Université de Montréal

Age, Period, and Cohort Effects on Adult Mortality due to Extrinsic Causes of Death

par

Enrique Acosta

Unité académique département de démographie

Faculté des arts et des sciences

Thèse présentée à la Faculté des études supérieures et postdoctorales

en vue de l'obtention du grade de

Philosophiæ Doctor (Ph.D.)

en démographie

Octobre 2019

Université de Montréal

Faculté des études supérieures

Cette thèse intitulée

Age, Period, and Cohort Effects on Adult Mortality due to Extrinsic Causes of Death

présentée par

Enrique Acosta

a été évaluée par un jury composé des personnes suivantes :

Simona Bignami

(président-rapporteur)

Alain Gagnon

(directeur de recherche)

Nadine Ouellette

(codirectrice de recherche)

Yves Carrière

(membre du jury)

Andrew Noymer

(examinateur externe)

Simona Bignami

(représentante du doyen de la FAS)

Résumé

Après des décennies d'amélioration, l'espérance de vie a stagné dans plusieurs pays à faible mortalité ces dernières années, avec, dans certains cas, quelques reculs. L'augmentation de la mortalité due à la grippe et aux surdoses de drogue, en particulier dans la génération des baby-boomers, a été le principal responsable de cette stagnation de l'espérance de vie. Cette découverte était inattendue, car il est considéré que la mortalité extrinsèque – par opposition à la mortalité intrinsèque due à des maladies dégénératives se déclarant souvent aux grands âges – joue un rôle négligeable dans les changements actuels d'espérance de vie. Pour la même raison, les tendances temporelles de la mortalité extrinsèque n'ont guère retenu l'attention des chercheurs. Les crises périodiques dues aux épidémies de grippe et à la crise des opioïdes sont considérées comme les principaux déterminants des variations de la mortalité extrinsèque. Cependant, des preuves récentes suggèrent que les effets de cohorte jouent un rôle important dans la modulation de la mortalité extrinsèque, mais que de telles influences sont encore mal connues.

L'objectif principal de cette thèse est d'examiner le rôle des effets de cohorte sur l'évolution de la mortalité extrinsèque dans les dernières décennies, avec un accent particulier mis sur la grippe et les causes de décès comportementales. Plus spécifiquement, elle vise à (1) déterminer les différences par cohorte de mortalité par la grippe et l'influence des expositions précoces au virus sur cette mortalité; (2) analyser le désavantage de mortalité des baby-boomers au Canada et aux États-Unis en identifiant la contribution des causes comportementales à ce désavantage; et (3) développer un outil méthodologique permettant à la fois l'analyse visuelle de la dynamique temporelle des effets non linéaires d'âge, de période et de cohorte (APC) et la comparaison entre divers phénomènes ou populations.

Pour ces analyses, nous utilisons des micro-données de mortalité provenant de systèmes de statistiques de l'état civil au Canada et aux États-Unis. Nous utilisons également les taux de mortalité et de fécondité de divers pays pour généraliser l'analyse visuelle des effets non linéaires à d'autres phénomènes démographiques que la mortalité. Les analyses ont été réalisées en appliquant des modèles de Serfling pour l'estimation de la mortalité par grippe, des mesures démographiques permettant une décomposition par cause des variations de la mortalité, des techniques de lissage pour identifier les tendances et des approches statistiques et visuelles sur des configurations de Lexis pour l'analyse des effets APC.

Les résultats, sous la forme de trois articles scientifiques, montrent que malgré des fluctuations marquées au cours des années calendrier (période), les cohortes de naissance ont une influence indépendante et durable sur la mortalité liée à la grippe ou due au comportement. Les principaux résultats du premier article suggèrent que deux mécanismes modulent la mortalité grippale au fil des cohortes. Pour la population jeune et adulte, les risques de mortalité par cohortes dépendent du contraste en le premier virus auquel on est vraisemblablement exposé (le virus laissant« l'empreinte antigénique ») et le virus rencontré à l'âge adulte, au moment de l'épidémie sous observation. Des modifications significatives du risque de décès ont ainsi été observées lors d'épidémies de grippes

pour les cohortes nées lors d'importants changements antigéniques (par exemple, une diminution significative du risque pour les cohortes nées entre 1957 et 1968). Pour les âges plus avancés, nous n'avons pas identifié de tels effets de cohorte « ponctuels », mais plutôt un effet de cohorte de plus longue haleine, qui aura conduit à un déclin progressif de la mortalité par grippe entre 1959 et 2016. En nous inspirant des théories dites de *technophysio* ou de *cohort morbidity phenotype*, nous attribuons ce déclin à des changements s'étant produit bien avant, c'est-à-dire à l'amélioration marqué des conditions sanitaires qui a eu lieu entre 1900 et 1930, au moment où les cohortes concernées venaient au monde et dont elles ont pu bénéficier.

Les travaux du deuxième article de cette thèse révèlent que la plupart des excès de mortalité chez les baby-boomers au Canada et aux États-Unis sont dus à des causes comportementales. Le désavantage des baby-boomers résulte de plusieurs effets de cohortes sur des causes comportementales différentes, et non pas d'effets de période ponctuels affectant la même cohorte aux âges différents, un mécanisme alternatif qui pourrait expliquer la «pénalité des boomers». Les baby-boomers présentaient respectivement un risque d'hépatite C et de mortalité par drogue trois fois et deux fois plus élevé que les cohortes voisines. La contribution méthodologique des *graphique de courbure APC*, présentée dans le troisième article, nous a permis d'analyser la dynamique des effets non linéaires au fil du temps, à travers divers phénomènes et populations. Cette technique offre une plus grande flexibilité que les modèles statistiques ou autres graphiques de Lexis.

Les résultats présentés dans cette thèse montrent l'importance d'analyser les effets de cohortes sur la mortalité extrinsèque. Nos résultats indiquent que même en présence de perturbations de période importantes affectant la mortalité extrinsèque à la plupart des âges, les effets de cohorte se sont maintenus au fil du temps. Ces résultats suggèrent également que les politiques publiques peuvent améliorer considérablement la santé de la population en formulant des politiques qui prennent en compte la sensibilité différentielle des cohortes aux facteurs de risque et en fournissant un soutien social aux cohortes les plus vulnérables.

Mots-clés : mortalité, effets d'âge-période-cohorte, causes extrinsèques, mortalité par influenza, baby-boomers, mortalité comportementale, surdose de drogues, effets de cohorte de naissance, identité générationnelle, surfaces de Lexis

Abstract

After decades of improvement, life expectancy momentarily declined during 2014-15 in several high income countries, with subsequent reversals in some cases. The main sources of this stagnation have been increases in mortality from influenza and drug overdoses, mainly for the baby-boomer generation. This trend is unexpected because it has long been assumed that extrinsic mortality, which is due to causes originating outside the body – in opposition to intrinsic mortality from degenerative diseases at old ages –, plays a negligible role in life expectancy changes. For this reason, the temporal patterns of extrinsic mortality have received little attention in demographic research. Period crises such as influenza epidemics and the opioid crisis are considered the main determinants of variations of extrinsic mortality. However, despite recent evidence suggesting that cohort effects have an important role in modulating extrinsic mortality, little is known about this relationship.

