Université de Montréal

Cigarette Smoking Trajectories in Adolescents

par Béatrice Lauzon

École de santé publique, Département de médecine sociale et préventive

Thèse présentée à la Faculté des études supérieures et postdoctorales
en vue de l'obtention du grade de Philosophiae Doctor (Ph.D.) en santé publique
Option épidémiologie

Septembre 2020

Université de Montréal
École de santé publique, Département de médecine sociale et préventive

Cette thèse intitulée

Cigarette Smoking Trajectories in Adolescents

Présentée par

Béatrice Lauzon

A été évaluée par un jury composé des personnes suivantes

Bernard Simon Leclerc
Président-rapporteur

Jennifer O'Loughlin
Directrice de recherche

Marie-Pierre Sylvestre
Codirectrice de recherche

Hélène Carabin
Membre du jury

Tara Elton-Marshall
Examinatrice externe

Résumé

Introduction

Malgré un progrès considérable durant les dernières années, beaucoup de jeunes Canadiens fument la cigarette. La plupart des fumeurs rapportent avoir initié le tabagisme à l'adolescence ou au début de l'âge adulte. Les trajectoires développementales du tabagisme présentent une description des changements du niveau de consommation de cigarettes durant de longues périodes. Celles-ci peuvent être modélisées à l'aide de programmes statistiques qui groupent les individus démontrant le même type de changement(s) à travers le temps en sous-groupes de trajectoires. L'analyse des trajectoires pourrait potentiellement être utile à la santé publique quant à ses efforts pour contrer le tabagisme. En effet, celles-ci pourraient permettre l'identification de sous-groupes qui diffèrent selon leur consommation tabagique à travers le temps. Des facteurs de risque pour et des conséquences de ces trajectoires pourraient donc être identifiés qui pourraient s'avérer utiles pour l'intervention pour réduire ou prévenir le tabagisme chez les jeunes. Les objectifs de cette thèse étaient de: (1) résumer la littérature portant sur les modèles de trajectoires de consommation de cigarette chez les adolescents; (2) au sein d'une cohorte de 1293 participants âgés de 12 et 13 ans au début de l'étude, de modéliser les trajectoires incidentes de consommation de cigarettes et de comparer celles-ci avec les trajectoires mixtes (c'est-à-dire qui combinent les fumeurs incidents et prévalents); (3) dans la même cohorte d'adolescents, d'étudier l'initiation de la cigarette et du cannabis en relation l'une à l'autre, ainsi que leur lien(s) potentiel(s) avec les trajectoires de consommation de la cigarette.

Méthodes

Nous avons effectué une revue systématique de la littérature portant sur les études présentant des modèles de trajectoires tabagiques chez les adolescents. Ces recherches ont fait usage de PubMed et EMBASE de 1980 à 2018 et 43 articles ont été retenus. Les données extraites de chaque article portaient sur la population à l'étude, le contexte et plan d'étude, les analyses statistiques et les résultats. Afin de déterminer si certains aspects du plan des études auraient pu avoir influencé le nombre ou la forme des trajectoires identifiées, nous avons groupé les études en catégories. Celles-ci étaient basées sur la taille de l'échantillon, le type de variable

tabagique utilisée lors de la modélisation des trajectoires, l'axe du temps et le nombre de points de données utilisés pour estimer les trajectoires. Nous avons alors examiné les distributions ainsi que le nombre et les formes des trajectoires identifiés selon ces caractéristiques.

Dans le deuxième manuscrit nous avons modélisé et comparé deux ensembles de trajectoires tabagiques. Le premier modélisait uniquement les fumeurs incidents alors que le second modélisait à la fois les fumeurs incidents et prévalents. Nos données proviennent d'une cohorte de 1293 étudiants en septième année au début de l'étude. Proc Traj et le logiciel SAS ont été utilisés afin de modéliser les trajectoires de consommation de cigarettes chez ces adolescents. L'analyse des trajectoires incidentes incluait 307 fumeurs incidents, alors que l'analyse des trajectoires dites «mixtes» incluait 307 fumeurs incidents et 338 fumeurs prévalents qui rapportaient avoir déjà essayé de fumer la cigarette au début de l'étude. Nous avons par la suite étudié plusieurs facteurs de risque potentiels pouvant être associés avec ces trajectoires dans les sphères socio-démographique, de la cigarette, psychosociale et du mode de vie. Le statut tabagique et la dépendance à la nicotine ont été étudiées comme conséquences potentielles à l'âge de 24 ans.

À l'aide des mêmes données, nous avons comparé les participants à travers les trajectoires de tabagiques obtenues lors du manuscrit 2, ainsi qu'avec les individus n'ayant jamais fumé durant l'adolescence, les participants qui avaient déjà tenté de fumer la cigarette lors de leur entrée dans l'étude et les fumeurs incidents qui ont cessé peu après l'initiation. À l'aide de méthodes descriptives, nous avons effectué une comparaison entre ces groupes de la séquence d'initiation pour la cigarette et le cannabis, ainsi que de l'âge au premier usage de cannabis. Avec des modèles de régression, nous avons identifié des prédicteurs du temps écoulé entre l'initiation de la cigarette et du cannabis.

Résultats

Les résultats de notre revue de la littérature ont révélé une hétérogénéité considérable entre les études, qui pourrait être le résultat de variations réelles de la consommation tabagique. Cependant celle-ci pourrait aussi avoir résulté de variations quant au plan d'études et des décisions quant à la modélisation des données. Un résultat clé était que seulement deux études avaient modélisé le tabagisme incident et ainsi représenté le cours naturel du tabagisme.

Cinq trajectoires furent identifiées dans nos analyses chez les fumeurs incidents: les fumeurs au tabagisme léger et stable, léger et décroissant, augmentant lentement, augmentant moyennement et augmentant de façon précoce et importante. Quatre trajectoires furent identifiées pour le modèle combinant les fumeurs incidents et prévalents. La vitesse de changement était généralement moins importante pour les trajectoires tabagiques obtenues à partir du modèle mixte. Dans les deux modèles, les trajectoires où le tabagisme allait en augmentant étaient associées à de plus hauts niveaux de consommation de cigarettes et de dépendance à la nicotine à l'âge (jeune) adulte.

Nous avons comparé les cinq groupes obtenus du modèle de trajectoires de fumeurs incidents avec les individus n'ayant jamais fumé durant l'adolescence, ainsi qu'avec les fumeurs prévalents et les fumeurs incidents qui ont cessé peu après l'initiation. Malgré le fait que l'initiation à la cigarette semble généralement avoir lieu avant l'initiation au cannabis, plusieurs des groupes avaient une proportion de participants qui avaient initié le cannabis avant la cigarette. L'initiation au cannabis avait généralement lieu à un âge moins élevé chez les participants ayant une consommation plus importante de cigarettes. L'âge à l'entrée dans l'étude était le seul facteur associé de façon statistiquement significative avec le temps écoulé entre l'initiation à la cigarette et l'initiation au cannabis chez les participants ayant initié la cigarette avant le cannabis. Aucun facteur n'était associé au temps écoulé entre l'initiation au cannabis et la première bouffée de cigarette chez les individus ayant initié le cannabis avant la cigarette. La proportion de participants rapportant avoir jamais consommé du cannabis était plus élevée dans les groupes tabagiques ayant une consommation plus importante de cigarettes.

Discussion

Les études publiées jusqu'à présent n'ont pas établi l'utilité de la modélisation des trajectoires tabagiques pour la santé publique: il s'agit d'une méthode utile quand il s'agit de résumer et de décrire la consommation tabagique à travers le temps. Cependant il n'est présentement pas clair que ce genre d'analyse puisse offrir des informations additionnelles au-delà des approches plus traditionnelles. Modéliser un mélange de fumeurs incidents et prévalents peut servir à camoufler le cours naturel du développement de l'habitude tabagique ainsi que des facteurs de risque y qui sont associés. Nous recommandons donc que les études futures dans ce domaine modélisent les trajectoires incidentes de consommation tabagique. Nos

résultats présentent aussi de nouvelles informations sur l'initiation de la cigarette et du cannabis qui devraient mener à une meilleure compréhension de l'interaction entre ces deux substances. L'usage de cannabis et le fait du fumer la cigarette sont liés l'un à l'autre de façon complexe: nos résultats suggèrent qu'il est important de considérer l'usage d'une substance dans son contexte, soit en présence d'autre(s) substances.

Mots-clés : Cigarette, tabagisme, adolescence, jeunes adultes, trajectoires développementales, incidence, prévalence, facteurs de risque, issues/conséquences, modélisation de trajectoires, cannabis

Abstract

Introduction

Despite undeniable progress, far too many Canadian youth still smoke cigarettes. Most smokers report initiation in adolescence or young adulthood. Developmental trajectories of cigarette smoking are descriptions of change in smoking over relatively long time-periods which can be modeled using software platforms which group individuals with similar developmental patterns into subgroups of trajectories. Trajectory analysis may be useful to public health efforts to curb smoking because it permits identification of subgroups that differ according to the pattern of growth in cigarette smoking. Risk factors for, and outcomes of these trajectories can be identified, which may be amenable to intervention to effect positive change in youth smoking. The objectives of this thesis were: (1) to synthesize the literature on studies of adolescent cigarette smoking trajectories; (2) in an adolescent cohort of 1293 participants age 12-13 years at inception, to model trajectories of incident cigarette smoking and compare incident trajectories with mixed (i.e. incident and prevalent smokers combined) trajectories; (3) in the same adolescent cohort, to study cannabis and cigarette initiation in relation to each other and to cigarette smoking trajectories.

Methods

We carried out a systematic review of studies of cigarette smoking trajectories in adolescents. PubMed and EMBASE were searched 1980–2018 and 43 articles retained. Data were extracted from each article relating to study population, setting and design, statistical analyses, and results. In order to assess whether study design features might have influenced the number or shapes of trajectories identified, we collapsed studies into categories based on study sample size, type of cigarette smoking indicator used, time axis, and number of data points used to estimate trajectories. We examined the distributions of number and shapes of trajectories identified according to these characteristics.

In Manuscript 2 we modeled and compared two sets of cigarette smoking trajectories. The first included incident cigarette smokers alone while the second included both incident and prevalent cigarette smokers. Data were from a cohort of 1293 grade 7 students at baseline. We used SAS Proc Traj to model trajectories of cigarette smoking in adolescence. Analysis of

incident trajectories included 307 incident smokers; analysis of "mixed" trajectories included 307 incident and 338 prevalent smokers who reported having ever smoked at baseline. We studied various potential sociodemographic, smoking-related, psychosocial, and lifestyle risk factors in relation to trajectory group. Smoking status and nicotine dependence outcomes were assessed at age 24.

Using these data, we compared participants across the cigarette smoking trajectories obtained in Manuscript 2, as well as never smokers during adolescence, baseline ever smokers, and incident smokers who stopped. Using descriptive methods, we compared these groups according to age at first cannabis use and determined the order of initiation of tobacco and cannabis among participants. Using regression, we identified predictors of elapsed time between tobacco and cannabis initiation.

Results

The findings of our review revealed considerable heterogeneity between studies which may have reflected real variations in cigarette smoking but which may also have resulted from variation in study design features and modelling decisions. A key finding was that only two studies modeled incident smoking and depicted the natural course of smoking.

Five trajectories were identified in incident smokers: stable-low consumers, low-level decreasers, slow escalators, moderate escalators, and early-rapid escalators. Four trajectories were identified in the mix of incident and prevalent smokers. The rate of change was generally attenuated across curves in the mixed trajectory analysis. Escalating trajectories in both analyses were associated with higher levels of cigarette consumption and nicotine dependence in early adulthood.

When comparing these five incident trajectory groups with never smokers, prevalent smokers at baseline, and incident smokers who stopped, we report that while first puff on a cigarette usually preceded cannabis use, several groups had a number of participants who initiated cannabis before cigarettes. Age at first cannabis use was generally lower in participants with heavier cigarette consumption. Age at baseline was the only significant risk factor for time to first cannabis use among ever smokers; no factors were associated with time to first cigarette

use among ever cannabis users. Ever use of cannabis was higher in trajectory groups with heavier cigarette consumption.

Discussion

The literature published thus far has not established the usefulness of this methodology to public health: it is useful for summarizing and describing cigarette smoking patterns, yet it is not clear whether trajectory analyses offer additional information useful to public health. Modeling a mix of incident and prevalent adolescent smokers obscures depiction of the natural course of smoking onset and identification of factors associated with the natural course of cigarette smoking: we therefore recommend that future studies in this area model incident trajectories of cigarette smoking. Our findings also present new information on the initiation of cigarettes and cannabis which should lead to a greater understanding of the interplay between these substances. Cannabis use and cigarette smoking relate to each other in complex ways: our results suggest that it is important to consider use of any one substance in the context of use with other substances.

Keywords: Cigarette smoking, adolescence, young adulthood, developmental trajectories, incidence, prevalence, risk factors, outcomes, trajectory modeling, cannabis.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

SES: Socio-economic status

U.S.: United States of America

LCGA : Latent class growth analysis

LGMM: Latent growth mixture modeling

SD: Standard deviation

N, *n*: Number of participants/subjects

CI: Confidence interval

SHS: Second-hand smoke

NDIT: Nicotine Dependence in Teens Study

RAPI: Rutgers Alcohol Problem Index

DNA : Deoxyribonucleic acid

CRCHUM: Centre de Recherche du Centre Hospitalier de l'Université de Montréal

CHUM: Centre Hospitalier de l'Université de Montréal

QCAHSS: Quebec Child and Adolescent Health and Social Survey

BMI: Body Mass Index

MVPA: Moderate and Vigorous Physical Activity

mFTQ: Modified Fagerstrom Tolerance Questionnaire

ICD-10: International Classification of Diseases – Tenth Revision

GRoLTS: Guidelines for Reporting on Latent Trajectory Studies

CEGEP: Collège d'enseignement général et professionnel

BIC: Bayes Information Criterion

SAS: Statistical Analysis System (software platform)

MeSH: Medical Subject Heading

EMBASE: Excerpta Medica Database

ND: Nicotine dependence

ANOVA: Analysis of variance

FRQS: Fonds de recherche du Québec – Santé

IQR : Interquartile range

NS: Not significant

NR: Not reported

NA: Not available

PRISMA : Preferred Reporting Items for Systematic Review and Meta-Analyses

GMM: Growth mixture modeling

LCA: Latent class analysis

LTA: Latent trajectory analysis

LCGM: Latent class growth modeling

LGCM: Latent growth curve modeling

LCPA: Latent class-profile analysis

LRT: Likelihood ratio test

AIC: Akaike Information Criterion

ICC: Intraclass correlation coefficient

ICC_2: Intracluster correlation coefficient

OR: Odds ratio

HR: Hazard ratio

Pour mes parents: je n'aurais pas pu le faire sans vous…

And in memory of Cynthia Jamal Isrep

Acknowledgements

I would like to express my sincere thanks and gratitude to my thesis supervisors, Drs. Jennifer O'Loughlin and Marie-Pierre Sylvestre for their encouragement, help, and patience. I am very grateful for their constant help in completing this thesis: I honestly could not have completed this without the valuable input and corrections.

I also thank my best friends Angela Brewer and Leslie Schneider, as well as my parents Maire and Denis Lauzon for and their constant support.

J'aimerais exprimer ma gratitude et remercier mes superviseures, Jennifer O'Loughlin et Marie-Pierre Sylvestre. Je les remercie pour leur encouragement, leur aide et leur patience lors des dernières étapes de ce processus. Je n'aurais pas pu réussir sans votre aide et vos corrections tout au long de ce processus.

Je tiens aussi à remercier mes amies Angela Brewer et Leslie Schneider, ainsi que mes parents Maire and Denis Lauzon pour leur précieux soutien durant cette période.

Chapter 1 – Introduction

Cigarette smoking has been referred to by the World Health Organization as “one of the biggest public health threats the world has ever faced”. [1] Tobacco kills up to half its users and causes more than 7 million deaths worldwide each year. More than 6 million deaths annually are the direct result of tobacco use, while the rest result from exposure to second-hand smoke. [1] Cigarettes are the most common form of tobacco used in most countries. [2] Approximately 80% of the more than 1 billion smokers in the world today live in low- and middle-income countries where the burden of tobacco-related illness and death is heaviest. [1]

There has been considerable progress in tobacco control in many countries over the past few decades, including in Canada and the United States (U.S.). Cigarette smoking among U.S. adults declined from 20.9% in 2005 to 15.5% in 2016. [3] In Canada approximately half of Canadians age ≥15 years smoked in 1965, compared to just 13% in 2015. [4] Use has also declined among youth. Current daily (i.e., survey participants who responded "every day" to the question: "At the present time do you smoke cigarettes every day, occasionally or not at all?") and non-daily cigarette smoking (i.e., survey participants who responded "occasionally") has declined among youth age 15-19 since 1999 in Canada [5], with prevalence estimated at 7.9% in 2017 (i.e., 2.9% daily and 4.9% non daily). [5], [6] In 2017, the prevalence of cigarette smoking among daily and non daily smokers in the province of Quebec aged ≥15 years was 15.7% (15.7 [12.4-19.1]). Four provinces had higher smoking prevalence estimates than Quebec (i.e., Newfoundland and Labrador, Alberta, Saskatchewan, and Nova Scotia). [7] (Current smoking was defined following the reply to the question, “At the present time do you smoke cigarettes every day, occasionally, or not at all?”, current smokers included individuals defined as occasional or daily smokers based on their replies to the question. [8]) Finally, despite undeniable progress, an important proportion of youth still smoke. Current cigarette smoking increases with age among youth [9] – the prevalence was 17.7% among 19-year-olds in Canada in 2014-2015, and daily cigarette smoking was 7.7%. [9]

Youth smoking is of paramount importance to public health since the vast majority of smokers report initiating cigarette smoking in adolescence or young adulthood. [10] In 2012, the U.S. Surgeon General’s Report reported that virtually all smokers acquire the habit by age

26; nearly 9 of 10 smokers start smoking by age 18, and 99% start by age 26. Progression from occasional to daily smoking almost always occurs by age 26. [11] Previously published data from the Nicotine Dependence in Teens (NDIT) Study (i.e., the study that provided the database used in two manuscripts presented in this thesis) suggest that the incidence of cigarette smoking initiation (i.e., reporting having ever smoked ≥1 puff(s) of a cigarette (lifetime)) decreases with age during adolescence and into young adulthood [12], although another study which investigated several forms of tobacco in addition to cigarettes [13], reported that the incidence of tobacco use is now higher in young adulthood. This latter study provides a compelling rationale for monitoring the natural course of cigarette smoking onset in a world where the forces that drive cigarette use in youth are constantly changing. New legislation including the legalization of cannabis in many parts of the world, and the emergence of new tobacco-related products such as e-cigarettes can have enormous impact on youth smoking. Addressing youth smoking is therefore critically important to public health, and there is an ongoing need to better understand the early natural course of cigarette smoking so that this knowledge can be incorporated into updating prevention policy and practice.

This PhD dissertation focuses on studies that use trajectory analyses to identify developmental patterns of cigarette smoking in adolescents. This analytic method has proliferated in the past two decades because of the appeal of summarizing longitudinal patterns into clear, easily-interpretable graphical representations, availability of easy-to-use statistical packages (e.g., Proc Traj in SAS) and ever-improving add-ons for handling time-varying covariates and attrition. [14], [15] In addition to depicting developmental patterns, trajectory analyses identify subgroups at higher risk of sustained and heavier smoking, and they help elucidate outcomes of specific trajectory patterns. Proponents of trajectory analyses argue that the differing risk profiles across developmental patterns increase understanding of the natural course of smoking onset [16], and that these analyses can pinpoint windows of opportunity for intervening to prevent addiction and long-term smoking.

The central aim of this thesis was to attempt to use trajectory modeling to increase understanding of cigarette smoking onset in youth. An important and related objective was to critically assess the usefulness of cigarette smoking trajectory modeling to public health. After this Introduction, Chapter 2 of this thesis introduces concepts relevant to adolescent cigarette

smoking trajectories, overviews the literature pertaining to youth cigarette smoking trajectories, and summarizes the literature relating to onset of cigarette smoking in relation to cannabis use. Chapter 3 presents a single objective relating to the systematic review carried out in Article 1. Article 1 (published in the International Journal of Drug Policy and presented in Chapter 4) presents a systematic review of the literature on cigarette smoking trajectories in adolescents. Chapter 5 then describes the objectives arising from the searches of the literature presented in Article 1 and section 2.3. Chapter 6 describes the methods used in Manuscripts 2 and 3 and Chapter 7 presents Manuscripts 2 and 3. Manuscript 2 presents our own analyses, wherein we modeled incident cigarette smoking trajectories in order to determine whether time window(s) of opportunity for intervention to reduce or prevent cigarette smoking can be identified. This manuscript also compared trajectories in new (incident) adolescent smokers and in a mix of incident and ever- (prevalent) smokers at baseline. Manuscript 3 sought to consider the important question of the influence of cannabis, a commonly used psychoactive substance in youth, on cigarette smoking status including incident trajectories. We described the order of initiation of cigarette smoking and cannabis use, as well as proportion of ever use and age at first cannabis use across smoking status categories (including incident smoking trajectories). We also sought to identify predictors of elapsed time between cannabis and cigarette smoking initiation among dual users. Chapter 8 discusses the main results, the strengths and limitations of this work, and the contributions of the findings to public health and Chapter 9 concludes the thesis.

Chapter 2 – Background

This section overviews the literature pertaining to youth cigarette smoking and cigarette smoking trajectories. It begins by describing how the smoking acquisition process has been conceptualized and introduces the concept of cigarette smoking trajectories. Risk factors and outcomes of cigarette smoking trajectories in youth are addressed next. Finally, current knowledge on co-use of cigarettes and cannabis is discussed as background for Manuscript 3.

2.1 Stages in cigarette smoking acquisition

Sections 2.1 and 2.2 present definitions and other concepts relating to the conceptualization of cigarette smoking trajectories used in this thesis.

An early conceptualization of cigarette smoking onset is the notion of stages of cigarette smoking. As described in the 1994 Surgeon General's Report [17], becoming a regular smoker is a process which can be conceptualized as consisting of a series of 'stages' representing increasing levels of cigarette smoking. These stages are described as follows: (i) during the first stage, attitudes and beliefs about the utility of cigarette smoking are formed; (ii) the trying stage encompasses the first two or three times an individual smokes; (iii) experimentation, which includes repeated but irregular cigarette smoking; (iv) regular use, where one smokes on a regular basis, usually at least weekly, and increasingly across a variety of situations and personal interactions; (v) the final stage, nicotine dependence and addiction, is characterized by a physiological need for nicotine. Numerous researchers have questioned this conceptualization and suggest that milestones such as taking smoke into the lungs for the first time, first whole cigarette, monthly cigarette smoking, weekly cigarette smoking, and daily cigarette smoking are more salient descriptors of the smoking onset process. [18], [19] An additional issue pertaining to the more traditional conceptualization of the smoking onset process, is that nicotine dependence is portrayed as occurring only in the later stages. However recent research suggests that symptoms of nicotine dependence develop soon after first puff and can precede monthly, weekly and daily smoking. [18], [19]

There is a substantial literature investigating risk factors for the early stages of cigarette smoking, including a recent systematic review (Wellman et al. 2016 [20]) of 53 longitudinal

studies that identified risk factors for initiation (i.e., first few puffs). An increased risk of smoking onset was reported for the following factors: increased age/grade, lower socioeconomic status (SES), poor academic performance, sensation-seeking or rebelliousness, intention to smoke in the future, receptivity to tobacco promotion efforts, susceptibility to smoking, family members' smoking, having friends who smoke, and exposure to films. Higher self-esteem and parental monitoring/supervision of the child were protective.

Although specific cigarette smoking stages may have different sets of risk factors, there are no systematic reviews of risk factors for stages other than initiation. O'Loughlin et al. 2009 [21] reported sets of risk factors that differed for cigarette smoking initiation: younger age, single-parent family status, cigarette smoking by parents, siblings, friends, and school staff, stress, impulsivity, lower self-esteem, feeling a need to smoke cigarettes, not doing well at school, susceptibility to tobacco advertising, alcohol use, use of other tobacco products, and attending a cigarette smoking-tolerant school were reportedly significant for initiation. For daily cigarette smoking risk factors reported were: cigarette smoking by siblings and friends, feeling a need to smoke cigarettes, susceptibility to tobacco advertising, use of other tobacco products, and self-perceived mental and physical addiction. [21] Roberts et al. 2015 [22] also reported differences in the sets of risk factors for first puff (i.e., availability of cigarettes, peer deviance) and first whole cigarette (i.e., availability of cigarettes, parental monitoring, having ever puffed at the first of the two assessments). [22]

That different stages of cigarette smoking have differing sets of risk factors raises questions about the public health relevance of the conceptualization of the acquisition of cigarette smoking as a series of stages. If the aim of public health intervention is to mitigate regular cigarette smoking, predictors of earlier stages of smoking may not be as relevant as predictors of regular smoking. Focusing intervention on an earlier stage may be less impactful on regular smoking if individuals who made the transition from never smoking to first puff, do not progress to regular smoking. An alternative to the Surgeon General's conceptualization of smoking onset that may be more meaningful to public health, is as a continuous process which can be modeled based on changes in cigarette consumption over time.

2.2 Adolescent cigarette smoking trajectories

Sections 2.1 and 2.2 present definitions and other concepts relating to the conceptualization of cigarette smoking trajectories used in this thesis.

This section defines adolescent cigarette smoking trajectories and describes what is currently known about their potential usefulness to public health. Also discussed are published guidelines on reporting trajectory studies which aim to assist in evaluating the existing literature. The concepts of risk factors for, and outcomes of, cigarette smoking trajectories in youth are presented next. These topics are particularly relevant to identifying heavy smokers, as well as in identifying consequences of adolescent smoking in adulthood (i.e., potential outcomes).

2.2.1 Definition of developmental trajectories

Developmental trajectories have been defined as a description of change, usually in a behavior or characteristic of an individual over a relatively long time-period. [23] An alternative definition suggests that trajectories represent the natural course of a behavior over age or time. [24] Estimating developmental trajectories avoids some of the difficulties of studying cigarette smoking stages. For example, rather than focusing on a single cigarette smoking transition (e.g., from first few puffs to first whole cigarette), this approach models the development of cigarette smoking as a continuous process over time. Developmental trajectories also permit identification of subgroups of individuals that differ according to the pattern of growth. Rapidly increasing heavier cigarette smokers for example, can be contrasted with short-term or lighter smokers.

2.2.2 Single versus multiple trajectories

Developmental trajectories can be modeled as a single, mean overall trajectory representing the entire analytical sample (i.e., with risk factors identified to explain deviation(s) from this mean trajectory) using latent growth curve modeling. [25], [26] For example, Mathur et al. 2013 [27] modeled smoking among youth ages 12–16 using multilevel modeling to account for clustering, and a linear growth function to model cigarette smoking data. This study reported increased cigarette smoking over time in participants with lower individual SES, as well as differential effects of individual SES on adolescent cigarette smoking for higher and

lower neighborhood SES. In this case, a single overall trajectory was modeled, with some variation around the overall curve explained by individual SES and gender.

Modeling can also involve separating participants into distinct trajectory groups. Some of the variance in the sample is represented by these trajectory groups. [24] It is the latter approach which is relevant to this thesis. For example, Roberts et al. 2014 [28] used data of children from the Nurses' Health Study II, where data on offspring cigarette smoking were obtained over seven study waves. Four cigarette smoking trajectories were identified, based on the average number of cigarettes smoked per week at each age. These trajectories were labelled non-smokers, experimenters, late initiators leading to moderate consumption, and early initiators leading to high consumption. [28]

2.2.3 Empirical versus pre-defined trajectories

Developmental trajectories can be also be modeled by defining a set of trajectories a priori, without reference to new data or results. Windle and Windle 2001 [29] modeled four waves of data from students in 10^{th} or 11^{th} grade during the first study assessment. Prior to examination of the data, three trajectory groups were defined as follows: first, at each of the four waves, cigarette smoking categories were developed using the following scheme: individual cigarette smoking was first classified as 0 = no cigarette smoking in the last 6 months; 1 = < ½ pack/day in the last 6 months; 2 = ≥ ½ pack/day in the last 6 months. Then, three smoking groups were identified using the four waves of data. Abstainers/light cigarette smokers received a score of 0 on at least two of the four measurement occasions and never received a score of 2. Moderate smokers, on the other hand, received a score of 1 on at least two of the four measurement occasions and received a score of 2 on no more than two occasions. Finally, heavy smokers received a score of 2 on at least three of the four assessments. [29] Alternatively, modeling techniques can be used to derive trajectory groups empirically a posteriori and several statistical models can be used to do so. [28], [30], [31] It is the latter approach which is relevant to this thesis.

2.2.4 Trajectories of incident or mixed (incident and prevalent) smoking

Porta [32] defines prevalence as: "[a] measure of disease occurrence: the total number of individuals who have an attribute or disease at a particular time (…) divided by the population at risk (…) at that time." Incidence is defined as: "[t]he number of instances of illness commencing, or of persons falling ill, during a given period in a specified population". [32] In the context of cigarette smoking, these two concepts are invoked in this thesis to refer to modeling smoking in all cigarette smokers over time (i.e., incident and prevalent smokers combined) or new smokers only (i.e., incident smokers), respectively. Modeling incident smoking captures the early natural course of cigarette smoking. Modeling incident and prevalent smoking (i.e., modeling the prevalence of smoking over time in a population) provides a snapshot of archetypical trajectories in a given population over time. These two models differ in fundamental ways (one important distinction is at the level of the time axes used: incident analyses model time since cigarette initiation, while combined incident and prevalent analyses use time axes such as age or calendar time). By far the majority of articles describing cigarette smoking trajectories to date focus on modeling the prevalence of smoking over time. One issue addressed in this thesis is whether these two approaches to modeling cigarette smoking trajectories in adolescents result in differing patterns (i.e., in the number or shapes) in the trajectories obtained, as well as in differing sets of risk factors and outcomes of the trajectories.

2.2.5 Guidelines for Reporting on Latent Trajectory Studies (GRoLTS)

Guidelines for reporting on modeling developmental trajectories (also referred to as "latent trajectory studies" [33]) were recently suggested by van de Schoot et al. 2017 [34], with the objective of "enhancing the uniformity of reporting in latent trajectory studies so that the results presented are transparent (…) and can be used for comparisons, replications, systematic reviews, and meta-analyses". These guidelines (Table 1) were developed using a four-round Delphi study [35] of a group of experts.

Table 1. Guidelines for Reporting Latent Trajectory Studies (GRoLTS) [34]

Number	Item
1	Is the metric of time used in the statistical model reported?
2	Is information presented about the mean and variance of time within a wave?
3a	Is the missing data mechanism reported?
3b	Is a description provided of what variables are related to attrition/missing data?
3c	Is a description provided of how missing data in the analyses were dealt with?
4	Is information about the distribution of the observed variables included?
5	Is the software mentioned?
6a	Are alternative specifications of within-class heterogeneity considered (e.g., LGCA versus LGMM)* and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration?
6b	Are alternative specifications of the between-class differences in variance–covariance matrix structure considered and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration?
7	Are alternative shape/functional forms of the trajectories described?
8	If covariates have been used, can analyses still be replicated?
9	Is information reported about the number of random start values and final iterations included?
10	Are the model comparison (and selection) tools described from a statistical perspective?
11	Are the total number of fitted models reported, including a one-class solution?
12	Are the number of cases per class reported for each model (absolute sample size, or proportion)?
13	If classification of cases in a trajectory is the goal, is entropy reported?
14a	Is a plot included with the estimated mean trajectories of the final solution?
14b	Are plots included with the estimated mean trajectories for each model?
14c	Is a plot included of the combination of estimated means of the final model and the observed individual trajectories split out for each latent class?
15	Are characteristics of the final class solution numerically described (i.e., means, SD/SE, n, CI, etc.)?
16	Are the syntax files available (either in the appendix, supplementary materials, or from the authors)?

*LGCA = latent class growth analysis; LGMM = latent growth mixture modeling.

2.2.6 Risk factors and outcomes of cigarette smoking trajectories

Identification of risk factors for adolescent cigarette smoking trajectories can help characterize individuals who will develop heavy sustained smoking. Outcomes of adolescent cigarette smoking trajectories can serve to identify later (negative) outcomes associated with each trajectory (i.e., what happens to the individuals in specific trajectory groups in adulthood?). This section reviews what is known about risk factors and outcomes of adolescent cigarette smoking trajectories.

2.2.6.1 Definition of risk factors and outcomes

According to van de Schoot et al. 2017 [34], covariates can be added to a model of developmental trajectories in three ways: (i) as predictors of the dependent variable to control or explain variability in the dependent variable at specific time points; (ii) as predictors of the growth parameters to identify latent classes that cannot be explained by individual differences in the covariates; or (iii) they can be used to predict class membership. Given the public health relevance of identifying risk factors for higher versus lower risk trajectories, it is this third approach which is relevant in the current thesis. For the purposes of this thesis, "risk factors" refer to factors positively or negatively associated with trajectory class membership.

In addition to risk factors, numerous studies model "distal outcomes that are predicted by class membership". [16], [34] Hampson et al. 2013 [36] modeled trajectories of cigarette smoking in grades 9-12 and studied the relationship between these trajectories and: (i) cigarette use at age 20 or 21 years; and (ii) hookah use at 20 or 21 years. Lynne-Landsman et al. 2010 [37] modeled trajectories of tobacco use in grade 9-12 and investigated a wide range of possible outcomes in young adulthood (i.e., graduating "on time" from high school, antisocial personality disorder, major depressive disorder, unprotected sex, pregnancy (for females), having made someone pregnant (for males), alcohol abuse, alcohol dependence, marijuana abuse, marijuana dependence, illicit drug use, having a criminal record, having committed a violent offence as a juvenile, having committed a nonviolent offence as a juvenile, having committed a violent offence as an adult, having committed a nonviolent offence as an adult). Several of these variables (i.e., graduating "on time", antisocial personality disorder (lifetime), having gotten someone pregnant (for male participants), alcohol abuse, marijuana dependence, illicit drug use,

criminal record, nonviolent juvenile criminal offences, violent juvenile criminal offences) were significantly associated with cigarette smoking trajectory.

The relationships between trajectory group membership and health outcomes is important for public health because earlier identification of risk factors amenable to prevention could change the natural course of some behaviors, which could in turn affect these distal outcomes. An outcome of particular relevance to the current thesis is the "tracking" of cigarette smoking or the potential association(s) between adolescent cigarette smoking trajectory group membership and cigarette smoking in (young) adulthood.

2.2.6.2 Modeling risk factors

van de Schoot 2017 et al. [34] report that risk factors for trajectory group or class membership in trajectory analyses can be identified in several ways. Potential risk factors for class membership can be added into a joint model in which the class solution and the prediction of class membership are estimated simultaneously. Alternatively, this can be carried out by first estimating the developmental trajectory model, followed by an additional analytic step to identify potential risk factors (hereafter referred to as the 3-step method).

One strategy that uses the 3-step method is as follows: after the number of latent classes is determined without covariates in the model, the most probable class membership for each participant is identified. Multinomial regression is then used to identify risk factors for class membership.

Other strategies using the 3-step method were discussed by van de Schoot et al. 2017. [34] These include a method developed by Vermunt 2010 [38], which adjusts for errors in trajectory group assignment. Another is to weight each participant by the posterior probability of assignment (i.e., the probability that they were correctly assigned to a particular trajectory group). [16] These two approaches avoid the drawback of simply assigning participants to the most probable trajectory group and treating these assignments as definitive rather than probable, since the latter ignores the uncertainty in class membership and could be problematic if the posterior probabilities of assignment are generally low for one or more groups. [16]

2.2.6.3 Modeling outcomes

Neither van de Schoot et al. 2017 [34] nor Nagin [16] specifically addressed modeling outcomes of trajectory group membership. Instead they consider this type of variable only within the larger category that is the associations between covariates and trajectory assignment, which also includes risk factors. Outcomes of trajectory membership are usually modeled in much the same way as risk factors, by first obtaining the trajectory model and assigning participants to the most probable trajectory group. This is followed by a regression model, with the outcome variable defined as the dependent variable in the model. [39] Other studies have used chi-square tests to compare levels of a variable between trajectory groups. [36] In general, few authors make recommendations specific to the outcomes of trajectory membership.

2.2.7 Gap(s) in knowledge on cigarette smoking trajectories

Our research group published an earlier analysis (in 2005) of cigarette smoking trajectories in adolescents followed for 3.5 years using data from the NDIT Study. [30] Many studies on this topic have been published since. We identified three review articles that attempted to synthesize the literature on youth cigarette smoking trajectories. [40]–[42] Two were narrative reviews - Schepis and Rao 2005 [42] included only two studies, and Nelson et al. 2015 [40] included 12 articles. de Leeuw et al. 2010 [41] systematically reviewed 17 articles published between 2000 and 2007 and reported that the number of cigarette smoking trajectories ranged between 3 and 6. All studies reported two specific trajectories including a group of non-smokers and one of stable regular smokers. Most studies also report a group that increase smoking during adolescence, and several studies described a trajectory of quitters. However, this latter review reported very little information on each article (i.e., the only variables abstracted from each article were age range of participants, number of trajectories identified by the best fitting model, sample size, and a very brief description of trajectory types (e.g., “never smokers”, “early experimenters”, etc.)). An important gap in this literature therefore is the absence of an up-to-date, comprehensive systematic review of the literature on youth cigarette smoking trajectories. Such a review would serve to synthesize the literature in this area and help assess the usefulness of this method to public health. This is therefore the objective of Manuscript 1 in this thesis. We then developed our objectives for Manuscript 2, an analysis of

cigarette smoking trajectories in adolescents using NDIT data, based on the results of the review presented in Manuscript 1.

2.3 Adolescent cigarette smoking trajectories and cannabis use

Young people often use more than one psychoactive substance [43], so that it is important to consider cigarette smoking trajectories in the context of using multiple psychoactive substances. We examined the literature on co-use of cigarettes and cannabis, a commonly used substance in youth, in relation to cigarette smoking status including incident trajectories. Cannabis users often add tobacco to cannabis in blunts or spliffs to lengthen and enhance the experience, which could exacerbate nicotine dependence and affect cigarette smoking status. [44] The long-term health effects of co-using cannabis and tobacco on smoking, compared with using cannabis-only or tobacco-only, are not well understood. [45]

2.3.1 Prevalence of cannabis use

Cannabis is one of the most commonly used drugs in North America and it is the most commonly used illicit drug in North America (although it should be noted that cannabis use, including recreational use, has been legalized in certain jurisdictions as described below, see also section 2.3.4.2): in Canada this assertion predates legalization of recreational cannabis in adults. [46], [47] As of 2019, eleven (as well as the District of Columbia in the U.S.) U.S. states and Canada had legalized recreational cannabis use. [48]–[61] In 2018, 10.1% of persons ages ≥12 years in the U.S. (i.e., 27 million Americans) used cannabis in the past month. [62], [63] In 2017, 46.6% of Canadians age ≥15 years had ever used cannabis, and 14.8% (i.e., 4.4 million Canadians) reported past-year use. [46], [64] Among 15-19-year-old Canadians, 26.9% had ever-used cannabis and 19.4% (i.e., 390,000 adolescents) had used cannabis in the past year. [46], [64] In 2009-10, a higher proportion of youth age 15 years in Canada had used cannabis than in any other country, both in terms of lifetime use and past 30-day use. [65] In Quebec in 2014-15, 15% of persons age ≥15 years reported past-year cannabis use, an increase of 3% since 2008. Among 15-24-year-olds in Quebec, 38.4% reported past-year use in 2014-5, which represents an increase from 33.3% over the prevalence in 2008. [66]

2.3.2 Co-use of cigarettes and cannabis

The following sections present the literature on co-use of cigarettes and cannabis. Section 2.3.2.1 presents tables summarizing: (i) several issues relating to study quality, and (ii) relevant results. These will be presented and discussed in the text of the following sections. (sections 2.3.2.2 – 2.3.6)

2.3.2.1 Co-use: tables

Table 2 summarizes both the quality of individual studies, as well as relevant results. Table 3 summarizes issues relating to quality and presents results of reviews of the literature presented in the following sections. (sections 2.3.2.2 – 2.3.6) Only the studies rated "acceptable" or "good" are discussed in the text of the following sections (as well as in the rest of the thesis, with some rare exceptions where the poor quality of the study would be noted). Where possible I have reported measures of association reported in this literature as well as ranges of measures of association. However in many instances summarizing these results in simple ranges was not possible due to: (i) the small number of studies available on these topics, (ii) the fact that different types of measures of measures of association were reported across studies (e.g., hazard ratios, odds ratios, beta coefficients), and (iii) the lack of similarity and comparability between studies when the same type of measure of association was reported (e.g., variables coded differently, using different reference categories, or examining different outcomes such as nicotine dependence vs. current cigarette smoking).

Table 2. Evaluation of the quality, and presentation of results, of individual studies presented in Chapter 2

First author, year of publication	Study sample size (statistical power)	Response rate (%), losses to follow-up[1] (selection bias)	(1) Questions reported (Y/N)?[2] (2) Information re: validation (Y/N)?[2] (Information bias) (3) Reference category reported (Y/N)?[2]	Adjustment for potential confounders (Y/N)? (Confounding bias)[3]	Nature of comparison (D = dependent variable; I = independent variable[4])	Reported measure(s) of association (CI)	Study quality (0: poor, 1: acceptable, 2: good)[5]	Relevant to section
Leatherdale, 2007 [67]	20,275	73, CS	Y, N, Y	Y	D = Past-year use of cannabis I = Current cigarette smoking vs. never smoked*	OR = 6.35 (5.65, 7.14)	2	2.3.2
Leatherdale, 2007 [67]	20,275	73, CS	Y, N, Y	Y	D = Past-year use of cannabis I = Former cigarette smokers vs. never smoked*	OR = 3.07 (2.54, 3.71)	2	2.3.2
Agrawal, 2012 [68]	NA	NA, CS	N, N, NA	--	Descriptive only	--	1	2.3.2
Dugas, 2010 [69]	1293	N, 32	Y, N, NA	N	D = Previous year waterpipe use I = Past-year use of cannabis	--	1	2.3.2
Schauer, 2015 [70]	77,002	73 - 76, CS	N, N, NA	--	Descriptive only	--	1	2.3.2
Schauer, 2018 [43]	31,336	71 - 76, CS	N, N, NA	--	Descriptive only	--	1	2.3.2
Bélanger, 2011 [44]	881	87.8 (schools) and 94.2 (individuals), CS	N, N, NA	--	Descriptive only	--	1	2.3.3
Fairman, 2019 [71]	615,710	65, CS	Y, N, Y	Y (including for no. substances used, age at tobacco initiation)	D = Nicotine dependence in cigarette smokers I = Cannabis initiated before tobacco vs. tobacco initiated before cannabis*	OR = 0.92 (0.83, 1.02)	2	2.3.4.2
Attaiaa, 2016 [72]	22,774	N, CS	N, Y, NA	--	Descriptive only	--	1	2.3.4.2
Aung, 2004 [73]	103	N, CS	N, N, NA	N	D = No. of cigarettes per day	--	0	2.3.4.2

					I = Comparison of tobacco initiated before cannabis vs. cannabis before tobacco vs. similar age at initiation of both substances			
Degenhardt, 2010 [74]	85,088	45.9 - 87.7, CS	N, N, NA	--	Descriptive only	--	1	2.3.4.2
Degenhardt, 2010 [74]	85,088	45.9 - 87.7, CS	N, N, N	N	D = Tobacco dependence among tobacco users I = Cannabis use before tobacco and alcohol	OR = 1.1 (0.6, 1.6)	0	2.3.4.2
Degenhardt, 2009 [75]	5,692	71, CS	N, Y, N	Y (including age at tobacco initiation) **(not including no. substances initiated)**	D = Tobacco dependence among tobacco users I = Cannabis use before tobacco and alcohol	OR = 1.3 (0.8, 2.0)	1	2.3.4.2
Kennedy, 2016 [76]	56,555	73 – 76, CS	Y, N, Y	Y **(not including age at tobacco initiation or no. substances initiated)**	D = Cannabis before tobacco vs. tobacco before cannabis/both substances initiated at same age (African Americans) I = Past-month combustible tobacco use (cigarette, cigar) cannabis use vs. no past-month use*	OR = 1.03 (0.90, 1.18)	1	2.3.4.2
Kennedy, 2016 [76]	56,555	73 – 76, CS	Y, N, Y	Y **(not including age at tobacco initiation or no. substances initiated)**	D = Cannabis before tobacco vs. tobacco before cannabis/both substances initiated at same age (whites) I = Past-month combustible tobacco use (cigarette, cigar) cannabis use vs. no past-month use*	OR = 0.68 (0.63, 0.72)	1	2.3.4.2
Kennedy, 2016 [76]	56,555	73 – 76, CS	Y, N, Y	Y **(not including age at**	D = Cannabis and tobacco initiated at same age vs. tobacco before cannabis/cannabis before tobacco (African Americans)	OR = 1.09 (0.95, 1.31)	1	2.3.4.2

				tobacco initiation or no. substances initiated)	I = Past-month combustible tobacco use (cigarette, cigar) cannabis use vs. no past-month use*			
Kennedy, 2016 [76]	56,555	73 – 76, CS	Y, N, Y	Y **(not including age at tobacco initiation or no. substances initiated)**	D = Cannabis and tobacco initiated at same age vs. tobacco before cannabis/cannabis before tobacco (whites) I = Past-month combustible tobacco use (cigarette, cigar) cannabis use vs. no past-month use*	OR = 0.95 (0.90, 1.00)	1	2.3.4.2
Kennedy, 2016 [76]	56,555	73 – 76, CS	Y, N, Y	Y **(not including age at tobacco initiation or no. substances initiated)**	D = Tobacco initiated before cannabis vs. tobacco and cannabis at same age/cannabis before tobacco (African Americans) I = Past-month combustible tobacco use (cigarette, cigar) cannabis use vs. no past-month use*	OR = 0.90 (0.79, 1.02)	1	2.3.4.2
Kennedy, 2016 [76]	56,555	73 – 76, CS	Y, N, Y	Y **(not including age at tobacco initiation or no. substances initiated)**	D = Tobacco initiated before cannabis vs. tobacco and cannabis at same age/cannabis before tobacco (whites) I = Past-month combustible tobacco use (cigarette, cigar) cannabis use vs. no past-month use*	OR = 1.35 (1.28, 1.46)	1	2.3.4.2
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cigarettes before cannabis vs. cigarettes and cannabis at same age (analytical *n* = 583) I = DSM-IV Nicotine Dependence	OR = 1.13 (0.73 – 1.76)	0	2.3.4.2
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cannabis before cigarettes vs. cigarettes and cannabis at same age (analytical *n* = 79)	OR = 0.56 (0.26 – 1.18)	0	2.3.4.2

					I = DSM-IV Nicotine Dependence			
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cigarettes before cannabis vs. cigarettes and cannabis at same age (analytical *n* = 583)	OR = 1.03 (0.94 – 1.13)	0	2.3.4.2
					I = #DSM-IV ND symptoms Current			
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cannabis before cigarettes vs. cigarettes and cannabis at same age (analytical *n* = 79)	OR = 0.80 (0.69 – 0.94)	0	2.3.4.2
					I = #DSM-IV ND symptoms Current			
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cigarettes before cannabis vs. cigarettes and cannabis at same age (analytical *n* = 583)	OR = 1.02 (0.55 – 1.88)	0	2.3.4.2
					I = Current smoker (in past 12 months)			
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cannabis before cigarettes vs. cigarettes and cannabis at same age (analytical *n* = 79)	OR = 1.43 (0.48 – 1.21)	0	2.3.4.2
					I = Current smoker (in past 12 months)			
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cigarettes before cannabis vs. cigarettes and cannabis at same age (analytical *n* = 583)	OR = 1.49 (0.92 – 2.41)	0	2.3.4.2
					I = Maximum cigarettes in 24 hours (≥40)			
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cannabis before cigarettes vs. cigarettes and cannabis at same age (analytical *n* = 79)	OR = 0.78 (0.36 –1.68)	0	2.3.4.2
					I = Maximum cigarettes in 24 hours (≥40)			
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cigarettes before cannabis vs. cigarettes and cannabis at same age (analytical *n* = 583)	OR = 1.36 (1.02 – 1.82)	0	2.3.4.2

					I = Cigarettes per day (≥40; refers to normal daily consumption)			
Agrawal, 2011 [77]	1,812	N, CS	N, N, N	N	D = Initiation of cannabis before cigarettes vs. cigarettes and cannabis at same age (analytical *n* = 79) I = Cigarettes per day (≥40; refers to normal daily consumption)	OR = 1.09 (0.67 – 1.76)	0	2.3.4.2
Sánchez-Niubò, 2020 [78]	2,069	~50, CS	N, N, NA	--	Descriptive only	--	0	2.3.4.3
Mayet, 2012 [79]	29,393	98, CS	Y, N, ?	N?	D = Cannabis initiation I = Level/degree of tobacco use (tobacco initiation without daily use?)	HR = 1.23 (1.18, 1.29)	1	2.3.4.3
Mayet, 2012 [79]	29,393	98, CS	Y, N, ?	N?	D = Cannabis initiation I = Level/degree of tobacco use (among those with daily use?)	HR=2.55 (2.43, 2.67)	1	2.3.4.3
Wang, 2018 [80]	2,104 (school 1) 1,024 (school 2)	N, 21	N, N, N	Y	D = (Cigarette) Smoking initiation? I = (Importance of) Cannabis use?	Beta (school 1) = 0.48[£]; Beta (school 2) = 0.24 **(No CIs)**	0	2.3.4.3
Wang, 2018 [80]	2,104 (school 1) 1,024 (school 2)	N, 21	N, N, N	Y	D = Cannabis initiation? I = (Importance of) Cigarette use?	Beta (school 1) = 0.10; Beta (school 2) = 0.08 **(No CIs)**	0	2.3.4.3
Mayet, 2013 [81]	4,208	97.6, CS	N, N, Y	Y?	D = Cannabis initiation (tobacco users) I = Female vs. male*	HR = 0.7 (0.5, 0.9)	1	2.3.4.3
Mayet, 2013 [81]	4,208	97.6, CS	N, N, Y	Y?	D = Cannabis initiation (tobacco users) I = 17 – 30 years of age vs. 10 – 17 years*	HR = 0.7 (0.6, 0.8)	1	2.3.4.3
Mayet, 2013 [81]	4,208	97.6, CS	N, N, Y	Y?	D = Tobacco initiation (cannabis users) I = Female vs. male*	HR = 1.6 (1.0, 2.5)	1	2.3.4.3
Mayet, 2013 [81]	4,208	97.6, CS	N, N, Y	Y?	D = Tobacco initiation (cannabis users)	HR = 1.1 (0.8, 1.4)	1	2.3.4.3

					I = 17 – 30 years of age vs. 10 – 17 years*			
Kokkevi, 2006 [82]	10,050	N, CS	N, N, NA	N	D = Very early (≤13 years) vs. early (13 – 15 years) cannabis initiation	--	0	2.3.5
					I = Daily (tobacco) smoking			
Heffner, 2008 [83]	134 (clinical sample with ↑ proportion of substance users)	N, CS	N, N, Y	N	D = Current smoker vs. nonsmoker	OR = 0.58 (0.37, 0.92)	0	2.3.5
					I = Age at onset of cannabis use			
Pilatti, 2017 [84]	4,083	~90, CS	N, N, NA	N	D = Past-month use of tobacco	--	0	2.3.5
					I = Initiation of cannabis at ≤16 years vs. >16 years			
Pilatti, 2017 [84]	4,083	~90, CS	N, N, NA	N	D = Past 7 day use of tobacco	--	0	2.3.5
					I = Initiation of cannabis at ≤16 years vs. >16 years			
Moore, 2001 [85]	174 (all were cannabis-dependent)	N, CS	N, N, Y	Y	D = Ex-(cigarette) smokers vs. current smokers	OR = 1.25 (1.06, 1.48)	0	2.3.5
					I = Age of 1st cannabis use (continuous?)			
Moore, 2001 [85]	174 (all were cannabis-dependent)	N, CS	N, N, Y	Y	D = Never (cigarette) smokers vs. current smokers	OR = 1.22 (1.04, 1.44)	0	2.3.5
					I = Age of 1st cannabis use (continuous?)			
Richmond-Rakerd, 2017 [86]	9,421	79, ~24.3	Y, N, NA	N	D = Tobacco use frequency (i.e., how many days smoked in past month)	Intercept = −0.31 ($p < 0.01$); slope = −0.29 ($p < 0.01$) **(No CIs)**	1	2.3.5
					I = Age of 1st cannabis use (continuous?)			
Richmond-Rakerd, 2017 [86]	9,421	79, ~24.3	Y, N, NA	N	D = Tobacco use quantity (no. cigarettes smoked per day in past month)	Intercept = −0.24 ($p < 0.001$); slope = 0.23 ($p < 0.01$) **(No CIs)**	1	2.3.5
					I = Age of 1st cannabis use (continuous?)			
Timberlake, 2007 [87]	5,963	N, 26.7	N, N, Y	Y	D = Nicotine dependence by 3rd wave/end of study (among never daily cigarette smokers at baseline, who had smoked ≥1 cigarette by final survey)	OR = 0.93 (0.85, 1.02) (all, analytical $n = 1171$)	1	2.3.5

					I = Age 1st cannabis use (continuous), among cannabis ever users			
Timberlake, 2007 [87]	5,963	N, 26.7	N, N, Y	Y	D = Nicotine dependence by 3rd wave/end of study (among never daily cigarette smokers at baseline, who had smoked ≥1 cigarette by final survey)	OR = 1.14 (0.95, 1.36) (18-22 years at end of study, analytical *n* = 527	1	2.3.5
					I = Age 1st cannabis use (continuous), among cannabis ever users			
Timberlake, 2007 [87]	5,963	N, 26.7	N, N, Y	Y	D = Nicotine dependence by 3rd wave/end of study (among never daily cigarette smokers at baseline, who had smoked ≥1 cigarette by final survey)	OR = 0.82 (0.73, 0.93) (23-27 years at end of study, analytical *n* = 644	1	2.3.5
					I = Age 1st cannabis use (continuous), among cannabis ever users			

[1]Longitudinal studies only. (This item is not applicable to cross-sectional studies.) Losses to follow-up in longitudinal studies were classified as follows: ≤10% excellent, 10-30% good, 30-50% acceptable, >50% unacceptable). The proportions shown do not take into account additional exclusions such as those relating to item non response regarding substance use variables of central importance to the article.

[2]Refers to whether the exact question(s) and associated response items were reported, whether the reference category(ies) used in the analyses was reported (in the case of continuous measures, this item refers to whether coding of the variable was specified), and whether any information regarding validity and/or reliability of variables used in the studies (i.e., specifically, those relating to the associations reported in this table) was reported. (NB: If only partial information on validity or reliability of relevant variables was reported, due to the lack of this type of information in published articles, this item was still coded as Y.) (For the definition of reliability and validity used in this thesis, please refer to section 8.3.2.)

[3]None of the reviewed studies presented directed acyclic graphs (DAGs) to show the probable relations between variables in the conceptual model of each study. It is therefore difficult to know whether confounders were likely to be true confounders vs. intermediate variables vs. colliders. (Confounding is generally defined as a situation where the exposure and outcome of interest share a common cause thereby biasing the association measure; an intermediate variable is a variable on the causal pathway between exposure and outcome; collider stratification bias occurs when conditioning on a common cause of exposure and outcome.)[88]–[90]

[4]Reference category is indicated with an asterisk.

[5]Ranking is based on the information reported in this table (the exception is Agrawal 2012, where little information was reported but the source of the data was the U.S. survey on National Drug Use and Health).

CI = confidence interval. NA = not applicable. CS = cross-sectional study. OR = odds ratio. HR = hazard ratio. Y: Yes. N: No. D: Dependent variable. I: Independent variable.
*Indicates reference category. £indicates a statistically significant association (no CI).

Table 3. Evaluation of the quality, and presentation of results, of reviews presented in Chapter 2

First author, year of publication	Is the article selection process described in the article (Y/N)?	Does the article include a diagram of the article selection process[1] (Y/N)?	Number of studies retained for review	Measure(s) of association described[2,3] (Y/N)? **(1)** Measure of association described? **(2)** Description of variables? Question(s) used in individual studies? **(3)** Reference category described? **(4)** Adjusted for confounding? **(5)** Confidence intervals reported? Individual study sample sizes?	Nature of comparison (D = dependent variable; I = independent variable[5])	Reported ranges for measure(s) of association (CI)[4]	Review quality (0: poor, 1: acceptable, 2: good)[4]	Relevant to section
Rabin, 2015 [91]	N	N	NA	(1) None (2) None (3) -- (4) -- (5) --	--	None	0	2.3.2
Ramo, 2012 [92]	Y	N	163 (NB: No. studies involved in each result NR)	(1) N (2) N, N (3) N (4) NR (5) NR, NR	--	None	0	2.3.2
Peters, 2012 [93]	Y	Y	28	(1) Y (2) Y, N (3) Y (4) Y (what variables adjusted for is NR) (5) N, Y	D = Cannabis use disorders I = Tobacco+ cannabis vs. cannabis alone*	ORs = 0.71 to 27 (CIs NR, sample size range: ~134-43,093)	1	2.3.2
Peters, 2012 [93]	Y	Y	28	(1) Y (2) Y, N (3) Y (4) Y (what variables adjusted for is NR) (5) N, Y	D = Tobacco use disorders I = Tobacco+ cannabis vs. tobacco alone*	ORs = 0.58 to 3.6 (CIs NR, sample size range: ~134-43,093)	1	2.3.2

[1]As recommended by the PRISMA guidelines. [94] Either the text or the figure should provide details regarding the inclusion and exclusion criteria used by the review.
[2]Refers to whether details regarding the measures of association were reported for each study (or whether this was attempted and reported for all studies for which the information was available)?
[3]None of the reviews presented directed acyclic graphs (DAGs) to show the probable relations between variables in the conceptual model of each study. It is therefore difficult to know whether confounders were likely to be true confounders vs. intermediate variables vs. colliders. (Confounding is generally defined as a situation where the exposure and

outcome of interest share a common cause thereby biasing the association measure; an intermediate variable is a variable on the causal pathway between exposure and outcome; collider stratification bias occurs when conditioning on a common cause of exposure and outcome.) [24]–[26]
[4]Ranking is based on the information reported in this table.
[5]Reference category is indicated with an asterisk.
NA = not available/reported. CI = confidence interval. *n* = sample size. NR = not reported. Y: Yes. N: No. NB: Note well.

2.3.2.2 Literature on co-use

Tobacco and cannabis use co-occur in individuals. (Agrawal et al., 2012; E. Dugas et al., 2010; Leatherdale et al., 2007; Schauer et al., 2015; Schauer & Peters, 2018) In 2013, Schauer and Peters 2018 [43] reported that 5.4% of U.S. youth ages 12-17 years reported past-month co-use of tobacco and marijuana, 2.2% reported marijuana-only use, and 3.9% reported tobacco-only use. In the U.S. population age ≥12 years in 2009, 57.9% of cigarette smokers compared to 11.9% of non-smokers, reported a lifetime history of cannabis use. Ninety percent of cannabis users versus 46.8% of nonusers, reported smoking cigarettes at some point during their lifetime. [68] In Canadian youth in grades 7-9 in 2014-5, ever use of cannabis was reported by 91.8% of current smokers. Only 3.3% of never smokers reported ever use of cannabis. [8], [95] According to the latest data available (2017) from the Canadian Tobacco, Alcohol and Drugs Survey, 22% of individuals ≥15 years who reported past-year use of cannabis reported mixing it with tobacco and 34% reported chasing (smoking a tobacco product right after smoking cannabis). [46]

Co-use likely occurs in a number of different ways. In a qualitative study of Seattle-area adults age 18-24 years, Schauer et al. 2016 [96] identified three modes of cannabis and tobacco co-use: (i) sequential use (i.e., using marijuana and tobacco in short succession, one after another); (ii) substitution (i.e., using both substances in different times and places); and (iii) co-administration (i.e., simultaneous use of both substances).

Relative to cannabis only use, co-use of cannabis and tobacco is associated with a greater likelihood of cannabis use disorders, more psychosocial problems and poorer cannabis cessation outcomes. [93] Relative to tobacco use only, co-occurring use with cannabis was not consistently associated with a greater likelihood of tobacco use disorders, more psychosocial problems or poorer tobacco cessation outcomes. [93] For the purposes of this thesis co-use refers to any co-use of cannabis with cigarettes, since much of the available data, including in NDIT (see below), does not specify whether the cannabis consumed also contained tobacco.

Overall results

Of the studies cited above, most provided descriptive (i.e., prevalence) results, which are described above. (Table 2 and current section) The exceptions are Leatherdale et al., 2007 [67]

and a review by Peters et al., 2012[93]. Leatherdale et al., 2007 [67] reported the following odds ratios (ORs) associated with risk of use of a second substance, given use of the first:

1. OR for **past-year use of cannabis**, according to **current vs. never cigarette smoking** (i.e., the latter was the reference category): 6.35 (5.65, 7.14);
2. OR for **past-year use of cannabis**, according to **former vs. never cigarette smoking** (reference category): 3.07 (2.54, 3.71).

Peters et al., 2012[93] reported the following range of associations for cannabis use disorders:

1. OR range for **cannabis use disorders,** according to **tobacco and cannabis use vs. cannabis alone:** 0.71 to 27 (no confidence limits);
2. OR range for **tobacco use disorders,** according to **tobacco and cannabis use vs. tobacco alone:** 0.58 to 3.6 (no confidence limits).

For both of these ranges study sizes varied widely (n = ~134 to 43,093). [93] These results suggest that risk of cannabis use increases according to cigarette smoking status and that risk of both cannabis and tobacco use disorders increases with co-use. The descriptive (prevalence) data above also suggests that co-use is a real phenomenon which can be observed in populations.

2.3.3 Cigarette smoking trajectories and cannabis use

Because young people often use more than one substance [43], it may be important to study cigarette smoking trajectories in conjunction with the use of other psychoactive substances. It is possible that co-use not considered in modeling cigarette trajectories results in inaccurate depictions of trajectory patterns of the use of specific substances and their associations with risk factors and outcomes of trajectory group membership. This could conceivably result from several phenomena including the following. Confounding is a biased measure of the association between risk factor and trajectory group membership resulting from the presence of a common cause (e.g., cannabis use may conceivably cause tobacco use given that tobacco is frequently added to cannabis as a result of mulling/adding tobacco to smoked cannabis [44]) of the exposure and the outcome. [32] Time-varying confounding of relationships with risk factors or outcomes of cigarette trajectory membership could occur if the risk factors or outcomes have associations with both cigarettes and cannabis which change over time (i.e.,

time-varying confounding occurs when there is a time-varying cause of an outcome which brings about changes in a time-varying exposure). [97] Effect modification [32] of the cigarette smoking trajectories could also result in differences in trajectories or in the associations of trajectories with risk factors and outcomes across levels of cannabis use. Given that both cigarettes and cannabis are commonly used substances (Chapter 1, Section 2.3.1) and co-use is also common (Section 2.3.2), this may be an issue worth considering. The following sections review the literature pertaining to trajectory models of cigarette use in relation to cannabis use and highlight research gaps in understanding the natural history of cannabis. We begin by considering the literature on joint models of cannabis and tobacco use.

2.3.3.1 Joint trajectory models of cannabis and tobacco use

We searched the literature on joint trajectories of tobacco and cannabis to determine whether the available studies provide information on the natural course of both substances in relation to each other by considering use of each substance from initiation onwards. The searches were carried out in Pubmed (they were repeated in 2019, in order to update the results and determine whether additional relevant articles had been published.)

1. Search #1: marijuana AND tobacco AND trajectories (no limits);
2. Search #2: cannabis AND tobacco AND trajectories (no limits).

The abstracts obtained were searched in order to identify the articles relevant to joint trajectories of tobacco and cannabis use. Articles published in a language other than French or English were excluded, as were articles which were not available online (for example, older articles may only be available as a paper copy at the University of Montreal libraries). We also included only those articles with ≥1 time point taking place prior to age 18 years. The reasons for this are that: (i) 9 of 10 smokers start smoking by age 18 [11]; (ii) social and health context in adolescence differs from social context in adulthood [98]; (iii) in Quebec, youth leave secondary school in grade 11 where students are age 17-18; and (iv) in Quebec, purchase of cigarettes is legal at ≥18 years. [99]

We identified 14 articles with at least one data collection cycle prior to age 18, which studied cannabis use in relation to tobacco use trajectories. [37], [40], [100]–[111] These articles generally obtained trajectories of tobacco and sometimes of cannabis and other drug use, to

characterize growth of substance use over time. Other aims were to study hypotheses regarding the number and types of trajectory groups obtained; to study comorbidity across substance types, associations of trajectory group membership with potential risk factors and outcomes, and whether risk factors could account for comorbid associations of substance use. Three studies [100], [104], [106], [108], [110] were re-analyses of the same data, and two (Brook et al. 2012, Brook et al. 2016 [109], [111]) presented re-analyses of a second data set. Two studies (Brook 2006, Stanton 2004 [104], [105]) examined the association between cigarette smoking trajectories and cannabis use measured at a single time point (both studies reported a significant association with trajectory group membership). Three articles [37], [106], [107] used cross-tabulations of the trajectories and two other articles (Valente et al. 2018, Brooks-Russell et al. 2015 [102], [103]) jointly modeled alcohol, tobacco, and cannabis use with additional drug use variables. Dual trajectory modeling of cannabis and tobacco was used in three [40], [108], [109] of the remaining seven articles. Nelson et al. 2015 [40] did however constrain the number of trajectory groups for cannabis and tobacco to the numbers previously identified in two separate models of each substance alone. Finally, the other four studies jointly modeled alcohol, tobacco and cannabis (Brook 2014, Brook 2016, Lee 2019, Martínez-Loredo 2018 [100], [101], [110], [111]). Table 4 details the studies reporting joint models of cannabis and tobacco use, with or without alcohol use.

Table 4. Articles reporting joint trajectories of cannabis and tobacco use, or of tobacco, alcohol and cannabis use

Reference (number)	Alcohol included[1]	No. of trajectory groups	Description of trajectories (% of sample)	Additional items	Study objectives
Lee 2019 [100]	Y	5	1. Heavy use of all 3 substances: Heavy use (use of alcohol was moderate, however) throughout (7%)	Same study population/data set as [108], [110]	To model triple joint trajectories of tobacco, cannabis, and alcohol. To test association of trajectories with certain outcomes.
			2. Increasing use of all 3 substances: Use began at zero/none and increased to high levels for all 3 substances (17%)		
			3. Tobacco and alcohol use: All 3 substances began at zero/none; tobacco increased to high levels, alcohol to moderate levels, while cannabis increased then decreased back to zero/none (19%)		
			4. Alcohol and cannabis use: Tobacco remained at zero/none throughout, while alcohol and cannabis increased to moderate levels (17%)		
			5. Moderate alcohol use only: Tobacco and cannabis remained at zero/none throughout while alcohol increased to moderate levels (40%)		
Martínez-Loredo 2018 [101]	Y	3	1. Early use: Use of tobacco and cannabis at baseline and an increase in alcohol, tobacco and cannabis use throughout; this study also modeled the number of (alcohol) intoxication episodes and the Rutgers Alcohol Problem Index score (RAPI began at moderate levels and increased to high levels, intoxication episodes began at approx.. 3-5 and increased then decreased slightly (remained at high levels/10-19) (9%)	This study modeled three alcohol use/abuse variables: (1) alcohol use, (2) intoxication episodes (i.e. in past month), and (3) Rutgers Alcohol Problem Index (RAPI)	To model joint trajectories of tobacco, cannabis, alcohol use, and problematic alcohol use. To test hypotheses about number and type of trajectories. To determine whether trajectories were associated with a particular risk factor (i.e., impulsivity).
			2. Experimental use: Moderate alcohol involvement (low RAPI and few or no intoxication episodes), no		

			tobacco or cannabis use (81.3%)			
			3. Telescoped use: Initially low substance use followed by an escalation in substance use to high polydrug use, intoxication episodes and problem drinking/RAPI (10%)			
Nelson 2015 [40]	N	7 for cannabis; 6 for tobacco (trajectories were determined previously in models with each substance alone)	1. Cannabis, abstainers: No use (52.5%)	1. Tobacco: Abstainers (38.8%)	84.9% of tobacco abstainers were also cannabis abstainers, other tobacco groups showed greater spread among the cannabis trajectory groups	To model trajectories of tobacco, alcohol, and cannabis (separately) and determine their prevalences and co-occurrence.
			2. Cannabis, early onset high decreasers (6.9%): Use ↑ through adolescence then ↓ in adulthood	2. Tobacco, very low users (10.0%): Steady low-level consumption in adolescence	65.8% of cannabis abstainers were cigarette abstainers and 65.7% of early onset high decreasing cannabis users were in the early onset steep increasing cigarette trajectory group, other cannabis groups showed greater spread among tobacco groups	
			3. Cannabis, high school onset steep increasers (10.5%): Began use in adolescence and ↑ to reach the highest levels of consumption of any trajectory group in young adulthood	3. Tobacco, young adult onset moderate increasers (11.5%): Steady low-level consumption in adolescence and ↑ consumption in young adulthood	---	
			4. Cannabis, post–high school onset	4. Tobacco, post-high school onset	---	

			high decreasers (6.5%): Initiated in late adolescence and ↑ in young adulthood before ↓	low decreasers (9.8%): Remained at low levels throughout but ↑ slightly during adolescence then ↓ during young adulthood		
			5. Cannabis, young adult onset steep increasers (8.8%): Had fluctuating low level use in adolescence then sharply ↑ consumption in young adulthood	5. Tobacco, post-high school onset steep increasers (18.9%): Smoked 2-3 packs in past month at 23 years	---	
			6. Cannabis, young adult onset low decreasers (9.4%): Initiated use in young adulthood and remained at low levels	6. Tobacco, early onset steep increasers (11.1%): Were using at age 12 and ↑ thereafter	---	
			7. Cannabis, early onset low decreasers (5.4%): Used cannabis throughout adolescence and young adulthood at relatively low levels, before finally ↓ in young adulthood	---	---	
Brook 2012 [108]	N	6	1. No use/low level use (39%): Little to no use throughout for both substances		Same study population/data set as [100], [110]	To model joint trajectories of cannabis and tobacco. To determine
			2. Infrequent use of both substances (12%): Began in			

			late adolescence and remained at relatively low levels thereafter		whether there are <7 trajectories obtained and to study hypotheses regarding whether certain specific trajectories will be present in the model. To study hypothesis regarding the most frequent trajectory group. To test study hypothesis regarding associations with several outcomes.
			3. Late onset tobacco/infrequent marijuana use (12%): Use of both began in late adolescence, then tobacco (but not cannabis) ↑ over time		
			4. Chronic tobacco use/maturing out cannabis (7%): Began both in early adolescence and ↑ tobacco thereafter while ↓ cannabis		
			5. Infrequent tobacco/late onset cannabis (5%): Started tobacco in early adolescence and tobacco remained at low levels (also started using cannabis in adolescence and ↑ to high levels thereafter)		
			6. Chronic use of both substances (25%): Started both in early adolescence and ↑ to high levels thereafter		
Brook 2012 [109]	N	5	1. No use/low level use of tobacco and cannabis (33%): Little to no use throughout for both substances	Same study population/data set as [111]	To determine whether the joint trajectories of tobacco and cannabis correspond to their hypotheses about number of trajectories and type of groups that would be present. To study certain hypotheses regarding associations with risk factors for trajectory membership.
			2. Late starting cigarettes/late starting cannabis (22.1%): Started both substances in late adolescence and ↑ to 1-5 cigs per day for tobacco and a few times per year or less for cannabis		
			3. Occasional tobacco/moderate cannabis use (17.9%): Started in adolescence for tobacco and remained at low levels; started in adolescence for cannabis and fluctuated between a few times per year or less and once a month throughout		
			4. Heavy continuous cigarette/occasional cannabis use (14.5%): Were smoking in adolescence and ↑ to reach high levels; cannabis began in adolescence and ↓ to low levels thereafter		
			5. Heavy continuous use of both substances (12.5%): Both		

			began in adolescence to reach high levels		
Brook 2016 [111]	Y	5	1. High levels of use (13.0%): Chronic moderate to heavy cigarette, alcohol, and cannabis use	Same study population/data set as [109]	To model triple joint trajectories of tobacco, cannabis, and alcohol use. To determine whether their hypotheses regarding number and types of trajectories are correct. To study association of trajectories with certain outcomes.
			2. Delayed/late onset of all three substances (23.5%): Use began in late adolescence/early adulthood and reached moderate levels of use thereafter		
			3. Little to no tobacco, moderate alcohol, low cannabis (17.7%): Use began in adolescence but remained low for tobacco and cannabis and was stable for alcohol throughout at moderate levels		
			4. Chronic heavy smoking/moderate alcohol/no cannabis (15%): Smoking began in adolescence, reached heavy levels in young adulthood and remained throughout at levels of ½ a pack per day, with moderate alcohol use throughout and low to no cannabis throughout		
			5. No smoking or cannabis/occasional alcohol (30.8%)		
Brook 2014 [110]	Y	5	1. Use of all 3 substances (23%): Alcohol use stable throughout at once a week or less, cannabis use stable at once a month, and tobacco ↑ from 1-5 cigs per day to ~ ½ pack per day throughout	Same study population/data set as [100], [108]	To model joint trajectories of tobacco, alcohol and cannabis. To determine whether their hypotheses regarding number and types of trajectories are correct. To study association of trajectories with certain outcomes.
			2. Cannabis and alcohol use (14%): No tobacco, alcohol initially ↑ to stabilize at once a week or less, cannabis also initially ↑ to stabilize at once a month		
			3. Tobacco and alcohol use (16%): Little to no cannabis use, tobacco 1-5 cigs per day throughout, alcohol once a week to several times a week throughout		
			4. Alcohol only (38%): No tobacco and cannabis, alcohol		

			use initially ↑ to stabilize at once a week or less		
			5. Non-use (9%): Little to no use of all three substances		

[1]All articles reported joint trajectories involving cannabis and tobacco. However some included alcohol use as an additional variable while others did not.
↑ = increasing. ↓ = decreasing. "Smoking" refers to cigarette smoking.

RAPI: Rutgers Alcohol Problem Index. Y: Yes. N: No.

In conclusion, several studies (Table 4) modeled joint trajectories of change in cannabis and tobacco use over time. However, there were few independent replications of these models; only three studies modeled cannabis and tobacco without the addition of other substances and one of these (Nelson et al. 2015 [40]) constrained the model to have the same number of trajectory groups as in models of each substance alone. Therefore while there were important similarities between the two studies (Brook et al. 2012, Brook et al. 2012 [108], [109]) (both studies reported groups with: (i) low to no use of both substances, (ii) chronic use of both substances, (iii) a group with moderate levels of both substances, and (iv) a group with chronic heavy tobacco use and decreasing cannabis use over time), no study modeled the natural course of cannabis and tobacco beginning at onset of use. Finally, we were unable to identify any study which considered initiation of one substance in relation to the other and/or continued use of the other. We therefore carried out searches outside the realm of cigarette smoking trajectories.

2.3.4 Cannabis and cigarettes – which comes first?

Three issues of interest relate to joint trajectories of cannabis and tobacco use: (i) whether cannabis or tobacco is initiated first; (ii) length of time between cannabis and tobacco initiation; and (iii) when cannabis use is initiated in relation to tobacco smoking trajectories.

We first consider the theories invoked in the literature, to explain the sequence of initiation of substance use. These are: (i) the gateway model, (ii) the common liability model, and (iii) the route of administration model. [112] We then present the extant studies on the sequence of initiation of cannabis and tobacco use and conclude by considering the time elapsed between cannabis and tobacco initiation, along with its potential risk factors.

2.3.4.1 Theories on sequence of initiation of substance use

Gateway Model

The Gateway Model suggests that youth follow a predictable sequence as they become increasingly involved in substance use, initially using tobacco or alcohol followed by cannabis, and then other illicit drugs. [113]–[115] The Gateway Model continues to be highly influential [113], [115], and has inspired additional or alternative "gateway" theories including the notions that e-cigarettes may serve as a gateway to cigarette smoking [116], and that prescription opioids are a gateway to heroin use. [117] A "reverse gateway" has also been proposed, whereby cannabis use would increase the risk of later tobacco initiation in non tobacco smoking adolescents. [118]

Common liability model

Use of multiple substances may represent a generalized liability or increase in the risk of drug use and it is addiction and not a specific drug that increases the risk of progression. [115], [119] In this model, liability is described as a latent and unobservable quantitative trait that follows a graded scale of the degree of affectedness or normality. [119] This model proposes that: (i) which substance is used first can be the result of a genetic or individual vulnerability (e.g., proneness to deviancy and familial liability to addiction); and (ii) no a priori order is expected in the sequence of drug use. [120]

Route of administration model

This model suggests that initiating use of a particular substance by one route of administration (e.g., inhalation) may account for future initiation of other substances via the same route. For example, inhaling tobacco can promote progression to other inhaled substances such as cannabis, possibly underpinning frequent co-use. [112], [120]

2.3.4.2 Beyond theory

The current section begins by describing the legal framework surrounding cannabis and tobacco use in North America. The section then summarizes what is known on the order of initiation of cannabis and tobacco: we identified studies, not limited to adolescence, which reported on cannabis initiation prior to tobacco initiation (i.e., since the proposed normative

pattern is tobacco initiation prior to first cannabis use. [113]–[115]) We also determined whether order of initiation was associated with later tobacco use or dependence.

Degenhardt 2010 [74] carried out a cross-sectional study on the extent and ordering of licit and illicit drug use across 17 countries. The results suggested variation in the patterns of substance use initiation across countries. While use of substances earlier in the "gateway" sequence (i.e., initially using tobacco or alcohol followed by cannabis, and then other illicit drugs) predicted use of drugs later in the sequence, the strength of these associations differed across countries. The prevalence of gateway "violations" or atypical patterns of substance use acquisition also varied across countries (e.g., in Japan, cannabis was rarely used prior to other illicit drugs, and alcohol and tobacco were not used prior to illicit drug use by 52.5% of respondents). Thus, while the Gateway Model is influential and may represent a normative behavior pattern, it may not represent the range of experiences leading to the acquisition of drug use and abuse.

Legal framework

One set of factors which may affect order of initiation of tobacco and cannabis and the prevalence of the two sequences in a population is the laws regarding tobacco and cannabis use in each country. In North America alone, there is considerable variation in laws across different regions.

When discussing cannabis use, it is important to distinguish the following three concepts: (i) decriminalization of use (i.e., this has been described as "policies that do not define possession for personal use or casual (nonmonetary) distribution as a criminal offense" [121]), (ii) use of cannabis for medical purposes (such measures remove penalties for the use of marijuana for medicinal purposes under specific conditions [121]), (iii) recreational use of cannabis. Recreational cannabis use was legalized in Canada in 2018: this law allows recreational use among individuals ≥18 years. [48] It is however important to note that use of recreational cannabis in Canada is also subject to provincial or territorial restrictions [48], and there is considerable variation in these restrictions across provinces and territories: for example, Quebec has restricted use of recreational cannabis to individuals ≥21 years and smoking/vaping of cannabis is not permitted in public spaces (indoor and outdoor). Growing cannabis plant(s)

for recreational use is also forbidden. [122] In Ontario, recreational use is restricted to ≥19 years, is allowed in many outdoor public places, and growing ≤4 plants per residence is permitted. [122] Use of cannabis for medical purposes was legalized in Canada in 2001 [123] and access to cannabis for medical purposes in both Ontario and Quebec continues to be regulated by federal (i.e., government of Canada) law. [122], [124] (The laws and regulations also specify that individuals of ≥21 years in Quebec and ≥19 years in Ontario may have in their possession small amounts of cannabis in public spaces, effectively decriminalizing cannabis in these specific circumstances. [122], [124])

In the United States as of 2019, eleven (as well as the District of Columbia in the U.S.) U.S. states and Canada had legalized recreational cannabis use. [48]–[61] Regulations regarding recreational cannabis vary across states: for example, in Alaska recreational use and possession is limited to ≥21 years of age and use is banned in all public spaces. Cannabis can be purchased for recreational use in designated stores. [125] In Vermont, sale of cannabis remains illegal, however residents ≥21 years may grow up to 6 cannabis plants (two mature and four immature) legally in their homes. [52] In addition to the eleven states mentioned above, some states have legalized cannabis use for medical purposes (one example is the state of Montana). [49], [126], [127] An important contradiction in laws exists in the United States however, in that federal law still defines cannabis as a "Schedule I Drug", which are drugs "with no currently accepted medical use and a high potential for abuse". [128]

Tobacco use in Canada: federal law prohibits sale of tobacco and vaping products to individuals <18 years. There are many additional restrictions on sale of tobacco imposed by federal law, including for example various restrictions with regards to packaging of tobacco. [129], [130] The province of Quebec also bans sales of tobacco to individuals <18 years and has laws which specify various additional restrictions regarding tobacco, such as those regarding use in public spaces (i.e., smoking is prohibited in many public spaces). [99] The government of Ontario also restricts smoking in public places but has banned sale of tobacco to individuals ≤19 years. [131] In the United States, the federal Family Smoking Prevention and Tobacco Control Act gives the Food and Drug Administration (FDA) authority to regulate the manufacture, distribution, and marketing of tobacco products. This law prohibits sales to minors. [132] Sale to individuals <21 years is in general prohibited at the federal level. [133]

Some regulations regarding tobacco vary by state, such as bans on smoking in public places. [134] Laws regarding both tobacco and cannabis therefore vary across the various regions of the United States and Canada.

Studies reporting on order of initiation

Many studies have reported "atypical" sequences consisting of patterns of substance use acquisition that do not conform to the Gateway Model. [72], [135], [75], [74], [71], [136], [137], [138], [76], [112], [139], [79], [81], [140], [141], [142], [143], [144] Eleven of these studies described initiation of cannabis prior to tobacco [71], [72], [76], [79], [81], [112], [136], [139], [141]–[143], while additional studies described cannabis initiation prior to tobacco and alcohol [74], [75], [135], [140], [144]. Ten studies [71], [72], [75], [79], [112], [136], [139]–[141], [144] reported that tobacco use prior to cannabis initiation was more common than the reverse.

