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The association between childhood attention-deficit/hyperactivity disorder medication use and symptoms of mental health problems in adolescence: A 15-year longitudinal population-based study

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Mémoire présenté
en vue de l'obtention du grade de maîtrise
en santé publique
option mémoire

Avril 2017

Résumé

Au cours des 30 dernières années, l'utilisation de médicaments pour le traitement du trouble de déficit de l'attention avec ou sans hyperactivité (TDAH) a considérablement augmenté dans les pays occidentaux. Cependant, on en sait peu sur les trajectoires de traitement du TDAH et sur l'association entre l'utilisation de médicaments TDAH durant l'enfance et les problèmes de santé mentale à l'adolescence. Les objectifs de ce mémoire sont d'identifier les trajectoires d'utilisation de médicaments TDAH dans des groupes distincts d'enfants âgés entre 3.5 et15 ans et de tester si l'utilisation de médicaments TDAH est associée à des symptômes d'hyperactivité, d'impulsivité, d'inattention, de dépression et d'anxiété à l'adolescence.

Les trajectoires d'utilisation de médicaments TDAH ont été estimées à partir d'un échantillon populationnel (n = 1443) au Québec. L'information sur l'utilisation de médicaments TDAH a été fournie par les parents (3.5 à 15 ans). Les symptômes d'hyperactivité, d'impulsivité, d'inattention, de dépression et d'anxiété ont été auto-déclarés par les participants à 15 ans. Des analyses de régression multiple ont été utilisées pour examiner l'association entre l'utilisation de médicaments TDAH pendant l'enfance et les symptômes de santé mentale à l'adolescence.

Trois trajectoires d'utilisation de médicaments TDAH ont été identifiées: « non-utilisation de médicaments TDAH », « utilisation tôt » et « utilisation tard » pendant l'enfance. La médication a généralement été initiée au cours de la moyenne enfance pour les enfants dans le groupe « utilisation tôt » et pendant l'adolescence pour ceux dans la trajectoire « utilisation tard ». Les enfants dans les trajectoires « utilisation tôt » et « utilisation tard » (ensemble) n'avaient pas des scores d'hyperactivité et d'impulsivité significativement plus élevés comparé à ceux dans le groupe « non-utilisation de médicaments TDAH » à 15 ans. Cependant, les garçons avaient des niveaux d'inattention et de dépression plus élevés.

L'utilisation de médicaments TDAH pendant l'enfance, était associée à une persistance de certains types de symptômes du TDAH à l'adolescence. De plus, c'était associé à des niveaux de dépression plus élevés chez les adolescents. Les études futures devraient examiner de plus

près l'efficacité à long terme des médicaments TDAH et leurs effets sur le développement de troubles affectifs chez les enfants atteint du TDAH, en incluant de plus grands échantillons de filles médicamentées pour des comparaisons de sexe significatives.

Mots-clés : Trouble de déficit de l'attention avec ou sans hyperactivité, médicament TDAH, étude longitudinale, enfance, adolescence, efficacité à long terme, effets à long terme, dépression, anxiété

Abstract

Over the past 30 years, the use of attention-deficit/hyperactivity disorder (ADHD) medication has drastically increased in Western nations. However, little is known about the longitudinal treatment patterns of ADHD and the long-term mental health outcomes associated with the use of ADHD medication in children. The objectives of this thesis are to identify groups of children with distinctive trajectory patterns of ADHD medication use between the ages of 3.5 and 15 years, and to test whether the use of ADHD medication during childhood is associated with symptoms of hyperactivity, impulsivity, inattention, depression and anxiety in adolescence.

Trajectories of ADHD medication use were estimated from a 15-year population-based longitudinal birth cohort (n=1443). Information on ADHD medication use was provided by the parents (of children aged 3.5-15 years). Symptoms of hyperactivity, impulsivity, inattention, depression and anxiety were self-reported by the participants at 15 years. Multiple regression analyses were used to examine the association between childhood ADHD medication use and symptoms of mental health problems in adolescence.

Three trajectories of ADHD medication use were identified in children: no/low ADHD medication use, early-onset use and late-onset use. Medication was generally initiated during middle childhood for individuals in the early-onset trajectory group and during adolescence for those following the late onset-trajectory. Children on the early and late trajectories (combined) did not have significantly higher hyperactivity nor impulsivity scores at 15 years compared to those on the no/low ADHD medication use trajectory. However, males had higher inattention and depression scores.

Childhood ADHD medication use was associated with the persistence of certain types of ADHD symptoms in adolescence as well as with higher levels of adolescent depression symptoms. Future studies should further examine the long-term effectiveness of ADHD medication and its effect on the subsequent development of affective disorders in children with ADHD. They should also include larger samples of medicated girls to allow for meaningful sex comparisons.

Keywords: Attention-deficit/hyperactivity disorder, ADHD medication, longitudinal study, childhood, adolescence, long-term effectiveness, long-term effects, depression, anxiety

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List of abbreviations

ADHD: Attention-deficit/hyperactivity disorder

BIC: Bayesian information criterion

CD: Conduct disorder

DSM: Diagnostic and Statistical Manual of Mental Disorders

ICD: International Classification of Mental and Behavioural Disorders

ISQ: Institut de la Statistique du Québec

MDD: Major depressive disorder

MTA: Multimodal Treatment study of ADHD

QLSCD: Quebec Longitudinal Study of Child Development

ODD: Oppositional defiant disorder

SD: Standard deviation

SE: Standard error

Chapter 1: Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity beyond the range of developmental norms (American Psychiatric Association 2013). The difference between ADHD and normal behavior lies in the severity and frequency of inattention, hyperactivity and impulsivity symptoms, and whether these symptoms interfere with normal functioning or development (National Institute of Mental Health 2016). Individuals with ADHD can have variable presentations of the disorder. For instance, some may present a predominantly inattentive type of ADHD while others have both inattention and hyperactivity-impulsivity. Furthermore, an individual's presentation of ADHD can also change across time. During early childhood, children with ADHD are predominantly hyperactive-impulsive. As they age, however, hyperactivity decreases whereas symptoms of inattention become more prominent (American Psychiatric Association 2013). Inattention can be identified when a person fails to complete tasks, has difficulty sustaining attention during activities, is easily distracted, is forgetful and has trouble organizing activities. Hyperactivity refers to fidgeting, tapping or squirming in seat, excessive talking and having difficulty to remain seated when expected. Individuals with impulsivity often have difficulties waiting their turn, interrupt or intrude on others and blurt out answers before questions have been completed (American Psychiatric Association 2013).

Currently, ADHD is the most common psychiatric disorder in children, affecting 5.3% of the child population worldwide (Polanczyk et al. 2007). Multiple factors have been found to play a role in the etiology of ADHD, including genetic, biological and environmental influences (Cortese and Morcillo Penalver 2010; Daviss et al. 2009; Faraone and Doyle 2001). ADHD often co-occurs with other externalizing and internalizing disorders such as oppositional defiant disorders (ODD), conduct disorders (CD), mood and anxiety disorders (Jensen et al. 2001; Kessler et al. 2005; Spencer et al. 2007). In fact, 50-90% of children diagnosed with ADHD have at least one comorbid psychiatric disorder (Spencer et al. 1999). Recent studies indicate that ADHD in childhood is associated with poor academic performance, poor peer relationships,

low self-esteem, family problems and emotional difficulties (Barkley 1997; Coghill et al. 2008; Edbom et al. 2008; Smith et al. 2002). Furthermore, persistence of the disorder over time is related to substance use disorders, marital difficulties, and antisocial and criminal behaviors in adulthood (Barkley et al. 2004; Eakin et al. 2004; Klein et al. 2012). The risks of long-term impairment, morbidity and mortality are even greater when ADHD co-occurs with depression (Daviss 2008).

Given the significant negative impact of ADHD on patients' lives, their families and society, appropriate treatment is deemed necessary. To this day, ADHD has been primarily treated with stimulant medication such as methylphenidate (Ritalin) and amphetamines (Adderall) (Chirdkiatgumchai et al. 2013; Galera et al. 2014). Numerous clinical practice guidelines support their use and safety for the treatment of ADHD in children (American Academy of Child and Adolescent Psychiatry 2007; American Academy of Pediatrics 2011; National Institute of Mental Health 2016). The exact mechanism of action of ADHD drugs is not fully understood, but they are believed to increase dopamine signaling in the brain: a process that is dysfunctional in individuals with ADHD (Del Campo et al. 2011). Hence, it is unsurprising that many short-term clinical trials have reported the effectiveness of medication in reducing core symptoms of ADHD (hyperactivity, impulsivity and inattention), enhancing cognitive functioning and improving academic performance (Coghill et al. 2014; Greenhill et al. 2002; Loe and Feldman 2007).

Over the past 30 years, the prescription of ADHD medication has steadily increased. For example, in the USA, the percentage of medicated children grew from 0.6% in 1987 to 3.5% in 2008 (Zuvekas and Vitiello 2012). In Canada, a similar upward trend was observed from 1994 to 2007, specifically for school-age children with a two-fold increase in prescribed ADHD medication (Brault and Lacourse 2012). Interestingly, an expansion of insurance coverage for prescription drugs in Quebec has been associated with a greater increase in ADHD medication use relative to the rest of Canada (Currie et al. 2014). According to the latest National Survey of Children's Health, 69% or 3.5 million children in the USA aged 4-17 and diagnosed with

ADHD take medication for ADHD (Visser et al. 2014). Since the long-term effects of ADHD drugs have not been extensively researched, their expanding use remains controversial.

While the prevalence of ADHD medication use is well documented, little is known about its longitudinal patterns in children. There is evidence showing that medication is not used continuously over time and that adherence is poor, despite ADHD being a chronic condition (Adler and Nierenberg 2010; Gajria et al. 2014; Zetterqvist et al. 2013). Furthermore, the rates of treatment differ between boys and girls (Brault and Lacourse 2012; Galera et al. 2014; McCarthy et al. 2012; Prosser et al. 2015; Zuvekas and Vitiello 2012). Studying longitudinal trends during childhood potentially allows for a characterization of distinctive patterns of ADHD medication use trajectories, which can help describe the changes and sex differences in the use of ADHD drugs over time. Thus, identifying different childhood trajectories of ADHD medication use could provide additional knowledge on the current treatment patterns of ADHD, which can eventually help improve the outcomes of children affected by this disorder.

Because pharmacological treatment of ADHD is often required over extended periods of time, it is important to examine the long-term outcomes of ADHD medication use in children as well. This can provide information from which to assess whether the current management of ADHD with medication should be supported or reviewed. Previous studies indicate that ADHD often persists into adulthood (Faraone et al. 2006) and that it is associated with the development of depression and anxiety later in life (Angold et al. 1999; Blackman et al. 2005; Pliszka 1998; Smith et al. 2010; Spencer et al. 1999). The persistence of ADHD symptoms leads to a range of problems that affect the quality of life and overall health of affected children (Barkley 2002; Caci et al. 2014; Peasgood et al. 2016). Moreover, the development of co-morbid depression in children with ADHD is related to even worse outcomes (Daviss 2008). Thus, the long-term mental health outcomes associated with the use of ADHD medication in children need to be thoroughly understood. Unfortunately, the existing body of research in this area is limited and inconsistent. Findings from pre-clinical studies have fueled speculations that ADHD medication may have detrimental effects on brain development. Using animal models, researchers have

shown that stimulants cause profound, long-lasting, cognitive and behavioral changes. The most important consequences reported were impaired working memory, spatial learning problems (i.e., reduced focus and attention), and anxiety- and depressive-like behaviors (Bolanos et al. 2003; Carlezon et al. 2003; Scherer et al. 2010; van der Marel et al. 2015). In humans, several cases of depression and suicidality have been associated with the use of ADHD drugs (Arun and Sahni 2014; Kim et al. 2011; Lafay-Chebassier et al. 2015; Lakic 2012). Consequently, Health Canada has issued a warning on the safety of these medications (Health Canada 2015). Some studies examining the association between ADHD medication and the development of depression in youth with ADHD supported the suggestive findings in animal models and case reports (Currie et al. 2014; Jerrell et al. 2015; Molina et al. 2009). In contrast, other investigations reported that ADHD medication was not associated with (Smith et al. 2010; Staikova et al. 2010) or related to a reduced risk of later depression (Biederman et al. 2009; Chang et al. 2016; Daviss et al. 2008). Information regarding the long-term effectiveness of medication for the treatment of ADHD in children is also contradictory. For instance, two studies found that ADHD medication continuously improved core symptoms of ADHD (Charach et al. 2004; Gillberg et al. 1997) while other reports determined that its treatment benefits were not long-lasting (Molina et al. 2009; Smith et al. 2010). Overall, the inconsistent findings on the long-term outcomes of ADHD medication use in children indicate that definite conclusions have not yet been reached on this topic.

In summary, a better understanding of the longitudinal treatment patterns of ADHD and the long-term mental health outcomes associated with the use of ADHD medication in children can contribute to the prevention of the negative health consequences of this disorder and its comorbidities. Studies that examined the trends of medication use for ADHD have often used a cross-sectional design, which does not allow for the identification of distinct developmental patterns of ADHD medication use in children. Moreover, these studies failed to describe how differences in the medication treatment of ADHD between boys and girls develop and change over time. With regard to the long-term effectiveness of ADHD medication and its association with the development of mood disorders, current research findings are inconclusive. Previous studies often relied on clinically referred or highly selected samples and rarely included non-

ADHD comparison groups. Another important limitation of long-term treatment studies of ADHD is that they did not examine whether the mental health outcomes associated with the use of medication differed by sex. Considering that samples in such studies are often small and predominantly male, most researchers have unfortunately excluded sex comparisons from their analyses. Hence, investigations that examine the association between childhood ADHD medication use and symptoms of mental health problems in adolescence, separately by sex, are needed.

Consistent with the above limitations of existing studies on the utilization of ADHD medication in children and on the long-term mental health outcomes of medication treatment of ADHD, many questions remain unanswered: What are the temporal trajectories of childhood ADHD medication use? To what extent do the trajectories of use differ between boys and girls? Is the use of ADHD medication in children associated with long-term improvements in core symptoms of ADHD, such as reduction of hyperactivity, impulsivity and inattention? Is there a relationship between the use of medication for ADHD during childhood, and depression and anxiety symptoms in adolescence? Finally, do sex differences in the associations between childhood ADHD medication use and symptoms of mental health problems in adolescence exist?

The present study addresses these questions. Specifically, we used longitudinal data from the Quebec Longitudinal Study of Child Development (QLSCD), which followed a representative population-based cohort of children from birth until the age of 15 years to address two objectives. First, we used an innovative approach called group-based trajectory modeling to systematically measure the use of ADHD medication during childhood. Ultimately, this method allowed us to identify groups of boys and girls in a large population sample, with distinct trajectories of ADHD medication use from 3.5 to 15 years. Second, we investigated the association between the use of ADHD drugs during childhood and five mental health problems in adolescence: hyperactivity, impulsivity, inattention, depression and anxiety.