The main objective of this dissertation is to help fill this gap by examining cohort influences on extrinsic mortality change, with a particular emphasis on influenza and behavioral causes. More specifically, we aim (1) to quantify cohort differences in mortality from influenza and the influence of early life exposures to the virus on subsequent influenza mortality; (2) to analyze the baby boomers' disadvantage in mortality in Canada and the United States, while identifying the contributions of behavioral causes to this disadvantage; and (3) to develop a methodological tool that can be used to both conduct visual analysis of the temporal dynamics of nonlinear Age-Period-Cohort (APC) effects, and compare these dynamics across various phenomena or populations.

To achieve these goals, we use micro-level mortality data from vital statistics in Canada and the United States. We also employ death and fertility rates from various countries to generalize the visual analysis of nonlinear effects to other demographic phenomena. The analyses were conducted by applying Serfling models for the estimation of influenza mortality, demographic measures for the decomposition of cause-specific mortality changes, smoothing techniques for the identification of trends, and statistical and visual approaches on the Lexis configuration for the analysis of APC effects.

The results, in the form of three scientific articles, show that despite marked fluctuations over calendar years (periods), birth cohorts have an independent and sustained influence on influenza and mortality from behavioral causes. The main results from the first paper suggest that two mechanisms modulated influenza mortality over cohorts. For the young and adult population, the mortality risks over cohorts depend of the contrast between the first virus to which individuals were exposed (the virus producing an *antigenic imprinting*) and the virus encountered in adulthood during the observed epidemic. For this age segment, significant changes in risk were found during influenza epidemics among cohorts born during important antigenic shifts (e.g., a decrease in risk for cohorts born between 1957 and 1968). For older ages, we did not identify such "punctual" cohort effects but rather a smooth and monotonic change in cohort effects that might have driven a progressive decline in influenza mortality between 1959 and 2016. Inspired by so-called cohort morbidity phenotype and technophysio evolution theories, we attributed this decline to changes produced

earlier, i.e., to the sharp sanitary improvements occurred between 1900 and 1930, when the concerned cohorts were born and when they could have benefited.

Findings from the second paper revealed that most of the baby boomers' excess mortality in Canada and the United States is driven by behavioral causes of death. The "boomer disadvantage" resulted from multiple cohort effects on behavioral-related mortality, and not from punctual period effects affecting the same cohort at different ages. Among the baby boomers, the risk of dying from hepatitis C was almost three times higher, and the risk of dying from drug-related causes was almost two times higher, than among the adjacent cohorts. These results were obtained using an innovative methodology developed in the third paper, which allowed us to analyze the dynamics of nonlinear effects over time through APC curvature plots. This technique provides greater flexibility than statistical models or other Lexis plots, and it has been shown to be applicable to other demographic phenomena, such as fertility.

The findings presented in this dissertation offer evidence of the importance of analyzing cohort effects on extrinsic mortality. Our results indicate that even in the presence of substantial period disturbances affecting extrinsic mortality at most ages, cohort effects were sustained over time. These findings also suggest that public policies can significantly improve the health of the population by formulating policies that take into account the differential sensitivity of cohorts to risk factors and by providing social support to the most vulnerable cohorts.

Keywords (10/10): mortality, age-period-cohort effects, extrinsic causes, influenza mortality, baby boomers, behavioral mortality, drug overdoses, birth cohort effects, generational identity, Lexis surfaces

Contents

List of Figures

List of Tables

Dédicace

A mi mamá,

Por tu inmenso amor y apoyo incondicional, por haberme engañado haciéndome creer que era inteligente, por sacar parte de tu salario mínimo de profesora de preescolar en Colombia para comprar tomos y tomos de enciclopedias carísimas con la esperanza de que sirvieran para algo. ¡Parece que sí sirvieron!

A Ana,

Mi persona favorita del universo universal, compañera de batallas en esta locura de vida que nos inventamos juntos y que tanto me gozo a tu lado. ¡Te amo!

Remerciements

Nombreux ont été les complices de cette odyssée académique et émotionnelle qu'est le doctorat.

J'exprime mes plus vifs remerciements à Alain Gagnon, mon directeur de thèse, qui depuis mon arrivé au département de démographie de l'Université de Montréal m'a fait confiance et m'a apporté un soutien gigantesque sans lequel ce marathon n'aurait même pas commencé. Tout d'abord, son invitation à participer en tant qu'assistant de recherche au projet sur la mortalité par grippe m'a permis d'avoir le soutien financier pour commencer le doctorat. Sous sa supervision et durant le travail conjoint, j'ai énormément appris sur la rigueur scientifique et la passion pour la recherche. Mais surtout, j'ai appris par son exemple sur les responsabilités éthiques des chercheurs.

À Nadine Ouellette, ma co-directrice de thèse, pour son soutien, son exigence, sa rigueur et sa patience face à mon entêtement. Dans toutes les interactions que nous avons eues, en plus de ses précieux conseils et observations académiques, l'aspect humain a toujours prévalu.

I thank Alyson van Raalte, my research supervisor at the Max Planck Institute for Demographic Research (MPIDR), who offered financial and invaluable academic support during the final stages of this thesis, without which it would have been impossible to accomplish this mission. Her support was also crucial for obtaining the SSHRC and FRQSC postdoctoral grants, as well as the postdoctoral position at the MPIDR. I was enormously lucky for being supervised by her in the Lifespan Inequalities group and for having the opportunity to work with amazingly talented women within this team.

Le soutien financier par plusieurs organismes a été aussi vital pour faire aboutir ce projet. Je remercie le Conseil de recherches en sciences humaines (CRSH) du Canada pour le soutien financier avec la bourse des études doctorales Joseph-Armand Bombardier, aux projets de recherche IRSC sur la mortalité par grippe dirigés par Alain Gagnon, au département de démographie et à la Faculté d'études supérieures et postdoctorales de l'UdeM pour les bourses de soutien académique, au Centre interuniversitaire québécois de statistiques sociales (CIQSS), to the European Research Council (ERC) project Lifespan Inequalities, directed by Alyson van Raalte, and to the Population Health Laboratory at the MPIDR, directed by Mikko Myrskylä.

Merci au département de démographie à l'Université de Montréal. À Robert Bourbeau pour sa générosité en étant toujours disponible pour la discussion des méthodes démographiques, ainsi que

pour m'inviter à travailler à ses côtés. À Thomas Legrand, qui m'a donné l'opportunité d'apprendre beaucoup en tant qu'assistant d'enseignement et enseignant substitut dans plusieurs de ses cours, et grâce aux jumelages linguistiques que nous avons partagés. À Simona Bignami pour son soutien et amitié arrosée de très bons cafés. À l'équipe de mortalité et longévité. À Micheline Côté et Élaine Gingras, qui ont énormément facilité les démarches administratives au département et qui ont toujours eu la meilleure disposition pour l'aide.

I also must thank the MPIDR. The courses that I attended at the International Advanced Studies in Demography (IDEM) program, funded by the MPIDR, were essential for my training as a researcher in demography.

Merci à mes collègues et amis au département de démographie, Astrid, Rafael, Julie, Linh, Marianne, Lorena, Jonathan, Cristina, Michael, Catalina et Gabriel, entre autres. To all my colleagues and friends at the MPIDR, specially Marilia, Daniel, Pinar, Lunita, Rosie, Angelo, Silvia, Nicola, Viorela, Ugo, Andreas, Marcus, Tim, Ainhoa, Nicolas, and the great CineMax combo; Andrés, Chia, Diego, Emanuele, Maarten, Samin, and Sofía. Gracias mil a la familia montrealesa, sin la cual esto habría sido inaguantable. A Andrés, Lina, Nadia, Geneviève, Andres, Steph, Alejo y Stefa por tanta sabrosura. Le debo mucho a mi pex Diego, con quien compartí tantas peinadas y Sapporos demográficas que tanto definieron esta tesis.