Potential outcomes of order of initiation

In our review of the literature on this topic, three studies reported no association between initiation sequence and later tobacco use or dependence. [71], [72], [75] One study (Kennedy et al. 2016 [76]) reported a significant association between initiation sequence and later tobacco use or dependence.

The measures of association reported by the few studies reporting on the (potential) association between order of initiation of tobacco and cannabis with heavier use and/or dependence on tobacco reported in the literature were difficult to summarize: indeed, of those studies reporting measures of association:

1. **OR for risk of nicotine dependence** among cigarette smokers, according to **initiation of cannabis before initiating tobacco (vs. tobacco before cannabis)** of 0.92 (0.83, 1.02) [71];
2. **OR for tobacco dependence** among tobacco users, according to **initiation of cannabis before initiating tobacco or alcohol** (reference category not reported) of 1.3 (0.8, 2.0) [75];
3. **OR for cannabis before tobacco vs. tobacco before cannabis/both substances initiated at same age** (dependent variable), according to **past-month**

combustible tobacco use (reference = no past-month use) of 0.68 (0.63, 0.72) for whites [76];

4. **OR for cannabis before tobacco vs. tobacco before cannabis/both substances initiated at same age** (dependent variable), according to **past-month combustible tobacco** use (reference = no past-month use) of 1.03 (0.90, 1.18) for African American participants [76].

Overall, although initiation of cannabis use prior to tobacco has been reported in the literature, tobacco initiation prior to first cannabis use appears to be the most frequent pattern. A small number of studies suggest that order or sequence of initiation may not be associated with later tobacco use and dependence.

2.3.4.3 Time elapsed between cannabis and cigarette smoking initiation

The current section describes variation in the length of time between cannabis and tobacco initiation (i.e., referred to hereafter as "time elapsed") and predictors of time elapsed.

We identified four studies with analyses related to time elapsed between cannabis and cigarette smoking initiation. [136], [141], [79], [81] Two of these studies (Green 2016, Richmond-Rakerd 2015 [136], [141]) reported the mean time between tobacco and cannabis initiation (i.e., 2.9 and 5.5 years between tobacco and cannabis initiation when tobacco was initiated first; 2.4 and 2.4 years among those who initiated cannabis first). No study described the distribution of time elapsed between initiation of both substances.

Regarding potential risk factors for initiation of one substance among ever users of the other, or predictors of time elapsed between initiation of the first and the second substance, one article reported that heavier smoking was associated with cannabis initiation among ever smokers: hazard ratios (HR) of 1.23 (1.18, 1.29) and 2.55 (2.43, 2.67) were reported for level of tobacco use for individuals without daily use and with daily use, respectively (the details of the coding of the variables involved was unclear). [79] A second (with a different study population) reported that, among adults entering the military, predictors of cannabis initiation among ever tobacco users included: gender (i.e., being female was protective, HR = 0.7 (0.5, 0.9)) and younger age (i.e., being younger increased the risk, HR = 0.7 (0.6, 0.8)). [81]

There were even fewer published studies identifying risk factors for time elapsed from cannabis initiation to cigarette initiation: one poor quality study [80] stated that the importance or degree of cannabis use may be associated with cigarette initiation (significant beta from a stochastic actor-based model of 0.48). A second study [81] reported results suggesting gender might be a predictor of cigarette initiation: marginally significant hazard ratios (from a Markov multi-state model) was reported for gender of 1.6 (1.0, 2.5). Overall there was little information available on distributions of time elapsed between cannabis and tobacco use, or on risk factors for initiation of a second substance among ever users of the first.

2.3.5 Cannabis and cigarettes: age at initiation

A further issue of interest relating to joint trajectories of cannabis and tobacco use is when cannabis use is initiated in relation to tobacco smoking trajectories. This section considers the available literature on this topic.

We were unable to identify any study which considered initiation of cannabis in relation to trajectories of tobacco use. We therefore searched for studies reporting on age at initiation of cannabis use in relation to heavier cigarette smoking.

Few studies examine whether earlier cannabis initiation relates to heavier cigarette smoking or tobacco use. Two longitudinal studies reported on this topic. Richmond-Rakerd et al. 2017 [86] found that individuals with an older age of cannabis initiation decreased their use of tobacco at steeper rates than individuals with an earlier age of initiation (referring specifically to tobacco use frequency). They reported beta (regression) coefficients of -0.31 for tobacco use frequency and of -0.24 for tobacco use quantity, according to age at 1st cannabis use (which appeared to be continuous, though this was not explicitly stated). No confidence intervals were reported.

Timberlake et al. 2007 [87] reported that individuals with earlier cannabis initiation were more nicotine dependent in adulthood (these analyses were limited to ever smokers, making it more likely that the dependence noted was at least partly the result of tobacco use apart from cannabis). The OR for younger 18-22 year-olds was 1.14 (0.95, 1.36), while that for older participants was 0.82 (0.73, 0.93).

Therefore the few available studies on this topic suggest that earlier cannabis initiation may be associated with later heavier cigarette use.

2.3.6 Gap(s) in knowledge on tobacco trajectories and cannabis use

Several studies have been published which have modeled joint trajectories of change in cannabis and tobacco use over time. However, only two studies (Brook et al. 2012, Brook et al. 2012 [108], [109]) presented models where the relationship between cannabis and tobacco, without consideration of other substances, was freely estimated. No studies examined the initiation of one substance in relation to the other and/or continued use of the other.

We sought to determine: (i) whether cannabis or tobacco use is initiated first; (ii) length of time between cannabis and tobacco initiation; and (iii) when cannabis use is initiated in relation to tobacco smoking trajectories.

While initiation of cannabis prior to tobacco has been reported, tobacco initiation prior to first cannabis use is most frequent. A small number of studies suggest that order or sequence of initiation may not be associated with later tobacco use and dependence. There was little evidence on the distribution of time elapsed between cannabis and tobacco use, or on risk factors for initiation of a second substance among ever users of the first. The available literature suggests that earlier cannabis initiation may be associated with later heavier cigarette use.

Chapter 3 – Review Objective

The central aim of the current thesis was to attempt to use trajectory modeling to increase understanding of cigarette smoking onset in youth, a further related aim was to ascertain the usefulness of cigarette smoking trajectory modeling to public health. An important gap in the literature on cigarette smoking trajectories in youth (section 2.2.7) is the absence of an up-to-date, comprehensive systematic review of the literature. A single initial objective relating to the review of the literature on the topic of cigarette smoking trajectories in adolescents, is presented in this chapter.

3.1 Objective 1

Objective: To synthesize the literature on adolescent cigarette smoking trajectories to determine the number and describe the shape of trajectories, to identify risk factors for specific trajectory groups, to identify cigarette smoking-related outcomes of specific trajectory groups, to compare incident versus mixed trajectories with respect to the aforementioned factors, and to determine whether specific time window(s) propitious for intervention can be identified.

Chapter 4 – Article 1

Contributions to Article 1 by the Candidate

BL carried out all literature searches 1980–2017 (a final search and selection of articles was later carried out specifically for the year 2018, to update the review). BL reviewed all titles, abstracts, and articles retained from the 1980–2017 searches and selected a final list of articles which was compared with that obtained by CBC and SE. Discussions between BL, CBC, SE, and JO'L led to a final consensus on the list of articles to include for the years 1980–2017. BL calculated inter-rater reliability values between CBC and BL and between SE and BL, for the 1980–2017 articles. BL extracted information from the articles published 1980–2017 and created initial versions of Figure 1 and Tables 23–29. These were later edited to the version presented in Appendix 1 and represent the source material for the tables included in the article (i.e., Tables 1 and 2). (Results for the 2018 search were later added to the tables.) BL drafted the initial version of all sections of the article. BL created Tables 7 and 8 with JO'L. Finally, BL reviewed and commented in detail on several versions of the manuscript and created Table 29.

4.1 Systematic review of cigarette trajectories

Clarification

Please note that because of the considerable heterogeneity in trajectory numbers and shapes reported between articles retained in the following review, we categorized each trajectory in each article retained into one of three broadly defined groups based on visual inspection of the curves, although heterogeneity in shapes within these groups remained substantial. Trajectories representing the lowest level of smoking across all time-points in each article were categorized as "low-stable." An "increasing" group comprised trajectories in which level of smoking increased; although the time-point at which the slope increased, and rate of increase differed. All other trajectories, which generally comprised trajectories that increased and then decreased or decreased and then increased were labelled "other".

The ranges of proportions of participants reported correspond to the proportions of participants (i.e., proportion of the analytical sample) reported to be in each type of trajectory (i.e., low-stable, increasing, or other) compiled across the individual studies.

International Journal of Drug Policy 83 (2020) 102838

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

A systematic review of cigarette smoking trajectories in adolescents

Marilyn N. Ahun[a,b], Béatrice Lauzon[a,b], Marie-Pierre Sylvestre[a,b,*], Cassi Bergeron-Caron[a,b], Sherif Eltonsy[c,d], Jennifer O'Loughlin[a,b]

[a] Université de Montréal Hospital Research Centre Tour Saint-Antoine, 850 rue Saint-Denis, Montréal, Québec, Canada H2X0A9
[b] Université de Montréal School of Public Health, 7101 Avenue du Parc, Montréal, Québec, Canada H3N1X9
[c] University of Moncton, J.-Raymond Frenette Building. 18 rue Antonine Maillet, Moncton, New Brunswick, Canada E1A3E9
[d] College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, 750 McDermot Avenue, Winnipeg, Manitoba, Canada R3E0T5

ARTICLE INFO

Keywords:
Trajectory analysis
Smoking
Adolescence
Systematic review
Natural history of smoking
Longitudinal method

ABSTRACT

Trajectory analyses differentiate subgroups of smokers based on early patterns of cigarette use, but no study has summarized this literature. We systematically reviewed the literature on adolescent cigarette smoking trajectories to document the number and shapes of trajectories identified, assess if certain study characteristics influence the number or shapes of trajectories identified, summarize factors associated with and outcomes of trajectory group membership, and assess whether the results of trajectory analyses help identify windows of opportunity for intervention. We searched PubMed and EMBASE (1/1/1980 to 1/11/2018) and identified 1695 articles. Forty-three articles with data from 37 unique datasets were retained. Each trajectory was categorized into one of three groups (i.e., low-stable, increasing, other). Number of trajectories ranged from 2 to 6 (mode = 4); 44–76% of participants were low-stable cigarette consumers, 11–21% increased consumption, and 3–11% were categorized as "other." Number of data points, smoking indicator used, and time axis influenced the number of trajectories identified. Only two articles depicted the natural course of smoking since onset. Factors associated with trajectory membership included age, sex/gender, race/ethnicity, parental education, behavior problems, depression, academic performance, baseline cigarette use, parental and friends smoking, alcohol use, and cannabis use. Outcomes included illicit drug and alcohol use. Beyond parsimoniously describing cigarette smoking patterns, it is not clear whether trajectory analyses offer increased insight into the natural course, determinants or outcomes of cigarette smoking in ways that inform the development of intervention.

Introduction

Nearly all cigarette smoking begins in adolescence (US Department of Health Human Services, 2012), and research over decades has attempted to describe how smoking becomes habitual. Herein we focus on studies that use trajectory analyses to identify developmental patterns of cigarette smoking in adolescents. This analytic method has proliferated in the past two decades because of the appeal of summarizing longitudinal data into clear easily-interpretable graphical representations, the availability of easy-to-use statistical packages (e.g., Proc Traj (SAS), TRAJ (STATA)), and ever-improving add-ons for handling time-varying covariates and attrition (Haviland, Jones & Nagin, 2011; Jones, Nagin & Roeder, 2001). The increasing number of such studies has led to Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) (Van De Schoot, Sijbrandij, Winter, Depaoli & Vermunt, 2017), a checklist of items to report in articles describing trajectory analyses. In addition to depicting developmental patterns, trajectory analyses help identify subgroups at higher risk of sustained and heavier smoking, and they elucidate outcomes of specific trajectory patterns. Proponents of trajectory analyses argue that the differing risk profiles across developmental patterns increase understanding of the natural course of smoking onset (Nagin, 2005), and that these analyses can pinpoint windows of opportunity for intervening to prevent addiction and long-term smoking.

Although smoking trajectory studies are on the increase, there are no systematic reviews of this literature, possibly because trajectory analyses cannot be easily pooled or meta-analyzed. The co-existence of two types of trajectories also complicate synthesis. The first type uses calendar time as the time axis among adolescents who initiate smoking either before or after baseline (i.e., "age/grade" analyses), and the

* Corresponding author at: Center de recherche du center hospitalier de l'Université de Montréal (CrCHUM). Tour Saint-Antoine, bureau S03.458. 850 rue Saint-Denis, Montréal Québec, Canada H2X0A9.
E-mail addresses: marilyn.ahun@umontreal.ca (M.N. Ahun), marie-pierre.sylvestre@umontreal.ca (M.-P. Sylvestre), cassi.bergeron-caron@umontreal.ca (C. Bergeron-Caron), sheriff.eltonsy@umoncton.ca (S. Eltonsy), jennifer.oloughlin@umontreal.ca (J. O'Loughlin).

https://doi.org/10.1016/j.drugpo.2020.102838

second uses time since smoking onset as the time axis among smokers who begin smoking after baseline (i.e. "time-since-onset" analyses). It is unclear if use of different time axes influences the number, shape, factors associated with, or outcomes of trajectories identified.

Herein we explore these issues by reviewing studies that describe smoking trajectories across adolescence. The objectives were to: (i) document the number and shapes of trajectories identified, (ii) assess if sample size, number of data points, indicator of cigarette smoking used, or time axis influence the number or shapes of trajectories identified, (iii) summarize factors associated with membership in specific trajectory groups, (iv) summarize trajectory-related outcomes, and (v) assess whether trajectories identify windows of opportunity for intervention.

Methods

PubMed and EMBASE were searched up to November 23, 2018 for articles published between January 1, 1980 and November 1, 2018 using key words *smoking* OR *tobacco* AND *trajectories*. The detailed search terms were: (i) PubMed (limited to 'humans', 'English language', 'publication date 01/01/1980 – 1/11/2018′): (("smoking"[MeSH Terms] OR "smoking"[All Fields]) **OR** ("tobacco"[MeSH Terms] OR "tobacco"[All Fields] OR "tobacco products"[MeSH Terms]) **OR** (("tobacco"[All Fields] AND "products"[All Fields]) OR ("tobacco products"[All Fields])) **AND** trajectories[All Fields]; and (ii) EMBASE (limited to 'humans', 'English language', 'publication year 1980 – 2018′, as well as to journal articles): ['smoking' ('smoking', 'smoking habit', 'adolescent smoking', "smoking and smoking related phenomena" as subject headings, 'smoking' as a keyword) **OR** 'tobacco' ('tobacco', 'tobacco consumption', 'tobacco dependence', 'tobacco smoke', "tobacco use" as subject headings, 'tobacco' as a keyword)] **AND** ['trajectories' ('illness trajectory', 'model' as subject headings, 'trajectories' as a keyword)].

Titles and abstracts of the 1695 articles identified were scanned by four authors (BL, MNA, SE, CBC) to filter out articles that were not relevant. Articles mentioning adolescent cigarette smoking trajectories in the title or abstract, and those in which the title or abstract was not sufficiently informative to determine relevance (n = 359), were retained for the next stage of review. The same four authors then reviewed each article according to pre-established inclusion and exclusion criteria. The single inclusion criterion was that the article reported more than one empirically derived cigarette smoking trajectory based on prospective participant self-reports of cigarette smoking over time. Exclusion criteria included that the study was a review, that its design or analysis was cross-sectional, that the data or analyses were qualitative, that they estimated joint trajectories of smoking and another behavior, or that they estimated trajectories of e-cigarette smoking. In addition, to assure that changes in cigarette smoking during adolescence were captured, we excluded studies that had < 3 data points between ages 12 and 18 (Curran & Muthen, 1999). Disagreements between the four authors at the abstract/title and full review stages were resolved in team discussions with MPS and JOL. Fig. 1 presents a PRISMA flow chart of the results of the article selection process (Moher, Liberati, Tetzlaff & Altman, 2009).

In the next step, BL and MNA used a two-step verification process to extract data from each article retained on study population (i.e., sample size, age range of participants, cohort/sample used); setting and design (i.e., country, age at assessments, number of data points required to be included in the analysis); statistical analyses (i.e., statistical model, software, number of trajectory groups considered, polynomial orders considered, if and how attrition and missingness were dealt with, the statistical and non-statistical criteria used for model selection); and results (i.e., number of trajectories reported in the final model, average posterior probability of trajectory group membership, prevalence of each trajectory in the analytical sample, reported trajectory shapes, factors associated with trajectories, outcomes of trajectory membership investigated and which factor(s) were statistically significant) (Tables S1–S4).

To assess whether study design features might have influenced the number or shapes of trajectories, we collapsed articles into categories based on sample size (<500, 500–2000, >2000), type of cigarette smoking indicator (intensity, frequency, a metric combining intensity and frequency, any use), time axis (time since cigarette smoking onset, age/grade or other measure of calendar time) and number of data points used to estimate trajectories (<5, 5–10, >10), and examined the distributions of the number and shapes of trajectories identified according to these characteristics.

GRoLTS

We used the GRoLTS to assess the quality of reporting in the articles retained (Van De Schoot et al., 2017). This checklist comprises 21 yes/no items assessing whether details such as the time metric used and how missing data were dealt with, are reported. No article reported all 21 items (mean (SD) number of items reported = 7.4 (1.7), range 4–11). Items reported in ≥50% of articles included time metric, variables related to attrition/missing data, how missing data were dealt with, distributions of observed variables, software, model comparison tools, total number of fitted models considered, and a plot of the final model solution. No article reported the mean or variance of time within a data collection wave, plots of the mean estimated trajectories for each model considered, plots of the observed individual trajectories split for each latent class, and none made the syntax files for their models available (Fig. 2). Table S5 describes whether each item is reported in each article.

Results

A total of 1695 articles were identified in the bibliographic databases reviewed; 43 articles were retained (Fig. 1). The references of all 43 articles can be found in the Online Supplementary Material. These articles used data from 37 unique datasets including longitudinal birth cohorts (e.g., Avon Longitudinal Study of Parents and Children), longitudinal national surveys (e.g., [Canadian] National Longitudinal Survey of Children and Youth), and community samples (Table 1). Twenty-eight articles used data from studies conducted in the US, six were conducted in Canada, two in Sweden, and one in each of the Czech Republic, China, the United Kingdom, South Korea, New Zealand, Taiwan, and The Netherlands. Sample size ranged from 203 to 15 828 (median = 975), and the youngest and oldest age of participants at first smoking assessment was 9 and 17 years, respectively (median age = 13 years). Duration of follow-up varied between 1.5 to 23 years (median = 5 years). Most articles tracked smoking into later adolescence and 28 continued assessments past age 18. In articles where it was ascertainable, the minimum time window between data points was three months and the maximum was 4.5 years (median = 1 year). Number of data points used to estimate trajectories ranged from 3 to 16 (median = 6); the range was 1 to 4 (median = 1) per year, and 0.5 to 5 (median = 1.3) per year from age 12 to 18. While an adequate number of data points are needed to capture inflections in the estimated trajectories, denser follow-up (beyond a certain point) will not impact the number or shape of the trajectories – it only makes them smoother (Tan, Dierker, Rose, Li & Network, 2011). Articles with more data points and shorter time intervals between data points had smoother trajectories (e.g., (Riggs, Chou, Li & Pentz, 2007; White, Nagin, Replogle & Stouthamer-Loeber, 2004)). Table 1 reports the countries in which articles were conducted, the cohorts/samples used, sample size, age range of participants, and labels used to describe trajectories identified.

Smoking indicator

Smoking was generally assessed using one of four indicators.

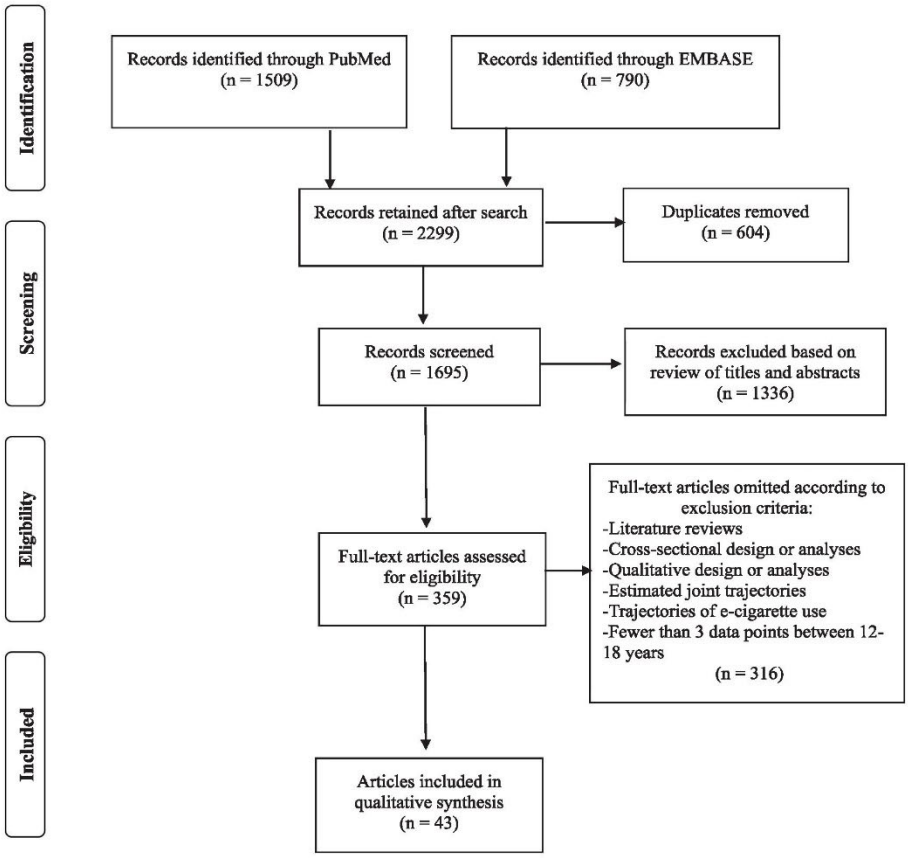


Fig. 1. PRISMA flow diagram showing the number of articles retained at each step in the article selection process.

Frequency (n = 16 articles) was defined as number of days on which participants had smoked in a given time period (e.g., past 7 days, past 30 days, past year, lifetime). Intensity (n = 17 articles) was defined as the number of cigarettes smoked in a given time period, and "any use" (n = 4 articles) indicated whether participants had smoked any cigarettes (yes, no) in a given time period. Eight articles created a metric combining intensity and frequency. One article (Maggi, Hertzman & Vaillancourt, 2007) conducted three trajectory analyses with different numbers of participants from the same sample, using indicators of frequency, intensity, and "any use".

Number of trajectories

The number of smoking trajectory groups reported ranged from 2 to 6. The most frequently reported number of trajectories (i.e., in 15 of 43 articles) was four. Four articles reported two trajectories, 12 reported three trajectories, 9 reported five trajectories, and 5 reported six trajectories. The article that investigated three smoking indicators (Maggi et al., 2007) reported two trajectories for the smoking intensity model (n = 260), five for the frequency model (n = 280), and three for the "any use" model (n = 2886).

Articles reporting studies with <5 data points identified three trajectories on average, compared to four in studies with more data points (Table 2). The 41 models with intensity, frequency, or a metric combining intensity and frequency as the y-axis had an average of four trajectory groups; the four models that used "any use" reported three.

Trajectory shapes

To enable comparison across articles, we categorized each trajectory in each article into one of three broadly defined groups based on visual inspection of the curves (Table 2), although heterogeneity in shapes within these groups remained substantial. Trajectories representing the lowest level of smoking across all time-points in each article were categorized as "low-stable." An "increasing" group comprised trajectories in which level of smoking increased; although the time-point at which the slope increased, and rate of increase differed. All other trajectories, which generally comprised trajectories that increased and then decreased or decreased and then increased were labelled "other". The time-point at which these slopes increased or decreased, and rates of increase or decrease varied across articles. The highest proportion of participants was categorized as "low-stable" (median range: 44.1–75.8%), followed by "increasing" (11.1–21.0%) and then "other" (3.1–10.8%). Not all articles reported participants in all three trajectory groups (e.g., some such as Vitaro et al.(2004) reported trajectories in the "low-stable" and "increasing" groups, but none in the "other" group). Also, some articles (e.g., Rosendahl et al.(2008)) provided number of participants for some trajectories, but not for others.

Regardless of sample size, number of data points, smoking indicator, or time axis, most participants were categorized as low-stable

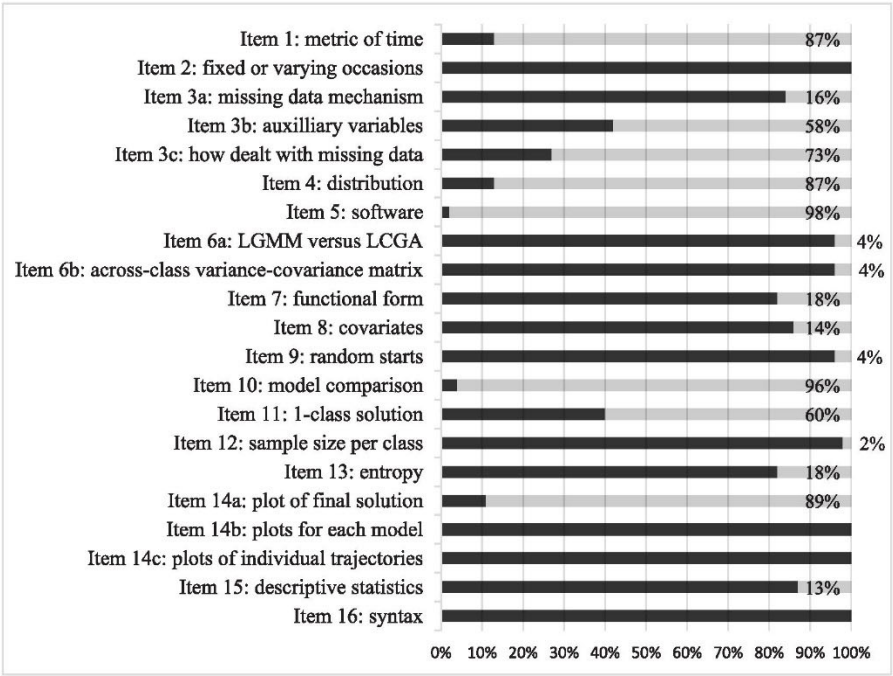


Fig. 2. Percent of all articles included in the systematic review (n = 43) reporting each item of the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS). Percentages are reported in the light grey bar.

(44–76%), followed by increasing (11–21%), and then "other" (3–11%), suggesting that although many adolescents tried cigarettes, only 1 in 3 or 4 increased use over time. Appendix Table S1 provides details on trajectory shapes and number of participants in each trajectory group. Table S2 provides data on years of follow-up, age at assessments, minimum number of data points required to estimate trajectories, density of data points from age 12 to 18, whether information on the distribution of the smoking measure was provided in the article, and methods used to account for missing values and attrition. Table S3 describes number of trajectories considered and used in the final model, polynomial orders considered, model comparison tools used, range of average posterior probabilities, software used, and whether alternative specifications of within-class heterogeneity were considered. While several articles reported using latent growth mixture modeling, most described results from models in which the variance and covariance estimates for the growth factors within each group were set to zero (Van De Schoot et al., 2017), akin to latent class growth analysis.

Factors associated with trajectories

All but nine (Cance, Talley, Morgan-Lopez & Fromme, 2017; Chang et al., 2018; Chung & Chun, 2010; Colder et al., 2001; Guo et al., 2002; Huang, Lanza & Anglin, 2013; Maggi, 2008; Maggi et al., 2007; Orpinas, Lacy, Nahapetyan, Dube & Song, 2015) of the 43 articles identified factors associated with trajectory group membership. Table S4 describes factors and outcomes potentially associated with trajectories investigated in each article. Table 3 summarizes the number of articles that examined each factor and that reported a significant association with trajectory group membership for that factor. The direction of the associations is not reported due to heterogeneity across articles in the trajectory group used as the reference and use of omnibus tests that do not distinguish direction of associations.

Of 86 distinct concepts investigated, 73 were examined in <5 articles. Among the 13 concepts examined in ≥ 5 articles, at least half of the articles reported a significant difference between at least two trajectories for age (6 of 7 articles), sex/gender (12 of 24), race/ethnicity (10 of 13), parental education (7 of 10), behavior problems (6 of 7), depression/depressive symptoms (6 of 8), academic performance (8 of 8), baseline cigarette use (5 of 5), parental smoking (9 of 14), friend's smoking (12 of 13), alcohol use (6 of 7), and cannabis use (6 of 6). In general, older age at baseline, being male, and being Caucasian were associated with membership in trajectory groups with higher cigarette consumption. For the remaining factors, the least favorable categories were associated with membership in trajectory groups with higher cigarette consumption. Only one of six articles that investigated school-related attitudes, and only two of six that investigated family functioning reported significant differences across trajectories.

Trajectory-related outcomes

Sixteen (Chang et al., 2018; Chassin, Presson, Pitts & Sherman, 2000; Dutra, Glantz, Lisha & Song, 2017; Guo et al., 2002; Hampson, Tildesley, Andrews, Barckley & Peterson, 2013; Huang et al., 2013; Karp, O'Loughlin, Paradis, Hanley & Difranza, 2005; Lessov-Schlaggar et al., 2008; Lynne-Landsman, Bradshaw & Ialongo, 2010; Nelson, Van Ryzin & Dishion, 2015; Orlando, Tucker, Ellickson & Klein, 2004; Orpinas et al., 2015; Riggs et al., 2007; Tucker, Ellickson, Orlando & Klein, 2006; Tucker, Ellickson, Orlando, Martino & Klein, 2005; Vuolo & Staff, 2013) of the 43 articles investigated outcomes of trajectory group membership. Of 21 outcomes examined, four were statistically significant in ≥ 5 articles (Table 4). Higher cigarette consumption trajectories were associated with illicit drug use and alcohol use, lower levels of education, and being unmarried.

Only the two articles that used "time since smoking onset" as the

Table 1
Number and description of smoking trajectory studies in 43 studies of cigarette smoking trajectories.

First author & year of publication; Country; Cohort/study sample[a]	Sample size[b]	Age range[c], y	Number of trajectories	Description of cigarette smoking trajectories (prevalence)[d]
AGE/GRADE ANALYSES				
Outcome variable[e]: Intensity of smoking				
Colder 2001; US Project STAR	260	12–16.6	5	Stable puffers (25%), stable light smokers, late slow escalators, late moderate escalators, early rapid escalators
Guo 2002; US Seattle Social Development Project	786	13–18	5	Non-smokers (73.0%), experimenters (7.3%), late-onsetters (10.9%), escalators (7.5%), chronic smokers (1.3%)
Vitaro 2004; Canada Quebec sample (1)	812	9–11.5 to 12.5–15	4	Never (75.4%), 13–14y starters (7.9%), 12–13y starters (11.1%), 11–12y starters (5.7%)
Stanton 2004; New Zealand Dunedin Multidisciplinary Health and Development Study	307	9–18	6	Late slow-escalators [puffers] (11.4%), stable puffers (12.7%), late slow escalators [smokers] (11.4%), late moderate escalators (14.3%), late rapid escalators (38.8%), early rapid escalators (11.4%)
White 2004; US Pittsburgh Youth Study	983	10–25	European Americans: 3 African Americans: 3	European Americans – Non-smokers (44.3%), light smokers (23.7%), heavy smokers (32%). African Americans – Non-smokers (55.9%), light smokers (27.3%), heavy smokers (16.7%)
Maggi 2007; Canada National Longitudinal Survey of Children and Youth	260	10–11 to 16–17	2	Late slow escalators (97.7%), early rapid escalators (2.3%)
Riggs 2007; US Kansas City sample	1 017	12–24	4	Abstainers (47%), low users (24%), late heavy users (16%), early heavy users (12%)
Lessov-Schlaggar 2008; US Smoking in Families Study	481	13.1–24	5	Experimenters (48.5%), late increasers (16.3%), early increasers (15.5%), quitters (9.2%), persistent (10.5%)
Otten 2008; Canada Quebec sample (2)	203	12–14	3	Low-rate (71.4%), increasing-rate (18.2%), high-rate (10.3%)
Chung 2010; South Korea Youth Panel Survey		13–17	4	Non-initiator (85.1%), late onsetter (7.0%), experimenter (4.5%), escalator (3.4%)
Gabrhelik 2012; Czech Republic Czech sample	1 874	11–13 to 13.6–15.6	2	Slow cigarette smoking escalators (91%), rapid/moderate cigarette smoking escalators (9%)
Vuolo 2013; US Youth Development Study	1 010	15–38	4	Stable non-smokers (54.1%), early onset light smokers who quit/reduce (16.2%), late onset persistent smokers (13.5%), early onset persistent heavy smokers (16.2%)
Roberts 2014; US Nurses' Health Study II and Growing Up Today Study	15 828	12–23	4	Non-smoker, experimenter, late initiator/moderate consumption, early initiator/high consumption
Nelson 2015; US Northwest sample	890	12–23	6	Abstainers (38.8%), very low users (10%), post-high school onset low decreasers (9.8%), young adult onset moderate increasers (11.5%), post-high school onset steep increasers (18.9%), early onset steep increasers (11.1%)
Orpinas 2015; US Healthy Teens Longitudinal Study	611	Grade 6–12	4	Abstainers/sporadic users (71.5%), late starters (11.3%), experimenters (9%), continuous users (8.2%)
Outcome variable[e]: Frequency of smoking				
First author & year of publication; Country; Cohort/study sample[a]	Sample size[b]	Age range[c], y	Number of trajectories	Description of cigarette smoking trajectories (prevalence)[d]
Abroms 2005; US Maryland sample (1)	1 320	Grade 6–9	5	Never smokers (41.2%), intenders (33.5%), delayed escalators (8.9%), early experimenters (13.9%), early users (2.5%)
Simons-Morton 2005; US Maryland sample (1)	1 320	Grade 6–9	Control Group:5; Treatment Group:5	Control Group – Class 1 (41.7%), class 2 (32.2%), class 3 (11.9%), class 4 (11%), class 5 (3.2%) Treatment Group – Class 1 (44.5%), class 2 (31.5%), class 3 (10.7%), class 4 (11.2%), class 5 (2%)
Maggi 2007; Canada National Longitudinal Survey of Children and Youth	280	10–11 to 16–17	5	Late infrequent experimenters (6.1%), late frequent smokers (38%), early frequent experimenters (5.2%), early frequent smokers (34%), early infrequent experimenters (6.8%)
Bernat 2008; US Minnesota Adolescent Community Cohort		12–16 to 15–19	6	Non-smokers (54%), late established (8%), triers (17%), occasional users (10%), early established (7%), decliners (4%)
Maggi 2008; Canada National Longitudinal Survey of Children and Youth	3 959	10–11 to 20–21	6	Stable non-smokers (48.4%), late experimenters-non-smokers (17.2%), late experimenters (13.9%), late experimenters-daily smokers (4.1%), early experimenters-daily smokers (5.8%), early experimenters-occasional smokers (10.5%)
Kimber 2009; Sweden Stockholm sample	662	13–14 to 15–16	3	Largely non-users (40%), largely moderate users (39%), heavy users (21%)
de Leeuw 2010; Netherlands Family and Health Project	428	15–18	4	Non-smokers (62.3%), stable smokers (13.7%), increasers (17.7%), decreasers (6.3%)
Lynne-Landsman 2010; US Maryland sample (2)	533	Grade 9–12	2	Abstaining (82%), increasing (18%)
Heron 2011; UK Avon Longitudinal Study of Parents and Children	3 038	14–16	4	Non-smokers (85.4%), experimenters (8.7%), late-onset regular smokers (4.3%), early-onset regular smokers (1.7%)
Hampson 2013; US Oregon Youth Substance Use Project	963	Grade 9–12	4	Stable non-smokers (71%), experimenters (15%), rapid escalators (8%), stable high smokers (6%)
Metzger 2013; US Family Talk about Smoking Study	344	15.6–17.9	3	Non-smokers (18.6%), infrequent/non-escalators (53.8%), escalators (27.6%)
Xie 2013; China Wuhan Smoking Prevention Trial	3 521	12–15 to 14–17	3	Non-smokers (48.7%), stable light/occasional smokers (48.6%), accelerating smokers (2.7%)
Musci 2015; US Maryland sample (3)		12–21	2	Low but increasing users (68%), moderate users (32%)

(*continued on next page*)

Table 1 (*continued*)

First author & year of publication; Country; Cohort/study sample[a]	Sample size[b]	Age range[c], y	Number of trajectories	Description of cigarette smoking trajectories (prevalence)[d]
Cance 2017; US Southwestern sample	2 244	17–19 to 23–25	5	Abstaining (68%), low-increasing (11%), decreasing (11%), moderate-increasing (6%), steady high (4%)
Dutra 2017; US National Longitudinal Survey of Youth 1997	8 791	12–16 to 26–30	4	Experimenters (13.6%), quitters (8.1%), early established smokers (39.0%), late escalators (5.2%)
; Chang 2018; Taiwan Child and Adolescent Behaviors in Long-term Evolution Project	2 510	13–18	3	Non-smokers (71%), late increasing (22%), escalating smokers (7%)
Outcome variable[e]: Intensity and frequency of smoking				
First author & year of publication; Country; Cohort/study sample[a]	Sample size[b]	Age range[c], y	Number of trajectories	Description of cigarette smoking trajectories (prevalence)[d]
Chassin 2000[f]; US Midwest sample	6 929	Grade 6–12 to age 21–31	4	Experimenter (6%), quitter (5%), late stable (16%), early stable (12%)
White 2002; US New Jersey sample	374	12–30/31	3	Non/experimental smokers (39.6%), occasional/maturing out smokers (19%), heavy/regular smokers (41.4%)
Audrain-McGovern 2004; US Virginia sample (1)	968	14–15 to 17–18	4	Never smokers (45%), early/fast adopters (8%), late/slow adopters (24%), experimenters (23%)
Orlando 2004; US RAND Adolescent/Young Adult Panel Study	5 914	13–23	5	Triers (55%), late increasers (14%), decreasers (9%), early increasers (14%), stable highs (8%)
Tucker 2005; US RAND Adolescent/Young Adult Panel Study	4 245	13–23	5	Triers (55.3%), stable highs (7.8%), early increasers (14%), decreasers (8.7%), steady increasers (14.2%)
Tucker 2006[g]; US RAND Adolescent/Young Adult Panel Study	1 442	13–23	6	Abstainers (29.5%), triers (40.5%), early increasers (8.5%), late increasers (11%), decreasers (5.7%), stable highs (4.8%).
Audrain-McGovern 2009; US Virginia sample (1)	909	15–20	3	Non-smokers (61.2%), fast adopters (12.3%), slow progressors (26.5%)
Otten 2009; Canada Quebec sample (3)	312	13–15	3	Low-rate (38.4%), medium-rate (46.5%), high-rate (15.1%).
Outcome variable[e]: Any use of cigarettes				
First author & year of publication; Country; Cohort/study sample[a]	Sample size[b]	Age range[c], y	Number of trajectories	Description of cigarette smoking trajectories (prevalence)[d]
Maggi 2007; Canada National Longitudinal Survey of Children and Youth	2 886	10–11 to 16–17	3	Late onset (40.5%), middle onset (49.3%), early onset (10.2%)
Weden 2012; US National Longitudinal Survey of Youth 1979	6 349	14–15 to 24–25	4	Non-smokers (63.7%), late onset (18.8%), early-experiment smokers (2.7%), early-onset smokers (14.7%)
Huang 2013; US National Longitudinal Survey of Youth 1979	5 141	12–18	3	Low (75.8%), increased (21.1%), high-decreasing (3.1%)
Lynne-Landsman 2016; US Cherokee Nation sample	684	<14–16 to <15–17	3	None (82%), increasing (3%), high (15%)
TIME SINCE ONSET ANALYSES				
Outcome variable[e]: Intensity of smoking				
First author & year of publication; Country; Cohort/study sample[a]	Sample size[b]	Age range[c], y	Number of trajectories	Description of cigarette smoking trajectories (prevalence)[d]
Rosendahl 2008; Sweden Children's Smoking and Environment in the Stockholm County (BROMS) Study	2 175	11–18	Males: 4; Females: 4	Males – Group 1, early extinction, Group 3, early escalation (21.1%) Females – Late trial (14.7%), early extinction (26.1%), late escalation (18.3%), early escalation (25.2%)
Karp 2005; Canada Natural History of Nicotine Dependence Study	369	13–16.9	4	Low-intensity non-progressing (72.4%), slow escalators (11.1%), moderate escalators (10.8%), rapid escalators (5.7%)

Note: Missing information (i.e. empty cells) indicates that information was not clearly provided in the article.

[a] Refers to cohort data used to estimate trajectories. Where cohorts were not used, the city/state/country where data was collected was specified. Studies using the same data from a given city/state/country have the same number (e.g. Quebec sample (1)).

[b] Number of participants in the model used to estimate smoking trajectories.

[c] Age range of all participants from baseline to last data point. Some studies provided school grade rather than age.

[d] Refers to the trajectories identified in the final model (using labels as reported in the article) and percentage of participants in each trajectory (if reported).

[e] Refers to the way in which smoking was assessed: intensity was assessed as the number of cigarettes smoked over a given time period (day(s), week(s), month(s), year); frequency was assessed as the number of days on which participants smoked over a given time period (week(s), month(s), year); any use was assessed by asking participants whether they had ever smoked cigarettes or whether they had smoked in the past week/month/year with a yes/no response option.

[f] An "erratic" group was determined a priori and was not included in trajectory analyses.

[g] The "abstainer" group was determined a priori and therefore not included in trajectory analyses.

Table 2
Shape of cigarette smoking trajectories in 43 articles and median percentage[a] of participants in each trajectory shape grouping according to selected characteristics of articles included in the review.

	No. articles	No. trajectories Median	Range	Trajectory shape Low stablemedian %	Increasingmedian %	Othermedian %
Sample size[b]						
Small (<500)	11	3.5	2–6	39.6	17.7	10.8
Medium (500–2000)	17	4	2–6	51.5	11.9	9.9
Large (>2000)	14	4	3–6	63.7	14.0	8.4
Cigarette smoking indicator[c]						
Intensity	17	4	2–6	55.9	14.3	10.0
Frequency	16	4	2–6	48.6	11.1	8.7
Metric combining intensity and frequency	8	4	3–6	42.3	14.0	8.4
Any use	4	3	3–4	75.8	18.8	3.1
Time axis used						
Time since onset	2	4	4,4	72.4	18.3	10.8
Age/grade	41	4	2–6	54.0	13.9	9.0
Number of data points used to estimate trajectories						
<5	12	3	2–3	62.3	21.0	6.8
5–10	27	4	2–6	54.1	12.0	9.2
>10	4	4	3–4	47.0	20.2	8.1

[a] Articles which did not report the percent of participants in a given trajectory group are not included in the calculations of median percentages.
[b] Excludes 3 articles (Bernat et al., 2008; Chung & Chun, 2010; Musci, Uhl, Maher, & Ialongo, 2015) that did not report the number of participants included in trajectory analyses. Maggi et al. (2007) used three different sample sizes for the three trajectory models estimated, two sample sizes were <500 and one was >2000.
[c] Maggi et al. (2007) estimated three trajectory models, one using intensity as the cigarette smoking indicator, one using frequency, and the third using any use. This article is counted in the intensity, frequency, and any use rows.

time metric (Karp et al., 2005; Rosendahl, Galanti & Gilljam, 2008) investigated the natural course of smoking onset. Of the 13 concepts examined in these articles (Table 3), sex/gender and peer smoking were significantly associated with trajectory group membership in both articles. Rosendahl et al.(2008) reported a significant association between trajectory group and each of parental education, parental tobacco use, and school smoking environment. Only Karp et al.(2005) examined potential outcomes – members of trajectory groups with higher cigarette consumption were more likely to develop nicotine dependence and tolerance.

Modeling approaches for testing factors and outcomes across trajectories differed. Nelson et al.(2015) included factors in the model that estimated trajectories, thereby accounting for the uncertainty associated with trajectory assignment. Others (e.g., Dutra et al., 2017; Lessov-Schlaggar et al., 2008) used post-hoc testing after individuals were classified into groups. This method does not account for this uncertainty unless posterior probabilities (e.g., Otten et al.(2009)) or more sophisticated approaches (see GRoLTS list (Van De Schoot et al., 2017)) are used, which is uncommon. Further, the assumptions underlying post-hoc testing varied across articles. While some used omnibus chi-square tests that considered trajectory groups as a nominal variable (Lessov-Schlaggar et al., 2008), others (Dutra et al., 2017) imposed an implicit ordering (e.g., from low to high) on the trajectories.

Windows of opportunity for intervention

Twelve of 43 articles discussed implications of trajectories for prevention; only two (Dutra et al., 2017; Orlando et al., 2004) described critical windows for high-risk trajectories. Orlando et al.(2004) suggested that the period between high school and young adulthood was a critical intervention period for "late increasers", but that "early increasers" would benefit from earlier intervention. Dutra et al.(2017) suggested interventions in early childhood and young adulthood for "early established smokers" and "late escalators", respectively. In the remaining 10 articles, some authors advocated that interventions should target the entire adolescent period (Audrain-McGovern et al., 2004; Lynne-Landsman et al., 2010; Nelson et al., 2015), while others – given the increased likelihood of smoking uptake (Abroms, Simons-Morton, Haynie & Chen, 2005) and experimentation (Bernat, Erickson, Widome, Perry & Forster, 2008) at specific time points – argued for late childhood or early adolescence (Abroms et al., 2005; Audrain-McGovern et al., 2009; Bernat et al., 2008; Gabrhelik et al., 2012; Hampson et al., 2013; Riggs et al., 2007). Others (Huang et al., 2013; Tucker et al., 2005) suggested late adolescence or emerging adulthood due to the transition to increased autonomy and adult roles.

Discussion

The main findings of this review are that: (i) in addition to possibly reflecting real patterns of cigarette smoking, heterogeneity across articles in trajectory number and shape may relate to study design features and modeling decisions; (ii) "risk" factors and outcomes identified in trajectory studies mirror those from studies that do not use trajectory analyses; (iii) few articles report windows of opportunity for intervention; (iv) only two articles depict the natural course of smoking since most used age/grade as the time axis; and (v) only two of 43 articles reported at least half of items in the GRoLTS checklist so that it is generally difficult to understand how the final models were selected, thereby decreasing the possibility of replicability.

This review comes at a time when trajectory analyses are apparently increasingly popular despite warnings that modeled trajectories may not represent real constructs (Sher, Jackson & Steinley, 2011; Vachon, Krueger, Irons, Iacono & McGue, 2017; Van De Schoot et al., 2017). Their appeal is explained by three key potentials including ease of summarizing longitudinal data into easily interpretable graphical presentations, increased understanding of factors associated with different patterns of smoking, and informing intervention by identifying at-risk subgroups and windows of opportunity for intervention.

Summarizing data

Trajectory analyses identify patterns in complex data which facilitate describing longitudinal data succinctly. However, differences across datasets such as in the density of measurements, may affect the number and shape of the estimated trajectories (e.g., having fewer data points or longer time intervals between data points could result in detecting fewer smoking patterns). Given the data-driven nature of the decision-making process in selecting a latent growth model, researchers should provide clear and detailed reports of the methods used to

Table 3
Number of articles[a] that investigated a potential factor associated with trajectory group membership, and among these articles, the number that reported a statistically significant association.

	Age/grade analyses			Time since onset analyses		
	First author, date	n	Reported significant association[b] n	First author, date	n	Reported significant association n
SOCIODEMOGRAPHIC FACTORS[c]						
Baseline age, grade (education level, school enrollment)4	Lessov-Schlaggar 2008, Bernat 2008, Orpinas 2016, de Leeuw 2010, Weden 2012, Dutra 2017	6	6	Karp 2005	1	0
Sex, gender	Vitaro 2004, Lessov-Schlaggar 2008, Otten 2008, Nelson 2015, Bernat 2008, Otten 2009, Orpinas 2016, White 2002, Gabrhelik 2012, Abroms 2005, de Leeuw 2010, Lynne-Landsman 2010, Heron 2011, Metzger 2013, Musci 2015, Hampson 2013, Audrain-McGovern 2004, Orlando 2004, Audrain-McGovern 2009, Weden 2012, Lynne-Landsman 2016, Dutra 2017	22	10	Karp 2005, Rosendahl 2008	2	2
Race, ethnicity (white, black, Hispanic, Asian, other, non-white)	White 2004, Nelson 2015, Bernat 2008, Orpinas 2016, Abroms 2005, Metzger 2013, Audrain-McGovern 2004, Weden 2012, Lynne-Landsman 2016, Orlando 2004, Tucker 2006, Audrain-McGovern 2009, Dutra 2017	13	10	–	–	–
Socioeconomic status	White 2004, Otten 2009, White 2002	3	1	–	–	–
Parental education	Vitaro 2004, Lessov-Schlaggar 2008, Lynne-Landsman 2010, Heron 2011, Orlando 2004, Tucker 2006, Weden 2012, Dutra 2017	8	6	Karp 2005, Rosendahl 2008	2	1
Household income	Lessov-Schlaggar 2008, Otten 2008, Dutra 2017	3	2	Karp 2005	1	0
Father's occupation	Stanton 2004	1	0	–	–	–
Free or reduced lunch	Musci 2015, Hampson 2013	2	2	–	–	–
Housing tenure	Heron 2011	1	1	–	–	–
No. of address changes in past 2yrs	Stanton 2004	1	1	–	–	–
Overcrowding	Heron 2011	1	1	–	–	–
Community type (urban, rural, small city)	Bernat 2008	1	1	–	–	–
Parity	Heron 2011	1	1	–	–	–
PSYCHOSOCIAL FACTORS						
	First author, date	n	Reported significant association[b] N	First author, date	n	Reported significant association n
Behavior problems (maladjustment, delinquency, conduct disorder score)	Stanton 2004, Otten 2009 , Vitaro 2004, White 2002, Weden 2012, Heron 2011, Dutra 2017	7	6	–	–	–
Sensation-seeking, disinhibition	Hampson 2013. White 2002	2	2	–	–	–
Novelty-seeking, impulsivity	Audrain-McGovern 2004, Audrain-McGovern J. 2009	2	2	Karp 2005	1	0
Tolerance for deviance	Chassin 2000, Abroms 2005, Orlando M. 2004	3	3	–	–	–
Locus of control	Chassin 2000	1	1	–	–	–
Delay discounting	Audrain-McGovern 2009	1	1	–	–	–
Child's sexual, physical, emotional abuse	Roberts 2014	1	1	–	–	–
Life satisfaction	Stanton 2004	1	0	–	–	–
Social competence	Stanton 2004, Abroms 2005	2	0	–	–	–
Social preference (popularity among peers, isolation from peers)	Otten 2008, Otten 2009 , Xie 2013	3	1	–	–	–
Friend-related psychosocial factors						
Peers' antisocial behavior, friends' disruptiveness, problem-behaving friends	Otten 2009, Abroms 2005	2	1	–	–	–
Attachment to friends	Stanton 2004	1	1	–	–	–
Friend support	Chassin 2000	1	0	–	–	–
Friend strictness	Chassin 2000	1	0	–	–	–
Peers' social preference	Otten 2008	1	0	–	–	–
Smoking-related psychosocial factors						
Low self-efficacy for smoking resistance	Orlando 2004	1	1	–	–	–

(*continued on next page*)

Table 3 (*continued*)

	Age/grade analyses	Time since onset analyses				
Beliefs about smoking (belief in smoking benefits, outcome expectations, smoking difficulty, lack of belief in smoking costs, psychological beliefs, social beliefs, functional meaning of smoking	Bernat 2008, Chassin 2000, Abroms 2005 , Orlando M. 2004,	4	4	–	–	–
Attitude(s) toward smoking	Otten 2008, White 2002, Xie 2013	3	1	–	–	–
Intention to smoke	Stanton 2004	1	1	–	–	–
Smoking social norms	Abroms 2005	1	1	–	–	–
Perception of tobacco industry (tobacco ad receptivity)	Bernat 2008, Audrain-McGovern 2004	2	2	–	–	–
MENTAL HEALTH						
	First author, date	n	Reported significant association[b] N	First author, date	n	Reported significant association n
Depression, depressive symptoms	White 2002, Xie 2013, Stanton 2004, Abroms 2005 , Audrain-McGovern 2004 , Audrain-McGovern 2009 , Dutra 2017	7	6	Karp 2005	1	0
Anxiety	Stanton 2004	1	0	–	–	–
Stress		–	–	Karp 2005	1	0
Self-esteem, self-derogation	White 2002	1	0	Karp 2005	1	0
Attention deficit disorder score, ADHD-attention, ADHD-hyperactivity	Stanton 2004, Audrain-McGovern 2009	2	1	–	–	–
Help-seeking for emotional or behavioral problem	Stanton 2004	1	0	–	–	–
Internalizing problems (depressive symptoms, social anxiety, and social loneliness)	Chang 2018	1	1	–	–	–
ACADEMIC-RELATED VARIABLES						
Academic performance (grades, GPA, school performance, school qualification)	White 2002, Xie 2013, Audrain-McGovern 2004 , Orlando 2004 , Audrain-McGovern 2009 , Lessov-Schlaggar ,2008 Stanton 2004	7	7	Karp 2005	1	1
School-related attitudes (value/expectations placed on academic success and independence, confident in ability to succeed at school, academic engagement, school adjustment, school attachment, perceived trouble with teachers, likes school	Chassin 2000, Abroms 2005, White 2002, Stanton 2004, Xie 2013	5	1	Karp 2005	1	0
Year level intending to leave school	Stanton 2004	1	0	–	–	–
School climate	Abroms 2005	1	0	–	–	–
College attendance[c]	Nelson 2015	1	1	–	–	–
SMOKING-RELATED FACTORS						
(Prior to) Baseline cigarette use, age first tried smoking	Riggs 2007, Lessov-Schlaggar 2008 , Heron 2011, Metzger 2013, Hampson	5	5	–	–	–
Baseline nicotine dependence	Lessov-Schlaggar 2008	1	1	–	–	–
SMOKING IN SOCIAL ENVIRONMENT						
	First author, date	n	Reported significant association[b] N	First author, date	n	Reported significant association n
No. of adults who smoke	Bernat 2008	1	1	–	–	–
School-related smoking (school has clear smoking rules, teachers/staff smoke near school, attends school where breaking smoking rules results in punishment, attends school where many students smoke where they are not allowed to, teachers sanction smoking, baseline prevalence of tobacco use in class	Xie 2013	1	1	Karp 2005, Rosendahl K. I. 2008	2	1
Family-related smoking						
Home smoking rules (smoking policies, non-smoking agreement, family rules about substance use)	Bernat 2008, de Leeuw 2010. Metzger 2013	3	2	–	–	–
Sibling smoking	White 2002	1	0	–	–	–
Parents' smoking, tobacco use, ever smoker, no. parents who smoke, household smoking, persons at home smoke, adult smoking	Vitaro 2004, Lessov-Schlaggar C. N. 2008, Otten R. 2008, Bernat D. H. 2008, Otten R. 2009, Chassin 2000, White 2002, Xie 2013, Abroms L. 2005, de Leeuw 2010, Orlando M. 2004, Audrain-McGovern J. 2009	12	8	Karp 2005, Rosendahl K. I. 2008	2	1
Mother smokes	Stanton 2004, Heron 2011, Metzger 2013, Weden 2012	4	3	–	–	–
Father smokes	Stanton 2004, Metzger 2013	2	0	–	–	–

(*continued on next page*)

Table 3 (*continued*)

	Age/grade analyses	Time since onset analyses				
Parental disapproval/sanctioning of smoking	Xie 2013, Orlando M. 2004, Metzger 2013	3	3	–	–	–
Parent communication (about smoking)	de Leeuw 2010, Metzger 2013	2	2	–	–	–
Parental smoking expectancies	Metzger 2013	1	0	–	–	–
Friend-related smoking						
Peer and friends smoking	Vitaro 2004, Otten R. 2008, Bernat D. H. 2008, Chassin 2000, White 2002, Stanton 2004, Abroms L. 2005, Audrain-McGovern J. 2004, Orlando M. 2004, Audrain-McGovern J. 2009, Dutra L. M. 2017	11	10	Karp 2005, Rosendahl K. I. 2008	2	2
Peer smoking attitudes, peer sanctioning of smoking, friend smoking norm	Otten 2008, Xie 2013	2	1	–	–	–
FAMILY-RELATED VARIABLES						
	First author, date	n	Reported significant association[b] n	First author, date	n	Reported significant association n
Family functioning (family relationships, parent-child conflict, family disharmony, parental involvement, monitoring, support, strictness, expectation, warmth)	Xie 2013, Stanton 2004, Abroms L. 2005, de Leeuw 2010, Chassin 2000, Metzger 2013	6	2	–	–	–
Nuclear family, two-parent family	Bernat 2008, Orlando M. 2004, Tucker 2006, Dutra L. M. 2017	4	4	–	–	–
Attachment to family	Stanton 2004	1	0	–	–	–
Maternal characteristics						
Obtained prenatal care	Weden 2012	1	0	–	–	–
Age at birth	Weden 2012	1	1	–	–	–
Breastfed child	Weden 2012	1	0	–	–	–
Smoked during pregnancy	White 2002	1	0	–	–	–
Marital status when child was age 14	Weden 2012	1	1	–	–	–
Maternal weekly alcohol use when child was age 12	Heron 2011	1	0	–	–	–
Maternal alcohol binge when child was age 12	Heron 2011	1	1	–	–	–
Maternal cannabis use when child was age 9	Heron 2011	1	1	–	–	–
Mother's psychological symptoms	Stanton 2004	1	1	–	–	–
Mother's abuse (sexual, physical, emotional)	Roberts 2014	1	1	–	–	–
SUBSTANCE USE						
	First author, date	n	Reported significant association[b] n	First author, date	n	Reported significant association n
Alcohol use (been drunk, binge drinking)	Xie 2013, Stanton 2004, Audrain-McGovern J. 2004, Audrain-McGovern J. 2009, Orlando M. 2004, Heron 2011	7	6	–	–	–
Intention to get drunk	Stanton 2004	1	0	–	–	–
Cannabis use (marijuana, pot)	Stanton 2004, Heron 2011, Audrain-McGovern J. 2004, Orlando M. 2004, Audrain-McGovern J. 2009, Dutra L. M. 2017	6	6	–	–	–
Drug use (other illicit drugs)	White 2002, Dutra L. M. 2017	2	2	–	–	–
Team sport	Audrain-McGovern 2004	1	1	–	–	–
MISCELLANEOUS						
Extracurricular activities (belongs to organized club, regular part-time job)	Stanton 2004	1	1	–	–	–
Genetics (polygenic score, population stratification)	Musci 2015	1	1	–	–	–
Environmental profile (parental monitoring, peer substance use)	Musci 2015	1	1	–	–	–

[a] When two or more articles used the same data, they were included as separate articles.
[b] The direction of associations is not reported due to heterogeneity across articles in the trajectory group used as the reference group.
[c] If a factor was studied in both univariate and multivariate models, results from the latter are reported.
[d] Variables in parentheses are the labels used by the authors to describe the concept of interest.
[e] It is not clear how "college" is defined in this study. Authors indicate college attendance both as a baseline variable and as an outcome.

Table 4
Number of articles[a] that report the association between trajectory group membership and a potential outcome, and among these articles, the number that reported a statistically significant association.

Potential outcome	First author, date	Total articlesn	Articles reporting a significant association[b]n
SOCIODEMOGRAPHIC FACTORS			
Education (college, high school dropout, graduate on time)[c]	Lessov-Schlaggar C. N. 2008, Chassin 2000 Orlando M. 2004, Tucker J. S. 2005, Tucker 2006 Orpinas 2016 Lynne-Landsman 2010, Dutra L. M. 2017	8	7
Income (welfare recipient)	Lessov-Schlaggar C. N. 2008, Tucker 2006	2	2
Employment (job problems)	Tucker 2006, Chassin 2000	2	0
Marital status	Lessov-Schlaggar C. N. 2008, Chassin 2000, Orlando M. 2004, Tucker J. S. 2005, Tucker 2006, Dutra L. M. 2017	6	3
Parenthood	Chassin 2000, Tucker 2006, Dutra L. M. 2017	3	3
PSYCHOSOCIAL FACTORS			
Personality risk (extroversion, conscientiousness)	Chassin 2000	1	1
Life satisfaction	Chassin 2000	1	1
Affect (negative, positive)	Chassin 2000	1	1
Stress	Chassin 2000	1	0
Major depressive disorder	Lynne-Landsman 2010	1	0
PHYSICAL AND MENTAL HEALTH			
Physical or mental health (respiratory symptoms, obesity)	Orlando M. 2004, Tucker J. S. 2005, Tucker 2006, Huang D. Y. 2013	4	4
Antisocial behavior (arrest history, criminal record stealing, selling drugs, violence)	Lynne-Landsman 2010, Tucker 2006 Orlando M. 2004, Tucker J. S. 2005	4	4
Sexual activity (no. sex partners, condom use, unsafe sex, pregnant, early sex, abortion)	Guo 2002, Lynne-Landsman 2010, Tucker 2006	3	3
SMOKING-RELATED FACTORS			
Smoking health and psychological beliefs	Chassin 2000	1	1
Nicotine dependence[4]	Riggs 2007, Lessov-Schlaggar C. N. 2008	2	2
Cigarette (or tobacco) use	Riggs 2007, Nelson 2015, Hampson S. E. 2013	3	3
Hookah use	Hampson S. E. 2013	1	1
Family smoking (offspring smoking)	Lessov-Schlaggar C. N. 2008, Vuolo M. 2013	2	2
SUBSTANCE USE			
Cannabis (marijuana (problematic use, dependence))	Orpinas 2016, Lynne-Landsman 2010, Nelson 2015	3	3
Illicit drug use (cocaine, methamphetamine, problematic use)	Orlando M. 2004, Tucker J. S. 2005, Tucker 2006	5	5
Alcohol use (inebriated, problematic use, dependence)	Orpinas, 2016 Nelson 2015, Lynne-Landsman 2010, Orlando M. 2004, Tucker J. S. 2005, Tucker 2006	6	6

[a] When two or more articles used data from the same cohort, they were included as separate articles.
[b] The direction of associations is not reported due to heterogeneity across articles in the trajectory group used as the reference group.
[c] Variables in parentheses are the labels used by the authors to describe the concept of interest.

facilitate replicability and critical appraisal of the results. The GRoLTS checklist (Van De Schoot et al., 2017) includes detailed yet concise items concerning each step of the model selection process and reporting these items will increase understanding on how the models were derived and the quality of the model selection process. However, few studies report these details – only two of the 43 studies in this review (Audrain-McGovern et al., 2004; Otten, Wanner, Vitaro & Engels, 2008) reported at least half of the GRoLTS items. Key information (e.g., missing data mechanism used, consideration of alternative specifications of within-class heterogeneity) was not reported in most studies, and these omissions make it harder to understand how the final models were selected, decreasing the possibility of replication. Reporting the details of the decision-making process will increase transparency and enable other researchers to replicate the findings and evaluate the quality of the latent growth models.

Factors associated with trajectories

Synthesizing evidence on factors associated with trajectories is challenged by using different smoking indicators across articles and the choice of which trajectory is used as a reference. In addition, most factors were investigated in a few articles only. However, factors associated with "riskier" trajectories mirrored predictors of cigarette smoking onset identified in a recent systematic review (Wellman et al., 2016), suggestive that risk factors for smoking onset may also discriminate smoking trajectories. Because trajectories represent patterns of smoking over time, they are necessarily more complex than single point-in-time indicators of smoking such as onset or sustained use. Studying factors associated with trajectories in their entirety likely obscures identification of factors associated with single point-in-time smoking indicators and may therefore complicate rather than clarify our understanding of smoking. Future work will need to ascertain whether identification of factors associated with trajectories add value to analyses identifying risk factors for single point-in-time smoking indicators.

Outcomes of smoking trajectories identified herein are convergent with those identified in non-trajectory studies (Chassin, Presson, Sherman & Edwards, 1990), but may be more useful than single point-in-time outcomes if for example, they distinguish early initiators who sustain smoking from early initiators who decrease. However, the feasibility of collecting data over time and plotting an individual's trajectory likely limits the utility of trajectory analyses in practice.

Are trajectories real?

Our review (and the trajectory approach in general) cannot determine whether smokers remain in a single trajectory over time, and several authors warn against considering trajectories as real constructs (Sher et al., 2011; Vachon et al., 2017; Van De Schoot et al., 2017). Most trajectories in our review were estimated using latent class growth analysis which assumes that individual trajectories within each group are homogeneous. However, the assumption of homogeneity may not be met, and estimated trajectories may not represent meaningful entities. Vachon et al.(2017) argue that for distinct *true* trajectories to exist,

strong, discriminating, categorical factors (e.g., a specific risk allele or event) must set individuals on a deterministic course. Smoking behavior may have a more dynamic nature than what trajectory analyses model (i.e., it may be fluid and subject to change across development, rather than static within a single trajectory) (Van De Schoot et al., 2017). This concern (Zuk, Hechter, Sunyaev & Lander, 2012) is augmented by the tendency for trajectory analyses to provide the same four forms (i.e., increasing, decreasing, stable high, stable-low), regardless of participant age at time zero or study duration, suggesting that some findings may be artefacts of the trajectory method (Sher et al., 2011). These four patterns were not systematically observed in the articles reviewed herein, although this could relate to the fact that no single strong discriminating categorial factor was identified across articles that sets adolescents on a deterministic course of smoking.

Time axis

If there is important variation in the natural course of smoking, time of smoking onset may be a more meaningful time zero in trajectory analyses than calendar time (Sher et al., 2011). Trajectory groups in age/grade analyses include members with different durations and levels of cigarette consumption at a single time-point, whereas "time-since-onset" trajectory groups include members with the same duration of smoking. This could explain our observation that 72% of smokers in "time-since-onset" studies were stable-low smokers, compared to 54% in age/grade studies. The proportion of smokers that initiate smoking after baseline may differ in each trajectory in age/grade studies, thus obscuring comparison across trajectory groups and across studies of persons with different ages at baseline. Further, risk factors for smoking onset and continuing to smoke at a given age may not coincide (Sher et al., 2011).

Recommendations for future research

Future studies on youth smoking trajectories should begin measuring smoking during childhood to ensure that smoking onset is observed. Further, they should incorporate frequent measurement of smoking to capture critical changes in smoking patterns. Continuous measures of smoking (i.e., mean number of cigarettes smoked per month) should be favored over categorical measures since they provide more nuanced data that can be easily measured and compared across studies (Royston, Altman & Sauerbrei, 2006). We recommend that researchers use the GRoLTS checklist (Van De Schoot et al., 2017) to report each step of the model selection process. Addressing the issue of heterogeneity of results across studies necessitates transparency in data-driven decisions, but also requires replication studies that reproduce the analytical plan in independent datasets that share the same design features as the initial studies including age range, frequency and timing of measuring smoking, as well as measurement of factors associated with smoking such as sex and socioeconomic status. Further, depending on the study objectives, future studies should consider using smoking onset as time zero. In addition to improving understanding of the natural course of smoking, knowledge on the timing of onset can facilitate comparison of results across studies. Finally, future work will need to critically appraise the usefulness of trajectory modeling against other statistical approaches that aim to describe longitudinal patterns of smoking (e.g., to ascertain whether identification of factors associated with trajectories add value to analyses identifying risk factors for single point-in-time smoking indicators).

Implications for intervention and policy

Our work has two important implications for intervention and policy. First, program planners and policy makers should consider the high proportion of young people who begin smoking in late childhood or early adolescence (Maggi et al., 2007; Riggs et al., 2007). Emerging evidence suggests that education and counselling at these ages may prevent initiation (Harvey, Chadi, & Canadian Paediatric Society Adolescent Health Committee, 2016). Second, the extant smoking trajectory literature does not provide consistent messages on at-risk individuals or windows of opportunity for intervention. Pinpointing the intervention needs of specific subgroups necessitates identifying factors amenable to intervention that differentiate trajectory groups at specific points-in-time. If trajectories depend on age, sex, and contextual factors, then using the current trajectory literature to inform policy could be harmful because of lack of specificity. Even if windows of opportunity are identified, it is unclear whether differences across trajectories at a given point-in-time are sufficiently important to warrant targeted intervention (Vachon et al., 2017). Recommendations from the two articles (Dutra et al., 2017; Orlando et al., 2004) that identified time windows for intervention differed, and only one article (Dutra et al., 2017) discussed specific intervention strategies. Therefore, we suggest that the potential of trajectory analyses to inform intervention and policy has yet to be identified.

Limitations

Study limitations include the methodological heterogeneity which made it difficult to synthesize the 43 articles retained. Despite the existence of objective criteria (e.g. the Bayesian Information Criterion), many articles used subjective criteria (e.g., substantive relevance of trajectories) to select the optimal model. Further, the criteria used were not always reported. Modeling decisions (e.g., dropping higher order polynomials which do not attain significance; requiring each trajectory group to have a minimum sample size) may also affect results and should be reported. Only two articles investigated individuals who initiated smoking after baseline, which limited detection of critical windows of opportunity relevant to intervention (Sher et al., 2011). Categorizing trajectories into three groups was necessary to facilitate summarizing trajectory shapes, but limited capturing unique trajectory patterns across articles. Finally, we did not adhere to the Cochrane recommendation of vote-counting based on direction-of-effect (as opposed to statistical significance) when meta-analysis is not possible (McKenzie & Brennan, 2019). Although direction-of-effect is useful in reviews of intervention studies, this approach cannot be used in synthesizing trajectory studies because of differences in the smoking indicator used, variation in the reference trajectory group, and use of different methods to test associations. Collating information on risk factors and outcomes across articles was also limited by differing indicators used for specific risk factors and outcomes across articles and because most factors or outcomes were investigated in only a few articles. Future reviews of specific factors associated with smoking trajectories using small subsets of articles reviewed herein might be better suited to this exercise.

Conclusion

Differences across studies in trajectory number and shape may reflect real-life smoking patterns, study design features, MNA and BL are co-first authors, and/or the data-driven nature of trajectory modeling. Factors and outcomes associated with trajectory membership mirror those reported in non-trajectory studies, so that the added value of trajectory analyses with these objectives remains to be demonstrated. Trajectory analysis may prove more useful in describing smoking patterns in a given population, than in identifying specific subgroups or specific time windows of opportunity for intervention.

Author contributions according to credit roles

Marilyn N. Ahun: Conceptualization, Writing – Original draft, Investigation. **Béatrice Lauzon**: Writing – Review and editing, Investigation. **Marie-Pierre Sylvestre**: Conceptualization, Writing –

Review and editing, Supervision, Funding Acquisition. **Cassi Bergeron-Caron**: Writing – Review and editing, Investigation. **Sherif Eltonsy**: Writing – Review and editing, Investigation. **Jennifer O'Loughlin**: Conceptualization, Writing – Review and editing, Supervision, Funding Acquisition

Declaration of Competing Interest

None.

Acknowledgements

Dr. Sylvestre holds a Chercheur-Boursier career award from the Fonds de Recherche du Québec–Santé. Dr O'Loughlin holds a Tier 1 Canada Research Chair in the Early Determinants of Adult Chronic Disease.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2020.102838.

References

Abroms, L., Simons-Morton, B., Haynie, D. L., & Chen, R. (2005). Psychosocial predictors of smoking trajectories during middle and high school. *Addiction (Abingdon, England), 100*(6), 852–861.

Audrain-McGovern, J., Rodriguez, D., Epstein, L. H., Cuevas, J., Rodgers, K., & Wileyto, E. P. (2009). Does delay discounting play an etiological role in smoking or is it a consequence of smoking. *Drug and Alcohol Dependence, 103*(3), 99–106.

Audrain-McGovern, J., Rodriguez, D., Tercyak, K. P., Cuevas, J., Rodgers, K., & Patterson, F. (2004). Identifying and characterizing adolescent smoking trajectories. *Cancer Epidemiology and Prevention Biomarkers, 13*(12), 2023–2034.

Bernat, D. H., Erickson, D. J., Widome, R., Perry, C. L., & Forster, J. L. (2008). Adolescent smoking trajectories: Results from a population-based cohort study. *Journal of Adolescent Health, 43*(4), 334–340.

Cance, J. D., Talley, A. E., Morgan-Lopez, A., & Fromme, K. (2017). Longitudinal conjoint patterns of alcohol and tobacco use throughout emerging adulthood. *Substance Use & Misuse, 52*(3), 373–382. https://doi.org/10.1080/10826084.2016.1228677.

Chang, L.-Y., Chang, H.-Y., Wu, W.-C., Lin, L. N., Wu, C.-C., & Yen, L.-L. (2018). Dual trajectories of sleep duration and cigarette smoking during adolescence: Relation to subsequent internalizing problems. *Journal of Abnormal Child Psychology, 46*(8), 1651–1663. https://doi.org/10.1007/s10802-018-0414-x.

Chassin, L., Presson, C. C., Pitts, S. C., & Sherman, S. J. (2000). The natural history of cigarette smoking from adolescence to adulthood in a midwestern community sample: Multiple trajectories and their psychosocial correlates. *Health Psychology, 19*(3), 223.

Chassin, L., Presson, C. C., Sherman, S. J., & Edwards, D. A. (1990). The natural history of cigarette smoking: Predicting young-adult smoking outcomes from adolescent smoking patterns. *Health Psychology, 9*(6), 701.

Chung, I. J., & Chun, J. (2010). Co-occurring Patterns of Smoking and Alcohol Consumption among Korean Adolescents. *The American Journal on Addictions, 19*(3), 252–256.

...Colder, C. R., Mehta, P., Balanda, K., Campbell, R. T., Mayhew, K., Stanton, W. R., & Flay, B. R. (2001). Identifying trajectories of adolescent smoking: An application of latent growth mixture modeling. *Health Psychology, 20*(2), 127.

Curran, P. J., & Muthen, B. O. (1999). The application of latent curve analysis to testing developmental theories in intervention research. *American Journal of Community Psychology, 27*(4), 567–595. https://doi.org/10.1023/a:1022137429115.

Dutra, L. M., Glantz, S. A., Lisha, N. E., & Song, A. V. (2017). Beyond experimentation: Five trajectories of cigarette smoking in a longitudinal sample of youth. *PloS One, 12*(2), Article e0171808.

Gabrhelik, R., Duncan, A., Lee, M. H., Stastna, L., Furr-Holden, C. D., & Miovsky, M. (2012). Sex specific trajectories in cigarette smoking behaviors among students participating in the unplugged school-based randomized control trial for substance use prevention. *Addictive Behaviors, 37*(10), 1145–1150. https://doi.org/10.1016/j.addbeh.2012.05.023.

Guo, J., Chung, I.-J., Hill, K. G., Hawkins, J. D., Catalano, R. F., & Abbott, R. D. (2002). Developmental relationships between adolescent substance use and risky sexual behavior in young adulthood. *Journal of Adolescent Health, 31*(4), 354–362.

Hampson, S. E., Tildesley, E., Andrews, J. A., Barckley, M., & Peterson, M. (2013). Smoking trajectories across high school: Sensation seeking and hookah use. *Nicotine & Tobacco Research, 15*(8), 1400–1408.

Harvey, J., & Chadi, N. Committee, Canadian Paediatric Society Adolescent Health. (2016). Preventing smoking in children and adolescents: Recommendations for practice and policy. *Paediatrics & Child Health, 21*(4), 209–214.

Haviland, A. M., Jones, B. L., & Nagin, D. S. (2011). Group-based trajectory modeling extended to account for nonrandom participant attrition. *Sociological Methods & Research, 40*(2), 367–390.

Huang, D. Y., Lanza, H. I., & Anglin, M. D. (2013). Association between adolescent substance use and obesity in young adulthood: A group-based dual trajectory analysis. *Addictive Behaviors, 38*(11), 2653–2660.

Jones, B. L., Nagin, D. S., & Roeder, K. (2001). A SAS procedure based on mixture models for estimating developmental trajectories. *Sociological Methods & Research, 29*(3), 374–393.

Karp, I., O'loughlin, J., Paradis, G., Hanley, J., & Difranza, J. (2005). Smoking trajectories of adolescent novice smokers in a longitudinal study of tobacco use. *Annals of Epidemiology, 15*(6), 445–452.

Lessov-Schlaggar, C. N., Hops, H., Brigham, J., Hudmon, K. S., Andrews, J. A., Tildesley, E., et al. (2008). Adolescent smoking trajectories and nicotine dependence. *Nicotine & Tobacco Research, 10*(2), 341–351.

Lynne-Landsman, S. D., Bradshaw, C. P., & Ialongo, N. S. (2010). Testing a developmental cascade model of adolescent substance use trajectories and young adult adjustment. *Development and Psychopathology, 22*, 933–948.

Maggi, S. (2008). Changes in smoking behaviours from late childhood to adolescence: 4 years later. *Drug and Alcohol Dependence, 94*(1–3), 251–253.

Maggi, S., Hertzman, C., & Vaillancourt, T. (2007). Changes in smoking behaviors from late childhood to adolescence: Insights from the Canadian National Longitudinal Survey of Children and Youth. *Health Psychology, 26*(2), 232.

McKenzie, J. E., & Brennan, S. E. (2019). Chapter 12: Synthesizing and presenting findings using other methods. Draft version (29 January 2019). In J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, & M. J. Page (Eds.). *Cochrane handbook for systematic reviews of interventions*. London: Cochrane.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine, 151*(4), 264–269.

Nagin, D. S. (2005). *Group-based modeling of development*. Harvard University Press.

Nelson, S. E., Van Ryzin, M. J., & Dishion, T. J. (2015). Alcohol, marijuana, and tobacco use trajectories from age 12 to 24 years: Demographic correlates and young adult substance use problems. *Development and Psychopathology, 27*(01), 253–277.

Orlando, M., Tucker, J. S., Ellickson, P. L., & Klein, D. J. (2004). Developmental trajectories of cigarette smoking and their correlates from early adolescence to young adulthood. *Journal of Consulting and Clinical Psychology, 72*(3), 400–410. https://doi.org/10.1037/0022-006x.72.3.400.

Orpinas, P., Lacy, B., Nahapetyan, L., Dube, S. R., & Song, X. (2015). Cigarette smoking trajectories from sixth to twelfth grade: Associated substance use and high school dropout. *Nicotine & Tobacco Research, 18*(2), 156–162.

Otten, R., Wanner, B., Vitaro, F., & Engels, R. C. (2008). Own and friends' smoking attitudes and social preference as early predictors of adolescent smoking. *Journal of Clinical Child and Adolescent Psychology, 37*(4), 808–819.

Otten, R., Wanner, B., Vitaro, F., & Engels, R. C. (2009). Disruptiveness, peer experiences and adolescent smoking: A long-term longitudinal approach. *Addiction (Abingdon, England), 104*(4), 641–650.

Riggs, N. R., Chou, C. P., Li, C., & Pentz, M. A. (2007). Adolescent to emerging adulthood smoking trajectories: When do smoking trajectories diverge, and do they predict early adulthood nicotine dependence. *Nicotine & Tobacco Research, 9*(11), 1147–1154. https://doi.org/10.1080/14622200701648359.

Rosendahl, K. I., Galanti, M. R., & Gilljam, H. (2008). Trajectories of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents: Differences and implications. *Nicotine & Tobacco Research, 10*(6), 1021–1027.

Royston, P., Altman, D. G., & Sauerbrei, W. (2006). Dichotomizing continuous predictors in multiple regression: A bad idea. *Statistics in Medicine, 25*(1), 127–141.

Sher, K. J., Jackson, K. M., & Steinley, D. (2011). Alcohol use trajectories and the ubiquitous cat's cradle: Cause for concern. *Journal of Abnormal Psychology, 120*(2), 322.

Tan, X., Dierker, L., Rose, J., Li, R., & Network, T. E. R. (2011). How spacing of data collection may impact estimates of substance use trajectories. *Substance Use & Misuse, 46*(6), 758–768.

Tucker, J. S., Ellickson, P. L., Orlando, M., & Klein, D. J. (2006). Cigarette smoking from adolescence to young adulthood: Women's developmental trajectories and associates outcomes. *Women's Health Issues, 16*(1), 30–37.

Tucker, J. S., Ellickson, P. L., Orlando, M., Martino, S. C., & Klein, D. J. (2005). Substance use trajectories from early adolescence to emerging adulthood: A comparison of smoking, binge drinking, and marijuana use. *Journal of Drug Issues, 35*(2), 307–332.

US Department of Health Human Services. (2012). *Preventing tobacco use among youth and young adults: A report of the Surgeon General, 3*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Vachon, D. D., Krueger, R. F., Irons, D. E., Iacono, W. G., & McGue, M. (2017). Are alcohol trajectories a useful way of identifying at-risk youth? A multiwave longitudinal-epidemiologic study. *Journal of the American Academy of Child & Adolescent Psychiatry, 56*(6), 498–505.

Van De Schoot, R., Sijbrandij, M., Winter, S. D., Depaoli, S., & Vermunt, J. K. (2017). The GRoLTS-checklist: Guidelines for reporting on latent trajectory studies. *Structural Equation Modeling: A Multidisciplinary Journal, 24*(3), 451–467.

Vitaro, F., Wanner, B., Brendgen, M., Gosselin, C., & Gendreau, P. L. (2004). Differential contribution of parents and friends to smoking trajectories during adolescence. *Addictive Behaviors, 29*(4), 831–835.

Vuolo, M., & Staff, J. (2013). Parent and child cigarette use: A longitudinal, multigenerational study. *Pediatrics, Peds* 2013-0067.

Wellman, R. J., Dugas, E. N., Dutczak, H., O'Loughlin, E. K., Datta, G. D., Lauzon, B., et al. (2016). Predictors of the onset of cigarette smoking: A systematic review of longitudinal population-based studies in youth. *American Journal of Preventive Medicine, 51*(5), 767–778.

White, H. R., Nagin, D., Replogle, E., & Stouthamer-Loeber, M. (2004). Racial differences in trajectories of cigarette use. *Drug & Alcohol Dependence, 76*(3), 219–227.

Zuk, O., Hechter, E., Sunyaev, S. R., & Lander, E. S. (2012). The mystery of missing heritability: Genetic interactions create phantom heritability. *Proceedings of the National Academy of Sciences of the United States of America, 109*(4), 1193–1198. https://doi.org/10.1073/pnas.1119675109.