We expected to identify three main trajectories in both sexes: children who never used ADHD medication, those who started using medication during childhood and those who began receiving medication during adolescence. We also expected to detect differences in the developmental patterns of ADHD medication use between boys and girls. We predicted that the use of ADHD medication during childhood would be associated with symptoms of depression and anxiety, but not with higher levels of hyperactivity, inattention and impulsivity in adolescence. Finally, we did not hypothesize whether the long-term mental health outcomes associated with the use of ADHD medication during childhood would differ by sex, due to the lack of previous research on this matter.

Chapter 2: Literature review

This literature review presents an overview of existing research on the etiology, diagnosis, treatment, long-term effectiveness of ADHD medication and its long-term effects on the development of affective disorders in children. Others risk factors of persistent ADHD and affective disorders in adulthood are discussed as well. Finally, this review provides relevant information about group-based trajectory modeling: an innovative statistical method used in this study.

2.1 Etiology of ADHD

The etiology of ADHD is very complex and still subject to research. There is, however, substantial evidence supporting that genetics strongly contribute to the disorder. For example, twin studies estimated that the heredity of ADHD is as high as 76% (Faraone and Mick 2010; Larsson et al. 2013; Larsson et al. 2014) and family studies found that the rate of ADHD is three to four times higher in siblings of children with ADHD than in siblings of children without the disorder (Nolen-Hoeksema 2013). Moreover, several genes have been associated with ADHD, many of which directly impact dopamine neurotransmission (Faraone et al. 2014). In addition to genetics, multiple environmental factors may potentially play a role in the pathogenesis of the disorder. Early risk factors include prenatal tobacco or alcohol exposure, premature birth, low birth weight and lead exposure during childhood (Burger et al. 2011; Daneshparvar et al. 2016; Froehlich et al. 2009; Galera et al. 2011; Heinonen et al. 2010; Kotimaa et al. 2003; Langley et al. 2007; O'Malley and Nanson 2002). Socioeconomic disadvantages such as non-intact family, lower maternal education, lower social class and maternal depression have been linked with the development of ADHD as well (Galera et al. 2011; Langley et al. 2007; Russell et al. 2016). Ultimately, it is believed that ADHD is caused by complex interactions between genetic and environmental factors that affect the neurobiological basis of the disorder (Brookes et al. 2006; Grizenko et al. 2012; Larsson et al. 2013; Larsson et al. 2014; Neuman et al. 2007; Retz et al. 2008; Thapar et al. 2013). Current research suggests that the neurobiology of ADHD is associated with structural, functional and neurotransmitter abnormalities in the brain.

Structural imaging studies found that children with ADHD have significantly smaller brains and a reduced volume in certain brain structures (Emond et al. 2009; Hoogman et al. 2012; Valera et al. 2007). ADHD patients also have a delayed cortical maturation during development, specifically in prefrontal regions involved in the control of cognitive processes such as attention and motor planning (Shaw et al. 2007; Shaw et al. 2006). Alterations of certain brain regions implicated in ADHD are also linked with functional impairment in neural networks (Purper-Ouakil et al. 2011). Finally, impairments in neurotransmitter systems involving dopamine and noradrenaline appear to play a part in the pathophysiology of the disorder (Chandler et al. 2014). People with ADHD typically have lower levels of dopamine receptors and transporters in some parts of the brain (Volkow et al. 2009; Volkow et al. 2007). In sum, the etiology of ADHD is likely multifactorial, arising from an interplay of genetic, environmental and biological factors.

2.2 Diagnosis

Two main classification systems can be used by qualified healthcare professionals to diagnose ADHD: The International Classification of Mental and Behavioural Disorders 10th revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders -5th Edition (DSM-V). The ICD-10 is most commonly used in European countries and refers to ADHD as hyperkinetic disorder (Taylor et al. 2004) whereas the DSM-V is used in North America (American Psychiatric Association 2013). When clinicians use the ICD-10, all three features of ADHD (inattention, hyperactivity and impulsivity) must be present in order to make a diagnosis (World Health Organization 1992). The DSM-V on the other hand, describes ADHD as a pattern of inattention and/or hyperactivity-impulsivity and further categorizes the disorder into three main presentations: predominantly inattentive, predominantly hyperactive/impulsive or combined (American Psychiatric Association 2013). Differences in these two classification systems lead to a situation in which ADHD is three to four times more likely to be diagnosed with the DSM-IV criteria than with the ICD-10 criteria (Rohde et al. 2005; Santosh et al. 2005). Furthermore, with the introduction of the 5th edition of DSM, rates of ADHD diagnosis are expected to increase even more (Steinau 2013; Vande Voort et al. 2014). Indeed, the diagnostic criteria for ADHD in DSM-V are less stringent than those in the previous DSM version. For example, while

DSM-IV required clinically significant impairment in functioning (American Psychiatric Association 2004), the newer DSM edition only requires that symptoms interfere or reduce functioning for an individual to qualify for an ADHD diagnosis (American Psychiatric Association 2013). In sum, this information shows that the diagnosis of ADHD is based on how it is initially conceptualized.

A formal diagnosis of ADHD requires prior assessment of the disorder. There are numerous ways to asses ADHD, but no standardized methods exist. Hence, a diagnosis of ADHD depends on clinical judgement that clinicians make based on the information they obtain using the methods they choose (Rabiner 2013). Nonetheless, clinical guidelines recommend using a multi-step process for the assessment of ADHD (Canadian ADHD Resource Alliance (CADDRA) 2011; Kooij et al. 2010; National Institute for Health and Care Excellence 2016; Taylor et al. 2004), which involves clinical examinations, interviews with parents, teachers and the child, behavioral observations and the use of rating scales. Rating scales can be used for diagnostic purposes, to measure symptom severity or improvement in symptoms over time (DuPaul et al. 1998; Guy 1976; Kooij and Francken 2010). However, they should never be used alone to diagnose ADHD as they lack sensitivity and specificity for diagnosis (National Institute for Health and Care Excellence 2016).

2.3 Treatment

The first line of treatment for ADHD is with stimulant medications, which have been found to improve symptoms of inattention, hyperactivity and impulsivity on the short-term (Coghill et al. 2014). Medication can be delivered via an immediate-release or an extended-release form (Conley et al. 2006; Gupta et al. 2009). The former is usually required to be taken two to three times a day whereas the latter needs to be used only once a day (Pliszka 2007). Regardless of the option, medication must be administered on a daily basis (Pliszka 2007). Additionally, due to the chronic nature of the disorder, pharmacological treatment is extended over long periods

of time. Adherence to medication (i.e. taken as prescribed) is particularly important because it has been associated with better treatment outcomes (Barner et al. 2011).

2.4 Long-term effectiveness of ADHD medication in children

Studying the long-term effectiveness of ADHD medication is challenging. The main problems are the high non-adherence treatment rates and the loss to follow-up (Gajria et al. 2014). Therefore, existing knowledge on the subject is limited. Moreover, studies researching the long-term effectiveness of pharmacological treatment for ADHD have yielded inconsistent results. Some researchers found ADHD medication to have sustained benefits over time. For instance, the first long-term randomized double-blind placebo-controlled trial on stimulant treatment in children (n=61) determined that amphetamine was superior to placebo in reducing hyperactivity and inattention problems up to 15 months (Gillberg et al. 1997). However, this study included subjects with pervasive developmental disorders, which may have undermined the true effect of medication on non-comorbid ADHD children. Furthermore, despite dysthymia (persistent mild depression) being a common reported negative effect of medication, the authors did not further investigate on this issue. Nonetheless, this report still showed that medication had continuous beneficial effects on core symptoms of ADHD over time. An observational five-year follow-up study also provided evidence that medication treatment of ADHD may be effective on the long-term (Charach et al. 2004). Specifically, the authors observed in a clinical sample of 79 children that individuals who adhered to medication had greater improvements in ADHD symptoms compared to non-adherents and those not taking medication (Charach et al. 2004). Yet, children who were medicated continuously over the five-year study period also had higher ADHD scores than non-adherents at the end of the research (Charach et al. 2004). Consistent with previous reports an observational follow-up study by Biederman et al. determined that medicated ADHD adolescents and adults performed better than non-medicated ADHD subjects on sustained attention and verbal learning tests. Additionally, in comparison to a normal control group, non-medicated subjects had greater impairments in cognitive functioning than medicated subjects (Biederman et al. 2008). Overall, the authors showed that individuals who received medical treatment for ADHD had better ADHD outcomes than non-treated ADHD individuals. The

long-term effectiveness of ADHD medication was also observed in a large population-based cohort of children with ADHD, indicating that medication treatment in the community is as equally effective as in short-term controlled clinical trials (Barbaresi et al. 2006).

On the other hand, a number of studies suggested that ADHD medication use may not be associated with long-term improvements in ADHD symptoms. A comprehensive Multimodal Treatment Study of ADHD (MTA) initially randomized 579 children with ADHD into four treatment groups: 1) medication management, 2) behavioral therapy, 3) combined medication and behavioral therapy and 4) community care and followed them for eight years in order to determine the long-term effects of ADHD medication. At the eight-year follow-up, the researchers found that there was no significant difference in ADHD symptoms across the groups, suggesting that medication did not have long-lasting treatment benefits. Moreover, children from the MTA study fared worse on hyperactivity/impulsivity and inattention symptoms compared to their non-ADHD peers (Molina et al. 2009). A UK cohort study, published in 2010, reported that children who continued to use ADHD medication into adolescence had significantly higher ADHD scores and greater rates of ADHD diagnosis than those who no longer used medication (Langley et al. 2007). In line with previous findings, van Lieshout et al. found that medication treatment of ADHD in children had no positive impact on ADHD related outcomes. In fact, continued pharmacological treatment predicted worse outcomes in terms of ADHD severity (van Lieshout et al. 2016). Lastly, based on a 14-years longitudinal study examining the change in ADHD symptoms from childhood to adolescence in a sample of ADHD children, investigators concluded that the use of ADHD medication was not associated with long-term improvement in core ADHD symptoms (Smith et al. 2010).

2.5 Long-term effects of ADHD medication on the development of affective disorders in children

There are different opinions about the long-term effects of ADHD medication on the development of mood disorders later in life. For instance, two longitudinal studies suggested that there was no association between pharmacological treatment of ADHD during childhood and the risk of developing depression in adolescence (Smith et al. 2010; Staikova et al. 2010). However, the research by Staikova et al. had an important limitation: 10% of children in their sample were diagnosed with depression before the onset of treatment with ADHD medication. The inclusion of children with pre-existing depression may have biased the results of this study.

One longitudinal and two case-control studies (prospective and retrospective in design) indicated that childhood ADHD medication use was associated with a reduced risk of subsequent affective disorders (Biederman et al. 2009; Chang et al. 2016; Daviss et al. 2008). Daviss et al. further suggested that earlier pharmacological intervention may be related to a delay in the onset of depression in adolescence (Daviss et al. 2008). However, it is important to note that Daviss et al. did not provide direct evidence that ADHD drugs have a protective effect against depression since they did not compare children who were under medication to those who were not. Instead, they compared the rates of pharmacological treatment in groups of individuals with ADHD with and without a history of depression. The findings of Biederman et al. should also be interpreted with caution because as subjects who were already diagnosed with depression before starting ADHD pharmacotherapy were categorized into the no treatment group. This may have generated results that falsely indicated that depression occurred at higher rates in children with ADHD who did not receive medication treatment.

Finally, some researches provided evidence that ADHD medication may be associated with an increased risk of later depression and anxiety. In an ecological study, a correlation was found between an increase in stimulant medication use in girls with ADHD and depression in adolescence (Currie et al. 2014). The previously described MTA study reported that, at the six-

year follow-up, medicated children had higher rates of anxiety and depression diagnosis (19.1%) compared to children who received behavioral therapy (4.3%) (Molina et al. 2009). A retrospective cohort research, published in 2014, determined that certain ADHD medications such as amphetamines (Adderall) were specifically associated with increased risks of subsequent major depression disorder (MDD) in children (Jerrell et al. 2015). Additionally, the authors of this study noted that longer treatment durations with methylphenidate and amphetamines were related to a higher risk of subsequent MDD (Jerrell et al. 2015).

2.6 Other risk factors of persistent ADHD and affective disorders

Previous studies have identified that childhood ADHD, comorbid anxiety and depression and low socioeconomic status predicted the persistence of ADHD in adulthood (Caye et al. 2016; Cheung et al. 2015; Lara et al. 2009; Roy et al. 2016; Tandon et al. 2016; Taylor et al. 1996; van Lieshout et al. 2016). Moreover, children with ADHD are more likely to develop depression and anxiety later in life (Blackman et al. 2005; Smith et al. 2010; Williams et al. 2008). Low socioeconomic status and non-intact family are other risk factors of adult mood disorders (Brook and Schmidt 2008; Gilman et al. 2003; Laukkanen et al. 2016)

2.7 Group-based trajectory modeling

Group-based trajectory modeling (GBTM) is a procedure that allows to identify distinct groups of people who follow similar trajectories on a specific outcome (Nagin et al. 1999). While this technique has been extensively used in developmental psychology to study the progression and causes of various mental disorders such as depression and hyperactivity/impulsivity (Cote et al. 2009; Jester et al. 2008), it has been less frequently applied in research with dichotomous outcomes. To our knowledge, this is the first study to perform trajectory analyses to uncover distinctive developmental trends of ADHD medication use in both boys and girls. Certain advantages are associated with this statistical method. First, it allowed us to observe the longitudinal patterns of medication use in distinct groups of children over a 10-year period in

Quebec. Furthermore, it did not exclude individuals with missing values since only available data were used for model estimations.

2.8 Summary of previous findings

In summary, there are no clear conclusions about the long-term effects of ADHD medication in children. The few studies that have examined the relationship between the use of ADHD medication and long-term mental health outcomes are contradictory, often weakened by small sample sizes and lack meaningful sex comparisons. Moreover, most studies in this area of research were performed in limited clinical settings and consequently had poor generalizability. Therefore, large population-based studies that include sex comparisons are needed. This study identifies distinct trajectories of childhood ADHD medication use and examines the association between the use of medication during childhood and symptoms of mental health problems in adolescence, separately for boys and girls.

Chapter 3: Methodology

3.1 Participants

The current research is based on data drawn from the Quebec Longitudinal Study of Child Development (QLSCD). The QLSCD is a continuing longitudinal study directed by the Institut de la Statistique du Québec (ISQ) that follows children prospectively born in 1997-1998 from 5 months to the present day. The target population of 2917 infants, randomly selected from the Quebec Master Birth registry, represented five-month-old children born to mothers living in the province of Quebec between October 1997 and July 1998. Newborns whose mothers resided in Northern Quebec, Cree territory and Indian reserves and those who were highly premature or had major health problems were excluded. The initial sample included 2120 children and was representative of 96.5% of the target population. These children were monitored yearly until they were eight years-old and bi-annually from age 10 to 15 years. Information on child, parent and family characteristics were provided by the person most knowledgeable (PMK) about the child (the mother in 98% of cases) through home interviews with trained research assistants. Assessments at the following ages were used in this study: 5 months, 1.5, 2.5, 3.5, 4.5, 5, 6, 7, 8, 10, 12, 13 and 15 years.