A la mujer más fuerte y dulce que conozco, mi mamá, cuyo coraje nos sacó a los dos de la tormenta, nos puso en buena mar, y siempre ha estado ahí, empujando y amando como nadie. A mi papá, que se echó al hombro una responsabilidad ajena y gigante con tanto amor. A Xavier, que ayudó con la grata y necesaria tarea del desorden, en tantos lugares tan improbables como dispersos. A Pamela, quien fue testigo directa de la maratón de comienzo a fin, quien trajo más sol a Montreal y fue un gran apoyo a punta de amor y cereales empiyamados. A Claudia y Luis, por tanta bacanería y, sobre todo, por el apoyo y soporte durante el tsunami.

Y principalmente, quedo en deuda impagable con Ana, la más de las mases, la mera mera, quien ha estado siempre ahí, enfrentando codo a codo el vendaval, remando con verraquera a contracorriente, enseñándome tantas cosas, moliéndome el ego a golpes, ayudándome a parar cuando caigo y siempre recordándome que esto es un paseo… el mejor de los paseos con esa compañía. ¡Gracias bonita!

Chapter 1 - General Introduction

Life expectancy has almost doubled in most Western societies since the turn of the 20th century (HMD 2019; Roser 2019) – an achievement that is nothing short of spectacular. Improvements in life expectancy over the past one hundred years have surpassed any gains in longevity made during the previous thousands of years of human history (Deaton 2015; Floud et al. 2011; Fogel and Costa 1997). Although some perceptive observers have pointed to the possibility that changes in mortality might stem from improvements in early life conditions as early as 1934 (Kermack et al. 1934), most have assumed that the changes were essentially secular, affecting the survival prospects of all age groups in real time, in response to medical innovations and improvements in sanitation (Szreter 1988).

It has been well-established that from the end of the 19th century to the middle of the 20th century, improvements in life expectancy resulted mainly from reductions in mortality from "extrinsic" causes – those originating outside the body, such as infectious diseases. These developments had the greatest impact among infant and children. Since the mid-20th century, however, improvements in life expectancy have principally stemmed from reductions in mortality at older ages, primarily from causes that can be considered "intrinsic" in nature – those originating within the body – (Carnes et al. 2006; Meslé and Vallin 2000; Olshansky and Ault 1986; Omran 1971).

Demographers' understanding of mortality changes has benefited from the development of conceptual frameworks that take into account the three temporal dimensions of mortality: that is, the changes occurring over age (age effects), periods (period effects), and cohorts (cohort effects). Age variations in mortality are typically associated with developmental processes in the life course. Mortality changes over periods are associated with short-term impacts (e.g., shocks) around the moment of death that affect most age groups simultaneously. Cohort effects originate from an event that occurred in the past, experienced collectively by a set of individuals born at the same time, and that leaves distinctive lingering effects for a significant portion of the life cycle of the cohort (Glenn 1976; Hobcraft et al. 1982; Keyes et al. 2010; Yang 2008). The decomposition of effects into so-called Age-Period-Cohort (APC) components provides valuable information on factors responsible for mortality changes that are not directly observable.

The mechanisms that have contributed to decreases in intrinsic mortality at old ages have received considerable attention. At the turn of the 21st century, three theoretical frameworks, i.e., the *fetal origins* (Barker and Osmond 1986), the *technophysio evolution* (Fogel and Costa 1997), and the *cohort morbidity phenotype* (Finch and Crimmins 2004), proposed that changes over cohorts have been primarily responsible for the reduction of intrinsic mortality at old ages. According to these frameworks, the gradual improvement of early life conditions – namely, better nutritional intake and reduction of infection load – led to physiological and health improvements, which, in turn, resulted in progressive reductions in intrinsic mortality at old ages. In the literature on mortality change, the relative importance of period- and cohort-based factors in the reduction of intrinsic mortality at old ages has been subject to considerable discussion, and the debate continues (Barbi and Vaupel 2005; Crimmins and Finch 2006; Ouellette et al. 2014; Yang 2008).

While the analyses of mortality change have concentrated on the impact of period- and cohort-based factors on variations in intrinsic mortality at older ages, the contributions of young and adult extrinsic mortality to changes in all-cause mortality did not receive much attention until very recently. It is sometimes assumed that extrinsic mortality plays a negligible role in current and future all-cause mortality trends (Bongaarts 2005, 2006). Furthermore, the few existing studies that investigated extrinsic mortality often limited their attention to period-based determinants of change. However, recent trends in life expectancy in several western countries demonstrate that this approach failed to anticipate the recent reversal in long-term mortality improvements, or to identify its underlying causes, which – like influenza and drug-related mortality – are largely extrinsic (Ho and Hendi 2018; Raleigh 2019; Statistics Canada 2019). In fact, evidence has recently been accumulating that cohort-based factors play an important role in the temporal dynamics of these extrinsic causes of death, even in the presence of marked variations over periods (Arevalo et al. 2019; Gagnon et al. 2018a; Gostic et al. 2019; Huang et al. 2017; Zang et al. 2019).

In this dissertation, we argue that the analysis of cohort effects on extrinsic mortality in adulthood is an important issue that should be given more attention in demography and connected disciplines. We feel that it may represent a valuable step toward deepening our understanding of the challenges contemporary populations face. Improving our knowledge of the temporal patterns of extrinsic mortality can help to mitigate the dramatic outcomes of mortality crises, such as the ongoing opioid epidemic in Canada and the United States, and to suggest ways to prevent the spread of high levels of extrinsic mortality to other populations.

The dissertation is structured as follows. In the second chapter, we present our theoretical background. We start by introducing the conceptual partitioning of total mortality into intrinsic and extrinsic causes of death, and then discuss their impact on recent and future changes in mortality. We also review the underlying mechanisms reflected in the APC variations in mortality, the challenges associated with decomposing mortality changes into APC components, and the debate about the contributions of period- and cohort-based factors to recent mortality trends. Finally, we present some limitations of the dominant paradigms for the analysis of mortality change. This review is intended to paint a broad picture of the main approaches that are currently being used to study mortality, and to identify the gaps that our work tries to fill.

The third chapter describes the data and the methods employed for the analyses. This section pays particular attention to the methods used in the APC analysis of mortality change, which have a central role in this dissertation.

Chapters 4, 5, and 6 consist of the three scientific articles that together constitute the main contribution of this dissertation. In the first article (chapter 4), we analyzed the APC patterns of influenza mortality in the United States between 1959 and 2016. The main objective of this analysis was to investigate the interactions between the first influenza virus subtype to which the cohort members were exposed – the *antigenic imprint* – and the influenza virus subtypes they encountered later in life, during the observed epidemics. This work included analyses of linear and nonlinear effects of mortality, i.e., the long-term trends and the divergences from these trends. Such analyses enabled us to identify the cohorts who experienced significant changes in their mortality risks.