Chapter 5 – Objectives

The central aim of the current thesis was to attempt to use trajectory modeling to increase understanding of cigarette smoking onset in youth, a further related aim was to ascertain the usefulness of cigarette smoking trajectory modeling to public health. The objectives and hypotheses presented in the current chapter follow directly from both the background chapter (chapter 2) and the conclusions of Article 1 (chapter 4). Objective 2 and its associated hypotheses relate directly to the topic of cigarette smoking trajectories and onset of cigarette smoking in youth. Objective 3 and its hypotheses relate to the potential association between cigarette trajectories, onset of cigarette use, and cannabis use.

5.1 Objective 2

A major finding of the systematic review conducted in Article 1 was that most studies modeled incident and prevalent smoking combined or mixed trajectories, and that few model incident smoking. The time axis used is the fundamental difference between these types of trajectory analyses: models of incident cigarette smoking model the time since smoking onset, while mixed trajectories model changes in smoking over time and use axes such as age or calendar time. Incident trajectories should theoretically present the clearest picture of the development of smoking over time in an individual. For this reason, we elected to carry out our own comparison of incident and mixed cigarette smoking trajectory models.

Objective: In an adolescent cohort of 1293 participants aged 12-13 years at inception in Montreal (Canada) in 1999-2000, to: (i) model trajectories of incident cigarette smoking; and (ii) to compare incident trajectories with mixed trajectories modeled using both incident and prevalent novice smokers, to ascertain whether the number or shape of trajectories differ and whether the risk factors or outcomes differ.

Hypothesis 1: Modeling trajectories of incident cigarette smoking in adolescence identifies high-risk smokers who begin smoking earlier and in addition sustain high levels of cigarette consumption during adolescence.

Hypothesis 2: Risk factors for incident cigarette smoking trajectories enable identification of novice smokers at risk of becoming heavy and sustained cigarette smokers.

Hypothesis 3: Novice smokers in higher risk/heavier cigarette smoking trajectories in adolescence are more likely to smoke cigarettes in adulthood, as well as to smoke more often and/or smoke more cigarettes per day/week/month in adulthood.

Hypothesis 4: Trajectories of incident cigarette smoking differ from trajectories combining incident and prevalent cigarette smokers. The number, shape, and risk factors differ between models of incident cigarette smoking versus models of incident and prevalent cigarette smoking.

5.2 Objective 3

Objective: In an adolescent cohort of 1293 participants age 12-13 years at inception in Montreal (Canada) in 1999-2000, to: (i) describe order of initiation of tobacco and cannabis; (ii) describe age at first cannabis use across cigarette smoking trajectories; and (iii) identify predictors of elapsed time between tobacco and cannabis initiation.

Hypothesis 1: Most individuals who initiate both cannabis and cigarettes will initiate cigarette smoking first. Order of initiation of cannabis and cigarettes is not associated with cigarette smoking trajectory group.

Hypothesis 2: The proportion of ever-cannabis use is higher in trajectories with heavier compared to lighter cigarette smoking. Cannabis use is initiated at younger ages in heavier smoking trajectories.

Hypothesis 3: Risk factors for time elapsed between initiation of one substance and initiation of the second can be identified. Risk factors for time to cigarette smoking initiation among ever cannabis users differ from those for time to cannabis initiation among ever cigarette smokers.

Chapter 6 – Methods

The current chapter presents methods pertaining to Manuscripts 2 and 3 of the current thesis. Sections 6.1 and 6.2 relate to Objectives 2 and 3 and describe the data source (i.e., an adolescent sample of 1293 participants age 12-13 years at inception) and variables used to: (i) model trajectories of incident cigarette smoking; (ii) compare incident and prevalent adolescent cigarette smoking trajectories; (iii) study cannabis and cigarette initiation in relation to each other and to cigarette smoking trajectories in high school. Section 6.3 presents an overview of the analyses presented in Chapter 7.

6.1 Data source

The following two sections report the data source and variables used to address Objectives 2 and 3. Data were drawn from an adolescent sample of 1293 participants age 12-13 years at inception to: (i) model trajectories of incident cigarette smoking, (ii) compare incident and prevalent adolescent cigarette smoking trajectories during high school, (iii) describe order of initiation of tobacco and cannabis; (iv) describe age at first cannabis use across cigarette smoking trajectories; and (v) identify predictors of elapsed time between tobacco and cannabis initiation.

NDIT study

The data to address Objectives 2 and 3 originate from the Nicotine Dependence in Teens (NDIT) Study. [145], [146] The following sections describe the NDIT Study including its design, data collection methods, and the study variables used in this thesis.

6.1.1 Study design

NDIT is an ongoing longitudinal investigation of 1293 students recruited in 1999–2000 from all grade 7 classes in a purposive sample [147] of 10 high schools in or near the city of Montreal, Quebec, Canada. The objectives of the study were to investigate the natural course and the determinants of cigarette smoking and nicotine dependence in novice smokers. NDIT also incorporated collection of data on obesity, blood pressure, physical activity, team sports,

sedentary behaviour, diet, genetics, alcohol use, use of illicit drugs, second-hand smoke, gambling, sleep and mental health. [145]

6.1.2 Sample of schools

Thirteen high schools in the Montreal area were selected with the assistance of local school boards and school principals, to ensure a mix of schools of differing socioeconomic status (high, moderate, low), language (French, English), and place of residence (urban, suburban, rural). [145] Schools selected were also purported to have a low level of in- and out-migration of students. [145] Private schools were excluded. Ten of 13 schools participated in the study (three schools were excluded because of low student participation or for logistical reasons) and students in grade 7 in 1999-2000 constituted the target study population.

6.1.3 Data collection

All grade 7 students in participating schools were given a take-home package that included a letter addressed personally to them and their parent(s)/legal guardian(s) describing the NDIT study, as well as a consent form for their parent(s)/legal guardian(s) to sign. The Principal Investigator gave a presentation in each school to explain the study to students, teachers and other school staff. Self-report questionnaires were administered at school every 3-4 months during the 10-month school year between grades 7-11 (1999–2005), for a total of 20 cycles. Self-report questionnaires were also completed after graduation from high school in 2007–08 and 2011–12 (cycles 21 and 22, respectively) when participants were age 20 and 24 years on average, respectively. Additional measures were collected in selected cycles including anthropometric measures, blood pressure measures, food frequency questionnaires, blood and/or saliva samples for genetics testing and cotinine, observation of school neighborhoods, and objective measures of physical activity collected using accelerometers. [145], [146] Questionnaires were also completed by parents and school administrators, and parental blood or saliva samples were obtained for DNA extraction. [145], [146]

6.1.4 Ethical considerations

This study was approved by the Montreal Department of Public Health Ethics Review Committee, the McGill University Faculty of Medicine Institutional Review Board, the Ethics Research Committee of the Centre de Recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), and the Ethics Research Committee of the University of Toronto. Parents or guardians provided written informed consent at baseline and participants provided assent. Participants provided written informed consent in post-high school surveys when they had attained legal age. [145], [146] (Appendix 10)

6.1.5 Participants

Response

Response rate in NDIT was relatively low (1294 of 2325 eligible students (56%)). (1293 of 2325 eligible students participated at baseline and a single individual participated only at survey cycle 22.). This was due partly to the need for blood samples for genetic analysis and to a labour dispute in Quebec that resulted in several teachers refusing to collect consent forms. [145]

Characteristics of participants

Nearly half (48%) of study participants were male, 30% reported speaking French at home, and 92% were born in Canada. Their mean age at baseline was 12.8 years. When compared with data from 13 year-olds in the Quebec Child and Adolescent Health and Social Survey (QCAHSS) [148], a representative sample of Quebec youth of three different ages (i.e., age 9, 13, and 16) in 1999 and a lower proportion spoke French at home (i.e., 30% versus 85%). Their parents were also more highly educated (58% versus 30% university-educated, respectively); and indicators of smoking were lower at baseline (e.g. 32% versus 53% had ever smoked, respectively). [145] Characteristics of NDIT participants at baseline are presented in Table 9. [145]

Table 9. Comparison of baseline characteristics of NDIT participants with those of a provincially representative sample of Quebec youth aged 13 years, NDIT 1999–2000; Quebec Child and Adolescent Health and Social Survey (QCAHSS) 1999 (Reproduced from reference [145])[e,f]

Characteristic	NDIT (*n* = 1293)	QCAHSS (*n* = 1186) [a]
Age, mean years (SD) (CI)	12.8 (0.6) (12.77, 12.83)	12.9 (0.3) (12.88, 12.92)
Male, % (CI)	48 (45, 51)	50 (47, 53)
French spoken at home, % (CI)	30 (27, 33)	85
Born in Canada, % (CI)	92 (90, 94)	95
Caucasian, % (CI)	82	100[b]
Parent(s) university educated, % (CI)	58	30
Ever smoked, even just a puff, % (CI)	32	53
Smoked ≥100 cigarettes lifetime (among smokers), % (CI)	27	37
No. cigarettes/week (among past-week smokers), mean (SD)	17.5 (24.3)	20.9 (25.8)
BMI, mean (SD)	20.1 (3.8)	20.6 (4.1)
Systolic blood pressure, mean mmHg (SD)	105.3 (10.2)	112.5 (11.8)
Diastolic blood pressure, mean mmHg (SD)	56.6 (6.2)	59.2 (7.0)
No. physical activities/week,[a] mean (SD)	8.4 (8.6)	8.0 (7.8)
TV viewing (h/week), mean (SD)	20.5 (14.7)	24.7 (14.1)
Drank alcohol,[b] % (CI)	44 (41, 47)	51

[a] Includes children age 13 years.
[b]Non-Caucasians were excluded by design.
[c]Excludes physical education classes at school.
[d]Time frame was past 3 months in NDIT and past 12 months in QCAHSS.
[e]Confidence intervals for proportions were obtained using the normal approximation to the binomial distribution. For continuous variables known to be normally distributed in NDIT a standard CI using the normal distribution was calculated.
[f]Confidence intervals were calculated for variables which were known to be normally distributed (continuous variables) and for which the degree of item nonresponse was known. (Not considering item nonresponse could lead to the confidence interval obtained being too narrow.)
SD: Standard deviation. CI: Confidence interval. TV: Television. BMI: Body mass index. h/week: Hours per week. NDIT: Nicotine Dependence in Teens study. QCAHSS: Quebec Child and Adolescent Health and Social Survey.

6.2 Description of study variables

6.2.1 Study variables used in Objectives 2 and 3

Table 10 describes the variables used in Manuscript 2 and 3.

Table 10. Detailed description of variables used in manuscripts addressing Objectives 2 and 3, NDIT 1999-2012

Variable	Available in cycle(s)	Item (s)	Response choices/ creation of score	Recoded for analysis	Relevant to manuscript
Sociodemographic					
Age	1-20	Date of birth, date of survey	-		2, 3
Sex	1-20	Are you a boy or a girl?	Male, female	-	2, 3
Lives with one parent	1-20	Do you live with your: biologic mother, biologic father, step-mother, step-father	No, yes (for each person)	No, yes	2, 3
Born in Canada	1-11	Were you born…?	In Canada, outside Canada	-	2, 3
French-speaking	1-11	What language do you speak most often at home? Check one box.	English, French, English and French, Other (specify)	French, other	2, 3
Mother university-educated	13,17, mother questionnaire	How much education has your mother had?	Did not finish high school, high school graduate, vocational, technical school, CEGEP, university, don't know, not applicable, other	No, yes	2, 3
Smoking indicators					
Mean number of cigarettes smoked per month in the past 3 months[149]	1-22	For each of the past 3 months: During _____, on how many days did you smoke cigarettes, even just a puff? On the days that you smoked during last month, how many cigarettes did you usually smoke each day?	0, 1, 2-3, 4-5, 6-10, 11-15, 16-20, 21-30, every day, don't know <1, 1, 2-3,4-5, 6-10, 11-15, 16-20, 21-25, >25, don't know	No. days was multiplied by no. cig/day and averaged across months (see section 8.1 of Appendix 8 for additional details)	2, 3
Baseline ever/never smoked		Have you ever in your life smoked a cigarette, even just a puff (drag, hit, haul)? Check the box that describes you best…."),	Yes, no I have never smoked, even just a puff, I have smoked	Never smoker (no+ I have never smoked, even just a puff), ever smoker (everyone else)	2, 3

		at baseline. Responses to the same question in cycles 1-20 were used to identify participants who remained never smokers during adolescence.)	cigarettes, but not at all in the past 12 months, I smoked cigarettes once or a couple of times in the past 12 months, I smoke cigarettes once or a couple of times each month, I smoke cigarettes once or a couple of times each week, I smoke daily		
Age at cigarette initiation	21	How old were you when you puffed on a cigarette for the first time?			3
Used other tobacco products	1-20	During the past 3 months, how often did you: (i) smoke a cigar or cigarillo; (ii) use chewing tobacco or snuff	Never, a bit to try, once or a couple of times a month, once or a couple of times a week, every day	No (never), yes (a bit to try or more)	2
Parent(s) smoke	1-20	Does your father currently smoke cigarettes? Does your mother currently smoke cigarettes?	No, yes (for each parent)	Yes (1 or 2 parents smoke), no	2, 3
Friends smoke	1-20	Now, think about your friends. How many of the people whom you usually hang out with smoke cigarettes?	None, a few, about half, more than half, most or all	Yes, no	2, 3
Sibling(s) smoke	1-20	You have ___sisters ___brothers who smoke cigarettes.	0,1,2,3,4,5,6+ 0,1,2,3,4,5,6+	No, yes (≥1 sibling smokes)	3
Physically and/or mentally addicted	1-22	How physically addicted to smoking cigarettes are you? How mentally addicted to smoking cigarettes are you?	Not at all, a little, quite, very Not at all, a little, quite, very	Yes (a little, quite, very for either), no (not at all for both)	2
Really need a cigarette	1-20	How often have you felt like you really need a cigarette?	Never, rarely, sometimes, often	No (never), yes (rarely, sometimes, often)	2
Quit smoking (among past 3-month smokers)	22	Think about the last time you tried to quit smoking. Did you quit smoking completely (for a while)?	Never tried to quit, no but I cut down a lot, no but I cut down a little, no the amount I smoke didn`t change at all, yes	No, yes (I quit smoking completely and have remained non-	2

			I quit completely for_____days, yes I quit completely and have remained non-smoking ever since	smoking ever since)	
Want a cigarette [150]	22	Even if you do not currently smoke cigarettes, how often do you…want to smoke a cigarette?	Never, rarely, sometimes, often	Yes (rarely, sometimes, often), no (never)	2
Need a cigarette [150]	22	Even if you do not currently smoke cigarettes, how often do you…need a cigarette?	Never, rarely, sometimes, often	Yes (rarely, sometimes, often), no (never)	2
Crave a cigarette [150]	22	Even if you do not currently smoke cigarettes, how often do you…crave a cigarette?	Never, rarely, sometimes, often	Yes (rarely, sometimes, often), no (never)	2
mFTQ (7-item modification of mFTQ) [151], [152]	22	How many cigarettes a day do you smoke?	<1 (0), 1-15 (0), 16-25 (1), > 25 (2)	Responses for each of the 7 items were summed to create a score of 0-9. Participants were categorized as nicotine dependent (yes, no) if they met ≥4 criteria.	2
		Do you inhale?	Never (0), seldom (1), quite often (1), always (2)		
		How soon after you wake up do you smoke your first cigarette?	<30 min (1), >30 min but before noon (0), in the afternoon (0), in the evening (0)		
		Which cigarette would you hate to give up?	First in the morning (1), any other cigarette before noon (0), any other cigarette in the afternoon (0), any other cigarette in the evening (0)		
		Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes, very difficult (1), yes, somewhat difficult (1), no, not usually difficult (0), no, not at all difficult (0)		
		Do you smoke if you are so ill that you are in bed most of the day?	Yes, always (1), yes, quite often (1), no, not usually (0), no,		

			never (0)		
		Do you smoke more during the first 2 hours than during the rest of the day?	Yes (1), no (0)		
ICD-10	22			An item was coded positive if the most extreme response option was endorsed. A criterion was coded positive if any of its items were positive (the withdrawal syndrome required that ≥2 of 4 items be endorsed). Participants were categorized as tobacco dependent (yes, no) if they met ≥3 criteria	2
Strong desire or sense of compulsion to take tobacco [153], [154]		1. Have you ever had strong cravings to smoke cigarettes? 2. How physically/mentally addicted to smoking are you? 3. How often have you felt like you really need a cigarette? 4. Do you find it difficult not to smoke in places where it's not allowed (at a movie theatre, at home if your parents don't know you smoke)?	No, yes Not at all, a little, quite, very Never, rarely, sometimes, often Not at all difficult/I don't know, a bit difficult, very difficult		
Difficulty controlling tobacco taking behaviour in terms of onset, termination, or level		1. In the past 3 months, did you seriously try to quit smoking completely and forever? 2. Do you smoke cigarettes now because it is really hard to quit?	Yes, I quit completely and have remained non-smoking, I never tried to quit, yes, I tried to quit but failed, other/I don't know/I smoke so little, I don't know because I have never tried to quit No; sometimes; often/always		
Physiological withdrawal state when tobacco use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for tobacco; or use of the		Now think about the times when you have cut down or stopped using cigarettes or when you haven't been able to smoke for a long period (like most of the day). How often did you experience. . .? (i) feeling irritable or angry; (ii) feeling restless/Feeling	never, rarely, sometimes, often		

same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms		nervous, anxious or tense; (iii) trouble concentrating; (iv) feeling a strong urge or need to smoke			
Evidence of tolerance, such that increased doses of tobacco are required to achieve effects originally produced by lower doses		How true are each of the following for you? 1. Compared to when I first started smoking, I need to smoke a lot more now to be satisfied. 2. Compared to when I first started smoking, I can smoke much more now before I start to feel nauseated or ill.	I've never felt nauseated or ill from smoking, not at all true, a bit true, very true Not at all true, a bit true, very true		
Progressive neglect of alternative pleasure or interests because of tobacco use, increased amount of time necessary to obtain or take the substance or to recover from its effects		How true are each of the following for you? (1) I spend a lot of time getting cigarettes (going out of my way to a store where I know they will sell to me; trying to find someone who will buy them for me); (2) I've stopped hanging out with certain people because of my smoking; (3) I avoid going to a friend's house where you're not allowed to smoke even though I might enjoy hanging out with him/her; (4) I have cut down or stopped physical activity or sports because of my smoking	Not at all true, a bit true, very true		

Persisting with tobacco use despite clear evidence of overtly harmful consequences		How true are each of the following for you? 1. In situations where I need to go outside to smoke, it's worth it even in cold or rainy weather 2. If you are sick with a bad cold or sore throat, do you smoke?	Not at all true, a bit true, very true No, I don't have to, I smoke so little; no, I stop smoking when I'm sick; yes, but I cut down on the amount I smoke; yes, I smoke the same amount as when I am sick		
Psychosocial indicators					
Depressive symptoms [155]	1-20	During the past 3 months how often have you: (i) felt too tired to do things (ii) had trouble going to sleep or staying asleep (iii) felt unhappy, sad or depressed (iv) felt hopeless about the future (v) felt nervous or tense (vi) worried too much about things	Never, rarely, sometimes, often	Score (range 1-4) created by summing responses and dividing by no. of items responded to	2, 3
Family stress [156], [157]	1-20	During the past 3 months, have you been worried or stressed by: (i) your parents separating or divorcing; (ii) your relationship with your father; (iii) your relationship with your mother; (iv) your relationship with your brother(s)/sister(s) (v) your new family (parents remarried)	Not at all/not applicable, a little bit, quite a bit, a whole lot	Score (range 1-4) created by summing responses and dividing by no. of items responded to	2

Other stress [156], [157]	1-20	During the past 3 months, have you been worried or stressed by: (i) breaking up with your boyfriend/girlfriend; (ii) your relationship with your friends; (iii) a health problem (acne, asthma); (iv) sex; (v) school work	Not at all/not applicable, a little bit, quite a bit, a whole lot	Score (range 1-4) created by summing responses and dividing by no. of items responded to	2
Impulsivity (measured using a shortened version of the Eysenck Impulsivity Scale) [158], [159]	14,18	How true are each of the following statements for you: (i) I often do things without stopping to think (ii) I am an impulsive person (iii) I often talk quickly, before thinking things out (iv) I often get involved in things I later wish I could get out of (v) I need to use a lot of self-control to keep out of trouble (vi) I often get into trouble because I do things without thinking (vii) I get carried away by new and exciting ideas, but I don't think of the possible problems	Not at all true, a little true, somewhat true, quite true, very true	Score (range 1-5) created by summing responses and dividing by no. of items responded to	2
Novelty-seeking [160]	14,18	How true are each of the following statements for you: (i) I often try new things just for fun or thrills, even if most people think it is a waste of time (ii) When nothing new is happening, I usually start looking for something that is exciting (iii) I can usually get people to believe me, even when what I'm saying isn't quite true (iv) I often do things based on how I feel at the moment (v) I sometimes get so excited that I lose	Not at all true, a little true, somewhat true, pretty true, very true	Score (range 1-5) created by summing responses and dividing by no. of items responded to	2

		control of myself (vi) I like it when people can do whatever they want, without strict rules and regulations (vii) I often follow my instincts, without thinking through all the details (viii) I can do a good job of "stretching the truth" when I'm talking to people (ix) I change my interests a lot, because my attention often shifts			
Self-esteem [161]	12	Indicate the response which best describes your situation. (i) I think I am someone who has something valuable to offer, at least as much as other people do (ii) I think I have a certain number of good qualities (iii) Everything considered, I tend to think I'm a failure (iv) I think I am capable of doing things as well as other people my age (v) There's little reason to be proud of myself; (vi) I have a positive attitude towards myself; (vii) I find it difficult to accept myself as I am; (viii) Sometimes I think I'm really useless; (ix) I've thought of myself as a good-for-nothing on occasion	Not at all true, a little true, very true	Score (range 1-3) created by summing responses and dividing by the no. of items responded to	2, 3
Lifestyle indicators					
Body mass index (BMI)	1, 12, 19	Height and weight were measured twice by trained technicians	If there was a discrepancy between the 2 measures (i.e., > 0.5 cm for height or > 0.5 lbs for weight) a 3rd measure was taken.	Mean computed (if there were 3 measures, the 2 closest measures were used). BMI: weight	2

				(kg)/height (m)^2. Age- and sex-specific BMI z-scores were computed using the CDC guidelines. [14,15]	
Alcohol use	1-20	During the past 3 months, how often did you drink alcohol (beer, wine, hard liquor)	Never, a bit to try, once or a couple of times a month, once or a couple of times a week, every day	No, yes (a bit to try or more)	2, 3
Ever used cannabis	21	Have you ever done any of the following? …used marijuana, cannabis, hashish	No, yes		3
Age at first cannabis use	21	Have you ever done any of the following? *(as above)* If yes, how old were you when you did it the first time? …used marijuana, cannabis, hashish	No, yes *(as above)* When I did it the first time I was ____ years old		3
Moderate or vigorous physical activity (MVPA) [162]	1-20	Think about the physical activities that you did last week from Monday to Sunday outside your regular school gym class. For each activity that you did for 5 min or more at one time, mark an "X" to show the day(s) on which you did that activity	No, yes for each activity. 21 of 29 activities were designated moderate (3-6 METs) and 6 of 29 activities were designated vigorous (>6 METs).	Activities summed to create a continuous score (range 0-189)	2
Participated in team sport(s)	1-20	Since September of this school year, did you belong to any of the following intramural or extramural school sports teams (teams that were not part of your regular gym class)? (list of 13 teams). Now think	No, yes (for each team or lesson)	No, yes (≥1 team)	2

		about sports teams and lessons outside of school. In the past 3 months, did you belong to a…? (list of 12 teams)			

MVPA: Moderate and vigorous physical activity. BMI: Body mass index. METS: Metabolic equivalent. CDC: Centers for Disease Control (U.S.). kg: kilograms. m: meters. lbs: pounds. mFTQ: Modified Fagerström Tolerance Questionnaire.

6.2.2 Reliability of cigarette measure

Reliability has been defined as the degree of stability exhibited when a measurement is repeated under identical conditions (see also section 8.3.2 for the difference between the concepts of reliability and validity). [32]

Test-retest reliability was measured by administering the questionnaire twice to a subset of NDIT participants (n = 63, mean age 14.1 years). Due to the study design, some participants provided data on cigarette use for the identical month in two different questionnaires administered 3 months apart. [163]

Frequency and intensity of cigarette use had the following test–retest reliability: kappa = 0.78 (0.66, 0.91) and 0.75 (0.61, 0.89), respectively. This corresponds to relatively good agreement (i.e., "moderate", near "strong" agreement) according to one published reference. [164] According to a second, this corresponds to "good" to "excellent" reliability. [165]

The ICC (used to measure test-retest reliability of the continuous cigarette smoking measure) for the combined measure representing the number of cigarettes smoked in the past month was however lower, at 0.64 (0.46, 0.77), indicating fair to good reliability according to one published scale. The measure should therefore be reliable. [163], [165]

6.3 Data analysis

Analyses were conducted using SAS versions 9.3, 9.4, and SAS University Edition. [166] Truncated regression analyses were carried out in R, using the Truncreg package. [167], [168] Trajectories were estimated using Proc Traj. [14]

6.3.1 Modeling smoking trajectories

Modeling cigarette smoking trajectories (incident and mixed models)

Group-based trajectory modeling was used to identify groups of smokers (i.e., incident smokers for incident trajectories; incident and prevalent smokers for the mixed trajectories) that were homogeneous in the pattern of mean number of cigarettes smoked per month over time. Time since smoking initiation, in 3-month intervals, comprised the time axis for the incident trajectories; this was converted to time in months after first puff (range 0 to 48 months) in Manuscript 2. The time axis for the mixed trajectories was data collection cycle (1 to 20); this was transformed to median age at each cycle in Manuscript 2. The number and shape of trajectories was not specified *a priori* but rather estimated from the data. We considered models with 1 to 6 trajectories, and selected the model which minimized the Bayes factor derived from the Bayesian Information Criterion (BIC) [14], [16], with the requirement that the average posterior probability assigning each individual to a group be more than 70%. The number of trajectory groups was determined using cubic polynomials; the model was then simplified by excluding higher order polynomial terms that were not statistically significant at the 5% level, except when this simplification resulted in an unstable model. Once the model was estimated, we assigned each individual to the trajectory group for which their posterior probability was highest.

6.3.2 Data analysis: Objective 2

The appearance of the incident and mixed trajectory models was compared. Potential risk factors were compared between trajectory groups in both the incident and the mixed cigarette smoking trajectory models. Smoking-related outcomes in young adulthood were compared across trajectory groups in both models.

6.3.3 Data analysis: Objective 3

We compared the 307 participants included in the incident cigarette smoking trajectories across trajectory groups, as well as with individuals who had never smoked across cycles 1–20, baseline ever smokers, and with participants who reported having initiated cigarette smoking during high school but stopped and reported zero for average monthly smoking throughout. (Figures 5 and 6) Participants were compared in order to describe order of initiation of cigarette smoking and cannabis use and to compare age at first cannabis use across participants

categorized into one of eight cigarette smoking categories. We also attempted to identify factors associated with elapsed time between cannabis initiation and cigarette smoking initiation. .

Chapter 7 - Results

7.2 Manuscript 2

Contributions to Manuscript 2 by Candidate

BL carried out all initial analyses, which originally involved only incident cigarette smoking trajectory models. BL drafted several initial versions of all sections of the article. The article was later extended to include a comparison of incident and mixed trajectories. BL participated in discussions and provided detailed feedback on all later versions of the article.

Note on manuscript references*

***Please note that references in the current manuscript are indicated by rounded parentheses (i.e., (and)) and refer to the list of references presented at the end of section 7.2.**

Title: Cigarette smoking trajectories in adolescent smokers: Does modeling incident or prevalent smoking make a difference?

Running head: Adolescent cigarette smoking trajectories

Authors: Lauzon B[1,2], Sylvestre MP[1,2] (co-first author), Dugas E N[1], Hanusaik N[1], Mesidor M[1,2], O'Loughlin JL[1,2]

Author affiliations: [1]Centre de recherche du centre hospitalier de l`Université de Montréal (CRCHUM), Montréal, QC, Canada; [2]Department of Social and Preventive Medicine, Université de Montréal, Montréal, QC, Canada

Corresponding author: Marie-Pierre Sylvestre, CRCHUM, 850 Saint-Denis (S03-458), Montreal, Quebec H2X 0A9. Tel: 514-890-8000, extension 31473; Fax: 514-412-7953; Email: marie-pierre.sylvestre@umontreal.ca

Word count (abstract): 297

Word count (body): 3495

Number of Tables: 4

Number of Figures: 2

Declaration of competing interest: none

Supplementary data: 7

Abbreviations: BMI - body mass index; mFTQ - modified Fagerstrom Tolerance Questionnaire; ICD-10 - International Classification of Diseases – Tenth Revision; MVPA -

moderate and vigorous physical activity; ND - nicotine dependence; NDIT - Nicotine Dependence in Teens

7.2.1 Abstract

Aims: Most studies modeling adolescent cigarette smoking trajectories use age or grade as the time axis, possibly obscuring depiction of the natural course of cigarette smoking onset. We compared trajectories in new (incident) adolescent smokers and (as in most trajectory studies) a mix of incident and ever- (prevalent) smokers at baseline.

Design: Data were drawn from a prospective investigation of adolescents recruited in 1999-2000 and followed in 22 data collection cycles from age 12 to 24.

Setting: Montreal, Canada

Participants: 1293 grade 7 students from 10 high schools. Analysis of incident trajectories included 307 incident smokers; analysis of "mixed" trajectories included 307 incident and 338 prevalent smokers (who reported ever-smoking at baseline).

Measurements: Cigarette consumption was measured every 3 months during high school, and 6 years after graduation. We studied whether baseline sociodemographic, smoking-related, psychosocial, and lifestyle indicators were associated with trajectory group. Smoking status and nicotine dependence (ND) were assessed at age 24.

Findings: Five trajectories were identified in incident smokers: stable-low consumers (45.6%), low-level decreasers (37.5%), slow escalators (8.1%), moderate escalators (6.2%), early-rapid escalators (2.6%). Four trajectories were identified in the mix of incident and prevalent smokers (the model did not differentiate stable-low and low-level decreasers). The rate of change was generally attenuated across curves in the mixed trajectory analysis. Escalating trajectories in both analyses were associated with higher levels of cigarette consumption and ND in early adulthood, although 35.6% and 60.6% of incident low-level decreasers and stable-low consumers continued to smoke respectively, and 10% and 16% reported ND into adulthood.

Conclusions: Modeling a mix of incident and prevalent adolescent smokers obscures depiction of the natural course of smoking onset and identification of factors associated with the natural course. Even stable-low consumers and low-level decreasers continue to smoke and experience ND into early adulthood.

Key words: adolescents, cigarette smoking, cohort, longitudinal, nicotine dependence, trajectories, young adults, incident, prevalent

7.2.2 Introduction

Despite recent decreases in North America (1, 2), cigarette smoking in youth remains a major public health burden. Recent reports indicate that 8% of Canadians ages 15-19 years and of US high school students currently smoke cigarettes. (2-4) While 75% of youth initiate smoking (5), not all become dependent or sustain smoking into adulthood. Increased understanding of early life factors that differentiate youth who progress to long-term smoking from those who initiate, but do not progress could enable targeting preventive intervention to novice smokers at risk of long-term smoking.

Trajectory analyses such as group-based approaches used to identify distinct developmental pathways of a behavior and to profile the characteristics of individuals within each homogeneous subgroup (6), have been useful in understanding the development of cigarette smoking behavior. In the last two decades, this method has flourished, in part due to the availability of analytic software that has facilitated its use. (7) These analyses provide support for the existence of multiple cigarette use trajectories suggestive of heterogeneity in the natural course of cigarette smoking. However, two aspects of this literature warrant attention.

First, despite the burgeoning literature, 41 of 43 studies in a recent systematic review (8) estimate cigarette smoking trajectories as a function of age or grade and thus include both current (prevalent) smokers, as well as new (incident) smokers. Only two studies (9, 10) estimate trajectories of incident smokers alone and thus capture the early natural course of cigarette smoking. Mixed trajectory studies (including both prevalent and incident smokers) result in trajectory groups that include members with different durations of smoking at a given point in time or age, and thus more variable levels of cigarette consumption and nicotine dependence (ND). Such studies provide a snapshot of archetypical trajectories in a given population (e.g., adolescents during high school) over time but, given the arbitrary anchoring of time zero, may not provide an accurate depiction of the natural course of smoking. (9) The question therefore arises as to whether incident and mixed trajectories can be used interchangeably to depict the natural course of smoking and identify windows of opportunity for intervention.

Second, it is generally accepted that, although other factors contribute to long-term smoking, ND is a central reason why smokers cannot quit. While several studies investigate

outcomes of adolescent smoking trajectories in adulthood such as smoking-related beliefs(11), cigarette smoking (12, 13), and family smoking (14, 15), only three investigate ND. Riggs et al., (16) reported significant differences across four trajectories in the likelihood of ND in early adulthood, suggesting even smokers with low cigarette use (0-4 cigarettes weekly) throughout adolescence were at risk of becoming addicted. Similarly, Karp et al. found that the majority of youth in trajectories with rapid increasing intensity of cigarette smoking over time developed some ND within a few years of initiation. (9) Lessov-Schlaggar et al., (14) however, reported "that regardless of trajectory group membership, smoking more than a few cigarettes per week throughout adolescence resulted in similar levels of lifetime nicotine dependence...". This inconsistency needs resolution because, if all trajectories result in similar proportions of ND adult smokers, the need for targeting intervention to specific subgroups of higher-risk adolescents is obfuscated. If only one or two trajectories result in high proportions of (dependent) adult smokers, planning targeted rather than population-wide programs may be more useful.

To address these gaps, we built on our earlier study (9) that tracked incident smokers from smoking initiation (at approximately age 13) to age 15. Because we continued intense follow-up (four data collection cycles per grade) during the five years of high school, the current study extends these earlier trajectories to age 17. We estimated trajectories in incident smokers only, as well as in both incident and baseline prevalent smokers, we identified factors associated with trajectory groups, and we examined the association between trajectories and smoking-related outcomes in young adulthood including ND.

7.2.3 Methods

Data were drawn from the Nicotine Dependence in Teens (NDIT) Study (17), a longitudinal investigation of 1293 grade 7 students recruited in 1999-2000 in 10 Montreal-area high schools. Schools selected included a mix of students by socioeconomic status (high, moderate, low), language (French, English), and place of residence (urban, suburban, rural). Participation at baseline (56% of eligible students) was affected by a labour dispute that resulted in some teachers refusing to collect consent forms. Participants completed self-report questionnaires at school every 3 months over five years in high school, for a total of 20 data collection cycles. (17) Questionnaires were also completed in 2007–08 (cycle 21) and 2011–12 (cycle 22) when participants were age 20 and 24, respectively. We refer to "baseline" in this manuscript as the first cycle that participants completed.

This study was approved by the Montreal Department of Public Health Ethics Committee and the McGill University Faculty of Medicine Institutional Review Board. It was also approved by the Ethics Research Committee of the Centre de recherche du Centre hospitalier de l'Université de Montréal. Parents/guardians provided written consent prior to baseline and participants provided consent post-high school.

Study design

We undertook two sets of trajectory analyses – one including incident cigarette smokers only (hereafter referred to as "incident trajectories"), and one including both incident and prevalent cigarette smokers (hereafter referred to as "mixed trajectories"). To create the analytic samples, we distinguished never- and ever-smokers at baseline based on responses to two questions: (i) "Have you ever in your life smoked a cigarette, even just a puff (drag, hit, haul)?" (yes, no); and (ii) "Check the box that describes you best…" (I have never smoked, even just a puff, I have smoked cigarettes, but not at all in the past 12 months, I smoked cigarettes once or a couple of times in the past 12 months, I smoke cigarettes once or a couple of times each month, I smoke cigarettes once or a couple of times each week, I smoke daily). (Table 10) Of 1293 NDIT participants, 869 had never smoked at baseline; the 424 ever-smokers were defined as prevalent smokers. (Figure 9)

To identify incident smokers, we examined responses in cycles 2 to 20 to the two questions: (i) "Have you ever in your life smoked a cigarette, even just a puff (drag, hit, haul)?" and (ii) "Check the box that describes you best…" (I have never smoked, even just a puff, versus any other answer) among the 869 baseline never smokers. The 415 (out of 869) participants who reported smoking for the first time in cycles 2 to 20 were defined as incident smokers. (Figure 9) Because trajectories cannot be estimated reliably with only one or two data points (18), 108 of 415 incident smokers without data on cigarettes smoked per month in at least 3 cycles (i.e., n = 42 participants were excluded because they did not provide data on cigarette smoking in ≥3 data collection cycles and n = 66 had zero values for number of cigarettes smoked in the past month for survey cycles 1-20 and could therefore not contribute to the trajectory estimation) were excluded. Data were therefore available for 307 incident smokers. (Figure 9) The 108 excluded were older at baseline than the 307 included, a higher proportion was male, relatively fewer were Canada-born, they smoked fewer cigarettes per month, reported fewer depressive and "other stress" symptoms, and they had lower novelty-seeking scores. (Table 32) A total of 645 participants (307 incident smokers and 338 of the 424 baseline prevalent smokers) were included in the mixed trajectory analyses. Eighty-six of the 424 prevalent smokers were excluded because they did not have cigarette consumption data in ≥3 cycles. (Figure 9) Excluded smokers in the mixed trajectory model (108 incident and 86 prevalent smokers) were older, a higher proportion was male, relatively fewer were Canada-born, fewer had friends who smoke, and they had lower novelty-seeking and impulsivity scores. (Table 33) Relatively fewer excluded participants smoked at baseline, but those who did smoke reported a higher median number of cigarettes per month than included participants.

Study variables

Number of cigarettes smoked per month was measured in a 3-month recall. (19) For each of the three months preceding each cycle, participants reported number of days on which they had smoked and usual number of cigarettes smoked per day on the days they smoked. The two items were multiplied to obtain number of cigarettes smoked per month; these were summed across the three months and averaged to obtain mean number of cigarettes smoked per month. Test-retest reliability of mean number of cigarettes smoked per month as measured by the intraclass correlation coefficient, was 0.64 (section 6.2.2). (20) Characteristics investigated in

association with trajectory groups included sociodemographic indicators (age, sex, mother university-educated, lives with one parent, born in Canada, French speaking) and smoking-related indicators (number of cigarettes smoked per month, used other tobacco products, parent(s) smoke, friend(s) smoke, physically/mentally addicted, really need a cigarette). Also investigated were psychosocial indicators (depressive symptoms, family-related stress, other stress, self-esteem, impulsivity, novelty-seeking) and lifestyle indicators (sex- and age-standardized body mass index (BMI) z-score (21, 22), alcohol use, moderate and vigorous physical activity (MVPA), participated in team sport(s)). Values for time-invariant characteristics (sex, mother university-educated, French-speaking, born in Canada) were drawn from baseline. Impulsivity and novelty-seeking (measured in cycles 14 and 18) and self-esteem (measured in cycle 12) were considered to be relatively time-invariant; the earliest value preceding cigarette smoking initiation was used, otherwise the variable was set to missing. Similarly, the earliest value of the BMI z-score (measured in cycle 1, 12 and 19) was used in the analyses or set to missing if unavailable. Values for all other characteristics were drawn from the cycle in which cigarette smoking was initiated in the incidence analysis. (Table 10)

Smoking-related outcomes were measured in cycle 22. Smoked in the past 3 months was measured in the 3-month recall. Quit smoking was coded yes for smokers who responded, "I have smoked cigarettes, but not at all in the past 12 months" to: "Check the box that describes you best" and, then, for past 3-month smokers who responded yes to: "Think about the last time you tried to quit smoking cigarettes. Did you quit smoking completely and remain non-smoking ever since?" Other outcomes investigated included: how mentally or physically addicted to smoking cigarettes are you (recoded yes (a little bit, quite, very) or not at all), how often do you want a cigarette (recoded yes (rarely, sometime, often) or never), how often do you need a cigarette (recoded yes (rarely, sometime, often) or never), how often do you crave a cigarette (recoded yes (rarely, sometime, often) or never), mFTQ (modified Fagerstrom Tolerance Questionnaire) nicotine dependent (yes, no) and ICD-10 (International Classification of Diseases – Tenth Revision) tobacco dependent (yes, no). Detailed descriptions of variables are provided in Table 10. (See also Appendices 4, 5, and 8 for further details on variables, as well as regarding included and excluded participants.)

Data analysis

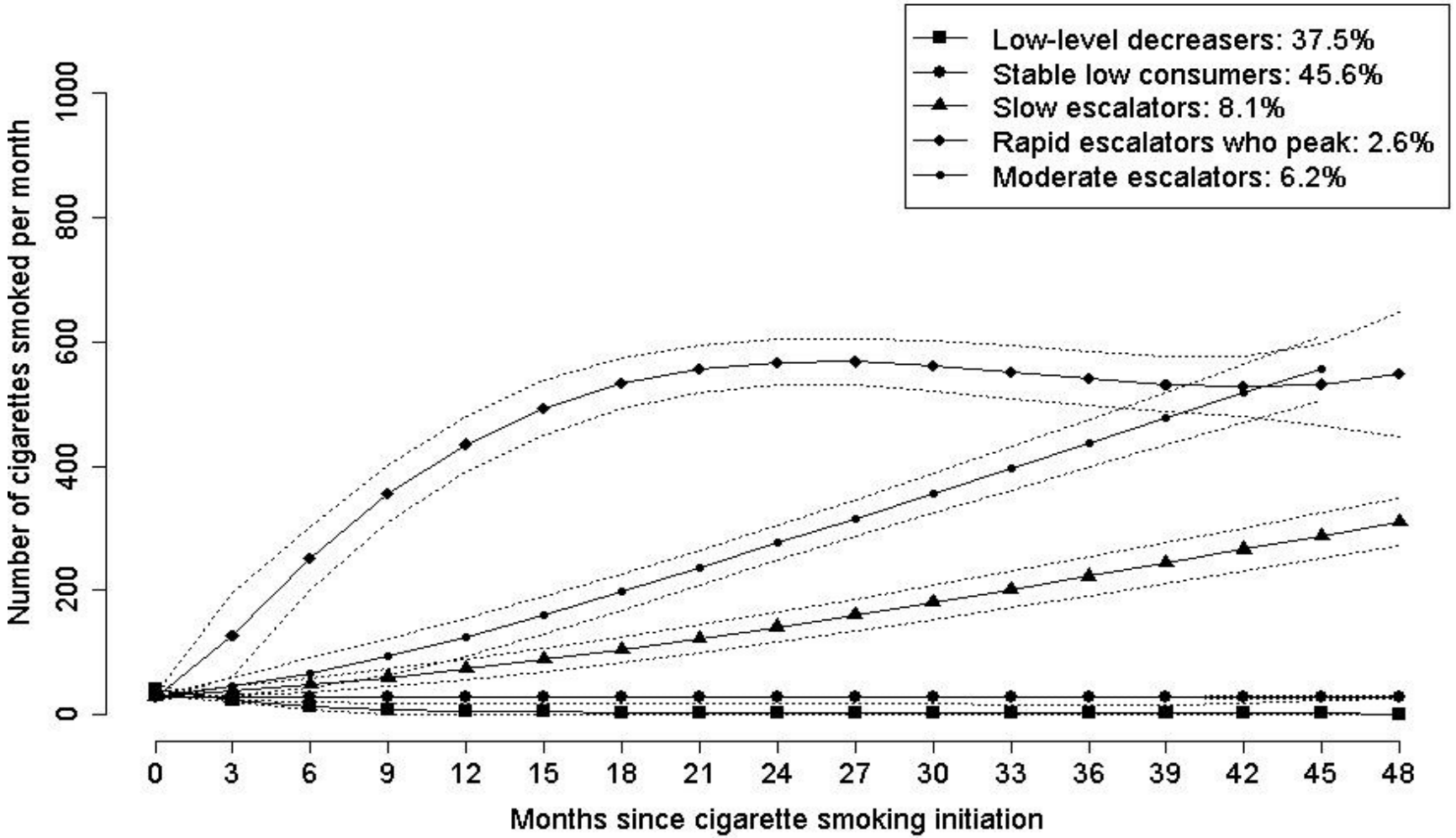
Group-based trajectory modeling was used to identify groups of incident smokers (for the incident trajectory analyses), or incident and prevalent smokers (for the mixed trajectories), that were homogeneous in terms of the pattern in mean number of cigarettes smoked per month over time. The time axis for the incident trajectories corresponded to time since cigarette smoking initiation, and the time axis for the mixed trajectories was data collection cycle (1 to 20). To facilitate interpretation of the figures, we converted time in 3-month intervals (i.e., number of cycles) to time in months after first puff (range 0 to 48 months) for the incident trajectories and to median age at each survey cycle (range 12.7 to 16.4 years) for the mixed trajectories.

The number and shape of trajectories was not specified a priori, but rather estimated from the data. We considered models with one to five trajectories and selected the model that led to the best improvement in the Bayes factor (23), if the average posterior probability assigning each individual to a trajectory group was more than 70%. Each trajectory was initially modeled using cubic polynomials and simplified by excluding higher order polynomial terms that were not statistically significant at the 5% level. Once the model was estimated, we assigned each participant to the trajectory group for which their posterior probability was highest. Trajectories were estimated using the SAS PROC TRAJ command, version 9.3. (7)

We contrasted characteristics of participants in each trajectory group at the time of cigarette smoking initiation (for the incident trajectories) or baseline (for the mixed trajectories), as well as smoking-related outcomes in cycle 22, using ANOVA or Kruskall-Wallis procedures for continuous variables and chi-squared tests for categorical variables. (It should be noted however that for comparison of incident trajectory groups, baseline values for time-invariant variables were used, while the earliest value available preceding cigarette smoking initiation was used for impulsivity, novelty-seeking, self-esteem, and BMI z-score. If the variable was not measured prior to initiation it was set to missing with regards to comparison of incident trajectories. When comparing mixed trajectory groups, the earliest values available for impulsivity, novelty-seeking, self-esteem, and BMI z-score were used, while all other variables were measured at baseline.) Trajectory groups with less than 10 participants were excluded from the testing procedures (a difference between the two models therefore was the exclusion of rapid escalators who peak from the risk factor and outcome comparisons in the incident model).

(Additional information on methods and reporting relating to this manuscript is provided in Appendices 4, 5, 6, and 8.)

Figure 3. (Manuscript 2, Figure 1) Trajectories with 95% confidence intervals of number of cigarettes smoked per month among incident adolescent smokers (*n* = 307), NDIT 1999-2005



7.2.4 Results

Incident trajectories

The 5-group model was the best fit to the data in the incident trajectory analyses. (Figure 3) The largest group (45.6% of 307 included incident cigarette smokers) consistently reported low cigarette consumption, fluctuating around 28 cigarettes per month. This group is referred to herein as "stable-low consumers." A second group, the "low-level decreasers" (37.5%) reported 40 cigarettes per month at the first survey following initiation and then steadily decreased their consumption to 1-2 cigarettes a month after 40 months of follow-up. "Slow escalators" (8.1%) and "moderate escalators" (6.2%) increased their consumption until the end of follow-up at a rate of approximately 6 and 12 cigarettes per month, respectively. Their maximum consumption, attained 48 months after initiation, was 310 and 558 cigarettes per month, respectively. Finally, "early-rapid escalators who peaked" (2.6%) began increasing consumption shortly after initiation, continued increasing for 24 months to peak at 548 cigarettes per month 48 months after initiation, before the curve leveled off for the duration of follow-up.

Two ND symptoms (physically/mentally addicted, really need a cigarette) differed across incident trajectory groups, but few other variables were associated with incident trajectory group. (Table 11) Specifically, there were no statistically significant differences across groups in sociodemographic, psychosocial or lifestyle indicators. The only exceptions were that slow escalators were younger on average at initiation, low-level decreasers were more likely to be male and low level decreasers and stable-low consumers participated in MVPA less frequently than other trajectories. (As a reminder, trajectory groups with <10 participants were excluded from the statistical testing procedures, so the early-rapid escalators were not compared with other groups in the incident trajectory model.)

Considering actual variable values (regardless of statistical significance), in general the smoking-related indicators showed a less favorable/higher risk profile in the increasing trajectories and a more favorable/lower risk profile in the low-level trajectories: for example 77.2% and 84.3% had friends who smoked in the low-level trajectories (i.e., low-level decreasers and stable-low consumers trajectory groups, respectively), while 88.0-100% had friends who smoked in the increasing trajectories (i.e., slow escalators, moderate escalators, and

early-rapid escalators who peaked). Use of other tobacco products was 42.5% and 36.1% in the low-level trajectories and 48-83% in the increasing trajectories. This was not the case for other risk factor categories: for example in the sociodemographic indicator category, mother university education was 46.0% and 52.0% in the low-level smoking and 0-60.9% in the increasing trajectories. As another example team sports participation (in the lifestyle indicators category) was also not clearly different: 64.3% and 55% had participated in the low-level trajectories while 48-57.9% reported participation in the increasing trajectories.

Table 11. (Manuscript 2, Table 1) Characteristics[1] of smokers across incident trajectory groups (*n* = 307), NDIT 1999-2005

	Low-level decreasers (*n* = 99-115)	Stable-low consumers (*n* = 110-140)	Slow escalators (*n* = 21-25)	Moderate escalators (*n* = 14-19)	p-value[2]	Rapid escalators who peak (*n* = 5-8)	Missing values n
Sociodemographic indicators							
Age, y, mean (SD)	14.1 (1.1)	14.1 (1.2)	13.4 (0.7)	14.0 (0.9)	0.0340	13.6 (0.5)	0
Male, %	48.7	30.7	40.0	36.8	0.0344	5/8 (0.625)	0
Mother university-educated, %	46.0	52.0	60.9	40.0	0.4705	0/6	40
Lives with one parent, %	8.7	17.3	12.0	10.5	0.2318	1/8 (0.125)	1
Born in Canada, %	93.0	97.1	100.0	94.7	0.2435	8/8	0
French-speaking, %	24.3	19.3	24.0	36.8	0.3486	2/8 (0.25)	0
Smoking-related indicators							
No. cig/month, median (IQR)	0.5 (0.5, 1)	0.5 (0, 1)	3.3 (0.6, 34.6)	1 (0.5, 12.2)	0.0004	27.2 (0.4, 65.7)	5
Used other tobacco products, %	42.5	36.1	48.0	58.8	0.2440	5/6 (0.83)	13
Parent(s) smoke, %	24.6	31.9	48.0	33.3	0.1271	4/8	4
Friends smoke, %	77.2	84.3	88.0	94.7	0.1522	8/8	1
Physically/mentally addicted, %	19.1	24.5	60.0	42.1	0.0001	5/7 (0.714)	2
Really need a cigarette, %	35.6	38.1	68.0	68.4	0.00168	78	1
Psychosocial indicators							
Depressive symptoms, mean (SD)	2.2 (0.8)	2.2 (0.7)	2.5 (0.7)	2.1 (0.5)	0.2307	2.1 (0.9)	0
Family-related stress, mean SD)	1.3 (0.5)	1.4 (0.4)	1.6 (0.5)	1.4 (0.5)	0.1372	1.3 (0.4)	2
Other stress, mean (SD)	1.6 (0.6)	1.6 (0.5)	1.8 (0.7)	1.6 (0.6)	0.2121	1.6 (0.5)	2
Self-esteem, mean (SD)	2.5 (0.4)	2.5 (0.4)	2.4 (0.4)	2.5 (0.4)	0.8927	2.4 (0.4)	35
Impulsivity[1], mean (SD)	2.4 (1.0)	2.5 (0.9)	2.5 (1.1)	2.7 (1.3)	0.7115	2.0 (0.8)	49

Novelty-seeking[1], mean (SD)	3.0 (0.7)	3.1 (0.8)	2.9 (1.0)	3.4 (0.8)	0.2774	2.9 (1.4)	48
Lifestyle indicators							
BMI z-score, mean (SD)	0.1 (1.0)	0.2 (1.0)	0.4 (1.2)	0.2 (0.9)	0.5320	0.4 (1.2)	18
Alcohol use, %	67.5	75.6	80.0	83.3	0.2863	6/8 (0.75)	7
MVPA, times/week, mean (SD)	21.1 (14.8)	19.4 (14.3)	27.8 (20.5)	28.3 (25.3)	0.0236	30.0 (26.4)	2
Participated in team sport(s), %	64.3	55.0	52.0	57.9	0.4293	48	0

Percents, means and the median for no. cig/month were computed excluding missing values.

[1]Baseline values for time-invariant variables (sex, mother university-educated, French spoken at home, born in Canada) were used. The earliest value available preceding cigarette smoking initiation was used for impulsivity and novelty-seeking (both measured in cycles 14 and 18), and BMI z-score (measured in cycles 1, 12 and 19) was used.

[2]p-value for difference across stable-low consumers, later escalators and parabolic escalators (early-rapid escalators were excluded from the p- value computation because of the low n). For categorical variables, differences across trajectory groups were assessed using chi-square. ANOVA was used to test for differences in means (of normally distributed variables); the Kruskal-Wallis test was used to test for differences in no. cig/month (which was not normally distributed).

MVPA: Moderate and vigorous physical activity. SD: Standard deviation. BMI: Body mass index. IQR: Interquartile range.

Data on smoking-related outcomes in young adulthood were available for 235 of the 307 incident smokers. Participants with (n = 235) and without (n = 72) outcome data were similar on all characteristics, except that a higher proportion of those without outcome data had parents who smoked cigarettes. (Table 34)

At age 24, approximately 35.6% of low-level decreasers and 60.6% of stable-low consumers reported smoking in the past 3 months, compared to 94.7% and 73.3% of slow and moderate escalators. (Table 12) Three of five early rapid escalators reported smoking at age 24. Median number of cigarettes per month ranged from 0 to 1 in low-level decreasers and stable-low consumers to 193 to 240 (9-10 cigarettes per day) among other trajectory groups. There was a consistent increase from low-level decreasers and stable-low consumers to the three escalator trajectories across all ND symptoms and indicators (e.g., 28.3% and 47.5% in the low-level trajectories reported craving a cigarette, whereas 78.6-84.2% reported cravings in the increasing trajectories). The proportion of incident smokers who were ND (according to the mFTQ and ICD-10 indicators) at age 24 ranged from 20-50% in the three escalating trajectories, although a lower number (10.3% of low-level decreasers and approximately 16% of stable-low consumers) of low-level trajectory participants were ND in adulthood.

Table 12. (Manuscript 2, Table 2) Smoking-related outcomes in early adulthood across incident trajectory groups (*n* = 235), NDIT 1999-2012

	Low-level decreasers (*n* = 78-92)[1]	Stable-low consumers (*n* = 98-104)[1]	Slow escalators (*n* = 19)[1]	Moderate escalators (*n* = 14-15)[1]	p-value[1]	Rapid escalators who peak (proportion) (*n* = 4-5)	Missing values[2] *n*
Smoked in past 3 months, %	35.6	60.6	94.7	73.3	<0.0001	3/5 (0.6)	2
No. cig/month, median (IQR)	0 (1.2)	1.1 (0,62.5)	240 (32.7,390)	193 (0,390)	<0.0001	240 (0,240)	2
Quit smoking cigarettes, %	65.2	41.3	10.5	26.7	<0.0001	2/5 (0.4)	0
Want a cigarette, %	46.7	68.0	94.7	86.7	<0.0001	4/5 (0.8)	1
Need a cigarette, %	24.2	40.6	84.2	80.0	<0.0001	3/5 (0.6)	4
Crave a cigarette, %	28.3	47.5	84.2	78.6	<0.0001	4/5 (0.8)	4
Physically or mentally addicted, %	29.3	49.0	89.5	80.0	<0.0001	4/5 (0.8)	0
mFTQ ≥ 4, %	10.3	16.3	42.1	35.7	0.0032	2/4 (0.5)	22
ICD-10 tobacco dependent, %	10.3	15.7	47.4	42.9	0.0002	1/5 (0.2)	17

Percents and the median for no. cig/month were computed excluding missing values.

[1]p-value for differences between stable-low consumers, later escalators and parabolic escalators (early-rapid escalators were excluded from the p-value computation because of the low n). For categorical variables, differences across trajectory groups were assessed using chi-square. The Kruskal-Wallis test was used for no. cig/month (which was not normally distributed). (We used parametric tests where possible and non parametric tests where assumptions of parametric tests were violated.)

[2]Data were missing because of loss-to-follow-up, participants not completing a questionnaire, or missing data on specific variables.

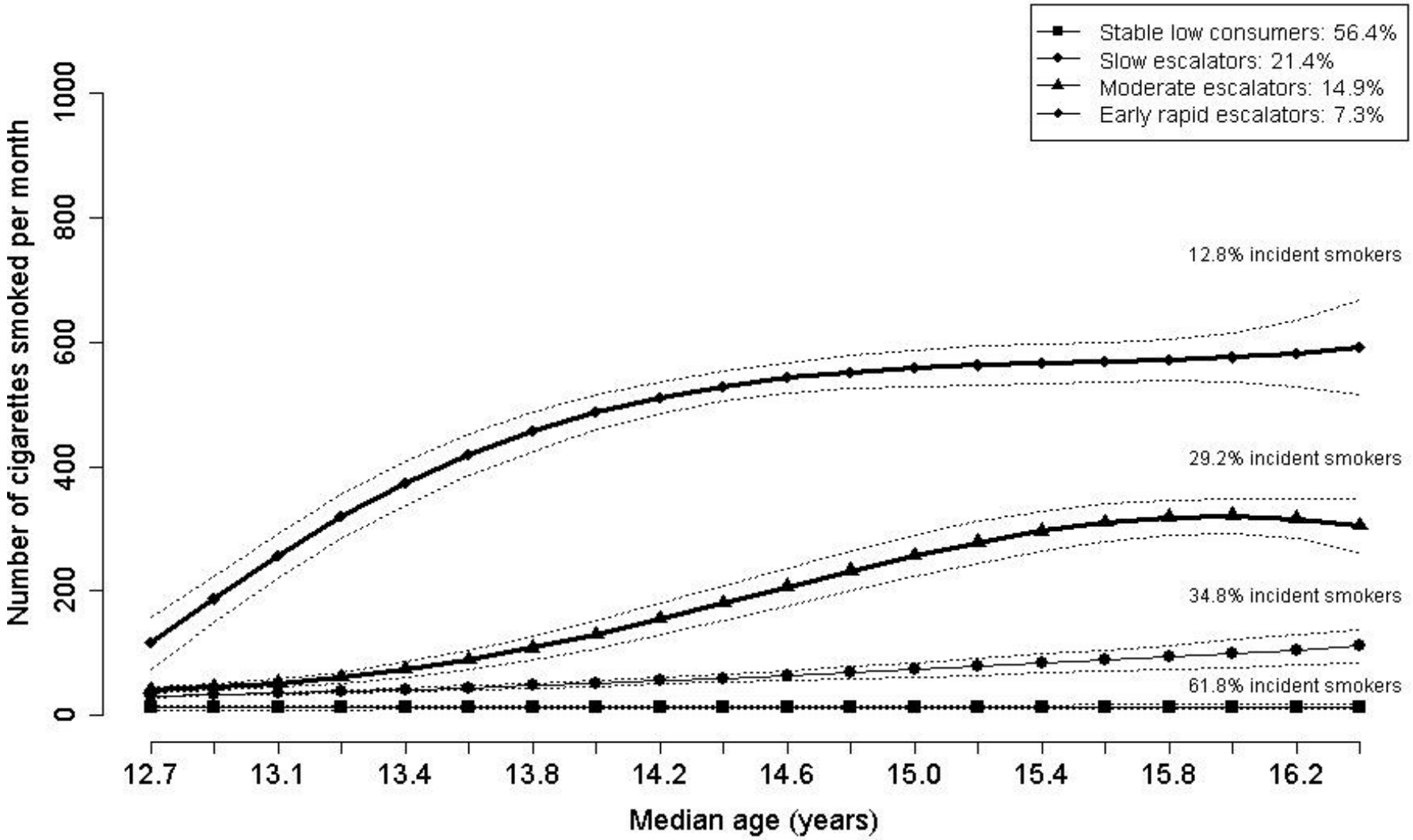
ICD-10: International classification of diseases, 10th revision. IQR: Interquartile range. mFTQ: Modified Fagerström Tolerance Questionnaire.

Mixed trajectories

The 4-group model was selected in the mixed trajectory analyses. The largest group (56.4% of the n = 645 included participants in the mixed trajectory model) reported consistent stable-low cigarette consumption throughout the study ("stable-low consumers"). (Figure 4) Slow, moderate and early-rapid escalators represented 21.4%, 14.9% and 7.3% of smokers included in this analysis. The proportion of incident smokers (i.e., the mixed trajectories included both incident and prevalent cigarette smokers) in the four trajectory groups varied from 12.8% of early-rapid escalators to 61.8% in the stable-low consumers group.

The mixed trajectory groups were discriminated by all smoking-related indicators measured at baseline. (Table 13) Unlike the incident trajectories, other characteristics including mother university-educated, French-speaking, depressive symptoms, family- and other stress, self-esteem, BMI z-score, alcohol use and participated in team sport(s) were statistically significantly different across trajectory groups. (As a note, a difference between the comparisons carried out for the incident and the mixed trajectory models was that the early-rapid escalators who peaked trajectory was excluded from statistical testing in the incident trajectory model, while no trajectory group was excluded from the comparisons in the case of the mixed trajectory model, because no trajectory group had an n of <10 in the mixed model.)

Figure 4. (Manuscript 2, Figure 2) Trajectories with 95% confidence intervals of number of cigarettes smoked per month among incident and prevalent adolescent smokers (*n* = 645), NDIT 1999-2005



Considering actual variable values (aside from the sociodemographic indicators), in general the majority of risk factors were both statistically significant and had values suggesting more unfavorable/higher risk profiles for heavier cigarette smoking trajectories. For example, among the smoking-related indicators, use of other tobacco products was 10.3% among the stable-low consumers trajectory, while percentages ranged 21.4-38.6% in the increasing trajectories (i.e., slow-, moderate-, and early-rapid escalators). Among the psychosocial indicators, the depressive symptoms mean was very slightly lower (i.e., 2.1, indicating lower depression) in the low-level group than in the increasing trajectories (2.2-2.5). Similar patterns were observed for the anxiety, novelty-seeking, and impulsivity variables. Among lifestyle indicators, BMI z-score was again slightly higher in the increasing trajectories (0.3-0.6) than among low-level cigarette smokers (0.2). Alcohol use was more common in the increasing trajectories (58.6-82.6%) than in the low-level trajectory group (50.3%). Among sociodemographic indicators several variables showed consistent patterns when stable-low consumers and increasing cigarette smoking trajectories were compared. For example, mean age was slightly lower in stable-low consumers (12.7 years) than in the increasing trajectory groups (12.8-13.2%). The proportion of participants born in Canada was lower in stable-low consumers (94.5%) than in the increasing trajectory groups (95.8-100%).

Outcome data were available for 448 of the 645 incident and prevalent smokers (i.e., *n* = 645 smokers were included in the mixed trajectory model). Compared to participants with outcome data, those without were older, reported higher family-related stress, were more likely to report smoking at baseline, and a higher proportion had parents and friends who smoked cigarettes. (Table 35) Similar to the incident trajectories, patterns of associations with smoking outcomes suggested that low-level smokers (i.e., low-stable consumers in this model) tended to maintain lower levels of smoking and dependence in adulthood: 43.9% of stable-low consumers had smoked in the past 3 months at age 24, compared to 67.7-84.8% of participants in the three escalating mixed trajectories. (Table 14) Cigarette consumption was low in stable-low consumers (median 0 cigarettes per day and per month), compared to 1, 7 and 8 cigarettes per day (i.e., 36-240 cigarettes per month) in slow, moderate and early-rapid escalators. One-third (i.e., 34.2% and 36.5%) of stable-low consumers reported craving and physical or mental addiction, compared to 64.8% to 86.4% of participants in the three escalating trajectory groups.

According to the mFTQ and ICD-10 indicators, 11.2-13.4% of stable-low consumers were ND at age 24, compared to 25.8-76.2% in the escalating trajectories.

Table 13. (Manuscript 2, Table 3) Baseline characteristics[1] of participants across mixed trajectory groups (*n* = 645), NDIT 1999-2005

	Stable-low consumers (*n* = 300-364)	Slow escalators (*n* = 98-138)	Moderate escalators (*n* = 60-96)	Early-rapid escalators (*n* = 18-47)	p- value[2]	Missing values *n*
Sociodemographic indicators						
Age, y, mean (SD)	12.7 (0.5)	12.8 (0.6)	12.8 (0.6)	13.2 (0.8)	<0.0001	0
Males, %	47.3	34.1	22.9	29.8	<0.0001	0
Mother university-educated, %	44.0	45.9	41.8	13.6	0.0408	147
Lives with one parent, %	10.6	11.3	12.1	6.7	0.8020	19
Born in Canada, %	94.5	97.1	95.8	100.0	0.2554	0
French-speaking, %	31.6	39.1	35.4	66.0	<0.0001	0
Smoking-related indicators						
No. cig/month, median (IQR)	0 (0,0)	0 (0,1.3)	0.5 (0,11.8)	8.7 (0,236)	<0.0001	28
Used other tobacco products, %	10.3	21.4	26.7	38.6	<0.0001	36
Parent(s) smoke, %	37.0	44.7	62.2	73.2	<0.0001	28
Friends smoke, %	40.6	61.9	71.4	84.4	<0.0001	18
Physically or mentally addicted, %	12.1	29.3	44.4	58.7	<0.0001	20
Really need a cigarette, %	15.8	42.0	53.9	82.2	<0.0001	33
Psychosocial indicators						
Depressive symptoms, mean (SD)	2.1 (0.6)	2.3 (0.6)	2.2 (0.6)	2.5 (0.8)	0.0001	18
Family-related stress, mean SD)	1.3 (0.4)	1.4 (0.4)	1.4 (0.5)	1.7 (0.6)	<0.0001	22
Other stress, mean (SD)	1.5 (0.4)	1.6 (0.4)	1.6 (0.5)	1.8 (0.6)	<0.0001	22
Self-esteem, mean (SD)	2.5 (0.4)	2.4 (0.4)	2.3 (0.4)	2.3 (0.4)	0.0103	144
Impulsivity[1], mean (SD)	2.4 (0.9)	2.6 (0.9)	2.7 (1.1)	2.7 (1.2)	0.0662	163
Novelty-seeking[1], mean (SD)	3.0 (0.8)	3.1 (0.8)	3.2 (0.9)	3.1 (1.3)	0.2038	161
Lifestyle indicators						
BMI z-score, mean (SD)	0.2 (1.0)	0.4 (1.0)	0.3 (0.9)	0.6 (1.0)	0.0382	52
Alcohol use, %	50.3	64.2	58.6	82.6	<0.0001	24
MVPA, times/week, mean (SD)	19.6 (13.2)	20.0 (18.1)	20.0 (14.9)	18.9 (13.9)	0.9693	17
Participated in team sport(s), %	65.9	55.1	53.1	51.1	0.0174	0

Percents, means and the median for no. cig/month were computed excluding missing values.

[1]The earliest values available for impulsivity and novelty-seeking (both measured in cycles 14 and 18), self-esteem (measured in cycle 12) and BMI z-score (measured in cycles 1, 12 and 19) were used.

[2]Chi-square was used to test for differences across trajectory groups in categorical variables. ANOVA was used to test for differences in means of normally distributed variables; the Kruskal-Wallis test was used to test for differences across trajectory group in the median no. cig/month (which was not normally distributed).

SD: Standard deviation. MVPA: Moderate and vigorous physical activity. BMI: Body mass index. IQR: Interquartile range.

Table 14. (Manuscript 2, Table 4) Smoking-related outcomes in early adulthood across mixed trajectory groups (*n* = 448), NDIT 1999-2012

	Stable-low consumers (*n* = 238-264)	Slow escalators (*n* = 89-95)	Moderate escalators (*n* = 62-67)	Early-rapid escalators (*n* = 10-22)	p-value[1]	Missing values[2]
Smoked in past 3 months, %	43.9	67.7	84.8	81.8	<0.0001	5
No. cig/month, median (IQR)	0 (0,18)	36 (0,240)	223 (0,390)	240 (0,390)	<0.0001	5
Quit smoking cigarettes, %	57.2	36.8	20.9	22.7	<0.0001	0
Want a cigarette, %	52.3	80.6	92.4	85.7	<0.0001	6
Need a cigarette, %	29.1	67.4	80.3	76.2	<0.0001	11
Crave a cigarette, %	34.2	64.8	86.4	80.0	<0.0001	11
Physically or mentally addicted, %	36.5	69.9	83.6	76.0	<0.0001	4
mFTQ ≥ 4, %	13.4	30.8	51.6	76.2	<0.0001	36
ICD-10 tobacco dependent, %	11.2	25.8	45.5	42,6	<0.0001	30

Percents and the median for no. cig/month were computed excluding missing values.

[1]Chi-square was used to test for differences in categorical variables across trajectory groups. The Kruskal-Wallis test was used to test for differences across trajectory groups in the median no. cig/month. (We used parametric tests where possible and non parametric tests where assumptions of parametric tests were violated.)

[2]Data were missing because of loss-to-follow-up, participants not completing a questionnaire, or missing data on specific variables.

IQR: Interquartile range. mFTQ: Modified Fagerström Tolerange Questionnaire.

7.2.5 Discussion

In this paper, we extended the length of follow-up of our earlier trajectory work (Karp et al.) from a mean of 24 to 48 months. (9) Unique features of this current study include that we modeled and compared incident vs. mixed trajectories and that we examined smoking-related outcomes including ND, 6 years after the last data point used in the trajectory modeling.

Incident trajectories

Unlike the two other trajectory studies of incident smokers (9, 10), we identified five incident trajectory groups rather than four, including low-level decreasers, stable-low consumers, slow escalators , moderate escalators , and early-rapid escalators . Three of the five trajectory patterns identified resemble those reported by Karp et al (2005). (9) However, extending follow-up of the Karp et al. (2005) study, we now differentiate between stable-low consumers and low-level decreasers while Karp et al. reported only stable-low consumers. Extended follow-up also showed that early-rapid escalators did not decrease their cigarette consumption, but continued to smoke at high levels until the end of high school. Reflected by the wider confidence bands around the estimated trajectories, the precision of estimates in Karp et al. was lower for follow-up exceeding two years after smoking onset. Extending the follow-up likely provided more stable estimates of the trajectories more than two years after smoking onset by increasing the number of data points available for estimation. As in Rosendahl et al (2008) who reported sex-specific trajectories that evolved into non-smoking and which they labeled “early extinction”, we identified low-level decreasers who slowly decreased cigarette consumption to one cigarette a month after 48 months. (10)

Incident vs. mixed trajectories

An important novelty in this study was the difference in time axes across trajectory analyses (time since smoking onset in the incidence analysis vs. age in the mixed analysis). Although similar in shape, the rate of change in the mixed trajectories was generally attenuated across curves, reflecting the mix of cigarette consumption levels and ND across incident and prevalent smokers. In the incident analysis, 3% of participants were early-rapid escalators, compared to 7% in the “mixed” model reflecting that adolescents at different stages in the natural course of smoking and ND were studied in the mixed analyses (13% of early-rapid

"mixed" escalators were incident smokers, compared to 100% in the incidence analysis). Further the curve of early rapid escalators in the incident trajectory was steeper at smoking onset, suggestive that the "window of intervention opportunity" for preventing escalation in cigarette consumption is not as wide as the mixed analysis would suggest.

The importance of differentiating incident vs. mixed trajectories is further underscored in the stable-low consumer group. Compared to 56% of participants in the mixed trajectory analyses, 83.1% of incident smokers reported low levels of smoking, whether as stable-low consumers (45.6%) or low-level decreasers (37.5%). This is expected since higher risk adolescents had already initiated smoking prior to baseline (in NDIT, 29% of males and 35% of females reported smoking at baseline, and therefore were not included in the incident trajectory analyses). Overall an important finding of this work is that trajectory analyses incorporating a mix of incident and prevalent smokers yield trajectories that differ from those that depict the natural course of onset, and the differences in shape likely depend on the proportion of incident smokers in the sample, and more specifically, in each trajectory group.

Factors associated with trajectories

A notable finding of this study is the different profile of factors associated with incident vs. mixed trajectories. Other than sex, age and well-known smoking-related factors, the only significant finding in the incidence analysis was that relatively more slow and moderate escalators participated in MVPA.

In the mixed trajectories, inclusion of prevalent smokers may have enabled detecting factors associated with both onset and sustained smoking. Aside from the smoking-related indicators which appear to be "dose-dependent", most significant results seem attributable to differences between the first three groups and early-rapid escalators. This group comprised prevalent smokers primarily for whom factors measured at baseline represents values during (and not before) their natural course of smoking, and therefore could be consequences of smoking. Alternatively, increased power in the mixed analysis might have permitted detection of additional variables (over the incident analysis). It is however interesting to note that the values for the various measures (discussed in the results section, such comparisons are akin to comparisons of point estimates of measures of association) suggest that the difference in patterns

of risk factor associations between the incident and mixed cigarette trajectory models may not be due entirely to chance and sample size.

Outcomes

Outcomes of both the incident and mixed trajectories were unambiguous in that any escalation in cigarette consumption was associated with higher levels of smoking and ND in early adulthood. While quit rates were higher than in the three escalating trajectories, 36% of low-level decreasers and 61% of stable-low consumers were still smoking in young adulthood, one-third to nearly half reported ND symptoms and 10-16% were addicted according to well-established indicators. These patterns of associations are supported by the actual values for the outcome variables, as discussed in the results section above.

Limitations of this study include that self-report data are subject to misclassification bias. Loss to follow-up could have resulted in selection bias in the association analyses and use of a purposive sample may have rendered the results less generalizable across diverse jurisdictions. For prevalent smokers, factors measured at baseline do not necessarily precede smoking onset. Finally, some results are imprecise because of small numbers of participants in some groups and by loss to follow-up, which would have affected the later time points in both models.

Conclusion

Trajectory analyses that include a mix of incident and prevalent smokers must be interpreted considering the time axis (age/calendar time or time since onset). Only incident trajectories can unambiguously depict the natural course of smoking onset. Although not negligible in stable-low consumers, ND is a major issue in adolescent smokers who escalate cigarette consumption.

Acknowledgements

Dr. Sylvestre was supported by a Chercheurs-Boursier career award from the Fonds de Recherche du Québec–Santé (FRQS). Dr. O'Loughlin holds a Canada Research Chair in the Early Determinants of Adult Chronic Disease.

Funding

This work was supported by the Canadian Cancer Society (grant numbers 010271, 017435) and the Cancer Research Society (grant number 21098). The funders were not involved in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

References

1. Reid JLHD, Rynard VL, Madill CL, Burkhalter R. Tobacco Use in Canada: Patterns and Trends, Waterloo, ON: Propel Centre for Population Health Impact, University of Waterloo. 2017.
2. Office on Smoking and Health (National Centers for Chronic Disease Prevention and Health Promotion). Trends in Current Cigarette Smoking Among High School Students and Adults - United States, 1965-2014; 2018.
3. Centers for Disease Control and Prevention. Youth and Tobacco Use; 2018.
4. Statistics Canada. Canadian Tobacco, Alcohol and Drugs Survey: 2017 summary, Ottawa, Ontario, Canada: Health Canada; 2018.
5. O'Loughlin JL, Dugas EN, O'Loughlin EK, Karp I, Sylvestre MP. Incidence and determinants of cigarette smoking initiation in young adults. *Journal of Adolescent Health* 2014: 54:26-32.e24.
6. Nagin D. Analyzing developmental trajectories: A semi-parametric, group-based approach. *Psychological Methods* 1999: 4: 139-177.
7. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociological methods & research* 2001; 29:374-393.
8. Lauzon B, Ahun MN, Sylvestre MP, Hanusaik N, Bergeron-Caron C, Eltonsy S. O'Loughlin J. A systematic review of cigarette smoking trajectories in adolescents; 2018.
9. Karp I, O'Loughlin J, Paradis G, Hanley J, DiFranza J. Smoking trajectories of adolescent novice smokers in a longitudinal study of tobacco use. *Annals of Epidemiology* 2005: 15:445-452.
10. Rosendahl K. I., Galanti M. R., Gilljam H. Trajectories of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents: differences and implications, *Nicotine and Tobacco Research* 2008: 10:1021-1027.
11. Chassin L, Presson CC, Pitts SC, Sherman SJ. The natural history of cigarette smoking from adolescence to adulthood in a midwestern community sample: multiple trajectories and their psychosocial correlates. *Health Psychology* 2000; 19:223.
12. Nelson SE, Van Ryzin MJ, Dishion TJ. Alcohol, marijuana, and tobacco use trajectories from age 12 to 24 years: Demographic correlates and young adult substance use problems. *Developmental Psychopathology* 2015; 27:253-277.
13. Hampson SE, Tildesley E, Andrews JA, Barckley M, Peterson M. Smoking trajectories across high school: sensation seeking and hookah use. *Nicotine and Tobacco Research* 2013; 15:1400-1408.
14. Lessov-Schlaggar CN, Hops H, Brigham J, Hudmon KS, Andrews JA, Tildesley E, McBride D, Jack LM, Javitz HS, Swan GE. Adolescent smoking trajectories and nicotine dependence. *Nicotine and Tobacco Research* 2008; 10:341-351.
15. Vuolo M, Staff J. Parent and child cigarette use: a longitudinal, multigenerational study. *Pediatrics* 2013; 132(3):e568-77.
16. Riggs NR, Chou CP, Li C, Pentz MA. Adolescent to emerging adulthood smoking trajectories: when do smoking trajectories diverge, and do they predict early adulthood nicotine dependence? *Nicotine and Tobacco Research* 2007; 9:1147-1154.

17. O'Loughlin J, Dugas EN, Brunet J, DiFranza J, Engert JC, Gervais A, Gray-Donald K, Karp I, Low NC, Sabiston C, Sylvestre MP, Tyndale RF. Cohort Profile: The Nicotine Dependence in Teens (NDIT) Study. *International Journal of Epidemiology* 2015; 44:1537-1546.
18. Curran PJ, Muthén BO. The application of latent curve analysis to testing developmental theories in intervention research. *American Journal of Community Psychology* 1999; 27:567-595.
19. Centers for Disease Control Prevention. Selected cigarette smoking initiation and quitting behaviors among high school students--United States, 1997, MMWR*Morbidity and Mortality Weekly Report* 1998; 47:386.
20. Eppel A, O'Loughlin J, Paradis G, Platt R. Reliability of self-reports of cigarette use in novice smokers. *Addictive Behaviors* 2006; 31:1700-1704.
21. Hammer LD, Kraemer HC, Wilson DM, Ritter PL, Dornbusch SM. Standardized percentile curves of body-mass index for children and adolescents. *American Journal of Diseases of Children* 1991; 145:259-263.
22. Kuczmarski RJ. 2000 CDC growth charts for the United States; methods and development, 2002.
23. Nagin D. Group-based modeling of development: Harvard University Press; 2005.

PLEASE NOTE that additional methodological details regarding Manuscript 2 are presented in Appendices 4, 5, 6, and 8.

7.3 Manuscript 3

Contributions to Manuscript 3 by Candidate

BL carried out all analyses and drafted all versions of the manuscript. BL participated in discussions of the article with co-authors.

Title: Age at first cannabis use in relation to cigarette smoking initiation and smoking trajectories in adolescents.

Running head: Cannabis use and cigarette smoking

Authors: Lauzon B, Sylvestre MP, O'Loughlin J.

Author affiliations:

Declaration of interest: The NDIT study was supported by the Canadian Cancer Society (grant numbers 010271, 017435). Dr Sylvestre was supported by a Chercheur-Boursier career award from the Fonds de Recherche du Québec–Santé (FRQS). Dr. O'Loughlin holds a Canada Research Chair in the Early Determinants of Adult Chronic Disease. The funders were not involved in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. The authors declare no competing interests.

Corresponding author: O'Loughlin J.
Centre de recherche du Centre Hospitalier de l'Université de Montréal. (CRCHUM)
850 rue Saint-Denis
Montréal (Québec)
Canada. H2X 0A9
Tel: (514) 890-8000, ext. 15858.
jennifer.oloughlin@umontreal.ca

Word count (abstract):
Word count (body):
Key words:
Abbreviations:

7.3.1 Abstract

Aims: Our aims were to: (i) describe the order of initiation of cigarette smoking and cannabis use among adolescents, (ii) compare age at first cannabis use across participants categorized into one of eight cigarette smoking categories, and (iii) identify factors associated with elapsed time between cannabis initiation and cigarette smoking initiation.

Design: Data were drawn from the Nicotine Dependence in Teens (NDIT) Study, a prospective investigation of adolescents recruited in 1999-2000 and followed in 22 data collection cycles from age 12 to 24 years.

Setting: Montreal, Canada

Participants: 1293 grade 7 students were recruited in 10 Montreal-area high schools. The analytic sample included 857 participants with data on cigarette smoking collected prospectively during high school and data on cannabis use collected retrospectively at age 20. Of the 857, 454 never smoked cigarettes during high school, 424 students had already initiated smoking at baseline, and 373 students initiated during high school. This latter group included 66 incident cigarette smokers who stopped smoking and 307 incident smokers categorized into five trajectory groups (i.e., stable-low consumers (45.6%), low-level decreasers (37.5%), slow escalators (8.1%), moderate escalators (6.2%) and early-rapid escalators (2.6%)).

Measurements: Cigarette consumption in the past 3 months was measured in four cycles in each of grade 7 to 11 for a total of 20 data collections cycles. Ever use of cannabis, age at first cannabis use and age at first cigarette use were measured in cycle 21 post-high school at age 20 years.

Findings: The proportion of participants who had ever used cannabis ranged from 38.3% in never smokers to 100% in slow escalators and early rapid increasers who peaked. Among users of both cigarettes and cannabis, 15.6% initiated cannabis before cigarettes, 26.1% initiated both substances during the same year, and 58.3% initiated cigarettes before cannabis. Median age at first cannabis use ranged from 13 years to 16 years among differing cigarette smoking categories representing different levels of use. Median age at first cannabis appeared to decrease with increasing level of cigarette consumption, in that the four trajectory groups with the lowest

consumption had the highest median age at cannabis initiation. Age at baseline predicted time elapsed from cigarette initiation to cannabis initiation.