3.2 Ethics statement

Written informed consent was obtained from all participants at each assessment (**Appendix A & B:** parent and teenager consent forms). The QLSCD study and protocol were previously approved by the ethics committees of Santé Québec (**Appendix C**) and the Quebec Institute of Statistics (**Appendix D**). The present study was approved by the University of Montreal Health Research Ethics Committee (**Appendix E**).

3.3 Attrition analyses

In this study, we retained participants with at least one valid data on ADHD medication use between 3.5 and 15 years. Hence, 1995 children (1007 boys and 988 girls) were included in the ADHD medication use trajectory estimation models. It is important to note, however, that individuals with a history of medication never exceeding 12 months were classified as not having use ADHD medication. At 15 years of age, 1443 youngsters reported on their symptoms of hyperactivity, impulsivity, inattention, depression and anxiety. These adolescents differed from the 677 excluded individuals on various characteristics, as shown in **Table I**. Thus, males, participants of non-Caucasian ethnicity, whose mothers did not obtain a high-school diploma (low maternal education), came from families with insufficient income and with mothers who experienced higher levels of depression symptoms were less represented in our study sample. Overall, the sample size used for trajectory modeling consisted of 1995 children but in subsequent analyses it was reduced to 1443 children.

Non-response at 15 years resulted in an attrition rate of 31.9%. To address sample attrition, we performed our analysis with and without inverse probability weights. Each child was given a weight, inversely proportional of being included in the study sample, based on variables predicting missingness, which are listed in the table below. Since the results with and without weights were similar, the latter are presented in this report.

Table I. Characteristics of included and excluded families

Variables % or mean	Included (n=1443)	Excluded (n=677)	p value
Child characteristics			
Sex (male)	47.8	57. 6	<0.001
Non-Caucasian ethnicity	16.7	24.4	<0.001
Maternal characteristics			
Maternal depression, mean	1.35	1.52	0.007
Sociodemographic variables			
Low maternal education	14.0	20.3	<0.001
Insufficient family income	20.4	33.7	<0.001

*Mothers without a high school diploma

3.4 Measures

Outcome variable: adolescent mental health symptoms at 15 years

At 15-years old, adolescents self-assessed their symptoms of hyperactivity, impulsivity, inattention, depression and anxiety with the Mental Health and Social Inadaptation Assessment for Adolescents (MIA) Questionnaire (Côté et al. 2017). The use of this measurement tool in this study presents several advantages. First, because the MIA was specifically designed to assess DSM-V symptoms of mental disorders in a general population of adolescents, it allowed to screen for subclinical problems that would have remained undetected with a categorical diagnostic tool (presence vs. absence of disorder) in our community-based sample. Moreover, this questionnaire is more reliable than other continuous scales for estimating internalizing symptoms in adolescents because it is based on self-reports (Côté et al. 2017). A total of four items were used to assess hyperactivity, six for impulsivity, six for inattention, eight for depression and nine for anxiety (see **Appendix F** for items). Teenagers were asked to rate whether their symptoms occurred never (1), sometimes (2) or often (3) over the past 12 months. Total scores were re-scaled on a 0 to 10 scale, with higher scores corresponding to higher levels

of symptoms. The scales presented adequate psychometric properties. The Cronbach's alpha values were 0.60, 0.76, 0.57, 0.84 and 0.81 for hyperactivity, impulsivity, inattention, depression and anxiety respectively.

Exposure variable: Childhood ADHD medication use trajectories

Information of ADHD medication use was obtained by asking the PMK about the child "In the past 12 months, did [your child] take any of the following prescribed medication on a regular basis: Ritalin or any other medication for treating hyperactivity or inattention?" at ages (years) 3.5, 4.5, 5, 6, 7, 8, 10, 12, 13 and 15. Since this data was reported at each wave by the mother, who most accurately knew whether or not her child was taking his/her medication on a regular basis, and because this information was collected by trained interviewers, it is the most valid possible measure.

Confounding variables

Potential confounding factors were selected based on their associations in the literature. Specifically, we considered sociodemographic and childhood behavioral problems. Since ADHD medicated children differ from non-medicated children on various factors (Galera et al. 2014), there is a risk that differences in the outcome variables may be caused by systematic differences between the groups and not by the independent effect of ADHD medication. For instance, children with high ADHD ratings are more likely to receive ADHD medication, but also have a greater risk of having persistent ADHD or developing affective disorders in adolescence, independently of medication use. Hence, if we do not control for childhood ADHD, our results will wrongly show that medication use is related to negative adolescent mental health outcomes. To minimize this potential bias effect, we adjusted our analyses for childhood behavioral problems (hyperactivity-impulsivity, inattention, depression and anxiety). The best way to control for these variables would before the initiation of ADHD medication since it may affect the rating of these behaviors and in turn bias the results. Consequently, we selected the age range of 2.5 to 5 years as the control period. Only eight individuals (0.6% of

the final sample) used ADHD medication during this period. In addition, we adjusted for sociodemographic measures (family structure, maternal education and family income) when participants were five months old.

Children's behavioral problems between 2.5 and 5 years

At 2.5, 3.5, 4 and 5 years, mothers assessed their child's symptoms of hyperactivity-impulsivity, inattention, depression and anxiety with the early childhood behavior scale from the Canadian National Longitudinal Study of Children and Youth (NLSCY) (Statistics Canada 1995). This tool incorporates items from the Child Behavior Checklist (Achenbach 1991), the Ontario Child Health Study Scales (Boyle et al. 1993), a modified version of the Children's Behavioural Questionnaire (Behar 1977), and the Preschool Behavior Questionnaire (Tremblay et al. 1987). These questionnaires have demonstrated good psychometric properties and have been used in large cohort studies to evaluate internalizing disorders in children (Boyle et al. 1993). Each behavior item was rated on a three-point scale (never: 0; sometimes: 1; often: 2). In general, mothers are regarded as valid sources of information regarding children's behaviors since they are acquainted with their child's behavior in various situations (Carter et al. 2003; Earls 1980). Hyperactivity-impulsivity was defined by six items, inattention by three items, depression by four items and anxiety by four items (See **Appendix G** for corresponding items). Scores were re-scaled on a 0 to 10 scale, with higher scores indicating greater levels of symptoms. The scales had satisfying psychometric properties since their mean Cronbach's values over four years of assessments were above 0.70. Specifically, they were 0.89, 0.85, 0.72 and 0.79 for hyperactivity-impulsivity, inattention, depression and anxiety respectively. The average score between 2.5 and 5 years in each scale was calculated for each child. This generated four variables: hyperactivity-impulsivity (2.5 to 5 years), inattention (2.5 to 5 years), depression (2.5 to 5 years) and anxiety (2.5 to 5 years).

Sociodemographic variables

Sociodemographic measures were collected when children were 5 months of age.

Family structure: Coded 1 if the family was not intact (single parent families or stepfamilies) and 0 if the family was intact.

Maternal education: Coded 1 if low (no high school diploma) and 0 if medium or high (high-school/post-secondary diploma or university degree).

Family income: Calculated according to Statistics Canada's guidelines which consider the family's income in the past year, the number of people living in the household and the family zone of residence (Statistics Canada 2009). Family income was coded 1 if insufficient and 0 if sufficient.

3.5 Data analyses

The current study had two main objectives. The first was to identify groups of children with distinct patterns of ADHD medication use between 3.5 and 15 years, separately by sex. The second was to determine whether the use of ADHD medication was associated with adolescent symptoms of hyperactivity, impulsivity, inattention, depression and anxiety. The first goal was achieved by using group-based trajectory modeling analysis and the second by performing multiple regression analyses. Each procedure is described in more details below.

3.5.1 Group-based trajectory modeling

Group-based trajectories were modeled by using a semi-parametric mixture approach (Nagin et al. 1999) in the SAS Proc Traj program. The optimal model that best fit the data was chosen by testing combinations of trajectory shapes (curvilinear, quadratic, or cubic) with several possible numbers of trajectories groups (two to four groups). The model with the highest Bayesian Information Criterion (BIC) value was selected (Kass and Raftery 1995; Raftery 1995). The BIC measures improvements in the model when the number of groups is increased but also favors model simplicity (Kass and Raftery 1995). The trajectory model is identified with the use of empirical data alone and not based on any prior hypothesis. Ultimately, three key outputs are

generated from the model: the parameters describing the trajectory for each group, the estimated proportion of children in each group and the posterior probability of group membership for each child in the sample. The Proc Traj program classifies children into groups according to the highest probability of belonging to one of the groups (Nagin et al. 1999). Children with at least one valid data on ADHD medication use were included in the analysis.

Comparisons between Childhood ADHD medication use trajectory groups

Student t-tests were carried out to compare the ADHD medication use (combined the early and the late onset trajectories of use) and the no/low ADHD medication use groups on continuous variables and Chi Square tests on categorical variables. These analyses were performed with SPSS-PC version 22.0 (SPSS Inc., Chicago, LT).

3.5.2 Multiple regression analyses

Multiple regression analyses were performed to examine the associations between childhood ADHD medication use and adolescent hyperactivity, impulsivity, inattention, depression and anxiety symptoms, separately for boys and girls. The ADHD medication use group (combining early- and late-onset trajectories of use) was contrasted to the no/low ADHD medication use group (reference group). Associations were also adjusted for sociodemographic variables (family structure, maternal education and family income) when children were five months old and for childhood behavioral problems (hyperactivity-impulsivity, inattention, depression and anxiety) between 2.5 and 5 years.

Chapter 4: Article

The association between childhood attention-deficit/hyperactivity disorder medication use and symptoms of mental health problems in adolescence: A 15- year longitudinal population-based study

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Author Contributions: The first author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Côté is the senior author. Study concept and design: Sabirova, Côté, Boivin and Tremblay. Statistical expertise and support: Liu. Analysis and interpretation of the data: Sabirova. Drafting of the manuscript: Sabirova. Critical revision of the manuscript for important intellectual content: Sabirova, Côté and Galéra. Final approval of the manuscript to be published: Sabirova, Côté, Boivin and Tremblay.

Disclosures: The authors have no financial relationships or conflicts of interest to disclose.

Status of article: In preparation for publication.

Abstract

Objectives: To model the patterns of attention-deficit/hyperactivity disorder (ADHD) medication use in distinct groups of boys and girls aged 3.5 to 15 years and to test whether the use of ADHD medication during childhood is associated with adolescent symptoms of hyperactivity, impulsivity, inattention, depression and anxiety.

Methods: A sample of 1443 children born in the Canadian Province of Quebec in 1997-1998 was followed for 15 years. Information on ADHD medication use was obtained from the parents between the ages of 3.5 and 15 years. Hyperactivity, impulsivity, inattention, depression and anxiety were self-reported by the participants at 15 years. Multiple regression analyses were used to determine the association between childhood ADHD medication use and symptoms of mental health problems in adolescence, adjusting for confounding factors.

Results: Three trajectories of ADHD medication use were identified in both boys and girls: no/low ADHD medication use, early-onset use and late-onset use. Medication was generally initiated during middle childhood for individuals in the early-onset trajectory and during adolescence for those following a late-onset trajectory. After controlling for sociodemographic factors and childhood behavioral problems, children on the early- and late-onset trajectories (combined) did not have significantly higher hyperactivity nor impulsivity scores at 15 years compared to those on the no/low ADHD medication use trajectory. However, males had higher inattention and depression scores.

Conclusion: Childhood ADHD medication use was associated with the persistence of certain types of ADHD symptoms in adolescence. Moreover, it was associated with higher levels of adolescent depression symptoms. Further research is needed on the long-term effectiveness and effects of ADHD medication on the risk of developing comorbid depression, including larger samples of medicated females for meaningful sex comparisons.

Key-words: Attention-deficit/hyperactivity disorder, ADHD medication, longitudinal study, childhood, adolescence, long-term effectiveness, long-term effects, depression, anxiety

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder in children, affecting 5.3% of the child population worldwide (Polanczyk et al. 2007). ADHD is characterized by symptoms of impulsivity, inattention and/or hyperactivity (American Psychiatric Association 2004). The first line of treatment is with stimulant drugs such as methylphenidate (Ritalin) (Chirdkiatgumchai et al. 2013; Galera et al. 2014). On the short-term, ADHD medication has been shown to be effective in reducing ADHD symptoms and improving academic performance (Coghill et al. 2014; Greenhill et al. 2002; Loe and Feldman 2007). As prescription rates of ADHD medication have increased for children (Brault and Lacourse 2012; Castle et al. 2007; Scheffler et al. 2007; Zuvekas and Vitiello 2012), concerns have been raised about their long-term effects, especially since pharmacological treatment can be maintained for years due to the persistence of the disorder (Sibley et al. 2016). Given the negative impact of ADHD on quality of life and overall health (Barkley 2002; Caci et al. 2014; Peasgood et al. 2016), a better understanding of the longitudinal treatment patterns of ADHD and the long-term mental health outcomes associated with the use of ADHD medication may help improve the outcomes for children with ADHD.

Pre-clinical studies using animal models showed that stimulants cause profound and long-lasting, cognitive and behavioral changes. The most important consequences reported were impaired working memory, spatial learning problems (i.e. reduced focus and attention), and anxiety- and depressive-like behaviors (Bolanos et al. 2003; Carlezon et al. 2003; Scherer et al. 2010; van der Marel et al. 2015). These findings underlie the importance of studying the long-term outcomes of ADHD medication use in children.

Long-term effectiveness of ADHD medication in children

Studies focusing on the long-term effectiveness of pharmacological treatment for ADHD have yielded contradictory results. For example, one randomized double-blind placebo-controlled trial that followed children with ADHD for 15 months (n=61) found that amphetamine treatment was superior to placebo in reducing hyperactivity and inattention problems (Gillberg et al. 1997). Through a large population-based cohort study of children with ADHD, Barbaresi et al.

later suggested that the long-term effectiveness of ADHD medication in the community is comparable to the efficacy of ADHD medication observed in randomized control trials (Barbaresi et al. 2006). An observational follow-up study of 79 subjects provided further evidence on this matter by showing that children who adhered to stimulant treatment showed greater improvements in ADHD symptoms than those who did not continuously take medication for five years (Charach et al. 2004). On the other hand, in a UK cohort study, Langley et al. reported that children who were using ADHD medication at the five-year follow-up in adolescence had significantly higher ADHD scores and greater rates of ADHD diagnoses compared to those who were no longer taking the medication (Langley et al. 2010). In 2009, with the aim of determining the long-term effects of ADHD medication, a longitudinal Multimodal Treatment Study of ADHD (MTA) initially randomized 579 children with ADHD into four treatment groups: medication management, behavioral therapy, combined medication and behavioral therapy or community care. The eight-year follow-up did not reveal any significant difference in ADHD symptoms across the groups, indicating that medication did not have long-lasting treatment benefits. Furthermore, participants in the MTA study fared worse than the non-ADHD classmate sample on hyperactivity/impulsivity and inattention symptoms (Molina et al. 2009). Consistent with previous findings, in a 6-year comprehensive investigation, researchers found that pharmacological treatment of ADHD in children had no positive impact on ADHD related outcomes. In fact, continued medication treatment predicted greater symptom severity (van Lieshout et al. 2016). Lastly, a 14-year longitudinal study, examining the change in ADHD symptoms from childhood to adolescence, determined that stimulant medication use was not associated with long-term improvement in core symptoms of ADHD (Smith et al. 2010).