In the second article (chapter 5), we analyzed baby boomers' excess mortality in the United States and Canada. Several studies have independently proposed that drug overdoses (Huang et al. 2017; Miech et al. 2011; Remund et al. 2018; Zang et al. 2019) and suicides (Chauvel et al. 2016) are more prevalent among boomers. However, there is little research on the causes of deaths that have contributed the most to what could be called "the boomer penalty." The objective of our work was to provide a comprehensive analysis of these causes, and to determine whether the boomers' penalty resulted from sustained disadvantages during the life course of the cohort or from a sequence of unrelated mortality crises, experienced at different ages by the same cohorts.

The aim of the third article (chapter 6) was to fill a methodological gap in the analysis of the nonlinear APC effects identified in the first two articles. Statistical methods for the analysis of

nonlinear effects that were already available allowed us to estimate an average of these effects, but not their changes over time. In this work we proposed a visualization tool that allows for the analysis of the temporal dynamics of nonlinear APC effects, and the comparison of several phenomena or populations in one single plot. To generalize this methodological contribution to the study of other demographic phenomena, we show how the tool can be applied to the analysis of nonlinear period effects, and include an example related to fertility.

In chapter 7, we conclude with a discussion of our findings, highlighting the similarities and the differences between the cohort effects on influenza and behavioral mortality; the advantages of the methods we employed for the analysis of mortality; as well as the potential implications of the mortality patterns we have detected for population health. Finally, we describe the general limitations we encountered and offer a few ideas for further research.

It is noteworthy that during my doctoral studies, in addition to writing this dissertation, I co-first-authored one paper and second-authored two papers analyzing cohort effects on influenza mortality that were published: one in *PLOS Pathogens* (Gagnon et al. 2015), a second in *mBio* (Gagnon, Acosta, Hallman, et al. 2018), and a third in *Vaccine* (Gagnon et al. 2018b). A fourth paper is currently under revision at *Clinical Infectious Diseases* (Gagnon et al. 2019). In all these articles, I wrote, in collaboration with Alain Gagnon, significant portions of the code in R and the code in Stata. I also participated in the research design, the implementation of figures in R and Excel, the analyses of the results, and the revision of the manuscripts. Additionally, a fifth paper analyzing the impacts of violence on external mortality in Colombia (Acosta et al. 2018) is finished and currently in preparation for publication. The research design, analysis strategy, discussion of results, and the writing of this article were made in collaboration with Catalina Torres and Rafael Silva-Ramírez. Robert Bourbeau participated in the revision of the manuscript.

Following the *open science* principles of transparency and accessible knowledge, the analyses and the methodological contributions contained in this dissertation are entirely reproducible. Most of the data are openly available from official websites and other published scientific works. The programming code written to perform the quantitative and visual analyses presented here are openly

available through Open Science Framework (OSF) repositories[1]. The information for accessing data and scripts is detailed within each article.

[1] OSF is an open source software project of the Center for Open Science to increase the openness, integrity, and reproducibility of scientific research. The OSF offers cloud-based repositories for documenting and sharing materials and data to facilitate open access science.

Chapter 2 - Theoretical Background

This section presents the concepts and the theoretical issues surrounding existing analyses of mortality change. First, we define intrinsic and extrinsic mortality, and discuss their respective contributions to recent and future mortality trends. Second, we introduce the basic concepts related to age, period, and cohort (APC) analyses of mortality. We begin by examining the methodological challenges associated with decomposing mortality change into APC effects. Next, we examine the biological, epidemiological, and social factors that underlie APC changes in mortality, and provide a brief account of the debate surrounding the role of period- and cohort-based factors in recent mortality trends. Finally, we discuss some limitations of the existing approaches in the analysis of mortality change, and some of the gaps that this dissertation aims to fill.

2.1. Mortality partitions and epidemiological transition

2.1.1. Intrinsic and extrinsic mortality

For more than 200 years, biologists, actuaries, and demographers have proposed several conceptual partitions of all-cause mortality to explain the mortality process itself, and to improve the mathematical modeling of mortality change over age and time (Carnes et al. 2006; Carnes and Olshansky 1997). The distinction between intrinsic and extrinsic causes of death was originally proposed by Gompertz (1825) as a way to study the aging process, particularly as it pertains to the limits of life. Since then, several conceptual frameworks for alternative mortality partitions have been proposed (Bongaarts 2005; Carnes and Olshansky 1997; Makeham 1860; Shryock et al. 1973). Carnes and Olshansky (1997) put forward a biological-based partitioning of mortality between intrinsic and extrinsic causes of death that merged 20th-century theoretical developments in demography, actuarial science, and evolutionary biology. According to the authors, intrinsic mortality originates from inside the body, and is thus due to failure of the organism's functions; whereas extrinsic mortality originates from outside the body, and is thus due to environmental factors. The authors acknowledged, however, that there is a large gray area in the proposed classification because it fails to recognize the potential interaction of intrinsic and extrinsic factors. For instance, environmental exposures during critical periods of an individual's development – i.e.,

extrinsic factors – may have long-term effects on chronic or degenerative diseases – i.e., intrinsic factors – at older ages (Barker and Osmond 1986; Finch and Crimmins 2004; Gluckman et al. 2005). Carnes and colleagues (2006) pointed out, however, that although a perfect partitioning of mortality is not attainable, analyses that use an imperfect partitioning approach offer greater insights into mortality and a better modeling fit than analyses performed on all-cause mortality that do not employ partitioning.

Throughout this dissertation, the concepts of intrinsic and extrinsic mortality are used to refer to deaths that mainly originate from, respectively, intrinsic or extrinsic factors. Accounting for the interactive dynamics between intrinsic and extrinsic stressors is essential for the analysis of cohort effects on mortality. As we will explain later in this dissertation, these effects result from shared exposures to extrinsic factors that have long-term consequences for both intrinsic and extrinsic mortality.

2.1.2. The contributions of intrinsic and extrinsic causes of death to mortality change

In the original formulation of the epidemiological transition theory, Omran (1971, 1983) proposed three stages in the mortality and disease patterns in human history: *the age of pestilence and famine*, *the age of receding pandemics*, and *the age of degenerative and man-made diseases*. Applying the partitioning approach proposed by Carnes and Olshansky (1997), we argue that the three stages of Omran's theory correspond to a transition in which extrinsic causes were gradually replaced by intrinsic causes as the main killers. However, Omran's model predicted that an important component of extrinsic mortality, called "man-made diseases" – and denoted here as human-made diseases –, would gradually expand and come to play a more important role in all-cause mortality.

Later, Olshansky and Ault (1986) added a fourth stage to the epidemiological transition theory that would have begun in the second half of the 20th century: *the age of delayed degenerative diseases*. In this stage, the ranking of the principal causes of death was not modified, as degenerative diseases continued to be the leading killers; but the risk of dying from these diseases was shifted to older ages. Another important feature of this fourth stage was the gradual reduction of deaths from human-made diseases (Olshansky and Ault 1986).