In this study of Montreal-area youth followed from high school into young adulthood, first puff on a cigarette usually preceded cannabis use. However, some participants initiated cannabis before cigarettes in most cigarette smoking categories. Ever cannabis use was in most (with the exception of stable low consumers) cases higher and first cannabis use generally occurred at a younger age, in cigarette smoking categories which likely had heavier lifetime cigarette consumption including cigarette smoking escalators and prevalent smokers. Finally, age at baseline was significantly associated with time to first cannabis use among ever cigarette smokers.

Conclusions: NDIT data provide support for the Gateway Model, which states that tobacco use precedes cannabis initiation. A minority of participants did however initiate cannabis prior to cigarettes. Age at first cannabis use was lower in cigarette smoking groups with heavier smoking. These smokers may constitute a higher risk group that may benefit from targeted intervention as a "vulnerable population".

Key words: adolescents, cigarette smoking, cannabis use, cohort, longitudinal, initiation

7.3.2 Introduction

Despite considerable progress in population-based tobacco control over the past three decades [3], [4], an important proportion of youth still smoke cigarettes [9] and many of these young people also use cannabis. Schauer and Peters 2018 [43] reported that 5.4% of U.S. youth ages 12-17 years reported past-month co-use of tobacco and marijuana. In the current North American context, which is characterized by a high prevalence of co-use, increasing numbers of jurisdictions legalizing cannabis for recreational purposes, constant evolution in the types of tobacco products available (i.e., e-cigarettes) and aggressive marketing of these products by the tobacco industry specifically targeting youth [116], it is critical to better understand evolving patterns in the co-use of cigarettes and cannabis.

Issues which could be affected by this evolving context include, among others, the order of initiation of cigarettes and cannabis (i.e., which substance is generally used first). According to the Gateway Model [113]–[115], youth follow a predictable sequence as they become increasingly involved in substance use, initially using tobacco and/or alcohol followed by cannabis, and then other illicit drugs. [114], [115] Several studies [113]–[115] support this theory, but many report initiation of cannabis prior to tobacco [71], [72], [143], [76], [79], [81], [112], [136], [139], [141], [142] or prior to tobacco and alcohol [74], [75], [135], [140], [144]. Monitoring patterns in substance use initiation is critical to developing deeper understanding on how legislation affecting product availability may (for example) affect youth substance use or whether the introduction of new products such as e-cigarettes affects the prevalence of cannabis use.

Another understudied issue is the time elapsed between initiation of one substance and the next. In two [136], [141] of six studies [79], [81], [136], [141], [169], [170] that examined time elapsed between tobacco and cannabis initiation, the mean time was 2.9 and 5.5 years when tobacco was initiated first, and 2.4 years in both studies when cannabis was initiated first. Shorter time lapse between initiation of psychoactive substances may have a more profound impact on a developing brain than products tried over longer time periods. How an evolving context affects the natural course of substance initiation and co-use is likely critical to planning public health programs that can effectively reduce the harmful effects of youth substance use.

Finally little is known about factors that influence time elapsed between cannabis and cigarette smoking initiation. Among the few studies that have addressed this issue, risk factors for cannabis initiation reported in ever smokers were heavier smoking [79], male gender [81] and younger age [81]. No study to date has reported risk factors for tobacco initiation among ever cannabis users.

Our aims in this current paper were to address these understudied issues in adolescents. The specific objectives were to: (i) describe the order of initiation of cigarette smoking and cannabis use, (ii) compare age at first cannabis use across participants categorized into one of eight cigarette smoking categories, and (iii) identify factor(s) associated with elapsed time between cannabis initiation and cigarette smoking initiation.

7.3.3 Methods

Data were drawn from the Nicotine Dependence in Teens (NDIT) Study [145], a prospective investigation of 1293 grade 7 students recruited in 1999-2000 in 10 high schools in Montreal, Canada. Schools were purposively selected to ensure a mix of students by socioeconomic status (high, moderate, low), language (French, English), and place of residence (urban, suburban, rural). Baseline participation (i.e., 56% of eligible students) was affected by a labour dispute in Quebec that resulted in some teachers refusing to collect consent forms. Participants completed self-report questionnaires in the language of instruction in their school every 3-4 months over five years during secondary school for a total of 20 data collection cycles. [145] Self-report mailed questionnaires were also completed post high school in 2007–08 (i.e., cycle 21). Cycle/survey 21 covered a median of 3.1 years post high school, when participants were age 20 years on average. [171]

The current analysis included 857 participants with data on cigarette smoking in cycles 1 to 20 and data on retrospectively recalled cannabis use in cycle 21. Individuals (n = 394, see figure 6) who did not complete cycle 21 or who were missing data on cannabis use in cycle 21 were excluded. Figures 5 and 6 describe the derivation of the analytic sample. (See also Appendix 7)

The NDIT study was approved by the Montreal Department of Public Health Ethics Review Committee, the McGill University Faculty of Medicine Institutional Review Board, and the Ethics Research Committee of the Centre de Recherche du Centre Hospitalier de l'Université de Montréal. Parents or guardians provided written informed consent at baseline; participants provided written informed consent for cycle 21.

Figure 5. (Manuscript 3, Figure 1a) Exclusions for cigarette use trajectories model, NDIT 1999-2008

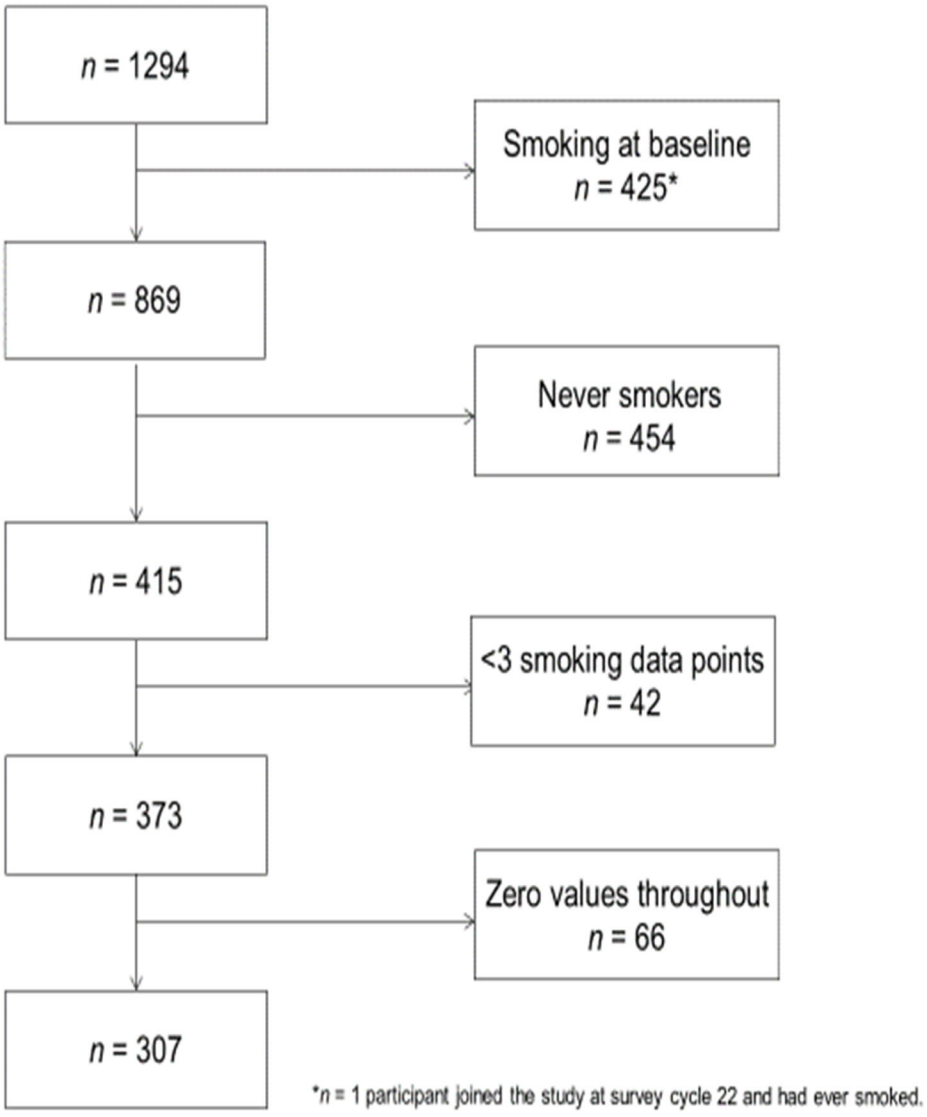
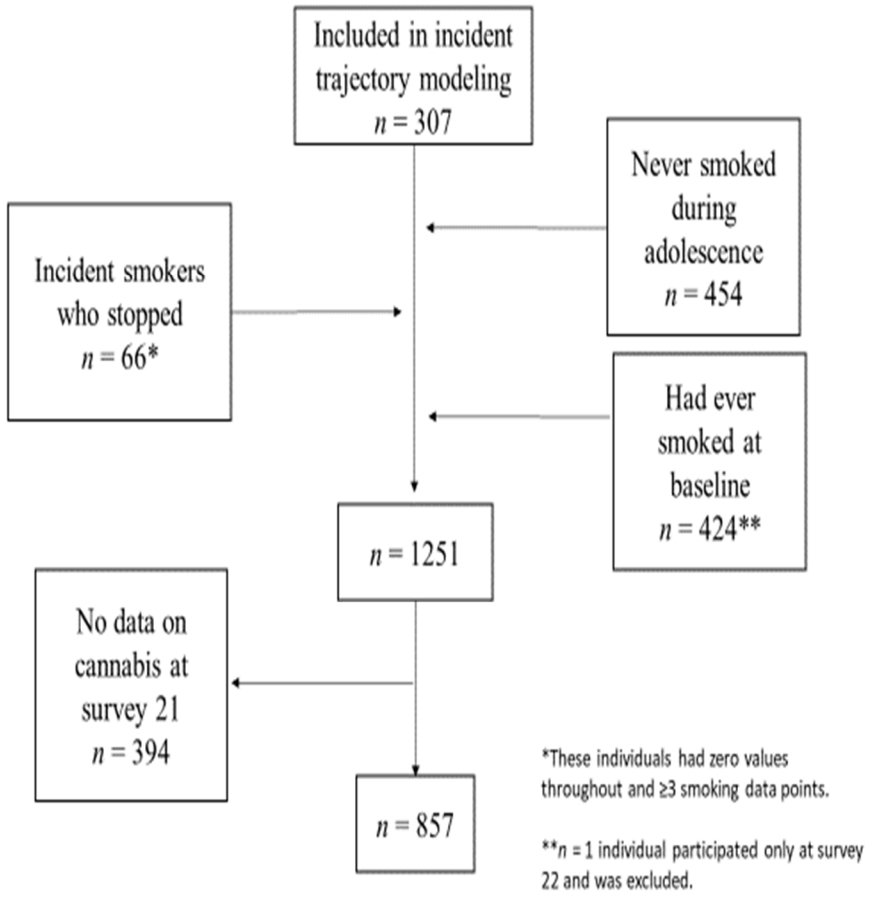


Figure 6. (Manuscript 3, Figure 1b) Participants included and excluded in the analytic sample, NDIT 1999-2008



Study variables

Cigarettes smoked in past month - was measured in a 3-month recall. [149] For each of the three months preceding each data collection cycle, participants reported number of days on which they had smoked and the usual number of cigarettes smoked per day on the days when they smoked. (Table 10) The two items were multiplied to obtain mean number of cigarettes smoked per month; these were averaged across the three months of recall at each cycle/survey to obtain a value for mean number of cigarettes smoked per month. Test-retest reliability of the mean number of cigarettes smoked per month based on the 3-month recall as measured by the intraclass correlation coefficient, was 0.64 (section 6.2.2). [163]

Age at cigarette smoking initiation - In cycle 21, participants were asked, *"*How old were you when you puffed on a cigarette for the first time?".

Ever used cannabis - In cycle 21, participants were asked, "Have you ever done any of the following? (…) used marijuana, cannabis, hashish". Response choices were "yes" or "no".

Age at first cannabis use - In cycle 21, participants who reported they had ever used marijuana, cannabis or hashish were asked how old they were when they used it for the first time, with the response worded: "When I used it the first time, I was… (age) years old".

Cigarette smoking categories – We classified individuals in terms of their cigarette consumption and created an 8-category variable called "cigarette smoking categories" which included:

(1) Never smokers (n = 454) who never reported any smoking in cycles 1 to 20;

(2) Participants who had already initiated cigarette smoking at baseline, referred to herein as "prevalent smokers" (n = 424);

(3) Participants who initiated cigarette smoking during follow-up in cycles 2-20 but did not smoke again after initiation, referred to herein as "incident smokers who stopped" (n = 66, these participants were not included in the incident trajectory model presented herein and in Manuscript 2, these are referred to as 'zero values throughout in Figure 5);

(4) The remaining individuals in our sample (n = 350) included n = 1 individual who participated only at survey 22 which we excluded; also excluded were n = 42 participants who had <3 data point for cigarette smoking between surveys 1 and 20. Using the remaining 307 incident cigarette smokers (i.e., who were incident cigarette smokers during high school, it should also be noted this group excluded the n = 66 participants who initiated in high school but stopped after initiation), we reproduced the 5-group incident cigarette smoking trajectories modeled in a previous article (Manuscript 2) using SAS Proc Traj. [14] The five groups retained included:

- Stable-low consumers
- Low-level decreasers
- Slow escalators

- Moderate escalators
- Early-rapid escalators who peaked

(It should be noted that incident cigarette smokers were the 5 groups obtained from our model, as well as the $n = 66$ "incident smokers who stopped", as all 6 groups initiated cigarette smoking during high school.)

Elapsed time between cannabis and tobacco initiation - We calculated time elapsed among participants who had used both substances as (age at 1st cannabis use) – (age at cigarette smoking initiation). The proportion of participants that initiated cannabis prior to tobacco (defined as (age 1st cannabis – age 1st cigarette) < 0, while cigarettes initiated before cannabis was defined as (age 1st cannabis – age 1st cigarette) > 0) was compared across cigarette smoking categories (in ever cannabis users, and excluding never and baseline ever smokers). The value of time elapsed between cigarette smoking initiation and cannabis use initiation is also presented separately according to whether cannabis or tobacco was initiated first.

Factors associated with elapsed time

Factors potentially associated with elapsed time between initiation of cannabis and cigarette smoking investigated included: age, gender, and mean number of cigarettes smoked per month in the past 3 months (at initiation). We also studied predictors of cigarette smoking initiation previously identified in a systematic review [20] and/or of cannabis initiation identified in a second review [172], including friend(s) smoke cigarettes, parent(s) smoke cigarettes, sibling(s) smoke cigarettes, mother university-educated (in this analysis, data were obtained from a combination of cycles 13, 17, and maternal questionnaires), French spoken at home, born in Canada, lives with one parent, depression, self-esteem (measured at cycle 12), and alcohol use. Aside from the exceptions mentioned just above (i.e., mean number of cigarettes smoked per month in the past 3 months, mother university-educated, and self-esteem), all variables were measured at baseline. (Table 10) (Additional details on variables, as well as on participants included and excluded from our analyses, is presented in Appendices 5 to 8.)

Statistical analysis

We undertook two regression analyses. The first used values of time elapsed in cannabis "primo-initiators" (i.e., participants who initiated cannabis before cigarettes) as the dependent variable. The second regression analysis used time elapsed in cigarette "primo-initiators" (i.e., who initiated cigarettes before cannabis). Since the distributions of these variables were truncated at zero, we used truncated Gaussian models for both outcomes. [167], [168]

All analyses except the truncated regression models were conducted using SAS version 9.4 for Windows and SAS University Edition [166] and cigarette smoking trajectories were obtained using Proc Traj. [14] Truncated regression models were carried out in R using the truncreg package. [167], [168] (Additional information on methods and reporting is provided in Appendices 5 to 8.)

Additional analyses

The following additional analyses were carried out as sensitivity analyses. One potential issue was the clustering of data by school in NDIT. First, we determined the intracluster correlation coefficient (ICC_2), which is a measure of the relatedness of clustered data, and is calculated by comparing the variance within clusters with the variance between clusters. ICC_2 was calculated using the formula:

ICC_2 or $\rho = \frac{{S_b}^2}{({S_b}^2 + {S_w}^2)}$, where ${S_b}^2$ was the variance between clusters (i.e., the random effect) and ${S_w}^2$ the variance within clusters. [173]–[175] This was calculated using mixed modeling in SAS (SAS proc mixed). [166]

In order to examine further the potential effect of clustering within these data (clustering, when ignored, can reduce the observed variance and thereby affect inference but should not affect point estimates) [175], we used multilevel modeling to account for the clustering effect by school in certain analyses. These were the analyses of time elapsed between cannabis and cigarette initiation: our analyses relating to order of initiation of cigarettes and cannabis and to age at cannabis initiation according to cigarette smoking category were descriptive and therefore the "point estimates" involving the comparisons of sample measures and proportions across cigarette categories should not be greatly affected. Given the distribution of time elapsed (i.e., truncated distribution) we used a multilevel model with gamma distribution [176] and modeled

this using the lme4 package in R. [177] We modeled only the variables which were significant in the initial truncated regression models in Tables 20 and 21.

7.3.4 Results

Sample characteristics

Table 15 compares selected characteristics at baseline across cigarette smoking categories, prior to deletion of individuals without data for cannabis use (cycle/survey 21). Prevalent smokers were older (13.02 years) than incident and never smokers (12.55-12.86 years) (Table 15, see also Table 40 for a comparison of mean ages between never, incident, and prevalent smokers prior to deletion of individuals without data on cannabis use) and more likely to live in a single-parent family (14.4% vs. 0-12.1% for prevalent vs. incident and never smokers). They were more likely to speak French at home (47.4% vs. 19.3-36.8% for prevalent vs. incident and never smokers) and to have friend(s) who smoke (71.0% vs. 15.0-57.1% for prevalent vs. incident and never smokers) and parent(s) who smoke (58.6% vs. 26.1-50.0% for prevalent vs. incident and never smokers). They were also less likely to have a university-educated mother (35.6% vs. 40-60.9% for prevalent vs. incident and never smokers). (It should be noted however that for this comparison, early rapid escalators who peaked did however have a percentage of 0%.) Early rapid escalators who peaked and incident smokers who stopped had the lowest proportions of female participants (37.5% and 37.9%, respectively) while stable low smokers had the highest (69.3%). Slow escalators had the lowest mean age (12.55 years) while prevalent smokers had the highest (13.02 years). Table 39 compares selected characteristics of the n = 857 included participants who had data on cigarette use during high school and on cannabis use at cycle 21, with excluded participants. Tables 40 and 41 provide other information relevant to these analyses. Group sample sizes and missing data are provided in the results tables.

Ever used cannabis

A total of 583 participants out of n = 857 included participants (56.3% of these ever cannabis users were female) reported ever use of cannabis in cycle 21. The proportion of ever use ranged from 38.3% in never smokers to 100% in both slow escalators and early rapid escalators who peaked. (Table 16)

Order of initiation of cannabis use and cigarette smoking

Among users of both cigarettes and cannabis who reported a value for age at initiation for both substances (n = 441), n = 69 (15.6%) initiated cannabis before cigarettes, n = 115 (26.1%) initiated both substances the same year, and n = 257 (58.3%) initiated cigarettes before cannabis.

Table 15. (Manuscript 3, Table 1) Baseline characteristics of never, incident, and prevalent cigarette smokers, NDIT 1999-2008[2]

	Never smokers (*n* = 454)	Incident smokers[1]						Prevalent smokers (*n* = 424)	Missing *n*
		Incident smokers who stopped (*n* = 66)	Low-level decreasers (*n* = 115)	Stable low (*n* = 140)	Slow escalators (*n* = 25)	Moderate escalators (*n* = 19)	Early rapid escalators who peaked (*n* = 8)		
Age*, y (mean (CI))[4]	12.70 (12.65, 12.75)	12.63 (12.53, 12.73)	12.65 (12.57, 12.73)	12.62 (12.55, 12.68)	12.55 (12.42, 12.67)	12.64 (12.47, 12.81)	12.86 (12.45, 13.27)	13.02 (12.95, 13.10)	0
Female*, %	43.8 (39.2, 48.4)	37.9 (26.2, 49.6)	51.3 (42.2, 60.4)	69.3 (61.7, 76.9)	60.0 (40.8, 79.2)	63.2 (41.5, 84.9)	37.5 (3.9, 71.0)	56.6 (51.9, 61.3)	0
Single-parent family*, % (CI)	6.2 (4.0, 8.4)	12.1 (4.2, 20.0)	7.8 (2.9, 12.7)	8.6 (4.0, 13.2)	8.0 (0, 18.6)	5.3 (0, 15.4)	0	14.4 (11.0, 17.7)	5
Born in Canada*, % (CI)	87.9 (84.9, 90.9)	92.4 (86.0, 98.8)	93.0 (88.3, 97.7)	97.1 (94.3, 99.9)	100	94.7 (84.6, 100)	100	94.6 (92.4, 96.7)	0
French spoken at home*, % (CI)	20.3 (16.6, 24.0)	24.2 (13.9, 34.5)	24.3 (16.5, 32.1)	19.3 (12.8, 25.8)	24.0 (7.3, 40.7)	36.8 (15.1, 58.5)	25.0 (0, 55.0)	47.4 (42.6, 52.1)	0
Mother university-educated*, (%) (CI)[3]	47.7 (42.5, 52.9)	46.5 (33.7, 59.3)	46.0 (36.2, 55.8)	52.0 (43.2, 60.8)	60.9 (41.0, 80.8)	40.0 (15.2, 64.8)	0	35.6 (30.0, 41.2)	293
Parent(s) smoke*, % (CI)	26.6 (22.5, 30.7)	31.8 (20.6, 43.0)	26.1 (18.1, 34.1)	33.6 (25.7, 41.5)	40.0 (20.8, 59.2)	38.9 (16.4, 61.4)	50.0 (15.3, 84.6)	58.6 (53.8, 63.3)	22
Friend(s) smoke*, % (CI)	15.0 (11.7, 18.3)	21.5 (11.5, 31.5)	29.6 (21.3, 37.9)	27.9 (20.5, 35.3)	32.0 (13.7, 50.3)	31.6 (10.7, 52.5)	57.1 (20.4, 93.8)	71.0 (66.7, 75.3)	3

[1]Incident smokers were *n* = 307 participants included in the Proc Traj model and *n* = 66 incident smokers who stopped.
[2]A Kruskal-Wallis test was used for age, while a chi-square test was used for all other variables. Factors for which there was a statistically significant difference ($p < 0.05$) between group(s) are marked with an asterisk next to the variable name. All comparisons excluded early rapid escalators who peaked because of the small size of this group.
[3]Mother's education was created from information provided in cycles 13 and 17 by participants and in questionnaires completed by participants' mothers.
[4]Data were normally distributed.
CI = 95% confidence interval. y: year.

The proportion of participants who initiated cannabis before cigarette smoking according to cigarette smoking category is presented in Table 16. The proportion ranged from 0% in moderate escalators to 28.6% in incident smokers who stopped.

Table 17 describes the proportion of participants who initiated cannabis and cigarettes in the same year according to cigarette smoking category. Moderate escalators and rapid escalators who peaked had the highest proportions of participants who initiated cannabis and cigarettes the same year (i.e., 50.0% and 42.9%, respectively), while incident smokers who stopped had the lowest (17.9%).

Table 16. (Manuscript 3, Table 2) Number and percent of participants who tried cannabis and tried cannabis before cigarettes[3], by cigarette smoking category, NDIT 1999-2008

Cigarette smoking category	*n*[1]	Tried cannabis[1] *n* (%)[2]	Tried cannabis before cigarettes[3,4] (total *n* = 69) *n* (%)[5]
Never smokers	321	123 (38.3)	--
Incident smokers			
Incident smokers who stopped	42	28 (66.7)	8 (28.6)
Low-level decreasers	91	76 (83.5)	11 (12.1)
Stable low consumers	104	100 (96.1)	11 (10.6)
Slow escalators	18	18 (100)	1 (5.5)
Moderate escalators	14	12 (85.7)	0 (0)
Early rapid escalators who peaked	7	7 (100)	1 (14.3)
Prevalent smokers	260	219 (84.2)	--

[1]Refers to ever users of cannabis, as reported at survey 21.
[2]After listwise deletion of participants in each group who had missing data on ever cannabis use at cycle 21.
[3]Tried cannabis prior to cigarette smoking initiation (both cigarette and cannabis initiation were reported at cycle 21).
[4]Never smokers and prevalent smokers were excluded from this table with regards to order of initiation. However *n* = 69 individuals who were never smokers, incident smokers, and prevalent cigarette smokers tried cannabis before cigarettes.
[5]Denominator of the percentages was the number of participants in each group which had tried cannabis.

Age at first use of cannabis

The median age at first cannabis use was 15 years (range 9 to 23 years). Table 18 shows median (range) age at first cannabis use according to cigarette smoking category. Median age at first cannabis appeared to decrease with increasing level of cigarette consumption. The four trajectory groups with the lowest consumption (i.e., never smokers, incident smokers who stopped, low level decreasers, and stable low consumers) had the highest median age at cannabis initiation (16, 16, 16, and 15 years, respectively). Early rapid escalators who peaked had the lowest median age at first cannabis use (13 years). Figure 7 presents these same data using

boxplots: the length of each box corresponds to the interquartile range, while the symbol in the box interior represents the group mean and the horizontal line in the box interior the group median. [178]

Table 17. (Manuscript 3, Table 3) Percent of participants who initiated cannabis the same year as cigarettes[3], by cigarette smoking category, NDIT 1999-2008

Cigarette smoking category	Tried cannabis[1] *n*[2]	Tried cannabis and cigarettes same year[3,4] (total *n* = 115) *n*, %[5]
Never smokers	123	--
Incident smokers		
Incident smokers who stopped	28	5 (17.9)
Low-level decreasers	76	16 (21.0)
Stable low consumers	100	31 (31.0)
Slow escalators	18	6 (33.3)
Moderate escalators	12	6 (50.0)
Early rapid escalators who peaked	7	3 (42.9)
Prevalent smokers	219	--

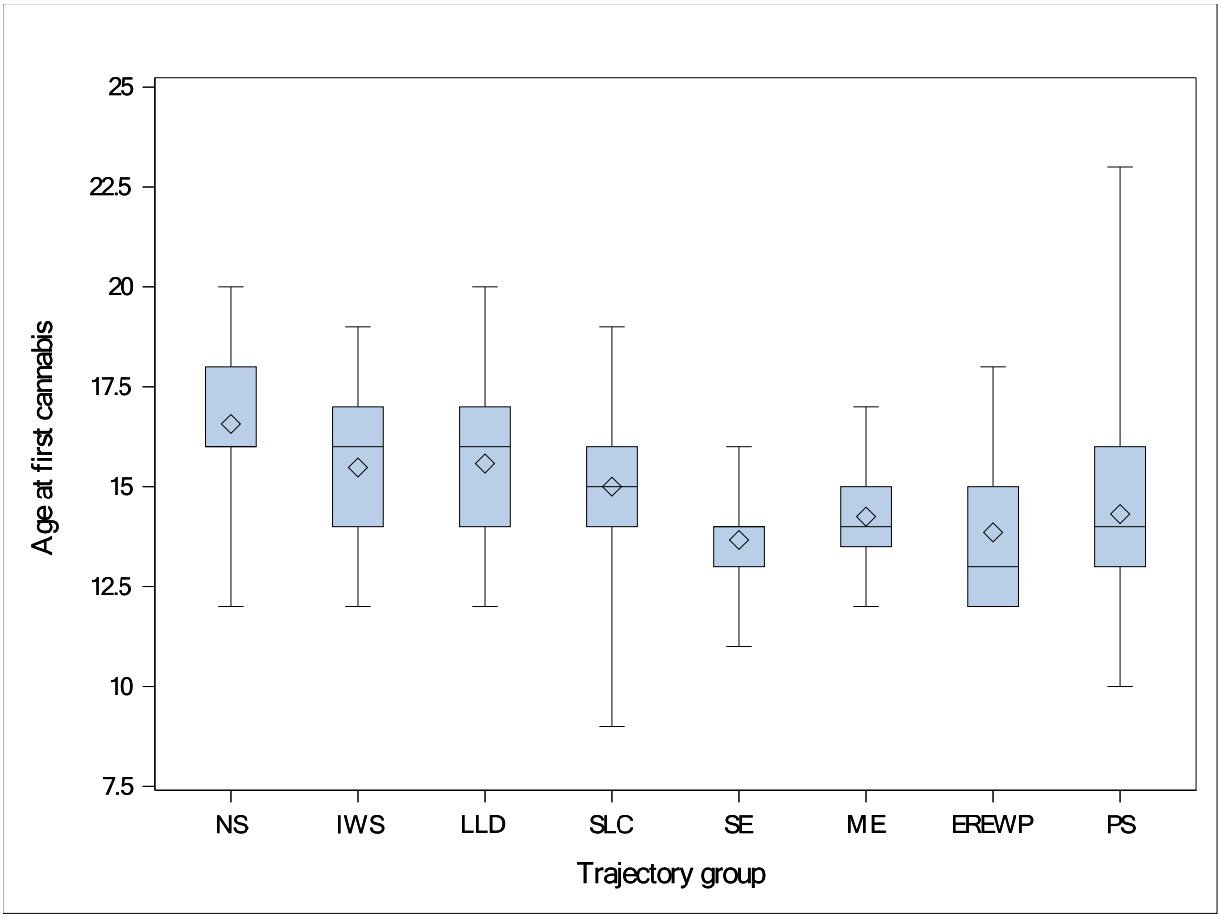
[1]Refers to ever users of cannabis, as reported at survey 21.
[2]After listwise deletion of participants in each group who had missing data on ever cannabis use at cycle 21.
[3]Initiated cannabis in the same year as cigarette smoking initiation (both cigarette and cannabis initiation were reported at cycle 21).
[4]Never smokers and prevalent smokers were excluded from this table with regards to order of initiation. However *n* = 115 individuals who were never smokers, incident smokers, and prevalent cigarette smokers tried/initiated cannabis and cigarettes at the same age.
[5]Denominator of the percentages was the number of participants in each group which had tried cannabis.

Table 18. (Manuscript 3, Table 4) Median age at first cannabis use, among cannabis ever-users, by cigarette smoking category, NDIT 1999-2008[2]

	Group *n*[3]	*n*[1]	Median age (range) at first cannabis use, y
Never smokers	454	121	16 (12–20)
Incident smokers			
Incident smokers who stopped	66	27	16 (12–19)
Low level decreasers	115	75	16 (12-20)
Stable low consumers	140	100	15 (9-19)
Slow escalators	25	18	14 (11-16)
Moderate escalators	19	12	14 (12-17)
Early rapid escalators who peaked	8	7	13 (12-18)
Prevalent smokers	424	219	14 (10–23)

[1]Number of participants after listwise deletion of participants with missing data for age at first cannabis use at cycle 21 (includes participants who reported that they had never tried cannabis, and who therefore did not report an age at first use).
[2]A Kruskal-Wallis test was used to test for differences between groups, which was statistically significant ($p < 0.0001$).
[3]Total number in each cigarette category prior to listwise deletion.

Figure 7. (Manuscript 3, Figure 2) Age at first cannabis use by cigarette smoking category, NDIT 1999-2008



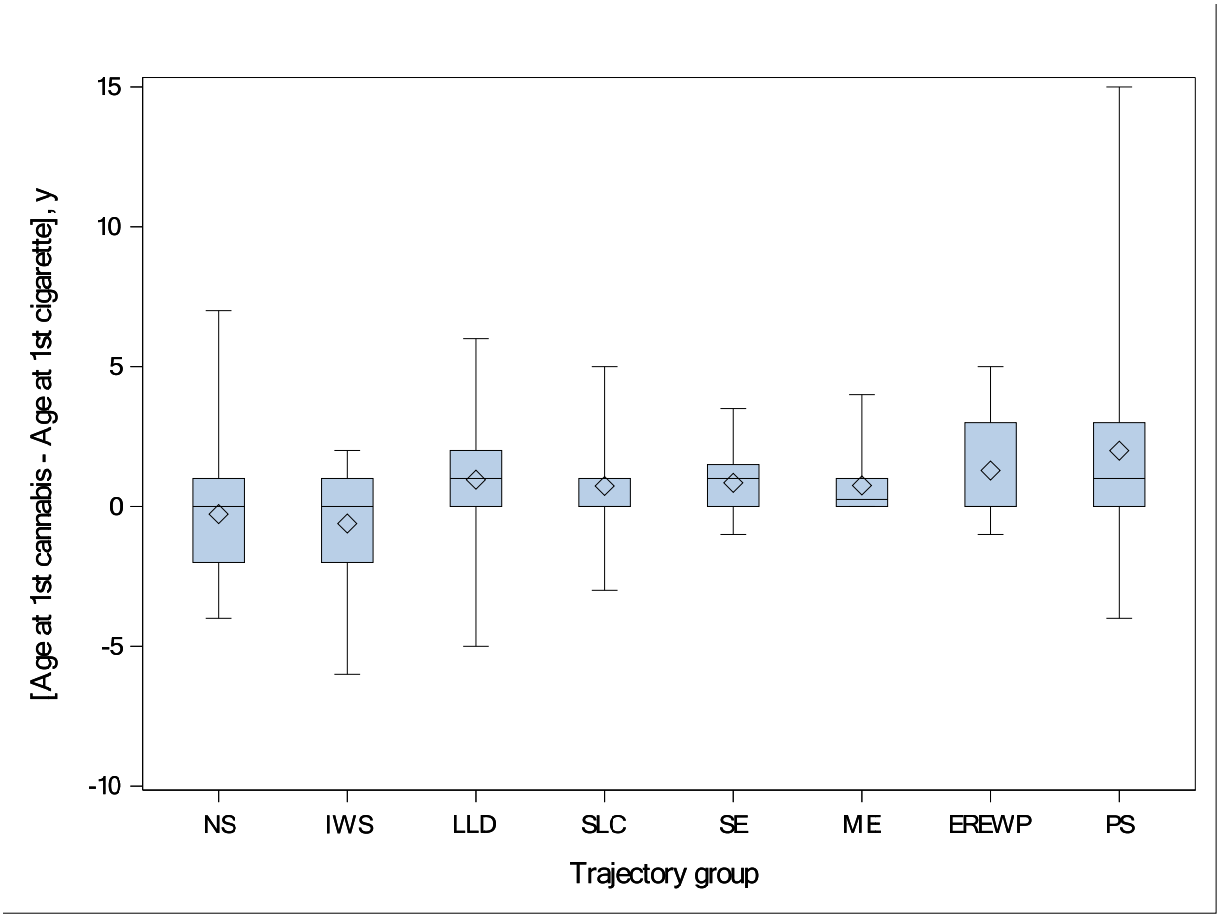
NS=never smokers, IWS=incident smokers who stopped, LLD=low level decreasers, SLC=stable low consumers, SE=slow escalators, ME=moderate escalators, EREWP=early rapid escalators who peaked, PS=prevalent smokers.

Time elapsed

Boxplots of (age at 1st cannabis use) – (age at smoking initiation) by cigarette smoking category are presented in Figure 8. The median and range of time elapsed between first cannabis use and cigarette smoking initiation according to cigarette smoking category are presented in Table 19. Note that these results are driven by both the order of initiation of cannabis and cigarette as well as by the absolute value of the difference between age at first cannabis use and age at cigarette smoking initiation.

All median values were ≥0. There did not appear to be a (descriptive) relationship between level of cigarette consumption and time elapsed.

Figure 8. (Manuscript 3, Figure 3) (Age at first cannabis use) – (age at smoking initiation), by cigarette smoking category, NDIT 1999-2008



IWS=incident smokers who stopped, LLD=low level decreasers, SLC=stable low consumers, SE=slow escalators, ME=moderate escalators, EREWP=early rapid escalators who peaked.

Factors associated with time elapsed

In the analyses of factors potentially associated with time to cigarette initiation among ever cannabis users, no factors were statistically significant and confidence intervals were wide, encompassing zero. (Table 20) In the analyses of factors potentially associated with time to cannabis initiation among ever cigarette smokers, increased age (at baseline) was the only factor associated with increased elapsed time ($p<0.05$) (parents' smoking was marginally significant). (Table 21)

Table 19. (Manuscript 3, Table 5) Median (range) of (age at 1st cannabis use) – (age at cigarette smoking initiation), by cigarette smoking category, NDIT 1999-2008[4]

	Group *n*[5]	*n*[1]	Median (range) of (age at 1st cannabis – age at 1st cigarette[3])[2]
Never smokers	454	55	--
Incident smokers			
Incident smokers who stopped	66	18	0 (-6, 2)
Low level decreasers	115	58	1 (-5, 6)
Stable low consumers	140	80	0 (-3, 5)
Slow escalators	25	16	1 (-1, 3.5)
Moderate escalators	19	12	0.25 (0, 4)
Early rapid escalators who peaked	8	7	0 (-1, 5)
Prevalent smokers	424	180	--

[1]Actual number of participants in each category, after listwise deletion of individuals with missing information for age at 1st cannabis and/or age at 1st cigarette (both self-reported at survey 21).
[2]A negative sign indicates cannabis was initiated prior to smoking.
[3]Self-reported age at cigarette initiation (i.e., at cycle 21).
[4]A Kruskal-Wallis test was used to test for differences between groups, which was not statistically significant (p = 0.1348).
[5]Total number in each cigarette category prior to listwise deletion.

Interpretation of coefficients

The coefficient for age at study baseline (model of cigarette primo-initiators) was 2.62 (1.19, 4.06), which implies that in a comparison of two participants with an age difference of 1 year at study baseline (among cigarette primo-initiators who used both substances), on average a value of +2.6 years would be added to the time to cannabis initiation for the older of the two participants.

Clustering and ICC_2 values

The ICC_2 values obtained for the school effect were as follows. At baseline (more specifically, participant baseline at surveys 1 and 2, the first available value was used for all participants), ICC_2 was 4.4% for number of cigarettes smoked per month (3-month recall). Therefore at baseline, 4.4% of the variance in this variable was due to clustering. At survey 18, ICC_2 was 2.7% and was 2.2% in adulthood (i.e., at survey 22 or approximately 24 years). For age at 1st cannabis, ICC_2 was 5.6% (i.e., survey 21).

Multilevel modeling

Results of a multilevel model with a gamma distribution (in R) suggested that the effect of age at baseline on time elapsed between cigarette and cannabis (among cigarette primo-initiators who used both substances) was not due to clustering. The beta coefficient obtained was -0.083 (exp(-0.083) = 0.920) and suggests that a 1 year increase in age at baseline was associated (on average, among cigarette primo-initiators who used both substances) with the

addition of +0.920 years to the time elapsed between cigarette and cannabis initiation (the result was also statistically significant).

Table 20. (Manuscript 3, Table 6) Regression coefficient[1] and confidence interval from bivariate linear regression models of (age at 1st cannabis use) – (age at 1st cigarette use)[2], among users of both substances who initiated cannabis prior to cigarette use, NDIT 1999-2008 (*n* = 70)

	Regression coefficient[1] (Confidence interval)	Missing *n*[4]
Age (baseline), years	0.58 (-0.19, 1.34)	0
Female	0.71 (-0.19, 1.63)	0
Mother university educated[3]	-0.07 (-0.97, 0.83)	9
French spoken at home	-0.54 (-1.43, 0.36)	0
Born in Canada	-1.27 (-3.11, 0.57)	0
Self-esteem	-0.99 (-2.44, 0.45)	10
Mean no. cigs smoked per month, in past 3 months[5]	-0.0013 (-0.008, 0.006)	13
Friend(s) smoked	0.55 (-0.48, 1.59)	0
Parent(s) smoked	-0.18 (-1.09, 0.73)	1
Sibling(s) smoked	-0.06 (-1.27, 1.14)	0
Single-parent family	0.06 (-1.86, 1.98)	0
Depression	0.45 (-0.28, 1.18)	0
Alcohol use	0.06 (-0.82, 0.95)	0

[1]Unstandardized regression coefficients.
[2]Truncated regression was used to examine the length of time elapsed between cannabis initiation and cigarette smoking initiation, among participants who had initiated cannabis prior to cigarettes (defined as (age at 1st cannabis use) – (age at 1st cigarette use) > 0.
[3]Mother's education was created from information provided in cycles 13 and 17 by participants and in questionnaires completed by participants' mothers.
[4]*n* = 70 participants were included in these models. Missing correspond to listwise deletion for each independent variable in the table, so total missing and excluded data would be 1224 + the number indicated.
[5]Measured at initiation. All other variables were obtained at baseline, except for self-esteem (survey 12) and mother's education (surveys 13, 17, and mother questionnaires).

7.3.5 Discussion

In this study of Montreal-area youth followed from high school into young adulthood, first puff on a cigarette usually preceded cannabis use. However, some participants initiated cannabis before cigarettes in most cigarette smoking categories. Ever cannabis use was in most (with the exception of stable low consumers) cases higher and first cannabis use generally occurred at a younger age, in cigarette smoking categories which likely had heavier lifetime cigarette consumption including cigarette smoking escalators and prevalent smokers. Finally, age at baseline was significantly associated with time to first cannabis use among ever cigarette smokers.

Table 21. (Manuscript 3, Table 7) Regression coefficient[1] and confidence interval from bivariate linear regression models of (age at 1st cannabis use) – (age at 1st cigarette use)[2], among users of both substances who initiated cigarette use prior to cannabis, NDIT 1999-2008 (*n* = 248)

	Regression coefficient[1] (Confidence interval)	Missing *n*[4]
Age (baseline), years	**2.62 (1.19, 4.06)**	0
Female	-0.35 (-2.44, 1.74)	0
Mother university educated[3]	-0.24 (-2.07, 1.60)	40
French spoken at home	1.78 (-0.31, 3.87)	0
Born in Canada	-3.41 (-11.09, 4.26)	0
Self-esteem	1.15 (-1.36, 3.66)	60
Mean no. cigs smoked per month, in past 3 months[5]	-0.00036 (-0.0093, 0.0086)	135
Friend(s) smoked	0.52 (-1.46, 2.49)	0
Parent(s) smoked	2.69 (0.41, 4.99)	6
Sibling(s) smoked	1.82 (-0.62, 4.27)	2
Single-parent family	0.49 (-2.50, 3.48)	1
Depression	0.87 (-0.69, 2.42)	0
Alcohol use	0.84 (-1.14, 2.82)	3

[1]Unstandardized regression coefficients.
[2]Truncated regression was used to examine the length of time elapsed between cannabis initiation and cigarette smoking initiation, among participants who had initiated cannabis prior to cigarettes (defined as (age at 1st cannabis use) – (age at 1st cigarette use) < 0.
[3]Mother's education was created from information provided in cycles 13 and 17 by participants and in questionnaires completed by participants' mothers.
[4]*n* = 70 participants were included in these models. Missing correspond to listwise deletion for each independent variable in the table, so total missing and excluded data would be 1045 + the number indicated.
[5]Measured at initiation. All other variables were obtained at baseline, except for self-esteem (survey 12) and mother's education (surveys 13, 17, and mother questionnaires).

A theory frequently invoked to explain order of substance use initiation is the Gateway Model, which suggests that youth follow a predictable sequence as they become increasingly involved in substance use, initially using tobacco or alcohol followed by cannabis, and then other illicit drugs. [114], [115] NDIT data support that first puff on a cigarette usually precedes cannabis use, although cannabis use preceded cigarette initiation in 69 of 857 participants or slightly fewer than 10% of participants, suggestive that initiation sequence is not necessarily (always) reflective of an inherent natural course of substance initiation. The Gateway Model could reflect that easily accessible or available substances will naturally be those tried first. It will be interesting to assess whether the prevailing order of initiation changes if legalization of cannabis makes cannabis more accessible to young people.

Models other than the Gateway Model also provide explanations for the order of initiation. The "common liability model" suggests that use of multiple substances represents a

generalized increase in the risk of drug use, and that it is addiction and not a specific drug that increases the risk of progression. [115], [119] The "route of administration model" proposes that initiating use of a particular substance by one route of administration (e.g., inhalation) accounts for future initiation of other substances via the same route. [112], [120] Finally a "reverse gateway model" has been proposed, whereby cannabis use increases the risk of later tobacco initiation in non-tobacco smoking adolescents. [118] Overall, while these models provide insight on alternate explanations, it is likely that multiple social and biological factors within a large complex network of influences (e.g., history of substance use for the gateway model, biological and behavioral effects via route of administration) are at play. Our results also accord with those of several earlier studies in that order of initiation did not appear to be associated with heavier cigarette use (heavier cigarette smokers initiated both cigarettes and cannabis earlier, but this did not appear to affect order of initiation). [71], [72], [75], [76] The gateway model deals with sequence of substance use initiation and does not explicitly deal with the importance of substance use beyond initiation. [113], [119] The liability to addiction or substance use disorder model does however explicitly state that it "pertain[s] to the entire course of development of the disorder and changes in the risk" [119]). The route of administration model was proposed to explain reverse sequences (i.e., cannabis to tobacco) and does not provide much guidance on later importance of substance use. [112], [120] Given that initiation of each of these two substances is only the first step in a process of acquisition of substance use, it stands to reason that any model of the interaction between cannabis and tobacco should take into account the longitudinal nature of the interactions between and natural course of these two substances.

NDIT data suggest that first cannabis use generally occurred at a younger age among smokers in riskier cigarette consumption categories. This could reflect that some adolescents have easier access to cannabis (e.g., have (older) friends who use cannabis; their parents use cannabis; they live in a neighbourhood where cannabis is easy to access) and therefore are able to try this substance at an earlier age. Alternatively (or in conjunction with easier access), this subgroup could actively seek out alternative psychoactive substances. Impulsivity, novelty-seeking or self-medication for psychosocial symptoms could underpin this search. These smokers likely constitute a higher risk group since earlier initiation of cannabis has been

associated with a negative outcomes such as lower education attainment [179], early-onset psychosis [180], and increased use of substances [181].

Age at baseline was the only factor associated with time to cannabis initiation among ever cigarette smokers: younger age decreased time to cannabis initiation and additional modeling confirmed that this effect was not due solely to the clustering effect in our data. While age is not modifiable (or would be difficult to modify), it may help target preventive intervention, possibly using a "vulnerable populations" approach whereby intervention is targeted to higher risk subgroup(s) with shared social characteristics. [182] Future analyses of this topic could further help to refine the list of factors associated with time to initiation of the second substance among primo initiators of cannabis or cigarette users, which may help with intervention.

Limitations of our analyses include that self-report data are subject to misclassification bias. Because age at first cannabis use was measured retrospectively in young adulthood, telescoping bias (i.e., temporal displacement of an event whereby people perceive distant events as being more recent than they are [183]) may be at play. Misclassification may also have occurred in regard to the order of initiation with relatively short elapsed time between initiation of the first and second substance, since the imprecision of reported age at cannabis initiation renders accurate determination of the order of initiation in such cases difficult. Loss to follow-up could have resulted in selection bias and use of a purposive sample may limit generalizability. Some results are imprecise given the small numbers of participants involved. Clustering by school should have played a small role in our results however, given that both the 3-month recall of cigarette use and cannabis had relatively small ICC_2 values (the clustering effect of cigarette smoking also declined over time). (Clustering should not have affected point estimates, therefore the descriptive analyses of order at initiation and age at first cannabis use according to cigarette smoking categories would not have been greatly affected.) [175][184] Finally, a major limitation of our data was that we had no information on use of cannabis post initiation.

In conclusion, the results of the analyses presented herein suggest that the Gateway Model prevails in terms of the order of substance use initiation among Montreal-area adolescents in the early 2000s. However, a minority of participants did initiate cannabis prior to cigarettes. Age at first cannabis use was lower in cigarette smoking groups with heavier

smoking. These smokers may constitute a higher risk group at risk of several negative outcomes and may benefit from targeted intervention as a "vulnerable population". Whether these observations will change as increasing numbers of jurisdictions legalize cannabis, and whether changing order of initiation affects physical and/or mental health are open questions.

References

Note: References in Manuscript 3 refer to the thesis Reference section, after Chapter 9.

PLEASE NOTE that additional methodological details regarding Manuscript 3 are presented in Appendices 5 to 8.

Chapter 8 - Discussion

The central aim of the current thesis was to attempt to use trajectory modeling to increase understanding of cigarette smoking onset in youth, a further related aim was to ascertain the usefulness of cigarette smoking trajectory modeling to public health. This Chapter begins by reviewing the objectives and main results of this thesis and discusses whether the results align with the hypotheses linked to objectives 2 and 3 (Section 8.1). Results pertaining to Article 1 are discussed alone (section 8.1.1), as well as in the context of our findings in objective 2 (section 8.1.2). Results of Manuscript 3 are discussed in section 8.1.3. Recommendations for future research are presented in section 8.1.4, considering the findings of Article 1 and Manuscripts 2 and 3. In Section 8.2, we consider the contributions of this work to public health. We discuss the strengths and limitations of these analyses in Section 8.3. This is followed by a Conclusion section (Chapter 9).

8.1 Summary of results

8.1.1 Manuscript 1: Systematic literature review

In the first manuscript of this thesis, we conducted a systematic review of the literature on studies of adolescent cigarette smoking trajectories to describe the number and shapes of trajectories. We also sought to assess whether sample size, number of data points, indicator of cigarette smoking used, or time axis influenced the number or shapes of trajectories identified. A third aim was to summarize risk factors and outcomes associated with membership in specific trajectory groups. Finally, we attempted to assess whether this literature identifies time window(s) for intervention to prevent or reduce cigarette smoking. The current section summarizes the main findings of our review.

Main findings

In our review the number of smoking trajectory groups reported ranged from 2 to 6, with the most frequent number of trajectories being four. The highest proportion of participants was categorized as low-stable smokers, followed by increasing trajectories, followed by all “other” trajectory types.

Studies with a small (<500) sample size reported a median of number of trajectories (3.5), which was only very slightly less than the number for the rest (four). Articles reporting trajectory models using <5 data points for cigarette smoking identified a median of 3 trajectories while studies with ≥5 points identified a slightly higher median of 4. The studies where the cigarette smoking variable used to model trajectories related to smoking intensity, frequency, or some combination of intensity and frequency had a slightly higher median number of trajectory groups reported (four) than studies reporting models with a variable relating to "any use" (median of three). Studies of incident cigarette smoking (i.e., referred to as "time since onset" time axis in Article 1) and of cigarette smoking prevalence (referred to as "age/grade" time axis analyses in Article 1) both had the same median number of reported trajectory groups. In general, across all categories of sample size, number of data points, smoking indicator, and time axis, most participants were categorized as belonging to a "low-stable" trajectory type, followed by the "increasing" trajectory type and then "other". An important finding and caveat of our review, however, is that only two studies modeled incident cigarette smoking/"time since onset". [30], [31]

The following risk factors were investigated in ≥5 articles and were reported to be statistically significant risk factors of trajectory group membership in at least half of the articles where they were studied: age, sex/gender, race/ethnicity, parental education, behavior problems, depression/depressive symptoms, academic performance, baseline cigarette use, parental smoking, friend(s) smoking, alcohol use, and cannabis use. In general, older age at baseline, being male, and being Caucasian were associated with membership in trajectory groups with higher cigarette consumption. For the remaining factors, the least favorable categories were associated with membership in trajectory groups with higher cigarette consumption. Fewer articles examined outcomes of trajectory group membership and of 21 outcomes examined, four were significant in ≥5 articles. Higher cigarette consumption trajectories were associated with illicit drug use and alcohol use, lower levels of education, and being unmarried. Finally, only two studies described time windows relating to high risk trajectories of cigarette smoking.

An important limitation of this literature is that it was not possible to determine whether smokers remain within a single trajectory over time or shift between trajectories. It was therefore unclear whether differences across trajectories at a given point in time are sufficiently important

to warrant targeted intervention. Further, several authors have warned against considering trajectories as real constructs. [34], [185], [186]

The central findings of our review were: (i) that while variation across studies in trajectory number and shape may reflect actual underlying variability in cigarette smoking, this may also be an "artefact" of variation in study design features and modelling decisions; (ii) the risk factors and outcomes identified in our review of trajectory studies mirror those from studies that do not use trajectory analyses; (iii) interpretations on windows of opportunity for intervention are not consistent and this topic was also understudied; (iv) few studies (only two of those reviewed) depicted the natural course of smoking since most studies modeled mixed cigarette smoking trajectories (i.e., "age/grade" time axis studies) rather than incident smoking; and (v) there was considerable missing information on how the final trajectory model was selected, which should affect replicability from one study to the next.

Therefore, while the public health potential of modeling cigarette smoking trajectories is considerable and while this approach could eventually provide useful information regarding cigarette smoking onset in youth (i.e., notably by studying cigarette smoking onset as a longitudinal process and potentially identifying high risk individuals), this potential has to date not been realized in the literature.

8.1.2 Manuscript 2: Modeling incident and mixed trajectories

Section 8.1.1 summarizes the results obtained of the systematic review of the literature presented in Article 1. One important limitation of this literature is that the vast majority of studies did not model the onset of cigarette smoking: rather, these studies used "age/grade" time axes and modeled prevalence of cigarette smoking over time. Manuscript 2 therefore sought to compare trajectories of incident and prevalent (i.e., so-called "mixed" trajectories) of cigarette smoking in a single dataset, in order to ascertain the effect(s) this difference has on results.

Our objectives for Manuscript 2 were to model incident trajectories of cigarette smoking and to compare incident with mixed trajectories to determine whether the number, shape, risk factors or outcomes differ across types of trajectories. We used data from a prospective investigation of 1293 grade 7 adolescents recruited in 1999-2000 who were followed in 22 data collection cycles from age 12 to 24. The first 20 data collection cycles, in which cigarette

consumption was measured every 3 months, were used to model cigarette smoking trajectories. We first report the main findings of our analyses; we then discuss what can be specifically concluded in response to our hypotheses relating to Objective 2. (Chapter 5) (Additional information regarding our analyses is presented in Appendices 4-6 and 8.)

Main findings

We identified five incident trajectory groups rather than four as reported by previous analyses: low-level decreasers (37.5%), stable-low consumers (45.6%), slow escalators (8.1%), moderate escalators (6.2%), and early-rapid escalators (2.6%). Three of the five trajectory patterns resembled those reported by Karp et al (2005) [30] although our analysis identified two trajectories of low-level smokers rather than one. High-risk smokers in Karp et al (2005) [30] increased smoking rapidly and early following smoking onset. The results in Manuscript 2 suggest that these early-rapid escalators do not decrease their cigarette consumption during adolescence. As in Rosendahl et al (2008) [31] who reported sex-specific trajectories that evolved into non-smoking, we identified a trajectory of smokers who slowly decreased cigarette consumption. [31]

The final model in the mixed analysis was a 4-group model: stable-low consumption (56%), slow (21%) escalators, moderate (15%) escalators, and early-rapid escalators (7%).

Different sets of risk factors were associated with both models: sex, age and smoking-related factors, as well as MVPA were the only factors which were significant in the incident model. In the mixed model, smoking-related factors were significant but several additional factors were also significant which were not so in the incident model. Overall, any escalation in cigarette consumption was associated with higher levels of smoking and nicotine dependence in early adulthood. Considering actual variable values (regardless of statistical significance, a comparison which is akin to comparisons of point estimates of measures of association), in general in the incident model the smoking-related indicators showed a less favorable/higher risk profile in the increasing trajectories and a more favorable/lower risk profile in the low-level trajectories. This was not the case for other risk factor categories. In the mixed model however, in general the majority of risk factors were both statistically significant and had values suggesting more unfavorable/higher risk profiles for heavier cigarette smoking trajectories

(sociodemographic indicators also showed a consistent pattern of differences when values associated with low-level and increasing cigarette smoking trajectories were compared, although these categories cannot be referred to as corresponding to 'higher risk"). In general both statistical significance and actual variable value comparisons, akin to comparison of point estimates of measures of association, suggest that risk of continuing to smoke, heavier smoking, and nicotine dependence in young adulthood increases with increasing smoking/higher risk trajectory groups.

A central finding of Manuscript 2 was that incident and mixed trajectory analyses yield trajectories that differ from each other, including with regards to the fact that the rate of change in the mixed trajectories was generally attenuated across the curves in comparison to the incident model, and that the differences observed likely depend on the proportion of incident smokers in each trajectory group in the mixed model. Finally, another crucial finding was that the curve of early rapid escalators was steeper at smoking onset in the incident model, suggesting that any window of intervention opportunity for preventing escalation in cigarette consumption is not as wide as the mixed analysis would suggest.

Hypotheses: Objective 2

Our first hypothesis was that when modeling incident cigarette smoking trajectories, high risk novice smokers begin smoking earlier and sustain high levels of cigarette consumption during adolescence and that modeling trajectories of incident cigarette smoking in adolescence can be used to identify these high-risk smokers. (In general, the studies reviewed in Article 1 also reported results which support this assertion, however only two of these studies modeled incident cigarette smoking. [30], [31]) Both our current (i.e., Manuscript 2) and previously published analyses of the same data (Karp et al., 2005 [30]) provide support for this assertion, as do the results presented by the only other study presenting a model of incident cigarette smoking trajectories (Rosendahl et al., 2008 [31]). In all three of these analyses, the models presented differentiate between high risk smokers who increase their smoking to reach high levels during adolescence, and those who smoke at lower levels.

Our second hypothesis posited that, when modeling incident cigarette smoking trajectories, risk factors can be identified which would enable the identification of novice

smokers at risk of becoming heavy and sustained cigarette smokers. The results of our review in Article 1 (maintaining the caveats discussed above) revealed that relatively few potential risk factors were studied in ≥5 studies. The issue of methodological heterogeneity across studies also made aggregation of results regarding potential risk factors difficult. Our conclusions in regard to objective 2, in light of the previous discussion, focus on studies of incident smoking. Our analyses of incident cigarette smokers did reveal certain statistically significant risk factors: age, sex/gender, number of cigarettes per month at initiation, and physically/mentally addicted and really need a cigarette measured at cigarette initiation, were significantly different between trajectory groups. MVPA was statistically significant but the results were somewhat paradoxical in that lower MVPA appeared to be protective against being in a heavier cigarette smoking trajectory. (This was contrary to previously published results suggesting that physical activity [187] and MVPA [188] are associated with a reduction in cravings among cigarette smokers. Additionally, a previous analysis of our data which included $n = 319$ novice smokers and used Cox regression to model time from cigarette initiation to each of cravings, withdrawal symptoms and tolerance found no association with physical activity. [189] This divergence from our current results may however be due to differences in the two analyses in terms of both methods as well as in the exposure and outcome studied.) These risk factors could conceivably be used to identify high risk cigarette smokers. Three caveats however apply to this conclusion: first, given that the curve of early rapid escalators in the incident mode was quite steep at smoking onset, any window of opportunity for preventing escalation in cigarette consumption may be limited and intervention relative to risk factors equally difficult. A second caveat is that the risk factors identified in our incident trajectory model differ from those identified in previously published analyses of incident trajectories of cigarette smoking: some factors were however not studied in all three studies. This difference may also result from differing risk factor definitions (Rosendahl et al. 2008 [31]) and a shorter length of follow-up than in our data (Karp et al. 2005 [30]). (In the case of Rosendahl et al. 2008 [31], differences may also be the result of differences between the two study populations, for example in terms of context or culture as pertains to substance use.) Finally/thirdly, given the small number of published studies reporting incident trajectory models of cigarette smoking, further studies of this type would be needed to affirm our results.

Our third hypothesis stated that when modeling incident cigarette smoking trajectories, novice smokers in higher risk/heavier smoking trajectories in adolescence would be more likely to continue smoking cigarettes in adulthood, as well as to smoke more often and/or smoke more cigarettes per day/week/month in adulthood. In our review of the literature, there were only four articles [36], [40], [190], [191] which studied cigarette smoking-related outcomes, all of which were of the "mixed"/"age/grade time axis" type. This hypothesis was however supported by our results in Manuscript 2, which provide novel results on this topic.

Our final hypothesis, that trajectories of incident cigarette smoking differ from trajectories combining incident and prevalent smokers in terms of the number, shapes, and risk factors of these trajectories, was supported by our analysis. In our review of the literature our comparison of incident and mixed trajectory models suggested that the number of trajectories did not differ according to the time axis used: our analysis however differed from this result in that different time axes did appear to result in different numbers of trajectories. The proportions of smokers in each trajectory type did however vary according to the time axis used in our systematic review (this was also the case in our analysis). Risk factors identified as statistically significant also appeared to vary according to whether incident or mixed trajectories of cigarette smoking were modeled in both our review of the literature (Article 1) and our analysis (Manuscript 2). Relatively few studies have examined outcomes of cigarette smoking trajectories and only a single study [30] reporting incident trajectories did so, so our results present new information. Cigarette smoking-related outcomes were significant in both incident and mixed trajectories of cigarette smoking.

In conclusion, our results suggest that modeling incident cigarette smoking trajectories does identify high risk individuals and our analysis of risk factors suggests that these may be of use in the identification of these individuals. As previously mentioned, our results are however tempered by the consideration that cigarette smokers may not remain in a single trajectory over time, and that several authors have warned against considering trajectories as real constructs. [34], [185], [186]

8.1.3 Manuscript 3: Cannabis, cigarettes, and cigarette trajectories

Manuscript 3 sought to describe order of initiation of tobacco and cannabis as well as whether this order appeared to be associated with cigarette category; to describe age at first cannabis use across cigarette smoking categories including the cigarette smoking trajectories modeled in Manuscript 2; and to identify predictors of elapsed time between tobacco (i.e., combustible cigarette) and cannabis initiation.

Our first hypothesis was that most individuals who initiate both cannabis and cigarettes will initiate cigarette smoking first and that order of initiation is not associated with cigarette smoking trajectory group. A theory frequently invoked to explain order of substance use initiation is the Gateway Model, which suggests that youth follow a predictable sequence as they become increasingly involved in substance use, initially using tobacco or alcohol followed by cannabis, and then other illicit drugs. [114], [115] Our results support that first puff on a cigarette does usually precede cannabis use, although cannabis use preceded cigarette initiation in a minority of participants (69 of 857); the proportion of participants who initiated cannabis before cigarette smoking according to cigarette smoking category ranged from 0% in moderate escalators to 28.6% in incident smokers who stopped. These values/proportions did not follow a clear pattern according to degree of smoking/cigarette smoking category: the second highest proportion was in early rapid escalators who peaked at 14.3%. Therefore the highest proportion was in the group with the lowest degree of smoking while the second highest proportion was in the group with the group with the highest. (Recently published analyses of trends over time do however suggest that cannabis primo-initiation may be increasing in more recent cohorts, as patterns of combustible cigarette, cannabis, other tobacco, and e-cigarette use change over time. [192]) Our results and those of others [71], [72], [143], [76], [79], [81], [112], [136], [139], [141], [142] suggest that cannabis can be initiated before tobacco, which provides theoretical support for models other than the Gateway Model. Our results also accord with those of several earlier studies in that order of initiation did not appear to be associated with heavier cigarette use. [71], [72], [75], [76] Three studies reported ORs relating tobacco dependence or later tobacco use (in tobacco users) to order of initiation which suggested that initiating cannabis before other tobacco may not increase risk of tobacco dependence or later tobacco use (it was not possible to summarize these ORs across studies due to differences between studies with

regards to the measures reported). For example, Fairman et al., 2009 reported an OR for risk of nicotine dependence among cigarette smokers, according to initiation of cannabis before initiating tobacco (vs. tobacco before cannabis) of 0.92 (0.83, 1.02) [71]. All three studies reported ORs whose confidence intervals encompassed 1.0.

We also hypothesized (Hypothesis 2) that cannabis use is initiated at younger ages in heavier cigarette smoking trajectories, which appeared to be supported by our results (the four trajectory groups with the lowest consumption of cigarettes had the highest median ages at cannabis initiation (16 and 15 years) while the group with the highest consumption had the lowest median age at first cannabis use (13 years)). This suggests that heavier smokers may constitute a group at higher risk of substance use and negative outcomes beyond the risk posed from heavier cigarette smoking alone: earlier initiation of cannabis has been associated with a variety of negative outcomes such as lower education attainment [179], early-onset psychosis [180], and increased substance use [181]. This group may therefore constitute a "vulnerable population" which could benefit from targeted intervention. [182] In our analyses, the use of trajectories provided a longitudinal summary of cigarette use over several time points, thereby providing information on the importance of cigarette smoking which goes well beyond a single time point. The two relevant studies on this topic, Richmond-Rakerd et al. 2017 [86] and Timberlake et al. 2007 [87] reported differing results which do however suggest that age at 1st cannabis use may be associated with heavier cigarette smoking. Timberlake et al. 2007 [87] reported ORs for (age of initiation appeared to be continuous but this was not explicitly stated) initiation in younger individuals/18-22 year-olds was 1.14 (0.95, 1.36), while that for older participants was 0.82 (0.73, 0.93). There was therefore a small number of studies suggesting that age at first cannabis might be associated with later heavier use of and/or dependence on tobacco, which accords with our results.

Our observation that a higher proportion of ever users of cannabis was (generally, but not always) found in the trajectory groups with heavier cigarette smoking aligned with our second hypothesis and provided some evidence for the liability to substance use model (i.e., that use of multiple substances may represent a generalized liability or increase in the risk of drug use and that it is addiction and not a specific drug that increases the risk of progression [115], [119]). It also aligned with the Gateway Model (although this model did not align with our other

results as discussed above) and the route of administration model (i.e., that initiating use of a particular substance by one route of administration such as inhalation may account for future initiation of other substances via the same route [112], [120]). This finding also aligned with the "reverse gateway" (i.e., that cannabis use increases the risk of later tobacco initiation in non-tobacco smoking adolescents [118]). This is the case because our observation does not imply an order of initiation and may for example result from initiation of cigarettes leading to initiation of cannabis or the reverse, or may result from a general increase in risk of substance use. This result is also aligns with that of two studies [104], [105] which examined the association between cigarette smoking trajectories and cannabis use measured at a single time point, both of which reported a significant association. Finally, these results also align with the results of the studies by Richmond-Rakerd et al. 2017 [86] and Timberlake et al. 2007 [87] discussed above

Our final hypothesis was that risk factors for time elapsed between initiation of one substance and initiation of the second can be identified (carrying out analyses separately for primo-initiators of cannabis vs. primo-initiators of cigarettes), and that these two sets of risk factors will differ. The only factor which appeared significant was age at baseline (associated with time to first cannabis among cigarette primo-initiators). The coefficient for age at study baseline of 2.62 (1.19, 4.06) suggested that a comparison of two participants with an age difference of 1 year at study baseline (among cigarette primo-initiators) would result in +2.6 years being added to the time to cannabis initiation for the older of the two participants. The identification of age as a risk factor aligns with the results of one previous study which examined risk factors for cigarette initiation among cannabis ever users (adults). [81] This study reported that hazard ratios suggesting that younger age increased the risk of initiation of cannabis among ever tobacco users, HR = 0.7 (0.6, 0.8)). [81] This study also identified gender as a risk factor (i.e., it was reported that being female was protective, HR = 0.7 (0.5, 0.9)), which was not significant in our analyses (we obtained a coefficient of -0.35 for gender, so the magnitude of this coefficient was also not very large). [81] One study [79] presented results suggesting heavier cigarette smoking may be a risk factor for cannabis initiation (hazard ratios (HR) of 1.23 (1.18, 1.29) and 2.55 (2.43, 2.67) were reported for level of tobacco use for individuals without daily use and with daily use, respectively), while heavier cigarette smoking was not a significant risk factor in our analyses (the coefficient obtained in our analyses was very small (-0.00036)).

There were even fewer published studies identifying risk factors for time elapsed from cannabis initiation to cigarette initiation: one poor quality study [80] (see Table 2, section 2.3.2.1) reported that the importance or degree of cannabis use may be associated with cigarette initiation (significant beta from a stochastic actor-based model of 0.48). A second study [81] reported results suggesting gender might be a predictor of cigarette initiation: marginally significant hazard ratios (from a Markov multi-state model) was reported for gender of 1.6 (1.0, 2.5). No variables were significant in our analyses of potential risk factors for time elapsed among individuals who had initiated cannabis before cigarettes (the small sample size was likely to be a factor in this observation). Other interpretations of differences between our results (Tables 20 and 21) and those of previous studies, may of course be at play including the use of samples and study populations, differing variable definitions and analytical techniques, as well as other differences between our sample and those of the published studies discussed above.

Finally, our results in this manuscript are timely given the high incidence and prevalence of cigarette and cannabis use [9], [65] as well as the current context (e.g., the legalization of recreational cannabis use in adults in Canada in 2018 [48]) and the noted co-use of these substances in individuals. [43], [67]–[70]

8.1.4 Recommendations

The current section presents recommendations for future research, based on the results presented in Article 1, Manuscript 2, and Manuscript 3.

One difficulty with regards to the literature on cigarette smoking trajectories in youth is the relative absence of studies modeling the onset of cigarette smoking (i.e., incident trajectories). Indeed, "mixed" models of cigarette smoking trajectories do not provide information on how long individuals in the various trajectories have been smoking cigarettes: prior to study baseline, individuals with a previous history of smoking can have smoked for varying periods of time and at different levels of intensity as well as frequency and these differences are not taken into account by mixed trajectory models. It is therefore not clear that any time window(s) of intervention to prevent or reduce cigarette smoking could be identified using mixed trajectories: what would time window(s), identified on the basis of this type of model, represent?

Both our review in Article 1 and the analyses of Manuscript 2 suggest that it may be possible to identify risk factors for high risk trajectory groups. Keeping in mind the limitations of the identification of likely windows of intervention discussed just above, there were a number of factors which were studied in ≥5 studies and were identified as significant in more than half of these studies. Therefore while the issue of the identification of time window(s) for potential intervention has not been resolved to date in this literature, it does appear likely that if such windows exist, appropriate risk factors (these would also need to be measured at time point(s) relevant to intervention) could be identified.

The results of Manuscript 2 suggest that cigarette smoking trajectories may relate to future smoking and/or nicotine dependence. Four additional articles presenting "mixed" trajectories of cigarette use also reported significant results. [36], [40], [190], [191] provided data pertaining to cigarette smoking-related outcomes of cigarette smoking trajectories. These results suggest that individuals in different cigarette smoking trajectories continue to have differing cigarette smoking experiences into adulthood.

The review presented in Article 1 suggests that methodological differences may result in differing findings between studies. For example, while the median number of trajectories did not differ according to the time axis used in this review, the proportions of smokers in each trajectory type (i.e., low-stable vs. increasing vs. other) did. This difference was also confirmed by our results in Manuscript 2. Additionally, our systematic review suggests that studies with fewer than 5 data points may yield fewer trajectory groups and that studies that use a dichotomous rather than a continuous cigarette smoking indicator may also yield fewer trajectory groups. Alongside the considerable methodological heterogeneity in this literature was the finding of heterogeneity across studies in the number and shape of the trajectories identified, as well as in the risk factors and outcomes associated with trajectory groups. This concurrence does at least raise the possibility that methodological heterogeneity across studies contributed to heterogeneity of results in our review. Finally, risk factors identified as statistically significant also varied according to whether incident or mixed trajectories were modeled, both in our review/Article 1 and in Manuscript 2.

Manuscript 3 presents several analyses relating to the co-use of cigarette and cannabis, with particular emphasis on cigarette trajectories. An important aim of these analyses was to

study the potential impact of use of cannabis on cigarette smoking trajectories. It is however important to note that the results presented do not pertain to the heaviness/importance of use of cannabis in our sample and only deal with initiation and ever use of cannabis. These results do however suggest that co-use is a phenomenon that exists and which should be considered in relation to cigarette smoking trajectories: in particular, our (descriptive) results suggest that both ever use of cannabis and younger age at initiation of cannabis may be more common in cigarette smoking trajectories with heavier use. Few studies of cannabis use in relation to cigarette smoking trajectories have been published, however an association has been reported. [104], [105]

Based on our conclusions, we state the following recommendations.

Recommendations for future research

i. The potential impact of methodological heterogeneity on this literature (i.e., complicating synthesis of this literature) and lack of completeness in reporting information pertaining to the selection of the final model suggest a need for better reporting in this type of study (to assist in synthesizing and understanding this literature), as recommended by the GRoLTS guidelines [34];

ii. Given that a central aim of this literature is the eventual reduction of cigarette smoking in youth, studies should attempt to identify potential time window(s) useful for intervention;

iii. Future studies should model incident cigarette smoking trajectories, since these present the clearest picture of the natural course of cigarette smoking and given that results may vary (both in terms of the trajectories obtained as well as the risk factors associated with individual trajectory(ies)) between models of mixed vs. incident smoking (Manuscript 2);

iv. Future studies should measure and consider the role of cannabis use in relation to cigarette smoking trajectories, given the close and complex ties between initiation and ever use of both substances (Manuscript 3);

v. Finally, future studies on youth cigarette smoking trajectories should consider the overall impact of their results on public health: both at the level of study

design (i.e., by beginning to measure cigarette smoking at an age at which onset is likely to be observed (childhood), frequent numerous measurements of cigarette smoking, use of continuous measures of cigarette smoking) and at the level of analysis (by attempting to maximize reproducibility in this literature) and reporting (GRoLTS checklist [34]).

8.2 Contributions to public health

The current section presents the contributions to public health provided by the current thesis.

8.2.1 Usefulness of adolescent cigarette smoking trajectories to public health

Because trajectory analyses have been used extensively in research on cigarette smoking in youth, their contribution to advancing the science on youth smoking is an issue of interest. This approach also has considerable potential with regards to public health and could (hypothetically) provide useful information regarding cigarette smoking onset in youth.

By (i) synthesizing the literature on cigarette smoking trajectories in adolescence, (ii) modeling incident trajectories of cigarette smoking in adolescence, and (iii) comparing incident and mixed trajectories of cigarette smoking in adolescence, we have raised questions on the usefulness of this approach to public health above and beyond more traditional approaches to studying the development of youth cigarette smoking. We carried out a systematic literature review, in which we provided a detailed, up-to-date and comprehensive review of this literature (Article 1). We also carried out our own analysis of data drawn from a prospective investigation of 1293 adolescents followed in 22 data collection cycles from age 12 to 24. (Manuscript 2) Our review of the literature identified several questions for future research, notably in relation to difficulties posed by the methodological heterogeneity present in this literature, incomplete reporting of information pertaining to the final selected trajectory model, and with regards to the lack of studies modeling incident trajectories of cigarette smoking which would be the model presenting the clearest view of the natural course of cigarette use. One aim of both our review and our analysis of NDIT data was to determine whether specific time window(s) useful for intervention to prevent or reduce cigarette smoking could be identified.

The extant literature could not respond to this question. In our analysis of NDIT data we raised the possibility that any time window of opportunity for intervention may be limited, since the trajectory was steeper at smoking onset in the highest risk group of smokers in the incident analysis, than in the mixed model.

We considered several questions relating to the use of cannabis in relation to cigarette smoking and cigarette trajectories. We report certain results which do not provide support for the influential Gateway Model. We also report that heavier cigarette smoking trajectories tended to initiate cannabis use at a younger age, which suggests that this group may constitute a group at higher risk of substance use and negative outcomes beyond the risk posed from heavier cigarette smoking alone, potentially requiring targeted intervention. Finally, we also attempted to identify risk factors for initiation of cannabis among ever cigarette smokers and for the initiation of cigarette smoking among ever cannabis users (such risk factors could have the potential to be of use to future intervention, although it should be noted that aside from age at baseline, no factor appeared to be a meaningful and significant predictor in our analyses). The importance of these results also lies beyond their immediate scope, in that they point to the need to consider cigarette smoking trajectories in the wider context of use of other substances.

8.3 Strengths and limitations

8.3.1 Main strengths

Systematic review

We used a transparent, systematic approach to review the literature on cigarette smoking trajectories in adolescents. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [94] (Appendix 3) and reported whether each of the studies reviewed followed the GRoLTS checklist [34] for reporting on latent trajectory studies. (Table 29) We also calculated inter-rater reliabilities to estimate variation in ratings across reviewers. (Appendix 2)

Our review addresses an important gap in this literature. It is the first to provide a detailed, up-to-date and comprehensive systematic review of the literature on adolescent

cigarette smoking trajectories. The results identified several important gaps in this literature and we have provided suggestions to assist future research in this area.

Data source

The data source used in our analyses for Manuscripts 2 and 3 (i.e., the NDIT study) was a particularly rich source of data for cigarette smoking trajectories in adolescence: smoking was measured every 3 months for five years in high school, so that the time lag between cigarette smoking assessments was smaller than in most studies reporting cigarette smoking trajectories during adolescence.

Novelty

Manuscript 2 presents the first study to compare incident and mixed cigarette smoking trajectories in adolescents and Manuscript 3 presents evidence on initiation of cannabis use in relation to cigarette smoking trajectories, which may raise questions on the importance of considering cigarette smoking trajectories in the context of other use of substances.

8.3.2 Internal validity

This section considers the potential for systematic error in Manuscripts 2 and 3, including information, selection and confounding bias. The detail reflect my attempt to (as completely as possible) address any potential concerns regarding the validity of the current work. In this section it is important to understand and differentiate between the concepts of reliability and validity: reliability has been defined as the degree of stability exhibited when a measurement is repeated under identical conditions. [32] Validity is an expression of the degree to which a measurement measures what it purports to measure. [32] Finally, effect modification can be defined as variation in the selected effect measure for the factor under study across levels of another factor while confounding bias has been defined as bias of the estimated effect of an exposure on an outcome due to the presence of common causes of the exposure and the outcome. [32]

8.3.2.1 Information bias

Non differential misclassification

There are two broad types of error or deviation from the "true" measurement, namely random error and bias/systematic error: bias is a systematic deviation from the "true" value. [32] Misclassification has been defined as, "the erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned". [32] Non differential misclassification has been defined as misclassification that is independent of other variables. This condition is not met in the case of differential bias. [193]

Except for BMI (Manuscript 2), all our measures were self-reported which could have led to misclassification of results. Many factors such as social desirability can affect the validity of self-reported measures. [194] Comparisons with biochemical measures do however suggest that self-report measures of cigarette smoking are valid in adolescents. [195], [196] Our cigarette smoking measure was shown to have acceptable test-retest reliability in youth (section 6.2.2). [163]

Non differential misclassification may result in a reduction in the measure of association, but may also in certain circumstances result in an increase in the measure of association. [193] One strategy used in order to minimize the possibility of information bias was the fact that we used established and published measures (one exception was socio-demographic variables). (Please see Table 10 in section 6.2.1 for the list of variables, as well as for a list of relevant references. The references for each of the variables used are also listed in O'Loughlin et al, 2015 [145]: the appendix of the article gives an exhaustive list of all the variables of the NDIT / NICO study, as well as the references for each variable.)

Finally, the measures used in Manuscript 2 (as well as to reproduce the trajectories in Manuscript 3) were obtained shortly after the event, which should increase their reliability (some studies suggest that the reliability and validity of self-reported measurements decreases with increasing time since the event). [197]–[199] An important consideration with regards to misclassification of age at first use of cannabis and cigarettes retrospectively reported at 20 years of age however, is that of telescoping bias (i.e., temporal displacement of an event whereby, as it has been suggested, people may perceive distant events as being more recent than they are). [183] The retrospective nature of the measures used in Manuscript 3 is, however, a limitation of our analyses. We did however attempt to minimize this potential bias by using retrospective data as little as possible in our analyses: cannabis use as well as age of initiation of cannabis and

tobacco were retrospective measures, however other measures including tobacco categories were obtained closer to the event (i.e., during adolescence). Potential risk factors for time elapsed were obtained at baseline.

Telescopic bias

An overview of the literature on this topic is provided in Appendix 9.

Probable consequences of telescopic bias

Rothman [193] suggests that non-differential classification errors may result in a bias that is not in the direction of a null association: this may occur as a consequence of random fluctuations/sampling error, and in other cases may even affect the expected value of a measure. The result of random fluctuation would be difficult to predict and could cause a spurious effect to be observed at the sample level, however such a phenomenon would become less likely with increasing study replication and/or sample size. The effect(s) of random fluctuation cannot be excluded given the size of our sample and could have resulted in a "false" association being observed, or in the observation of a null association when a positive or negative association did in fact exist. This is an acknowledged weakness of our data and one which could only be remedied through repetition of our analyses.

The main conclusions of Manuscript 3 (i.e., the manuscript wherein retrospective data were used) were as follows:

1. That some participants initiated cannabis before smoking in most smoking categories and that initiation order did not appear to be related to the smoking category;
2. That ever use of cannabis was higher, and age at first use of cannabis lower, in the cigarette smoking categories who had higher consumption during adolescence.

In the case of a binary exposure, a bias not due to sampling error may occur in the following situations [193]:

- In the case of a binary/dichotomous measure, reversing the value of the association measure would require a measure whose quality would be worse than a purely random classification of participants;

- In the case of a measure with >2 categories, reversing a trend would also be rather difficult.

Indeed, Rothman, Greenland, and Lash [193] describe results [200] suggesting that a trend could not be reversed if the average of the true exposure increases or decreases at the same time (i.e., monotonically) as the "real" exposure.

For items 1 and 2 above, the exposures (i.e., the order of initiation for item 1 and the age at initiation of cannabis for item 2) should be the measures most affected by misclassification, given to their retrospective nature. In order for non differential misclassification to have affected or modified the observed conclusions however, the (non-random) classification errors at the level of the order of initiation (item 1) would have to be worse than a purely random classification of order of initiation, which is relatively unlikely given that self-report of use of cannabis and cigarettes has been shown to be valid and better than random assignment of values [163], [195], [196] for cigarette use and [201]–[204] for cannabis use (although limitations of course exist and these measures are imperfect).

In order to have reversed the (descriptive) association observed between age at initiation of cannabis and cigarette smoking categories, the mean age reported should not increase at the same time as the "true" age at initiation of cannabis, which also seems unlikely (i.e., it seems relatively unlikely that self-reported age at initiation would be of such low validity, which would imply that the measure would be as bad as a purely random assignment of values, given that self-reported use of cannabis has been shown to be valid in general [201]–[204], although of course the effect of time since event with regards to age at initiation cannot be discounted). (Appendix 9 provides a review of the literature on telescoping bias and the accuracy of data which involves dating and which is more distant in time. In general this literature did not enable me to draw any conclusions other than that the literature does suggest that accuracy of reporting may diminish according to time since the event.)

Differential misclassification

Finally, differential bias refers to a situation where the misclassification is not independent of other variables. [32], [193] The numbers in our sample suggest a potential association between mother's education with cigarette smoking trajectory, as well as French

language with trajectory, although the relation was not statistically significant in the incident model. (Manuscript 2, Tables 11 and 13) A possible bias therefore, could arise if accuracy of reporting of cigarette smoking (or cannabis use) varied across categories of SES and/or language spoken at home: it has been suggested that prevalence may be higher in Francophones in Canada [205], as well as in individuals with lower SES [206]. Prevalence of use could, in theory, affect social desirability [194] of reporting cigarette smoking.