Long-term effects of ADHD medication on the development of affective disorders in children

Existing studies examining the relationship between the use of ADHD medication in children and the development of affective disorders later in life also highlight a similar lack of consensus. Since several cases of depression and suicidality have been reported with the use of ADHD drugs, (Arun and Sahni 2014; Kim et al. 2011; Lafay-Chebassier et al. 2015; Lakic 2012) Health Canada has recently issued a warning on the safety of these medications (Health Canada 2015).

However, two longitudinal studies found that pharmacological treatment of ADHD during childhood was not associated with depression in adolescence (Smith et al. 2010; Staikova et al. 2010). Furthermore, two case-control studies (prospective and retrospective in design) and a longitudinal cohort study indicated that medication use in ADHD children was associated with a reduced risk of subsequent affective disorders (Biederman et al. 2009; Chang et al. 2016; Daviss et al. 2008). Interestingly, in the retrospective case-control report, the authors suggested that earlier pharmacological intervention may be related to a delay in the onset of depression in youth with ADHD (Daviss et al. 2008). In contrast, the abovementioned MTA study showed that medicated children had higher rates of anxiety and depression diagnosis (19.1%) than children who received behavioral therapy (4.3%) at the six-year follow-up (Molina et al. 2009). In 2014, Jerrell et al. provided additional evidence to support the findings from the MTA report. For instance, they determined which ADHD medication was specifically associated with the development of major depression disorder (MDD) in children with ADHD. They also found that longer durations of treatment with methylphenidate and mixed amphetamine salts (Adderall) was related to a higher risk of subsequent MDD (Jerrell et al. 2015). Finally, in line with these findings, an ecological study showed that an increase in ADHD medication use in girls was correlated with depression in adolescence (Currie et al. 2014).

Overall, no clear conclusions can be made on this subject. The few studies that have investigated the long-term mental health outcomes associated with ADHD medication use in children are contradictory, limited to clinical samples and lack meaningful sex comparisons. Furthermore, studies examining the trends of medication use for ADHD often used a cross-sectional design, which does not allow for the identification of distinct patterns of ADHD medication use in children. These studies also failed to describe how differences in medication treatment of ADHD develop and change over time between boys and girls. This research aims to address these issues. We used data from a population-based study in Quebec that followed children from birth until the age of 15 years to accomplish two objectives. The first was to identiy groups of boys and girls with distinct trajectories of ADHD medication use from 3.5 to 15 years. The second was to test the association between the use of ADHD medication during childhood and five mental health problems in adolescence: hyperactivity, impulsivity, inattention, depression and anxiety.

Methods

Participants

The present study is a secondary analysis of data drawn from the Quebec Longitudinal Study of Child Development (QLSCD). The initial sample was selected from the Quebec Master Birth registry to represent all the children born in Quebec (Canada) in 1997-1998 and consisted of n=2120 five-month-old infants. These children were monitored yearly until they were eight years-old and bi-annually from age 10 to 15 years. Trained interviewers conducted home interviews with the person most knowledgeable (PMK) about the child (the mother in 98% of cases) to collect information on child, parent, and family characteristics and behaviors. Informed written consent was obtained from all participants at each follow-up. The QLSCD protocol was approved by the ethics committees of Quebec Institute of Statistics and the St Justine Hospital Research Center and this study by the University of Montreal Health Research Ethics Committee. Assessments at the following ages were retained for this research: 5 months, 2.5, 3.5, 4, 5, 6, 7, 8, 10, 12, 13 and 15 years.

Accounting for attrition

Of the 2120 participants in the initial sample, we included those with data on at least one time point (3.5 to 15 years) for ADHD medication use (n=1995) and those who self-reported hyperactivity, impulsivity, inattention, depression and anxiety symptoms at 15 years. The final study sample consisted of 1443 individuals (incurred 31.9% attrition). To adjust for this problem, we performed our analysis with and without inverse probability weights. Each child was given a weight, inversely proportional of being included in the study sample, based on variables related to attrition. The 1443 individuals used in our research differed from the excluded 677 individuals in the proportion of male children [47.8% included vs. 57.6% excluded, X^2=17.67, p<0.001], non-Caucasian ethnicity [16.7% included vs. 24.4 % excluded, X^2=17.50, p<0.001], maternal depressive symptoms [1.35 included vs. 1.52 excluded, T (1205.62)=2.70, p=0.007], families with insufficient income [20.4% included vs. 33.7% excluded, X^2=42.98, p<0.001], and mothers without a high-school diploma [14.0% included vs. 20.3% excluded, X^2=13.52, p<0.001]. As the results with and without weights were similar, the

latter are presented here. **Table I** describes the sociodemographic characteristic of the 1443 participants at five months.

Table I. Sociodemographic characteristics of the sample at five months (n=1443).

	%
Sex of the child (female)	52.2
Ethnic origins[a]	
Canadian	74.2
French	34.4
European	7.8
British	6.8
First Nations	2.8
African or Haitian	1.7
Other[b]	12.8
Maternal education (no high school diploma)	14.0
Non-intact family	17.9
Family income	
<$30,000	26.4
$30,000-$60,000	41.6
>$60,000	32.0
Insufficient family income	20.4

	Mean	SD
Maternal depression	1.35	1.29

[a] Children may be classified in more than one category

[b] "Other" includes all categories of ethnic origin with less than 2% membership

Outcome variables: Adolescent mental health symptoms at 15 years

Participants self-reported their DSM-V symptoms of hyperactivity, impulsivity, inattention, depression and anxiety at 15 years using the Mental Health and Social Inadaptation Assessment for Adolescents (MIA) Questionnaire (Côté et al. 2017). The following items defined each outcome:

1) Hyperactivity: "I felt very restless, I was constantly on the move", "I often stood up in class or in other situations where I was supposed to remain seated", "I often had trouble staying calm during games or leisure activities" and "I moved my hands and feet, I wriggled in my chair".
2) Impulsivity: "I was impulsive (reacted quickly without thinking)", "I said things before thinking them through", "I did or said things without stopping to think", "I had difficulty waiting for my turn in games or group activities", "I often blurted out the answer to a question that hadn't yet been completely asked" and "I got into trouble because I did things without thinking".
3) Inattention: "I was inattentive, I had difficulty paying attention to what someone was saying or doing", "I completed all of my tasks or homework, I was able to stay focused. (reverse coding)", "I had trouble keeping my mind on what I was doing for more than a few minutes", "I forgot what I was supposed to be doing or what I had planned to do", "I avoided doing things where I needed to pay attention for a long time" and "I made a lot of mistakes because it was hard for me to do things carefully".
4) Depression: "Nothing was fun for me, I wasn't interested in anything", "I felt sad and unhappy", "I lacked energy or felt tired", "I lost interest in things I usually like", "I felt I couldn't do anything well", "I wasn't as good-looking or as smart as other people", "Doing even little things made me feel really tired" and "I had trouble thinking clearly".
5) Anxiety: "I was too fearful or nervous", "I had worries that interfered with my everyday life", "I worried about my past behaviour", "I worried about my school work", "I worried about my own health", "I worried about my loved ones (family, friends)", "I worried about my relationships with my friends (i.e. making and keeping friends)", "I was concerned about my appearance or weight" and "I found it difficult to control the worry".

All items refer to the preceding 12 months and were rated on a frequency scale (never: 1; sometimes: 2; often: 3). Total scores were then re-scaled on a 0 to 10 scale, with higher scores corresponding to higher levels of symptoms. The Cronbach's alpha values were 0.60, 0.76, 0.57, 0.84 and 0.81 for hyperactivity, impulsivity, inattention, depression and anxiety respectively.

Exposure variable: Childhood ADHD medication use trajectories

ADHD medication use was reported by the PMK about the child (the mother in 98% of cases) in a question referring to the preceding 12 months "Does [your child] take any of the following prescribed medication on a regular basis: Ritalin or any other medication for treating hyperactivity or inattention?" at ages (years) 3.5, 4.5, 5, 6, 7, 8, 10, 12, 13 and 15 years.

Confounding variables

Given that medicated children differ from non-medicated children on various factors (Galera et al. 2014), there is a risk that a difference in the outcome variables may be caused by systematic differences between the groups and not by the independent effect of ADHD medication. To reduce the potential effect of bias, we controlled for childhood behavioral problems. The best way to adjust for these confounding factors is before the exposure to medication, since its mitigating effect on ADHD symptoms may change the ratings of these symptoms and subsequently confound the results. Hence, we selected the ages of 2.5 to 5 years as the control period. Only eight subjects (0.6% of the final sample) were exposed to ADHD medication during that age range. In addition, we adjusted for sociodemographic measures when participants were five months old. The confounding factors were selected based on their associations in the literature with childhood ADHD medication use (Galera et al. 2014) and with the development of ADHD (Caye et al. 2016; Cheung et al. 2015; Lara et al. 2009; Roy et al. 2016; Tandon et al. 2016; Taylor et al. 1996; van Lieshout et al. 2016), depression and anxiety later in life (Blackman et al. 2005; Brook and Schmidt 2008; Gilman et al. 2003; Laukkanen et al. 2016; Smith et al. 2010; Williams et al. 2008).

Childhood behavioral problems between 2.5 and 5 years

Symptoms of hyperactivity-impulsivity, inattention, depression and anxiety were reported by the mother as never (0), sometimes (1), or often (2) over the last 12 months when their child was 2.5, 3.5, 4.5 and 5 years old. In general, mothers are regarded as valid sources of information regarding children's behaviors since they are acquainted with their child's behavior in various situations (Carter et al. 2003; Earls 1980) . Ratings were based on the early childhood behavior scale from the Canadian National Longitudinal Study of Children and Youth (NLSCY)

(Statistics Canada 1995), which combines items from the Child Behavior Checklist (Achenbach 1991), the Ontario Child Health Study Scales (Boyle et al. 1993), a modified version of the Children's Behavioural Questionnaire (Behar 1977) and the Preschool Behavior Questionnaire (Tremblay et al. 1987). Each mental health problem was defined by the following corresponding items:

1) Hyperactivity-impulsivity: "could not sit still, was restless and hyperactive", "could not stop fidgeting", "was impulsive and acted without thinking'", "had difficulty waiting for his/her turn in games", "could not settle down to do anything for more than a few moments" and "was unable to wait when someone promised him/her something".
2) Inattention: "was unable to concentrate, could not pay attention for long", "was easily distracted, had trouble sticking to any activity" and "was inattentive".
3) Depression: "seemed to be unhappy or sad", "was not as happy as other children", "had trouble enjoying him/herself" and "had no energy, was feeling tired".
4) Anxiety: "was too fearful or anxious", "was worried", "cried a lot" and "was nervous, high strung or tense".

Scores were re-scaled on a 0 to 10 scale, with higher scores indicating greater levels of symptoms. The mean alpha levels over the five years of assessments were 0.89 for hyperactivity-impulsivity ratings, 0.85 for inattention, 0.72 for depression and 0.79 for anxiety. For each scale, the average score between 2.5 and 5 years was calculated for every child. This generated four variables: hyperactivity-impulsivity (2.5 to 5 years), inattention (2.5 to 5 years), depression (2.5 to 5 years) and anxiety (2.5 to 5 years).

Sociodemographic variables

Sociodemographic measures were assessed when the child was five months of age and included sex of the child, family structure, maternal education and family income. Family structure was coded 1 if the family was not intact (single parent families or stepfamilies) and 0 if the family was intact. Maternal education was coded 1 if low (no high-school diploma) and 0 if medium or high (high-school/post-secondary diploma or university degree). Family income, coded 1 for insufficient and 0 for sufficient, was calculated based on Statistics Canada's guidelines by taking into consideration the family's income in the past year, the number of people living in the household and the family zone of residence (Statistics Canada 2009).

Statistical analyses

Group-based trajectory modeling (GBTM) was the method applied to identify groups of boys and girls with distinct developmental patterns of ADHD medication use from 3.5 to 15 years. To accomplish this, we used a semiparametric mixture model (Nagin et al. 1999) with a trajectory model program called SAS Proc Traj. The optimal model is determined based on the Bayesian Information Criterion (BIC), which identifies the number and shapes (curvilinear, quadratic, or cubic) of the trajectory groups that best fit the data. This is done by testing a combination of trajectory shapes with several possible numbers of trajectories. After the number of trajectory groups was established by the model, each individual was given a probability of group membership. The Proc Traj program classifies children into groups according to the highest probability of belonging to one of the groups (Nagin et al. 1999). The trajectory model is identified with the use of empirical data alone and not based on any prior hypothesis.

Student t-tests and Chi Square tests were carried out to compare the ADHD medication use group (combining early- and late-onset trajectories of use) and the no/low ADHD medication use group on continuous and categorical variables, respectively. The analyses were performed separately by sex.

Multiple regression analyses contrasting the ADHD medication use group (combined early and later trajectories) to the no/low ADHD medication use group (reference group) were performed to estimate the association between the use of ADHD medication during childhood and adolescent hyperactivity, impulsivity, inattention, depression and anxiety symptoms, separately for boys and girls. The associations were adjusted for sociodemographic variables (family structure, maternal education and family income) when children were five months old and for childhood behavioral problems (hyperactivity-impulsivity, inattention, depression and anxiety) at ages between 2.5 and 5 years. The above analyses were executed with SPSS-PC version 22.0 (SPSS Inc., Chicago, LT)

Results

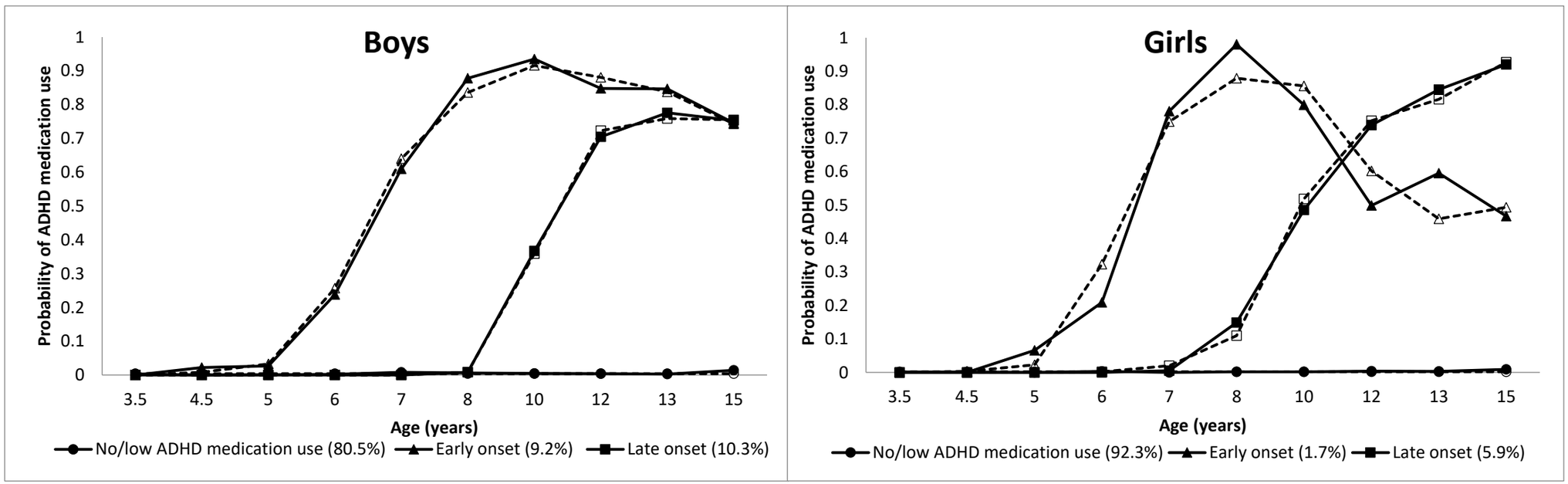
Childhood ADHD medication use trajectory models

Since we used individuals with at least one valid data on ADHD medication use to model the trajectory group estimations, 1995 participants from the initial sample (n=2120) were included in the models, specifically 1007 boys and 988 girls.