As an alternative to the epidemiological transition model, several authors put forward the concept of a *sanitary* or *health transition* (Frenk et al. 1991; Meslé and Vallin 2000). Instead of focusing on the composition of mortality by cause of death alone, these authors expanded the scope of the analysis to the periods, the age structure, and the causes of death that contributed to the substantial improvements in life expectancy. More precisely, in the *first health transition*, increases in life expectancy resulted mainly from massive reductions in mortality from infectious disease. In the *second health transition*, gains in life expectancy were primarily attributable to substantial reductions in cardiovascular diseases at older ages, and gradual declines in mortality from human-made diseases (Meslé and Vallin 2000). A *third health transition*, which is currently beginning in some Western countries, consists in considerable decreases in mortality risk for elderly population (Vallin and Meslé 2004). Similar to Olshansky and Ault (1986), within the second stage of the *sanitary transition* framework, deaths from human-made diseases were expected to recede to very low levels, and to play a small role in all-cause mortality (Meslé and Vallin 2000, Vallin and Meslé 2004).

In addition to being useful for the analysis of previous changes in mortality, the intrinsic/extrinsic partition is a core concept in the projection of mortality trends. Scholars have argued that when attempting to project future mortality trends in countries with high life expectancy, the main focus should be on changes in intrinsic mortality, because these causes of death are currently the leading killers, and are likely to remain the largest contributors to life expectancy variations. It has also been posited that because extrinsic mortality has been decreasing, reaching insignificant levels during the last phase of the health transition, it will continue to decline to the point where it has virtually no impact on population-level mortality (Bongaarts 2005, 2006).

This shift in the leading causes of death has been widely analyzed and conceptualized through the prisms of the epidemiological and health transition theories. However, a significant challenge researchers face is that many of the factors that contribute to mortality changes are normally not observable. The identification of unique APC contributions to mortality changes can offer important clues about the effects of underlying and often unobserved biological, epidemiological, social, and economic factors (Fosse and Winship 2019a; Hobcraft et al. 1982; Holford 1983; W. M. Mason and Fienberg 1985; Murphy 2010; Tarone and Chu 1996). In the sections that follow, we will describe some characteristics of APC analysis, and explore the factors that underlie such variations in mortality.

2.2. Age, period, and cohort determinants of mortality

2.2.1. APC analysis of mortality change

The APC decomposition of change indicates the contributions from variations occurring over the life course of individuals (age effects), from the events occurring in the same period of observation (period effects), or from particular characteristics that uniquely shape the individuals born at a given time and that endure over time (cohort effects). Identifying the APC effects on any given socio-demographic phenomenon has long been a methodological challenge that has sparked disagreement. The question of whether it is possible to isolate the APC components of mortality change has been debated since the beginning of the 20th century (Keyes et al. 2010; Murphy 2010; O'Brien 2014a). This is because, given the perfect linear dependence between the three temporal variables (*age* = *period - cohort*), there is no unique solution, but rather an infinite number of solutions that provide the exact same fitting (Fosse and Winship 2018; Glenn 1976; Holford 1983; K. O. Mason et al. 1973; O'Brien 2014a). Therefore, it is impossible to estimate a unique solution describing APC effects without the imposition of additional constraints. This inability to identify a unique solution is the well-known *identification problem* that is inherent in APC analyses.

For more than a century, demographers, sociologists, and epidemiologists have been proposing different ways to overcome this identification problem, with at least four waves of theoretical and methodological developments emerging. In the 1870s, several mathematical and graphical advances providing analytical and visual descriptions of mortality were introduced; including, notably, the Lexis diagram (Keiding, 2011). In the 1920s and 1930s, influential works in epidemiology (Andvord 1921; Andvord et al. 1930; Derrick 1927; Frost 1939; Kermack et al. 1934) tried to disentangle the age, period, and cohort components of the rapid decrease in mortality observed at the end of the 19th century and the beginning of the 20th century. During the 1970s and 1980s, a third wave of methodological advancements included the first statistical propositions to account simultaneously for age, period, and cohort effects; and the formal recognition of the identification problem (Glenn 1976). In addition, during the same period, the first methodological attempts were made to overcome the identification problem by adding theoretically-based constraints to the models. More recently, Fu (2000) started a fourth wave of methodological production that has been widely

popularized by the work of Yang and colleagues (Yang et al. 2004; Yang and Land 2013a). These ongoing developments of the APC methodology suggest that a unique solution could be estimated by assigning arbitrary constraints that do not require the subjective intervention of the researcher. However, this proposed solution is far from being universally accepted, and a debate currently surrounds these methodological developments (Fosse and Winship 2018; Luo 2013; O'Brien 2013; Tolnay 2013; Yang and Land 2013b).

A considerable achievement in the development of APC analyses is the possibility of decomposing each APC component into *linear* and *nonlinear* effects (Holford 1983; Rodgers 1982). The *linear* effects refer to the slope of the linear trend of change. The *nonlinear* effects, also known in the APC literature as *curvatures* or *nonlinear fluctuations*, refer instead to divergences from the linear trend in each APC dimension. *Nonlinear* effects are indicative of the relative risk of each age, period, or cohort category compared to the respective overall linear trend. The distinction between linear and nonlinear effects is important because the identification problem exclusively concerns the linear effects component. By contrast, the nonlinear effects are unambiguously identifiable because their shape and magnitude do not vary in response to the model constraints that are imposed in order to find a unique solution (Clayton and Schifflers 1987; Fosse and Winship 2019a; Holford 1983; O'Brien 2014b; Rodgers 1982). It follows that it is much easier and more reliable to distinguish APC effects when mortality trends have accelerated, decelerated, or changed direction – i.e., nonlinear effects – than when changes are steady and monotonic – i.e., linear effects (Kuh et al. 2003). Although the analysis of nonlinear effects provides substantial information about the phenomenon under observation, this aspect has been greatly underappreciated in the APC literature (Fosse and Winship 2019a). A more detailed discussion of the identification problem inherent in APC analyses and the methodological attempts to overcome it is presented in the methods section of Chapter 3.

Although they provide substantial information about the demographic components of variation, ages, periods, and cohorts have no effect on mortality by themselves. Instead, they are markers of the unobserved factors underlying the temporal dynamics of mortality. We turn to these factors in the next section.

2.2.2. Age-, period-, and cohort-based factors underlying mortality change

Age-based factors influence mortality in several ways. An individual's physiological frailty varies considerably with age due to the maturation and deterioration of the organism. In parallel, the gradual accumulation of permanent damages over the life course – resulting from diseases, injuries, the environment, and behaviors – contribute to the physiological deterioration of the individual with age. In addition, each life stage corresponds to specific behaviors and exposures that can increase or decrease the risk of death, such as the risk of work-related mortality.

Period-based factors typically stem from environmental variations or shocks that can be either natural or human-caused, such as natural disasters, epidemics, wars, famines, changes in sanitary conditions, and advances in medical technology. These period disturbances may produce contemporary shifts in mortality at most ages, albeit to varying degrees. Over the last three centuries, the management of environmental factors was responsible for massive reductions of mortality, first at the youngest ages, and then at all other (Finch and Crimmins 2004; Fogel and Costa 1997; Meslé and Vallin 2000; Omran 1983; Szreter 1988, 2004). Nevertheless, in addition to triggering direct, contemporary shifts in mortality, period disturbances can have long-term implications that uniquely shape the mortality experience of the cohorts who lived through the disturbance, especially the youngest cohort members (Keyes et al. 2010; Yang 2008). In other words, these extrinsic period disturbances may produce not only period effects, but also cohort effects on mortality. Because of the difficulties in distinguishing between the short- and long-term implications of such disturbances, identifying the changes in mortality that result from period- and cohort-based factors that change gradually over time is challenging.