An important note with regards to cigarette use however, is that the current (strict) laws regarding cigarette smoking in public places were adopted in Quebec in 1998. [207] The NDIT cohort, which began high school in 1999-2000 would therefore have largely spent their adolescence in an environment that had denormalized cigarette smoking. It is therefore worth raising the question of whether there would indeed be considerable differences in social desirability with regards to adolescents' cigarette smoking according to SES, or language. While the familial environment may have been more permissive for lower SES and Francophone individuals, this would likely not have been generalized to all aspects of the tobacco use environment (e.g., peers, school climate and rules regarding cigarette smoking). It is therefore at best unclear to what degree participants with lower SES and/or who were Francophone would have experienced more social desirability to report cigarette smoking. (Cannabis use was illegal in Canada, aside from use for medical use purposes, during the data collection period covered by the NDIT study. (Section 2.3.4.2))

Finally, in order to modify our main conclusions, a differential bias caused by varying degree of social desirability (i.e., with cigarette smoking being more undesirable in participants with higher SES and/or who spoke a language other than French at home) would have to have caused the observed difference of one trajectory of low-level smokers observed in the mixed model of Manuscript 2 vs. two trajectories in the incident model. Such a bias would also have to have caused the differences in associations with risk factors observed when comparing the incident and mixed models (Manuscript 2). This is relatively unlikely because 61.8% of the low-level trajectory in the mixed model were actually incident cigarette smokers (implying that the differences in reporting between incident and prevalent cigarette smokers would have to be major/extreme to spuriously cause these results to be observed).

Sensitivity analyses

I carried out some sensitivity analyses to evaluate the possibility of differential bias according to SES and/or language spoken at home. In Table 22, relevant conclusions are numbered as follows:

1. Manuscript 2: The incident cigarette smoking trajectory model had 2 low-level smoking trajectories, while the mixed trajectory model had one;
2. Manuscript 2: The incident cigarette smoking trajectory model had a different pattern of risk factor associations (both at the level of "estimates"/comparisons of percentages or risk factor values, as well as with regards to statistical significance) than the mixed trajectory model and more factors appeared to be associated with trajectory group(s) in the mixed trajectory model;
3. Manuscript 2: Most cigarette smoking-related outcomes in adulthood (i.e., survey 22) appeared to be associated (both at the level of "estimates"/comparisons of percentages or risk factor values, as well as with regards to statistical significance) with cigarette smoking trajectory group for both the incident and mixed trajectory models;
4. Manuscript 3: Order of initiation of cigarette and cannabis did not appear to be (descriptively) associated with cigarette smoking "category";
5. Manuscript 3: Age at 1st cannabis use did not appear to be (descriptively) associated with cigarette smoking "category".

(Results relating to time elapsed between initiation of the 1st and 2nd substance in Manuscript 3, were of an exploratory nature and sought to determine whether risk factors could be identified. It was always our intention that these results should be confirmed by additional/further study(ies).)

Table 22. Sensitivity analysis results: examination of NDIT data, in relation to possible differential bias according to SES (i.e., mother university educated vs. not)[4] and/or language spoken at home[3], NDIT 1999-2008

Dependent variable	Independent variable	Limited to…?	Results	Details	Relevant to manuscript(s) (conclusion(s) no.[1])
(From Manuscript 3, Table 15) Prevalent cigarette smoker (adolescence) vs. incident and never cigarette smokers (adolescence)	French spoken at home (vs. other language)	No limits	• **Difference in proportion speaking French at home (vs. other language)** when comparing prevalent vs. other cigarette "categories" (i.e., incident and never smokers, adolescence)	• 47.4% (prevalent) • 19.3-36.8% (incident and never smokers)	2 (1 - 3)
(From Manuscript 3, Table 15) Prevalent cigarette smoker (adolescence) vs. incident and never cigarette smokers (adolescence)	Mother university educated (Y/N)	No limits	• **No difference in proportion with mother university-educated** when comparing prevalent vs. other cigarette "categories" (i.e., incident and never smokers, adolescence)	• 35.6% (prevalent) • 0-60.9% (incident and never smokers)	2 (1 - 3)
Past 3-month cigarette smoking	Mother university educated (Y/N)	Baseline ever cigarette smokers (adolescence) (n = 424)	• **No variation in median past 3-month cigarette smoking** according to mother's education **(surveys 1, 2, 10, 11, 18)** • **↑ median past 3-month cigarette smoking** if mother not university educated **(survey 22)**	• None (median value was exactly equal) • No university education median (survey 22) = 0.833 cigarettes per month • University-educated mother median (survey 22) = 1.17 cigarettes per month	2 (1, 2)
Past 3-month cigarette smoking	Mother university educated (Y/N)	Baseline ever cigarette smokers (adolescence) (n = 424)	• **No variation in range of past 3-month cigarette smoking** according to mother's education **(surveys 10, 11, 18)** • **↓ maximum value in range of past 3-month cigarette**	• None (range of values was exactly equal) • Survey 1, mother no university education,	2 (1, 2)

			smoking if mother was university educated **(surveys 1, 2, 22)**	cigarettes per month range = 0 – 720 **(max. average cigarette per day of 24)** • Survey 1, mother university-educated, cigarettes per month range = 0 – 255 **(max. number of average cigarettes per day of 8.5)** • Survey 2, mother no university education, cigarettes per month range = 0 – 900 **(max. average cigarettes per day of 30)** • Survey 2, mother university-educated, cigarettes per month range = 0 – 750 **(max. average cigarettes per day of 25)** • Survey 22, mother no university education, cigarettes per month range = 0 – 900 **(max. average cigarettes per day of 30)** • Survey 22, mother university-educated, cigarettes per month range = 0 – 690 **(max. average cigarettes per day of 23)**	
Past 3-month cigarette smoking	French spoken at home (vs. other language)	Baseline ever cigarette smokers (adolescence) (n = 424)	• **No variation in median past 3-month cigarette smoking** according to language spoken at home **(surveys 10, 11, 18)** • **↑ median past 3-month cigarette smoking** if French spoken at home **(survey 1, 2, 22)**	• None (median value was exactly equal) • French spoken at home median (survey 1) = 0.3333 • Other language spoken at home median (survey 1) = 0 • French spoken at home median (survey 2) = 0.3333	2 (1, 2)

				• Other language spoken at home median (survey 2) = 0 • French spoken at home median (survey 22) = 6.8750 • Other language spoken at home median (survey 22) = 0.5833	
Past 3-month cigarette smoking	French spoken at home (vs. other language)	Baseline ever cigarette smokers (adolescence) (*n* = 424)	• **No variation in range of past 3-month cigarette smoking** according to language spoken at home **(surveys 2, 10, 18, 22)** • **↓ maximum value in range of past 3-month cigarette smoking** if language other than French spoken at home **(surveys 1, 11)**	• None (range of values was exactly equal) • French spoken at home (ranged, survey 1) = 0 – 900 **(max. average cigarettes per day of 30)** • Other language spoken at home (ranged, survey 1) = 0 – 720 **(max. average cigarette per day of 24)** • French spoken at home (ranged, survey 11) = 0 – 540 **(max. average cigarette per day of 18)** • Other language spoken at home (ranged, survey 11) = 0 – 900 **(max. average cigarettes per day of 30)**	2 (1, 2)
Past 3-month cigarette smoking (survey 22)	Mother university educated (Y/N)	No limits	• **No difference in median (range)** of past 3-month cigarette smoking according to mother's education	• Median (range) past 3-month cigarette smoking (survey 22, mother university-educated) = 0 (0 - 900) • Median (range) past 3-month cigarette smoking (survey 22, mother not university-educated) = 0 (0 - 900)	2 (3)
Past 3-month cigarette smoking (survey 22)	French spoken at home (vs. other language)	No limits	• **No difference in median (range)** of past 3-month cigarette smoking according to language spoken at home	• Median (range) past 3-month cigarette smoking (survey 22, French spoken at home) = 0 (0 - 900)	2 (3)

				• Median (range) past 3-month cigarette smoking (survey 22, other language spoken at home) = 0 (0 - 900)	
Mother university educated (Y/N)	Order of initiation of cigarettes and cannabis[2]	No limits	• **% whose mother was not university educated was ↑ (vs. % university educated)**, overall among participants who reported data on age at initiation of both substances	• % mother university-educated = 45.7 • % mother not university-educated = 54.2%	3 (4)
Mother university educated (Y/N)	Order of initiation of cigarettes and cannabis[2]	No limits	• **(Minor) differences in % whose mother was not university educated** when comparing participants who initiated cannabis ≥1 year before cigarettes, vs. both substances the same year, vs. who initiated cigarettes ≥1 year before	• % mother not university-educated (cannabis ⩾1 year before cigarettes) = 53.3% • % mother not university-educated (both substances the same year) = 49.5% • % mother not university-educated (cigarettes ≥1 year before cannabis) = 56.9%	3 (4)
French spoken at home (vs. other language)	Order of initiation of cigarettes and cannabis[2]	No limits	• **% who spoke French at home was ↑ (vs. % other language)**, overall among participants who reported data on age at initiation of both substances	• % who spoke French at home = 35.2% • % who spoke other language at home = 64.8%	3 (4)
French spoken at home (vs. other language)	Order of initiation of cigarettes and cannabis[2]	No limits	• **(Minor) differences in % French spoken at home** when comparing participants who initiated cannabis ≥1 year before cigarettes, vs. both substances the same year, vs. who initiated cigarettes ≥1 year before	• % French spoken at home (cannabis ≥1 year before cigarettes) = 36.2% • % French spoken at home (both substances the same year) = 37.4% • % French spoken at home (cigarettes ≥1 year before cannabis) = 33.9%	3 (4)
Age at 1st cannabis use	Mother university educated (Y/N)	No limits	• **Median (range) for age at 1st cannabis was very similar,** according to mother university educated (vs. not)	• Median (range), mother university-educated = 15.0 (9 - 20) • Median (range), not university-educated = 15.0 (11 - 21)	3 (5)

Age at 1st cannabis use	French spoken at home (vs. other language)	No limits	• **Median (range) for age at 1st cannabis was similar,** according to French spoken at home (vs. other)	• Median (range), French spoken at home = 14.0 (9 - 23) • Median (range), other = 16.0 (10 - 21)	3 (5)

[1]The conclusions are numbered as in page 149 just above.
[2]Was cigarettes initiated ≥1 year before cannabis, both substances initiated same year, cannabis initiated ≥1 year before cigarettes.
[3]Language spoken at home was measured at baseline.
[4]Mother university-educated was created by combining information obtained at surveys 13 and 17 with maternal questionnaires, in order to maximize response rate for this variable.
Y: yes. N: no. ↑: increased. ↓: decreased.

Conclusions based on Table 22

One potential effect of underreporting according to SES would be to cause underreporting of more extreme values of cigarette smoking in the higher SES group, relative to the lower SES group. If this had caused major restrictions of the range in prevalent/baseline ever cigarette smokers, the possibility exists that our findings of differences in Manuscript 2 with regards to trajectory models and risk factor profiles could have been affected. This did not appear to be the case in our data however, for while there were some surveys where the range was restricted in the higher SES group, the range of values in the higher SES group was in most cases still wide (with the single exception being survey 1 where range for low SES indicated an average for the most extreme values of 8.5 cigs/day). The median values between both groups were in all cases either quite similar or identical.

A similar conclusion can be drawn, based on the above data, for language spoken at home (i.e., regarding the hypothesis that underreporting according to language spoken at home could have caused underreporting of more extreme values of cigarette smoking in the group which spoke language(s) other than French at home), as the medians and ranges did not differ to any great extent between the two groups (i.e., French spoken at home vs. other language).

Another potential effect of SES and/or language spoken at home could have been to cause underreporting of more extreme values of cigarette smoking in the higher SES/other language(s) spoken at home for the cigarette-smoking outcomes at survey 22. While it is unclear what effect(s) this could have had on observed associations had this been the case, the data presented in Table 22 for past 3-month cigarette smoking suggests that this was not an issue in our data.

Order of initiation of cigarette smoking and cannabis use did not appear (descriptively) to vary according to SES or to language spoken at home. The proportion of participants reporting data on initiation of both substances (and therefore having ever used both substances) was higher in the lower SES/mother not university educated group, as well as in the group which spoke French at home. Further examination of the data, however, did not support the assertion that this could have affected our results and that SES and/or language spoken at home obscured an existing association between order of initiation and cigarette smoking category (i.e.,

"trajectory"). Indeed, the proportion of participants whose mother did not have any university education, and the proportion of participants who reported speaking French at home, did not vary appreciably according to order of initiation. If order of initiation was in fact associated with cigarette smoking category in Manuscript 3, and this was obscured by differential reporting across SES and/or language spoken at home, there should be an association with both exposure (i.e., order of initiation) and outcome (i.e., cigarette category). Since this does not appear to be the case in our data with regards to the exposure, such a bias appears unlikely. A similar conclusion can be drawn for age at 1st use of cannabis according to cigarette smoking category, as median and range of age at 1st cannabis did not appear to vary according to mother's education or language spoken at home in our data.

8.3.2.2 Selection bias

The participation rate at baseline was low in the NDIT study (i.e., 56% of eligible participants). Participants however appeared to be representative of the Quebec population (with the notable exception of the % who spoke French at home), as evidenced by a comparison of many variables between NDIT and data from 13 year-olds in the Quebec Child and Adolescent Health and Social Survey (QCAHSS) [148], a representative sample of Quebec youth carried out in 1999. (Table 9)

Losses to follow-up

Trajectories (Manuscripts 2 and 3): The trajectories should be more affected by losses to follow-up over time (i.e., from left to right along the time axis) in the figures presenting the trajectories, since in both models (i.e., incident and mixed) the losses to follow-up would increase over time. (This is the case in both the mixed trajectory model where the time axis corresponds to the median of the participants' age, as well as in the incident model. This would be the case since being able to progress further from cigarette smoking initiation in the incident model requires longer follow-up/observation.) This implies that the figures representing the cigarette smoking trajectories would be more vulnerable the effects of losses to follow-up for time points further to the right on the time axes of both models. Losses to follow-up could affect the right side/end of trajectories if participants lost to follow-up differ systematically from those included with regards to the progression of their cigarette smoking habit (i.e., if those

excluded/lost had individual trajectories which differed from those who were included). The trajectories could also be modified if losses to follow-up at the ends of the trajectories resulted in changes in the overall appearance of the trajectories. We did however attempt to minimize the effect of losses on the trajectories by limiting the modeling to the first 16 data points in both the incident and mixed trajectory models (i.e., the last 4 data points in both models were therefore excluded from our models). This corresponds to the first 16 surveys for the mixed trajectory model, and to the first 16 time points after cigarette smoking initiation in the incident trajectory model.

Risk factors (Manuscript 2): Our conclusions include that several risk factors appeared to be associated with cigarette smoking trajectory group in the mixed model which were not associated with trajectory group in the incident model. In order to modify this conclusion, losses to follow-up would have to have affected many associations, which makes such a possibility less likely. Additionally, measurement of most risk factors was carried out prior to or at cigarette smoking initiation (incident model) or at baseline (mixed trajectory model). It is therefore unlikely that their measurement would have been greatly affected by losses to follow-up.

Cigarette smoking outcomes (Manuscript 2): Our conclusions state that the majority of cigarette smoking-related outcomes in survey 22 appeared to be associated with cigarette smoking trajectory group (both models). In order to have modified this conclusion, any losses to follow-up would again have to have acted on a pattern of associations involving several variables, rather than a single association. In addition, in young adulthood we attempted to recontact all participants who had been lost to follow-up during high school (mostly, this occurred because of participants changing schools or leaving school). [171], [208]

Manuscript 3: We modeled the incident cigarette smoking trajectories in the same way as in article 2, in order to minimize the effect of losses to follow-up on the trajectories. In addition, the losses to follow-up probably did not greatly affect the other three groups compared (which were not part of manuscript 2):

1. The prevalent smokers were defined by their cigarette smoking behavior when they entered the study (therefore none in this group were excluded, aside from those who had missing information for other variables such as cannabis use in cycle 21);

2. The “never smokers” had never smoked at baseline and maintained this status during their subsequent participation (adolescence): the median and the 75th percentile for the number of cycles of data available for the questions on cigarette smoking in high school (i.e., for the first 20 surveys) were both equal to 19 (only n = 12 participants in this group had <3 data points for cigarette smoking during high school/adolescence);
3. Incident cigarette smokers who quit shortly after initiation (n = 66) had never smoked when they entered the study but reported having subsequently initiated and did not smoke post initiation. None of these incident smokers had <3 surveys of data in high school after cigarette smoking initiation. The median number of surveys available for these participants, post initiation (high school), was 11 while the 75th percentile was 14 surveys.

Overall it can therefore be concluded that the losses to follow-up probably had a minimal effect on the observation of smoking behavior in these groups.

With regards to the information on cannabis in Manuscript 3, efforts were made to minimize losses to follow-up in our study. In adulthood (i.e., when the cannabis use data were obtained) efforts were made to contact all participants who were lost to follow-up during high school but who had not refused participation. Participation was therefore slightly higher at survey 21 in young adulthood where cannabis information was obtained, than at the end of secondary school (i.e., 68% participation in survey 21 vs. 65% in survey 20/end of high school). [145]

The main conclusions of Manuscript 3 were as follows.

1. That some of the participants initiated cannabis before cigarette smoking in most cigarette categories, and that initiation order did not appear to be related to the cigarette smoking category;
2. That proportion of ever use was (in most cases) higher and that age at 1st cannabis use was lower, in the cigarette smoking categories who had a heavier use during adolescence.

In order to modify these conclusions, the losses in follow-up would have had to not only simultaneously affect the initiation and/or use reported for cannabis and cigarettes, but to have

affected these differently depending on the cigarette smoking trajectory. This appears relatively unlikely. Furthermore, although the literature suggests that the use of each both substances may be associated with leaving school (i.e., dropping out of school) [209] it is not clear that this association exists for the act of changing from one school to another, which was an important reason for the loss of follow-up for many of our participants. [145]

Is selection bias likely?

In addition to potential losses to follow-up, various exclusions were applied to generate the analytical samples for the various analyses. Analyses are presented relating to Manuscripts 2 and 3 (Manuscript 2 and Appendices 4-8), which do suggest that certain differences exist between included and excluded participants. It is however unlikely that the results relating to the modeling of trajectories (e.g., the number and shape of the trajectories) were subject to selection bias. It is clear that the exclusion of certain types of participants caused certain differences between the subjects included and excluded from the model of incident trajectories as well as that of mixed trajectories (Tables 32 and 33) and that the analytical samples were not representative of the initial sample. The trajectories obtained, as well as the percentages of subjects in each trajectory, may not be fully representative (see Figure 9 of Appendix 4) of the trajectories that would be found in the study population [210] of the same age. An unrepresentative sample is not necessarily, however, a biased sample. Furthermore, the vast majority of excluded participants were excluded because they had never smoked in adolescence (n = 454) or because they had already tried to smoke prior to study baseline (see Figure 9 of Appendix 4). It is likely that the inclusion of the n = 454 participants who were never cigarette smokers during adolescence would not have changed the trajectories obtained: rather, it would most likely have simply added an additional trajectory of non-use to the trajectory models. In addition, the effect(s) of excluding baseline ever cigarette smokers was studied in Manuscript 2 and was therefore not a source of bias but rather a central topic of the manuscript (Manuscript 2, comparisons of incident and mixed models).

<u>Manuscript 2:</u>

Finally, an important difference between the two incident and mixed trajectory models (Manuscript 2) was the presence of two distinct groups of light cigarette smokers in the incident

model (vs. only one in the mixed model). The two low-level incident trajectories included 37.5% and 45.6% of the analytical sample, while the single low-level trajectory in the mixed model included 56.4% of the analytical sample. In order for this difference between the two models to be the result of missing data/exclusions, most or all of those excluded would have to be light smokers different from the light cigarette smokers included in the two models, and this difference would need to be able to create a difference between the two models where no difference would otherwise exist. This would mean that the fact of combining the excluded light smokers with the included light smokers would have to result in an absence of observed difference(s) between the trajectories obtained in the two models. This would be possible if the prevalent light smokers excluded were sufficiently different from the included prevalent cigarette smokers with regards to their cigarette smoking trajectories, to result in a second decreasing trajectory in the mixed model when they were included. Alternatively, the inclusion of excluded incident light cigarette smokers could result in a single trajectory being observed in the incident model. In general, both of these possibilities appear unlikely as (see above) a majority of smokers in the light trajectories in the mixed model were incident smokers. Any differences between excluded and included smokers would therefore have to be of considerable magnitude.

Some of the associations between trajectory group(s) and potential risk factors and outcomes could have been susceptible to selection bias. However, it is less likely that such a bias would have affected all of the associations tested. It is important to note that in our analyses we were more interested in the potential differences in the patterns of associations identified between the two types of trajectories (i.e., the incident vs. the mixed trajectories) as a whole, than in the association of a specific measure with one or several trajectory group(s). It is therefore relatively unlikely that our main results (i.e., of differences in the overall risk factor profiles between the two models) would have been greatly affected by a selection bias resulting from the exclusions carried out to generate our analytical sample. Additionally, a careful examination of the different proportions and other measures between trajectory groups in both models (without considering statistical significance which can be affected by sample size) suggests that patterns of associations do indeed differ between both models. Indeed, these values support the assertion that (aside from sex, age, and MVPA) smoking-related factors were the

only factors which appeared to be associated with the incident trajectories, whereas additional associations (judging only by values of proportions of participants and other values/point estimates) are likely to be present in the mixed trajectory model. With regards to trajectory outcomes, another important conclusion of both models in Manuscript 2 was that any increase in smoking appeared to increase the risk of later heavier smoking as well as nicotine dependence. In order for this conclusion to be significantly biased, our exclusions would have had to bias the vast majority of associations observed between cigarette outcomes and trajectory groups in order to significantly modify our results.

Manuscript 3: Unlike Manuscript 2, most NDIT study participants were included in Manuscript 3. Indeed, apart from the process of modeling incident trajectories in the same way as described in Manuscript 2 (as well as the exploratory analyses relating to time elapsed between initiation of the first and second substance), never cigarette smokers during adolescence (n = 454) were compared with other participants. Also compared with others in our analyses were participants who had already tried smoking at baseline (n = 424) and a third group of individuals who were incident smokers but who were excluded from the modeling of incident trajectories in Manuscript 2 (n = 66). (The only exception to this was with regards to the models of time elapsed between primo-initiation of cannabis and secondary initiation of cigarettes and models of the time elapsed between primo-initiation of cigarettes and secondary initiation of cannabis. These particular results should therefore be considered with caution and would require confirmation by additional studies.) Therefore with regards to most of our results in Manuscript 3, selection bias as a result of exclusions to generate our analytical samples was relatively unlikely.

8.3.2.3 Confounding

Confounding (please refer to the beginning of section 8.3.2 for a definition of this concept) could have resulted in biased measures of association: we did not control for confounding in our analyses, so this possibility must be considered. Time-varying confounding may also have affected the observed cigarette smoking trajectories differently across time. The emphasis of the current thesis was however descriptive: can trajectories of cigarette smoking inform about cigarette smoking onset? We sought to determine whether the usefulness of

adolescent cigarette smoking trajectories to public health can be clearly and easily ascertained, or whether further study is required. Is there any suggestion of a potential role of cannabis use on these trajectories (i.e., so as to determine the potential importance of the use of a substance frequently used by adolescents and young adults on cigarette smoking trajectories)?

Trajectories

It is possible that the cigarette smoking trajectories would have been modified by not considering the effects variables that could modify the trajectories (i.e., confounding or effect modification of the trajectories). (It should be noted that when discussing 'warping' of the observed trajectories in manuscripts 2 and 3, I am emphasizing the fact that this phenomenon may result from either: (i) confounding bias of the estimated effect of a given variable/exposure such as SES or impulsivity on the 'outcome' of cigarette an outcome due to the presence of common causes of the exposure and the outcome), or (ii) effect modification of the trajectories where a given variable/effect modifier acts on the 'outcome' of cigarette smoking such that trajectories differ at different levels of the effect modifier.) These confounding or modifying factors could have affected the trajectories in a constant or variable way over time (i.e., time-dependent confounding or effect modification). An example would be the co-use of substances such as cannabis (as use of tobacco and cannabis are associated appears to co-occur [67]): it would certainly be possible for cannabis use to modify the observed trajectories. (The existence of bias may however not applicable to the context of modeling of trajectories: such a consideration requires the existence of "real" trajectories, against which we can compare the trajectories obtained. However some researchers have raised doubts regarding the existence of "true" trajectories.[185])

Manuscript 2

In order to modify our main conclusion that adolescent cigarette smoking trajectories differed between the incident model and the prevalent models, the variable (s) responsible for the confounding or effect modification of the trajectories (please refer to the paragraph above for why these terms are used together in this instance) would have to have resulted in the differences that we observed between the two models. In other words, any such variable(s) would have to have resulted in the observation of two trajectories of light smokers in the incident

model vs. only one in the mixed model. This possibility is made not very likely as a result of the fact that the trajectories of light smokers were by far the largest in our analytical sample such that any "bias" or differences resulting in the observed differences between the incident and mixed models, both as a result of random variation due to sampling error at the level of a potential confounder or effect modifier and at the level of a systematic error, would need to be both relatively large and widespread in our sample. One important difference between the two models was the presence of the trajectories of light cigarette smokers in the incident model, whereas a single such trajectory was observed in the mixed trajectory model. Again, it is important to note that 61.8% of the participants included in the light smoker trajectory in the mixed trajectory model were in fact incident cigarette smokers, which further emphasizes the fact that any difference between the two groups with regards to confounders or effect modifiers would need to be large. The possibility of confounding or effect modification of our results cannot be entirely excluded however and a next step following the current work would be to model cigarette smoking trajectories in adolescents while controlling for variables which could potentially confound or modify the observed trajectories.

With regards to our conclusion that the incident and the mixed models had differing sets of risk factor associations, any potential confounding biases would have to affect associations with several or all of these variables simultaneously in order to change our main conclusions. This is therefore relatively unlikely, partly because this would involve such potential confounder(s) biasing not one but many observed associations. (The same argument can be applied to the observed associations with cigarette-related outcomes in survey 22.)

Manuscript 3

Our main conclusions were that:

1. Some of the participants initiated cannabis before smoking in most cigarette smoking categories and that the initiation order did not appear to be related to cigarette smoking category;
2. Ever use of cannabis was in most cases higher and age at 1st use of cannabis was lower in the cigarette smoking categories who had a heavier tobacco use during adolescence.

With regards to the results relating to the order of initiation in relation to cigarette smoking category (conclusion 1 above) the question to ask would be: could the lack of observed association have been induced by confounding bias? This would be possible if the associations between a potential confounder with the order of initiation of cannabis, and between this potential confounder and cigarette use category were essentially opposite to the (hypothetical) association that would actually exist between the order of initiation of cannabis and tobacco and the smoking categories. Therefore the two associations (i.e., one with the confounding factor and the second between order of initiation and the cigarette smoking category) would have an essentially opposite effect: this appears unlikely, however (as a completely opposite trend with caused by the confounder, when compared to the "true" trend, is a rather extreme scenario).

In order to modify the second conclusion, a potential confounder would need to affect the (potential, given the descriptive nature of our results) association between age at initiation and/or ever use of cannabis and the cigarette smoking categories. This would have to happen in such a way as to cause a (spurious) association to be observed between the extent of cigarette smoking (determined by smoking category) and age at initiation or ever cannabis use. This would be possible and constitutes a significant limitation of the results presented in this manuscript: a variable associated with initiation and/or ever use of cannabis as well as with cigarette smoking category trajectory could affect the associations observed. This limitation is discussed below.

As a sensitivity analysis, a small number of additional models were carried out, modeling a (restricted) list of potential confounders. In particular, the possibility that heavier cigarette users represent a "vulnerable" population for substance use in general raises the possibility that personality variables may be associated with both cannabis initiation and cigarette use. For example, both novelty seeking and impulsivity have been linked with cannabis [211], [212] and cigarette use [213], [214]. An association in the reverse direction has also been extensively discussed: cannabis use may also cause increased impulsivity. [215] (Given the fact that the direction of association and potential causality is unclear, I ran models with and without these variables.) Finally, it is important to note that impulsivity and novelty seeking were strongly correlated ($r = 0.72$, $p < 0.0001$). In a model an ordinal logistic regression model of cigarette smoking category (dependent variable) according to age at 1st cannabis use (independent

variable), controlling only for age and sex at baseline, the OR obtained for age at 1st use of cannabis was OR = 0.62 (0.56, 0.67), which again suggested that increasing age at 1st cannabis use reduced the risk of being in a cigarette category with heavier smoking. Controlling for either impulsivity, novelty seeking, or both simultaneously did not change this result: OR = 0.61 (0.55, 0.67), OR = 0.61 (0.55, 0.67), OR = 0.61 (0.55, 0.67), respectively. It is however important to note that these results did not include a complete/exhaustive list of potential confounders of this association.

It is possible that the risk factors associated with the time elapsed between the initiation of cannabis and smoking may be subject to confounding bias. This constitutes an important limitation of these analyses, and our analyses in relation to time elapsed between initiation of the first and second substance should be seen as exploratory.

8.3.2.4 Additional issues

Manuscript 2: Differences in risk factor and outcome analyses between incident and mixed trajectory models

A further difference between the incident and mixed trajectory models resides in the fact that, due to the small number of participants in the heaviest smoking group in the incident model, this group was excluded from risk factor comparisons. It should be noted that, given its small size, including it in risk factor comparisons would probably not have resulted in more significant risk factors (incident model). Furthermore, when the actual risk factor values for this group are contrasted with those of the other groups of the incident trajectory model, these values suggest that the inclusion of this group (small group size aside) would likely not have resulted in any appreciable difference in our overall conclusion that the incident and mixed trajectory models had differing patterns of risk factors.

An important additional point is that analyses relating to the incident model had in fact a different objective than those relating to the mixed model. The incident model (as well as its risk factors and outcomes) refers to new smokers, while the mixed analyses refer to all individuals who were cigarette smokers during a given period, divided by all individuals at risk of smoking during that same period. [32] In other terms, “prevalent” cigarette smokers will be those who initiated smoking prior to the study baseline. The mixed trajectory models were of

the prevalence of smoking at different points in the study, combining incident and prevalent smokers at each point on the time axis (we used calendar time as the time axis for these models). Incident models model smokers' journey from initiation (i.e., the time axis was time from smoking initiation/first puff lifetime), so time zero will actually correspond to several different calendar time values. Therefore these analyses differed not only in terms of the individuals included but in a fundamental and conceptual way, and it is important to note that the exclusion of baseline ever smokers/prevalent smokers is not a limitation, as it enabled us to focus on modeling the onset of individuals who had been observed at smoking onset.

Clustering by school

One potential additional issue was the potential clustering of data by school in NDIT. As a sensitivity analysis, we calculated the intracluster correlation coefficient (ICC_2), which is a measure of the relatedness of clustered data, and is calculated by comparing the variance within clusters with the variance between clusters. ICC_2 was calculated using SAS proc mixed. [166], [173]–[175]

Clustering, when ignored, can reduce the observed variance and thereby affect inference but should not affect point estimates. [175] Our analyses relating to order of initiation of cigarettes and cannabis and to age at cannabis initiation according to cigarette smoking category (Manuscript 3) were descriptive and therefore the "point estimates" involving the comparisons of sample measures across categories should not be greatly affected. The same justification can be provided for not adjusting for clustering in Manuscript 2: while the confidence intervals around the trajectories may be affected, this should not affect the estimate of the trajectories themselves, which represent "point estimates". In a similar vein, this should not unduly affect the observed pattern of associations with risk factors and outcomes in Manuscript 2 (i.e., which differed between the incident and the mixed models) given that these association patterns are supported by the value of the "point estimates" (i.e., the comparisons of proportions and other variable values discussed in Manuscript 2 and section 8.1.2).

The ICC_2 values obtained for the school effect were as follows. At baseline (more specifically, baseline at surveys 1 and 2, the first available value was used), ICC_2 was 4.4% for number of cigarettes smoked per month (3-month recall). Therefore at baseline, 4.4% of the

variance in this variable was due to clustering. At survey 18, ICC_2 was 2.7% and was 2.2% in adulthood (i.e., at survey 22). For age at 1st cannabis, ICC^2 was 5.6%. This implies that most of the variance observed in our data was not a result of systematic differences between clusters (i.e., schools). [175]

We also used multilevel modeling to account for the clustering effect by school in certain analyses (i.e., the analyses of time elapsed between cigarette and cannabis initiation among cigarette primo-initiators). We modeled the only significant variable in the models presented in Tables 20 and 21 (i.e., age at baseline among cigarette primo-initiators). The results of this model suggests that the effect of age at baseline on time elapsed between cigarette and cannabis (among cigarette primo-initiators) was not due to clustering. The beta coefficient obtained was -0.083 (exp(-0.083) = 0.920) suggested that a one year increase in age at baseline was associated with the addition of +0.920 years to the time elapsed between cigarette and cannabis initiation (result was also statistically significant).

Chapter 9 - Conclusion

Cigarette smoking in adolescence and young adulthood is of crucial importance to public health, as the vast majority of smokers report adopting the habit in adolescence or young adulthood. [10] Reaching an understanding of how and why youth smoke cigarettes is therefore of critical importance to public health, given that many youth still smoke. [9] Developmental trajectories provide a description of change (usually in a behavior or characteristic of an individual) over a long time-period. [23] Trajectories of cigarette smoking can be modeled using software packages such as Mplus [216] or Proc Traj [217]; these serve to describe the data succinctly and accessibly to researchers in the area of youth cigarette smoking and may provide insight into the developmental process that is the onset of cigarette smoking.

Despite their potential usefulness to public health our results have however raised several questions as to the usefulness of cigarette smoking trajectories to public health. In particular, it is currently unclear whether modeling cigarette smoking trajectories provides additional useful information beyond that provided by research which does not make use of this method. Given that this approach necessitates the availability of longitudinal data, its use may also prove unduly costly and labor intensive.

Several issues were raised with regards to cigarette smoking trajectories which suggest the need for further study: in particular, the lack of studies of incident cigarette smoking trajectories, which would present the clearest picture of the natural course of cigarette smoking; the methodological heterogeneity of the studies in this area and the missing information regarding final trajectory model selection which complicated the process of summarizing this literature; and the fact that few researchers considered the idea of potential time windows for intervention. We have provided four suggestions for future research in this area. (Section 8.1.4)

Our analysis of a cohort of adolescents support the conclusions of our literature review. This analysis also suggests that incident and mixed trajectory analyses yield trajectories that differ from each other, with the rate of change in the mixed trajectories being generally attenuated across the curves in comparison to the mixed trajectory model. Additionally, we noted that the curve at cigarette smoking onset was steeper in the heaviest cigarette smokers in the incident model than the mixed model, suggesting that any window of intervention opportunity for preventing escalation in cigarette consumption is not as wide as the literature, which consists mainly of mixed trajectory models of cigarette smoking, would suggest.

Our results also suggest that considering the research question is important when deciding whether to model incident or prevalent (i.e., mixed) cigarette smoking, notably since our results suggest important differences in both trajectories and risk factor profiles associated with trajectories between both types of model. Both models did appear to discriminate between higher and lower risk cigarette smoking however, underscoring the (potential) usefulness of this approach, as suggested by the fact that both models were associated with several cigarette smoking related outcomes in young adulthood.

Finally, we have shown that cannabis and cigarette initiation and cigarette use trajectories are interrelated in youth, in ways which are not made manifest by modeling cigarette smoking trajectories alone. Our results also suggest that some individuals may be at higher risk of heavier substance use and other negative outcomes and may require intervention specific to their needs. These results emphasize the importance of situating the use of one substance (in this case, cigarette smoking depicted using trajectory modeling) in the wider context of use with other substances.

The results of this thesis therefore provide valuable insight, by raising questions about a popular and frequently used approach to the study of adolescent cigarette smoking and providing suggestions for future research in this area.

References

[1] World Health Organization, "Tobacco. Key facts.," *27 May*, 2020. http://www.who.int/mediacentre/factsheets/fs339/en/ (accessed Aug. 21, 2020).

[2] U.S. Department of Health and Human Services, "How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA," 2010. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK53013/.

[3] Centers for Disease Control and Prevention (US), "Smoking is down, but almost 38 million American adults still smoke," 2018. https://www.cdc.gov/media/releases/2018/p0118-smoking-rates-declining.html (accessed May 22, 2020).

[4] University of Waterloo, "Tobacco use in Canada. Historical trends in smoking prevalence. 1965-2017," 2020. https://uwaterloo.ca/tobacco-use-canada/adult-tobacco-use/smoking-canada/historical-trends-smoking-prevalence (accessed May 22, 2020).

[5] University of Waterloo, "Tobacco use in Canada. Current smoking. 2017," 2020. https://uwaterloo.ca/tobacco-use-canada/youth-tobacco-use/current-smoking (accessed May 22, 2020).

[6] R. Reid, D. Hammond, V. L. Rynard, C. L. Madill, and B. R, "Reid JL, Hammond D, Rynard VL, Madill CL, Burkhalter R. Tobacco Use in Canada: Patterns and Trends, 2017 Edition. Waterloo, ON: Propel Centre for Population Health Impact, University of Waterloo.," 2017. [Online]. Available: https://uwaterloo.ca/tobacco-use-canada/sites/ca.tobacco-use-canada/files/uploads/files/2017_tobaccouseincanada_final_0.pdf.

[7] University of Waterloo, "Tobacco Use in Canada. Smoking in the provinces. Smoking prevalence by province. (2017)," 2017. https://uwaterloo.ca/tobacco-use-canada/adult-tobacco-use/smoking-provinces (accessed May 25, 2020).

[8] Government of Canada, "Canadian Tobacco, Alcohol and Drugs Survey (CTADS): 2017

definitions," 2017. https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2017-summary/2017-definitions.html (accessed May 25, 2020).

[9] University of Waterloo, "Tobacco Use in Canada. Smoking prevalence by age. 2016-2017," 2020. https://uwaterloo.ca/tobacco-use-canada/youth-tobacco-use/current-smoking/smoking-prevalence/smoking-prevalence-age (accessed May 22, 2020).

[10] J. E. Schulenberg, L. D. Johnston, P. M. O'Malley, J. G. Bachman, R. A. Miech, and M. E. Patrick, "Monitoring the Future national survey results on drug use, 1975–2019: Volume II, College students and adults ages 19–60. Ann Arbor: Institute for S," 2020. [Online]. Available: http://monitoringthefuture.org/pubs.html#monographs.

[11] U.S. Department of Health and Human Services, "Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta, GA," 2012. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK99237/.

[12] J. L. O'Loughlin, E. N. Dugas, E. K. O'Loughlin, I. Karp, and M.-P. Sylvestre, "Incidence and determinants of cigarette smoking initiation in young adults.," *J. Adolesc. Heal.*, vol. 54, no. 1, pp. 26–32, Jan. 2014, doi: 10.1016/j.jadohealth.2013.07.009.

[13] C. L. Perry *et al.*, "Youth or Young Adults: Which Group Is at Highest Risk for Tobacco Use Onset?," *J. Adolesc. Heal.*, vol. 63, no. 4, pp. 413–420, 2018, doi: 10.1016/j.jadohealth.2018.04.011.

[14] B. L. Jones, D. S. Nagin, and K. Roeder, "A SAS procedure based on mixture models for estimating developmental trajectories," *Sociol. Methods Res.*, vol. 29, no. 3, pp. 374–393, 2001, doi: 10.1177/0049124101029003005.

[15] A. M. Haviland, B. L. Jones, and D. S. Nagin, "Group-based trajectory modeling extended to account for nonrandom participant attrition.," *Sociol. Methods Res.*, vol. 40, no. 2, pp. 367–390, 2011, doi: 10.1177/0049124111400041.

[16] D. S. Nagin, *Group-based modeling of development.* Cambridge, Massachusetts: Harvard University Press, 2005.

[17] U.S. Department of Health and Human Services, "Preventing Tobacco Use Among Young People: A Report of the Surgeon General. Atlanta, Georgia," 1994.

[18] J. O'Loughlin, A. Gervais, E. Dugas, and G. Meshefedjian, "Milestones in the process of cessation among novice adolescent smokers," *Am. J. Public Health*, vol. 99, no. 3, pp. 499–504, 2009, doi: 10.2105/AJPH.2007.128629.

[19] A. Gervais, J. O'Loughlin, G. Meshefedjian, C. Bancej, and M. Tremblay, "Milestones in the natural course of onset of cigarette use among adolescents," *CMAJ*, vol. 175, no. 3, pp. 255–261, 2006, doi: 10.1503/cmaj.051235.

[20] R. J. Wellman *et al.*, "Predictors of the Onset of Cigarette Smoking: A Systematic Review of Longitudinal Population-Based Studies in Youth," *Am. J. Prev. Med.*, vol. 51, no. 5, pp. 767–778, 2016, doi: 10.1016/j.amepre.2016.04.003.

[21] J. O'Loughlin, I. Karp, T. Koulis, G. Paradis, and J. DiFranza, "Determinants of first puff and daily cigarette smoking in adolescents," *Am. J. Epidemiol.*, vol. 170, no. 5, pp. 585–597, 2009, doi: 10.1093/aje/kwp179.

[22] M. E. Roberts, S. M. Colby, and K. M. Jackson, "What predicts early smoking milestones?," *J. Stud. Alcohol Drugs*, vol. 76, no. 2, pp. 256–266, 2015, doi: 10.15288/jsad.2015.76.256.

[23] D. S. Nagin and R. E. Tremblay, "Developmental trajectory groups: Fact or a useful statistical fiction?," *Criminology*, vol. 43, no. 4, pp. 873–904, 2005, doi: 10.1111/j.1745-9125.2005.00026.x.

[24] D. S. Nagin, "Analyzing developmental trajectories: A semiparametric, group-based approach," *Psychol. Methods*, vol. 4, no. 2, pp. 139–157, 1999, doi: 10.1037//1082-989x.4.2.139.

[25] K. J. Grimm and K. F. Widaman, "Residual structures in latent growth curve modeling," *Struct. Equ. Model.*, vol. 17, pp. 424–442, 2010, doi: 10.1080/10705511.2010.489006.

[26] T. E. Duncan and S. C. Duncan, "An introduction to latent growth curve modeling," *Behav. Ther.*, vol. 35, pp. 333–363, 2004, doi: 10.1016/S0005-7894(04)80042-X.

[27] C. Mathur, D. J. Erickson, M. H. Stigler, J. L. Forster, and J. R. J. Finnegan, "Individual and neighborhood socioeconomic status effects on adolescent smoking: a multilevel cohort-sequential latent growth analysis.," *Am. J. Public Health*, vol. 103, no. 3, pp. 543–

548, Mar. 2013, doi: 10.2105/AJPH.2012.300830.

[28] A. L. Roberts, S. Galea, S. B. Austin, H. L. Corliss, M. A. Williams, and K. C. Koenen, "Women's experience of abuse in childhood and their children's smoking and overweight," *Am. J. Prev. Med.*, vol. 46, no. 3, pp. 249–258, 2014, doi: 10.1016/j.amepre.2013.11.012.

[29] M. Windle and R. C. Windle, "Depressive Symptoms and Cigarette Smoking Among Middle Adolescents: Prospective Associations and Intrapersonal and Interpersonal Influences," *J. Consult. Clin. Psychol.*, vol. 69, no. 2, pp. 215–226, 2001, doi: 10.1037//0022-006X.69.2.215.

[30] I. Karp, J. O'Loughlin, G. Paradis, J. Hanley, and J. Difranza, "Smoking trajectories of adolescent novice smokers in a longitudinal study of tobacco use," *Ann. Epidemiol.*, vol. 15, pp. 445–452, 2005, doi: 10.1016/j.annepidem.2004.10.002.

[31] K. I. Rosendahl, M. Rosaria Galanti, and H. Gilljam, "Trajectories of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents: Differences and implications," *Nicotine Tob. Res.*, vol. 10, no. 6, pp. 1021–1027, 2008, doi: 10.1080/14622200802097522.

[32] M. Porta, *A Dictionary of Epidemiology.*, 5th ed. Oxford, 2008.

[33] R. van de Schoot, "Latent trajectory studies: the basics, how to interpret the results, and what to report.," *Eur. J. Psychotraumatol.*, vol. 6, p. 27514, 2015, doi: 10.3402/ejpt.v6.27514.

[34] R. van de Schoot, M. Sijbrandij, S. D. Winter, S. Depaoli, and J. K. Vermunt, "The GRoLTS-Checklist: Guidelines for Reporting on Latent Trajectory Studies," *Struct. Equ. Model.*, vol. 24, no. 3, pp. 451–467, 2017, doi: 10.1080/10705511.2016.1247646.

[35] The British Psychological Society, "The British Psychological Society. The Psychologist. The Delphi Method," 2009. https://thepsychologist.bps.org.uk/volume-22/edition-7/delphi-method (accessed May 22, 2020).

[36] S. E. Hampson, E. Tildesley, J. A. Andrews, M. Barckley, and M. Peterson, "Smoking trajectories across high school: Sensation seeking and hookah use," *Nicotine Tob. Res.*,

vol. 15, no. 8, pp. 1400–1408, 2013, doi: 10.1093/ntr/nts338.

[37] S. D. Lynne-Landsman, C. P. Bradshaw, and N. S. Ialongo, "Testing a developmental cascade model of adolescent substance use trajectories and young adult adjustment," *Dev. Psychopathol.*, vol. 22, no. 4, pp. 933–948, 2010, doi: 10.1017/S0954579410000556.

[38] J. K. Vermunt, "Latent class modeling with covariates: Two improved three-step approaches," *Polit. Anal.*, vol. 18, no. 4, pp. 450–469, 2010, doi: 10.1093/pan/mpq025.

[39] J. Guo, I.-J. Chung, K. G. Hill, J. D. Hawkins, R. F. Catalano, and R. D. Abbott, "Developmental Relationships Between Adolescent Substance Use and Risky Sexual Behavior in Young Adulthood," *J. Adolesc. Heal.*, vol. 31, no. 4, pp. 354–362, 2002.

[40] S. E. Nelson, M. J. Van Ryzin, and T. J. Dishion, "Alcohol, marijuana, and tobacco use trajectories from age 12 to 24 years: Demographic correlates and young adult substance use problems," *Dev. Psychopathol.*, vol. 27, no. 1, pp. 253–277, 2015, doi: 10.1017/S0954579414000650.

[41] R. de Leeuw, R. Scholte, A. Vermulst, and R. Engels, "The relation between smoking-specific parenting and smoking trajectories of adolescents: How are changes in parenting related to changes in smoking?," *Psychol. Health*, vol. 25, no. 8, pp. 999–1021, 2010, doi: 10.1080/08870440903477204.

[42] T. S. Schepis and U. Rao, "Epidemiology and etiology of adolescent smoking," *Curr. Opin. Pediatr.*, vol. 17, no. 5, pp. 607–612, 2005, doi: 10.1097/01.mop.0000176442.49743.31.

[43] G. L. Schauer and E. N. Peters, "Correlates and trends in youth co-use of marijuana and tobacco in the United States, 2005–2014," *Drug Alcohol Depend.*, vol. 185, pp. 238–244, 2018, doi: 10.1016/j.drugalcdep.2017.12.007.

[44] R. E. Bélanger, C. Akre, E. Kuntsche, and G. Gmel, "Adding Tobacco to Cannabis—Its Frequency and Likely Implications," *Nicotine Tob. Res.*, vol. 13, no. 8, pp. 746–750, 2011, doi: 10.1093/ntr/ntr043.

[45] G. L. Schauer, Z. R. Rosenberry, and E. N. Peters, "Marijuana and tobacco co-administration in blunts, spliffs, and mulled cigarettes: A systematic literature review,"

Addict. Behav., vol. 64, pp. 200–211, 2017, doi: 10.1016/j.addbeh.2016.09.001.

[46] Government of Canada, "Canadian Tobacco, Alcohol and Drugs Survey (CTADS): summary of results for 2017.," 2017, [Online]. Available: https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2017-summary.html.

[47] National Institute on Drug Abuse, "NIH. National Institute on Drug Abuse. Advancing addiction science. Most commonly used addictive drugs.," 2018. https://www.drugabuse.gov/publications/media-guide/most-commonly-used-addictive-drugs (accessed May 24, 2020).

[48] Government of Canada, "Cannabis legalization and regulation.," 2018. https://www.justice.gc.ca/eng/cj-jp/cannabis/ (accessed May 24, 2020).

[49] G. Lopez, "Marijuana has been legalized in 11 states and Washington, DC. (U.S.)," *Vox.com*, 2019. https://www.vox.com/identities/2018/8/20/17938336/marijuana-legalization-states-map (accessed May 24, 2020).

[50] State of Nevada (U.S.), "Cannabis Compliance Board. State of Nevada.," 2020. https://ccb.nv.gov/ (accessed May 24, 2020).

[51] State of Oregon (U.S.), "Marijuana and Hemp (Cannabis).," 2020. https://www.oregon.gov/olcc/marijuana/Pages/default.aspx (accessed May 24, 2020).

[52] State of Vermont (U.S.), "Lt. Governor Zuckerman Newsletter. On July 1st cannabis will become legal in Vermont.," 2018. https://ltgov.vermont.gov/sites/zuckerman/files/June18NLOnline.pdf (accessed May 24, 2020).

[53] State of Washington (U.S.), "Washington State. Liquor and cannabis board. Know the law.," 2020. https://lcb.wa.gov/mj-education/know-the-law (accessed May 24, 2020).

[54] District of Columbia (U.S.), "Metropolitan Police Department. The Facts on DC Marijuana Laws.," 2015. https://mpdc.dc.gov/marijuana (accessed May 24, 2020).

[55] State of Alaska (U.S.), "Alaska Department of Health and Social Services. Division of Public Health. Get the facts about marijuana.," 2019.

http://dhss.alaska.gov/dph/Director/Pages/marijuana/facts.aspx (accessed May 24, 2020).

[56] State of California (U.S.), “California Cannabis Portal.,” 2020. https://cannabis.ca.gov/ (accessed May 24, 2020).

[57] State of Colorado (U.S.), “Colorado. Marijuana. Laws about marijuana use.,” 2019. https://www.colorado.gov/pacific/marijuana/laws-about-marijuana-use (accessed May 24, 2020).

[58] State of Illinois (U.S.), “Cannabis Regulation and Tax Act.,” 2020. https://ilga.gov/legislation/publicacts/101/101-0027.htm (accessed May 26, 2020).

[59] State of Maine (U.S.), “Maine State Legislature. Recreational marijuana use in Maine.,” 2020. https://legislature.maine.gov/lawlibrary/recreational_marijuana_in_maine/9419 (accessed May 24, 2020).

[60] State of Massachusetts (U.S.), “Massachusetts law about marijuana. A compilation of laws, regulations, cases, and web sources on recreational and medical use of marijuana in Massachusetts.,” 2020. https://www.mass.gov/info-details/massachusetts-law-about-marijuana#massachusetts-laws- (accessed May 24, 2020).

[61] State of Michigan (U.S.), “MICHIGAN REGULATION AND TAXATION OF MARIHUANA ACT. Initiated Law 1 of 2018.,” 2018. https://www.legislature.mi.gov/(S(rzzqvpcp54ovl4wkfuumnqwk))/documents/mcl/pdf/mcl-Initiated-Law-1-of-2018.pdf (accessed May 26, 2020).

[62] National Institute on Drug Abuse, “NIH. National Institute on Drug AbuseNational Survey of Drug Use and Health. National Survey on Drug Use and Health: Trends in Prevalence of Various Drugs for Ages 12 or Older, Ages 12 to 17, Ages 18 to 25, and Ages 26 or Older; 2016 - 2018 (in percent).,” 2018. https://www.drugabuse.gov/drug-topics/trends-statistics/national-drug-early-warning-system-ndews/national-survey-drug-use-health (accessed May 24, 2020).

[63] Substance Abuse and Mental Health Services Administration (SAMHSA) (U.S.), “2018 NSDUH Detailed Tables. Published Date: August 20, 2019. Collected Date: 2018. Data

Source: National Survey on Drug Use and Health. Report Type: Data Table. Description: Results from the 2018 National Survey on Drug Use and Health.," 2018. https://www.samhsa.gov/data/report/2018-nsduh-detailed-tables (accessed May 24, 2020).

[64] Government of Canada, "CTADS. Illicit drug use (past 12-month and lifetime), by age group and sex, 2017," 2017. https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2017-summary/2017-detailed-tables.html#t13 (accessed May 26, 2020).

[65] World Health Organization, "Currie C et al., eds. Social determinants of health and well-being among young people. Health Behaviour in School-aged Children (HBSC) study: international report from the 2009/2010 survey.," Copenhagen, 2012. [Online]. Available: https://www.euro.who.int/__data/assets/pdf_file/0003/163857/Social-determinants-of-health-and-well-being-among-young-people.pdf.

[66] Institut de la statistique du Québec, "L'Enquête québécoise sur la santé de la population, 2014-2015: pour en savoir plus sur la santé des Québécois.," Montreal, 2016. [Online]. Available: https://www.stat.gouv.qc.ca/statistiques/sante/etat-sante/sante-globale/sante-quebecois-2014-2015.pdf.

[67] S. T. Leatherdale, D. G. Hammond, M. Kaiserman, and R. Ahmed, "Marijuana and tobacco use among young adults in Canada: Are they smoking what we think they are smoking?," *Cancer Causes Control*, vol. 18, pp. 391–397, 2007, doi: 10.1007/s10552-006-0103-x.

[68] A. Agrawal, A. J. Budney, and M. T. Lynskey, "The Co-occurring Use and Misuse of Cannabis and Tobacco: A Review," *Addiction*, vol. 107, no. 7, pp. 1221–1233, 2012, doi: 10.1111/j.1360-0443.2012.03837.x.

[69] E. Dugas, M. Tremblay, N. C. P. Low, D. Cournoyer, and J. O'Loughlin, "Water-pipe smoking among North American youths," *Pediatrics*, vol. 125, no. 6, pp. 1184–1189, 2010, doi: 10.1542/peds.2009-2335.

[70] G. L. Schauer, C. J. Berg, M. C. Kegler, D. M. Donovan, and M. Windle, "Assessing the overlap between tobacco and marijuana: Trends in patterns of co-use of tobacco and

marijuana in adults from 2003-2012," *Addict. Behav.*, vol. 49, pp. 26–32, 2015, doi: 10.1016/j.addbeh.2015.05.012.

[71] B. J. Fairman, C. D. Furr-Holden, and R. M. Johnson, "When Marijuana Is Used before Cigarettes or Alcohol: Demographic Predictors and Associations with Heavy Use, Cannabis Use Disorder, and Other Drug-related Outcomes.," *Prev. Sci.*, vol. 20, no. 2, pp. 225–233, Feb. 2019, doi: 10.1007/s11121-018-0908-3.

[72] L.-A. Attaiaa, F. Beck, J.-B. Richard, C. Marimoutou, and A. Mayet, "Relationships between substance initiation sequence and further substance use: A French nationwide retrospective study.," *Addict. Behav.*, vol. 57, pp. 1–5, Jun. 2016, doi: 10.1016/j.addbeh.2016.01.009.

[73] A. T. Aung, W. B. Pickworth, and E. T. Moolchan, "History of marijuana use and tobacco smoking topography in tobacco-dependent adolescents.," *Addict. Behav.*, vol. 29, no. 4, pp. 699–706, Jun. 2004, doi: 10.1016/j.addbeh.2004.02.012.

[74] L. Degenhardt *et al.*, "Evaluating the drug use 'gateway' theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys.," *Drug Alcohol Depend.*, vol. 108, no. 1–2, pp. 84–97, Apr. 2010, doi: 10.1016/j.drugalcdep.2009.12.001.

[75] L. Degenhardt *et al.*, "Does the 'gateway' matter? Associations between the order of drug use initiation and the development of drug dependence in the National Comorbidity Study Replication.," *Psychol. Med.*, vol. 39, no. 1, pp. 157–167, Jan. 2009, doi: 10.1017/S0033291708003425.

[76] S. M. Kennedy, R. P. Patel, P. Cheh, J. Hsia, and I. V. Rolle, "Tobacco and Marijuana Initiation Among African American and White Young Adults.," *Nicotine Tob. Res.*, vol. 18, no. Supplement 1, pp. S57–S64, Apr. 2016, doi: 10.1093/ntr/ntv194.

[77] A. Agrawal *et al.*, "Patterns of use, sequence of onsets and correlates of tobacco and cannabis.," *Addict. Behav.*, vol. 36, no. 12, pp. 1141–1147, Dec. 2011, doi: 10.1016/j.addbeh.2011.07.005.

[78] A. Sánchez-Niubò, L. Sordo, G. Barrio, B. Indave, and A. Domingo-Salvany, "Onset and

progression of drug use in the general population of Catalonia, Spain.," *Adicciones*, vol. 32, no. 1, pp. 32–40, Jan. 2020, doi: 10.20882/adicciones.1089.

[79] A. Mayet, S. Legleye, B. Falissard, and N. Chau, "Cannabis use stages as predictors of subsequent initiation with other illicit drugs among French adolescents: use of a multi-state model.," *Addict. Behav.*, vol. 37, no. 2, pp. 160–166, Feb. 2012, doi: 10.1016/j.addbeh.2011.09.012.

[80] C. Wang, J. R. Hipp, C. T. Butts, and C. M. Lakon, "The interdependence of cigarette, alcohol, and marijuana use in the context of school-based social networks.," *PLoS One*, vol. 13, no. 7, p. e0200904, 2018, doi: 10.1371/journal.pone.0200904.

[81] A. Mayet *et al.*, "Is serving in the armed forces associated with tobacco or cannabis initiation? A study of onset sequences before and after joining the French armed forces.," *Addict. Behav.*, vol. 38, no. 9, pp. 2437–2444, Sep. 2013, doi: 10.1016/j.addbeh.2013.04.001.

[82] A. Kokkevi, S. N. Gabhainn, M. Spyropoulou, and Risk Behaviour Focus Group of the HBSC, "Early Initiation of Cannabis Use: A Cross-national European Perspective," *J. Adolesc. Heal.*, vol. 39, no. 5, pp. 712–719, 2006, doi: 10.1016/j.jadohealth.2006.05.009.

[83] J. L. Heffner, M. P. DelBello, D. E. Fleck, R. M. Anthenelli, and S. M. Strakowski, "Cigarette smoking in the early course of bipolar disorder: Association with ages-at-onset of alcohol and marijuana use," *Bipolar Disord.*, vol. 10, no. 7, pp. 838–845, 2008, doi: 10.1111/j.1399-5618.2008.00630.x.

[84] A. Pilatti, J. P. Read, and R. M. Pautassi, "ELSA 2016 Cohort: Alcohol, Tobacco, and Marijuana Use and Their Association with Age of Drug Use Onset, Risk Perception, and Social Norms in Argentinean College Freshmen.," *Front. Psychol.*, vol. 8, p. 1452, 2017, doi: 10.3389/fpsyg.2017.01452.

[85] B. A. Moore and A. J. Budney, "Tobacco smoking in marijuana-dependent outpatients.," *J. Subst. Abuse*, vol. 13, no. 4, pp. 583–596, 2001, doi: 10.1016/s0899-3289(01)00093-1.

[86] L. S. Richmond-Rakerd, W. S. Slutske, and P. K. Wood, "Age of initiation and substance

use progression: A multivariate latent growth analysis.," *Psychol. Addict. Behav.*, vol. 31, no. 6, pp. 664–675, Sep. 2017, doi: 10.1037/adb0000304.

[87] D. S. Timberlake *et al.*, "Progression from marijuana use to daily smoking and nicotine dependence in a national sample of U.S. adolescents.," *Drug Alcohol Depend.*, vol. 88, no. 2–3, pp. 272–281, May 2007, doi: 10.1016/j.drugalcdep.2006.11.005.

[88] M. A. Hernán, S. Hernández-Díaz, and J. M. Robins, "A structural approach to selection bias.," *Epidemiology*, vol. 15, no. 5, pp. 615–625, Sep. 2004, doi: 10.1097/01.ede.0000135174.63482.43.

[89] E. F. Schisterman, S. R. Cole, and R. W. Platt, "Overadjustment bias and unnecessary adjustment in epidemiologic studies.," *Epidemiology*, vol. 20, no. 4, pp. 488–495, Jul. 2009, doi: 10.1097/EDE.0b013e3181a819a1.

[90] S. R. Cole *et al.*, "Illustrating bias due to conditioning on a collider.," *Int. J. Epidemiol.*, vol. 39, no. 2, pp. 417–420, Apr. 2010, doi: 10.1093/ije/dyp334.

[91] R. A. Rabin and T. P. George, "A review of co-morbid tobacco and cannabis use disorders: Possible mechanisms to explain high rates of co-use," *Am. J. Addict.*, vol. 24, pp. 105–116, 2015, doi: 10.1111/ajad.12186.

[92] D. E. Ramo, H. Liu, and J. J. Prochaska, "Tobacco and marijuana use among adolescents and young adults: A systematic review of their co-use," *Clin. Psychol. Rev.*, vol. 32, no. 2, pp. 105–121, 2012, doi: 10.1016/j.cpr.2011.12.002.

[93] E. N. Peters, A. J. Budney, and K. M. Carroll, "Clinical Correlates of Co-Occurring Cannabis and Tobacco Use: A Systematic Review," *Addiction*, vol. 107, no. 8, pp. 1404–1417, 2012, doi: 10.1111/j.1360-0443.2012.03843.x.

[94] PRISMA, "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Transparent reporting of systematic reviews and meta-analyses.," 2015. http://www.prisma-statement.org/ (accessed May 24, 2020).

[95] C. Leos-Toro, J. L. Reid, C. L. Madill, V. L. Rynard, S. R. Manske, and H. D., "Cannabis in Canada - Tobacco Use in Canada: Patterns and Trends, 2017 Edition, Special Supplement.," 2017. [Online]. Available: https://uwaterloo.ca/tobacco-use-

canada/sites/ca.tobacco-use-canada/files/uploads/files/cannabissupplement_2017_final_accessible.pdf.

[96] G. L. Schauer, C. D. Hall, C. J. Berg, D. M. Donovan, M. Windle, and M. C. Kegler, "Differences in the relationship of marijuana and tobacco by frequency of use: A qualitative study with adults aged 18-34 years.," *Psychol. Addict. Behav.*, vol. 30, no. 3, pp. 406–414, May 2016, doi: 10.1037/adb0000172.

[97] R. W. Platt, E. F. Schisterman, and S. R. Cole, "Time-modified confounding.," *Am. J. Epidemiol.*, vol. 170, no. 6, pp. 687–694, Sep. 2009, doi: 10.1093/aje/kwp175.

[98] Society for Adolescent Health and Medicine, "Young Adult Health and Well-Being: A Position Statement of the Society for Adolescent Health and Medicine.," *J. Adolesc. Heal.*, vol. 60, no. 6, pp. 758–759, Jun. 2017, doi: 10.1016/j.jadohealth.2017.03.021.

[99] Government of Quebec, "Québec. Loi concernant la lutte contre le tabagisme.," 2020. https://www.quebec.ca/sante/conseils-et-prevention/saines-habitudes-de-vie/mode-de-vie-sans-tabac/loi-concernant-la-lutte-contre-le-tabagisme/#c431 (accessed Aug. 28, 2020).

[100] J. Y. Lee, J. S. Brook, S. J. Finch, W. Kim, and D. W. Brook, "Single and dual diagnoses of major depressive disorder and posttraumatic stress disorder predicted by triple comorbid trajectories of tobacco, alcohol, and marijuana use among urban adults," *Subst. Abus.*, vol. 40, no. 2, pp. 221–228, 2019, doi: 10.1080/08897077.2019.1572047.

[101] V. Martínez-Loredo, J. R. Fernández-Hermida, A. de La Torre-Luque, and S. Fernández-Artamendi, "Polydrug use trajectories and differences in impulsivity among adolescents.," *Int. J. Clin. Heal. Psychol.*, vol. 18, no. 3, pp. 235–244, 2018, doi: 10.1016/j.ijchp.2018.07.003.

[102] J. Y. Valente, H. Cogo-Moreira, W. Swardfager, and Z. M. Sanchez, "A latent transition analysis of a cluster randomized controlled trial for drug use prevention.," *J. Consult. Clin. Psychol.*, vol. 86, no. 8, pp. 657–665, Aug. 2018, doi: 10.1037/ccp0000329.

[103] A. Brooks-Russell *et al.*, "Dynamic Patterns of Adolescent Substance Use: Results From a Nationally Representative Sample of High School Students," *J. Stud. Alcohol Drugs*,

vol. 76, no. 6, pp. 962–970, Nov. 2015, doi: 10.15288/jsad.2015.76.962.

[104] J. S. Brook, Y. Ning, and D. W. Brook, "Personality risk factors associated with trajectories of tobacco use," *Am. J. Addict.*, vol. 15, no. 6, pp. 426–433, 2006, doi: 10.1080/10550490600996363.

[105] W. R. Stanton, B. R. Flay, C. R. Colder, and P. Mehta, "Identifying and predicting adolescent smokers' developmental trajectories," *Nicotine Tob. Res.*, vol. 6, no. 5, pp. 843–852, 2004, doi: 10.1080/14622200410001734076.

[106] J. S. Brook, J. Y. Lee, S. J. Finch, and E. N. Brown, "Course of comorbidity of tobacco and marijuana use: Psychosocial risk factors," *Nicotine Tob. Res.*, vol. 12, no. 5, pp. 474–482, 2010, doi: 10.1093/ntr/ntq027.

[107] K. M. Jackson, K. J. Sher, and J. E. Schulenberg, "Conjoint Developmental Trajectories of Young Adult Substance Use," *Alcohol. Clin. Exp. Res.*, vol. 32, no. 5, pp. 723–737, 2008, doi: 10.1111/j.1530-0277.2008.00643.x.

[108] J. S. Brook, J. Y. Lee, E. N. Brown, and S. J. Finch, "Comorbid Trajectories of Tobacco and Marijuana Use as Related to Psychological Outcomes," *Subst. Abus.*, vol. 33, no. 2, pp. 156–167, 2012, doi: 10.1080/08897077.2011.640202.Comorbid.

[109] J. S. Brook, E. Rubenstone, C. Zhang, and D. W. Brook, "Maternal predictors of comorbid trajectories of cigarette smoking and marijuana use from early adolescence to adulthood," *Addict. Behav.*, vol. 37, no. 1, pp. 139–143, 2012, doi: 10.1016/j.addbeh.2011.09.004.

[110] J. S. Brook, J. Y. Lee, E. Rubenstone, D. W. Brook, and S. J. Finch, "Triple comorbid trajectories of tobacco, alcohol, and marijuana use as predictors of antisocial personality disorder and generalized anxiety disorder among urban adults," *Am. J. Public Health*, vol. 104, no. 8, pp. 1413–1420, 2014, doi: 10.2105/AJPH.2014.301880.

[111] J. S. Brook, C. Zhang, E. Rubenstone, B. A. Primack, and D. W. Brook, "Comorbid Trajectories of Substance Use as Predictors of Antisocial Personality Disorder, Major Depressive Episode, and Generalized Anxiety Disorder," *Addict. Behav.*, vol. 62, pp. 114–121, 2016, doi: 10.1016/j.addbeh.2016.06.003.

[112] A. Mayet, S. Legleye, F. Beck, B. Falissard, and N. Chau, “The Gateway Hypothesis, Common Liability to Addictions or the Route of Administration Model A Modelling Process Linking the Three Theories.,” *Eur. Addict. Res.*, vol. 22, no. 2, pp. 107–117, 2016, doi: 10.1159/000439564.

[113] M. T. Lynskey and A. Agrawal, “Denise Kandel’s classic work on the gateway sequence of drug acquisition,” *Addiction*, vol. 113, no. 10, pp. 1927–1932, Oct. 2018, doi: 10.1111/add.14190.

[114] D. Kandel, “Stages in adolescent involvement in drug use.,” *Science (80-.).*, vol. 190, no. 4217, pp. 912–914, Nov. 1975, doi: 10.1126/science.1188374.

[115] E. R. Kandel and D. B. Kandel, “Shattuck Lecture. A molecular basis for nicotine as a gateway drug.,” *N. Engl. J. Med.*, vol. 371, no. 10, pp. 932–943, Sep. 2014, doi: 10.1056/NEJMsa1405092.

[116] J. O’Loughlin, R. J. Wellman, and L. Potvin, “Whither the e-cigarette?,” *Int. J. Public Health*, vol. 61, no. 2, pp. 147–148, Mar. 2016, doi: 10.1007/s00038-016-0800-5.

[117] W. M. Compton, C. M. Jones, and G. T. Baldwin, “Relationship between Nonmedical Prescription-Opioid Use and Heroin Use.,” *N. Engl. J. Med.*, vol. 374, no. 2, pp. 154–163, Jan. 2016, doi: 10.1056/NEJMra1508490.

[118] G. C. Patton, C. Coffey, J. B. Carlin, S. M. Sawyer, and M. Lynskey, “Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence.,” *Addiction*, vol. 100, no. 10, pp. 1518–1525, Oct. 2005, doi: 10.1111/j.1360-0443.2005.01220.x.

[119] M. M. Vanyukov *et al.*, “Common liability to addiction and ‘gateway hypothesis’: theoretical, empirical and evolutionary perspective.,” *Drug Alcohol Depend.*, vol. 123, no. Supplement 1, pp. S3–S17, Jun. 2012, doi: 10.1016/j.drugalcdep.2011.12.018.

[120] A. P. van Leeuwen, F. C. Verhulst, S. A. Reijneveld, W. A. M. Vollebergh, J. Ormel, and A. C. Huizink, “Can the gateway hypothesis, the common liability model and/or, the route of administration model predict initiation of cannabis use during adolescence? A survival analysis--the TRAILS study.,” *J. Adolesc. Heal.*, vol. 48, no. 1, pp. 73–78, Jan.

2011, doi: 10.1016/j.jadohealth.2010.05.008.

[121] R. L. Pacula and R. Smart, “Medical Marijuana and Marijuana Legalization.,” *Annu. Rev. Clin. Psychol.*, vol. 13, pp. 397–419, May 2017, doi: 10.1146/annurev-clinpsy-032816-045128.

[122] Government of Quebec, “Québec. Cadre légal. Cadre légal en bref. (Cannabis),” 2020. https://encadrementcannabis.gouv.qc.ca/loi/cadre-legal-en-bref/ (accessed Aug. 28, 2020).

[123] Government of Canada, “Justice Laws Website. Marihuana Medical Access Regulations. Registration 2001-06-14.,” 2020. https://laws-lois.justice.gc.ca/eng/regulations/sor-2001-227/20140307/P1TT3xt3.html (accessed Aug. 28, 2020).

[124] Government of Ontario, “Ontario. Cannabis laws. Learn about Ontario’s rules to keep people safe when buying and consuming recreational cannabis.,” 2019. https://www.ontario.ca/page/cannabis-laws#section-0 (accessed Aug. 28, 2020).

[125] State of Alaska (U.S.), “Responsible Alaska Consumer. What you need to know about using marijuana in Alaska.,” 2020. [Online]. Available: http://dhss.alaska.gov/dph/Director/Documents/marijuana/ResponsibleConsumerFactBook.pdf.

[126] State of Montana (U.S.), “Montana.gov. Official State Website. Montana Medical Marijuana Program Rules and Regulations.,” 2020. https://dphhs.mt.gov/marijuana/rulesandregulations (accessed Aug. 28, 2020).

[127] National Conference of State Legislatures (U.S.), “National Conference of State Legislatures. (U.S.) State Medical Marijuana Laws.,” 2020. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (accessed Aug. 28, 2020).

[128] Drug Enforcement Administration (U.S.), “Drug Scheduling. Drug Schedules. DEA (United States Drug Enforcement Administration).,” 2020. https://www.dea.gov/drug-scheduling (accessed Aug. 28, 2020).

[129] Government of Canada, “Loi sur le tabac et les produits de vapotage. PARTIE I.1,” 2018.

https://laws-lois.justice.gc.ca/fra/lois/T-11.5/page-3.html?txthl=jeunes+jeune#s-9 (accessed Aug. 28, 2020).

[130] Government of Canada, "Loi sur le tabac et les produits de vapotage. Définitions.," 2018. https://laws-lois.justice.gc.ca/fra/lois/T-11.5/page-1.html#h-438600 (accessed Aug. 28, 2020).

[131] Government of Ontario, "Ontario. Rules for selling tobacco and vapour products.," 2020. https://www.ontario.ca/page/rules-selling-tobacco-and-vapour-products (accessed Aug. 28, 2020).

[132] U.S. Food and Drug Administration (FDA), "U.S. Food and Drug Administration (FDA). Family Smoking Prevention and Tobacco Control Act - An Overview.," 2020. https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/family-smoking-prevention-and-tobacco-control-act-overview (accessed Aug. 28, 2020).

[133] Cornell Law School, "Cornell Law School. Legal Information Institute. LII U.S. Code Title 21. FOOD AND DRUGS Chapter 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT.," 2020. https://www.law.cornell.edu/uscode/text/21/387f (accessed Aug. 28, 2020).

[134] American Lung Association, "American Lung Association. Smokefree Air Laws. (U.S.)," 2020. https://www.lung.org/policy-advocacy/tobacco/smokefree-environments/smokefree-air-laws (accessed Aug. 28, 2020).

[135] A. E. Barry, J. King, C. Sears, C. Harville, I. Bondoc, and K. Joseph, "Prioritizing Alcohol Prevention: Establishing Alcohol as the Gateway Drug and Linking Age of First Drink With Illicit Drug Use.," *J. Sch. Health*, vol. 86, no. 1, pp. 31–38, Jan. 2016, doi: 10.1111/josh.12351.

[136] K. M. Green, R. M. Johnson, A. J. Milam, D. Furr-Holden, N. S. Ialongo, and B. A. Reboussin, "Racial differences and the role of neighborhood in the sequencing of marijuana and tobacco initiation among urban youth.," *Subst. Abus.*, vol. 37, no. 4, pp. 507–510, 2016, doi: 10.1080/08897077.2016.1178680.

[137] L. M. Guerra, P. S. Romano, S. J. Samuels, and P. H. Kass, "Ethnic differences in

adolescent substance initiation sequences.," *Arch. Pediatr. Adolesc. Med.*, vol. 154, no. 11, pp. 1089–1095, Nov. 2000, doi: 10.1001/archpedi.154.11.1089.

[138] M. Herrera-Vázquez, F. A. Wagner, E. Velasco-Mondragón, G. Borges, and E. Lazcano-Ponce, "[Onset of alcohol and tobacco use and transition to other drug use among students from Morelos, Mexico].," *Salud Publica Mex.*, vol. 46, no. 2, pp. 132–140, 2004, doi: 10.1590/s0036-36342004000200007.

[139] A. Mayet, S. Legleye, N. Chau, and B. Falissard, "Transitions between tobacco and cannabis use among adolescents: a multi-state modeling of progression from onset to daily use.," *Addict. Behav.*, vol. 36, no. 11, pp. 1101–1105, Nov. 2011, doi: 10.1016/j.addbeh.2011.06.009.

[140] B. Myers, M. S. van Heerden, A. Grimsrud, L. Myer, D. R. Williams, and D. J. Stein, "Prevalence and correlates of atypical patterns of drug use progression: findings from the South African Stress and Health Study.," *Afr. J. Psychiatry*, vol. 14, no. 1, pp. 38–44, Mar. 2011, doi: 10.4314/ajpsy.v14i1.65467.

[141] L. S. Richmond-Rakerd *et al.*, "Progression in substance use initiation: A multilevel discordant monozygotic twin design.," *J. Abnorm. Psychol.*, vol. 124, no. 3, pp. 596–605, Aug. 2015, doi: 10.1037/abn0000068.

[142] L. M. Tullis, R. Dupont, K. Frost-Pineda, and M. S. Gold, "Marijuana and tobacco: a major connection?," *J. Addict. Dis.*, vol. 22, no. 3, pp. 51–62, 2003, doi: 10.1300/J069v22n03_05.

[143] M. Vaughn, J. Wallace, B. Perron, V. Copeland, and M. Howard, "Does marijuana use serve as a gateway to cigarette use for high-risk African-American youth?," *Am. J. Drug Alcohol Abuse*, vol. 34, no. 6, pp. 782–791, 2008, doi: 10.1080/00952990802455477.

[144] H. R. White, N. Jarrett, E. Y. Valencia, R. Loeber, and E. Wei, "Stages and sequences of initiation and regular substance use in a longitudinal cohort of black and white male adolescents.," *J. Stud. Alcohol Drugs*, vol. 68, no. 2, pp. 173–181, Mar. 2007, doi: 10.15288/jsad.2007.68.173.

[145] J. O'Loughlin *et al.*, "Cohort Profile: The Nicotine Dependence in Teens (NDIT) Study.,"

Int. J. Epidemiol., vol. 44, no. 5, pp. 1537–1546, Oct. 2015, doi: 10.1093/ije/dyu135.

[146] University of Montreal, "Étude NICO. NDIT Study.," 2020. https://www.webdepot.umontreal.ca/Usagers/oloughlj/MonDepotPublic/en/history.html (accessed May 25, 2020).

[147] P. J. Lavrakas, *Encyclopedia of survey research methods. Thousand Oaks, CA: Sage Publications, Inc.* Thousand Oaks, California: Sage Publications, Inc., 2008.

[148] G. Paradis *et al.*, "The Québec Child and Adolescent Health and Social Survey: design and methods of a cardiovascular risk factor survey for youth.," *Can. J. Cardiol.*, vol. 19, no. 5, pp. 523–531, Apr. 2003.

[149] Centers for Disease Control and Prevention (US), "Selected cigarette smoking initiation and quitting behaviors among high school students—United States, 1997.," *MMWR Morb. Mortal. Wkly. Rep.*, vol. 47, no. 19, pp. 386–389, 1998, [Online]. Available: https://www.cdc.gov/mmwr/preview/mmwrhtml/00052816.htm.

[150] J. R. DiFranza, W. W. S. Ursprung, and L. Biller, "The developmental sequence of tobacco withdrawal symptoms of wanting, craving and needing.," *Pharmacol. Biochem. Behav.*, vol. 100, no. 3, pp. 494–497, Jan. 2012, doi: 10.1016/j.pbb.2011.10.018.

[151] J. O'Loughlin, J. Tarasuk, J. Difranza, and G. Paradis, "Reliability of selected measures of nicotine dependence among adolescents.," *Ann. Epidemiol.*, vol. 12, no. 5, pp. 353–362, Jul. 2002, doi: 10.1016/s1047-2797(01)00312-x.

[152] T. F. Heatherton, L. T. Kozlowski, R. C. Frecker, and K. O. Fagerström, "The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire.," *Br. J. Addict.*, vol. 86, no. 9, pp. 1119–1127, Sep. 1991, doi: 10.1111/j.1360-0443.1991.tb01879.x.

[153] World Health Organization, "International statistical classification of diseases and related health problems. 10th revision. Geneva: World Health Organization," 2020. [Online]. Available: http://www.who.int/classifications/icd/en/.

[154] J. O'Loughlin *et al.*, "Assessment of nicotine dependence symptoms in adolescents: a comparison of five indicators.," *Tob. Control*, vol. 11, no. 4, pp. 354–360, Dec. 2002,

doi: 10.1136/tc.11.4.354.

[155] D. B. Kandel and M. Davies, “Epidemiology of depressive mood in adolescents: an empirical study.,” *Arch. Gen. Psychiatry*, vol. 39, no. 10, pp. 1205–1212, Oct. 1982, doi: 10.1001/archpsyc.1982.04290100065011.

[156] M. Deschenes, S. Demers, and P. Finès, “Styles de vie des jeunes du secondaire en Outaouais, 1991 – 1996 - 2002,” 2003. [Online]. Available: http://www.santecom.qc.ca/bibliothequevirtuelle/hyperion/2895770085.pdf.

[157] E. Dugas *et al.*, “Early predictors of suicidal ideation in young adults.,” *Can. J. psychiatry*, vol. 57, no. 7, pp. 429–436, Jul. 2012, doi: 10.1177/070674371205700706.

[158] S. B. Eysenck and H. J. Eysenck, “The place of impulsiveness in a dimensional system of personality description.,” *Br. J. Soc. Clin. Psychol.*, vol. 16, no. 1, pp. 57–68, Feb. 1977, doi: 10.1111/j.2044-8260.1977.tb01003.x.

[159] T. A. Wills, J. M. Sandy, and O. Shinar, “Cloninger’s constructs related to substance use level and problems in late adolescence: a mediational model based on self-control and coping motives.,” *Exp. Clin. Psychopharmacol.*, vol. 7, no. 2, pp. 122–134, May 1999, doi: 10.1037//1064-1297.7.2.122.

[160] T. A. Wills, M. Windle, and S. D. Cleary, “Temperament and novelty seeking in adolescent substance use: convergence of dimensions of temperament with constructs from Cloninger’s theory.,” *J. Pers. Soc. Psychol.*, vol. 74, no. 2, pp. 387–406, Feb. 1998, doi: 10.1037//0022-3514.74.2.387.

[161] E. F. Vallieres and R. J. Vallerand, “Traduction et Validation Canadienne-Française de L’échelle de L’estime de Soi de Rosenberg.,” *Int. J. Psychol.*, vol. 25, no. 2, pp. 305–316, 1990, doi: 10.1080/00207599008247865.

[162] R. R. Pate *et al.*, “Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine.,” *JAMA*, vol. 273, no. 5, pp. 402–407, Feb. 1995, doi: 10.1001/jama.273.5.402.

[163] A. Eppel, J. O’Loughlin, G. Paradis, and R. Platt, “Reliability of self-reports of cigarette use in novice smokers.,” *Addict. Behav.*, vol. 31, no. 9, pp. 1700–1704, Sep. 2006, doi:

10.1016/j.addbeh.2005.11.006.

[164] M. L. McHugh, “Interrater reliability: the kappa statistic.,” *Biochem. medica*, vol. 22, no. 3, pp. 276–282, 2012.

[165] D. V. Cicchetti, “Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instruments in Psychology,” *Psychol. Assess.*, vol. 6, no. 4, pp. 284–290, 1994, doi: https://doi.org/10.1037/1040-3590.6.4.284.

[166] SAS Institute Inc., “SAS (statistical software).” SAS Institute Inc., Cary, NC, U.S., 2020.