For both sexes, three distinct groups of ADHD medication use were identified from the ages of 3.5 to 15 years (See **Figure 1**): no/low ADHD medication use, early-onset use and late-onset use. Solid lines represent observed data while dashed lines represent estimated values. Many distinctions between the trajectory models of boys and girls were identified. First, the proportions of subjects in each group were different for male and female participants: 80.5% vs 92.3%, 9.2% vs 1.7% and 10.3% vs 5.9% in the no/low ADHD medication use, the early-onset and the late-onset groups, respectively. Second, the developmental patterns of medication use were different for male and female participants. As expected, the no/low ADHD medication female and male groups comprised individuals who generally never used ADHD medication or in rare cases had a short and inconsistent history of pharmacological treatment, which never exceeded 12 months. Thus, the probability that they were medicated remained 0 throughout the observation period. The early- and the late-onset trajectories, on the other hand, were very dissimilar between the sexes. Boys in the early-onset group had a probability of using medication close to 0 until the age of five years. Between 6 and 10 years their probability increased and from 12 years onward it gradually decreased. Overall, this early-onset group consisted of boys who started using medication for ADHD between six and eight years but did not necessarily continue to use it at the age of 15 years. Male children following a late-onset trajectory were not exposed to medication across the ages of 3.5 and 8 years. However, from 10 to 12 years, ADHD medication use rose noticeably in this group. Thus, this group was mainly comprised of males who began receiving ADHD pharmacotherapy at 10 years or later and tended to stay on medication until the age of 15 years. As for girls, the early-onset trajectory exhibited an exponential growth in the probability of using ADHD medication between six and eight years, followed by a marked decline up to the age of 15 years. This category can be described as a group of girls for whom ADHD pharmacotherapy was initiated from six to eight years of age and ended, for the majority, before age 15. However, it is important to note that the

trajectory of this group was estimated only from the data of 14 subjects. Females classified in the late-onset group started using ADHD medication only after the age of seven years. From then on, their probability of medication use increased with time. Unlike those in the early-onset trajectory, most girls in the late-onset group continued to be treated with ADHD medication at the age of 15 years. For detailed information on medication use for the 1995 children included in the trajectory models at each time point see **Supplementary Table I**.

Figure 1. Childhood ADHD medication use trajectory groups in boys (n=1007) and girls (n=988).



Childhood ADHD medication use trajectory groups between 3.5 and 15 years.

As the number of participants in the early- and late-onset categories within the final sample (n=1443) was relatively low for both sexes (early-onset: 59 boys and 12 girls, late-onset: 72 boys and 40 girls), we combined these two groups into one (for specific numbers, see **Supplementary Table II**). Therefore, the childhood ADHD medication use variable included two groups for each sex: 1) No/low ADHD medication use: 81.0% boys (n=559) and 93.1% girls (n=701) and 2) ADHD medication use: 19.0% boys (n=131) and 6.9% girls (n=52). **Supplementary Table III** provides a detailed description of the number of medicated children in each group at each time point.

Childhood behavioral problems and sociodemographic characteristics at baseline

Table II compares the no/low ADHD medication use and ADHD medication use groups regarding childhood behavioral problems before medication use (i.e. between 2.5 and 5 years) and sociodemographic data (at five months) for boys and girls separately. Group comparisons are expressed as means (standard deviations) or numbers (percentages). Hyperactivity-impulsivity and inattention scores were significantly higher in the ADHD medication use group for both sexes ($p<0.001$ for all four comparisons). In general, male children had higher levels of hyperactivity-impulsivity symptoms than female children (boys: m=4.28(SD=1.75), girls: m=3.73(SD=1.69), $p<0.001$) and greater inattention ratings (boys: m=3.27(SD=1.79), girls: m=2.89(SD=1.73), $p<0.001$). Medicated boys did not differ from non-medicated boys on depression, but were more anxious before the onset of treatment ($p=0.028$). As for girls, no difference in depression and anxiety was detected between groups. Regarding sociodemographic variables, boys treated with ADHD medication were more likely to come from non-intact families than boys not treated with ADHD medication ($p=0.002$). Finally, medicated girls were more likely to come from families with insufficient family income compared to non-medicated girls ($p=0.038$).

Table II. Childhood behaviors and sociodemographic characteristics according to childhood trajectory of ADHD medication use.

	Boys				Girls			
Variables [n, (%)] or [mean (SD)]	No/low ADHD medication use (n=559)	ADHD medication use[c] (n=131)	Total (n=690)	*p* value[d]	No/low ADHD medication use (n=701)	ADHD medication use[c] (n=52)	Total (n=753)	*p* value[d]
Childhood behaviors (2.5-5 years)[a]								
Hyperactivity-impulsivity, mean (SD)	4.06(1.72)	5.21(1.57)	4.28(1.75)	<0.001	3.65(1.67)	4.81(1.73)	3.73(1.69)	<0.001
Inattention, mean (SD)	3.07(1.73)	4.13(1.75)	3.27(1.79)	<0.001	2.81(1.68)	3.92(2.01)	2.89(1.73)	<0.001
Depression, mean (SD)	1.41(0.97)	1.48(0.90)	1.42(0.96)	0.459	1.47(0.96)	1.34(0.86)	1.46(0.96)	0.353
Anxiety, mean (SD)	1.91(1.34)	2.19(1.19)	1.97(1.32)	0.028	2.00(1.30)	2.22(1.02)	2.02(1.28)	0.158
Sociodemographic variables[b]								
Non-intact family	88(15.7)	36(27.5)	124(18.0)	0.002	124(17.7)	10(19.2)	134(17.8)	0.680
Low maternal education	70(12.5)	22(16.8)	92(13.3)	0.195	98(14.0)	12(23.1)	110(14.6)	0.062
Insufficient family income	119(21.3)	34(26.0)	153(22.2)	0.250	123(17.6)	15(28.9)	138(18.3)	0.038

[a]Childhood behaviors very measured at 2.5, 3.5, 4.5 and 5 years old. Scores were averaged across those ages.

[b]Sociodemographic measures were collected when the child was 5 months of age.

[c]ADHD medication use group combines children from the early and late onset of ADHD medication use trajectories

[d]*p* values were calculated by using χ^2 test for categorical variables or two-sample (independent) *t*-test for continuous variables.

Adolescent mental health symptoms at 15 years

In adolescence, the self-assessed mental health problems showed a different picture, as depicted in **Table III**. Overall, hyperactivity and impulsivity ratings were similar between sexes. However, adolescent girls reported significantly higher levels of depression than adolescent boys (girls: 4.27(2.22), boys: 2.64(1.95), $p<0.001$) and higher anxiety scores (girls: 4.86(2.08), boys: 3.27(1.97), $p<0.001$). Surprisingly, non-medicated girls appeared to be considerably more inattentive than non-medicated boys (girls: 3.44(2.01), boys: 2.94(1.88), $p<0.001$), whereas medicated girls and medicated boys did not differ on inattention scores (girls: 3.98(1.95), boys: 3.97(1.83), $p=0.979$). Most unexpectedly, while girls in the ADHD medication use group had lower ratings of depression and anxiety than girls in the no/low use group, they still had higher symptoms scores than boys of the same group.

Associations between childhood ADHD medication use and adolescent mental health symptoms at 15 years

Multiple regression analyses, controlling for sociodemographic measures and childhood characteristics, were performed to examine the independent relationship between childhood ADHD medication use and mental health problems in adolescence. The ADHD medication use group (combining early- and late-onset trajectory of use) was contrasted with the no/low ADHD medication use group in the models. The results are summarized in **Table IV** for boys and girls separately. For male participants, medication use during childhood was not significantly associated with hyperactivity nor with impulsivity symptoms at 15 years. However, it was related to higher levels of inattention ($\beta=0.935$, $p<0.001$). Moreover, boys treated with ADHD medication reported significantly greater depression scores in adolescence than those not treated with ADHD medication ($p=0.029$). In contrast, the use of medication was not associated with increased male anxiety. For females, childhood ADHD medication use was not correlated with worse ADHD outcomes in adolescence (i.e., higher hyperactivity, impulsivity or inattention). Lastly, no relationship was found between the use of ADHD medication during childhood, and female adolescent depression and anxiety. Although the results were not significant, higher depression and anxiety scores were reported by girls in the no/low ADHD medication use. The estimated marginal means are provided in **Supplementary Table IV**.

Table III. Adolescent mental health symptoms according to childhood trajectory of ADHD medication use.

	Boys				Girls			
Number of mental health symptoms at 15 years	No/low ADHD medication use (n=559)	ADHD medication use[a] (n=131)	Total (n=690)	*p* value[b]	No/low ADHD medication use (n=701)	ADHD medication use[a] (n=52)	Total (n=753)	*p* value[b]
Hyperactivity, mean (SD)	2.50(2.07)	3.03(2.35)	2.60(2.14)	0.017	2.60(2.11)	2.91(2.45)	2.62(2.13)	0.310
Impulsivity, mean (SD)	2.64(1.95)	3.01(2.33)	2.71(2.03)	0.098	2.84(1.87)	2.95(2.18)	2.85(1.89)	0.699
Inattention, mean (SD)	2.94(1.88)	3.97(1.83)	3.13(1.91)	<0.001	3.44(2.01)	3.98(1.95)	3.48(2.01)	0.067
Depression, mean (SD)	2.54(1.88)	3.04(2.18)	2.64(1.95)	0.018	4.30(2.22)	3.85(2.20)	4.27(2.22)	0.160
Anxiety, mean (SD)	3.24(1.95)	3.40(2.04)	3.27(1.97)	0.409	4.88(2.08)	4.49(2.00)	4.86(2.08)	0.185

[a]ADHD medication use group combines children from the early and late onset of ADHD medication use trajectories

[b]*p* values were calculated by using χ^2 test for categorical variables or two-sample (independent) *t*-test for continuous variables.

Table IV. Multiple regression analysis of the association between childhood ADHD medication use trajectory and adolescent hyperactivity, impulsivity, inattention, depression and anxiety at 15 years.

	Boys (n=690)														
	Hyperactivity			Impulsivity			Inattention			Depression			Anxiety		
Variables	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*
ADHD medication use[a] vs. No/low ADHD medication use	0.329	0.215	0.126	0.184	0.205	0.370	0.935	0.190	<0.001	0.432	0.197	0.029	0.057	0.201	0.778
Family structure[b]	0.486	0.223	0.029	0.215	0.212	0.311	0.449	0.197	0.023	0.309	0.205	0.131	0.086	0.208	0.679
Maternal education[c]	-0.528	0.248	0.034	-0.319	0.236	0.178	-0.460	0.219	0.036	-0.554	0.228	0.015	-0.393	0.231	0.090
Family income[d]	0.041	0.211	0.846	0.204	0.201	0.311	0.206	0.186	0.270	-0.056	0.194	0.773	-0.086	0.197	0.663
Hyperactivity-impulsivity (2.5 to 5 years)	0.185	0.066	0.006	0.236	0.063	<0.001	0.123	0.059	0.037	0.088	0.061	0.148	0.047	0.062	0.452
Inattention (2.5 to 5 years)	0.009	0.067	0.897	-0.083	0.064	0.197	-0.052	0.059	0.380	-0.042	0.062	0.494	0.049	0.063	0.434
Depression (2.5 to 5 years)	0.018	0.102	0.860	0.110	0.097	0.257	0.129	0.090	0.150	0.164	0.093	0.080	-0.016	0.095	0.866
Anxiety (2.5 to 5 years)	-0.167	0.074	0.024	-0.097	0.070	0.167	-0.127	0.065	0.051	-0.061	0.068	0.363	0.028	0.069	0.687
F		4.07	<0.001		3.28	0.001		6.59	<0.001		2.55	0.010		1.03	0.412
R^2		0.046			0.038			0.073		0.029				0.012	
AdjR^2		0.035			0.026			0.062		0.018				0.000	
	Girls (n=753)														
	Hyperactivity			Impulsivity			Inattention			Depression			Anxiety		
Variables	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*
ADHD medication use[a] vs. No/low ADHD medication use	0.038	0.318	0.906	0.036	0.283	0.899	0.400	0.302	0.186	-0.592	0.332	0.076	-0.602	0.312	0.054
Family structure[b]	0.044	0.214	0.838	0.182	0.191	0.340	0.189	0.204	0.353	0.058	0.224	0.794	0.062	0.210	0.767
Maternal education[c]	0.303	0.235	0.197	0.191	0.209	0.361	0.176	0.224	0.431	0.246	0.246	0.316	0.158	0.230	0.494
Family income[d]	0.008	0.216	0.971	-0.065	0.192	0.736	0.183	0.205	0.371	-0.128	0.225	0.570	-0.074	0.211	0.727
Hyperactivity-impulsivity (2.5 to 5 years)	0.109	0.066	0.097	0.149	0.059	0.011	0.122	0.063	0.051	0.169	0.069	0.014	0.097	0.065	0.135
Inattention (2.5 to 5 years)	0.035	0.065	0.590	-0.047	0.058	0.421	-0.012	0.062	0.851	-0.085	0.068	0.212	0.032	0.064	0.619
Depression (2.5 to 5 years)	0.011	0.100	0.914	0.105	0.089	0.237	0.152	0.095	0.110	0.275	0.104	0.009	0.188	0.098	0.055
Anxiety (2.5 to 5 years)	-0.027	0.074	0.720	-0.058	0.066	0.382	-0.102	0.071	0.151	-0.162	0.078	0.037	-0.117	0.073	0.110
F		1.43	0.180		1.54	0.139		2.08	0.036		2.09	0.034		1.95	0.072
R^2		0.015			0.017			0.022			0.022			0.019	
AdjR^2		0.005			0.006			0.012			0.012			0.009	

[a]ADHD medication use group combines children from the early and late onset of ADHD medication use trajectories

[b]Family structure (1: non-intact; 0: intact)

[c]Maternal education (1: low [no high school diploma]; 0: medium or high [high-school/post-secondary diploma or university degree])

[d]Family income (1: insufficient; 0: sufficient)

Discussion

In this 15-year longitudinal population-based study, we observed specific longitudinal trends of ADHD medication use from 3.5 to 15 years in both boys and girls. Specifically, we identified three groups of children following distinct trajectories: 1) a group of children who did not use medication, 2) an early-onset use (between age 6 and 8 years) and 3) a late-onset use (age 10 years for boys and 8 years for girls). The proportion and developmental patterns of the trajectories were different for males vs. females: early- and late-onset boys represented respectively 9.2% and 10.3% of boys and followed sharply rising trajectories followed by a plateau (between 12 and 15 years), while early- and late-onset girls represented respectively 1.7% and 5.9% of girls. The late-onset trajectory was similar in shape to that of boys, but early-onset girls followed a sharply rising and then declining early-onset trajectory. Furthermore, we found that ADHD medication use during childhood was related to inattention and depression symptoms at 15 years. We did not document sex differences for the measured associations due to inconclusive results for females. However, our findings seem to suggest that boys and girls who were medicated for ADHD during childhood have comparable mental health outcomes in adolescence.