The identification of cohort-based factors requires a more complex conceptualization. Cohort-based factors operate through intricate interactions between extrinsic stressors that modify either the frailty composition of the cohort or the intrinsic characteristics of the cohort members. In other words, cohort-based variations may stem from either selection processes or long-term modifications of individuals' mortality risks (Preston et al. 1998). The idea behind selection is that extremely beneficial/adverse conditions early in life tend to increase the proportion of frail/robust individuals within the cohort, which may, in turn, translate into higher/lower levels of mortality later in life (Hobcraft et al. 1982; Preston et al. 1998; Vaupel et al. 1979). Other mechanisms may instead modify the individuals' mortality risks. Shared exposures to extrinsic factors during critical or sensitive life stages of the cohort members can lead to biological or behavioral modifications that increase or

decrease their later life mortality risks. This mechanism could explain the long-term effects of detrimental exposures early in life, producing cohort effects that are manifested through different temporal patterns. Several analyses that provide evidence for such an association will be detailed later.

Manifestation of cohort effects

Cohort effects do not all become apparent in the same way. There are important differences in the timing and the dynamics of cohort effects over time (Chauvel 2013; Chauvel et al. 2016; Hobcraft et al. 1982; Keyes et al. 2010). Hobcraft and colleagues (1982) distinguished three types of cohort effects.

The first type, denoted as the *cohort-inversion effect*, manifests itself as a gradual reversal of the effect over time. This pattern results from the selection process described above (Chauvel 2013; Chauvel et al. 2016; Hobcraft et al. 1982)[2]. In the second type of cohort effect pattern, called the *conventional linear model*, the magnitude of the effect is invariable during the whole period of observation. Although most of the current statistical methods for the analysis of APC effects assume this pattern, this cohort effect is unrealistic. It does not take into account variations over time, or the interactions with age- and period-based factors. The third and more common type of cohort effect is denoted as the *continuously-accumulating cohort effect*. This effect results from a period disturbance that affects the population "differentiated by age and becomes embodied in cohorts differentially" (1982, p. 10).

It is important to highlight at this point the difference between cohort and age-period interaction effects. Period disturbances that disproportionately affect some age groups may lead to either cohort or age-period interaction effects, depending whether the disturbance is differently embodied in the cohorts or not. According to Keyes et al. (2010, p. 1101), unlike in the *sociological perspective*, in the *epidemiological perspective,* "short-term fluctuations in health that result from age by period interactions" are also considered cohort effects. In this dissertation, only the age-period interactions that take the

[2] This effect was proposed by Canudas-Romo and Guillot (2015) for explaining the mortality patterns of baby boomers in the United States, who, compared to their neighboring cohorts, experienced lower mortality levels in early life and higher adult mortality. A more detailed discussion of this case, which compares the selection mechanism and the attributes of the boomer disadvantage, is presented in chapter 5.

form of lagged effects embodied in the cohorts will be considered cohort effects – as it is proposed in the *continuously-accumulating cohort effect* presented above.

In the following, we discuss some theoretical frameworks linking early life exposures and later life mortality that are useful for the analysis of cohort effects on mortality.

Early life exposures and adult mortality risks

A distinction between *critical* and *sensitive* periods is typically made in order to differentiate the time windows in which exposures affect, respectively, the biological or the behavioral development of individuals (Kuh et al. 2003; Montez and Hayward 2011). These periods usually refer to stages of the individuals' physiological and psychosocial development. *Critical* or *sensitive* periods are indispensable for the initiation of cohort effects. Given the age differences in susceptibility, period disturbances experienced by the whole population have an especially large impact on age groups going through critical or sensitive life stages. Thus, such disturbances may change the intrinsic characteristics of the susceptible groups, initiating cohort effects.

Another important distinction concerns the type of exposure that creates the cohort effects. Montez and Hayward (2011) have classified these exposures as either *physical* or *social*. They considered nutrition and infections to be key *physical exposures*, and socioeconomic conditions and family environment to be key *social exposures*. Compared to nutrition and exposure to infection, socioeconomic characteristics and family environment are expected to vary far less across cohorts, and are therefore rarely translated into cohort effects. Instead, large variations in social exposures are expected to result from rapid and extensive social changes, which can affect different birth cohorts very differently (Kuh et al. 2003; Ryder 1965).

The link between exposures during *critical* and *sensitive* periods and later life mortality could develop in several ways. Through the *imprinting* mechanism, exposures of the cohort members to extrinsic factors during *critical* stages could be inscribed into their physiological functions or structures, and leave biological imprints on their adult mortality risks (Ben-Shlomo and Kuh 2002; Montez and Hayward 2011). This *imprinting* mechanism could increase the cohort members' mortality risks as a result of past physiological insults, or it could provide them with long-term protection if their past antigenic exposures are similar to those they encounter later. These contrasting effects of permanent

harm and protection are denoted, respectively, as *scarring* and *acquired immunity* in Preston et al. (1998)'s typology. In contrast to the *imprinting* mechanism, the *pathway* mechanism – also denoted as *correlated environments* by Preston et al. (1998) – refers to exposures that are not directly linked to mortality risks at older ages, but rather to the accumulation of correlated risk factors through the life course (Ben-Shlomo and Kuh 2002; Montez and Hayward 2011; Palloni et al. 2009; Preston et al. 1998). Unlike the *imprinting* mechanism, in which early life insults leave permanent imprints affecting mortality risks in adulthood, in the *pathway* mechanism, the influence of early life conditions on adult mortality is indirect because individuals tend to experience similar environments during life. Because *imprinting* and *pathway* mechanisms are not mutually exclusive, other authors have proposed the existence of a *cumulative* mechanism. This mechanism allows for the possibility that interactions and the accumulation of stressors have an impact in both early and later life (Ben-Shlomo and Smith 1991; Montez and Hayward 2011). In this case, some early life exposures that are imprinted on individuals may be either mitigated or exacerbated by the conditions they encounter over their life course, and could influence their further exposures.

Numerous hypotheses have linked early life exposures and later life mortality. In the following, we present some of the hypotheses that could be related to the origination of cohort effects. We also offer a brief account of some empirical analyses that have attempted to identify and quantify such cohort effects.

Cohort effects from physical exposures

Related to the *scarring* mechanism concept, the *fetal origins* hypothesis (Barker and Osmond 1986) proposes that an individual's nutritional intake very early in life is a strong determinant of whether that individual develops chronic or non-transmissible diseases at older ages. The *cohort morbidity phenotype* hypothesis (Finch and Crimmins 2004) assigns a larger role to infection and inflammation during early life.

The *antigenic imprinting* hypothesis, originally formulated for influenza infections (Davenport et al. 1953; Francis 1960), states that early life exposure to a specific strain of influenza virus could compromise an individual's immune system. Strains that the person subsequently encountered would be stored in the immune repertoire, but with a lower position in the hierarchy than those he

or she encountered earlier (Henry et al. 2018). When the imprinted and the encountered virus are similar, the person is expected to have protection; but if these strains are very dissimilar, there is a considerable increase in the individual's risk of having severe outcomes from the influenza infection (Gagnon et al. 2013; Kobasa et al. 2007; Shanks and Brundage 2012).