[167] A. Henningsen and O. Toomet, “maxLik: A package for maximum likelihood estimation in R.,” *Comput. Stat.*, vol. 26, no. 3, pp. 443–458, 2011, doi: 10.1007/s00180-010-0217-1.

[168] Y. Croissant and A. Zeileis, “Truncreg: Truncated Gaussian Regression Models.,” 2018. https://cran.r-project.org/package=truncreg (accessed May 25, 2020).

[169] D. O. Dean, V. Cole, and D. J. Bauer, “Delineating prototypical patterns of substance use initiations over time.,” *Addiction*, vol. 110, no. 4, pp. 585–594, Apr. 2015, doi: 10.1111/add.12816.

[170] L. S. Richmond-Rakerd, K. A. Fleming, and W. S. Slutske, “Investigating Progression in Substance Use Initiation Using a Discrete-Time Multiple Event Process Survival Mixture (MEPSUM) Approach.,” *Clin. Psychol. Sci.*, vol. 4, no. 2, pp. 167–182, Mar. 2016, doi: 10.1177/2167702615587457.

[171] E. N. Dugas, “E. Dugas, NDIT study coordinator, personal communication, 2017.” 2017.

[172] M. Guxens, M. Nebot, C. Ariza, and D. Ochoa, “Factors associated with the onset of cannabis use: a systematic review of cohort studies.,” *Gac. Sanit.*, vol. 21, no. 3, pp. 252–260, 2007, doi: 10.1157/13106811.

[173] R documentation, “icc. Intraclass Correlation Coefficient (ICC).,” 2020. https://www.rdocumentation.org/packages/performance/versions/0.4.8/topics/icc#:~:text=Calculation,variance and the residual variance%2C . (accessed Sep. 12, 2020).

[174] D. M. Thompson, D. H. Fernald, and J. W. Mold, “Intraclass correlation coefficients

typical of cluster-randomized studies: estimates from the Robert Wood Johnson Prescription for Health projects.," *Ann. Fam. Med.*, vol. 10, no. 3, pp. 235–240, 2012, doi: 10.1370/afm.1347.

[175] S. Killip, Z. Mahfoud, and K. Pearce, "What is an intracluster correlation coefficient? Crucial concepts for primary care researchers.," *Ann. Fam. Med.*, vol. 2, no. 3, pp. 204–208, 2004, doi: 10.1370/afm.141.

[176] V. Ng and R. Cribbie, "Using the Gamma Generalized Linear Model for Modeling Continuous, Skewed and Heteroscedastic Outcomes in Psychology," *Curr. Psychol.*, Jan. 2016, doi: 10.1007/s12144-015-9404-0.

[177] D. Bates, M. Mächler, B. Bolker, and S. Walker, "Fitting Linear Mixed-Effects Models Using lme4," *J. Stat. Softw.*, vol. 67, no. 1, 2015, doi: 10.18637/jss.v067.i01.

[178] SAS Institute Inc., "SAS Institute Inc. 2008. SAS/STAT® 9.2 User's Guide. Cary, NC: SAS Institute Inc.," Cary, NC, U.S., 2008.

[179] M. Melchior, C. Bolze, E. Fombonne, P. J. Surkan, L. Pryor, and M. Jauffret-Roustide, "Early cannabis initiation and educational attainment: is the association causal? Data from the French TEMPO study.," *Int. J. Epidemiol.*, vol. 46, no. 5, pp. 1641–1650, Oct. 2017, doi: 10.1093/ije/dyx065.

[180] K. S. Bagot, R. Milin, and Y. Kaminer, "Adolescent Initiation of Cannabis Use and Early-Onset Psychosis.," *Subst. Abus.*, vol. 36, no. 4, pp. 524–533, 2015, doi: 10.1080/08897077.2014.995332.

[181] D. M. Fergusson and L. J. Horwood, "Early onset cannabis use and psychosocial adjustment in young adults," *Addiction*, vol. 92, no. 3, pp. 279–296, Mar. 1997, doi: 10.1111/j.1360-0443.1997.tb03198.x.

[182] K. L. Frohlich and L. Potvin, "Transcending the known in public health practice: the inequality paradox: the population approach and vulnerable populations.," *Am. J. Public Health*, vol. 98, no. 2, pp. 216–221, Feb. 2008, doi: 10.2105/AJPH.2007.114777.

[183] E. O. Johnson and L. Schultz, "Forward telescoping bias in reported age of onset: an example from cigarette smoking.," *Int. J. Methods Psychiatr. Res.*, vol. 14, no. 3, pp.

119–129, 2005, doi: 10.1002/mpr.2.

[184] A. C. Cameron, J. B. Gelbach, and D. L. Miller, "Bootstrap-Based Improvements for Inference with Clustered Errors," *Rev. Econ. Stat.*, vol. 90, no. 3, pp. 414–427, Jul. 2008, doi: 10.1162/rest.90.3.414.

[185] D. D. Vachon, R. F. Krueger, D. E. Irons, W. G. Iacono, and M. McGue, "Are Alcohol Trajectories a Useful Way of Identifying At-Risk Youth? A Multiwave Longitudinal-Epidemiologic Study.," *J. Am. Acad. Child Adolesc. Psychiatry*, vol. 56, no. 6, pp. 498–505, Jun. 2017, doi: 10.1016/j.jaac.2017.03.016.

[186] K. J. Sher, K. M. Jackson, and D. Steinley, "Alcohol use trajectories and the ubiquitous cat's cradle: cause for concern?," *J. Abnorm. Psychol.*, vol. 120, no. 2, pp. 322–335, May 2011, doi: 10.1037/a0021813.

[187] M. Haasova *et al.*, "The acute effects of physical activity on cigarette cravings: systematic review and meta-analysis with individual participant data.," *Addiction*, vol. 108, no. 1, pp. 26–37, Jan. 2013, doi: 10.1111/j.1360-0443.2012.04034.x.

[188] M. Haasova *et al.*, "The acute effects of physical activity on cigarette cravings: exploration of potential moderators, mediators and physical activity attributes using individual participant data (IPD) meta-analyses.," *Psychopharmacology (Berl).*, vol. 231, no. 7, pp. 1267–1275, Apr. 2014, doi: 10.1007/s00213-014-3450-4.

[189] P. Wileyto, J. O'Loughlin, M. Lagerlund, G. Meshefedjian, E. Dugas, and A. Gervais, "Distinguishing risk factors for the onset of cravings, withdrawal symptoms and tolerance in novice adolescent smokers.," *Tob. Control*, vol. 18, no. 5, pp. 387–392, Oct. 2009, doi: 10.1136/tc.2009.030189.

[190] N. R. Riggs, C.-P. Chou, C. Li, and M. A. Pentz, "Adolescent to emerging adulthood smoking trajectories: When do smoking trajectories diverge, and do they predict early adulthood nicotine dependence?," *Nicotine Tob. Res.*, vol. 9, no. 11, pp. 1147–1154, 2007, doi: 10.1080/14622200701648359.

[191] C. N. Lessov-Schlaggar *et al.*, "Adolescent smoking trajectories and nicotine dependence," *Nicotine Tob. Res.*, vol. 10, no. 2, pp. 341–351, 2008, doi:

10.1080/14622200701838257.

[192] Y. M. Terry-McElrath, P. M. O'Malley, and L. D. Johnston, "Changes in the Order of Cigarette and Marijuana Initiation and Associations with Cigarette Use, Nicotine Vaping, and Marijuana Use: U.S. 12th Grade Students, 2000–2019," *Prev. Sci.*, vol. 21, no. 7, pp. 960–971, 2020, doi: 10.1007/s11121-020-01150-2.

[193] K. J. Rothman, S. Greenland, and T. L. Lash, *Modern Epidemiology. 3rd edition.* Philadelphia, PA, USA: Lippincott Williams & Wilkins., 2008.

[194] N. D. Brener, J. O. G. Billy, and W. R. Grady, "Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: evidence from the scientific literature.," *J. Adolesc. Heal.*, vol. 33, no. 6, pp. 436–457, Dec. 2003, doi: 10.1016/s1054-139x(03)00052-1.

[195] D. L. Patrick, A. Cheadle, D. C. Thompson, P. Diehr, T. Koepsell, and S. Kinne, "The validity of self-reported smoking: a review and meta-analysis.," *Am. J. Public Health*, vol. 84, no. 7, pp. 1086–1093, Jul. 1994, doi: 10.2105/ajph.84.7.1086.

[196] S. L. Wong, M. Shields, S. Leatherdale, E. Malaison, and D. Hammond, "Assessment of validity of self-reported smoking status.," *Heal. reports*, vol. 23, no. 1, pp. 47–53, Mar. 2012.

[197] M. A. Bruijnzeels, J. C. van der Wouden, M. Foets, A. Prins, and W. J. van den Heuvel, "Validity and accuracy of interview and diary data on children's medical utilisation in The Netherlands.," *J. Epidemiol. Community Health*, vol. 52, no. 1, pp. 65–69, Jan. 1998, doi: 10.1136/jech.52.1.65.

[198] A. L. Betz and J. J. Skowronski, "Self-events and other-events: temporal dating and event memory.," *Mem. Cognit.*, vol. 25, no. 5, pp. 701–714, Sep. 1997, doi: 10.3758/bf03211313.

[199] T. S. Carey, J. Garrett, A. Jackman, L. Sanders, and W. Kalsbeek, "Reporting of acute low back pain in a telephone interview. Identification of potential biases.," *Spine (Phila. Pa. 1976).*, vol. 20, no. 7, pp. 787–790, Apr. 1995.

[200] C. R. Weinberg, D. M. Umbach, and S. Greenland, "When will nondifferential

misclassification of an exposure preserve the direction of a trend?," *Am. J. Epidemiol.*, vol. 140, no. 6, pp. 565–571, Sep. 1994, doi: 10.1093/oxfordjournals.aje.a117283.

[201] L. Harrison, "The validity of self-reported drug use in survey research: an overview and critique of research methods.," *NIDA Res. Monogr.*, vol. 167, pp. 17–36, 1997.

[202] B. J. Buchan, M. L. Dennis, F. M. Tims, and G. S. Diamond, "Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing.," *Addiction*, vol. 97, no. Suppl 1, pp. 98–108, Dec. 2002, doi: 10.1046/j.1360-0443.97.s01.1.x.

[203] F. R. Dillon, C. W. Turner, M. S. Robbins, and J. Szapocznik, "Concordance among biological, interview, and self-report measures of drug use among African American and Hispanic adolescents referred for drug abuse treatment.," *Psychol. Addict. Behav.*, vol. 19, no. 4, pp. 404–413, Dec. 2005, doi: 10.1037/0893-164X.19.4.404.

[204] G. W. Martin, D. A. Wilkinson, and B. M. Kapur, "Validation of self-reported cannabis use by urine analysis.," *Addict. Behav.*, vol. 13, no. 2, pp. 147–150, 1988, doi: 10.1016/0306-4603(88)90004-4.

[205] S. Kirkland, L. Greaves, and P. Devichand, "Gender Differences in Smoking and Self Reported Indicators of Health.," *BMC Womens Heal.*, vol. 4, no. Suppl.1, p. S7, 2004, doi: 10.1186/1472-6874-4-S1-S7.

[206] Centers for Disease Control and Prevention (US), "Smoking & Tobacco Use. Cigarette Smoking and Tobacco Use Among People of Low Socioeconomic Status.," 2019. https://www.cdc.gov/tobacco/disparities/low-ses/index.htm (accessed Sep. 14, 2020).

[207] Info-tabac.ca, "PETITE HISTOIRE DE LA LUTTE CONTRE LE TABAC AU QUÉBEC.," 2013. https://info-tabac.ca/petite-histoire-de-la-lutte-contre-le-tabac-au-quebec/ (accessed Sep. 07, 2020).

[208] B. Lauzon, "B. Lauzon, NDIT interviewer, personal communication." 2020.

[209] L. Townsend, A. J. Flisher, and G. King, "A systematic review of the relationship between high school dropout and substance use.," *Clin. Child Fam. Psychol. Rev.*, vol. 10, no. 4, pp. 295–317, Dec. 2007, doi: 10.1007/s10567-007-0023-7.

[210] D. Coggon, G. Rose, and D. J. P. Barker, *Epidemiology for the Uninitiated*, 4th editio.

Chennai, India: BMJ Publishing Group., 1997.

[211] A. M. Passarotti, N. A. Crane, D. Hedeker, and R. J. Mermelstein, "Longitudinal trajectories of marijuana use from adolescence to young adulthood.," *Addict. Behav.*, vol. 45, pp. 301–308, Jun. 2015, doi: 10.1016/j.addbeh.2015.02.008.

[212] P. D. Quinn and K. P. Harden, "Differential changes in impulsivity and sensation seeking and the escalation of substance use from adolescence to early adulthood.," *Dev. Psychopathol.*, vol. 25, no. 1, pp. 223–239, Feb. 2013, doi: 10.1017/S0954579412000284.

[213] J. Audrain-McGovern, D. Rodriguez, L. H. Epstein, J. Cuevas, K. Rodgers, and E. P. Wileyto, "Does delay discounting play an etiological role in smoking or is it a consequence of smoking?," *Drug Alcohol Depend.*, vol. 103, no. 3, pp. 99–106, 2009, doi: 10.1016/j.drugalcdep.2008.12.019.

[214] L. C. Masse and R. E. Tremblay, "Behavior of Boys in Kindergarten and the Onset of Substance Use During Adolescence," *Arch. Gen. Psychiatry*, vol. 54, no. 1, pp. 62–68, Jan. 1997, doi: 10.1001/archpsyc.1997.01830130068014.

[215] J. H. P. van Wel *et al.*, "Single doses of THC and cocaine decrease proficiency of impulse control in heavy cannabis users," *Br. J. Pharmacol.*, vol. 170, no. 7, pp. 1410–1420, Dec. 2013, doi: 10.1111/bph.12425.

[216] L. K. Muthén and B. O. Muthén, "Muthén, L. K., & Muthén, B. O. (1998-2011). Mplus User's Guide. Sixth Edition. Los Angeles, CA: Muthén & Muthén." https://www.statmodel.com/index.shtml (accessed May 25, 2020).

[217] B. L. Jones and D. S. Nagin, "Advances in Group-Based Trajectory Modeling and an SAS Procedure for Estimating Them," *Sociol. Methods Res.*, vol. 35, no. 4, pp. 542–571, 2007, doi: 10.1177/0049124106292364.

[218] The Cochrane Collaboration, "Ryan R, Hill S, Prictor M, McKenzie J; Cochrane Consumers and Communication Review Group. Study Quality Guide.," 2013. [Online]. Available: https://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/StudyQualityGu

ide_May 2013.pdf.

[219] The Cochrane Collaboration, "Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.," 2011. [Online]. Available: https://handbook-5-1.cochrane.org/.

[220] S. Sanderson, I. D. Tatt, and J. P. T. Higgins, "Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography.," *Int. J. Epidemiol.*, vol. 36, no. 3, pp. 666–676, Jun. 2007, doi: 10.1093/ije/dym018.

[221] P. J. Curran and B. O. Muthén, "The application of latent curve analysis to testing developmental theories in intervention research," *Am. J. Community Psychol.*, vol. 27, no. 4, pp. 567–595, 1999, doi: 10.1023/A:1022137429115.

[222] STROBE, "STROBE Statement—checklist of items that should be included in reports of observational studies," 2020. https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf (accessed Sep. 14, 2020).

[223] T. P. Johnson and J. A. Mott, "The reliability of self-reported age of onset of tobacco, alcohol and illicit drug use.," *Addiction*, vol. 96, no. 8, pp. 1187–1198, Aug. 2001, doi: 10.1046/j.1360-0443.2001.968118711.x.

[224] J. N. Soulakova, B. C. Bright, and L. J. Crockett, "Perception of Time Since Smoking Cessation: Time in Memory Can Elapse Faster.," *J. Addict. Behav. Ther. Rehabil.*, vol. 4, no. 4, 2015, doi: 10.4172/2324-9005.1000145.

[225] A. M. Shillington, S. I. Woodruff, J. D. Clapp, M. B. Reed, and H. Lemus, "Self-Reported Age of Onset and Telescoping for Cigarettes, Alcohol, and Marijuana Across Eight Years of the National Longitudinal Survey of Youth.," *J. Child Adolesc. Subst. Abuse*, vol. 21, no. 4, pp. 333–348, Sep. 2012, doi: 10.1080/1067828X.2012.710026.

[226] A. M. Shillington, M. B. Reed, and J. D. Clapp, "Self-Report Stability of Adolescent Cigarette Use Across Ten Years of Panel Study Data.," *J. Child Adolesc. Subst. Abuse*, vol. 19, no. 2, pp. 171–191, 2010, doi: 10.1080/10678281003635089.

[227] C. E. Kaestle, “Age of smoking milestones: longitudinal inconsistencies and recanting.,” *J. Adolesc. Heal.*, vol. 56, no. 4, pp. 382–388, Apr. 2015, doi: 10.1016/j.jadohealth.2014.12.005.

[228] B. C. Bright and J. N. Soulakova, “Evidence of telescoping in regular smoking onset age.,” *Nicotine Tob. Res.*, vol. 16, no. 6, pp. 717–724, Jun. 2014, doi: 10.1093/ntr/ntt220.

[229] A. Golub, B. D. Johnson, and E. Labouvie, “On Correcting Biases in Self-Reports of Age at First Substance Use with Repeated Cross-Section Analysis.,” *J. Quant. Criminol.*, vol. 16, no. 1, pp. 45–68, Mar. 2000, doi: 10.1023/A:1007573411129.

[230] S. A. Norman *et al.*, “Validation of self-reported screening mammography histories among women with and without breast cancer.,” *Am. J. Epidemiol.*, vol. 158, no. 3, pp. 264–271, Aug. 2003, doi: 10.1093/aje/kwg136.

[231] D. S. May and A. E. Trontell, “Mammography use by elderly women: a methodological comparison of two national data sources.,” *Ann. Epidemiol.*, vol. 8, no. 7, pp. 439–444, Oct. 1998, doi: 10.1016/s1047-2797(98)00010-6.

[232] E. Petridou, N. Dessypris, C. E. Frangakis, M. Belechri, A. Mavrou, and D. Trichopoulos, “Estimating the population burden of injuries: a comparison of household surveys and emergency department surveillance.,” *Epidemiology*, vol. 15, no. 4, pp. 428–432, Jul. 2004, doi: 10.1097/01.ede.0000129519.76945.0d.

[233] K. Dalziel, J. Li, A. Scott, and P. Clarke, “Accuracy of patient recall for self-reported doctor visits: Is shorter recall better?,” *Health Econ.*, vol. 27, no. 11, pp. 1684–1698, Nov. 2018, doi: 10.1002/hec.3794.

[234] A. E. Rhodes and K. Fung, “Self-reported use of mental health services versus administrative records: care to recall?,” *Int. J. Methods Psychiatr. Res.*, vol. 13, no. 3, pp. 165–175, 2004, doi: 10.1002/mpr.172.

[235] N. A. Pachana, S. L. Brilleman, and A. J. Dobson, “Reporting of life events over time: methodological issues in a longitudinal sample of women.,” *Psychol. Assess.*, vol. 23, no. 1, pp. 277–281, Mar. 2011, doi: 10.1037/a0021337.

Appendix 1

Supplementary Tables

Table 23. (Article 1, Table S1) Number and description of smoking trajectory studies in 43 studies of cigarette smoking trajectories[8]

First author & year of publication; Country	Sample size[1]	Age range[2], y	Cohort/study sample[3]	Number and description of cigarette smoking trajectories (prevalence)[4]
AGE/GRADE ANALYSES				
Outcome variable[5]: Intensity of smoking				
Colder 2001; US(1)	260	12-16.6	Project STAR	5 – Stable puffers (25%), stable light smokers, late slow escalators, late moderate escalators, early rapid escalators
Guo 2002; US(2)	786	13-18	Seattle Social Development Project	5 – Non-smokers (73.0%), experimenters (7.3%), late-onsetters (10.9%), escalators (7.5%), chronic smokers (1.3%)
Vitaro 2004; Canada(3)	812	9-11.5 to 12.5-15	Quebec sample (1)	4 – Never (75.4%), 13-14y starters (7.9%), 12-13y starters (11.1%), 11-12y starters (5.7%)
Stanton 2004; New Zealand(4)	307	9-18	Dunedin Multidisciplinary Health and Development Study	6 – Late slow-escalators [puffers] (11.4%), stable puffers (12.7%), late slow escalators [smokers] (11.4%), late moderate escalators (14.3%), late rapid escalators (38.8%), early rapid escalators (11.4%)
White 2004; US(5)	983	10-25	Pittsburgh Youth Study	European Americans: 3 – Non-smokers (44.3%), light smokers (23.7%), heavy smokers (32%). African Americans: 3 – Non-smokers (55.9%), light smokers (27.3%), heavy smokers (16.7%)
Maggi 2007; Canada(6)	260	10-11 to 16-17	National Longitudinal Survey of Children and Youth	2 – Late slow escalators (97.7%), early rapid escalators (2.3%)
Riggs 2007; US(7)	1 017	12-24	Kansas City sample	4 – Abstainers (47%), low users (24%), late heavy users (16%), early heavy users (12%)
Lessov-Schlaggar 2008; US(8)	481	13.1-24	Smoking in Families Study	5 – Experimenters (48.5%), late increasers (16.3%), early increasers (15.5%), quitters (9.2%), persistent (10.5%)
Otten 2008; Canada(9)	203	12-14	Quebec sample (2)	3 – Low-rate (71.4%), increasing-rate (18.2%), high-rate (10.3%)
Chung 2010; South Korea(10)		13-17	Korea Youth Panel Survey	4 – Non-initiator (85.1%), late onsetter (7.0%), experimenter (4.5%), escalator (3.4)
Gabrhelik 2012; Czech Republic(11)	1 874	11-13 to 13.6-15.6	Czech sample	2 – Slow cigarette smoking escalators (91%), rapid/moderate cigarette smoking escalators (9%)

Vuolo 2013; US(12)	1 010	15-38	Youth Development Study	4 – Stable non-smokers (54.1%), early onset light smokers who quit/reduce (16.2%), late onset persistent smokers (13.5%), early onset persistent heavy smokers (16.2)
Roberts 2014; US(13)	15 828	12-23	Nurses' Health Study II and Growing Up Today Study	4 – Non-smoker, experimenter, late initiator/moderate consumption, early initiator/high consumption
Nelson 2015; US(14)	890	12-23	Northwest sample	6 – Abstainers (38.8%), very low users (10%), post-high school onset low decreasers (9.8%), young adult onset moderate increasers (11.5%), post-high school onset steep increasers (18.9%), early onset steep increasers (11.1%)
Orpinas 2015; US(15)	611	Grade 6-12	Healthy Teens Longitudinal Study	4 – Abstainers/sporadic users (71.5%), late starters (11.3%), experimenters (9%), continuous users (8.2%)
Outcome variable[5]: Frequency of smoking				
Abroms 2005; US(16)	1 320	Grade 6-9	Maryland sample (1)	5 – Never smokers (41.2%), intenders (33.5%), delayed escalators (8.9%), early experimenters (13.9%), early users (2.5%)
Simons-Morton 2005; US(17)	1 320	Grade 6-9	Maryland sample (1)	Control Group (n = 628): 5 – Class 1 (41.7%), class 2 (32.2%), class 3 (11.9%), class 4 (11%), class 5 (3.2%) Treatment Group (n = 692): 5 – Class 1 (44.5%), class 2 (31.5%), class 3 (10.7%), class 4 (11.2%), class 5 (2%)
Maggi 2007; Canada(6)	280	10-11 to 16-17	National Longitudinal Survey of Children and Youth	5 – Late infrequent experimenters (6.1%), late frequent smokers (38%), early frequent experimenters (5.2%), early frequent smokers (34%), early infrequent experimenters (6.8%)
Bernat 2008; US(18)		12-16 to 15-19	Minnesota Adolescent Community Cohort	6 - Non-smokers (54%), late established (8%), triers (17%), occasional users (10%), early established (7%), decliners (4%)
Maggi 2008; Canada(19)	3 959	10-11 to 20-21	National Longitudinal Survey of Children and Youth	6 – Stable non-smokers (48.4%), late experimenters-non-smokers (17.2%), late experimenters (13.9%), late experimenters-daily smokers (4.1%), early experimenters-daily smokers (5.8%), early experimenters-occasional smokers (10.5%)
Kimber 2009; Sweden(20)	662	13-14 to 15-16	Stockholm sample	3 – Largely non-users (40%), largely moderate users (39%), heavy users (21%)
de Leeuw 2010; the Netherlands(21)	428	15-18	Family and Health Project	4 – Non-smokers (62.3%), stable smokers (13.7%), increasers (17.7%), decreasers (6.3%)
Lynne-Landsman 2010; US(22)	533	Grade 9-12	Maryland sample (2)	2 – Abstaining (82%), increasing (18%)
Heron 2011; UK(23)	3 038	14-16	Avon Longitudinal Study of Parents and Children	4 – Non-smokers (85.4%), experimenters (8.7%), late-onset regular smokers (4.3%), early-onset regular smokers (1.7%)
Hampson 2013; US(24)	963	Grade 9-12	Oregon Youth Substance Use Project	4 – Stable non-smokers (71%), experimenters (15%), rapid escalators (8%), stable high smokers (6%)

Metzger 2013; US(25)	344	15.6-17.9	Family Talk about Smoking Study	3 – Non-smokers (18.6%), infrequent/non-escalators (53.8%), escalators (27.6%)
Xie 2013; China(26)	3 521	12-15 to 14-17	Wuhan Smoking Prevention Trial	3 – Non-smokers (48.7%), stable light/occasional smokers (48.6%), accelerating smokers (2.7%)
Musci 2015; US(27)		12-21	Maryland sample (3)	2 – Low but increasing users (68%), moderate users (32%)
Cance 2017; US(28)	2244	17-19 to 23-25	Southwestern sample	5 – Abstaining (68%), low-increasing (11%), decreasing (11%), moderate-increasing (6%), steady high (4%)
Dutra 2017; US(29)	8791	12-16 to 26-30	National Longitudinal Survey of Youth 1997	4 – Experimenters (13.6%), quitters (8.1%), early established smokers (39.0%), late escalators (5.2%)
Chang 2018; Taiwan(30)	2510	13-18	Child and Adolescent Behaviors in Long-term Evolution Project	3 – Non-smokers (71%), late increasing (22%), escalating smokers (7%)
Outcome variable[5]: Intensity and frequency of smoking				
Chassin 2000[6]; US(31)	6 929	Grade 6-12 to age 21-31	Midwest sample	4 – Experimenter (6%), quitter (5%), late stable (16%), early stable (12%)
White 2002; US(32)	374	12-30/31	New Jersey sample	3 – Non/experimental smokers (39.6%), occasional/maturing out smokers (19%), heavy/regular smokers (41.4%)
Audrain-McGovern 2004; US(33)	968	14-15 to 17-18	Virginia sample (1)	4 – Never smokers (45%), early/fast adopters (8%), late/slow adopters (24%), experimenters (23%)
Orlando 2004; US(34)	5 914	13-23	RAND Adolescent/Young Adult Panel Study	5 – Triers (55%), late increasers (14%), decreasers (9%), early increasers (14%), stable highs (8%)
Tucker 2005; US(35)	4 245	13-23	RAND Adolescent/Young Adult Panel Study	5 – Triers (55.3%), stable highs (7.8%), early increasers (14%), decreasers (8.7%), steady increasers (14.2%)
Tucker 2006[7]; US(36)	1 442	13-23	RAND Adolescent/Young Adult Panel Study	6 – Abstainer (29.5%), trier (40.5%), early increasers (8.5%), late increasers (11%), decreasers (5.7%), stable highs (4.8%).
Audrain-McGovern 2009; US(37)	909	15-20	Virginia sample (1)	3 – Non-smokers (61.2%), fast adopters (12.3%), slow progressors (26.5%)
Otten 2009; Canada(38)	312	13-15	Quebec sample (3)	3 – Low-rate (38.4%), medium-rate (46.5%), high-rate (15.1%).
Outcome variable[5]: Any use of cigarettes				
Maggi 2007; Canada(6)	2 886	10-11 to 16-17	National Longitudinal Survey of Children and Youth	3 – Late onset (40.5%), middle onset (49.3%), early onset (10.2%)
Weden 2012; US(39)	6 349	14-15 to 24-25	National Longitudinal Survey of Youth 1979	4 – Non-smokers (63.7%), late onset (18.8%), early-experiment smokers (2.7%), early-onset smokers (14.7%)

Huang 2013; US(40)	5 141	12-18	National Longitudinal Survey of Youth 1979	3 – Low (75.8%), increased (21.1%), high-decreasing (3.1%)
Lynne-Landsman 2016; US(41)	684	<14-16 to <15-17	Cherokee Nation sample	3 – None (82%), increasing (3%), high (15%)
TIME SINCE ONSET ANALYSES				
Outcome variable[5]: Intensity of smoking				
Rosendahl 2008; Sweden(42)	2 175	11-18	Children's Smoking and Environment in the Stockholm County (BROMS) Study	Males: 4 – Group 1, early extinction, Group 3, early escalation (21.1%) Females: 4 – Late trial (14.7%), early extinction (26.1%), late escalation (18.3%), early escalation (25.2%)
Karp 2005; Canada(43)	369	13-16.9	Natural History of Nicotine Dependence Study	4 – Low-intensity non-progressing (72.4%), slow escalators (11.1%), moderate escalators (10.8%), rapid escalators (5.7%)

Note: Missing information (i.e. empty cells) indicates that information was not clearly provided in the article.
[1]Number of participants in the model used to estimate smoking trajectories
[2]Age range of all participants from baseline to last data point. Some studies provided school grade rather than age
[3]Refers to cohort data used to estimate trajectories. Where cohorts were not used, the city/state/country where data was collected was specified. Studies using the same data from a given city/state/country have the same number (e.g. Quebec sample (1)).
[4]Refers to the trajectories identified in the final model (using labels as reported in the article) and percentage of participants in each trajectory (if reported)
[5]Refers to the way in which smoking was assessed: intensity was assessed as the number of cigarettes smoked over a given time period (day(s), week(s), month(s), year); frequency was assessed as the number of days on which participants smoked over a given time period (week(s), month(s), year); any use was assessed by asking participants whether they had ever smoked cigarettes or whether they had smoked in the past week/month/year with a yes/no response option.
[6] An "erratic" group was determined a priori and was not included in trajectory analyses
[7] The "abstainer" group was determined a priori and therefore not included in trajectory analyses
[8]This table is retained in the current Appendix as it contains some additional information relative to Table 5 (Article 1)

ARTICLES INCLUDED IN SYSTEMATIC REVIEW

1. Colder CR, Mehta P, Balanda K, Campbell RT, Mayhew K, Stanton WR, et al. Identifying trajectories of adolescent smoking: an application of latent growth mixture modeling. Health Psychology. 2001;20(2):127.
2. Guo J, Chung I-J, Hill KG, Hawkins JD, Catalano RF, Abbott RD. Developmental relationships between adolescent substance use and risky sexual behavior in young adulthood. Journal of Adolescent Health. 2002;31(4):354-62.
3. Vitaro F, Wanner B, Brendgen M, Gosselin C, Gendreau PL. Differential contribution of parents and friends to smoking trajectories during adolescence. Addictive behaviors. 2004;29(4):831-5.
4. Stanton WR, Flay BR, Colder CR, Mehta P. Identifying and predicting adolescent smokers' developmental trajectories. Nicotine & Tobacco Research. 2004;6(5):843-52.
5. White HR, Nagin D, Replogle E, Stouthamer-Loeber M. Racial differences in trajectories of cigarette use. Drug & Alcohol

Dependence. 2004;76(3):219-27.
6. Maggi S, Hertzman C, Vaillancourt T. Changes in smoking behaviors from late childhood to adolescence: Insights from the Canadian National Longitudinal Survey of Children and Youth. Health Psychology. 2007;26(2):232.
7. Riggs NR, Chou CP, Li C, Pentz MA. Adolescent to emerging adulthood smoking trajectories: when do smoking trajectories diverge, and do they predict early adulthood nicotine dependence? Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2007;9(11):1147-54.
8. Lessov-Schlaggar CN, Hops H, Brigham J, Hudmon KS, Andrews JA, Tildesley E, et al. Adolescent smoking trajectories and nicotine dependence. Nicotine & Tobacco Research. 2008;10(2):341-51.
9. Otten R, Wanner B, Vitaro F, Engels RC. Own and friends' smoking attitudes and social preference as early predictors of adolescent smoking. Journal of Clinical Child & Adolescent Psychology. 2008;37(4):808-19.
10. Chung IJ, Chun J. Co-occurring Patterns of Smoking and Alcohol Consumption among Korean Adolescents. The American Journal on Addictions. 2010;19(3):252-6.
11. Gabrhelik R, Duncan A, Lee MH, Stastna L, Furr-Holden CD, Miovsky M. Sex specific trajectories in cigarette smoking behaviors among students participating in the unplugged school-based randomized control trial for substance use prevention. Addict Behav. 2012;37(10):1145-50.
12. Vuolo M, Staff J. Parent and child cigarette use: a longitudinal, multigenerational study. Pediatrics. 2013:peds. 2013-0067.
13. Roberts AL, Galea S, Austin SB, Corliss HL, Williams MA, Koenen KC. Women's experience of abuse in childhood and their children's smoking and overweight. American journal of preventive medicine. 2014;46(3):249-58.
14. Nelson SE, Van Ryzin MJ, Dishion TJ. Alcohol, marijuana, and tobacco use trajectories from age 12 to 24 years: Demographic correlates and young adult substance use problems. Development and psychopathology. 2015;27(01):253-77.
15. Orpinas P, Lacy B, Nahapetyan L, Dube SR, Song X. Cigarette smoking trajectories from sixth to twelfth grade: associated substance use and high school dropout. Nicotine & Tobacco Research. 2015;18(2):156-62.
16. Abroms L, Simons-Morton B, Haynie DL, Chen R. Psychosocial predictors of smoking trajectories during middle and high school. Addiction. 2005;100(6):852-61.
17. Simons-Morton B, Haynie D, Saylor K, Crump AD, Chen R. The effects of the going places program on early adolescent substance use and antisocial behavior. Prevention Science. 2005;6(3):187.
18. Bernat DH, Erickson DJ, Widome R, Perry CL, Forster JL. Adolescent smoking trajectories: results from a population-based cohort study. Journal of Adolescent Health. 2008;43(4):334-40.
19. Maggi S. Changes in smoking behaviours from late childhood to adolescence: 4 years later. Drug and alcohol dependence. 2008;94(1-3):251-3.
20. Kimber B, Sandell R. Prevention of substance use among adolescents through social and emotional training in school: A latent-class analysis of a five-year intervention in Sweden. Journal of Adolescence. 2009;32(6):1403-13.
21. de Leeuw R, Scholte R, Vermulst A, Engels R. The relation between smoking-specific parenting and smoking trajectories of

adolescents: How are changes in parenting related to changes in smoking? Psychology and Health. 2010;25(8):999-1021.
22. Lynne-Landsman SD, Bradshaw CP, Ialongo NS. Testing a developmental cascade model of adolescent substance use trajectories and young adult adjustment. Development and Psychopathology. 2010;22:933-48.
23. Heron J, Hickman M, Macleod J, Munafò MR. Characterizing patterns of smoking initiation in adolescence: comparison of methods for dealing with missing data. Nicotine & Tobacco Research. 2011;13(12):1266-75.
24. Hampson SE, Tildesley E, Andrews JA, Barckley M, Peterson M. Smoking trajectories across high school: sensation seeking and hookah use. Nicotine & Tobacco Research. 2013;15(8):1400-8.
25. Metzger A, Wakschlag LS, Anderson R, Darfler A, Price J, Flores Z, et al. Information management strategies within conversations about cigarette smoking: Parenting correlates and longitudinal associations with teen smoking. Developmental psychology. 2013;49(8):1565.
26. Xie B, Palmer P, Li Y, Lin C, Johnson CA. Developmental trajectories of cigarette use and associations with multilayered risk factors among Chinese adolescents. nicotine & tobacco research. 2013;15(10):1673-81.
27. Musci RJ, Uhl G, Maher B, Ialongo NS. Testing gene× environment moderation of tobacco and marijuana use trajectories in adolescence and young adulthood. Journal of consulting and clinical psychology. 2015;83(5):866.
28. Cance JD, Talley AE, Morgan-Lopez A, Fromme K. Longitudinal Conjoint Patterns of Alcohol and Tobacco Use Throughout Emerging Adulthood. Subst Use Misuse. 2017;52(3):373-82.
29. Dutra LM, Glantz SA, Lisha NE, Song AV. Beyond experimentation: Five trajectories of cigarette smoking in a longitudinal sample of youth. PloS one. 2017;12(2):e0171808.
30. Chang L-Y, Chang H-Y, Wu W-C, Lin LN, Wu C-C, Yen L-L. Dual trajectories of sleep duration and cigarette smoking during adolescence: Relation to subsequent internalizing problems. Journal of abnormal child psychology. 2018:1-13.
31. Chassin L, Presson CC, Pitts SC, Sherman SJ. The natural history of cigarette smoking from adolescence to adulthood in a midwestern community sample: multiple trajectories and their psychosocial correlates. Health Psychology. 2000;19(3):223.
32. White HR, Pandina RJ, Chen P-H. Developmental trajectories of cigarette use from early adolescence into young adulthood. Drug and alcohol dependence. 2002;65(2):167-78.
33. Audrain-McGovern J, Rodriguez D, Tercyak KP, Cuevas J, Rodgers K, Patterson F. Identifying and characterizing adolescent smoking trajectories. Cancer Epidemiology and Prevention Biomarkers. 2004;13(12):2023-34.
34. Orlando M, Tucker JS, Ellickson PL, Klein DJ. Developmental trajectories of cigarette smoking and their correlates from early adolescence to young adulthood. J Consult Clin Psychol. 2004;72(3):400-10.
35. Tucker JS, Ellickson PL, Orlando M, Martino SC, Klein DJ. Substance use trajectories from early adolescence to emerging adulthood: A comparison of smoking, binge drinking, and marijuana use. Journal of Drug Issues. 2005;35(2):307-32.
36. Tucker JS, Ellickson PL, Orlando M, Klein DJ. Cigarette smoking from adolescence to young adulthood: women's developmental trajectories and associates outcomes. Women's Health Issues. 2006;16(1):30-7.
37. Audrain-McGovern J, Rodriguez D, Epstein LH, Cuevas J, Rodgers K, Wileyto EP. Does delay discounting play an etiological

role in smoking or is it a consequence of smoking? Drug and alcohol dependence. 2009;103(3):99-106.
38. Otten R, Wanner B, Vitaro F, Engels RC. Disruptiveness, peer experiences and adolescent smoking: a long-term longitudinal approach. Addiction. 2009;104(4):641-50.
39. Weden MM, Miles JN. Intergenerational relationships between the smoking patterns of a population-representative sample of US mothers and the smoking trajectories of their children. American journal of public health. 2012;102(4):723-31.
40. Huang DY, Lanza HI, Anglin MD. Association between adolescent substance use and obesity in young adulthood: a group-based dual trajectory analysis. Addictive behaviors. 2013;38(11):2653-60.
41. Lynne-Landsman SD, Komro KA, Kominsky TK, Boyd ML, Maldonado-Molina MM. Early trajectories of alcohol and other substance use among youth from rural communities within the Cherokee nation. Journal of studies on alcohol and drugs. 2016;77(2):238-48.
42. Rosendahl KI, Galanti MR, Gilljam H. Trajectories of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents: differences and implications. Nicotine & Tobacco Research. 2008;10(6):1021-7.
43. Karp I, O'loughlin J, Paradis G, Hanley J, Difranza J. Smoking trajectories of adolescent novice smokers in a longitudinal study of tobacco use. Annals of epidemiology. 2005;15(6):445-52.

Table 24. (Article 1, Table S2) Description of cigarette smoking trajectories

First author and year of publication	Low stable[1] n (%)	Decreasers[2,7] n (%); age(s)[3]	Increasers[4] n (%); age(s)[3]	Stable smokers[5,7] n (%)	Other trajectory(ies)[6,7] n (%); age(s)[3]
AGE/GRADE ANALYSES					
Outcome variable[8]: Intensity of smoking					
Colder, 2001*	65(25%)		(1) Increasing 12-13 to 16 (2) Low stable 12 to ~13. Increasing 13-14 to 16 (3) Low stable 12 to ~14. Increasing 14-15 to 16	Stable light smokers	
Guo, 2002*	573(73%)		(1) 86(10.9%); low stable 12 to 16. Increasing 16 to 18; (2) 59(7.5%); low stable 13 to 14. Increasing 14 to 18		(1) 57(7.3%); stable 13 to 14 years. Increasing 14 to 15 years. Stable 15 to 16 years. Decreasing 16 to 18 years. (2) 10(1.3%); increasing 13 to 15. Decreasing 15 to 18.
Vitaro, 2004 †	612(75.4%)		(1) 64(7.9%); increasing 13-14 to 14-15 (2)90(11.1%); increasing 12-13 to 14-15 (3)46(5.7%); increasing 11-12 to 14-15		
Stanton, 2004*		39(12.7%); decreasing 9 to 18	(1) 35(11.4%); increasing 9 to 18 (2) 119(38.8%); low stable 9 to 11. Increasing 11 to 18 (3) 44(14.3%); low stable 9 to 13. Increasing 13 to 15 (4) 35(11.4%); stable 9 to 13. Increasing 13 to 18		35(11.4%); decreasing 9 to 15. Increasing 15 to 18
White, 2004*	African-Americans: 314(55.9%). European-Americans: 186(44.3%)		African-Americans: (1) 153(27.3%); low stable 10 to 14. Increasing 14 to 25 (2) 94(16.7%); low stable 10 to 12. Increasing 12 to 25 European-Americans: (1) 100(23.7%); low stable 10 to 12. Increasing 12 to 25 ;(2) 135(32%); low stable 10 to 11. Increasing 11 to 17. Stable 17 to 25		
Maggi, 2007*			(1) 254(97.7%); increasing 12-13 to 16-17; (2) 4(2.3%); increasing 12-13 to 14-15. Stable 14-15 to 16-17		
Riggs, 2007*	479(47%)		(1) 246(24%); increasing 12 to 24; (2) 167(16%); low stable 12 to 14. Increasing 14 to 21. Stable 21 to 24; (3) 125(12%); low stable 12 to 12.5. Increasing 12.5 to 16. Stable 16 to 24.		
Lessov-Schlaggar, 2008*	116(48.5%)	22(9.2%); stable 13.1 to 17.3.	(1) 39(16.3%); low stable 13.1 to 15.1. Increasing 15.1 to 24; (2) 37(15.5%); low stable 13.1 to 14.1. Increasing 14.1 to 24.		25(10.5%); increasing 13.1 to 15.1. Decreasing 15.1 to 16.3. Increasing 16.3 to 17.3. Decreasing 17.3 to 19.8.

		Decreasing 17.3 to 24			Increasing 19.8 to 24
Otten, 2008*	145(71.4%)		(1) 37(18.2%); increasing 12 to 14; (2) 21(10.3%); increasing 12 to 14		
Chung, 2010*	(85.1%)		(1) 7.0%; low stable 13 to 15. Increasing 15 to 17; (2) 3.4%; increasing 13 to 16. Stable 16 to 17		4.5%; increasing 13 to 15. Decreasing 15 to 17
Gabrhelik, 2012 ‡			(1) 1705(91%) – slow cigarette smoking escalators; (2) 169(9%) – rapid/moderate cigarette smoking escalators		
Vuolo, 2013‡	546(54.1%)		(1) 164(16.2%) – early onset persistent heavy smokers; (2) 136(13.5%) – late onset persistent smokers		164(16.2%) – early onset light smokers, who quit/reduce
Roberts, 2014 ‡	Non-smoker		(1) Late initiator, moderate consumption; (2) Early initiator, high consumption		Experimenter
Nelson, 2015*	345(38.8%)		(1) 102(11.5%); low stable 12 to 19. Increasing 19 to 23; (2) 168(18.9%); low stable 12 to 15. Increasing 15 to 23	(1) 89(10%) (2)87(9.8%)	99(11.1%); increasing 12 to 19. Stable 19 to 22. Decreasing 22 to 23
Orpinas, 2015*	437(71.5%)		(1) 69(11.3%); low stable grade 6 to grade 9. Increasing grade 9 to grade 12; (2) 50(8.2%); increasing grade 6 to grade 11. Stable grade 11 to grade 12		55(9%); increasing grade 6 to grade 9. Stable grade 9 to grade 10. Decreasing grade 10 to grade 12
Outcome variable[8]: Frequency of smoking					
Abroms, 2005*	544(41.2%)		(1) 442(33.5%); increasing fall 6th grade to spring 7th grade. Stable spring 7th grade to fall 9th grade; (2) 118(8.9%); low stable fall to spring 6th grade. Increasing spring 6th to 9th grade; (3) 184(13.9%); increasing fall 6th grade to 9th grade (4) 33(2.5%); increasing fall 6th to 9th grade		
Simons-Morton, 2005*	Treatment: 308(44.5%) Control: 262(41.7%)		Treatment: (1) 74(10.7%); increasing fall 6th grade to fall 9th grade (2) 78(11.2%); increasing fall to spring 6th grade. Stable spring 6th grade to fall 9th grade (3) 14(2%); increasing fall 6th grade to spring 7th grade. Stable spring 7th grade to fall 9th grade Control: (1) 75(11.9%): increasing fall 6th grade to fall 9th grade (2) 69(11%); increasing fall to spring 6th grade. Stable spring 6th grade to fall 9th grade (3) 20 (3.2%); increasing fall 6th grade to spring 7th grade. Stable spring 7th grade to fall 9th grade		Treatment: 218(31.5%); increasing fall 6th grade to spring 7th grade. Decreasing spring 7th grade to fall 8th grade. Increasing fall 8th grade to fall 9th grade. Control: 202(32.2%); increasing fall 6th grade to spring 7th grade. Stable spring 7th grade to fall 8th grade. Decreasing fall 8th grade to fall 9th grade.
Maggi, 2007*	46(6.8%)		106(38%); low stable 10-11 to 12-13. Increasing 12-13 to 16-17		(1) 17(6.8%); low stable 10-11 to 12-13. Increasing 12-13 to 14-15. Decreasing 16-17; (2) 15(5.2%); increasing 10-11 to 14-15.

					Decreasing 14-15 to 16-17 (3) 95(34%); increasing 10-11 to 12-13. Decreasing 12-13 to 14-15. Increasing 14-15 to 16-17
Bernat, 2008*	54%		(1) 17%; increasing 12 to 19; (2) 7%; increasing 12 to 16.5. Stable 16.5 to 19; (3) 8%; low stable 12 to 14. Increasing 14 to 18. Stable 18 to 19; (4) 10%; increasing 12 to 14. Stable 14 to 17. Increasing 17 to 19.		4%; increasing 12 to 15.5. Decreasing 15.5 to 19
Maggi, 2008*	1916(48.4%)		(1) 550(13.9%); low stable 10-11 to 14-15. Increasing 14-15 to 20-21; (2) 162(4.1%); low stable 10-11 to 14-15. Increasing 14-15 to 18-19. Stable 18-19 to 20-21; (3) 230(5.8%); increasing 10-11 to 16-17. Stable 16-17 to 20-21		(1) 681(17.2%); low stable 10-11 to 14-15. Increasing 14-15 to 18-19. Decreasing 18-19 to 20-21 (2) 416(10.5%); increasing 10-11 to 18-19. Decreasing 18-19 to 20-21
Kimber, 2009‡	264(40%)		(1) 258(39%) – largely moderate users; (2) 140(21%) – heavy users		
de Leeuw, 2010[8]*	267(62.3%)	27(6.3%); decreasing 15 to 18	76(17.7%); increasing 15 to 18	59(13.7%)	
Lynne-Landsman, 2010*	437(82%)		96(18%); increasing 9th to 12th grade		
Heron, 2011‡	2594(85.4%)		(1) 131(4.3%) – late-onset regular smokers; (2) 52(1.7%) – early-onset regular smokers		264(8.7%) - Experimenters
Hampson, 2013	684(71.0%)		(1) 141 (14.6%); increasing grade 9 to grade 12; (2) 82 (8.5%); increasing grade 9 to grade 11. Stable grade 11 to grade 12.	56(5.8%)	
Metzger, 2013*	64(18.6%)		(1) 185(53.8%); stable baseline to 15-month follow-up. Increasing 15-month follow-up to 24-month follow-up; (2) 95(27.6%); increasing baseline to 24-month follow-up		
Xie, 2013*	1715(48.7%)		(1) 1711(48.6%); increasing 12 to 13 years. Stable 13 to 15 years. Increasing 15 to 16 years; (2) 95(2.7%); increasing 12 to 16		
Musci, 2015‡			(1) 68% - low but increasing users; (2) 32% - moderate users		
Cance, 2017*	1526 (68%)	247 (11%)	(1) 247 (11%); low stable at 17-19. increasing 17-19 to 21-23. Stable 21-23 to 23-25; (2) 135 (6%); increasing 17-19 to 21-23. Stable 21-23 to 23-25		89 (4%); stable high 17-19 to 20-22. Decreasing 20-22 to 23-25
Dutra,	1205		(1) 533 (5.2%); low stable from 12-16 to 18-24 years.		701 (8.1%); increasing from 12-16 to

2017*	(13.6%)		Increasing from 18-24 to 26-30 years; (2) 3205 (39.0%); increasing from 12-16 to 22-26 years. Stable from 22-26 years to 26-30 years.		18-22 years. Decreasing from 18-22 to 25-29 years. Low stable from 26-30 years.
Chang, 2018*	1772 (71%)		(1) 560 (22%); increasing from 13 to 18 years; (2) 178 (7%); increasing from 13 to 17 years. Stable from 17 to 18 years		
Outcome variable[8]: Intensity and frequency of smoking					
Chassin, 2000* †[9]			(1) 843(12%); increasing 10 to 20. Stable 20 to 31; (2) 1108(16%); low stable 10 to 15. Increasing 15 to ~24. Stable ~24 to 31		(1) 367(5%); low stable 10 to 14. Increasing 14 to ~22. Decreasing ~22 to ~26. Stable ~26 to 31; (2) 393(6%); stable 10 to ~13. Increasing ~13 to ~17. Decreasing ~17 to 20. Stable 20 to 21
White, 2002*	148(39.6%)		155(41.4%); increasing 12 to 25. Stable 25 to 30-31		71(19%); increasing 12 to 18. Decreasing 18 to 30-31
Audrain-McGovern, 2004*	436(45%)		(1) 223(23%); increasing 9th to 12th grade; (2) 232(24%); increasing 9th to 12th grade; (3) 77(8%); increasing 9th to 10th grade. Stable 10th to 12th grade		
Orlando, 2004*	3253(55%)	532(9%); decreasing 13 to 18. Stable to 23	(1) 828(14%); Increasing 13 to 18. Stable 18 to 23; (2) 828(14%); Low stable 13 to 14. Increasing 14 to 23	473(8%)	
Tucker, 2005*		371(8.7%); decreasing 13 to 18. Stable to 23	(1) 593(14%); increasing 13 to 16. Stable 16 to 23; (2) 601(14.2%); increasing 13 to 23	333(7.8%)	2347(55.3%); increasing 13 to 15 years; decreasing 15 to 23 years.
Tucker, 2006*[10]	426(29.5%)	82(5.7%); decreasing 13 to 18. Stable to 23	(1) 123(8.5%); increasing 13 to 16. Stable 16 to 23; (2) 158(11%); increasing 13 to 23	69(4.8%)	584(40.5%); increasing 13 to 15 years; decreasing 15 to 23 years.
Audrain-McGovern, 2009*	556(61.2%)		(1) 241(26.5%); increasing 10th grade to 2 post high-school; (2) 112(12.3%); increasing 10th grade to 12th grade. Stable 12th grade to 2 post high-school		
Otten 2009*	120(38.4%)		145(46.5%); increasing 13 to 15	47(15.1%)	
Outcome variable[8]: Any use of cigarettes					
Maggi 2007*	1169(40.5%)		(1) 1423 (49.3%); increasing 10-11 to 14-15. Stable 14-15 to 16.17; (2) 294 (10.2%); increasing 10-11 to 16-17.		

Weden, 2012*	4044(63.7%)		(1) 933(14.7%); increasing 14 to 16. Stable 16 to 25; (2) 1194(18.8%); low stable 14 to 16. Increasing 16 to 25		171(2.7%); increasing 14 to 16. Decreasing 16 to 21. Increase 21 to 22, decrease 22 to 23, increase 23 to 24, and decrease 24 to 25.
Huang, 2013*	3897(75.8%)	159(3.1%); decreasing 12 to 18	1085(21.1%); increasing 12 to 18		
Lynne-Landsman, 2016*	561(82%)		21(3%); increasing baseline to 1-year follow-up	102(15%)	
TIME SINCE ONSET ANALYSES					
Outcome variable[8]: Intensity of smoking					
Rosendahl, 2008*			Males: (1) 21.1%; increasing 5th to 9th grade. Stable 9th grade to 3 after compulsory school; (2) Increasing 5th grade to 3 after compulsory school; (3) Low stable 5th to 9th grade. Increasing 9th grade to 3 after compulsory school. Females: (1) 159(14.7%); low stable 5th to 9th grade. Increasing 9th grade to 3 after compulsory school; (2) 198(18.3%); low stable 5th to 6th grade. Increasing 6th grade to 3 after compulsory school; (3) 273(25.2%); increasing 5th to 9th grade. Stable 9th grade to 3 after compulsory school		Males: Increasing 5th to 6th grade. Decreasing 6th to 7th grade. Increasing 7th to 8th grade. Decreasing 8th grade to 2 after compulsory school. Stable 2 to 3 after compulsory school Females: 283(26.1%); increasing 5th to 9th grade. Decreasing 9th grade to 3 after compulsory school
Karp, 2005*	267(72.4%)		41(11.1%); low stable baseline to 9-month follow-up. Increasing 9-month follow-up to end of follow-up		(1) 40(10.8%); increasing baseline to 18-month follow-up. Stable 18-month follow-up to 30-month follow-up. Decreasing 30-month follow-up to end of follow-up; (2) 21(5.7%); increasing baseline to 36-month follow-up. Decreasing 36-month follow-up to end of follow-up

Missing information (i.e. empty cells) in the table indicates that information was not clearly provided in the article. If articles do not provide the percentage or number of people in a given trajectory, the label assigned to that trajectory in the article is written in the appropriate column.

*Indicates studies which provided plots and descriptions of the shape of trajectories.

†Indicates studies which provide descriptions of the shape (including inflection points), but no plots of the trajectories.

‡Indicates studies which provide neither plots nor descriptions of the shape of trajectories.

[1]Refers to whether there was a trajectory of participants who remained at low levels of smoking throughout the study.

[2]Refers to whether there was a trajectory of smokers who decreased the frequency or intensity of smoking throughout the study.

[3]Refers to the age range over which participants decreased or increased their frequency or intensity of smoking. For studies which did not indicate age on the x-

axis, this range is given in terms of the value of the x-axis (e.g. school grade, months since baseline).
[4]Refers to whether there was a trajectory of smokers who increased their frequency or intensity of smoking throughout the study.
[5]Refers to whether there was a trajectory of smokers who consistently smoked, either at medium or high frequency or intensity, throughout the study.
[6]Provides a list and a brief description (i.e. inflection points, age ranges, etc.) of any additional reported trajectories.
[7]Trajectories in the "decreasing", "stable", and "other" groupings are included in the "other" grouping reported in the manuscript
[8]Refers to the way in which smoking was assessed: intensity was assessed as the number of cigarettes smoked over a given time period (day(s), week(s), month(s), year); frequency was assessed as the number of days on which participants smoked over a given time period (week(s), month(s), year); any use was assessed by asking participants whether they had ever smoked cigarettes or whether they had smoked in the past week/month/year with a yes/no response option.
[9]An "erratic" group was determined a priori and was not included in trajectory analyses
[10]The "abstainer" group was determined a priori and therefore not included in trajectory analyses

Table 25. (Article 1, Table S3) Further description of trajectories

First author and year of publication	Years of follow-up	Age at assessments[1]	Minimum no. data points required[2]	Density of measurements during adolescence (12-18 years)[3]	Information about distribution of smoking measure[4]	Dealt with attrition (Y/N) If Y, method used	Dealt with missing values (Y/N) If Y, method used
AGE/GRADE ANALYSES							
Outcome variable[5]: Intensity of smoking							
Colder 2001	4 years	12y, 12.6y, 13.6y, 14.6y, 15.6y, 16.6y	6	1.5	Y and N		
Guo 2002	5 years	13y, 14y, 15y, 16y, 18y	2	1	N		Y, multiple imputation
Vitaro 2004	3.5 years	9-11.5y, 9.5-12y, 10.5-13y, 11.5-14y, 12.5-15y		1.3	N		
Stanton 2004	9 years	9y, 11y, 13y, 15y, 18y	5	0.6	Y		Y, listwise deletion
White 2004	15 years	10y, 11y, 12y, 13y, 14y, 15y, 16y, 17y, 18y, 19y, 20y, 21y, 22y, 23y, 24y, 25y	1	1.2	N		N
Maggi 2007	6 years	10-11y, 12-13y, 14-15y, 16-17y	2-3	0.8	N		
Riggs 2007	12 years	12y, 12.5y, 13y, 14y, 15y, 16y, 17y, 18y, 19y, 20y, 21y, 22y, 23y, 24y		1.3	N		
Lessov-Schlaggar 2008	11 years	13.1y, 14.1y, 15.1y, 16.3y, 17.3y, 18.3y, 19.8y, 21.9y, 23y, 24y		1.2	N		
Otten 2008	2 years	12y, 13y, 14y	1	1.5	Y and N		
Chung 2010	4 years	13y, 14y, 15y, 16y, 17y		1.3	N		
Gabrhelik 2012	2.5 years	11-13y, 11.6-13.6y, 12-14y, 12.6-14.6y, 13-15y, 13.6-15.6y		2.4	N		Y, multiple imputation
Vuolo 2013	23 years	15y, 16y, 17y, 18y, 22y, 25y, 26y, 27y, 36y, 38y	1	1.3	N	N	N
Roberts 2014	11 years	T1 (12y) to T7 (23y)	1		N	Y, inverse probability weights	
Nelson 2015	11 years	12y, 13y, 14y, 15y, 17y, 18y, 19y, 22y, 23y	3	1	N		
Orpinas 2015	6 years	Grade 6, Grade 7, Grade 8, Grade 9 (14.8y), Grade 10, Grade 11, Grade 12			N		Y, maximum likelihood
Outcome variable[5]: Frequency of smoking							

Abroms 2005	3 years	T1(6th grade) to T5 (9th grade)	5		N		
Simons-Morton 2005	3 years	T1 (6th grade) to T5 (9th grade)	5		Y and N		
Maggi 2007	6 years	10-11y, 12-13y, 14-15y, 16-17y	2-3	0.8	N		
Bernat 2008	3 years	12-16y, 12.5-16.5y, 13-17y, 13.5-17.5y, 14-18y, 14.5-18.5y, 15-19y	4	2.4	N		
Maggi 2008	10 years	10-11y, 12-13y, 14-15y, 16-17y, 18-19y, 20-21y		0.7	N		
Kimber 2009	2 years	13-14y, 14-15y, 15-16y		1.5	Y and N		
de Leeuw 2010	3 years	15y, 16y, 17y, 18y		1.3	Y and N	Y, FIML	
Lynne-Landsman 2010	3 years	9th grade, 10th grade, 11th grade, 12th grade	1	1.3	Y	Y, FIML	
Heron 2011	2 years	14y, 15y, 16y	1-3	1.5	Y		Y, listwise deletion and multiple imputation
Hampson 2013	3 years	9th grade, 10th grade, 11th grade, 12th grade	1	1.3	N	Y; analysis of var related to attrition	Y, expectation maximization algorithm
Metzger 2013	2 years	15.6y, 16.1y, 17y, 17.9y		2.0	N		
Xie 2013	2 years	12-15y, 13-16y, 14-17y		1.5	Y (for sub-sample)	N	Y, expectation maximization algorithm
Musci 2015	9 years	12y, 13y, 14y, 15y, 16y, 17y, 18y, 19y, 21y		1.2	Y		Y, FIML
Cance 2017	6 years	17-19 fall, 17-19 spring, 18-20 fall, 18-20 spring, 19-21 fall, 19-21 spring, 20-22 fall, 21-23 fall, 22-24 fall, 23-25 fall	1	4	Y	Y; analysis of var related to attrition	Y; MLR missing data estimation
Dutra 2017	14 years	12-16y, 13-17y, 14-18y, 15-19y, 16-20y, 17-21y, 18-22y, 19-23y, 20-24y, 21-25y, 22-26y, 23-27y, 24-28y, 25-29y, 26-30y	3	1.2	N	N	Y; maximum likelihood
Chang, 2018	5 years	13y, 14y, 15y, 16y, 17y, 18y	4	1.2	N	Y, multiple imputation	Y, multiple imputation
Outcome variable[5]: Intensity and frequency of smoking							

Chassin 2000[6]	10 years	T1 (6th-12th grade) to T6 (21-31y)	2-3		N		
White 2002	18-19 years	12y, 15y, 18y, 25y, 30-31y	2	0.5	Y and N		
Audrain-McGovern 2004	3 years	14-15y, 15-16y, 16-17y, 17-18y	4	1.3	Y		Y, listwise deletion
Orlando 2004	10 years	13y, 14y, 15y, 16y, 18y, 23y	3	1	N	Y, weights	N
Tucker 2005	10 years	13y, 14y, 15y, 16y, 18y, 23y	3	1	N	Y, weights	N
Tucker 2006[7]	10 years	13y, 14y, 15y, 16y, 18y, 23y	3	1	N	Y, inverse probability weights	
Audrain-McGovern 2009	5 years	15y, 16y, 17y, 18y, 20y		1.3	N		N
Otten 2009	2 years	13y, 14y, 15y	2	1.5	N	Y; analysis of var related to attrition	Y, listwise deletion
Outcome variable[5]: Any use of cigarettes							
Maggi 2007	6 years	10-11y, 12-13y, 14-15y, 16-17y	2-3	0.8	N		
Weden 2012	10 years	14-15y, 16-17y, 18-19y, 20-21y, 22-23y, 24-25y	1	0.8	N		
Huang 2013	6 years	12y, 14y, 16y, 18y	8	0.7	Y and N		N
Lynne-Landsman 2016	1 year	T1 (<14-16y) to T5 (<15-17y)		5	N		Y, FIML
TIME SINCE ONSET ANALYSES							
Outcome variable[5]: Intensity of smoking							
Rosendahl 2008	7 years	11y, 12y, 13y, 14y, 15y, 17y, 18y		1.0	N	N	Y, replaced w/ 0 or left as missing
Karp 2005	4 years	13y, 13.3y, 13.6y, 13.9y, 14.2y, 14.5y, 14.8y, 15.1y, 15.4y, 15.7y, 16y, 16.3y, 16.6y, 16.9y	3	3.5	N	N	Y, listwise deletion

Note: Missing information (i.e. empty cells) in the table indicates that information was not clearly provided in the article. FIML = fill information maximum likelihood

[1]Age of participants at each time smoking was assessed. Some studies only reported age at baseline and end of follow-up or school grade rather than age.

[2]Minimum number of data points of smoking information required for participants to be included in the trajectory analyses
[3]Calculated as the number of data points during adolescence (12-18 years old) divided by the number of years covered during adolescence
[4]Refers to the variable used to generate the trajectories.
[5]Refers to the way in which smoking was assessed: intensity was assessed as the number of cigarettes smoked over a given time period (day(s), week(s), month(s), year); frequency was assessed as the number of days on which participants smoked over a given time period (week(s), month(s), year); any use was assessed by asking participants whether they had ever smoked or whether they had smoked in the past week/month/year with a yes/no response option.
[6] An "erratic" group was determined a priori and was not included in trajectory analyses
[7] The "abstainer" group was determined a priori and therefore not included in trajectory analyses. Y: yes. No: No. y: years.

Table 26. (Article 1, Table S4) Method used to estimate trajectories

First author and year of publication	No. traj considered; used[1]	Orders considered; used	Model comparison tools used[2]	Range of average posterior probabilities	Discussion of heterogeneity (Y/N)[3]	(Statistical Model) Software used
AGE/GRADE ANALYSES						
Outcome variable[4]: Intensity of smoking						
Colder 2001	; 5	Piecewise, linear, quadratic; quadratic	APP, BIC, substantive criteria		N	(LGMM) Mplus
Guo 2002	1-6; 5		BIC, substantive criteria		N	(LCGM) Proc Traj, SAS
Vitaro 2004	1-5; 4		BIC		N	(LCGM) Proc Traj, SAS
Stanton 2004	1-6; 6	Piecewise, linear, quadratic; quadratic	APP, BIC	0.87-0.98	N	(LGMM) Mplus
White 2004	2-4; 3	Quadratic; quadratic	BIC, APP	0.97-1.00	N	(LCGM) Proc Traj, SAS
Riggs 2007	--; 4	Linear, quadratic, cubic; cubic	BIC		N	(LCGM) Proc Traj, SAS
Lessov-Schlaggar 2008	3-6; 6		BIC, substantive criteria		N	(LCGM) Proc Traj, SAS
Otten 2008	1-4; 3	Zero order, linear, quadratic; quadratic	APP, BIC, LRT, substantive criteria	0.66-1.00	N	(LCGM) Proc Traj, SAS
Chung 2010	1-5; 4		BIC		N	(LCGM) Proc Traj, SAS
Gabrhelik 2012	1-4; 2		BIC, LRT, substantive criteria		Y	(GMM) Mplus
Vuolo 2013	1-7; 5		BIC, LRT, substantive criteria		N	(non-parametric LC trajectory A) Latent Gold
Roberts 2014	--; 4				N	(GMM) Mplus

Nelson 2015	2-8; 6		APP, BIC, OCC, substantive criteria		N	
Orpinas 2015	--; 4		APP, BIC, substantive criteria	0.97-1.00	N	(LCGM) Proc Traj, SAS
Outcome variable[4]: Frequency of smoking						
Abroms 2005	--; 5		BIC		N	(LGMM) Mplus
Simons-Morton 2005	--; 5		BIC		N	(LGCM) Mplus
Maggi 2007	--; 5		BIC		N	(LCGM) Proc Traj, SAS
Bernat 2008	2-7; 6	Linear, quadratic, cubic; cubic	APP, BIC		N	(LCGM) Proc Traj, SAS
Maggi 2008	1-8; 6		BIC, substantive criteria		N	(LCGM) Proc Traj, SAS
Kimber 2009	--; 3		BIC, substantive criteria		N	(non-parametric LCA for repeated measures) Latent Gold
de Leeuw 2010	2-6; 4	Linear, quadratic; quadratic	AIC, BIC, LRT, substantive criteria		N	(LCGA) Mplus
Lynne-Landsman 2010	--; 2		AIC, BIC, LRT, substantive criteria		N	(GMM) Mplus
Heron 2011	2-5; 4		Mplus: BIC, LRT, substantive criteria. Latent Gold: substantive criteria		N	(LCA for repeated analysis) Mplus & Latent Gold
Hampson 2013	1-5; 4		BIC, entropy, adjusted Lo-		N	(LCGA) Mplus

			Mendell-Rubin LRT			
Metzger 2013	--; 5	Linear, quadratic; quadratic			N	(GMM) Mplus
Xie 2013	2-4; 3		APP, BIC in SAS. BIC, LRT in Mplus	0.85-0.98	N	(LCGM) Proc Traj, SAS & Mplus
Musci 2015	1-4; 2		BIC, LRT, substantive criteria		N	(LCPA) Mplus
Cance 2017	--; 5	Linear, quadratic; quadratic	BIC, entropy, LRT, bootstrap LRT, APP, substantive criteria	0.88-0.99	Y	(LCGA) Mplus
Dutra 2017	1-5; 5		BIC, LRT, APP, substantive criteria	0.90-0.98	Y	(LCGA) Mplus
Chang 2018	2-4; 3		AIC, BIC, log Bayes factor, APP, substantive criteria	0.90-1.00	N	(LCGM) Proc Traj, SAS
Outcome variable[4]: Intensity and frequency of smoking						
Chassin 2000[5]	1-5; 6	Quadratic, cubic; cubic	BIC		N	(LCGM) Proc Traj, SAS
White 2002	2-4; 3	Linear, quadratic; quadratic	BIC		N	(LCGM) Proc Traj, SAS
Audrain-McGovern 2004	1-5; 4		BIC, LRT, substantive criteria		N	(LCGM) Mplus
Orlando 2004	--; 5	Linear, quadratic; quadratic	APP, BIC, substantive criteria	0.84-0.95		(LGMM) Mplus
Tucker 2005	--; 5	Linear, quadratic; quadratic	APP, BIC, substantive criteria		Y	(LGMM) Mplus

Tucker 2006[6]	4-5; 5		APP, BIC, substantive criteria	0.80-0.96	N	(LGMM) Mplus
Audrain-McGovern 2009	2-6; 5		APP, BIC, LRT, substantive criteria		N	(LGCM) Mplus Latent growth curve modeling followed by growth mixture modelling
Otten 2009	--; 3		BIC, LRT		N	(LCGM) Proc Traj, SAS
Outcome variable[4]: Any use of cigarettes						
Maggi 2007	--; 3		BIC		N	(LCGM) Proc Traj, SAS
Weden 2012	1-5; 4		AIC, BIC		N	mixture latent class analysis (LTA) Mplus
Huang 2013	2-4; 3	; linear	AIC, APP, BIC, substantive criteria		N	(LCGM) Proc Traj, SAS
Lynne-Landsman 2016	1-4; 3		AIC, BIC, LRT, substantive criteria		N	(GMM) Mplus
TIME SINCE ONSET ANALYSES						
Outcome variable[4]: Intensity of smoking						
Rosendahl 2008	--; 4		BIC	Males – 0.73-1.00. Females – 0.85-0.96	N	(LCGM) Proc Traj, SAS
Karp 2005	2-4; 4	Linear, quadratic, cubic; cubic	BIC	0.94-1.00	N	(LCGM) Proc Traj, SAS

Note: Missing information (i.e. empty cells) in the table indicates that information was not clearly provided in the article. LGMM: Latent growth mixture modeling. GMM: growth mixture modeling. LCA: Latent class analysis. LCGA: Latent class growth analysis. LTA: Latent trajectory analysis. LCGM: Latent class growth modeling. LGCM: Latent growth curve modeling. LCPA: Latent class-profile analysis

[1]Number of trajectories considered refers to the number of trajectories that were compared in the model selection process. Number used refers to the number of trajectories in the final model. If there was more than one model, then results from each trajectory model is reported

[2]Model comparison tools used include BIC (e.g. sample-adjusted BIC); LRT (e.g. (adjusted; Vuong or Lo-Mendell-Rubin likelihood ratio test, classification likelihood criterion, integrated completed likelihood criterion, (conditional) bootstrap likelihood ratio test, log-likelihood); APP; AIC; and substantive criteria (e.g. previous literature and previous cluster analyses of data, parsimony, selecting best-fitting model that maintained unique trajectories, utility of each trajectory group, trajectory group interpretability, theoretical understanding of trajectories, shape of trajectories, trajectory group sizes (i.e. proportion of people in each trajectory

group), entropy, maximum posterior probability, bivariate model fit information using Pearson's chi-square, bivariate residuals, % of standardized bivariate residuals > 4, number of (free) parameters, identification, scree test).

[3]Refers to whether alternative specifications of within-class heterogeneity were considered (e.g. some specifications can set this to zero, while others may allow it to be freely estimated). Wherever this information was not provided in the article the mention "N" would be listed.

[4]Refers to the way in which smoking was assessed: intensity was assessed as the number of cigarettes smoked over a given time period (day(s), week(s), month(s), year); frequency was assessed as the number of days on which participants smoked over a given time period (week(s), month(s), year); any use was assessed by asking participants whether they had ever smoked cigarettes or whether they had smoked in the past week/month/year with a yes/no response option.

[5] An "erratic" group was determined a priori and was not included in trajectory analyses

[6] The "abstainer" group was determined a priori and therefore not included in trajectory analyses

Table 27. (Article 1, Table S5) Risk factors and outcomes associated with trajectory group membership

First author and year of publication	Factors investigated as associated with trajectories[1]	Outcomes investigated[2]
AGE/GRADE ANALYSES		
Outcome variable[3]: Intensity of smoking		
Colder 2001		
Guo 2002		No. sexual partners past 12 months, inconsistent condom use past 12 months*
Vitaro 2004	Participant: maladjustment* (antisocial behavior and school maladjustment), sex. Parents: education, smoking*. Peers: smoking	
Stanton 2004	Participant: intention to smoke later in life*, no. of friends who smoke*, alcohol use, drunkenness, intention to get drunk later in life, smoked marijuana*, behaviour problems score*, social competence score, year level intending to leave school, attitude toward school, no. of changes to address in past 2 *, belongs to organized club*, attention deficit disorder score*, conduct disorder score*, trouble with police, help seeking for emotional or behavioural problem, depression score*, anxiety score, regular part—time job, life satisfaction scale, attachment to family, attachment to friends*, school qualification* Parents: smoking*, SES, occupation psychological symptoms*. Other: family relations index	
White 2004	Participant: race*, SES*	
Maggi 2007		
Riggs 2007	Participant: age/grade*, baseline cigarette use*, ethnicity*, intervention status, sex*	Adult nicotine dependence*, weekly cigarette use* at each wave of data collection
Lessov-Schlaggar 2008	Participant: age first smoked*, baseline age*, baseline nicotine dependence*, satisfaction with school performance*, sex*. Parents: education*, ever smoker*, income*.	Adult nicotine dependence*
Otten 2008	Participant: attitude, sex, SES, social preference. Parents: smoking. Peers: attitude, smoking involvement*, social preference.	
Chung 2010		
Gabrhelik 2012	Participant: sex*, intervention status*	
Vuolo 2013	Participant: age*, depressive affect, GPA, self-esteem, sex, race, close to parent respondent, older sibling smoker*. Parents: smoking trajectory*, marital status, education level, currently employed.	offspring smoking
Roberts 2014	Participant: history of sexual*, physical* and/or emotional* abuse. Mother: history of childhood sexual* and physical/emotional* abuse	
Nelson 2015	Participant: college attendance*, intervention status, sex*, race*	Problematic substance use*

Orpinas 2015		High school dropout*
Outcome variable[3]: Frequency of smoking		
Abroms 2005	Participant: social norms*, outcome expectations*, social competence, deviance acceptance*, depression*, friends who smoke*, problem behaving friends*, person at home smoke*, academic engagement, school adjustment, school climate, intervention status*, sex*, race. Parents: involvement, monitoring, expectation*. Other: parent-child conflict	
Simons-Morton 2005	Participant: race, sex*, intervention status*.	
Maggi 2007		
Bernat 2008	Participant: difficulty smoking in various places*, functional meaning of smoking*, no. of adults who smoke (belief)*, no. of teens who smoke (belief)*, perceptions of tobacco industry*, race*, sex. Parents: family structure*, smoking*. Peers: no. who smoke*. Other: community type*, adults smoke in home*	
Maggi 2008		
Kimber 2009	Participant: intervention status*, duration of intervention*, grade*, well-being, sex, neighbourhood SES	
de Leeuw 2010	Participant: sex, education*, Parents: smoking*, house rules. Both: quality* and frequency* of communication regarding smoking issues, non-smoking agreement*	
Lynne-Landsman 2010	Participant: sex*, lunch subsidy, intervention status. Parents: education*	Graduate on time*, antisocial personality disorder (lifetime)*, major depressive disorder, unsafe sex, pregnant*, alcohol abuse*, alcohol dependence, marijuana abuse, marijuana dependence*, illicit drug use*, criminal record*, non-violent juvenile crime(s)*, violent juvenile crime(s)*, non-violent adult crime(s), violent adult crime(s)
Heron 2011	Participant: sex*, parity*, baseline smoking*, baseline alcohol*, baseline maximum number of drinks*, baseline cannabis use*, conduct problems*. Mother: education*, adolescent alcohol use, adolescent binge drinking*, adolescent smoking*, adolescent cannabis*. Other: housing tenure*, overcrowding*	
Hampson 2013	Participant: sex*, smoking status (childhood/grade 4)*, received free or reduced-cost lunch*, initial level of sensation-seeking*, growth of sensation-seeking*	Smoking status (young adulthood)*, hookah smoking (young adulthood)*
Metzger 2013	Participant: baseline smoking*, problem communication with mother*, problem communication with father, less open communication with parents*, initiation of discussions about smoking behaviour, active secrecy with mothers*, information management (full disclosure vs concealment) strategies. Parents: initiation of discussions about smoking, maternal solicitation of teen smoking behaviour*, paternal	

	solicitation of teen smoking behaviour, maternal smoking disapproval*, paternal smoking disapproval	
Xie 2013	Participant: depressive symptoms*, attitudes toward smoking*, alcohol*, trouble with teachers*, like of school*, isolation, teacher sanctioning of smoking*, GPA*, school performance*. Parents: disapproval*, smoking*, sanctioning of smoking*. Family: relationships*, disharmony*. Peers: sanctioning of smoking*, smoking norm*	
Musci 2015	Participant: lunch subsidy*, intervention status, sex, genetic differences between sub-populations*	
Cance 2017		
Dutra 2017	Participant: race/ethnicity*, gender, employment status/school enrollment*, depression*, conduct problems/rebellion*, alcohol use*, marijuana use*, cocaine or other hard drugs use Parents: SES*, family stability* Peers: smoking*	Marital status*, number of children*, highest level of education
Chang 2018		Internalizing problems*
Outcome variable[3]: Intensity and frequency of smoking		
Chassin 2000[4]	Participant: health beliefs about smoking*, locus of control*, no. friends who smoke*, no. of parents who smoke*, psychological beliefs about smoking*, tolerance for deviance*, cohort*. Parents: support*	currently employed full-time, currently married, having children*, health beliefs*, life satisfaction, negative affect in past month*, personality risk*, positive affect in past month, psychological beliefs*, some college education*, stress
White 2002	Participant: sex*, SES, exposure to pregnancy smoking, self-esteem, self-derogation, depression, disinhibition*, cigarette attitudes, school attachment, grades*, drug use*, delinquency. Parent: smoking. Sibling: smoking. Peer: smoking	
Audrain-McGovern 2004	Participant: sex, novelty-seeking*, depressive symptoms*, alcohol use*, marijuana use*, GPA*, tobacco advertising receptivity*, team sport*, race*. Peers: smoking*	
Orlando 2004	Participant: exposure to adult smoking*, low resistance self-efficacy*, belief in smoking benefits*, marijuana use*, deviance*, poor grades*, lack of belief in smoking costs*, binge drinking*. Parents: smoking approval*. Peers: smoking*.	Currently married, college degree*, deviant behavior*, physical health*, mental health*, ever had alcohol problem*, ever had drug problem*
Tucker 2005[5]	Participant: sex, ethnicity, family status. Parents: education[4]	Currently married, college degree*, stealing*, selling drugs*, predatory violence*, mental health*, alcohol problem*, drug problem*, poor physical health*
Tucker 2006[6]	Participant: race*. Parents: education*. Other: family structure*	Early sexual activity*, early parenthood*, early marriage, college degree*, employment income in past year*, welfare

		assistance in past year*, physical health*, mental health*, arrest history*, job problems, alcohol abuse*, drug abuse*, abortion*
Audrain-McGovern 2009	Participant: sex, race, delay discounting*, novelty-seeking*, ADHD-attention*, ADHD-hyperactivity, depression symptoms, academic performance*, alcohol use*, marijuana use*. Household: smoking. Peer: smoking*.	
Otten 2009	Participant: disruptiveness (6y)*, disruptiveness (7-12y) sex*, SES, social preference*. Parents: smoking. Peers: disruptiveness	
Outcome variable[3]: Any use of cigarettes		
Maggi 2007		
Weden 2012	Participant: baseline age*, sex*, race/ethnicity*. Mother: smoking history*, age at birth*, education level, marital status*, breastfed child, prenatal care, adolescent delinquency score*.	
Huang 2013		Adult obesity trajectory*
Lynne-Landsman 2016	Participant: race, sex.	
TIME SINCE ONSET ANALYSES		
Outcome variable[3]: Intensity of smoking		
Rosendahl 2008	Participant: sex*. Parents: education*, tobacco use*. Peer: tobacco use*. School environment: tobacco use*.	
Karp 2005	Participant: age, sex*, poor academic performance*, >50% of friends smoke*, school with clear rules on smoking, confident in ability to succeed in school. Parents: tobacco use, education.	Nicotine dependence*, tolerance*

Note: Missing information (i.e. empty cells) in the table indicates that information was not clearly provided in the article.

[1]Refers to risk factors of smoking trajectory class membership. If both univariate and multivariate results are presented in the article, only the multivariate will be reported. (If no such results are reported, the column will be left blank). *Indicates a risk factor variable which was significantly associated with the smoking trajectories ($p<0.05$).

[2]Refers to whether the study examined the potential effect(s) of the smoking trajectory class membership on particular outcome(s). The particular outcomes studied are listed in the column. *Indicates an outcome variable which was significantly associated with the smoking trajectories ($p<0.05$).

[3]Refers to the way in which smoking was assessed: intensity was assessed as the number of cigarettes smoked over a given time period (day(s), week(s), month(s), year); frequency was assessed as the number of days on which participants smoked over a given time period (week(s), month(s), year); any use was assessed by asking participants whether they had ever smoked cigarettes or whether they had smoked in the past week/month/year with a yes/no response option.