Childhood ADHD medication use trajectories

To our knowledge, this is the first study that used group-based trajectory modeling to identify groups of children with differential patterns of ADHD medication use. Most studies, examining the relationship between the use of ADHD medication and long-term mental health outcomes have relied on arbitrary cut points to create medication groups. Trajectory modeling, on the other hand, generates groups from empirical data instead of categorizing actively required participants into predetermined groups, does not exclude subjects with missing data and allows for the observation of temporal patterns of each trajectory group over time. Overall, we obtained with this method a general portrait of the dynamic prevalence of childhood ADHD medication use among children in Quebec, between 2001 and 2013. Consistent with previous reports, this study also documented sex differences in the use of ADHD medication in children (Brault and

Lacourse 2012; Galera et al. 2014; McCarthy et al. 2012; Prosser et al. 2015; Zuvekas and Vitiello 2012). The sex differences were significant. Two groups were observed for boys: those who began medication treatment in the early school years (6-8 years old) and those who started taking medication during adolescent years (10-15 years old). For girls, however, there was only one sizable medication group: late-onset of ADHD medication use, which was initiated between 8 and 15 years. This confirms that, overall, boys are more medicated than girls (Galera et al. 2014; Zuvekas and Vitiello 2012), but especially during early childhood (3-8 years) (Brault and Lacourse 2012). This can perhaps be explained by the fact that girls with ADHD display less externalizing behavior problems and are thus less likely to be medicated (Levy et al. 2005) or because of a general belief that the disorder is more prevalent in boys (Quinn and Wigal 2004). Interestingly, in comparison to boys, girls in the late-onset category displayed a greater increase in probability of being medicated, more specifically between the age of 12 and 15 years. This decreasing sex disparity in the rate of ADHD medication use among adolescents has also been observed in a US study (Burcu et al. 2016), suggesting that this is not an isolated situation in Quebec but rather an ongoing world wide phenomenon (McCarthy et al. 2012; Prosser et al. 2015).

Associations between childhood ADHD medication use and adolescent hyperactivity, impulsivity and inattention symptoms at 15 years

We found that children in the ADHD medication use group (combining the early and late trajectories of use) did not have significantly higher hyperactivity nor impulsivity scores at 15 years compared to those in the no/low ADHD medication use group. However, our results also showed that the use of ADHD medication during childhood was related to higher levels of inattention in adolescent males. On the other hand, medicated and non-medicated girls did not differ on inattention ratings in adolescence. Yet, upon carefully examining adolescent mean scores between sexes, we observed that females had far higher inattention scores than males only in the no/low ADHD medication groups (see **Table III**). Thus, it is very likely that our results failed to detect a significant difference in inattention ratings between females in the ADHD medication use and the no/low use groups because of inherently high inattention scores

in the latter. Moreover, the fact that medicated boys and girls reported almost identical inattention scores at 15 years (see Table III) further indicates that the association between childhood ADHD medication use and inattention symptoms in adolescence does not differ by sex. In general, findings in the present study suggest that childhood ADHD medication use is associated with the persistence of certain types of ADHD symptoms in adolescence. Furthermore, our results indicate that children with ADHD have ongoing problems with inattention in adolescence, despite the use of medication treatment, relative to their non-medicated counterparts. Comparable observations were made in the MTA study, which reported that treated ADHD children had significantly greater ADHD symptom scores (particularly for inattention) compared to their non-ADHD classmates at the eight-year follow-up. Thus, researchers from that investigation concluded that medication generally failed to "normalize" ADHD children (Molina et al. 2009). In other studies of youth with ADHD, the use of medication during childhood was also associated with the persistence of ADHD symptoms in adulthood (Biederman et al. 2012; Caye et al. 2016; Kessler et al. 2005). Due to methodological limitations, we were unable to further investigate why childhood ADHD medication use was related to inattention but not hyperactivity nor impulsivity symptoms at 15 years. There is evidence showing that, in children with ADHD, hyperactivity/impulsivity decreases over time, while inattention persists (Biederman et al. 2000; Hart et al. 1995). In the present study, the use of medication for ADHD in children may therefore reflect the phenotypic presentation of ADHD rather than the normalization of its symptoms.

Associations between childhood ADHD medication use and adolescent depression and anxiety symptoms at 15 years

Lastly, based on the data for males, the use of medication for ADHD during childhood was associated with depression but not anxiety symptoms in adolescence. While the results from multiple regression analyses initially suggested that ADHD medication use was related to lower depression and anxiety in adolescent females, a more detailed examination of the data suggests otherwise. First, the elevated levels of depression and anxiety symptoms reported by adolescent girls in the no/low ADHD medication use group most likely reversed or obscured the direction of associations for females. Second, within the ADHD medication use groups, girls displayed

higher levels of depression and anxiety than boys in adolescence. This further supported that the association between childhood ADHD medication use and symptoms of mood disorders in adolescence does not differ by sex. In sum, our findings imply that children with ADHD are at an increased risk of higher levels of depression at 15 years, even with the use of medication, compared to their non-medicated peers. Existing research shows that children with ADHD are more likely to develop mood disorders (Blackman et al. 2005; Smith et al. 2010; Williams et al. 2008), especially affected girls (Gershon 2002; Lahey et al. 2007; Rucklidge and Tannock 2001). In the current study, we could not determine whether medication reduced or increased the risk of later depression in youth with ADHD, as suggested by some long-term treatment studies (Biederman et al. 2009; Chang et al. 2016; Currie et al. 2014; Daviss et al. 2008; Jerrell et al. 2015; Molina et al. 2009), because we did not have a non-medicated ADHD comparison group. However, our results suggest that childhood ADHD medication use is not associated with the normalization (referring to the no/low ADHD medication use group in males) of depression symptoms in adolescence.

Limitations

Several limitations should be considered when interpreting the findings of this study. First, due to the non-clinical nature of the current research, clinical diagnostic information on ADHD was not provided. Thus, without a separate sample of ADHD children, we were only able to compare participants who did not use ADHD medication during childhood to those who did. This approach is equivalent to comparing medicated children with ADHD to normal controls without ADHD. However, these two groups were likely to differ on many levels in addition to their medication status. To minimize potential bias associated with group differences, we adjusted for a range of factors such as childhood behavioral problems (before the initiation of medication treatment) and sociodemographic data. We did not control for childhood symptoms of hyperactivity/impulsivity, inattention, depression and anxiety during the period of treatment (6-15 years) since medication could have influenced their ratings and in turn confounded our results. Second, although symptoms of mental health problems in adolescence were measured by a well-validated questionnaire, it did not asses all DSM symptoms of hyperactivity,

impulsivity, inattention, depression and anxiety. Moreover, the scales used to measure inattention and hyperactivity had acceptable but not very strong psychometric properties. The limitations of this assessment tool suggest that more stringent measures of mental health problems should be used in this field of research. Third, findings relevant to female sex may have been underpowered due to the small number of medicated females. This limits the generalizability of our results to other samples of girls with ADHD. Fourth, the continued use of medication could not be assessed in this investigation due to missing data for different individuals at various time points. Nonetheless, group-based trajectory modeling enabled us to identify distinct ADHD medication groups and discern their patterns of use across time. Fifth, as with almost all longitudinal studies there was sample attrition. However, additional analyses with inverse probability weights showed that attrition bias was unlikely. Sixth, ADHD severity was not measured in this study. Existing research indicates that it is related to both medication use and persistence of ADHD later in life (Caye et al. 2016; Kessler et al. 2005; Langley et al. 2010). Hence, future studies should account for the severity of ADHD when examining the relationship between the use of ADHD medication in childhood and long-term mental health outcomes. Seventh, since there was no information on dosage, intensity of treatment and adherence to medication, we were unable to determine the impact of these factors on our results. Eighth, other factors that were not measured in this research, may have influenced the associations between childhood ADHD medication use and symptoms of mental health problems in adolescence. Finally, it is important to acknowledge that the correlational design of the current study prevents us from making any causal inferences.

Conclusion

In Quebec, boys generally began receiving ADHD medication during middle childhood or adolescence whereas girls mainly started during adolescence. Childhood ADHD medication use was associated with higher levels of inattention and depression in adolescence. These results indicate that, despite the use of medication, children with ADHD have persistent problems with inattention and depressive mood compared to their non-medicated peers at 15 years. Sex differences were not reported in this study due to inconclusive data for females. Yet, our data

seems to suggest that girls and boys medicated for ADHD have similar symptoms of mental health problems in their teens. Overall, our research clearly suggests that future studies should thoroughly examine the long-term effectiveness of ADHD drugs and their effect on the subsequent development of depression in children with ADHD.

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Chapter 5: Discussion

5.1 Summary and interpretation of main findings

The objectives of this research were two-fold: 1) To identify the longitudinal trends of childhood ADHD medication use in distinct groups of boys and girls over a 10-year period in a large Canadian (Quebec) population sample and 2) To determine whether the use of ADHD medication during childhood is associated with symptoms of hyperactivity, impulsivity, inattention, depression and anxiety in adolescence. As expected, we observed three main trajectories of medication use between the ages of 3.5 and 15 years in both sexes: no/low ADHD medication use, early- and late-onset use. Significant sex differences were noted in the shapes and proportions of individuals in each trajectory. Overall, we concluded that boys begin receiving pharmacological treatment for ADHD during middle childhood or adolescence. Girls, however, generally start using ADHD medication in adolescence. Contrary to our hypothesis, medication use during childhood was associated with higher levels of some symptoms of ADHD in adolescence. Specifically, children who used ADHD medication reported higher levels of inattention at 15 years compared to those who did no use ADHD medication. In line with our prediction, childhood ADHD medication use was positively related to depression symptoms in adolescence. Because of inconsistent results for females, we were unable draw any strong conclusions regarding sex differences in the associations between medication treatment of ADHD during childhood and symptoms of mental health problems in adolescence. Nevertheless, our data appears to indicate that boys and girls medicated for ADHD during childhood have similar mental health outcomes in adolescence.

5.1.1 Trajectories of childhood ADHD medication use

To our knowledge, this is the first study that used group-based trajectory modeling to identify groups of children with differential patterns of ADHD medication use. This method presents numerous advantages over traditional ways of measuring medication use. First, it allowed us to observe the temporal patterns of medication treatment in separate groups over time, which would not have been possible if we assigned children into different groups based on pre-

determined cut points. Second, it does not exclude subjects with missing data and instead uses their valid information for trajectory estimations. Overall, we obtained with this procedure a general portrait of the dynamic prevalence of childhood ADHD medication use among children in Quebec between 2001 and 2013.

Based on the models, three groups of children followed distinct trajectories: 1) no/low ADHD medication use, 2) early-onset use and 3) late-onset use. The no/low ADHD medication use group represented 80.5% of boys and 92% of girls and had a low probability of ADHD medication use across the whole 10-year assessment period. The early-onset trajectories were different between sexes: 9.2% of boys and only 1.7% of girls were in this group. The late-onset categories consisted of 10.3% and 5.9% of boys and girls respectively. Early- and late-onset boys followed sharply rising trajectories followed by a plateau (12-15 years). The late-onset trajectory for girls was similar in shape to that of boys, but early-onset girls followed a sharply rising and then declining early-onset trajectory.

In line with previous studies, we observed differences between boys and girls in ADHD medication use (Brault and Lacourse 2012; McCarthy et al. 2012; Zuvekas and Vitiello 2012). For example, we noted that boys began using medication for ADHD during early school years (6-8 years old) or adolescence (10-15 years old). Most girls, however, were not medicated during childhood: only 14 started using medication between six and eight years of age. They primarily started receiving ADHD medication during adolescence (8-15 years). These results show that, in general, males are more medicated than females, (Galera et al. 2014; Zuvekas and Vitiello 2012), but specifically during early childhood (Brault and Lacourse 2012). This can perhaps be explained by the fact that girls with ADHD display less externalizing behavior problems and are thus less likely to be medicated (Levy et al. 2005).

5.1.2 Associations between childhood ADHD medication use and adolescent hyperactivity, impulsivity and inattention symptoms at 15 years

Childhood ADHD medication use was not associated with hyperactivity nor impulsivity symptoms in adolescence. However, medicated boys self-reported higher levels of inattention at 15 years compared to non-medicated boys. The analysis did not indicate a significant difference in inattention scores between female medication groups. Yet, medicated girls reported inattention ratings equal to those of medicated boys in adolescence. Hence, these results suggest that females medicated for ADHD during childhood were more similar than different to medicated males in terms of their levels of inattention at 15 years. Overall, our findings indicate that childhood ADHD medication use is associated with the persistence of some types of symptoms of ADHD. Specifically, we noted that children with ADHD continue to have significant problems with inattention in adolescence, despite the use of medication, in comparison to their non-medicated peers. Our results are consistent with findings from the MTA study, in which researchers reported that children with ADHD who received treatment had poorer ADHD outcomes (especially inattention) than their normal non-ADHD counterparts, eight years into the study (Molina et al. 2009). This showed that treatment of ADHD failed to normalize children affected by the disorder (Molina et al. 2009). In other studies of youth with ADHD, the use of medication during childhood was also associated with the persistence of ADHD symptoms in adulthood (Biederman et al. 2012; Caye et al. 2016; Kessler et al. 2005). In the current study, the higher adolescent inattention scores observed in youth medicated for ADHD during childhood may be caused by the fact that children with more severe forms of ADHD are more likely to be treated with medication and thus display higher levels of inattention symptoms (Langley et al. 2010). This, nonetheless, does not explain why childhood ADHD medication use was not associated with other types of ADHD symptoms, at 15 years, such as hyperactivity and impulsivity. There is evidence, however, supporting that hyperactivity/impulsivity typically decreases in children with ADHD, while inattention persists in adolescence (Biederman et al. 2000; Hart et al. 1995). Hence, in the present study, the use of medication for ADHD in children may reflect the phenotypic presentation of ADHD, rather than the normalization of its symptoms.