Two observations can be offered about the mechanism proposed by the *antigenic imprinting* hypothesis. First, its double-edged aspect (i.e., protection/disadvantage) was not addressed by the *acquired immunity* typology proposed by Preston et al. (1998), according to whom previous exposure to a pathogen is always construed as protective when the same pathogen is encountered later in life. Second, contrary to the *scarring imprinting* hypothesis, the critical stage for *antigenic imprinting* is related more to the previous antigenic experience of the individual, and less to his or her physiological stage of development. Because influenza viruses constantly mutate and spread widely across the population, each cohort has its own particular and enduring *antigenic signature* (Ma et al. 2011), which translates into cohort effects on influenza mortality.

Likewise, exceptional periods of extreme adverse conditions, such as famines and epidemics, have served as natural experiments for analyzing the influence of nutrition shortages and infections experienced by cohorts early in life on their mortality over the life course (Mu and Zhang 2011). A large number of empirical analyses, some of which are reviewed below, have been conducted that sought to identify the cohort effects on mortality that result from shared exposures to such exceptional periods during critical life stages.

The results of studies that examined the long-term effects on later life mortality of being exposed to extreme nutritional deprivation due to famine early in life have been mixed. Analyses of early life exposure to famines in Finland in 1866-1868 (Kannisto et al. 1997), and in the Netherlands in 1944-1945 (Painter et al. 2005), found no effects on adult and old-age mortality. By contrast, higher mortality risks after age 50 were found for cohorts exposed early in life to the Dutch famines of 1846-1847 (Lindeboom et al. 2010). Previous research has found that the disease load experienced during the first years of life had a large impact on the later life mortality of cohorts in Sweden (Bengtsson and Broström 2009; Bengtsson and Lindström 2000, 2003) and in Quebec (Bilodeau Bertrand 2015).

In historical populations, season of birth offers proxy information about the epidemiological context and the availability of nutrition shared by cohorts during critical stages of their life course.

Individuals born during autumn and winter were shown to have longer lifespans in Denmark, Austria, Britain, and Australia (Doblhammer and Vaupel 2001); in the United States (Gavrilov and Gavrilova 2011); and in Quebec (Gagnon 2012; Jarry et al. 2013). The reason that is usually given for this seasonal advantage in historical contexts is that after the summer season, more food from crops was available and the incidence of infections was considerably lower.

Influenza pandemics have also offered opportunities to study the long-term effects of short-term shocks, which may affect cohorts through both scarring and acquired immunity mechanisms. Analyses of scarring effects resulting from early life exposure to the 1918 Spanish flu pandemic have found negative effects on health, educational attainment, and income in the United States (Almond 2006) and Taiwan (Lin and Liu 2014); and higher mortality from cardiovascular diseases in the United States (Mazumder et al. 2010; Myrskylä et al. 2013). Similarly, Kelly (2011) found evidence of negative cohort effects on child development for those cohorts exposed to the 1957 Asian flu pandemic in England.

Among the analyses of the cohort effects resulting from *antigenic imprinting* mechanisms are studies that examined the influence of exposure to influenza pandemics in infancy on mortality during subsequent influenza pandemics. Numerous studies (Oeppen and Wilson 2006; Gagnon et al. 2013; Hallman 2015; Shanks and Brundage 2012) have found a higher relative risk of death during the 1918 Spanish pandemic for those cohorts who were born during the 1890 Russian pandemic in Canada and the United States. Likewise, other analyses found higher relative risks of death during the 2009 flu pandemic in North America (US and Mexico) for those cohorts who were born during the 1957 Asian pandemic, as well as for those cohorts who were born during the 1957 Asian and the 1968 Hong Kong pandemics in Mexico (Gagnon et al. 2018a). These increased mortality risks likely resulted from the large antigenic differences between the priming influenza virus strains – H2N2 in 1957 and H3N2 in 1968 – and the strains these cohorts encountered later in life – pH1N1 in 2009. The opposite effect – i.e., a protective effect due to antigenic similarities – was also found in several countries during the 2009 North American pandemic for those cohorts born around the 1918 Spanish pandemic, and who were therefore primed by a similar subtype H1N1 (Fisman et al. 2009; Gagnon et al. 2018a; Ikonen et al. 2010; Lemaitre et al. 2012; Nguyen and Noymer 2013) .

Cohort effects from social exposures

The influences of family environments and socioeconomic status in early life on later life mortality have been extensively studied (Bengtsson and Broström 2009; Gagnon and Bohnert 2012; Hayward and Gorman 2004; Jarry et al. 2013). However, as we argued earlier in this chapter, such exposures do not lend themselves into cohort effects because the inter-cohort variations are not as substantial as the intra-cohort variation. The effects of sudden social changes in early life on mortality later in life have received less attention, but various theoretical frameworks have been proposed to analyze the translation of these social changes into cohort effects. The demographer Norman Ryder (1965) proposed the *birth cohort effect* and the sociologist Karl Mannheim (1952) proposed the *generational effect* as mechanisms for explaining social changes via the succession of cohorts through, respectively, demographic and social metabolism processes (Lutz 2013; Mayer 2009). Nevertheless, both effects have potential implications for mortality outcomes through their influence on mental health, attitudes, behaviors, and correlated environments.

According to Ryder (1965), birth cohort effects refer to the distinctive aspects of the cohort itself (i.e., cohort size, education) and to the uniqueness of the sociohistorical context that the members of a cohort experience simultaneously during their life cycle (i.e., economic cycles, increased participation of women in the workforce). Such shared social contexts leave permanent traces in the cohort members' lives (Alwin and McCammon 2003, 2007; Easterlin 1987; Ryder 1965). Thus, changes in population size and educational attainment across cohorts, as well as sudden institutional and economic transformations during sensitive life stages, can translate into cohort differences in the availability of material and social resources, and in cohort differences in perceived well-being, which are all widely recognized as important determinants of mortality (Canon 2018; Easterlin 1987; Hayward and Gorman 2004; Montez et al. 2012; Montez and Friedman 2015; Montez and Hayward 2011; Sasson 2016a, 2016b; van Raalte et al. 2012, 2014)

According to Mannheim (1952), generational effects may result from involvement in social movements at sensitive stages of life during sudden sociohistorical transformations. This participation could lead to the emergence of a shared and distinctive generational identity among the members of the generation, which is manifested through common dispositions, attitudes, and behaviors (Alwin and McCammon 2007; Eyerman and Turner 1998; Mannheim 1952). Sudden and

important changes in sociohistorical processes are expected to lead to important variations in attitudes and behaviors across generations, which could, in turn, shape the cohorts' mortality.

The baby boomer cohorts are clear examples of cohorts who experienced abrupt social changes that translated into cohort effects on several dimensions of life. Because of their social location and sociohistorical experience, the boomer cohorts have experienced marked *birth cohort* and *generational* effects (Alwin et al. 2014; Alwin and McCammon 2007). Through their large number and because they lived through an epoch of important social movements and transformations at young ages, the baby-boomers were exposed to conditions that turned into both birth cohort and generational effects. Following Ryder's concept of the birth cohort effect, Easterlin (1987) extensively analyzed the influence of the cohort size on the lives of the baby-boomers. According to Easterlin, the boomers experienced a sharp contrast between the expectations they developed during the prosperous period in which they grew up, and the harsh economic conditions they encountered later in life when they entered to the labor market in large numbers. This mismatch would then have led to a decrease in perceived well-being and to a considerable increase in levels of stress and frustration. For this reason, he predicted that the rates of suicide, homicide, and drug abuse would be higher among boomers than among adjacent cohorts (Easterlin 1987). Moreover, other researchers have argued that the involvement of boomers in the counterculture movements at younger ages led them to develop risky attitudes regarding sexual behavior and substances abuse, which might have translated into higher mortality risks from behavioral causes (Colliver et al. 2006; Crome and Rao 2018; Duncan et al. 2010; McBride 1990; Miech et al. 2011; Patterson and Jeste 1999; Puac-Polanco et al. 2016; R. Rao and Roche 2017; T. Rao 2019).]