[4] An "erratic" group was determined a priori and was not included in trajectory analyses

[5]Tucker 2005: authors indicate that these variables were used as risk factors of trajectory group membership but do not provide any information on whether they were significant risk factors or not

[6] The "abstainer" group was determined a priori and therefore not included in trajectory analyses

Table 28. (Article 1, Table S5a) Number of articles[1] that investigated a potential factor associated with trajectory group membership, and among these articles, the number that reported a statistically significant association

	Age/grade analyses			Time-since-onset analyses		
	First author, date	n	Reported significant association[2] n	First author, date	n	Reported significant association n
Sociodemographic factors[3]						
Baseline age, grade (education level, school enrollment)[4]	Lessov-Schlaggar 2008, Bernat 2008, Orpinas 2016, de Leeuw 2010, Weden 2012, Dutra 2017	6	6	Karp 2005	1	0
Sex, gender	Vitaro 2004, Lessov-Schlaggar 2008, Otten 2008, Nelson 2015, Bernat 2008, Otten 2009, Orpinas 2016, White 2002, Gabrhelik 2012, Abroms 2005, de Leeuw 2010, Lynne-Landsman 2010, Heron 2011, Metzger 2013, Musci 2015, Hampson 2013, Audrain-McGovern 2004, Orlando 2004, Audrain-McGovern 2009, Weden 2012, Lynne-Landsman 2016, Dutra 2017	22	10	Karp 2005, Rosendahl 2008	2	2
Race, ethnicity (white, black, Hispanic, Asian, other, non-white)	White 2004, Nelson 2015, Bernat 2008, Orpinas 2016, Abroms 2005, Metzger 2013, Audrain-McGovern 2004, Weden 2012, Lynne-Landsman 2016, Orlando 2004, Tucker 2006, Audrain-McGovern 2009, Dutra 2017	13	10	-	-	-
Socioeconomic status	White 2004, Otten 2009, White 2002	3	1	-	-	-
Parental education	Vitaro 2004, Lessov-Schlaggar 2008, Lynne-Landsman 2010, Heron 2011, Orlando 2004, Tucker 2006, Weden 2012, Dutra 2017	8	6	Karp 2005, Rosendahl 2008	2	1
Household income	Lessov-Schlaggar 2008, Otten 2008, Dutra 2017	3	2	Karp 2005	1	0
Father's occupation	Stanton 2004	1	0	-	-	-
Free or reduced lunch	Musci 2015, Hampson 2013	2	2	-	-	-
Housing tenure	Heron 2011	1	1	-	-	-
No. of address changes in past 2yrs	Stanton 2004	1	1	-	-	-
Overcrowding	Heron 2011	1	1	-	-	-
Community type (urban, rural, small city)	Bernat 2008	1	1	-	-	-

Parity	Heron 2011	1	1	-	-	-
Psychosocial factors						
Behavior problems (maladjustment, delinquency, conduct disorder score)	Stanton 2004, Otten 2009, Vitaro 2004, White 2002, Weden 2012, Heron 2011, Dutra 2017	7	6	-	-	-
Sensation-seeking, disinhibition	Hampson 2013. White 2002	2	2	-	-	-
Novelty-seeking, impulsivity	Audrain-McGovern 2004, Audrain-McGovern 2009	2	2	Karp 2005	1	0
Tolerance for deviance	Chassin 2000, Abroms 2005, Orlando 2004	3	3	-	-	-
Locus of control	Chassin 2000	1	1	-	-	-
Delay discounting	Audrain-McGovern 2009	1	1	-	-	-
Child's sexual, physical, emotional abuse	Roberts 2014	1	1	-	-	-
Life satisfaction	Stanton 2004	1	0	-	-	-
Social competence	Stanton 2004, Abroms 2005	2	0	-	-	-
Social preference (popularity among peers, isolation from peers)	Otten 2008, Otten 2009, Xie 2013	3	1	-	-	-
Friend-related psychosocial factors						
Peers' antisocial behavior, friends' disruptiveness, problem-behaving friends	Otten 2009, Abroms 2005	2	1	-	-	-
Attachment to friends	Stanton 2004	1	1	-	-	-
Friend support	Chassin 2000	1	0	-	-	-
Friend strictness	Chassin 2000	1	0	-	-	-
Peers' social preference	Otten 2008	1	0	-	-	-
Smoking-related psychosocial factors						
Low self-efficacy for smoking resistance	Orlando 2004	1	1	-	-	-
Beliefs about smoking (belief in smoking benefits, outcome expectations, smoking difficulty, lack of belief in smoking costs, psychological beliefs, social beliefs, functional meaning of smoking	Bernat 2008, Chassin 2000, Abroms 2005, Orlando 2004,	4	4	-	-	-
Attitude(s) toward smoking	Otten 2008, White 2002, Xie 2013	3	1	-	-	-
Intention to smoke	Stanton 2004	1	1	-	-	-
Smoking social norms	Abroms 2005	1	1	-	-	-
Perception of tobacco industry (tobacco ad receptivity)	Bernat 2008, Audrain-McGovern 2004	2	2	-	-	-
Mental health						
Depression, depressive symptoms	White 2002, Xie 2013, Stanton 2004, Abroms 2005, Audrain-McGovern 2004, Audrain-McGovern 2009, Dutra 2017	7	6	Karp 2005	1	0
Anxiety	Stanton 2004	1	0	-	-	-

Stress		-	-	Karp 2005	1	0
Self-esteem, self-derogation	White 2002	1	0	Karp 2005	1	0
Attention deficit disorder score, ADHD-attention, ADHD-hyperactivity	Stanton 2004, Audrain-McGovern 2009	2	1	-	-	-
Help-seeking for emotional or behavioral problem	Stanton 2004	1	0	-	-	-
Internalizing problems (depressive symptoms, social anxiety, and social loneliness)	Chang 2018	1	1	-	-	-
Academic-related variables						
Academic performance (grades, GPA, school performance, school qualification)	White 2002, Xie 2013, Audrain-McGovern 2004, Orlando 2004, Audrain-McGovern 2009, Lessov-Schlaggar 2008, Stanton 2004	7	7	Karp 2005	1	1
School-related attitudes (value/expectations placed on academic success and independence, confident in ability to succeed at school, academic engagement, school adjustment, school attachment, perceived trouble with teachers, likes school	Chassin 2000, Abroms 2005, White 2002, Stanton 2004, Xie 2013	5	1	Karp 2005	1	0
Year level intending to leave school	Stanton 2004	1	0	-	-	-
School climate	Abroms 2005	1	0	-	-	-
College attendance[5]	Nelson 2015	1	1	-	-	-
Smoking-related factors						
(Prior to) Baseline cigarette use, age first tried smoking	Riggs 2007, Lessov-Schlaggar 2008, Heron 2011, Metzger 2013, Hampson 2013	5	5	-	-	-
Baseline nicotine dependence	Lessov-Schlaggar 2008	1	1	-	-	-
Smoking in social environment						
No. of adults who smoke	Bernat 2008	1	1	-	-	-
School-related smoking (school has clear smoking rules, teachers/staff smoke near school, attends school where breaking smoking rules results in punishment, attends school where many students smoke where they are not allowed to, teachers sanction smoking, baseline prevalence of tobacco use in class	Xie 2013	1	1	Karp 2005, Rosendahl 2008	2	1
Family-related smoking						
Home smoking rules (smoking policies, non-	Bernat 2008, de Leeuw 2010. Metzger 2013	3	2	-	-	-

smoking agreement, family rules about substance use)						
Sibling smoking	White 2002	1	0	-	-	-
Parents' smoking, tobacco use, ever smoker, no. parents who smoke, household smoking, persons at home smoke, adult smoking	Vitaro 2004, Lessov-Schlaggar 2008, Otten 2008, Bernat 2008, Otten 2009, Chassin 2000, White 2002, Xie 2013, Abroms 2005, de Leeuw 2010, Orlando 2004, Audrain-McGovern 2009	12	8	Karp 2005, Rosendahl 2008	2	1
Mother smokes	Stanton 2004, Heron 2011, Metzger 2013, Weden 2012	4	3	-	-	-
Father smokes	Stanton 2004, Metzger 2013	2	0	-	-	-
Parental disapproval/sanctioning of smoking	Xie 2013, Orlando 2004, Metzger 2013	3	3	-	-	-
Parent communication (about smoking)	de Leeuw 2010, Metzger 2013	2	2	-	-	-
Parental smoking expectancies	Metzger 2013	1	0	-	-	-
Friend-related smoking						
Peer and friends smoking	Vitaro 2004, Otten 2008, Bernat 2008, Chassin 2000, White 2002, Stanton 2004, Abroms 2005, Audrain-McGovern 2004, Orlando 2004, Audrain-McGovern 2009, Dutra 2017	11	10	Karp 2005, Rosendahl 2008	2	2
Peer smoking attitudes, peer sanctioning of smoking, friend smoking norm	Otten 2008, Xie 2013	2	1	-	-	-
Family-related variables						
Family functioning (family relationships, parent-child conflict, family disharmony, parental involvement, monitoring, support, strictness, expectation, warmth)	Xie 2013, Stanton 2004, Abroms 2005, de Leeuw 2010, Chassin 2000, Metzger 2013	6	2	-	-	-
Nuclear family, two-parent family	Bernat 2008, Orlando 2004, Tucker 2006, Dutra 2017	4	4	-	-	-
Attachment to family	Stanton 2004	1	0	-	-	-
Maternal characteristics						
Obtained prenatal care	Weden 2012	1	0	-	-	-
Age at birth	Weden 2012	1	1	-	-	-
Breastfed child	Weden 2012	1	0	-	-	-
Smoked during pregnancy	White 2002	1	0	-	-	-
Marital status when child was age 14	Weden 2012	1	1	-	-	-
Maternal weekly alcohol use when child was age 12	Heron 2011	1	0	-	-	-
Maternal alcohol binge when child was age 12	Heron 2011	1	1	-	-	-

Maternal cannabis use when child was age 9	Heron 2011	1	1	-	-	-
Mother's psychological symptoms	Stanton 2004	1	1	-	-	-
Mother's abuse (sexual, physical, emotional)	Roberts 2014	1	1	-	-	-
Other						
Alcohol use (been drunk, binge drinking)	Xie 2013, Stanton 2004, Audrain-McGovern 2004, Audrain-McGovern 2009, Orlando 2004, Heron 2011	7	6	-	-	-
Intention to get drunk	Stanton 2004	1	0	-	-	-
Cannabis use (marijuana, pot)	Stanton 2004, Heron 2011, Audrain-McGovern 2004, Orlando 2004, Audrain-McGovern 2009, Dutra 2017	6	6	-	-	-
Drug use (other illicit drugs)	White 2002, Dutra 2017	2	2	-	-	-
Team sport	Audrain-McGovern 2004	1	1	-	-	-
Extracurricular activities (belongs to organized club, regular part-time job)	Stanton 2004	1	1	-	-	-
Genetics (polygenic score, population stratification)	Musci 2015	1	1	-	-	-
Environmental profile (parental monitoring, peer substance use)	Musci 2015	1	1	-	-	-

[1]When two or more articles used the same data, they were included as separate articles.
[2]The direction of associations is not reported due to heterogeneity across articles in the trajectory group used as the reference group.
[3]If a factor was studied in both univariate and multivariate models, results from the latter are reported.
[4]Variables in parentheses are the labels used by the authors to describe the concept of interest.
[5]It is not clear how "college" is defined in this study. Authors indicate college attendance both as a baseline variable and as an outcome.
[6]This table is the same as Table 7 (Article 1 Table 3), but is reproduced here as this earlier version was slightly clearer and easier to follow.

Table 29. (Article 1, Table S6) Items[1] reported from the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) checklist

First author and year of publication	1	2	3a	3b	3c	4	5	6a	6b	7	8	9	10	11	12	13	14a	14b	14c	15[2]	16
AGE/GRADE ANALYSES																					
Outcome variable[3]: Intensity of smoking																					
Colder 2001	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes		No	Yes	No	No	No	Yes	No	No	Yes	No
Guo 2002	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No
Vitaro 2004	No	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No
Stanton 2004	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No
White 2004	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No
Maggi 2007	Yes	No	No	Yes	Yes	No	Yes	No	No	No		No	Yes	No	No	No	Yes	No	No	No	No
Riggs 2007	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	Yes	No	No	No	No
Lessov-Schlaggar 2008	Yes	No	No	Yes	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No
Otten 2008	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No	Yes	No	No	Yes	No
Chung 2010	Yes	No	No	No	No	No	Yes	No	No	No		No	Yes	Yes	No	No	Yes	No	No	No	No
Gabrhelik 2012	Yes	No	No	No	Yes	No	Yes	Yes	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No
Vuolo 2013	No	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No
Roberts 2014	Yes	No	No	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Nelson 2015	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No
Orpinas 2015	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Outcome variable[3]: Frequency of smoking																					
Abroms 2005	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Simons-Morton 2005	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Maggi 2007	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No		No	Yes	No	No	No	Yes	No	No	No	No
Bernat 2008	Yes	No	No	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No
Maggi 2008	Yes	No	No	Yes	No	Yes	Yes	No	No	No		No	Yes	Yes	No	No	Yes	No	No	No	No
Kimber 2009	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
de Leeuw 2010	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No	Yes	No	No	No	No
Lynne-Landsman 2010	Yes	No	Yes	No	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Heron 2011	No	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	Yes	No	No	No	No	No
Hampson 2013	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No
Metzger 2013	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No

Xie 2013	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No
Musci 2015	No	No	Yes	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	No	No
Cance 2017	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No		No	Yes	Yes	No	Yes	Yes	No	No	No	No
Dutra 2017	Yes	No	No	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No	Yes	No	No	No	No
Chang 2018	Yes	No	No	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No
Outcome variable[3]: Intensity and frequency of smoking																					
Chassin 2000	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	No	Yes	No	No	No	No
White 2002	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No	Yes	No	No	No	No
Audrain-McGovern 2004	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No	No
Orlando 2004	No	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	Yes	No
Tucker 2005	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Tucker 2006	Yes	No	No	No	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Audrain-McGovern 2009	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No
Otten 2009	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Outcome variable[3]: Any use of cigarettes																					
Maggi 2007	Yes	No	No	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Weden 2012	Yes	No	No	No	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes	No	No	No	No
Huang 2013	Yes	No	No	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes	No	No	No	No
Lynne-Landsman 2016	Yes	No	Yes	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No
TIME SINCE ONSET ANALYSES																					
Outcome variable[3]: Intensity of smoking																					
Rosendahl 2008	Yes	No	No	No	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Karp 2005	Yes	No	No	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	Yes	No	No	Yes	No

Note: Missing information (i.e. empty cells) in the table indicates that information was not clearly provided in the article.

[1]1-Is the metric of time used in the statistical model reported? 2-Is information presented about the mean and variance of time within a wave? 3a-Is the missing data mechanism reported? 3b-Is a description provided of what variables are related to attrition/missing data? 3c-Is a description provided of how missing data in the analyses were dealt with? 4-Is information about the distribution of the observed variables included? 5-Is software mentioned? 6a-Are alternative specifications of within-class heterogeneity considered (e.g., LGCA vs LGMM) and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration? 6b-Are alternative specifications of the between-class differences in variance-covariance matrix structure considered and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration? 7-Are alternative shape/functional forms of the trajectories described? 8-If covariates have been used can analyses still be replicated? 9-Is information reported about the number of random start values and final iterations included? 10-Are the model comparison (and selection) tools described from a statistical perspective? 11-Are the total number of fitted models reported, including a one-class solution? 12-Are the number of cases per class reported for each model (absolute sample size, or proportion)? 13-If classification of cases in a trajectory is the goal, is entropy reported? 14a-Is a plot included with the estimated mean trajectories of the final solution? 14b-Are plots included with the estimated mean trajectories for each model? 14c-Is a plot included of the combination of estimated means of the final

model and the observed individual trajectories split out for each latent class? 15-Are characteristics of the final class solution numerically described (i.e., means, *SD/SE, n,* CI, etc.)? 16-Are the syntax files available (either in the appendix, supplementary materials, or from the authors)?

[2]Note that no article reported all the required information

[3]Refers to the way in which smoking was assessed: intensity was assessed as the number of cigarettes smoked over a given time period (day(s), week(s), month(s), year); frequency was assessed as the number of days on which participants smoked over a given time period (week(s), month(s), year); any use was assessed by asking participants whether they had ever smoked cigarettes or whether they had smoked in the past week/month/year with a yes/no response option.

Appendix 2

Additional Material (Manuscript 1)

The current appendix presents additional information relating to the literature review methods. (Manuscript 1)

The literature review was undertaken in nine steps: developing review criteria, carrying out the literature searches, selecting the articles for data abstraction, obtaining an inter-rater reliability coefficient for the article selection process (definition of the concepts of reliability and validity is provided in section 8.3.2), data abstraction, summarizing the abstracted data, and determining whether specific design features could have influenced the number or shape(s) of trajectories identified. The following paragraphs provide additional information on certain steps of this process. Guidelines suggested by van de Schoot 2017 [34] for reporting latent trajectory studies (i.e., described in Section 2.2.5), as well as the PRISMA (i.e., Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [94] were used to guide the review process. (See also Appendix 3)

Review criteria

Step 1: Following discussion of the aims of the literature review, three authors (BL, JO'L, MPS) developed a set of criteria to guide the article selection process. The central aim of these criteria was to focus the review on articles pertaining to trajectories of cigarette smoking in adolescence - defined herein as ages 12-18 years - which modeled population variability as separate trajectory groups. We sought to focus the review on articles dealing with empirically derived trajectory models (i.e., rather than trajectory models defined a priori, as described in Section 2.2.3).

The review criteria retained are listed in Table 30. As recommended by the PRISMA guidelines [94], a flow diagram of the article selection process and results is provided in Figure 1 of Article 1. (Chapter 4)

Table 30. Review criteria for the title, abstract, and article review stages[5]

Criterion relates to content, design, or analysis?	Criterion	Example(s)	Exclusion or inclusion criterion?
Content	Articles not reporting active cigarette smoking (articles pertaining only to e-cigarettes were also excluded)	Articles reporting environmental smoking only	Exclusion
		Studies dealing only with clinicians' practices in relation to patient smoking	
		Articles not dealing with cigarette smoking (e.g., cannabis use)	
Design	Cross-sectional design or analyses (no longitudinal analysis)	---	Exclusion
Design	Literature reviews (articles with no original data and/or no original analyses)	---	Exclusion
Design	Qualitative analyses only	---	Exclusion
Analyses	Analyses used < 3 data points between ages 12-18[1]	---	Exclusion
Analyses	Analyses with a single overall trajectory (i.e., no separate and empirically derived groups of cigarette smoking trajectories)[2,3]	---	Exclusion
Analyses	Studies where all the smoking trajectories were defined a priori, rather than empirically (i.e. using the data)[4]	One study[6] modeled four waves of data; prior to any examination of the data 3 trajectory groups were defined (at each of the 4 waves participants were placed into one of 3 cigarette smoking categories; smoking groups were then formed using the 4 waves of data (see also	Exclusion

		section 2.2.3))	
Analyses	Studied cigarette smoking trajectories (i.e., articles dealing only with joint trajectories of cigarette smoking with other variable(s) were not included)	---	Inclusion

[1]Where possible we used mean age as a basis for these decisions rather than the age range.
[2]Articles which examined specific risk factors(s) for a "mean" or "average" cigarette smoking trajectory were also excluded.
[3]Articles which determined whether a "mean" or "average" trajectory of cigarette smoking differed between intervention and control groups (i.e., in relation to a specific intervention) were excluded.
[4]Some trajectories could be defined a priori without this resulting in the exclusion of the article: an example is the exclusion of subjects who never smoked during the study which can be considered to be a cigarette smoking trajectory defined a priori.
[5]Articles which present only joint trajectories of smoking (i.e., of cigarette smoking with a second variable) were also excluded from our review.
[6]From the following reference: Windle M, Windle RC. Depressive Symptoms and Cigarette Smoking Among Middle Adolescents: Prospective Associations and Intrapersonal and Interpersonal Influences. *Journal of Consulting and Clinical Psychology* 2001; 69(2):215-26.

Article selection process

Steps 2 to 5: The article selection process is described in the Methods section of Article 1. (Chapter 4)

Inter-rater reliability

Step 6: Three authors (BL, SE, CBC) assessed a subset of titles, abstracts, and articles independently. The three final lists of articles retained were compared. Inter-rater reliability kappa values were computed using Proc Freq in SAS version 9.4 for Windows [166] with BL designated as the gold standard, and SE and CBC as separate comparatives. Kappa values were 0.79 between SE and BL and 0.85 between CBC and BL, which should correspond to "substantial" to "almost perfect" agreement, according to Cohen's recommendations. [164]

Data abstraction

Step 7: Following guidelines suggested by van de Schoot (2017) [34] for reporting latent trajectory studies, data were extracted from each article as described in chapter 4. The information is presented in Tables 5-8 (Article 1), as well as in Tables 23-29, in Appendix 1.

Study quality

We elected not to carry out a formal assessment of study quality in our review. An example of a guide to assessing potential bias in studies and study quality is provided/recommended by the Cochrane Consumers and Communication Review Group. [218] In the context of a previous systematic review [20], our research group conducted an extensive examination of tools for quality assessment. These, including the Cochrane Collaboration's tool for assessing risk of bias [219], were geared primarily to intervention studies and were therefore not relevant for the current review. The tools identified also typically scored studies based on an algorithm, however the distribution and weighting of similar domains across tools in one comparison carried out across 86 such tools were found to be variable and inconsistent. [220]

We did however use published recommendations for reporting latent trajectory studies [34] and created a table describing whether each of these items was reported in the studies retained. (Table 29) This information was later transformed into a figure for easier visual interpretation. (Figure 2 of Article 1)

Summarizing data, effect(s) of design features

Step 8: Given the wide variability in cigarette smoking measures used, Tables 23-29 (Appendix 1) as well as Tables 5-8 of Article 1 group the studies by type of outcome variable used in the trajectory models (i.e., intensity of smoking, frequency of smoking, intensity and frequency of smoking, any use of cigarettes). Studies were also grouped according to whether they presented models of incident or mixed (i.e., incident and prevalent combined) cigarette smoking trajectories.

We also grouped the reported trajectory shapes into broad categories selected to make our reporting of these groups as objective and reproducible as possible, including: low stable, decreasing, increasing, stable (i.e., stable at medium or high levels of smoking), and "other" types of trajectory shapes. (Table 24) This was later grouped further into the categories: low stable, increasing, and other. (Table 6) We also reported selected items pertaining to the methodologies used, as suggested by van de Schoot 2017. [34] (Table 26) Finally, we reported the risk factors for and outcomes of the trajectories reported for each article, as well as which

associations were statistically significant. (Table 27) We further summarized the information on risk factors and outcomes into two additional tables: the first table (Table 28) lists all articles which studied and reported results for each potential risk factor, as well as how many studies reported a statistically significant association (we separated these results according to whether studies reported incident or mixed cigarette smoking trajectories). The second/final table (Table 8 of Article 1) provides the same results for outcomes of cigarette smoking trajectories.

Step 9: To determine whether selected study design features might have influenced the number or shapes of trajectories identified, we collapsed studies into broad categories according to these features. These results are further described in Chapter 4 and results are presented in Table 6. (Article 1)

Categorization of trajectories

As stated in Article 1 (Chapter 4), "we categorized each trajectory in each article into one of three broadly defined groups based on visual inspection of the curves (…). Trajectories representing the lowest level of smoking across all time-points in each article were categorized as "low-stable." An "increasing" group comprised trajectories in which level of smoking increased; although the time-point at which the slope increased, and rate of increase differed. All other trajectories, which generally comprised trajectories that increased and then decreased or decreased and then increased were labelled "other"."

The ranges of proportions of participants reported correspond to the proportions of participants (i.e., proportion of the analytical sample) reported to be in each type of trajectory (i.e., low-stable, increasing, or other) compiled across the individual studies.

Risk factors, outcomes

The reason Tables 7, 8 (Article 1), and 28 (Appendix 1) do not report actual measures of association or confidence intervals is as follows.

With regards to potential risk factors for cigarette smoking trajectory group(s), there were several features of the literature on cigarette smoking trajectories which made it very difficult to summarize the reported associations beyond a simple statement recording how many studies reported a significant association for a particular variable. In general, there was

considerable missing information in the published studies with regards to how the potential risk factor variables were coded: for this reason it was frequently not possible to determine the reference category used, and frequently the way in which the variable was coded was not stated. Additionally, while articles did sometimes refer to a previous publication with regards to the coding of variables, it was frequently unclear whether the variable in question had been used exactly as described in the earlier reference in question as opposed to being further modified (e.g., dichotomized). Additional limitations also applied specifically to the variable race/ethnicity as a potential risk factor: one issue when attempting to summarize this variable was whether it could or should be summarized across countries (i.e., because different countries can vary quite extensively with regard to ethnic makeup). Furthermore, even within a country such as the United States, different comparisons such as African American (when compared with all other ethnicities) and Asian American (when compared with all other ethnicities) could not easily be amalgamated since the effect of ethnicity might well depend on the particular ethnicity(ies) being studied. A further difficulty which arose was the complexity of the outcome (i.e., cigarette smoking trajectory group): while we did attempt to limit our summary of risk factors to comparisons of increasing and high degree of smoking (compared with low level non increasing and/or non smokers) summarizing this literature was greatly complicated by the varying numbers and shapes of trajectories reported across individual studies.

(Most of the above issues also affected our ability to synthesize results across studies with regards to reported outcomes of cigarette smoking trajectory(ies).)

Appendix 3

PRISMA 2009 Statement Checklist (Article 1)

Table 31. PRISMA 2009 Statement Checklist (Article 1)[1]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	47
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	47
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	47, 48
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	47, 48
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	48
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	48
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	48
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	48; Appendix 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	48; Appendix 2

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	48; Appendix 1-2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**Appendix 2 (where applicable)**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	48; Appendix 1-2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**48; Appendix 1-2 (where applicable)**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**Appendix 2**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**48; Appendix 1-2**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Appendix 2 (where applicable)**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2, Tables 5-8 (Article 1)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**Not applicable**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	See Appendix 2 (where applicable); Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**Not applicable**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	53

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	58
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	53-59
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	59

[1]*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 4

Additional Tables and Figures (Manuscript 2)

Figure 9. (Manuscript 2, Figure S1) Flow chart indicating the derivation of the analytic samples

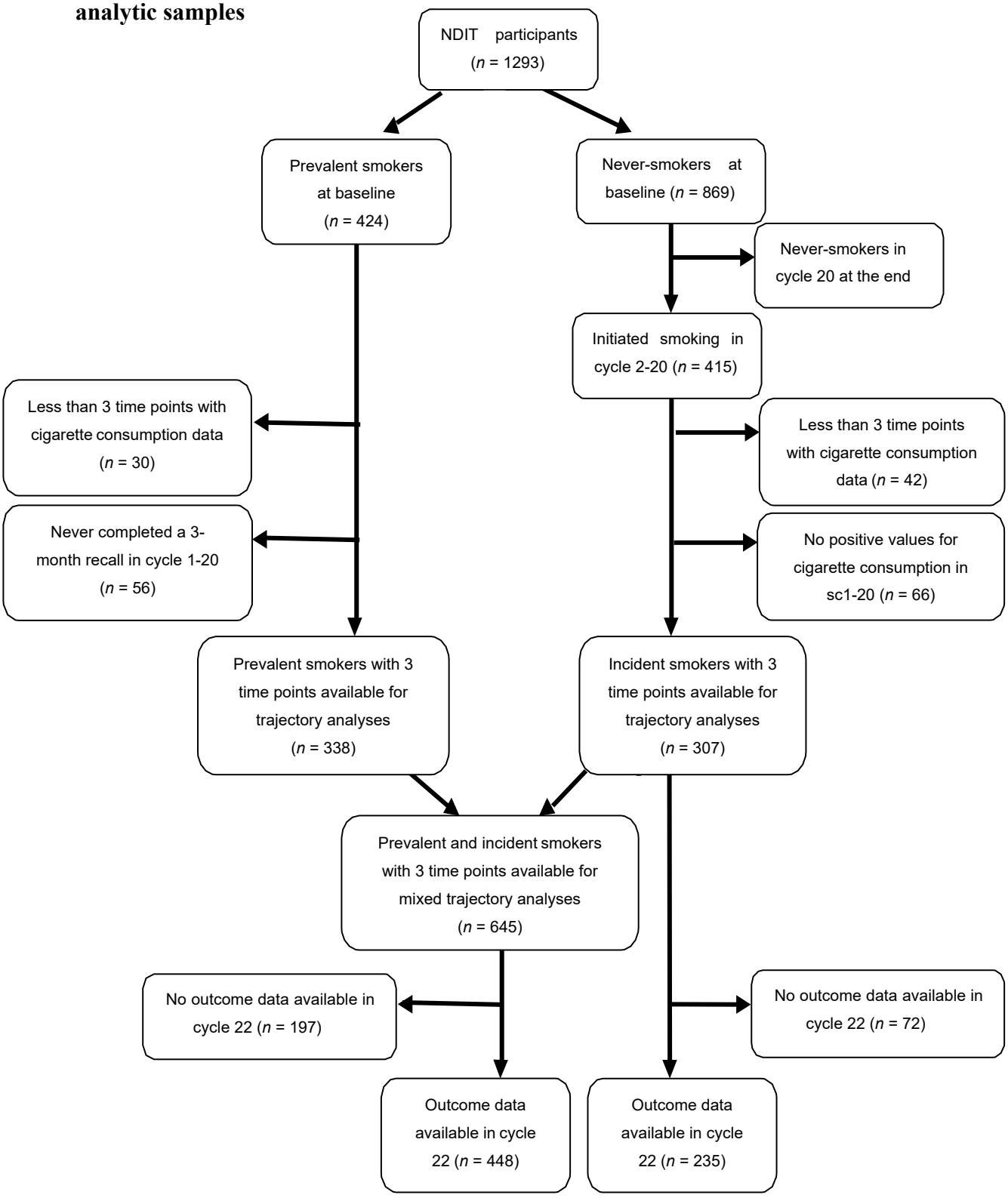


Table 32. (Manuscript 2, Table S1) Characteristics[a] of smokers included and excluded from the incident trajectory analyses. NDIT (Canada) 1999-2005

	Included in incident trajectory analyses		
	Yes (n = 307)	No[b] (n = 108)	p-value
Sociodemographic indicators			
Age, y, means (SD)	14.0 (1.1)	14.8 (1.5)	<0.0001
Male, %	39.4	58.3	0.0007
Mother university-educated, %	48.7	47.4	0.8455
Lives with one parent, %	13.1	11.3	0.6399
Born in Canada, %	95.8	89.8	0.0227
Language spoken at home (French), %	22.8	24.1	0.7873
Smoking-related indicators			
No. cig/month, median (IQR)	0.5 (0, 1.3)	0.0 (0.0, 0.5)	<0.0001
Used other tobacco products, %	41.8	33.3	0.1262
Parents smoke, %	31.0	27.6	0.5124
Friends smoke, %	83.0	80.6	0.5656
Psychosocial indicators			
Depressive symptoms, mean(SD)	2.2 (0.7)	2.0 (0.8)	0.0187
Family-related stress, mean (SD)	1.4 (0.5)	1.3 (0.5)	0.2737
Other stress, mean (SD)	1.6 (0.5)	1.5 (0.6)	0.0244
Self-esteem, mean (SD)	2.5 (0.4)	2.5 (0.4)	0.7121
Impulsivity, mean(SD)	2.5 (1.0)	2.3 (0.9)	0.1054
Novelty-seeking, mean (SD)	3.1 (0.8)	2.8 (1.0)	0.0120
Lifestyle indicators			
MVPA, times/wk, mean (SD)	21.6 (16.5)	22.1 (17.4)	0.7762
Participated in team sports, %	58.3	56.5	0.7412

[a]Values for time-invariant variables (sex, mother university-educated, French spoken at home, born in Canada) were drawn from baseline. The earliest values available for impulsivity and novelty-seeking (both measured in cycles 14 and 18) and self-esteem (measured in cycle 12) were used. All other characteristics were measured at the time of cigarette smoking initiation.[b]Includes incident smokers with <3 cycles of data on cigarette consumption or who never reported a non-zero value for number of cigarettes smoked per month.

[b]Chi-square was used to test for differences in categorical variables. ANOVA was used to test for differences in means of normally distributed variables; the Wilcoxon test was used to test for differences in no. cig/month (which was not normally distributed).

SD: Standard deviation. IQR: Interquartile range. MVPA: Moderate and vigorous physical activity.

Table 33. (Manuscript 2, Table S2) Baseline characteristics[a] of smokers included and excluded from the mixed trajectory analyses. NDIT (Canada) 1999-2005

	Included in mixed trajectory analyses		
	Yes (n = 645)	No[b] (n = 194)	p-value
Sociodemographic indicators			
Age, y, means (SD)	12.8 (0.6)	13.0 (0.7)	0.0002
Male, %	39.5	58.2	<0.0001
Mother university-educated, %	42.8	42.2	0.9052
Lives with one parent, %	10.7	13.1	0.3637
Born in Canada, %	95.7	90.2	0.0038
Language spoken at home (French), %	36.3	32.5	0.3312
Smoking-related indicators			
Smoked cigarettes, %	34.2	7.4	<0.0001
No. cig/month (among smokers), median (IQR)	2.5 (0.5, 20)	240 (2.5, 540)	<0.0001
Used other tobacco products, %	17.1	11.2	0.0599
Parents smoke, %	44.7	47.8	0.4703
Friends smoke, %	52.8	39.0	0.0011
Psychosocial indicators			
Depressive symptoms, mean(SD)	2.2 (0.6)	2.1 (0.6)	0.0554
Family-related stress, mean (SD)	1.4 (0.4)	1.3 (0.5)	0.3025
Other stress, mean (SD)	1.5 (0.4)	1.5 (0.4)	0.0575
Self-esteem[a], mean (SD)	2.4 (0.4)	2.5 (0.4)	0.1629
Impulsivity[a], mean(SD)	2.5 (1.0)	2.2 (0.8)	0.0100
Novelty-seeking[a], mean (SD)	3.0 (0.8)	2.8 (0.9)	0.0027
Lifestyle indicators			
MVPA, times/wk, mean (SD)	19.7 (14.6)	17.8 (14.6)	0.1244
Participated in team sports, %	60.6	57.2	0.3965

[a]The earliest values available for impulsivity and novelty-seeking (both measured in cycles 14 and 18) and self-esteem (measured in cycle 12) were used.

[b]Prevalent and incident smokers with <3 cycles of cigarette consumption data or who never reported a non-zero value for number of cigarettes smoked per month.

[c]Chi-square was used to test for differences in categorical variables. ANOVA was used to test for differences in means of normally distributed variables; the Wilcoxon test was used to test for differences in no. cig/month (which was not normally distributed).

SD: Standard deviation. IQR: Interquartile range. MVPA: Moderate and vigorous physical activity.

References (Appendix 4):

1. Control and Prevention. Selected cigarette smoking initiation and quitting behaviors among high school students – United States, 1997. Morb Mortal Wkly Rep 1998; 47(19): 386-9.
2. DiFranza, J.R., Ursprung, W.W., Biller, L. The developmental sequence of tobacco withdrawal symptoms of wanting, craving and needing. Pharmacol Biochem Behav 2012; 100(3): 494-7.
3. O'Loughlin, J., Tarasuk, J., Difranza, J., Paradis, G. Reliability of selected measures ofnicotine dependence among adolescents. Ann Epidemiol 2002; 12(5): 353-62.
4. Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerström, K.O. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991; 86(9): 1119-27.
5. O'Loughlin, J., DiFranza, J., Tarasuk, J., Meshefedjian, G., McMillan-Davey, E., Paradis, G., et al. Assessment of nicotine dependence symptoms in adolescents: a comparison of five indicators. Tob Control 2002; 11(4): 354-60.
6. World Health Organization. International statistical classification of diseases and related health problems. 10th revision. Geneva: World Health Organization. http://apps.who.int/classifications/ICD-10/browse/Content/statichtml/ICD-10Volume2_en_2010.pdf. Accessed 29 August 2018.
7. Kandel, D.B., Davies, M. Epidemiology of depressive mood in adolescents: an empirical study. Arch Gen Psychiatry 1982; 39(10): 1205-12.
8. Deschesnes, M. Life Style of Youth in Secondary Schools in Outaouais [in French]. Public Health Directorate, Regional Directorate of Health and Social Services; Hull, Quebec, Canada: 1997.
9. Dugas, E., Low, N.C., Rodriguez, D., Burrows, S., Contreras, G., Chaiton, M., et al. Early predictors of suicidal ideation in young adults. Can J Psychiatry 2012; 57(7): 429-36.
10. Eysenck, S.B., Eysenck, H.J. The place of impulsiveness in a dimensional system of personality description. Br J Soc Clin Psychol 1977; 16(1): 57–68.
11. Wills, T.A., Sandy, J.M., Shinar, O. Cloninger's constructs related to substance use level and problems in late adolescence: a mediational model based on self-control and coping motives. Exp Clin Psychopharmacol 1999; 7(2): 122-34.
12. Wills, T.A., Windle, M., Cleary, S.D. Temperament and novelty seeking in adolescent substance use: Convergence of dimensions of temperament with constructs from Cloninger's theory. J Pers Soc Psychol 1998; 74(2): 387–406.
13. Vallieres, E.F., Vallerand, R. Translation to French (Canadian) and validation of Rosenberg's self- esteem scale. (In French). Int J Psychol 1990; 25(2): 305-16.
14. Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11 2002; 1-190.
15. Hammer, L.D., Kraemer, H.C., Wilson, D.M., Ritter, P.L., Dornbusch, S.M. Standardized percentile curves of body-mass index for children and adolescents. Am J Dis Child 1991; 145: 259-63.
16. Pate, R.R., Pratt, M., Blair, S.N., Haskell, W.L., Macera, C.A., Bouchard, C., et al. Physical Activity and Public Health. A Recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA 1995; 273(5): 402-07.

Figure 10. (Manuscript 2, Figure S2) Amplification of the two lowest trajectories of the five-group model of incident trajectories with 95% confidence intervals, according to number of cigarettes smoked per month (*n* = 307 incident adolescent smokers), NDIT 1999-2005

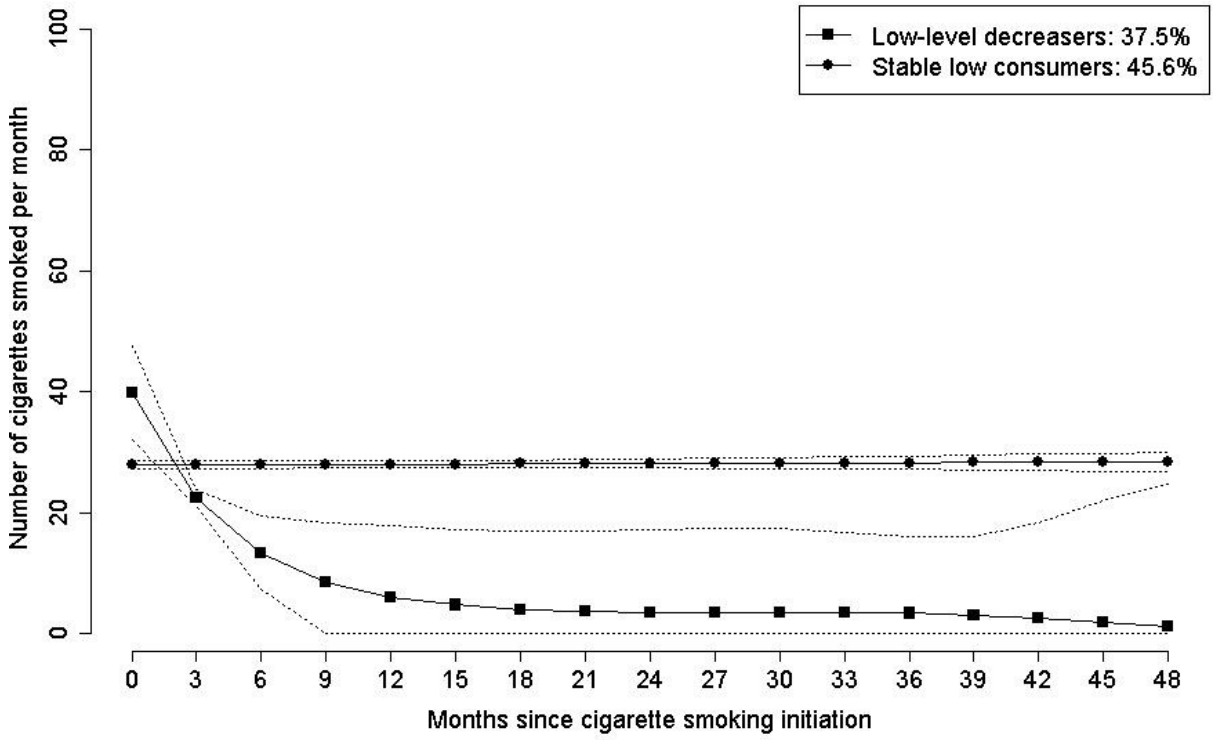


Table 34. (Manuscript 2, Table S3) Characteristics[a] of incident smokers with and without data for at least one smoking-related outcome in early adulthood. NDIT (Canada) 1999-2012

	With data (*n* = 235)	Without data (*n* = 72)	p-value[b]
Sociodemographic			
Age, y, mean (SD)	14.1 (1.2)	13.9 (1.0)	0.2029
Male, %	38.7	41.7	0.6548
Mother university-educated, %	50.0	41.9	0.3280
Lives with one parent, %	12.0	16.7	0.3008
Born in Canada, %	97.0	91.7	0.0857
French-speaking, %	23.0	22.2	0.8935
Smoking-related indicators			
No. cig/month, median (IQR)	0.5 (0, 1.3)	0.5 (0, 1)	0.6914
Used other tobacco products, %	42.1	40.8	0.8458
Parents smoke, %	26.6	45.7	0.0024
Friends smoke, %	83.8	80.6	0.5266
Psychosocial indicators			
Depressive symptoms, mean (SD)	2.2 (0.7)	2.2 (0.7)	0.9253
Family-related stress, mean (SD)	1.4 (0.5)	1.4 (0.4)	0.8849
Other stress, mean (SD)	1.6 (0.5)	1.6 (0.5)	0.5169
Self-esteem, mean (SD)	2.5 (0.4)	2.5 (0.4)	0.8101
Impulsivity, mean (SD)	2.5 (1.0)	2.4 (1.0)	0.8464
Novelty-seeking, mean (SD)	3.1 (0.8)	3.1 (0.8)	0.9094
Lifestyle indicators			
MVPA, times/wk, mean (SD)	22.1 (17.0)	202 (15.0)	0.4042
Participated in team sports, %	57.9	59.7	0.7806

[a]Values for time-invariant variables (sex, mother university-educated, French spoken at home, born in Canada) were drawn from baseline. The earliest values available for impulsivity and novelty-seeking (both measured in cycles 14 and 18) and self-esteem (measured in cycle 12) were used. Values for all other characteristics were drawn from the cycle in which the participant initiated cigarette smoking.

[b]Chi-square was used to test for differences in categorical variables. ANOVA was used to test for differences in means of normally distributed variables; the Wilcoxon test was used to test for differences in no. cig/month (which was not normally distributed).

SD: Standard deviation. IQR: Interquartile range. MVPA: Moderate and vigorous physical activity. wk: week.

Table 35. (Manuscript 2, Table S4) Baseline characteristics[a] of smokers included in the mixed trajectory analyses with and without data for at least one smoking-related outcome in early adulthood. NDIT (Canada) 1999-2012

	With data (*n* = 448)	Without data[b] (*n* = 197)	p-value
Sociodemographic			
Age, y, mean (SD)	12.7 (0.5)	12.9 (0.7)	<0.0001
Male, %	37.5	44.2	0.1109
Mother university-educated, %	44.6	35.6	0.1049
Lives with one parent, %	10.2	11.9	0.5331
Born in Canada, %	96.2	94.4	0.3044
French-speaking, %	36.6	35.5	0.7938
Smoking-related indicators			
Smoked cigarettes, %	30.1	43.8	0.0010
No. cig/month (among smokers), median (IQR)	2.4 (0.5, 19.2)	2.5 (0.5, 20.3)	0.5972
Used other tobacco products, %	15.9	19.9	0.2304
Parents smoke, %	42.0	51.4	0.0324
Friends smoke, %	49.1	61.5	0.0044
Psychosocial indicators			
Depressive symptoms, mean (SD)	2.2 (0.6)	2.2 (0.6)	0.2359
Family-related stress, mean (SD)	1.3 (0.4)	1.5 (0.5)	0.0054
Other stress, mean (SD)	1.5 (0.4)	1.6 (0.5)	0.0604
Self-esteem, mean (SD)	2.4 (0.4)	2.4 (0.4)	0.8535
Impulsivity, mean (SD)	2.5 (1.0)	2.5 (1.0)	0.9554
Novelty-seeking, mean (SD)	3.0 (0.8)	3.1 (0.9)	0.5255
Lifestyle indicators			
MVPA, times/wk, mean (SD)	19.8 (14.2)	19.4 (15.7)	0.7576
Participated in team sports, %	62.0	57.4	0.2612

[a]The earliest values available for impulsivity and novelty-seeking (both measured in cycles 14 and 18) and self-esteem (measured in cycle 12) were used.

[b]Chi-square was used to test for differences across groups in categorical variables. ANOVA was used to test for differences in means of normally distributed variables; the Wilcoxon test was used to test for differences in no. cig/month (which was not normally distributed).

SD: Standard deviation. IQR: Interquartile range. MVPA: Moderate and vigorous physical activity. wk: week.

Appendix 5

Additional Material (Manuscripts 2 and 3)

Trajectory variable

Table 36 presents the range, median, and number of missing values for the cigarette smoking trajectory variable, for each time point.

Table 36. Range, median, and missing values for mean number of cigarettes smoked per month in the past 3 months, by cycle among included participants[3] and by type of trajectory model[1], NDIT 1999-2012

Time[1]	Incident trajectories (*n* = 307)			Mixed trajectories (*n* = 645)		
	Range	Median	Missing	Range	Median	Missing
1	0-900	0	36	0-720	0	39
2	0-540	0	35	0-900	0	54
3	0-440	0	41	0-900	0	65
4	0-540	0	52	0-900	0	387
5	0-690	0	79	0-900	0	76
6	0-900	0	70	0-900	0	93
7	0-900	0	83	0-900	0	170
8	0-900	0	102	0-900	0	164
9	0-900	0	121	0-900	0	133
10	0-900	0	122	0-900	0	148
11	0-900	0	128	0-900	0	159
12	0-900	0	150	0-900	0	163
13	0-900	0	174	0-900	0	192
14	0-680	0	188	0-900	0	204
15	0-900	0	204	0-900	0	202
16	0-900	0	236	0-900	0	221
17	0-900[2]	0[2]	245[2]	0-900	0.166667	219
18	0-900[2]	0[2]	268[2]	0-900	0	228
19	-[2]	-[2]	307[2]	0-900	0	243
20	-[2]	-[2]	307[2]	0-900	0	244

[1]Time axis for incident trajectories was number of survey cycles since cigarette smoking onset, while for mixed trajectories this was survey/data collection cycle.
[2]These time points were excluded from the incident trajectory models.
[3]Excludes incident cigarette smokers who stopped. (Manuscript 3)

Missing values: additional information

Throughout the analyses presented in relation to objective 2, missing values (aside from the previously discussed exclusions) ranged between 0 and 52 in all but four cases (i.e., across

mixed trajectory groups, the comparisons of baseline variables resulted in larger numbers of missing values for mother university-educated, self-esteem, impulsivity, and novelty seeking - see Table 13). (Tables 11-14) An additional individual who participated only at survey cycle 22 was excluded from all analyses in Manuscripts 2 and 3, as well as the breakdown of participants in Figure 9.

Appendix 6

Additional Material (Manuscripts 2 and 3)

Further details regarding the incident cigarette smoking trajectory model

Table 37. Mean posterior probabilities by trajectory group, for the incident cigarette smoking trajectory model, NDIT 1999-2012

Trajectory group	Mean posterior probability
Consistently low consumption	0.80
Low-level decreasers	0.80
Slow escalators	0.90
Moderate escalators	0.83
Early-rapid escalators who peaked	0.93

Appendix 7

Additional material (Manuscript 3)

Cannabis and cigarette smoking

Table 38 presents information on the distribution and number of missing values for the cannabis and cigarette smoking variables relating to Objective 3.

Table 38. Distribution and number of missing values for cannabis and cigarette variables (other than cigarette category variable) among participants included and excluded from the incident cigarette smoking categories, NDIT 1999-2012

Variable	Included[1] *n* = 857	Excluded *n* = 436
Ever used cannabis[2] (*n*, %, (missing[3]))	583, 68.0 (N/A[4])	19, 86.4 (414)
Age at 1st cannabis use, y (median, range (missing[3]))	15, 9-23 (278)	16, 14-19, (417)
Age at 1st cigarette, y, reported (median, range (missing[3]))	13, 3-21 (367)	16, 13-18, (418)

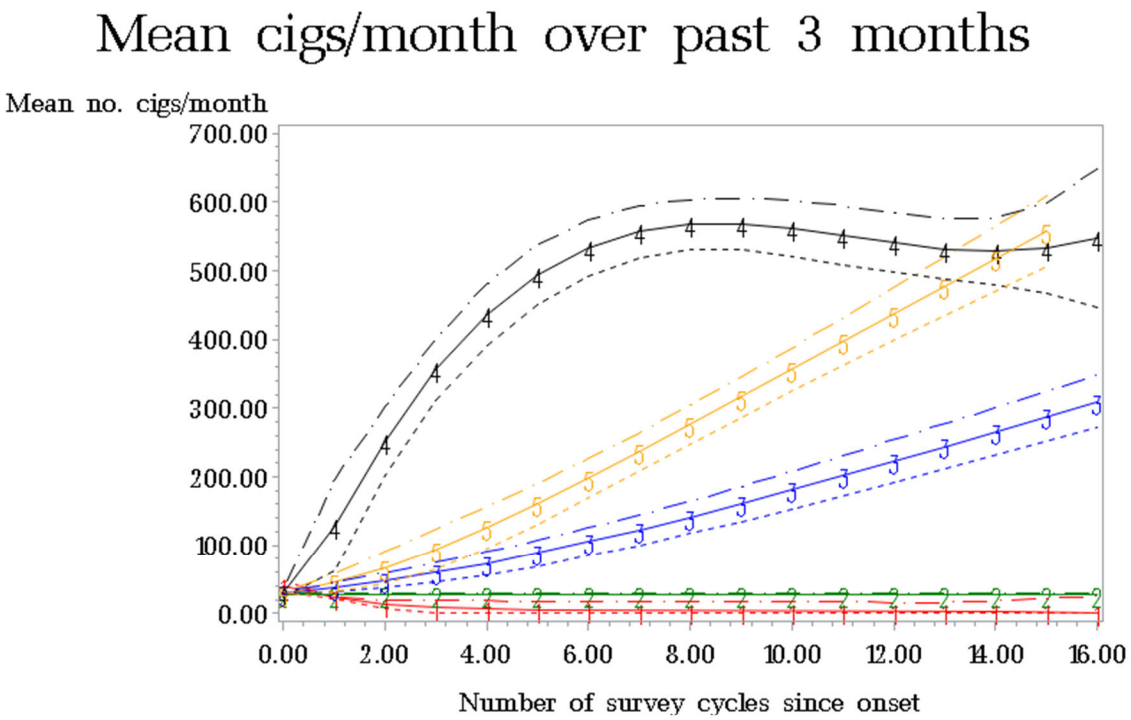
[1]Included participants were incident smokers who were included in the incident cigarette smoking trajectory model, as well as baseline ever smokers, incident smokers who stopped, and never smokers during adolescence, as described in Manuscript 3.
[2]This was obtained at cycle 21.
[3]Was the number missing among participants included and excluded from the cigarette smoking categories.
[4]N/A: Not applicable (i.e., given the way in which included participants were defined, there were zero missing values for this item).

Trajectories of incident smoking: included participants

The sample used to model incident cigarette smoking trajectories was restricted to participants who had never smoked at baseline, but who initiated smoking during follow-up in high school (i.e., incident cigarette smokers). (Figure 5, 6, and 11) Participants who had never smoked, not even a puff, during cycles 1-20 ($n = 454$) and those who had ever smoked at baseline (i.e., prevalent smokers, $n = 424$) were excluded. Baseline ever smokers were identified using the questions, "Have you ever in your life smoked a cigarette, even just a puff (drag, hit, haul)?" (yes, no) and "Check the box that describes you best…" ("I have never smoked, even just a puff"), at baseline. Responses to the same question in survey cycles 1-20 were used to identify participants who remained never smokers during adolescence. An additional individual who participated only at survey cycle 22 was excluded from all analyses. Among the 415 incident cigarette smokers, $n = 42$ participants were excluded because they did not provide data on

cigarette smoking in ≥3 data collection cycles and n = 66 had zero values for number of cigarettes smoked in the past month for all cycles in which smoking was reported (i.e., for cycles 1-20), and therefore could not contribute to the trajectory estimation. (Figure 5) We limited included participants to those who had three or more values for number cigarettes smoked in the past month and for whom at least one value for this variable was larger than zero, because trajectories cannot be estimated reliably with only one or two data points. [221] The analytical sample for the trajectory modeling, as in Manuscript 2, therefore included a total of 307 incident smokers. (Never smokers during adolescence, baseline ever smokers, and incident smokers who stopped were included in later analyses but were excluded from the trajectory model.)

Figure 11. Cigarette smoking trajectory model of incident smokers (*n* = 307), NDIT 1999-2008*



*Low-level decreasers (in red); stable low consumers (in green); slow escalators (in blue); moderate escalators (in yellow); early rapid escalators who peaked (in black)

Table 39. Baseline characteristics of included[1] and excluded participants, NDIT 1999-2008[2]

	Included[1] (*n* = 857)	Excluded[4] (*n* = 436)	Missing (*n*)
Age*, y, mean (SD) (CI)	12.7 (0.54) (12.66, 12.74)	12.9 (0.68) (12.84, 12.96)	0
Female*, % (CI)	54.5 (51.2, 57.8)	46.6 (41.9, 51.3)	0
Single-parent family, % (CI)	8.7 (6.8, 10.6)	11.5 (8.5, 14.5)	5
Born in Canada*, % (CI)	93.6 (92.0, 95.2)	89.2 (86.3, 92.1)	0
French spoken at home, % (CI)	31.3 (28.2, 34.3)	27.7 (23.5, 31.9)	0
Mother university-educated, (%) (CI)[3]	45.3 (41.8, 48.8)	41.7 (35.1, 48.2)	315
Parent(s) smoke, % (CI)	37.6 (34.3, 40.9)	41.9 (37.2, 46.6)	22
Friend(s) smoke*, % (CI)	35.6 (32.4, 38.8)	42.2 (37.6, 46.8)	3

[1]Included participants were *n* = 307 incident smokers, *n* = 66 incident cigarette smokers who stopped, *n* = 454 never smokers during adolescence, and *n* = 424 baseline ever smokers (minus *n* = 394 individuals who did not provide data on cannabis use at survey 21)
[2]A Kruskal-Wallis test was used for age, while a chi-square test was used for all other variables. Factors for which there was a statistically significant difference ($p < 0.05$) between group(s) are marked with an asterisk next to the variable name.
[3]Mother's education was not measured at baseline but was rather created from information provided in cycles 13 and 17 by participants and in questionnaires completed by participants' mothers.
[4]The data presented in the current table exclude *n* = 1 participant who entered the study at survey 22.
y: year(s). CI: Confidence interval.

Table 40. Baseline characteristics of never, incident and prevalent smokers, NDIT 1999-2008[4]

	Never smokers (*n* = 454)	Incident smokers[1] (*n* = 307)	Prevalent smokers (*n* = 424)	p-value[2]	Missing (*n*)
Age, y, mean (SD) (CI)	12.7 (0.5) (12.65, 12.75)	12.6 (0.4) (12.55, 12.64)	13.0 (0.7) (12.93, 13.07)	<.0001	0
Female, % (CI)	43.8 (39.2, 48.4)	60.6 (55.1, 66.1)	56.6 (51.9, 61.3)	<.0001	0
Single-parent family, % (CI)	6.2 (4.0, 8.4)	7.8 (4.8, 10.8)	14.4 (11.0, 17.7)	<.0001	5
Born in Canada, % (CI)	87.9 (84.9, 90.9)	95.8 (93.6, 98.0)	94.6 (92.4, 96.7)	<.0001	0
French spoken at home, % (CI)	20.3 (16.6, 24.0)	22.8 (18.1, 27.5)	47.4 (42.6, 52.1)	<.0001	0
Mother university-educated, (%) (CI)[3]	47.7 (42.5, 52.9)	48.7 (42.7, 54.7)	35.6 (30.0, 41.2)	0.0020	285
Parent(s) smoke, % (CI)	26.6 (22.5, 30.7)	32.0 (26.7, 37.2)	58.6 (53.8, 63.3)	<.0001	22
Friend(s) smoke, % (CI)	15.0 (11.7, 18.3)	29.7 (24.6, 34.8)	71.0 (66.7, 75.3)	<.0001	2

[1]Incident smokers were *n* = 307 participants included in the Proc Traj model.
[2]A Kruskal-Wallis test was used for age, while a chi-square test was used for all other variables.

[3]Mother's education was not measured at baseline but was rather created from information provided in cycles 13 and 17 by participants and in questionnaires completed by participants' mothers.
[4]The data presented in the current table exclude $n = 1$ participant who entered the study at survey 22.
SD: Standard deviation. y: years. CI: Confidence interval.

Table 41. Characteristics[1,2] of members of each incident smoking trajectory group (n = 307), NDIT 1999-2008

	Trajectory group						
	Stable-low consumers	Low-level decreasers	Slow escalators	Moderate escalators	p-value	Early-rapid escalators who peaked	Missing (n)
Measured at initiation							
Age (y), mean (SD) (CI)	14.1 (1.2) (13.90, 14.30)	14.1 (1.1) (13.90, 14.30)	13.4 (0.7) (13.13, 13.67)	14.0 (0.9) (13.59, 14.40)	0.0259	13.6 (0.5) (13.25, 13.95)	0
Single-parent family, % (CI)	17.3 (11.0, 23.6)	8.7 (3.5, 13.8)	12.0 (0, 24.7)	10.5 (0, 24.3)	0.2318[4]	12.5 (0, 35.4)	1
Parent(s) smoke, % (CI)	31.9 (24.1, 39.7)	24.6 (16.7, 32.5)	48.0 (28.4, 67.6)	33.3 (11.5, 55.1)	0.1271	50.0 (15.3, 84.6)	4
Friends smoke, % (CI)	84.3 (78.3, 90.3)	77.2 (69.5, 84.9)	88.0 (75.3, 100)	94.7 (84.6, 100)	0.1697[4]	100	1
Not measured at initiation[3]							
Female, % (CI)	69.3 (61.7, 76.9)	51.3 (42.2, 60.4)	60.0 (40.8, 79.2)	63.2 (41.5, 84.9)	0.0344	37.5 (3.9, 71.0)	0
Mother university-educated, % (CI)	52.0 (43.2, 60.8)	46.0 (36.2, 55.8)	60.9 (41.0, 80.8)	40.0 (15.2, 64.8)	0.4705	0	40
Born in Canada, % (CI)	97.1 (94.3, 99.9)	93.0 (88.3, 97.7)	100	94.7 (84.6, 100)	0.2435[4]	100	0
French spoken at home, % (CI)	19.3 (12.8, 25.8)	24.3 (16.5, 32.1)	24.0 (7.3, 40.7)	36.8 (15.1, 58.5)	0.3486	25.0 (0, 55.0)	0

[1]n = 42 participants who had <3 values for smoking during survey cycles 1-20, as well as participants who were never smokers at survey cycles 1-20 (n = 454), and participants who had ever smoked at baseline (n = 424) are excluded from this table.
[2]A Kruskal-Wallis test was used for age, while a chi-square test was used for all other variables. Early-rapid escalators who peaked were excluded from statistical inference, given the small size of this trajectory group.
[3]Whether the participant was born in Canada and whether French was spoken at home was measured at baseline, while mother's education was created from information provided in cycles 13 and 17 by participants and in questionnaires completed by participants' mothers.
[4]An exact chi-square was used in this instance, rather than an asymptotic chi-square, given the fact that a significant proportion of the cells had expected values of <5.
SD: Standard deviation. y: years.

Figure 12. Histogram of (age at 1st cannabis use) – (age at smoking initiation), NDIT 1999-2008

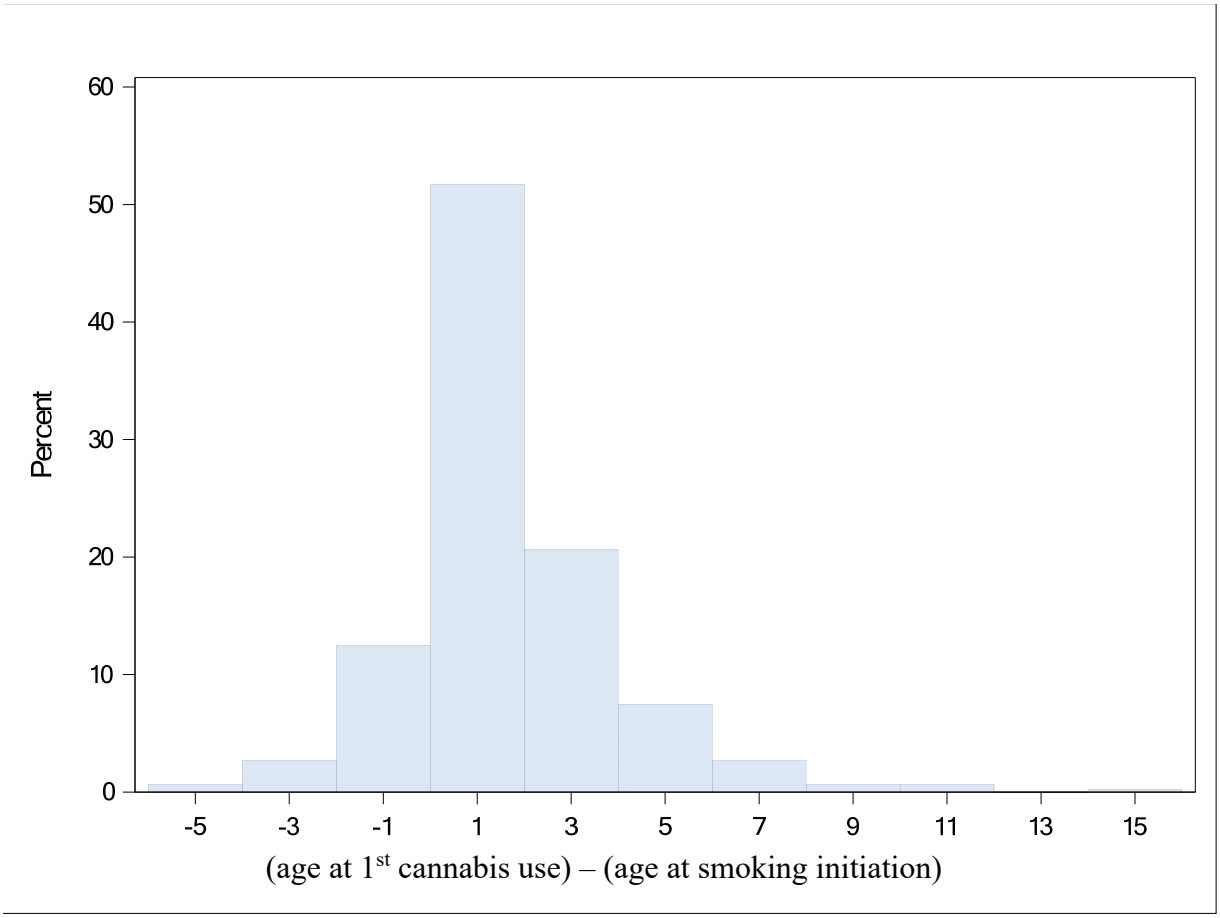
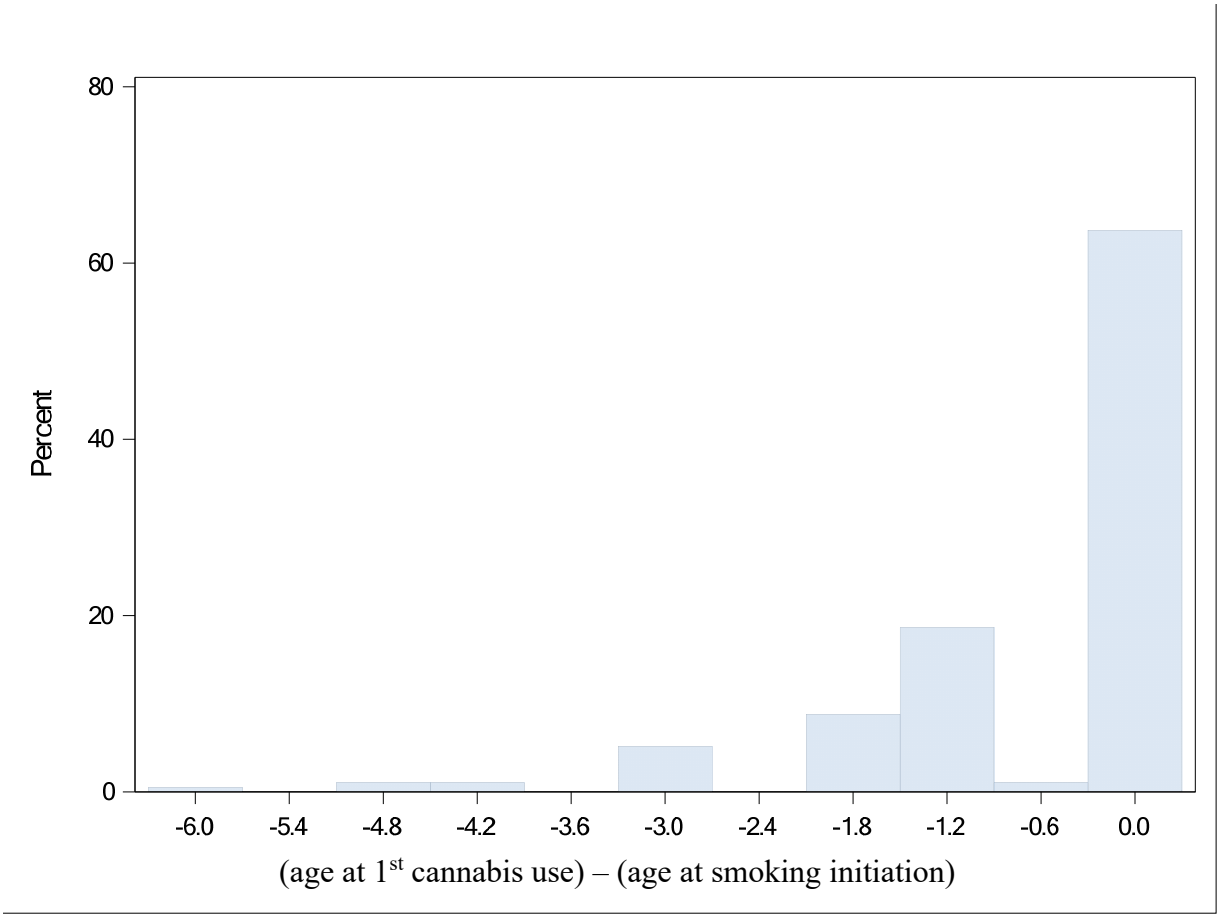
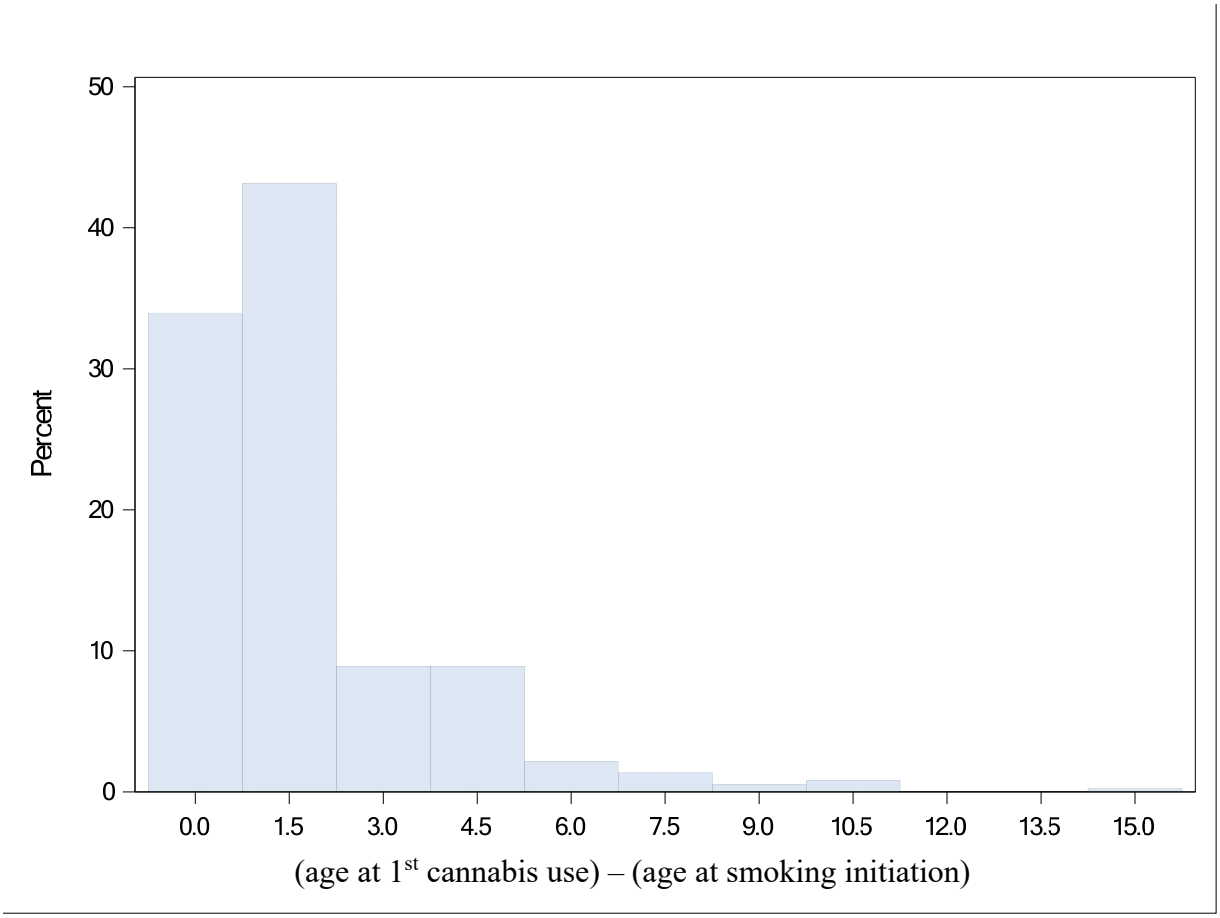


Figure 13. Histogram of (age at 1st cannabis use) – (age at 1st cigarette use)[1], among participants who initiated cannabis before cigarettes or who initiated both substances the same year, obtained using reported age at cigarette initiation, NDIT 1999-2008



[1]These negative values were used in the truncated regression models (Table 20), however zero values were removed from the model as these individuals were conceptually different (i.e., same year initiators had zero values while participants who initiated cannabis ≥1 year before cigarettes had negative values).

Figure 14. Histogram of (age at 1st cannabis use) – (age at 1st cigarette use)[1], among participants who initiated cigarettes before cannabis, obtained using reported age at cigarette initiation, NDIT 1999-2008



[1]Zero values were removed from the model as these individuals were conceptually different (i.e., same year initiators had zero values while participants who initiated cigarettes ≥1 year before cannabis had negative values).

Appendix 8

Additional material (Manuscripts 2 and 3)

8.1 Cigsurv Variable

Additional details regarding "cisgsurv" variable (i.e., mean number of cigarettes smoked per month in the past 3 months) are provided in this section. This variable was coded as follows.

Month 1 (no. of days smoked): "During ___, on how many days did you smoke cigarettes, even just a puff?"

Response choices and coding (original categories of variables are provided in Table 10):

- 0 = 0
- 1 = 1
- 2-3 = 2.5
- 4-5 = 4.5
- 6-10 = 8
- 11-15 = 13
- 16-20 = 18
- 21-30 = 25
- Every day = 30
- Don't know = missing
- (Missing information was coded as missing)

(The same coding was used for the other two months of the 3-month recall.)

Month 1 (no. of cigarettes smoked on days where participant smoked): "On the days that you smoked during last month, how many cigarettes did you usually smoke each day?"

Response choices and coding:

- <1 = 0.5
- 1 = 1
- 2-3 = 2.5

- 4-5 = 4.5
- 6-10 = 8
- 11-15 = 13
- 16-20 = 18
- 21-25 = 23
- >25 = 30
- Don't know = missing
- (Missing information was coded as missing)

(The same coding was used for the other two months of the 3-month recall.)

The recoded variable for number of days smoked (month 1) was then multiplied by the recoded variable for number of cigarettes smoked on days smoked (month 1). If participants replied that they had smoked on zero days, then the number of cigarettes smoked in that month was set to zero (regardless of their answer to the question on number of cigarettes smoked on days smoked). The same operations were carried out with the variables for month 2 and month 3 of the 3-month recall.

Finally, the mean of all three months was obtained to create the cigsurv variable. (cigsurv was recoded to zero if a participant replied, "No" to the question, "Have you ever in your life smoked a cigarette, even just a puff (drag, hit, haul)?" and cigsurv was missing. Additionally, cigsurv was also recoded to zero if a participant had replied "0" to the question regarding the number of days smoked, for all 3 months. This was to take into account the skip patterns in the questionnaire.)

8.2 Strobe Criteria

The following section details which individual STROBE criteria items were reported in manuscripts 2 and 3. [222]

Manuscript 2:

Table 42a. STROBE Statement. Checklist of items that should be included in reports of observational studies, Manuscript 2

	Item No	Recommendation	Present? (Y/N)[1]
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y
Methods			
Study design	4	Present key elements of study design early in the paper	Y
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Y
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	Not applicable

		Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y (Table 10)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Y (Table 10)
Bias	9	Describe any efforts to address potential sources of bias	Y (Section 8.3.2)
Study size	10	Explain how the study size was arrived at	Y (Figure 9)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y (Table 10)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y
		(*b*) Describe any methods used to examine subgroups and interactions	Y
		(*c*) Explain how missing data were addressed	Y Listwise deletion for risk factors and outcomes, we included all individuals with ≥3 data points AND ≥1 non zero value for past 3-month smoking in the cigarette trajectories (mixed model); for the incident model ≥3 data points AND ≥1 non zero value for past 3-month smoking were required AFTER initiation in order to be included in the trajectories
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	See item (c) above as well as section 8.3.2.2

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Please see section 8.3.2

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y (Figure 9)
		(b) Give reasons for non-participation at each stage	Y (Figure 9)
		(c) Consider use of a flow diagram	Y (Figure 9)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y (Table 10, Manuscript 2)
		(b) Indicate number of participants with missing data for each variable of interest	Y (Tables 10 and 36, Manuscript 2, Appendix 4)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Y Missing data for cigarette smoking is described in Table 36; *n* = 241 refused participation during cycles 1-22 [145]
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Y (Table 36, Figure 9)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y
		(*b*) Report category boundaries when continuous variables were categorized	Y (Table 10)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Y
Discussion			
Key results	18	Summarise key results with reference to study objectives	Y
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y (Manuscript 2, Sections 8.1, 8.3.2)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y (Manuscript 2, Section 8.1)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y Results are not fully representative as this was a convenience sample and additional exclusions were carried out to constitute our analytical sample
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Y

[1]When no further information was provided on location of relevant items, these were located in Manuscript 2.

Table 42b. STROBE Statement. Checklist of items that should be included in reports of observational studies, Manuscript 3

	Item No	Recommendation	Present?[1] (Y/N)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y
Methods			
Study design	4	Present key elements of study design early in the paper	Y
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Y
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y (Table 10, Manuscript 3)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Y (Table 10, Manuscript 3)

		Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	Y (Section 8.3.2)
Study size	10	Explain how the study size was arrived at	Y (Figure 9)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y (Table 10, Manuscript 3)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y
		(*b*) Describe any methods used to examine subgroups and interactions	Y
		(*c*) Explain how missing data were addressed	Y Listwise deletion for potential risk factors for time elapsed (both models), as well as of individuals with missing data on cannabis
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Y Only individuals with ≥3 data points for cigarette smoking AFTER initiation (as well as ≥1 non zero cigarette smoking value post initiation) were included in trajectory modeling; see also Manuscript 3; *n* = 241 refused participation during cycles 1-22 [145]
		(*e*) Describe any sensitivity analyses	Y (Section 8.3.2)

Results			**Present?[1]**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y
		(b) Give reasons for non-participation at each stage	Y
		(c) Consider use of a flow diagram	Y (Figures 5, 6)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y
		(b) Indicate number of participants with missing data for each variable of interest	Y (Tables 15-21)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable except for cigarette categories (Table 36, *n* = 241 refused participation during cycles 1-22 [145]
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Y (Table 36, Figures 5, 6)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y
		(*b*) Report category boundaries when continuous variables were categorized	Y (Manuscript 3, Table 10)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Y
Discussion			
Key results	18	Summarise key results with reference to study objectives	Y

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y (Manuscript 3, section 8.3.2)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y Results are not fully representative as this was a convenience sample and additional exclusions were carried out to constitute our analytical sample
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding is described in Manuscript 2

[1]When no further information was provided on location of relevant items, these were located in Manuscript 3.

Appendix 9

Telescoping bias: further details

The current state of the literature does not permit us to determine what the exact effect of telescoping bias would be. Indeed, the literature suggests in some cases a shift forward in time (i.e., the future) and in other cases backward (the past). What is however clear is that events which are farther away in time appear to be reported with less validity and reliability than more recent events (please note that the definition of both these concepts is provided in section 8.3.2).

Literature review

I searched Pubmed for the term, "telescoping bias" (no limits) and obtained 25 articles. (Searches carried out in April 2020.) The most relevant articles were retained following reading of the article abstracts. Additional articles were also obtained by searching for "tobacco" AND "telescoping" in Pubmed (May 2020, no limits). This search returned 9 articles of which 4 were duplicates of the previous search (no additional articles were retained from this search). Additional searches were carried out which yielded no additional relevant articles: (i) "cannabis" AND "telescoping"; (ii) "marijuana" AND "telescoping" in Pubmed (May 2020, no limits). These combined searches yielded a total of $n = 16$ relevant articles: $n = 7$ studied in the context of cigarette smoking and $n = 9$ studied telescoping bias within a context other than substance use. In general, with regards to the studies of telescoping bias in relation to tobacco use, there was no formal validation of the reported results. [223]–[228] One study [229] did not include truly longitudinal data and will therefore not be considered further). Indeed, several of these studies had repeated measures which were not validated by objective measures (e.g., biological measure(s) of tobacco or cannabis). No studies reported data on telescopic bias for cannabis initiation.

One additional article, not obtained from the searches described (i.e., this reference was suggested by a colleague) dealing with telescoping bias with regards to cigarette smoking did not use longitudinal data on participants: incidence rates from cross-sectional studies were used) to reconstruct incidence rates for smoking by age in several birth cohorts. [183]

Other studies which compared objective measures with self-reported behaviors other than tobacco or cannabis use reported either movement forward (i.e., reporting events as newer than they actually are) or backward/toward the past ("time expansion"). [197]–[199], [230]–[235]

Table 43. Summary of studies relating to telescoping bias

First author, year of publication	Study sample size (statistical power)	Response rate (%), losses to follow-up[1], additional exclusions (%) (selection bias)[4]	(1) Questions reported (Y/N)?[2] (2) Previous information re: validation of self-reported data (Y/N)?[2] (3) Gold standard measure described (including validation)? (4) Reference category reported (measures of association) (Y/N)?[2] (Information bias)	Adjustment for potential confounders (Y/N)? (Confounding bias)[3]	Nature of comparison (D = dependent variable; I = independent variable)	Information on effect of time since event (Y/N)?	Study quality (0: poor, 1: acceptable, 2: good)[5]	Relevant to telescoping bias (Y/N)?
Norman, 2003 [230]	2,960 (2,399+561)	NR, NA, 45% (cases) and 87% (controls)	Y, N, Y (N, negative reports of mammography not validated), NA	N	Test characteristics reported for self-reported screening mammography (compared with medical records) within (1) past year and (2) past 2 years	N	0	Maybe?
Petridou, 2004 [232]	4,079	50.9%, NA, none	N, N, Y (Y), NA	N	Comparison of point estimates and confidence intervals for rates of injuries in the past year (comparison between self-reported and The Emergency Department Injury Surveillance System in Greece)	N	1	Maybe?
Dalziel, 2018 [233]	4,399	NR, NA, 34.7%	Y, N, Y (N), NA	Y	Comparison of several error measures for number of doctor visits in the past year (comparison between self-reported and Australian Medicare records)	N	0	Maybe?
Rhodes, 2004 [234]	23,063	78.8% (household) and 94.4% (individuals), 37.5%, NA	Y, N, Y (Y), Y	Y	Percent difference in ORs comparing risk of use of mental health services (during past year) according to level of distress (SR OR - AD OR /AD OR) *100); overlap of associated confidence intervals	N	2	Maybe?
Bruijnzeels, 1998 [197]	1,765	NR (for physicians) and 89%	N, N, Y (N), Y?	Y	Test characteristics for parent interview and parent diary (comparison between parent reports of doctor visits and physician	Y	1	Y

		(families), 10%, 2.2%			information/records); ORs for prevalence of reasons for physician visits by category; ORs for parental under and over reporting according to respondent characteristics			
Betz, 1997 [198]	49	N, NR, NR	Y, N, Y (N), NA	N	Pooled within subjects regression used to compare recall of events (comparison between diary of life events kept by participants and later recall of these events)	Y	0	Y
Pachana, 2011 [235]	16,715 (6,839 and 9,876 in two cohorts)	NR, 52% and 28.1% (two cohorts), none?	Y, N, Y (N), NA	N	Consistency in reports between first report of an event and whether it was reported at subsequent waves of the study	N	0	Maybe?
May, 1998 [231]	4,472	NR, NA, 65.2%	N, N, N (Y), NA	N	Comparison of mammography reported in a survey vs. in medicare administrative data	N	1	Maybe?
Carey, 1995[5] [199]	367 (235 cases and 132 controls)	?	?	?	Consistency in reports of low back pain between patient reports (4-16 weeks post doctor visit) and physician records	Y	?	Y

NA: Not applicable. NR: Not reported. OR: Odds ratio. SR: Self reported. AD: Administrative data. D: Dependent variable. I: Independent variable. Y: Yes. N: No.

[1]Longitudinal studies only. (This item is not applicable to cross-sectional studies.) Losses to follow-up in longitudinal studies were classified as follows: ≤10% excellent, 10-30% good, 30-50% acceptable, >50% unacceptable). The proportions shown do not take into account additional exclusions such as those relating to item non response regarding substance use variables of central importance to the article.