5.1.3 Associations between childhood ADHD medication use and adolescent depression symptoms at 15 years

Lastly, while ADHD medication use during childhood was positively associated with depression in adolescent males, it was negatively correlated to depression and anxiety symptoms in adolescent females (associations for girls were not statistically significant). Nonetheless, we did not conclude that the association between childhood ADHD medication use, and symptoms of depression and anxiety in adolescence differed by sex. First, the elevated levels of depression and anxiety symptoms reported by adolescent girls in the no/low ADHD medication use group most likely reversed or obscured the direction of association for females. Second, medicated girls displayed higher depression and anxiety scores than medicated boys at 15 years. Therefore, our data rather supports that females who received medication treatment for ADHD during childhood are as likely to have problems with mood disorders as their male counterparts in adolescence. Overall, our findings indicate that children with ADHD are at an increased risk of depression symptoms at 15 years, even with the use of medication, compared to their non-medicated counterparts. Previous studies found that children with ADHD are at greater risk of developing affective disorders (Blackman et al. 2005; Pliszka 1998; Smith et al. 2010; Spencer et al. 1999; Williams et al. 2008), particularly affected girls (Gershon 2002; Lahey et al. 2007; Rucklidge and Tannock 2001). In the present study, we were unable to determine whether ADHD medication increased or decreased the risk of subsequent depression in youth with ADHD, as suggested by some long-term treatment studies (Biederman et al. 2009; Chang et al. 2016; Currie et al. 2014; Daviss et al. 2008; Jerrell et al. 2015; Molina et al. 2009), because we did not have a non-medicated ADHD comparison group. Nevertheless, our research results clearly suggest that the medication treatment of ADHD during childhood was not related to the normalization of depression symptoms in adolescence.

5.2 Strengths and limitations of the study

This sudy had several strengths. First, the large population-based sample allowed us to examine the long-term outcomes (at 15 years) associated with the use of ADHD medication during childhood in a community setting. Second, the repeated assessments of ADHD medication use across a 15-year period provided an unbiased measurement of medication use. Medication groups were further identified with an empirical method, avoiding any potential bias associated with subjective categorizations. Third, the yearly assessments of child hyperactivity-impulsivity, inattention, depression and anxiety symptoms before the initiation of ADHD pharmacotherapy enabled us to control for these confounding variables more reliably. Finally, the use of continuous scales to measure symptoms of mental health problems in adolescents detected small but significant differences between medicated and non-medicated children, which would not have been possible had a categorical diagnostic tool been employed.

This study also has limitations that should be considered when interpreting its findings. First, because we did not have access to diagnostic information on ADHD, we were only able to compare users of ADHD medication to non-user of ADHD medication, which is similar to comparing medicated children with ADHD to normal controls without ADHD. However, these two groups differ on many levels. To adjust for these differences, we controlled for childhood behavioral problems before the exposure to medication (2.5-5 years) and for sociodemographic variables (at five months). These variables were chosen based on their reported association with medication use and/or outcome variables. Since ADHD medication has a direct and immediate impact on core symptoms of ADHD, controlling for these symptoms during the treatment period would have confounded our results. Thus, we did not control for symptoms of hyperactivity/impulsivity, inattention, depression and anxiety between 6 and 15 years. Second, although symptoms of mental health problems in adolescence were measured by a well-validated questionnaire, it did not asses all DSM symptoms of hyperactivity, impulsivity, inattention, depression and anxiety. Additionally, some of the scales did not have strong psychometric properties, specifically those used to measure inattention and hyperactivity. Thus, future studies should employ more reliable and accurate assessment tools of mental health problems in adolescents. Third, sex bias in self-reports may have confounded our results because

symptoms of mental health problems were reported only by the adolescents. Fourth, our results for girls were likely underpowered because the number of medicated girls was very small, which limits the generalizability of our results to other samples of ADHD girls. Fifth, due to missing data on ADHD medication use for different individuals at different time points, an assessment of continued medication use was not possible in this study. Nonetheless, by using group-based trajectory modeling, we were able to identify distinct ADHD medication groups and characterize their trajectories of use across time. Sixth, as in many other longitudinal studies, there was sample attrition. However, as the results including weights did not differ, attrition bias was shown to be unlikely. Seventh, information on ADHD severity was not available in this research. As some studies reported that ADHD severity was associated with both medication use and persistence of ADHD (Caye et al. 2016; Kessler et al. 2005; Langley et al. 2010), future studies examining the association between childhood ADHD medication use and long-term mental health outcomes should take this factor into account. Eight, there was no information on dosage, intensity of treatment or adherence to medication, which prevented us from determining how these factors affected our results. Ninth, other variables, that were not measured in this investigation may explain some of the observed associations. Lastly, it is important to note that findings in the present study do not suggest causality: they only indicate associations.

5.3 Implications

Findings in this study have certain implications in the field of public health. As previously mentioned, we identified only one sizeable medication use group for girls. In fact, our data shows that girls mainly started receiving treatment for ADHD during adolescence. Only, a small number of girls were treated during childhood. Boys, on the other hand, were almost equally medicated during childhood and adolescence. Some researchers suggest that the disorder is simply more prevalent in boys, hence reflecting the disparities in treatment rates between sexes (Quinn and Wigal 2004). There is however a growing amount of evidence showing that ADHD does not primarily occur in males. In adult samples, researchers found that the male-to-female ratio of ADHD diagnoses decreases with age (Willcutt 2012). Boys are more likely to be medicated than girls because they display more externalizing behaviors of ADHD (Rucklidge

2010). Girls are characterized by having an inattentive type of ADHD with internalizing symptoms, hence making it difficult to identify and diagnose the disorder (Biederman et al. 2004; Levy et al. 2005). The underdiagnoses of ADHD in girls and their subsequent undertreatment is alarming since studies found that girls are more negatively affected by ADHD than their male counterparts. For instance, girls with ADHD are more likely to experience poor peer relationships, have lower self-esteem and be bullied in school than boys with ADHD (Elkins et al. 2011; Rucklidge 2010). This calls for the development of gender-appropriate diagnostic criteria and diagnostic tools to better identify ADHD in girls, thereby allowing them to receive appropriate treatment and prevent the occurrence of negative problems associated with ADHD.

This research also shows that children with ADHD have ongoing problems with inattention in adolescence despite the use of ADHD medication in comparison to their non-medicated counterparts. Although the limitations of this study prevented us from making any causal inferences, our study findings strongly suggest that the long-term effectiveness of ADHD medication should be further reviewed and researched. Moreover, our results highlight the importance of comparing the outcomes of children treated for ADHD to those without the disorder in order to determine whether medication "normalizes" children with ADHD. Since the persistence of ADHD symptoms is associated with academic, social and family problems (Biederman et al. 2006; Caci et al. 2014; Coghill et al. 2008), future studies should focus more on the development of effective sustainable treatments that seek to normalize, rather than simply improve symptoms of ADHD in affected youth (Steele et al. 2006).

Finally, we found that children with ADHD are at increased risk of depression symptoms in adolescence than their non-medicated counterparts, despite the use of ADHD medication. While depression is known to occur with ADHD at high rates (Angold et al. 1999; Pliszka 1998), it typically appears several years after the onset of ADHD (Biederman et al. 1995). Moreover, the co-occurrence of depression and ADHD is related to greater risks of long-term impairment, morbidity and mortality (Daviss 2008). Thus, consistent with this information, our findings

indicate that there is a great need to pursue further research in order to develop early interventions approaches that will prevent the onset of comorbid mood disorders in children with ADHD. Clinicians, treating youth with ADHD, should also monitor their patients very closely for signs of depression symptoms.

5.4 Further research

Due to the correlational design of this research, we were not unable to make any causal inferences about the long-term effects of ADHD medication in children. This study also relied on data drawn from the Quebec Longitudinal Study of Child Development (QLSCD). The QLSCD, however, had limited amount of available information. For instance, clinical diagnostic information on ADHD was not provided, which prevented us from comparing medicated ADHD children to non-medicated ADHD children.

An ideal study with the capacity to determine the long-terms effectiveness and effect of ADHD medication on the risk of developing affective disorders in children with ADHD would be a prospective, randomized, placebo-controlled trial. In such study, treatment would be continued for several years for a group of randomly selected children while simultaneously collecting data on child, family and environment characteristics longitudinally for non-medicated ADHD, medicated ADHD subjects and a normal control group without ADHD. Unfortunately, this type of research would raise numerous ethical issues because it requires withholding medical treatment for some ADHD children for an extended period time, as well as continuing to medicate individuals who no longer desire being medicated. Thus, such study is not feasible a real world setting.

Nonetheless, there are ways to improve future research designs by making certain methodological changes. First, a large population-based cohort sample should be identified, containing a subsample of ADHD children. Second, ADHD medication use should be measured yearly for all participants. Third, symptoms of hyperactivity, impulsivity, inattention and other

comorbid disorders should be assessed annually before, during and after medication exposure, for all participants. Other risk factors predicting ADHD, depression and anxiety later in life should be considered as well.

Chapter 6: Conclusion

The present study contributed to the existing knowledge regarding the use of ADHD medication in children and its association with long-term mental health outcomes. Specifically, it identified distinct trends of ADHD medication use in specific groups of children over time and tested the whether its use was associated with symptoms of mental health problems in adolescence. Children in the early-onset trajectory group mainly began using medication for ADHD during middle childhood whereas those in the late-onset trajectory started in adolescence. The trajectories of use also showed that boys start using ADHD medication during childhood or adolescence while girls mainly begin in adolescence. The use of ADHD medication during childhood was associated with higher levels of inattention at 15 years. Moreover, it was related to an increased risk of depression symptoms in adolescence. Thus, children with ADHD had ongoing problems with inattention and depressive mood in their teens even with the use of medication treatment. Because of inconclusive results for females, we were unable to conclude whether sex differences existed for the measured associations. However, our data tends to indicate that females medicated for ADHD during childhood were more similar rather than different to their male counterparts regarding their adolescent mental health outcomes. More rigorous research is needed to determine the long-term effects of ADHD medication on mental health.

At a time when prescription rates of ADHD drugs are greatly increasing, this study provides information on the patterns of medication use in children and on the long-term outcomes related with the use of ADHD medication. This knowledge can contribute to the future prevention of negative outcomes associated with ADHD.

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Appendix A: Parent consent form

2	-	0	3	-		-		-			-					-			
1		2	3		4		5		6	7		8	9	10	11		12	13	14

Québec Longitudinal Study of Child Development
QLSCD (E6) - Round 2003

Informed consent form

I understand that this form is part of the study entitled « In 2002… I was 5 years old! ». I have been advised that the PURPOSE of this study is to collect information about factors influencing child development in Québec.

I understand that my participation in this study is entirely VOLUNTARY, of MY OWN FREE WILL, and that the information I provide will be handled CONFIDENTIALLY and that I will NOT BE PERSONALLY IDENTIFIED in the reporting of the results. All information that I provide about ME, MY SPOUSE OR MY CHILD/CHILDREN or of which I authorize the use, will be handled and protected as required by the *Act respecting the INSTITUT DE LA STATISTIQUE DU QUÉBEC* and AN ACT RESPECTING ACCESS TO DOCUMENTS HELD BY PUBLIC BODIES AND THE PROTECTION OF PERSONAL INFORMATION. The Québec Access to Information Commission authorized the *ministère de la Santé et des Services sociaux* to give the *Direction Santé Québec* of the *Institut de la statistique du Québec* my address, which was used to contact me.

I understand that an interviewer selected by the *Direction Santé Québec* of the *ISQ/BIP* will call me at home to complete the questionnaires with me. I was informed that the telephone interview lasts about 1 hour and 30 minutes. I will also receive questionnaires by mail to be filled out by me/my spouse and returned by mail. A group of researchers from the *Université de Montréal* and their research assistants will invite my child to play some simple games with him/her, lasting about 35 to 45 minutes, at the daycare or kindergarten attended by my child or at home, whichever is more convenient for me.

I also understand that to confirm my participation in the other parts of this annual study, the *Direction Santé Québec* of the *ISQ* will contact me over the next year.

I, the undersigned, freely agree to take part in this longitudinal study. I certify that the study has been verbally explained to me, that all my questions have been answered and that I was given enough time to come to this decision on my own.

I, the undersigned, further understand that I may withdraw my consent to participate at any time without penalty to me in any way.

Signature of Respondent	Signature of Respondent	Date

Consent Form for Data Sharing

I hereby authorize the *Institut de la statistique du Québec* to send data collected on me or on the people I represent as long as it is not identified (i.e., not revealing the name, address and telephone number) to research groups affiliated with five Québec universities, that is: *Université Laval*, *Université de Montréal*, Concordia University, *Université de Sherbrooke* and McGill University, as well as the *ministères de la Santé et des Services sociaux, de la Famille et de l'Enfance, de l'Emploi et de la Solidarité sociale* and *de l'Éducation*. I understand that I can obtain the list of these researchers upon request, and that these researchers will have signed a confidentiality agreement before my data or that of the people I represent are transmitted to them.

Signature of Respondent	Date
Signature of Respondent	

Appendix B: Teenager consent form

Institut de la statistique Québec

I AM, I'LL BE
THE SURVEY ON THE FUTURE OF A GENERATION

Québec Longitudinal Study of Child Development
QLSCD (E18) – 2015 Round

Consent Form for the Teenage Participant

1. I authorize the Institut de la statistique du Québec (Statistique Québec) to:

1.1. Have me fill out an online questionnaire at home, by myself, with the goal of collecting data on my development and environment;

1.2. Send data collected on me, in an anonymous form (i.e., not revealing my name, address and telephone number) to affiliated researchers who will have committed to respecting Statistique Québec's standards regarding the security and confidentiality of information.

2. I understand that :

2.1. The list of affiliated researchers can be given to me upon request, and that these researchers will have signed a confidentiality agreement before anonymous data (i.e., not revealing my name, address and telephone number) on me are sent to them;

2.2. This consent form is part of the study entitled *I am, I'll be*. I have been advised that the purpose of this study is to collect information that will help gain a better understanding of factors that can influence youth development and success in school in Québec;

2.3. To confirm my participation in future rounds of this study, Statistique Québec will contact me in the coming years;

2.4. Statistique Québec will send me an email containing the information I need to access my online questionnaire, or a Statistique Québec employee will contact my parent and me to arrange a visit at home during which I can fill out my online questionnaire using a netbook provided by the interviewer. Completing the questionnaire will take 60 to 75 minutes;

2.5. My participation in this study is entirely VOLUNTARY, of MY OWN FREE WILL;

2.6. I freely consent to take part in this longitudinal study;

Continued on reverse

2.7. I am free to withdraw my consent to participate at any time without penalty to me in any way;

2.8. The information I provide will be treated as CONFIDENTIAL, handled and protected in accordance with the ACT RESPECTING THE INSTITUT DE LA STATISTIQUE DU QUÉBEC and the ACT RESPECTING ACCESS TO DOCUMENTS HELD BY PUBLIC BODIES AND THE PROTECTION OF PERSONAL INFORMATION.

Before filling out your questionnaire, you should consent to the following clause:

3. I agree:

3.1. To freely take part in this longitudinal study. I certify that I was given enough time to come to this decision on my own.

You don't have to send us back this form. However, please keep it for your files.

Appendix C: QLSCD study ethics approval

Montréal, le 10 mars 1998

Monsieur Richard Tremblay
Université de Montréal - GRIP
350, Édouard-Montpetit
C.P. 6128
Montréal (Québec) H3C 3J7

Objet: Enquête Santé Québec «En 2002 j'aurai 5 ans» Phase I

Cher monsieur Tremblay,

Lors de sa dernière réunion tenue le 12 février dernier, le comité d'éthique de Santé Québec a étudié le projet en titre.

Le comité, après discussion, réserve pour le moment sa décision quant à l'approbation du dit projet et désirerait obtenir des précisions supplémentaires. Le comité approuvera le projet dès que les précisions et correctifs seront apportés à sa satisfaction.

Les éléments suivants pourraient être précisés davantage :

- Simplifier la lettre de consentement éclairé dont les termes apparaissent comme hermétiques et peu accessibles au commun des mortels d'y inclure de l'information simplifiée expliquant la nature du projet.
- Présenter une procédure claire et finale de transfert et de garde des données.

Veuillez agréer, Cher Monsieur Tremblay, l'expression de nos sentiments distingués.

Pierre Durand
Président du comité d'éthique

c.c. Daniel Tremblay, directeur de Santé Québec
Mireille Jetté, coordonnateur du projet

Appendix D: QLSC protocol ethics approval

10-06-'10 16:08 DE- T-050 P0002/0002 F-119

Institut de la statistique Québec

Phase II : E7 à E13 (2004 à 2010)
→ Sur la base du protocole des collectes E7 (enquête) et P9 (pré-test).
PERTRAND PERRON

Montréal, le 21 janvier 2004

Monsieur Daniel Tremblay, directeur
Direction Santé Québec
Institut de la statistique du Québec
1200, avenue McGill College, 5e étage
Montréal (Québec) H3B 4J8

Monsieur,

Le comité d'éthique de l'Institut de la statistique du Québec vous remercie d'avoir participé à sa rencontre du 9 janvier dernier afin de lui présenter votre Protocole de recherche du nouveau cycle de l'étude longitudinale sur le développement des enfants au Québec (ELDEQ).

Le comité a approuvé ce protocole de recherche sous réserve des conditions suivantes :

1. S'assurer que l'ISQ possède l'autorisation des familles à les contacter de nouveau;
2. Produire une lettre, une note ou un dépliant à l'intention des répondants afin de les informer des détails et de leur implication réelle;
3. Produire un rapport annuel au comité d'éthique et lui soumettre toute modification majeur ou nouveau volet;
4. S'assurer que les listes nominatives soient retournées à l'ISQ à la fin de chaque collecte.

Le comité vous saurait gré de faire le suivi avec lui relativement aux conditions mentionnées ci-haut.

Veuillez agréer, Monsieur, l'expression de mes sentiments les meilleurs.

[redacted]

PD/JB

Pierre Durand, président
Comité d'éthique de l'Institut de la statistique du Québec

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Téléphone : (514) 864-8686
Télécopieur : (514) 873-4803

Appendix E: Ethics approval by the University of Montreal health research ethics committee

Université de Montréal

N° de certificat
16-094-CERES-D

Comité d'éthique de la recherche en santé

CERTIFICAT D'APPROBATION ÉTHIQUE

Le Comité d'éthique de la recherche en santé (CERES), selon les procédures en vigueur, en vertu des documents qui lui ont été fournis, a examiné le projet de recherche suivant et conclu qu'il respecte les règles d'éthique énoncées dans la Politique sur la recherche avec des êtres humains *de l'Université de Montréal.*

Projet	
Titre du projet	**A longitudinal study of the association between childhood ADHD medication use and adolescent depressive/anxiety symptoms**
Étudiante requérante	**Alina Sabirova** [redacted] Candidate à la M. Sc. en santé publique, École de santé publique - Département de médecine sociale et préventive
Sous la direction de	Sylvana Côté, professeure titulaire, École de santé publique - Département de médecine sociale et préventive, Université de Montréal

Financement	
Organisme	Non financé
Programme	
Titre de l'octroi si différent	
Numéro d'octroi	
Chercheur principal	
No de compte	

MODALITÉS D'APPLICATION

Tout changement anticipé au protocole de recherche doit être communiqué au CERES qui en évaluera l'impact au chapitre de l'éthique.

Toute interruption prématurée du projet ou tout incident grave doit être immédiatement signalé au CERES

Selon les règles universitaires en vigueur, un suivi annuel est minimalement exigé pour maintenir la validité de la présente approbation éthique, et ce, jusqu'à la fin du projet. Le questionnaire de suivi est disponible sur la page web du CERES.

[redacted]

Dominique Langelier, présidente
Comité d'éthique de la recherche en santé
Université de Montréal

7 juin 2016
Date de délivrance

1er juillet 2017
Date de fin de validité

Guillaume Pouliot, conseiller en éthique de la recherche pour Dominique Langelier.

adresse postale
C.P. 6128, succ. Centre-ville
Montréal QC H3C 3J7

3744 Jean-Brillant
4e étage, bur. 430-11
Montréal QC H3T 1P1

Téléphone : 514-343-6111 poste 2604
ceres@umontreal.ca
www.ceres.umontreal.ca

Appendix F: Items for Mental Health Assessments of Adolescents

1) Hyperactivity (4): “I felt very restless, I was constantly on the move”, “I often stood up in class or in other situations where I was supposed to remain seated”, “I often had trouble staying calm during games or leisure activities” and “I moved my hands and feet, I wriggled in my chair”.

2) Impulsivity (6): “I was impulsive (reacted quickly without thinking)”, “I said things before thinking them through”, “I did or said things without stopping to think”, “I had difficulty waiting for my turn in games or group activities”, “I often blurted out the answer to a question that hadn't yet been completely asked” and “I got into trouble because I did things without thinking”.

3) Inattention (6): “I was inattentive, I had difficulty paying attention to what someone was saying or doing”, “I completed all of my tasks or homework, I was able to stay focused. (reverse coding)”, “I had trouble keeping my mind on what I was doing for more than a few minutes”, “I forgot what I was supposed to be doing or what I had planned to do”, “I avoided doing things where I needed to pay attention for a long time” and “I made a lot of mistakes because it was hard for me to do things carefully”.

4) Depression (8): “Nothing was fun for me, I wasn't interested in anything”, “I felt sad and unhappy”, “I lacked energy or felt tired”, “I lost interest in things I usually like”, “I felt I couldn't do anything well”, “I wasn't as good-looking or as smart as other people”, “Doing even little things made me feel really tired” and “I had trouble thinking clearly”.

5) Anxiety (9): “I was too fearful or nervous”, “I had worries that interfered with my everyday life”, “I worried about my past behaviour”, “I worried about my school work”, “I worried about my own health”, “I worried about my loved ones (family, friends)”, “I worried about my relationships with my friends (i.e. making and keeping friends)”, “I was concerned about my appearance or weight” and “I found it difficult to control the worry”.

Appendix G: Items for Mental Health Assessments of Children

1) Hyperactivity-impulsivity (6): "could not sit still, was restless and hyperactive", "could not stop fidgeting", "was impulsive and acted without thinking'", "had difficulty waiting for his/her turn in games", "could not settle down to do anything for more than a few moments" and "was unable to wait when someone promised him/her something".

2) Inattention (3): "was unable to concentrate, could not pay attention for long", "was easily distracted, had trouble sticking to any activity" and "was inattentive".

3) Depression (4): "seemed to be unhappy or sad", "was not as happy as other children", "had trouble enjoying him/herself" and "had no energy, was feeling tired".

4) Anxiety (4): "was too fearful or anxious", "was worried", "cried a lot" and "was nervous, high strung or tense".

Appendix H: Supplementary tables

Supplementary Table I. Number of medicated children according to childhood ADHD medication use trajectory at each time point in the initial sample (n=1995)

	Boys (n=1007)				Girls (n=988)			
	Trajectory group				Trajectory group			
On medication [n, (%)]	No/low ADHD medication use* (n=847)	Early onset (n=74)	Late onset (n=86)	Missing data (n)	No/low ADHD medication use* (n=928)	Early onset (n=14)	Late onset (n=46)	Missing data (n)
3.5 years	2(0.2)	0(0)	0(0)	28	1(0.1)	0(0)	0(0)	17
4.5 years	0(0)	2(2.7)	0(0)	30	1(0.1)	0(0)	0(0)	21
5 years	1(0.1)	2(2.7)	0(0)	132	0(0)	1(7.1)	0(0)	104
6 years	1(0.1)	17(23.0)	0(0)	273	2(0.2)	3(21.4)	0(0)	231
7 years	4(0.5)	42(56.8)	0(0)	277	0(0)	12(85.7)	0(0)	190
8 years	2(0.2)	58(78.4)	0(0)	310	2(0.2)	13(92.9)	7(15.2)	234
10 years	2(0.2)	56(75.7)	26(30.2)	372	1(0.1)	11(78.6)	20(43.5)	290
12 years	3(0.4)	54(73.0)	48(55.8)	325	3(0.3)	6(42.9)	32(69.6)	275
13 years	0(0)	48(64.9)	50(58.1)	404	2(0.3)	7(50.0)	37(80.4)	301
15 years	1(0.1)	45(60.8)	58(67.4)	332	8(0.9)	5(35.7)	38(82.6)	265

*Children classified in the no ADHD medication use group never used ADHD medication or in rare cases had a short and inconsistent history of pharmacological treatment that never exceeded 12 month

Supplementary II. Number of medicated children according to childhood ADHD medication use trajectory at each time point in the final sample (n=1443)

	Boys (n=690)				Girls (n=753)			
	Trajectory group				Trajectory group			
On medication [n, (%)]	No/low ADHD medication use* (n=559)	Early onset (n=59)	Late onset (n=72)	Missing data (n)	No/low ADHD medication use* (n=701)	Early onset (n=12)	Late onset (n=40)	Missing data (n)
3.5 years	2(0.4)	0(0)	0(0)	18	1(0.1)	0(0)	0(0)	10
4.5 years	0(0)	1(1.7)	0(0)	15	1(0.1)	0(0)	0(0)	11
5 years	0(0)	2(3.4)	0(0)	60	0(0)	1(8.3)	0(0)	47
6 years	1(0.2)	12(20.3)	0(0)	107	1(0.1)	3(25.0)	0(0)	104
7 years	2(0.4)	32(54.2)	0(0)	94	0(0)	10(83.3)	0(0)	75
8 years	2(0.4)	50(84.7)	0(0)	109	1(0.1)	11(91.7)	7(17.5)	93
10 years	2(0.4)	50(84.7)	22(30.6)	131	1(0.1)	9(75.0)	19(47.5)	123
12 years	3(0.5)	44(74.6)	38(52.8)	83	3(0.4)	6(50.0)	28(70.0)	97
13 years	0(0)	43(72.9)	45(62.5)	130	2(0.3)	7(58.3)	33(82.5)	108
15 years	1(0.2)	41(69.5)	58(80.6)	30	8(1.1)	5(41.7)	37(92.5)	37

*Children classified in the no ADHD medication use trajectory never used ADHD medication or in rare cases had a short and inconsistent history of pharmacological treatment that never exceeded 12 month

Supplementary Table III. Number of medicated children accord no ADHD medication use and the ADHD medication use groups at each time point in the final sample (n=1443)

	Boys (n=690)			Girls (n=753)		
On medication [n, (%)]	No ADHD medication use[a] (n=559)	ADHD medication use[b] (n=131)	Missing data (n)	No ADHD medication use[a] (n=701)	ADHD medication use[b] (n=52)	Missing data (n)
3.5 years	2 (0.4)	0 (0)	18	1 (0.1)	0 (0)	10
4.5 years	0 (0)	1 (0.8)	15	1 (0.1)	0 (0)	11
5 years	0 (0)	2 (1.5)	60	0 (0)	1 (1.9)	47
6 years	1 (0.2)	12 (9.2)	107	1 (0.1)	3 (5.8)	104
7 years	2 (0.4)	32 (24.4)	94	0 (0)	10 (19.2)	75
8 years	2 (0.4)	50 (38.2)	109	1 (0.1)	18 (34.6)	93
10 years	2 (0.4)	72 (55.0)	131	1 (0.1)	28 (53.9)	123
12 years	3 (0.5)	82 (62.6)	83	3 (0.4)	34 (65.4)	97
13 years	0 (0)	88 (67.2)	130	2 (0.3)	40 (76.9)	108
15 years	1 (0.2)	99 (75.6)	30	8* (1.1)	42 (80.8)	37

[a]Children classified in the no ADHD use group never used ADHD medication or in rare cases had a short and inconsistent history of pharmacological treatment that never exceeded 12 month.

[b]ADHD medication use group combines children from the early and late onset of ADHD medication use trajectories.

Supplementary Table IV. Estimated marginal means for adolescent mental health symptoms by ADHD medication use groups

Number of mental health symptoms at 15 years	Stimulant medication use group	Boys					Girls				
		Mean	SE	95% CI		*p* value[b]	Mean	SE	95 % CI		*p* value[b]
Hyperactivity	No ADHD medication use	2.51	0.14	2.23	2.23	0.126	2.73	0.13	2.48	2.99	0.906
	ADHD medication use[a]	2.84	0.21	2.42	2.42		2.77	0.32	2.14	3.40	
Impulsivity	No ADHD medication use	2.69	0.14	2.42	2.96	0.370	2.96	0.12	2.73	3.18	0.899
	ADHD medication use[a]	2.87	0.20	2.48	3.27		2.99	0.29	2.43	3.55	
Inattention	No ADHD medication use	2.99	0.13	2.74	3.24	<0.001	3.63	0.12	3.39	3.88	0.186
	ADHD medication use[a]	3.92	0.19	3.55	4.29		4.03	0.30	3.44	4.63	
Depression	No ADHD medication use	2.43	0.13	0.13	0.13	0.029	4.37	0.14	4.11	4.64	0.076
	ADHD medication use[a]	2.86	0.20	0.20	0.20		3.78	0.33	3.13	4.44	
Anxiety	No ADHD medication use	3.12	0.13	2.86	3.38	0.778	4.95	0.13	4.70	5.20	0.054
	ADHD medication use[a]	3.18	0.20	2.79	3.57		4.35	0.31	3.73	4.9	

[a]ADHD medication use group combines children the early and late onset of ADHD medication use trajectories.
[b]*p* values were calculated by using two-sample (independent) *t*-tests.