[2]Refers to whether the exact question(s) and associated response items were reported, whether the reference category(ies) used in the analyses was reported (in the case of continuous measures, this item refers to whether coding of the variable was specified), and whether any previously available information regarding validity and/or reliability of self-reported variables used in the studies (i.e., specifically, those relating to the associations reported in this table) was reported. (Please note that a definition of both of these concepts is provided in section 8.3.2).

[3]None of the reviewed studies presented directed acyclic graphs (DAGs) to show the probable relations between variables in the conceptual model of each study. It is therefore difficult to know whether confounders were likely to be true confounders vs. intermediate variables vs. colliders. (Confounding is generally defined as a situation where the exposure and outcome of interest share a common cause thereby biasing the association measure; an intermediate variable is a variable on the causal pathway between exposure and outcome; collider stratification bias occurs when conditioning on a common cause of exposure and outcome.)[88]–[90]

[4]Ranking is based on the information reported in this table.

[5]Carey et al., 1995 was not available online, but was retained in this table given the relative lack of studies in this area.

Telescopic-type bias appears to affect dates of self-reported events and could be a cause of bias when self-reported information involves recalling a date: in other words this bias may act upon recall of information involving not only the presence or absence of a lifetime entity (e.g., ever used cannabis), but also involves the recall of one or more specific dates of events (e.g., age of first cannabis use). Telescopic bias may also affect rates of events when these are limited in time (e.g., any self-reported of cannabis use limited to a particular time period).

In conclusion, despite a lack of studies on telescopic bias in the particular context of self-reported data on tobacco and cannabis use, and despite the poor quality of this literature overall, there is a suggestion that rather than always causing a forward displacement in time, this bias might cause either backward or forward movement. (The state of the literature did not allow any conclusion as to the direction of this bias.) Finally, some studies (it should however be noted that these were not within the realm of questions relating to substance use) did suggest that validity and reliability of results might diminish according to time since the event. (Bruijnzeels et al., 1998; Carey et al., 1995) It therefore appears likely that the validity and reliability of self-reported data on initiation of cannabis and cigarette smoking would be reduced by the time fact that (in many cases) some years had passed between initiation and reporting of age at initiation by our participants (Manuscript 3).

Appendix 10

Ethics certificates, NDIT Study (Manuscripts 2 and 3)

RÉGIE RÉGIONALE DE LA SANTÉ ET DES SERVICES SOCIAUX
DE MONTRÉAL-CENTRE

APPROBATION DU PROJET PAR LE COMITÉ D'ÉTHIQUE

Le Comité d'éthique de santé publique de la Régie régionale de Montréal-Centre a examiné le projet de recherche :

A prospective study on the natural history of nicotine dependence

Soumis par: *Madame Jennifer O'Loughlin*

Le comité d'éthique a conclu que la recherche proposée respecte les règles éthiques en santé publique définies par la Régie régionale de Montréal-Centre.

Membres du comité:

M. Denis Allard	*Agent de recherche*
Dr. Robert Allard	*Médecin*
Mme Lorraine Bernier	*Agente de recherche sociosanitaire*
Dr. Nicole-Hébert-Croteau	*Médecin-conseil*
M. Alain Gauthier	*Secrétaire général, C.S. Marguerite Bourgeois*
Mme Marie Hirtle	*Avocate*
Mme Marcelle Monette	*Conseillère à la recherche et au développement professionnel*
Mme Francine Tardif	*Sociologue consultante*
M. Claudio Zanchettin	*Professeur en philosophie*
Dr. Bernard Heneman	*Médecin-conseil et président du comité*

[redacted]

Président du comité

99-04-07
Date

Note: Le présent certificat n'est valide que si une preuve d'acceptation du protocole pour son évaluation scientifique a été déposée auprès du comité d'éthique de la santé publique.

certifica.eth

RÉGIE RÉGIONALE
DE LA SANTÉ ET DES
SERVICES SOCIAUX
DE MONTRÉAL-CENTRE

November 18, 1999

MCGILL UNIVERSITY STUDY ON NICOTINE DEPENDENCE IN TEENS

Investigators: J. O'Loughlin, PhD., G. Paradis, MD, P. Clarke, PhD., J. Hanley, PhD, R. Tyndale, PhD., J. DiFranza, MD

Dear Parent/Guardian:

The Public Health Directorate of Montréal-Centre in collaboration with McGill University, and the Universities of Toronto and Massachusetts, is undertaking a 3-year study among Secondary I students in 12-15 Montreal high schools to study how smoking becomes an established habit in certain adolescents. All Secondary I students in your child's school have been asked to participate because we need to study children who smoke, as well as children who do not smoke. The ultimate purpose of this research is to help us develop more effective strategies to prevent the onset of smoking in children, as well as to help youth who want to quit smoking. In addition, this study will examine the relationship between smoking, weight, and blood pressure during adolescence. The study has 2 parts:

Part I - In the next few weeks, our research team will visit your child's classroom. Two interviewers will administer a 45-minute in-class questionnaire to all students about their smoking experiences. The interviewers will visit your child's class again 3-4 months later and every 3-4 months after that for the next 3 years (in Secondary I, II and III) to re-administer the questionnaire in order to collect updated information on the students' smoking experiences. Trained technicians will measure your child's height, weight, skinfold thickness, waist circumference and blood pressure once a year. All data will be stored in locked storage areas at the Public Health Directorate.

Part II - An important aspect of this study is to investigate if genetic factors are involved in smoking uptake. To explore this possibility, we will collect a blood sample from each student for genetic analysis. During data collection in March 2002, a nurse will draw 10 ml of blood (2 teaspoons) for genetic analysis. The samples will be analyzed and stored at the University of Toronto, which specializes in this type of genetic analysis. The blood samples will be labeled only by number and the results of the genetic test will remain completely confidential. A master list linking the child and the identification number will be stored securely at the Public Health Directorate. Only the principal investigator and the project coordinator will have access to the list. This list will be destroyed at the end of the study. It will be impossible to provide any individual results of the genetic testing to anyone because they will never be linked to a particular name. After the list is destroyed, all blood samples will be completely anonymous. The samples will be stored for a maximum of ten (10) years for future genetic analysis exclusively related to smoking.

Request for your consent - We are now asking for your and your child's consent for Part I of the study (the in-class questionnaire and the anthropometric measures). In February or March 2002, we will ask you separately and specifically for a consent for the blood sample. Both your school board and school principal fully support this project and have agreed that your child's class can participate. However your child's participation is completely voluntary, and it is entirely up to you and your child whether or not he/she participates. Your child can decide not to participate in the blood sample portion of the study and participate only in the questionnaires and anthropometric measures. Also, your child can withdraw from the study at any time and/or ask that his/her blood sample be destroyed before the end of the study by contacting the Project Coordinator (telephone number shown below). If you decide not to allow his/her participation, or if he/she withdraws from the study before it is completed, there will be no prejudice against your child.

Please complete the attached form to indicate whether or not your child will participate in Part I of the study, and return it to your child's teacher in the next 3 days. If you have any questions, please contact the Project Coordinator, Mrs. Elizabeth MacMillan-Davey at 528-2400 local 3976. We thank you and your child for your help in this important project.

[redacted]

Jennifer O'Loughlin, Ph.D.
Principal Investigator

[redacted]

Gilles Paradis, M.D.
Co-Investigator

Santé physique
1301, rue Sherbrooke Est
Montréal (Québec) H2L 1M3
Téléphone : (514) 528-2400
Télécopieur : (514) 528-2512
http://www.santepub-mtl.qc.ca
Hôpital général de Montréal
mandataire

RÉGIE RÉGIONALE
DE LA SANTÉ ET DES
SERVICES SOCIAUX
DE MONTRÉAL-CENTRE

MCGILL UNIVERSITY STUDY ON NICOTINE DEPENDENCE IN TEENS

Investigators: J. O'Loughlin, PhD., G. Paradis, MD, P. Clarke, PhD., J. Hanley, PhD, R. Tyndale, PhD., J. DiFranza, MD

CONSENT FORM - PART I

(In-class questionnaire and anthropometric measures)

Please complete and return this form to your child's teacher within 3 days.

Child's name:

First name (please print clearly) _____ Last name (please print clearly) _____

☐ **Yes,** my child will participate in Part I of this study (i.e. the classroom questionnaire and the measurement of height, weight, skinfold thickness, waist circumference and blood pressure).

☐ **No,** my child will not participate in this study.

PLEASE NOTE: You are <u>not</u> consenting to the blood sample at this time. You will receive a separate consent form to sign for Part II (blood sample) in February or March 2002, just before the blood sample will be taken.

Signatures

Parent's name (please print) _____ Parent's signature _____ Date _____

Child's name (please print) _____ Child's signature _____ Date _____

Santé physique
1301, rue Sherbrooke Est
Montréal (Québec) H2L 1M3
Téléphone : (514) 528-2400
Télécopieur : (514) 528-2512
http://www.santepub-mtl.qc.ca

Hôpital général de Montréal
mandataire

DIRECTION DE LA SANTÉ PUBLIQUE

PLEASE COMPLETE FORM ON REVERSE SIDE AND RETURN

September 21, 2001

MCGILL UNIVERSITY STUDY ON NICOTINE DEPENDENCE IN TEENS

Investigators: J. O'Loughlin, PhD., G. Paradis, MD, P. Clarke, PhD., J. Hanley, PhD, R. Tyndale, PhD., J. DiFranza, MD
McGill University, Direction de la santé publique de Montréal-Centre, University of Toronto, University of Massachusetts

Dear Parent/Guardian:

As you know your child has been participating in the McGill University Study on Nicotine Dependence in Teens, a project funded by the National Cancer Institute of Canada. An important aspect of this study is to investigate if genetic factors are involved in smoking uptake. To explore this possibility, we will collect a blood sample from each study participant for genetic analysis. During data collection in March 2002, after application of a local anaesthetic (Emla), a nurse will draw 10 ml of blood (2 teaspoons) for genetic analysis. Although the risk is very slight, there may be bruising where the needle pierces the skin or the child may faint. For this reason, the child will be in a reclining chair as the blood is drawn, and will be observed 10-15 minutes afterwards. As with any medication, some children might experience an allergic reaction to the local anaesthetic.

The blood samples will be labeled only by number. They will be analyzed at the University of Toronto, which specializes in this type of genetic analysis, and they will be stored at the Jewish General Hospital in Montreal. The results of the genetic test will remain completely confidential. A master list linking the child and the identification number will be stored securely at the Public Health Directorate. Only the principal investigator and the project coordinator will have access to the list, which will be destroyed at the end of the study. It will be impossible to provide any individual results of the genetic testing to anyone because they will never be linked to a particular name. After the list is destroyed, all blood samples will be completely anonymous.

The samples will be stored for a maximum of ten (10) years for future genetic analysis exclusively related to smoking. The blood samples, test results and consent forms are under the custody and control of Dr. Jennifer O'Loughlin, and will be kept under lock and key at all times. They will not, under any circumstances, be made available to any individual or organization not directly involved in this research project.

We are now asking for your and your child's consent for the blood sample. Your child's participation is completely voluntary, and it is entirely up to you and your child whether or not he/she participates. Your child can decide not to participate in the blood sample portion of the study and continue to participate only in the questionnaires and anthropometric measures. Also your child can withdraw from the study at any time and/or ask that his/her blood sample be destroyed before the end of the study by contacting the Project Coordinator (telephone number shown below). If you decide not to allow his/her participation, or if he/she withdraws from the study before it is completed, there will be no prejudice against your child.

Please complete the form on the reverse side of this letter, and return it in the enclosed addressed and stamped envelope. We have included an extra copy of the form for you to keep. If you have any questions, please contact the Project Coordinator, Mrs. Elizabeth McMillan-Davey at 528-2400 local 3976. Any complaints about the study can be discussed with Ms. Gloria Sacks-Silver at (514) 528-2400 local 3520. We thank you and your child for your help in this important project.

Jennifer O'Loughlin, Ph.D.
Principal Investigator

Gilles Paradis, M.D.
Co-Investigator

Please turn over ➢ ➢ ➢

RÉGIE RÉGIONALE
DE LA SANTÉ ET DES
SERVICES SOCIAUX
DE MONTRÉAL-CENTRE

MCGILL UNIVERSITY STUDY ON NICOTINE DEPENDENCE IN TEENS

Investigators: J. O'Loughlin, PhD., G. Paradis, MD, P. Clarke, PhD., J. Hanley, PhD, R. Tyndale, PhD., J. DiFranza, MD
McGill University, Direction de la santé publique de Montréal-Centre, University of Toronto, University of Massachusetts

CONSENT FORM FOR BLOOD SAMPLING

Please complete the 4 sections below and return by mail in the enclosed addressed, stamped envelope

1. Child's name:

First name (please print clearly) _____ Last name (please print clearly) _____

2. Blood sample and genetic analysis

☐ **Yes,** I have discussed this with my child and I accept that my child participate in the blood sampling and genetic analysis.

☐ **No,** my child will not participate in the blood sampling and genetic analysis.

3. Blood storage (complete only if YES in above section 2.)

☐ **Yes,** I have discussed this with my child and I accept that my child's blood sample may be stored for ten (10) years to study genetic factors associated with smoking.

☐ **No,** my child's blood sample must be destroyed at the end of the study.

4. Signatures

Parent's name (please print)	Parent's signature	Date
Child's name (please print)	Child's signature	Date

Santé physique
1301, rue Sherbrooke Est
Montréal (Québec) H2L 1M3
Téléphone : (514) 528-2400
Télécopieur : (514) 528-2512
http://www.santepub-mtl.qc.ca

Centre universitaire de santé McGill
McGill University Health Centre
mondialaire

DIRECTION DE LA SANTÉ PUBLIQUE

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

June 7, 2002

Dr. Jennifer O'Loughlin
Department of Epidemiology and Biostatistics
Purvis Hall
1020 Pine Avenue West
Montreal, Quebec
H3A 1A2

Dear Dr. O'Loughlin,

We have received correspondence in support of the research proposal AØØ-M48-02A entitled **"A Prospective Study on the Natural History of Nicotine Dependence: Request for Renewal"** which was reviewed by the Institutional Review Board, Faculty of Medicine at its meeting of May 13, 2002.

The responses and revisions were found to be acceptable and we are pleased to inform you that final approval for the clinical protocol (October 15, 2001), revised English and French questionnaires (May 28, 2002) and English and French study instruments was provided on June 7, 2002 valid until **May 2003**. The certification document (executed) is enclosed.

It is the responsibility of the investigator to assure that the approved research protocol and consent form is deposited with the Research Ethics Board of each hospital where patient recruitment or study data will be collected.

We ask you to take note that review of all research involving human subjects is required on an annual basis in accord with the date of initial approval. Should any modification to the study or unanticipated development occur prior to the next review, please advise IRB promptly.

Yours sincerely,

[redacted]

J. Lawrence Hutchison, M.D.
Chair,
Institutional Review Board

cc: A05 -M48-02A

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board consisting of:

LAWRENCE HUTCHISON, MD
PATRICIA DORKIN, PHD
CATHERINE GARDNER, BSC
CELESTE JOHNSTON, DED
WILSON MILLER, PHD, MD
ROBERT L. MUNRO, BCL
MARGARET SWAINE, BA

has examined the research project **AØ5-M48-02A** entitled **"A Prospective Study on the Natural History of Nicotine Dependence: Request for Renewal"**

as proposed by: Jennifer O'Loughlin (Applicant) to _____ (Granting Agency, if any)

and consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

June 7, 2002
Date

[redacted]
Chair, IRB

Dean of Faculty

Institutional Review Board Assurance Number: M-1458

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

May 13, 2002

Dr. Jennifer O'Loughlin
Department of Epidemiology and Biostatistics
Purvis Hall
1020 Pine Avenue West
Montreal, Quebec H3A 1A2

Dear Dr. O'Loughlin:

We are writing in response to your request for continuing review by the Institutional Review Board for the study **A05-M48-02A** entitled ***"A Prospective Study on the Natural History of Nicotine Dependence: Request for Renewal".***

The progress report was reviewed and we are pleased to inform you that full-board re-approval for the study was provided on ***May 12, 2002,*** valid until ***May 2004.*** The certification of annual review (executed) has been enclosed. We note that the current consent form is dated ***September 15, 2002.***

It is the Investigator's responsibility to assure that the current protocol and consent document are deposited, at the time of annual review, with the Research Ethics Board of each hospital where patient recruitment or data collection is carried out.

Should a study revision or unanticipated development occur prior to the next review, please advise the IRB promptly.

Yours sincerely,

[redacted]

Neil MacDonald, M.D.
Chair
Institutional Review Board

cc: A05-M48-02A

McGill Faculty of Medicine
Institutional Review Board
-Continuing Review-

Principal Investigator: Jennifer O'Loughlin Department/Institution: Epidemiology & Biostatistics
IRB Review Number: M-1458 Study Number (if any): AØ5-M48-02A Review Interval: June 7, 2002 – May 12, 2003

Title of Research Study: "A Prospective Study on the Natural History of Nicotine Dependence: Request for Renewal"

Date of initial IRB approval: June 7, 2002 Date of previous continuing review (if applicable): _____

INTERIM REPORT (PLEASE CHECK OR SPECIFY)

Current Status of Study:

Active Study: X On Hold: _____ Closed to Enrolment: X

Interim Analysis: X Final Analysis: _____ Study Not Activated*: _____

*If the study has not become active at McGill, please provide correspondence to explain; enclosed: _____

McGill hospital(s) where study is being conducted and has received approval of local Research Ethics Board(s) (if applicable):

JGH: ☐ MUHC/MCH: ☐ MUHC/MGH: ☐ MUHC/MNH-MNI: ☐

MUHC/RVH: ☐ SMH: ☐ Douglas ☐ Other: ☐ _____

McGill hospital(s) where study has not received approval of local Research Ethics Board(s) (if applicable): _____

If study sponsorship or financial support has changed, please provide correspondence to explain; enclosed: _____

Number of subjects to be enrolled by the McGill PI: 0 Number of subjects enrolled by the McGill PI to date: 1293

Number of subjects enrolled by the McGill PI since last review: 0

Have any of these subjects withdrawn from the study?: Yes

Has the study been revised since the last review?: No Have the study revisions been approved by the IRB?: _____

Has the consent form been revised since the last review?: No Date of the current consent form: September 15, 2002

Are there new data since the last review that could influence a subject's willingness to provide continuing consent?: No

Have there been any serious adverse experiences (SAEs)?: No

Have all serious adverse experiences (SAEs) and safety reports relevant to the study been reported to the IRB?: _____

SIGNATURES:

Principal Investigator: [redacted] Date: April 9, 2003

IRB Chair: [redacted] Date: May 12, 2003

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

May 11, 2004

Dr. Jennifer O'Loughlin
Department of Epidemiology and Biostatistics
Purvis Hall
1020 Pine Avenue West
Montreal, Quebec H3A 1A2

Dear Dr. O'Loughlin:

We are writing in response to your request for continuing review by the Institutional Review Board for the study **A05-M48-02A**, entitled: ***"A Prospective Study on the Natural History of Nicotine Dependence: Request for Renewal"***.

The progress report was reviewed and we are pleased to inform you that full-board re-approval for the study was provided on ***May 10, 2004***, valid until ***May 9, 2005***. The certification of annual review (executed) has been enclosed.

It is the Investigator's responsibility to assure that the current protocol and consent document are deposited, at the time of annual review, with the Research Ethics Board of each hospital where patient recruitment or data collection is carried out.

Should a study revision or unanticipated development occur prior to the next review, please advise the IRB promptly.

Yours sincerely,

[redacted]

Celeste Johnston, DEd.
Co-Chair
Institutional Review Board

cc: A05-M48-02A

DATE OF I.R.B. APPROVAL

MAY 10 2004

Faculty of Medicine
McGill University

McGill Faculty of Medicine
Institutional Review Board
-Continuing Review-

Principal Investigator: Jennifer O'Loughlin, Ph.D. Department/Institution: Epidemiology & Biostatistics

IRB Review Number: M - 1458 Study Number (if any): A05 – M48 – 02A Review Interval: May 2003 – May 2004

Title of Research Study: A Prospective study on the Natural History of Nicotine Dependence: Request for Renewal

Date of initial IRB approval: June 7, 2002 Date of previous continuing review (if applicable): May 12, 2003

INTERIM REPORT (PLEASE CHECK OR SPECIFY)

Current Status of Study:

Active Study: X On Hold: Closed to Enrolment: X

Interim Analysis: X Final Analysis: Study Not Activated*:

*If the study has not become active at McGill, please provide correspondence to explain; enclosed:

McGill hospital(s) where study is being conducted and has received approval of local Research Ethics Board(s) (if applicable):

JGH: ☐ MUHC/MCH: ☐ MUHC/MGH: ☐ MUHC/MNH-MNI: ☐

MUHC/RVH: ☐ SMH: ☐ Douglas ☐ Other: ☐

McGill hospital(s) where study has not received approval of local Research Ethics Board(s) (If applicable):

If study sponsorship or financial support has changed, please provide correspondence to explain; enclosed:

Number of subjects to be enrolled by the McGill PI: 0 Number of subjects enrolled by the McGill PI todate: 1293

Number of subjects enrolled by the McGill PI since last review: 0

Have any of these subjects withdrawn from the study?: Yes

Has the study been revised since the last review?: Yes Have the study revisions been approved by the IRB? Yes

Has the consent form been revised since the last review?: No Date of the current consent form: September 15, 2002

Are there new data since the last review that could influence a subject's willingness to provide continuing consent?: No

Have there been any serious adverse experiences (SAEs)?: No

Have all serious adverse experiences (SAEs) and safety reports relevant to the study been reported to the IRB?:

SIGNATURES:

Principal Investigator: [redacted] Date: April 23 2004

IRB Chair: [redacted] Date: 10 MAY 2004

PCW

National Cancer Institute of Canada
Application for Research Grant

Institut National du Cancer du Canada
Demande de subvention de recherche

October 15, 2001/Le 15 octobre 2001

Important! The *2001 Grant Application Guide* contains essential information for completing this form.
Important! *Le Guide de demande de subvention de 2001* contient des renseignements essentiels pour remplir ce formulaire.

Grant Category/Catégorie de la subvention

- ☒ Regular Research Grant / Subvention de fonctionnement
- ☐ New Investigator / Nouveau chercheur
- ☐ Feasibility/Faisabilité

Are you also applying for New Investigator Equipment? / Faites-vous également une demande d'équipement pour nouveau chercheur?
☐ Yes/Oui ☒ No/Non

Type of Application/Type de demande

- ☐ Initial Application/Première demande
- ☐ Re-Application/Nouvelle soumission d'une demande refusée
- ☒ Renewal/Renouvellement
  Current Grant # /Subvention actuelle no :010271

1. PRINCIPAL INVESTIGATOR/CHERCHEUR PRINCIPAL

Surname/Nom	Given Name/Prénom	Middle Name/2e prénom	Title/Titre
O'Loughlin	Jennifer	Lee	☒ Dr. ☐ Mr./M ☐ Ms. /Mme

2. MAILING ADDRESS OF PRINCIPAL INVESTIGATOR/ADRESSE POSTALE DU CHERCHEUR PRINCIPAL

Institution/Établissement	Department/Département
Régie régionale de la santé et des services sociaux	Direction de la santé publique de Montréal-Centre

Street Address/Adresse: 1301, rue Sherbrooke Est

City/Ville	Province	Postal Code/Code postal	E-Mail Address/Adresse c. élec.
Montréal	Québec	H2L 1M3	jennifer.oloughlin@mcgill.ca

Office Telephone/Téléphone bureau	Lab Telephone/Téléphone lab.	Fax Number/Télécopieur
(514)528-2400 ext. 3448	N/A	(514) 528-2425

3. TITLE OF PROJECT/TITRE DU PROJET

A prospective study on the natural history of nicotine dependence: a request for renewal

4. HOST RESEARCH INSTITUTION/ÉTABLISSEMENT HÔTE

Research Institute of the McGill University Health Centre (MUHC)

5. BUDGET INFORMATION/RENSEIGNEMENTS SUR LE BUDGET

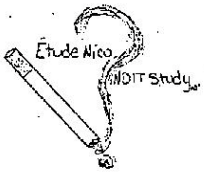
	$ Year One $ 1ère année	$ Year Two $ 2e année	$ Year Three $ 3e année	$ Year Four $ 4e année	$ Year Five $ 5e année
(I) Supplies & Expenses / Fournitures et dépenses	12,282	12,282	4,430		
(II) Salaries & Wages / Salaires	[redacted]				
(III) Permanent Equipment / Équipement permanent	0				
(IV) New Investigator Equipment (if applicable) / Équipement nouveau chercheur (le cas échéant)	0				
Yearly Totals Requested (I+II+III+IV) / Totaux annuels demandés (I+II+III+IV)	[redacted]				

FOR OFFICE USE ONLY / À L'USAGE DU BUREAU SEULEMENT	Year One 1ère année	Year Two 2e année	Year Three 3e année	Year Four 4e année	Year Five 5e année
(I) Supplies & Expenses / Fournitures et dépenses		DATE OF REC. APPROVAL			
(II) Salaries & Wages / Salaires					
(III) Permanent Equipment / Équipement permanent		JUN - 7 2002			
(IV) New investigator Equipment (if applicable) / Équipement nouveau chercheur (le cas échéant)		Faculty of Medicine			
Yearly Totals Recommended (I+II+III+IV) / Totaux annuels recommandés (I+II+III+IV)		McGill University			

PANEL/COMITÉ	REVIEWER/EVALUATEUR 1	REVIEWER/EVALUATEUR 2	EXTERNAL/EXTERNE 1	EXTERNAL/EXTERNE 2

27 C01

PLEASE PRINT YOUR NAME _____
First name Last name



DATE OF I.R.B. APPROVAL
JUN - 7 2002
Faculty of Medicine
McGill University

MCGILL UNIVERSITY STUDY ON NICOTINE DEPENDENCE IN TEENS

QUESTIONNAIRE VERSION [0][6]

SCHOOL [ ][ ]

DOSSIER NUMBER [ ][ ][ ]

SURVEY NUMBER [ ][ ]

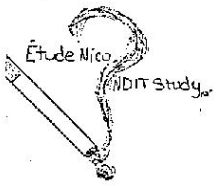
TODAY'S DATE [ ][ ] DAY [ ][ ] MONTH [ ][ ][ ][ ] YEAR

GRADE [ ][ ]

RECALL MONTHS [0][1]

INSCRIVEZ VOTRE NOM _____

Prénom Nom



ÉTUDE DE L'UNIVERSITÉ McGILL SUR LA DÉPENDANCE À LA NICOTINE CHEZ LES ADOLESCENTS

VERSION DU QUESTIONNAIRE [0][6]

ÉCOLE [ ][ ]

NUMÉRO DU DOSSIER [ ][ ][ ]

NUMÉRO DE L'ENQUÊTE [ ][ ]

DATE D'AUJOURD'HUI [ ][ ] JOUR [ ][ ] MOIS [ ][ ][ ][ ] ANNÉE

ANNÉE À L'ÉCOLE [ ][ ]

MOIS DE RAPPELS [0][1]

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

May 13, 2002

Dr. Jennifer O'Loughlin
Department of Epidemiology and Biostatistics
Purvis Hall
1020 Pine Avenue West
Montreal, Quebec H3A 1A2

Dear Dr. O'Loughlin:

We are writing in response to your request for continuing review by the Institutional Review Board for the study **A05-M48-02A** entitled ***"A Prospective Study on the Natural History of Nicotine Dependence: Request for Renewal".***

The progress report was reviewed and we are pleased to inform you that full-board re-approval for the study was provided on ***May 12, 2002***, valid until ***May 2004.*** The certification of annual review (executed) has been enclosed. We note that the current consent form is dated ***September 15, 2002.***

It is the Investigator's responsibility to assure that the current protocol and consent document are deposited, at the time of annual review, with the Research Ethics Board of each hospital where patient recruitment or data collection is carried out.

Should a study revision or unanticipated development occur prior to the next review, please advise the IRB promptly.

Yours sincerely,

[redacted]

Neil MacDonald, M.D.
Chair
Institutional Review Board

cc: A05-M48-02A

McGill Faculty of Medicine
Institutional Review Board
-Continuing Review-

Principal Investigator: Jennifer O'Loughlin Department/Institution: Epidemiology & Biostatistics
IRB Review Number: M-1458 Study Number (if any): AØ5-M48-02A Review Interval: June 7, 2002 – May 12, 2003

Title of Research Study: "A Prospective Study on the Natural History of Nicotine Dependence: Request for Renewal"

Date of initial IRB approval: June 7, 2002 Date of previous continuing review (if applicable): _____

INTERIM REPORT (PLEASE CHECK OR SPECIFY)

Current Status of Study:

Active Study: X On Hold: _____ Closed to Enrolment: X

Interim Analysis: X Final Analysis: _____ Study Not Activated*: _____

*If the study has not become active at McGill, please provide correspondence to explain; enclosed: _____

McGill hospital(s) where study is being conducted and has received approval of local Research Ethics Board(s) (if applicable):

JGH: ☐ MUHC/MCH: ☐ MUHC/MGH: ☐ MUHC/MNH-MNI: ☐
MUHC/RVH: ☐ SMH: ☐ Douglas ☐ Other: ☐ _____

McGill hospital(s) where study has not received approval of local Research Ethics Board(s) (if applicable): _____

If study sponsorship or financial support has changed, please provide correspondence to explain; enclosed: _____

Number of subjects to be enrolled by the McGill PI: 0 Number of subjects enrolled by the McGill PI to date: 1293

Number of subjects enrolled by the McGill PI since last review: 0

Have any of these subjects withdrawn from the study?: Yes

Has the study been revised since the last review?: No Have the study revisions been approved by the IRB?: _____

Has the consent form been revised since the last review?: No Date of the current consent form: September 15, 2002

Are there new data since the last review that could influence a subject's willingness to provide continuing consent?: No

Have there been any serious adverse experiences (SAEs)?: No

Have all serious adverse experiences (SAEs) and safety reports relevant to the study been reported to the IRB?: _____

SIGNATURES:

Principal Investigator: [redacted] Date: April 9, 2003

IRB Chair: [redacted] Date: May 12, 2003

Le 15 septembre 2002

ÉTUDE DE L'UNIVERSITÉ MCGILL SUR LA DÉPENDANCE À LA NICOTINE CHEZ LES ADOLESCENTS

Chercheurs: J O'Loughlin, PhD, G Paradis, md, P Clarke, PhD, J Hanley, PhD, B Tyndale, PhD, J DiFranza, md
Université McGill, Direction de la santé publique de Montréal-Centre, Université de Toronto, Université du Massachussetts

Chers parents/tuteurs,

Comme vous le savez, votre enfant a participé à l'étude de l'université McGill sur la dépendance à la nicotine chez les adolescents, un projet financé par l'Institut national du cancer du Canada.

L'objectif de cette étude, qui touche 1200 élèves de 10 écoles de la région de Montréal, est de mieux comprendre le processus qui amène certains adolescents à devenir fumeurs. Nous étudions à la fois les enfants qui fument et les enfants qui ne fument pas. De plus, cette étude explorera la relation entre le tabagisme, le poids corporel et la tension artérielle à l'adolescence.

Nous vous écrivons maintenant pour vous informer que l'étude a été subventionnée pour 3 années additionnelles par l'Institut national du cancer du Canada. Ce prolongement nous permettra de suivre les élèves jusqu'à la fin du secondaire et d'explorer la faisabilité de continuer à suivre le groupe d'élèves après la fin des études secondaires. Comme auparavant, notre équipe visitera l'école de votre enfant chaque 3-4 mois pour faire remplir un questionnaire de 40 minutes, portant sur les expériences face à la cigarette. De plus, à la fin du Secondaire V, des techniciens de recherche mesureront la taille, le poids, l'épaisseur des plis cutanés, la circonférence abdominale et la tension artérielle de votre enfant. Toutes les informations seront conservées sous clé à la Direction de la Santé publique de Montréal-Centre. Ce prolongement n'occasionnera aucun risque ou bénéfice pour les participants à l'étude. Cependant, les résultats augmenteront notre compréhension de l'histoire naturelle de la dépendance à la nicotine et nous aideront à développer des stratégies efficaces permettant aux enfants et adolescents d'éviter de commencer à fumer, ainsi que des moyens efficaces pour aider les jeunes qui désirent arrêter de fumer.

La Commission scolaire et le directeur de votre école ont approuvé cette étude. Cependant, la participation de votre enfant est tout à fait volontaire et il n'en tient qu'à vous et à votre enfant qu'il continue à y participer. Votre enfant peut se retirer de l'étude à n'importe quel moment. Si votre enfant ne participe pas à cette étude, ou se retire, il n'y aura aucun préjudice envers lui/elle.

S'il vous plaît complétez le formulaire ci-dessous seulement si vous ne voulez pas que votre enfant continue à participer à l'étude, et retourner le dans l'enveloppe-réponse affranchie. Si vous ne retournez pas le formulaire, ceci nous indique que vous consentez que votre enfant continue à participer à l'étude. Si vous avez des questions, s'il vous plait communiquer avec la coordonnatrice du projet, Mme Elizabeth McMillan-Davey, au (514) 528-2400, poste 3976. Nous vous remercions de votre aide précieuse et de celle de votre enfant dans cet important projet.

[redacted]

Jennifer O'Loughlin, Ph.D
Chercheure principale

Gilles Paradis, M.D.
Co-chercheur

✂ ✂ ✂ ✂ ✂ ✂

☐ Non, mon enfant _____
Nom de l'enfant

qui va à l'école _____
Nom de l'école

ne continuera pas à participer à l'Étude de l'Université McGill sur la dépendance à la nicotine chez les adolescents.

Nom du parent (en lettres moulées) _____ Signature du parent _____ Date _____

DATE OF C.R.E.
APPROVAL

JUN - 7 2002

September 15th, 2002

MCGILL UNIVERSITY STUDY ON NICOTINE DEPENDENCE IN TEENS

Investigators: J. O'Loughlin, PhD., G. Paradis, MD, P. Clarke, PhD., McGill University, R. Tyndale, PhD., J. DiFranza, MD
McGill University, Direction de la santé publique de Montreal-Centre, University of Toronto, University of Massachusetts

Dear Parent/Guardian:

As you know your child has been participating in the McGill University Study on Nicotine Dependence in Teens, a project funded by the National Cancer Institute of Canada. The purpose of this research, which is being conducted among 1200 students in 10 Montreal high schools, is to study how smoking becomes an established habit in some adolescents. We are studying children who smoke, as well as children who do not smoke. In addition, this study will examine the relationship between smoking, weight, and blood pressure during adolescence.

We are writing to you now to let you know that this project has been funded for another 3 years by the National Cancer Institute of Canada to enable us to follow our group of students until the end of high school. In this phase of the project we will also explore the feasibility of continuing to follow the group after they have completed high school.

As before, our team will visit your child's school every 3 to 4 months to administer a 40-minute in-class questionnaire which asks participants about their smoking experiences. In addition, at the end of Secondary V, trained technicians will measure your child's height, weight, skinfold thickness, waist circumference and blood pressure. All data are stored in locked storage areas at the Public Health Directorate. There are no risks or benefits expected for study participants in this extension of the project. However, the results will allow increased understanding of the natural history of nicotine dependence and will therefore help us to develop more effective strategies to prevent the onset of smoking in children, as well as to help youth who want to quit smoking.

Both your school board and school principal fully support the 3-year extension of this project. However, as before, your child's participation is completely voluntary, and it is entirely up to you and your child whether or not he/she continues to participate. Your child can withdraw from the study at any time. If you decide not to allow his/her participation in the extension of the study, there will be no prejudice against your child.

Please complete the form below only if you do not want your child to continue participating in the study, and return it in the enclosed, stamped, addressed envelope. If you do not return the form, it will indicate to us that you have consented to allow your child to continue to participate in the study. If you have any questions, please contact the Project Coordinator, Mrs. Elizabeth McMillan-Davey at (514) 528-2400 ext. 3976.

[redacted]
Jennifer O'Loughlin, Ph.D.
Principal Investigator

[redacted]
Gilles Paradis, M.D.
Co-Investigator

☐ No, my child _____
Name of the child

who attends _____
Name of school

will not continue to participate in the McGill University Study on Nicotine Dependence in Teens.

Name of parent (please print) _____ Signature of parent _____ Date _____

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

28 August 2006.

Dr. Jennifer O'Loughlin
Department of Epidemiology & Biostatistics
Purvis Hall
1020 Pine Avenue West
Montreal Quebec H3A 1A2

RE: IRB Study Number A05-B21-06B

Dear Dr. O'Loughlin,

Thank you for responding to the Initial Review Board's correspondence dated 31 May 2006 in reference to the study entitled, *Long-term follow-up of the Nicotine Dependence in Teens (NDIT) Cohort*. This study received full Board review on May 29, 2006.

The submitted revisions are acceptable and final ethics approval is provided on August 28, 2006 for the following:

- Study Protocol (IRB dated May 2006);
- Appendix 8: Consent form for Self-Administered Questionnaire dated May 2006;
- Revised Appendix 9: Consent form for DNA Sample Collection dated June 2006;
- Appendix 10: Data/DNA User's Manuel;
- Appendix 12: Self-Administered Questionnaire (May 2006).

Please ensure that an IRB acceptable French translation of the approved consent forms are available to subjects during the consent process.

The ethics approval for this study is valid until **May 2007.** The Certificate of Ethical Acceptability is enclosed.

All research involving human subjects is required to undergo an annual review in accordance with the date of initial approval. It is the responsibility of the investigator to submit a completed application form for Continuing Review to the IRB prior to the date of expiration of ethics approval. A copy of the Continuing Review Form is available on the IRB website at: http://www.medicine.mcgill.ca/research/irb/.

Any modifications or unanticipated developments that may occur to the study prior to the annual review must be reported to the IRB promptly. Regulation does not permit the initiation of a study modification prior to IRB review and approval of the change.

Sincerely,

[redacted]

Serge Gauthier, MD
Chair
Institutional Review Board

Cc: A05-B21-06B

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3585

CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board (IRB) is a registered University IRB working under the published guidelines of the Tri-Council Policy Statement, in compliance with the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique, (MSSS, 1998) and the Food and Drugs Act (17 June 2001); and acts in accordance with the U.S. Code of Federal Regulations that govern research on human subjects. The IRB working procedures are consistent with internationally accepted principles of good clinical practice.

At a full Board meeting on May 29, 2006, the Faculty of Medicine Institutional Review Board, consisting of:

SERGE GAUTHIER, MD	FRANCES ABOUD, PHD
MARTIN CHASEN, MB CHB, MPHIL	PIERRE DESCHAMPS, BCL, LSCR
MARYLNNE GURSKY, BN, M.ED.	MARIGOLD HYDE, BSC
PETR KAVAN, MD	HARVEY SIGMAN, MD

SALLY TINGLEY, BCOM

Examined the research project **A05-B21-06B** entitled ***Long-term Follow-up of the Nicotine Dependence in Teens (NDIT) Cohort***

As proposed by: Dr. Jennifer O'Loughlin (Applicant) to _____ (Granting Agency, if any)

And consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

August 28, 2006
Date

[redacted]
Chair, IRB

[redacted]
Dean of Faculty

Institutional Review Board Assurance Number: FWA 00004545

May 2006

TABLE OF CONTENTS

May 2006

APPENDIX 12

Self-Administered Questionnaire

DATE OF I.R.B.
APPROVAL

AUG 28 2006

Faculty of Medicine
McGill University

APPENDIX 10

McGill University Study on the Natural History of Nicotine Dependence
Data/DNA User's Manual

1. Introduction

The McGill University Study on the Natural History of Nicotine Dependence (NDIT Study) is a unique Canadian resource with a wealth of information about tobacco use onset and nicotine dependence in youth, as well as a DNA repository. While the NDIT research team has already, or will soon, complete the main effects analyses, it encourages others to learn about this database and to exploit it to its full potential. This document provides information to individuals who wish to have access to and use data/DNA from the NDIT Study to conduct secondary analyses. The intent is to assure that publications emanating from this database are consistent in the sample sizes and in the variables reported, and to assure that there is no overlap between publications. In addition to describing how to obtain access to the database, this Data User's Manual includes the following Appendices:

I. Questionnaires
II. Data Dictionary
III. List of Suppressed Variables
IV. List of Created Variables
V. List of Publications, Abstracts, and Reports (including documents in progress, submitted, and under review)

2. Access

Access to data/DNA collected in the NDIT Study is open to any university-affiliated investigator upon successful completion of the application procedure. Students may apply for use of the data/DNA though their primary supervisor. In order to obtain access, applicants must submit a proposal to the NDIT research team in Montreal using the format outlined in the Data Request Application. Proposals may be submitted by fax or electronically. Once the proposal is approved, Data Users must provide a certificate of ethics approval for the research from their Institutional Review Board to the NDIT research team.

3. Confidentiality

The NDIT research team has taken great care to protect the identity of cohort members and to safeguard their privacy and the confidentiality of the data/DNA they provided. Any secondary analyses undertaken using these data/DNA must also maintain the confidential nature of these data/DNA. To assure confidentiality, the data/DNA provided to Data Users will be stripped of identifiers such as name, geographic location, etc., that could permit a direct relation to be established between the data/DNA and specific respondents. Data Users must sign a confidentiality agreement in order to access these data/DNA.

4. Review of Proposal

Receipt of the proposal will initiate the review process by the NDIT research team. Approval of proposals will be based on scientific merit, relevance, and security provisions in place at the applicant's institution to protect the confidentiality of data/DNA. The review process will produce one of two outcomes – acceptance or rejection. Results of the review will be communicated by letter to applicants within two weeks of the date of application. If a project is rejected, the rationale for the decision will be included in the letter. Once the proposal has been approved, a written agreement between the NDIT research team and Data User will be developed, which describes the dataset/DNA to be provided and the Data User's agreement to abide by the security and confidentiality requirements. After proof of ethics review by the applicant's Institutional Review Board has been received by the NDIT research team, Data Users will be provided with an electronic copy of the variables requested in the proposal and/or DNA samples.

5. Data Security

The NDIT data set(s) must be stored in a password-protected location. Giving access to the dataset/DNA to other individuals not mentioned in the proposal is not permitted. NDIT data set(s)/DNA must be destroyed upon project completion.

may 2006

APPENDIX 8

Consent Form for Self-Administered Questionnaire

DATE OF I.R.B. APPROVAL
AUG 2 8 2006
Faculty of Medicine
McGill University

McGill

Joint Departments of Epidemiology and Biostatistics
and of Occupational Health
Départements unifiés d'épidémiologie et biostatistique,
et de santé au travail

1020 Pine Avenue West
Purvis Hall, room 46
Montréal, Québec H3A 1A2
Tel: (514) 398-8997 Fax: (514) 398-4503

Consent Form - Questionnaires
Principal Investigator: Jennifer O'Loughlin
Co-Investigators: Gilles Paradis, James Hanley, Rachel F. Tyndale, Joseph DiFranza
Funded by: National Cancer Institute of Canada

Project Title: McGill University Study on the Natural History of Nicotine Dependence: Long term follow-up of the nicotine dependence in teens (NDIT) cohort

Introduction: As you know, the NDIT study is a prospective investigation of 1293 students initially aged 12-13 years, recruited from grade 7 classes in 10 Montreal high schools in 1999. Our funding was renewed in 2002 and we are now entering the 3rd phase of the study. The purpose of this current extension is to study smoking in young adults and to continue investigating how genetic factors might be related to nicotine dependence.

Study Procedure: Every 6 months over the next 5 years, you will receive a self-administered questionnaire by mail. The questionnaire, which will take 10-15 minutes to complete, asks participants about their smoking experiences. You will be asked to return the questionniaret to McGill by mail in a stamped, addressed envelope. All identifying information will be removed from the questionnaire at McGill and then the data will be entered into an electronic database.

Benefits and Risks: There are no risks or benefits expected for study participants in this extension of the project. However, the results will allow increased understanding of the natural history of nicotine dependence and will therefore help us to develop more effective strategies to prevent the onset of smoking in young adults, as well as to help young adults who want to quit smoking.

Withdrawal from Study: Your participation in this extension of the NDIT Study is completely voluntary. You may withdraw from the study at any time. If you decide not to continue to participate, there will be no prejudice against you.

Confidentiality: All questionnaire data are completely confidential and data will stored in locked storage areas at McGill University. Only members of the research team will have access to the data.

Contact: Please complete the form below if you want to continue participating in the study, and return it in the enclosed, stamped, addressed envelope. If you have any questions, please contact the Project Coordinator, *Name of Coordinator* at *Phone Number*. We thank you for your help in this important project.

June 2006

APPENDIX 9

Consent Form for DNA Sample Collection

McGill

DATE OF I.R.B. APPROVAL

AUG 28 2006

Faculty of Medicine
McGill University

Joint Departments of Epidemiology and Biostatistics
and of Occupational Health
Départements unifiés d'épidémiologie et biostatistique,
et de santé au travail

1020 Pine Avenue West
Purvis Hall, room 46
Montréal, Québec H3A 1A2
Tel: (514) 398-8997 Fax: (514) 398-4503

Consent Form - DNA Sample
Principal Investigator: Jennifer O'Loughlin
Co-Investigators: Gilles Paradis, James Hanley, Rachel F. Tyndale, Joseph DiFranza
Funded by: National Cancer Institute of Canada

Project Title: McGill University Study on the Natural History of Nicotine Dependence: Long term follow-up of the nicotine dependence in teens (NDIT) cohort

Introduction: As you know, the NDIT study is a prospective investigation of 1293 students initially aged 12-13 years, recruited from grade 7 classes in 10 Montreal high schools in 1999. Our funding was renewed in 2002 and we are now entering the 3rd phase of the study. The purpose of this current extension is to study smoking in young adults and to continue investigating how genetic factors might be related to nicotine dependence.

Study Procedure: In the next week, you will receive a DNA sample kit through the mail, with an instruction manual. You will be asked to provide a saliva sample in a plastic container (for genetic analysis), seal it, and return it to McGill by mail in a stamped, addressed envelope.

Benefits and Risks: There are no risks or benefits expected for study participants in this extension of the project. However the results will allow increased understanding of the natural history of nicotine dependence and will therefore help us to develop more effective strategies to prevent the onset of smoking in young adults, as well as to help young adults who want to quit smoking.

Withdrawal from Study: Your participation in providing a DNA sample is completely voluntary. If you decide not to provide a sample, there will be no prejudice against you. You may withdraw from the study at any time with no prejudice.

Confidentiality: All DNA samples will be stored at the University of Toronto in locked filing cabinets. The samples will not have any identifying information. Only the members of the research team will have access to the DNA and the data. All identifying information will be removed from the sample at McGill and then the sample will be sent to Dr. Rachel Tyndale's laboratory at the University of Toronto, where it will be genotyped for selected genes suspected to be related to smoking.

CHUM

CENTRE DE RECHERCHE
Comités d'évaluation scientifique et d'éthique de la recherche
Édifice Cooper
3981, boulevard St-Laurent, Mezz 2
Montréal (Québec) H2W 1Y5

Téléphone : 514 - 890-8000 – Poste 14485
Télécopieur : 514 – 412-7394
Courriel : ghislaine.otis.chum@ssss.gouv.qc.ca

Le 21 février 2007

Dr Jennifer O'Loughlin
Épidémiologie
A/S Mme Erika Dugas
Édifice St-Urbain
3875, rue Saint-Urbain – 1e étage
Montréal (Québec) H2W 1T9

Objet : ***NDo6.087 – Approbation finale CÉR***

L'étude de la dépendance à la nicotine

Docteur,

J'accuse réception, en date du 21 février 2007, de votre lettre ainsi que des documents suivants en vue de l'approbation finale de l'étude décrite en rubrique :

- *Formulaire de consentement – Questionnaire – Version française – 8 février 2007*
- *Formulaire de consentement – Questionnaire – Version anglaise – 8 février 2007*
- *Formulaire de consentement – Échantillon d'ADN – Version française – 8 février 2007*
- *Formulaire de consentement – Échantillon d'ADN – Version anglaise – 8 février 2007*

Le tout est jugé satisfaisant. Je vous retourne sous pli une copie de chacun des formulaires portant l'estampille d'approbation du comité. Seuls ces formulaires devront être utilisés pour signature par les sujets.

La présente constitue l'approbation finale, ***valide pour un an à compter du 27 novembre 2007,*** *date de l'approbation initiale. Je vous rappelle que toute modification au protocole et/ou au formulaire de consentement en cours d'étude, doit être soumise pour approbation du comité d'éthique.*

Le comité suit les règles de constitution et de fonctionnement de l'Énoncé de Politique des trois Conseils et des Bonnes pratiques cliniques de la CIH.

Vous souhaitant la meilleure des chances dans la poursuite de vos travaux, je vous prie d'accepter, Docteur, mes salutations distinguées.

[redacted]

Brigitte St-Pierre, conseillère en éthique
Vice-présidente
Comité d'éthique de la recherche
Équipe Hôpital Notre-Dame du CHUM

BSTP/go
P. j. : Formulaires de consentement approuvés et estampillés

FORM 2

CHUM

Non-multicentrique – Renouvellement annuel

FORMULAIRE DE DEMANDE DE RENOUVELLEMENT ANNUEL DE L'APPROBATION D'UN PROJET DE RECHERCHE

SECTION 1 – Renseignements généraux

1.	Date de soumission du formulaire :	le 18 octobre 2011
2.	Numéro de référence donné au projet par le CÉR :	ND 06.087
3.	Numéro de protocole ou autre numéro d'identification :	N/A
4.	Nom du chercheur principal :	Dr. Jennifer O'Loughlin
5.	Titre en français du projet : L'étude de la dépendance à la nicotine	

6. Indiquez le statut actuel du projet de recherche

- ☐ Projet en cours pour lequel aucun sujet de recherche n'a encore été recruté dans l'établissement.
- ☐ Projet et recrutement en cours
- ☒ Projet en cours pour lequel le recrutement est terminé
- ☐ Projet interrompu
- ☐ Projet en attente

7. Selon les exigences de l'organisme subventionnaire (NIH, NCI, NCIC...), le renouvellement doit-il être approuvé lors d'une réunion plénière (Full Board)? ☐ Oui ☒ Non

SECTION 2 Renseignements relatifs au déroulement du projet de recherche depuis le début

8. Date de l'approbation initiale du projet de recherche par le CÉR : approbation initiale le 27 nov 2006; approbation finale le 21 fev 2007
9. Date à laquelle le projet de recherche a effectivement commencé : mars 2007
10. Date à laquelle le projet de recherche devrait se terminer : 30 juin 2013

11. Informations relatives aux sujets de recherche depuis le début du projet (incluant la dernière année)

Nombre de sujets à recruter initialement :	1208
Nombre de sujets qui ont effectivement été recrutés :	1208
Nombre de sujets dont la participation n'est pas terminée :	1063
Nombre de sujets dont la participation est terminée :	0
Nombre de sujets qui ont été exclus ou retirés du projet :	0
Nombre de sujets qui ont abandonné en cours de route :	145

12. Indiquez les motifs de l'exclusion ou du retrait des sujets de recherche ou de l'abandon du projet par ceux-ci.
Motifs des exclusions ou retraits
N/A

Motifs des abandons, si connus
Raisons des abandons non connues

SECTION 3 **Renseignements relatifs au déroulement du projet au cours de la dernière année**

13. Informations relatives aux sujets de recherche durant la dernière année

Nombre de sujets recrutés durant l'année :	N/A
Nombre de sujets qui ont terminé durant l'année :	N/A
Nombre de sujets qui ont abandonné ou été retirés :	0

14. Au cours de la dernière année, et par rapport à la situation au moment de la dernière approbation, y a-t-il eu des rapports soumis au CÉR concernant :

☐ Modifications (amendement) au protocole?
Si oui, précisez le nombre d'amendements soumis au CÉR :
☐ Incidents ou réactions indésirables (Essai clinique)?
☐ Accidents?

15. Au cours de la dernière année, y a-t-il eu :

☐ Nouveau renseignement susceptible d'affecter l'éthicité du projet ou d'influencer sur la décision d'un sujet de recherche quant à sa participation au projet :
☐ Modification de l'équilibre clinique à la lumière des données recueillies :
☐ Déviations au protocole de recherche :
☐ Interruption temporaire du projet :
☐ Problèmes constatés par un tiers au cours d'une activité de surveillance ou de vérification, interne ou externe, lesquels problèmes seraient susceptibles de remettre en question soit l'éthicité du projet, soit la décision du CÉR :
☐ Le CÉR a-t-il été avisé d'une situation de conflit d'intérêts – apparent, éventuel ou réel et touchant un ou plusieurs membres de l'équipe de recherche – qu'il ne connaissait pas au moment de sa dernier approbation du projet :
☐ Nouvelles informations dans la littérature ou dans des études récentes qui pourraient modifier l'équilibre entre les risque et les bénéfices du projet :
☒ Les résultats du projet ont-ils déjà été soumis pour publication, présentées ou publiés :
☐ Le CÉR a-t-il été avisé d'une situation de conflit d'intérêts – apparent, éventuel ou réel et touchant un ou plusieurs membres de l'équipe de recherche – qu'il ne connaissait pas au moment de sa dernière approbation du projet :
☐ Y a-t-il une allégation de manquement à l'éthique (ex. : plainte d'un sujet de recherche, non-respect des

FORM 2

CHUM

Non-multicentrique – Renouvellement annuel

règles relatives à l'éthique ou à l'intégrité) concernant un ou plusieurs chercheurs :
☐ Y a-t-il eu des problèmes dans l'exécution du projet de recherche ou des événements d'importance sont-ils survenus dans l'un des établissements où ce projet se déroule :
☐ Le projet a-t-il posé des problèmes ou soulevé des difficultés sur le plan éthique :
☐ Voulez-vous porter un autre élément à l'attention du CÉR :

Joindre toute information qui n'aurait pas encore été soumise au CÉR.

J'atteste que les renseignements fournis dans le présent formulaire sont exacts

[redacted]

S

le 18 octobre 2011
Date

SECTION 4 – Suivi donné par le Comité d'éthique de la recherche

Renouvellement accordé	
Du 27 novembre 2011	Au 27 novembre 2012

Approuvé par :

[redacted]

21 octobre 2011
Date

Commentaires :

CENTRE DE RECHERCHE
Comités d'évaluation scientifique et d'éthique de la recherche
Équipe Saint-Luc du CHUM
Édifice Cooper
3981, boulevard St-Laurent – Mezz 2
Montréal (Québec) H2W 1Y5

Téléphone : 514 890 8000 – Poste 14528
Télécopieur : 514 412 7394
Courriel : karima.bekhiti.chum@ssss.gouv.qc.ca

CHUM

Le 27 novembre 2006

Dre Jennifer O'Loughlin
Épidémiologie

a/s Mme Erika Dugas
3875 rue Saint-Urbain, 1er étage
Montréal (Québec) H2W 1V1

Objet : ND 06.087 – Approbation initiale CÉR
Titre : Étude de la dépendance à la nicotine
Protocole : N/A

Chère Docteure,

J'ai le plaisir de vous informer que le Comité d'éthique de la recherche, à sa réunion plénière du 27 novembre 2006, a évalué le projet mentionné ci-dessus.

À cette fin, ont notamment été examinés les documents suivants :

- Formulaire de présentation – Formulaire A – Annexe 2.1
- Formulaire de renseignements supplémentaires – Annexe 2.2
- Résumé du protocole
- Protocole de recherche (version de mai 2006)
- Data user's manual (version de juin 2006)
- Formulaire de consentement – Échantillons d'ADN - français et anglais
- Formulaire de consentement – Questionnaire - français et anglais
- Questionnaires (version anglaise)

Votre projet a été approuvé conditionnellement à ce que les précisions et modifications suivantes soient apportées.

Précisions demandées par le comité :

1. Nous comprenons que les échantillons mis en banque et les données recueillies à l'aide des questionnaires ✓ feront partie d'une banque constituée à des fins de recherches futures en plus de répondre aux objectifs de la recherche en cours. Si tel est le cas, les sujets doivent en être informés et consentir à ce que leurs échantillons et leurs données puissent faire l'objet de prêt à d'autres chercheurs.

CHUM

2. Y aura-t-il un lien entre les échantillons d'ADN et les données recueillies à l'aide des questionnaires (même code d'identification)? ✓

Si nous comprenons bien et qu'il s'agit d'une banque d'ADN et de données « psycho-sociales » associées qui servira à d'autres recherches dans le futur, il faudrait ajouter certaines informations à vos formulaires de consentement actuels :

Modifications demandées aux formulaires de consentement :

Formulaire pour l'échantillon d'ADN :

1. Indiquer une date de version du formulaire et la paginer sous la forme x/y ✓
2. Nous vous suggérons d'ajouter une section intitulée « Participation demandée » juste avant la section intitulée « procédures » et d'y inclure les informations suivantes : Nous vous demandons d'accepter de fournir un échantillon de salive dans le but d'en extraire l'ADN et d'accepter que cet échantillon soit conservé (indéfiniment ou X années?) dans une banque. Nous vous demandons également d'accepter qu'ils puissent servir à d'autres recherches dans le futur, soit par la même équipe de chercheurs, soit par d'autres équipes à qui les échantillons seraient prêtés (avec les informations recueillies à l'aide des questionnaires ?)... sans que votre identité ne soit révélée. ✓
3. Dans la clause de confidentialité, ajouter que le même numéro de code identifiera les données « psycho-sociales et d'habitudes de tabagisme » . ✓
4. Dans la section sur le consentement, ajouter un consentement spécifique à participer à la banque qui servira à des prêts et des recherches dans le futur. Adapter le texte de façon à continuer de vouvoyer les participants comme dans la partie précédente. ✓
5. Effectuer toute autre correction annotée au formulaire et effectuer les corrections correspondantes au formulaire en anglais

Formulaire pour les questionnaires :

1. Indiquer une date de version du formulaire et la paginer sous la forme x/y
2. Nous vous suggérons d'ajouter une section intitulée « Participation demandée » juste avant la section intitulée « procédures » et d'y inclure les informations suivantes : Nous vous demandons d'accepter de répondre à des questionnaires dont les résultats seront conservés dans une base de données pour une durée de ... Nous vous demandons également d'accepter que ces résultats puissent servir à d'autres recherches dans le futur, soit par la même équipe de chercheurs, soit par d'autres équipes, (en lien ou non avec les échantillons d'ADN?)... sans que votre identité ne soit révélée.
3. Vous pourriez ajouter une section dans laquelle vous mentionnez le tirage de prix en guise de remerciements pour la participation.
4. Si pertinent, dans la clause de confidentialité, ajouter que le même numéro de code identifiera également les échantillons d'ADN.
5. Dans la section sur le consentement, ajouter un consentement spécifique à participer à la banque qui servira à des prêts et des recherches dans le futur. Adapter le texte de façon à continuer de vouvoyer les participants comme dans la partie précédente.
6. Effectuer toute autre correction annotée au formulaire et effectuer les corrections correspondantes au formulaire en anglais.

CHUM

Vous voudrez bien nous faire parvenir la copie française des questionnaires dès qu'elle sera disponible, afin de compléter votre dossier au comité d'éthique de la recherche.

La version anglaise des formulaires de consentement doit correspondre à la version française.

Vous voudrez bien nous retourner un original et une copie – première page sur papier entête CHUM – des formulaires de consentement modifiés, dont la copie indiquera en surligné au crayon jaune les modifications demandées. L'original vous sera retourné avec l'estampille d'approbation.

Il est entendu que vous ne pouvez commencer le recrutement de sujets avant d'avoir reçu l'approbation finale du comité et que les formulaires de consentement modifiés n'aient été approuvés et estampillés.

Vous souhaitant la meilleure des chances dans la poursuite de vos travaux, je vous prie d'accepter, Docteure, mes salutations distinguées.

[redacted]

Brigitte St-Pierre, conseillère en éthique
Vice-présidente
Comité d'éthique de la recherche
Équipe Notre-Dame du CHUM

BSTP/kb

P.j. : Formulaires de consentement annotés

CENTRE DE RECHERCHE
Comités d'évaluation scientifique et d'éthique de la recherche
Édifice Cooper
3981, boulevard St-Laurent, Mezz 2
Montréal (Québec) H2W 1Y5

Téléphone : 514 – 890-8000 – Poste 14485
Télécopieur : 514 – 412-7394
Courriel : ghislaine.otis.chum@ssss.gouv.qc.ca

Le 21 février 2007

Dr Jennifer O'Loughlin
Épidémiologie
A/S Mme Erika Dugas
Édifice St-Urbain
3875, rue Saint-Urbain – 1e étage
Montréal (Québec) H2W 1T9

Objet : ***NDo6.087 – Approbation finale CÉR***

L'étude de la dépendance à la nicotine

Docteur,

J'accuse réception, en date du 21 février 2007, de votre lettre ainsi que des documents suivants en vue de l'approbation finale de l'étude décrite en rubrique :

- *Formulaire de consentement – Questionnaire – Version française – 8 février 2007*
- *Formulaire de consentement – Questionnaire – Version anglaise – 8 février 2007*
- *Formulaire de consentement – Échantillon d'ADN – Version française – 8 février 2007*
- *Formulaire de consentement – Échantillon d'ADN – Version anglaise – 8 février 2007*

Le tout est jugé satisfaisant. Je vous retourne sous pli une copie de chacun des formulaires portant l'estampille d'approbation du comité. Seuls ces formulaires devront être utilisés pour signature par les sujets.

La présente constitue l'approbation finale, ***valide pour un an à compter du 27 novembre 2006,*** *date de l'approbation initiale. Je vous rappelle que toute modification au protocole et/ou au formulaire de consentement en cours d'étude, doit être soumise pour approbation du comité d'éthique.*

Le comité suit les règles de constitution et de fonctionnement de l'Énoncé de Politique des trois Conseils et des Bonnes pratiques cliniques de la CIH.

Vous souhaitant la meilleure des chances dans la poursuite de vos travaux, je vous prie d'accepter, Docteur, mes salutations distinguées.

[redacted]

Brigitte St-Pierre, conseillère en éthique
Vice-présidente
Comité d'éthique de la recherche
Équipe Hôpital Notre-Dame du CHUM

BSTP/go
P. j. : Formulaires de consentement approuvés et estampillés

CHUM

Comité d'éthique de la recherche CHUM
APPROUVÉ le 2007/02/21
[redacted]

Formulaire de consentement - Questionnaire
Chercheur Principal: Jennifer O'Loughlin
Co-Chercheurs: Gilles Paradis, James Hanley, Rachel F. Tyndale, Joseph DiFranza
Subventionné par: l'Institut National du Cancer du Canada

Titre du projet: Étude sur l'histoire naturelle de la dépendance à la nicotine : Suivi à long terme de la dépendance à la nicotine chez une cohorte d'adolescents (NDIT)

Description: L'Étude NDIT est une enquête prospective de 1293 étudiants recrutés dans les classes de première secondaire de 10 écoles de Montréal en 1999. Notre subvention à été renouvelée en 2002 et en 2006. Les objectifs de cette dernière prolongation sont d'étudier le tabagisme chez les jeunes adultes et de continuer à examiner comment les facteurs génétiques sont liés à la dépendance à la nicotine.

Participation: À cette étape, nous vous demandons d'accepter de répondre à des questionnaires auto-administrés où les réponses seront conservées dans une base de données pendant 15 ans. Nous vous demandons également d'accepter que ces données (qui seront conservés sans informations susceptibles de révéler votre identité) soient utilisées pour des analyses additionnelles futures, soit par les mêmes chercheurs, soit par d'autres équipes de recherche, possiblement en lien avec les données tirées de l'ADN.

Procédure de l'étude: Au cours des 5 prochaines années, vous recevrez un questionnaire auto-administré par courrier (ou par Internet si vous préférez) à tous les ans, qui prendront 15-20 minutes à compléter. Ces questionnaires contiendront des questions par rapport à vos expériences concernant la consommation de cigarette, ainsi que sur les facteurs connus comme étant reliés au tabagisme. On vous demandera de nous retourner les questionnaires par la poste dans une enveloppe adressée et préaffranchie (ou par Internet si vous préférez). Si vous ne complétez pas le questionnaire, il est possible que notre équipe de recherche vous contacte par téléphone pour vous rappeler de le faire. Toutes les informations susceptibles de révéler votre identité seront retirées des questionnaires et les données seront entrées dans une base de données électronique.

Risques et bénéfices: Il n'y a aucuns risques ou bénéfices attendus pour les participants de cette étude. Toutefois, les résultats obtenus contribueront à l'avancement des connaissances sur l'histoire naturelle de la dépendance à la nicotine, ce qui pourra nous aider à développer des stratégies efficaces pour aider les jeunes adultes à cesser de fumer.

Liberté de consentement et liberté de se retirer: Votre participation est complètement volontaire. Vous pouvez vous retirer de l'étude à tout moment. Si vous décidez de vous retirer, il n'y aura aucun préjudice envers vous.

Confidentialité: Toutes les données tirées des questionnaires sont complètement confidentielles et seront conservées sous clé en tout temps. Les données ne contiendront aucune information personnelle et seront identifiées uniquement par un code numérique qui sera différent de celui relié aux données tirées de l'ADN. Seuls les chercheurs et la coordonnatrice du projet auront accès au code numérique et aux données.

Consentement: Veuillez compléter le formulaire ci-dessous pour indiquer si vous participerez au volet questionnaire de l'étude NDIT et nous le retourner dans l'enveloppe adressée et préaffranchie ci-jointe. Si vous avez des questions, n'hésitez pas à contacter la coordinatrice du projet, Érika Dugas, au *numéro de téléphone à confirmer*. Nous vous remercions de votre aide dans cet important projet.

[redacted]

Jennifer O'Loughlin
Chercheur Principal

[redacted]

Érika Dugas
Coordinatrice du Projet

- -

VEULLEZ REMPLIR LA SECTION CI-DESSOUS ET RETOURNER LE FORMULAIRE DANS L'ENVELOPPE ADRESSÉE ET AFFRANCHIE DANS LES 7 PROCHAINS JOURS

Consentement à participer au volet questionnaire de l'Étude NDIT

Veuillez cochez «Oui» ou «Non» ci-dessous

- **Oui**, j'accepte de participer au volet questionnaire auto-administré de l'Étude NDIT
- **Non**, je n'accepte pas de participer au volet questionnaire auto-administré de l'Étude NDIT

Si vous avez coché «Oui» ci-dessus, veuillez cocher «Oui» ou «Non» ci-dessous

- **Oui**, j'accepte que les données tirées de mes questionnaires soient conservés dans une base de données qui pourrait servir à d'autres recherches ultérieures.
- **Non**, je n'accepte pas que les données tirées de mes questionnaires soient conservés dans une base de données qui pourrait servir à d'autres recherches ultérieures.

____

Nom du Participant **(caractères d'imprimerie)** **Signature** **Date**

CHUM

Comité d'éthique de la recherche CHUM
APPROUVÉ le 2007/02/21
[redacted]

Consent Form - Questionnaires

Principal Investigator: Jennifer O'Loughlin
Co-Investigators: Gilles Paradis, James Hanley, Rachel F. Tyndale, Joseph DiFranza
Funded by: National Cancer Institute of Canada

Project Title: Study on the Natural History of Nicotine Dependence: Long term follow-up of the Nicotine Dependence In Teens (NDIT) cohort

Description: The NDIT Study is a prospective investigation of 1293 students recruited from grade 7 classes in 10 secondary schools Montreal in 1999. Our funding was renewed first in 2002, and then again in 2006. The purpose of this latest extension is to study smoking in young adults and to continue to investigate how genetic factors relate to nicotine dependence.

Participation: In this phase, we ask that you accept to complete self-administered questionnaires, the responses of which will be maintained in a database for 15 years. We also ask you to accept that these data (which will be stored with no information that could identify you) be used for additional analyses in the future, either by the same researchers or by other research teams, possibly in link with the DNA data.

Study Procedure: Every year over the next 5 years, you will receive a self-administered questionnaire by mail (or online through the Internet if you prefer), which will take 15-20 minutes to complete. It will ask you about your experience with smoking cigarettes, as well as about factors known to relate to smoking. You will be asked to return the questionnaires by mail in a stamped, addressed envelope (or online through the Internet if you prefer). If you do not complete the questionnaire, our research team may contact you by telephone to remind you to do so. All identifying information will be removed from the questionnaire and the data will be entered into an electronic database.

Benefits and Risks: There are no risks or benefits expected for participants in this project. However the results will allow increased understanding of the natural history of nicotine dependence, which will help us develop more effective strategies to help young adults quit smoking.

Withdrawal from Study: Your participation is completely voluntary. You may withdraw from the study at any time. If you decide to withdraw, there will be no prejudice against you.

Confidentiality: All questionnaire data are completely confidential and will be stored in locked storage areas. The data will not have any identifying information, and will be identified by a code, which is different from the one used for DNA data. Only the researchers and the project coordinator will have access to the codes and the data.

Consent: Please complete the form below to indicate if you will participate in the questionnaire component of the NDIT Study, and return it in the stamped, addressed envelope enclosed. If you have any questions, please contact the Project Coordinator,

Erika Dugas at *phone number to be confirmed*. We thank you for your help in this important project.

Jennifer O'Loughlin
Principal Investigator

Erika Dugas
Project Coordinator

PLEASE FILL IN THE BOX BELOW AND RETURN THE FORM IN THE STAMPED ADDRESSED ENVELOPE IN THE NEXT 7 DAYS

Consent to Participate in the Questionnaire Component of the NDIT Study

Please check either "Yes" or "No" below

- O **Yes,** I accept to participate in the self-administered questionnaire component of the NDIT Study
- O **No,** I do not accept to participate in the self-administered questionnaire component of the NDIT Study

If you checked "Yes" above, please check either "Yes" or "No" below

- O **Yes,** I accept that the data from my questionnaires be included in a database that could be used for other studies in the future.
- O **No,** I do not accept that the data from my questionnaires be included in a database that could be used for other studies in the future.

Name of Participant (Please Print) **Signature** **Date**

CHUM

Comité d'éthique de la recherche CHUM
APPROUVÉ le 2007/02/21
[redacted]

Formulaire de consentement - Échantillon d`ADN
Chercheur Principal: Jennifer O`Loughlin
Co-Chercheurs: Gilles Paradis, James Hanley, Rachel F. Tyndale, Joseph DiFranza
Subventionné par: l'Institut national du cancer du Canada

Titre du projet: Étude sur l'histoire naturelle de la dépendance à la nicotine : Suivi à long terme de la dépendance à la nicotine chez une cohorte d'adolescents (NDIT)

Description: L'Étude NDIT est une enquête prospective de 1293 étudiants recrutés dans les classes de première secondaire de 10 écoles de Montréal en 1999. Notre subvention à été renouvelée en 2002 et en 2006. Les objectifs de cette dernière prolongation sont d`étudier le tabagisme chez les jeunes adultes et de continuer à examiner comment les facteurs génétiques sont liés à la dépendance à la nicotine.

Participation: À cette étape, nous vous demandons d'accepter de fournir un échantillon de salive qui sera envoyé au laboratoire du Dr. Michael Philips au Centre Génome Québec. L'ADN sera extrait des échantillons et génotypé pour certains gènes pouvant être liés tabagisme. Nous avons besoin de cet échantillon que vous fumiez ou pas puisque nous désirons savoir si les fumeurs ont des gènes différents des non-fumeurs. Ces échantillons d'ADN seront conservés sans informations personnelles au Centre Génome Québec pendant 15 ans. Nous vous demandons également d'accepter que votre échantillon d'ADN (qui sera conservé sans informations susceptibles de révéler votre identité) soit utilisé pour des analyses additionnelles futures, soit par les mêmes chercheurs, soit par d'autres équipes de recherche, possiblement en lien avec les données tirées du questionnaire.

Procédures: Au cours de la semaine prochaine, vous recevrez un kit de collection d'ADN par la poste ainsi qu'un manuel d'instruction. On vous demandera de fournir un échantillon de salive dans un contenant de plastique, de le refermer et de nous le retourner par la poste dans une enveloppe préaffranchie et adressée. Il est possible que notre équipe de recherche vous contacte par téléphone afin de s'assurer que vous avez reçu le kit et pour savoir si vous avez des questions.

Risques et bénéfices: Il n'y a aucuns risques ou bénéfices attendus pour les participants de cette étude. Toutefois, les résultats obtenus contribueront à l'avancement des connaissances sur l'histoire naturelle de la dépendance à la nicotine, ce qui pourra nous aider à développer des stratégies efficaces pour aider les jeunes adultes à cesser de fumer.

Liberté de consentement et liberté de se retirer: Votre participation au volet-ADN est complètement volontaire. Si vous décidez de ne pas fournir un échantillon d'ADN, il n`y aura aucun préjudice envers vous. Vous êtes libre, en tout temps, de vous retirer du projet sans aucun préjudice. Les échantillons d'ADN seront détruits si vous décidez de vous retirer de l`étude.

Confidentialité: Les échantillons d'ADN seront conservés sans information personnelles. Ils seront identifiés uniquement par code numérique qui sera différent de celui utilisé pour identifier les données tirées de votre questionnaire. Une liste maîtresse liant le nom du participant et ses codes numériques sera conservée sous clé en tout temps. Seuls les chercheurs et la coordonnatrice du projet auront accès à l'ADN et aux données.

Consentement: Veuillez compléter le formulaire ci-dessous pour indiquer si vous fournirez un échantillon d'ADN et retournez le formulaire dans l'enveloppe adressée et préaffranchie ci-jointe. Si vous avez des questions, n'hésitez pas à contacter la coordinatrice du projet, Érika Dugas, au *numéro de téléphone à confirmer*. Nous vous remercions de votre aide dans cet important projet.

Jennifer O'Loughlin
Chercheur Principal

Érika Dugas
Coordinatrice du Projet

VEULLEZ REMPLIR LA SECTION CI-DESSOUS ET RETOURNER LE FORMULAIRE DANS L'ENVELOPPE ADRESSÉE ET AFFRANCHIE DANS LES 7 PROCHAINS JOURS

Consentement à participer au volet Échantillon d'ADN de l'Étude NDIT

Veuillez cochez «Oui» ou «Non»ci-dessous

- o **Oui**, j'accepte de participer à la collecte d'échantillons d'ADN de l'étude NDIT
- o **Non**, je n'accepte pas de participer à la collecte d'échantillons d'ADN de l'étude NDIT

Si vous avez cochez «Oui» ci-dessus, veuillez cochez «Oui» ou «Non»ci-dessous

- o **Oui**, j'accepte que mon échantillon fasse partie d'une banque qui servira possiblement à des recherches dans le futur.
- o **Non**, je n'accepte pas que mon échantillon fasse partie d'une banque qui servira possiblement à des recherches dans le futur.

Nom du Participant (caractères d'imprimerie) **Signature** **Date**

CHUM

Comité d'éthique de la recherche CHUM
APPROUVÉ le 2007/02/21

Consent Form - DNA Sample

Principal Investigator: Jennifer O'Loughlin [redacted]

Co-Investigators: Gilles Paradis, James Hanley, Rachel F. Tyndale, Joseph DiFranza

Funded by: National Cancer Institute of Canada

Project Title: Study on the Natural History of Nicotine Dependence: Long term follow-up of the Nicotine Dependence In Teens (NDIT) cohort

Description: The NDIT Study is a prospective investigation of 1293 students recruited from grade 7 classes in 10 secondary schools Montreal in 1999. Our funding was renewed first in 2002, and then again in 2006. The purpose of this latest extension is to study smoking in young adults and to continue to investigate how genetic factors relate to nicotine dependence.

Participation: In this phase, we ask that you agree to provide a saliva sample which will be sent to Dr. Michael Phillip's laboratory at Centre Genome Quebec. DNA will be extracted from the sample and genotyped for selected genes thought to be related to smoking. We need the sample whether or not you smoke because we need to compare is smokers have different genes from non-smokers. The DNA sample will be stored without any identifying information at Centre Genome Quebec for 15 years. We also ask you to accept that your DNA sample (which will include no information that could identify you) be used for additional analyses in the future, either by the same researchers or by other research teams, possibly in link with questionnaire data.

Procedure: In the next week, you will receive a DNA sample kit through the mail, with an instruction manual. You will be asked to provide a saliva sample in a plastic container, seal it, and return it to us by mail in a stamped, addressed envelope. Our research team may telephone you to make sure that you received the kit and to ask if you have any questions.

Benefits and Risks: There are no risks or benefits expected for participants in this phase of the project. However the results will allow increased understanding of the natural history of nicotine dependence, which will help us develop more effective strategies to help young adults quit smoking.

Withdrawal from Study: Your participation in providing a DNA sample is completely voluntary. If you decide not to provide a sample, there will be no prejudice against you. You may withdraw from the study at any time with no prejudice. The DNA sample will be destroyed if you decide to withdraw from the study.

Confidentiality: The DNA sample will be stored without any identifying information. It will be labeled with a code that is different from the code used to identify your questionnaire data. A Master List linking your name to your codes will be kept in locked filing cabinets. Only the researchers and the project coordinator will have access to the DNA and the data.

Consent: Please complete the form below to indicate if you will provide a saliva sample, and return the form in the stamped, addressed envelope enclosed. If you have any questions, please contact the Project Coordinator, Erika Dugas at *phone number to be confirmed*. We thank you for your help in this important project.

Jennifer O'Loughlin
Principal Investigator

Erika Dugas
Project Coordinator

PLEASE FILL IN THE BOX AND RETURN THE FORM IN THE STAMPED ADDRESSED ENVELOPE THE NEXT 7 DAYS

Consent to participate to the DNA Component of the NDIT Study

Please check either "Yes" or "No" below

- **Yes**, I accept to participate in the DNA sample collection component of the NDIT Study
- **No**, I do not accept to participate in the DNA sample collection component of the NDIT Study

If you checked "Yes" above, please check either "Yes" or "No" below

- **Yes**, I accept that my sample be part of a bank that could be used for other studies in the future.
- **No**, I do not accept that my sample be part of a bank that could be used for other studies in the future.

Name of Participant (Please Print) **Signature** **Date**

Comité d'éthique de la recherche du CHUM
Pavillon R, 900 rue St-Denis, 3e étage
Montréal (Québec) H2X 0A9

Formulaire de demande de renouvellement annuel de l'approbation d'un projet de recherche

Date de dépôt du formulaire: **2018-09-27 08:11**
Déposé par: **Dugas, Érika**
[redacted]
Date d'approbation du projet par le CER: **2007-02-21**
Numéro(s) de projet: **2007-2384, ND 06.087 - MJB**
Formulaire: **F9 - 42323**
Statut du formulaire: **Approuvé**

Suivi du BCER

1. **Statut de la demande:**
   Demande approuvée

2. **La demande a été traitée par :**
   Lynda Ferlatte
   date de traitement:
   2018-10-02

3. **Renouvellement accordé**
   du 27 novembre 2018 au 27 novembre 2019

Section 1 - Renseignements généraux

1. **Indiquez, en français, le titre complet du projet de recherche**

   L'étude de la dépendance à la nicotine

2. **Indiquez le nom du chercheur responsable local (CHUM)**

   Oloughlin, Jennifer

3. **Y a-t-il des co-chercheurs du CHUM qui collaborent au projet de recherche?**

Oui

Indiquez le nom et les coordonnées des co-chercheurs et collaborateurs CHUM connus au moment de soumettre le projet.

Sylvestre, Marie-Pierre

Désignation

Co-chercheur

Statut

Chercheur

Veuillez préciser le rôle du co-chercheur/collaborateur dans le projet:

Autre

Veuillez préciser:

Dr Sylvestre est le co principal investigator donc agit comme chercheur principal

4. **Est-ce que le formulaire et/ou documents soumis au CER doivent être vus en réunion plénière (Full Board) selon les exigences des organismes subventionnaires (NIH, RTOG, NCIC, etc.)**

Non

5. **Indiquez le statut actuel du projet de recherche**

Projet en cours dont le recrutement est terminé

Section 2 - Projet de recherche

1. **Date à laquelle le projet de recherche a commencé:**

2007-02-21

2. **Date à laquelle le projet de recherche devrait se terminer:**

2020-10-31

3. **Quel est le profil des participants de recherche?**

Quel est le sexe des participants à la recherche?

- [x] Hommes
- [x] Femmes
- [ ] Autres

Quel est le niveau d'aptitude des participants à la recherche?

- [x] Majeurs aptes
- [ ] Majeurs inaptes
- [ ] Mineurs
- [ ] Majeurs, mais dont l'inaptitude est subite

Informations complémentaires des participants à la recherche?

- [ ] Membres du personnel de l'établissement
- [ ] Personnes recrutées dans un groupe témoin
- [ ] Personnes hospitalisées
- [ ] Personnes vues en consultation (consultation externe, clinique privée, hôpital de jour, etc.)
- [ ] Personnes qui se présentent à l'urgence de l'établissement
- [ ] Personnes proches des sujets
- [ ] Personnes touchées par un programme ciblé (précisez)
- [x] Autre, spécifiez

Précisions complémentaires

Participants population générale (écoles secondaires Montréal 1999)

4. **Veuillez cocher "oui" si votre projet est une RECHERCHE SUR DOSSIERS. Si vous avez cochez "OUI" à cette question, vous devez répondre aux questions ci-dessous.**

Non

5. **Veuillez cocher "oui" si votre projet est une banque. Si vous cochez "OUI", vous pouvez répondre "0" aux demandes obligatoires de la question suivante "Informations relatives aux participants CHUM/CRCHUM".**

Non

6. **Informations relatives aux PARTICIPANTS CHUM/CRCHUM:**

Nombre de participants à recruter initialement:

1293

Nombre de participants qui ont effectivement été recrutés:

1208

Nombre de participants dont la participation n'est pas terminée (suivi en cours):

1053

Nombre de participants dont la participation est terminée:

155

Nombre de participants ayant abandonné (retrait volontaire):

155

Donnez-en la raison:

non connue

Nombre de participants exclus ou retirés du projet:

155

Donnez-en la raison:

non connue

Section 3 - Informations autres centres

1.

S'agit-il d'un projet multicentrique ?

Non

Section 4 - Dernière année

1. **Au cours de la dernière année et par rapport à la situation au moment de la dernière approbation du CÉR :**

Avez-vous rapporté tous les effets indésirables graves au Comité d'éthique depuis la dernière approbation du CÉR ?

- [x] OUI
- [ ] NON
- [ ] N/A

Avez-vous rapporté tous les changements ou amendements (protocole, formulaire de consentement, etc.) depuis la dernière approbation du CÉR ?

- [x] OUI
- [ ] NON
- [ ] N/A

Signature

1. **J'atteste que les renseignements fournis dans le présent formulaire sont exacts.**

Nom et prénom de la personne qui a complété ce formulaire

Erika Dugas