Starting in the early 20th century, the formulation of numerous theoretical frameworks linking period- and cohort-based factors to mortality, like those presented above, have had a strong influence on the analysis of mortality change and the underlying factors. Several deliberations broke out in the scientific community about the extent to which these factors had contributed to mortality reductions in western populations since the 19th century. Numerous shifts between the period and cohort paradigms in the analysis of mortality change took place during the century, which had substantial implications for research. A detailed account of these discussions and shifts in paradigms can be found in Murphy (2010) and Smith and Kuh (2001). We will focus now on those pertaining to period- and cohort-based factors of mortality change.

2.2.3. The role of period- and cohort-based factors in mortality change

Because the variation in mortality risk over the life course is widely considered to be the most significant determinant of variation in vital rates (Carstensen 2007; Clayton and Schifflers 1987; Hobcraft et al. 1982; Holford 1991; Yang 2008), most of the studies on secular mortality changes have concentrated on the decomposition between period and cohort components. However, it has been very difficult to dissociate period and cohort contributions to these secular changes because mortality improvements in Western societies since the mid-19th century have been mostly monotonic (i.e., dominated by linear effects).

During most of the 20th century, the perspective attributing a greater influence to period-based factors on mortality changes remained dominant. Nevertheless, at the end of the century, the confluence of the theoretical frameworks presented above, which privileged the role of cohorts in mortality changes, helped the cohort paradigm regain credibility (Murphy 2010; Smith and Kuh 2001).

The concepts of *generation* developed by Mannheim (1952) and *birth cohort* developed by Ryder (1965) were appealing frameworks for explaining social changes through generation and cohort replacement mechanisms. Finch and Crimmins (2006; 2004) not only proposed a mechanism linking early life exposures to mortality at old ages with the *cohort morbidity phenotype*; they also argued that the declines in old-age mortality during the 20th century were the consequence of the gradual improvements experienced by those same cohorts earlier in life during the 19th century. Moreover, in addition to developing the theory of *technophysio evolution*, Fogel and Costa (1997) proposed a cumulative mechanism, which stated that improvements occurred over cohorts through the intergenerational transmission of improvements experienced at the individual level (Floud et al. 2011; Fogel and Costa 1997).

However, the debate over the relative contributions of period- and cohort-based factors is far from concluded. Barbi and Vaupel (2005) challenged the association between child and elderly mortality within the same cohorts proposed by Finch and Crimmins (2004). Instead, they argued that period effects, such as medical technology improvements during adulthood, had a larger influence than cohort-based factors on decreases in mortality at older ages. The position of Barbi and Vaupel (2005) was consistent with that of Szreter (1988, 2004), who argued that most of the mortality

reductions observed during the end of the 19th century in England were far more responsive to period-based factors, such as improvements in sanitary conditions and the implementation of public health policies, than to cohort effects. To examine the influence of period- and cohort-based factors on the mortality of historical populations, Gagnon and Mazan (2009) analyzed the mortality of cohorts born in Quebec during the 17th and 18th centuries. In contrast with previous analyses, which only observed decreases in both infant and old-age mortality within the same cohorts, their study was able to analyze the influence of increases in infant mortality, as was the case in 17th century Quebec, on later life mortality. Their analysis did not find that increases in infant mortality levels were followed with increases in old-age mortality within the same cohorts, as the *cohort morbidity phenotype* hypothesis would have predicted. In a study that examined more recent mortality trends and at a wider geographical scale, Myrskylä (2010) found that early life experiences had little influence on old-age mortality in cohorts born during the late 19th century and the early 20th century in six European countries.

The contrasting results about the role of period- and cohort-based factors are not limited to mortality changes in the past; indeed, there is also a lack of convergence of results in more recent mortality changes or trends. In accordance with the *cohort morbidity phenotype* hypothesis and the *technophysio evolution* theory, Yang (2008) proposed that decreases in U.S. intrinsic mortality during the second half of the 20th century were dominated by cohort effects. Similar conclusions were reported by Masters (2012) based on an analysis of the mortality crossover between white and black populations in the United States. Some of these findings were challenged by a study from Ouellette and colleagues (2014), who demonstrated that most of the accelerated adult mortality decline that occurred in the late 1960s simultaneously affected most age groups in several high-income countries. They argued that period-based factors, such as improved measures of prevention and better diagnostic methods, were the main determinants of these reductions.

Given the biological, epidemiological, social, and economic factors that are known to determine mortality changes (and for which APC variables are just markers), it is clear that both period- and cohort-based factors have jointly contributed to mortality changes over time (Murphy 2010; Ouellette et al. 2014; Yang 2008). Most researchers are aware that there are both period and cohort influences on mortality changes, and that a complete and exclusive attribution of mortality changes to any of these dimensions would be an oversimplification of the complex and intricate process of mortality, and of its resulting temporal patterns.

2.3. Implications of current paradigms for the analysis of mortality change

The approaches presented above have considerable influence in guiding research on mortality. Analyses of mortality changes generally focus their attention on long-term trends of chronic degenerative mortality at old ages. This approach focuses on one set of causes (i.e., intrinsic), one age group (i.e., old ages), one temporal pattern (i.e., linear effects), and one category of cohort effects (i.e., *scarring* mechanisms contemplated in the *fetal origins* and *cohort morbidity phenotype* hypotheses). In the following, we argue that these approaches are poorly suited for addressing many of the challenges certain populations face that can affect their current and future mortality trends.

2.3.1. Role of young and adult extrinsic mortality in the contemporary population health trends

As we discussed earlier in this chapter, the temporal dynamics of non-communicable and degenerative diseases have received considerable attention as the primary contributors to life expectancy improvements during the second and third phases of the health transition – or as the leading causes of death in the fourth stage of the epidemiological transition. According to these theoretical frameworks, extrinsic causes of death are expected to progressively decline to very low levels, and to play a marginal role in changes at the macro population level (Bongaarts 2005, 2006; Meslé and Vallin 2000; Olshansky and Ault 1986; Vallin and Meslé 2004).

However, some analyses have offered evidence that recent changes in mortality patterns do not support this hypothesis. After decades of improvements in life expectancy, several high-income countries experienced a decline in mortality between 2014 and 2015 (Raleigh 2019). This deterioration was unexpected because those populations were not suffering from wars, famines, or infectious pandemics. A comprehensive analysis by Ho and Hendi (2018) identified two extrinsic causes – i.e., influenza infection and drug overdoses – as the leading contributors to mortality increases in at least 12 high-income countries (out of 18) between 2014 and 2015. The majority of these countries have seen their life expectancy rise again in later years, except in the United States, where life expectancy has declined for three years in a row, and the United Kingdom, where life

expectancy stagnated between 2015 and 2016. The 2015-2016 improvements that occurred in most high income countries suggest that the observed deterioration between 2014 and 2015 was a divergence from the long-term trend of mortality improvements rather than a reversal of this trend. Nevertheless, the decline in life expectancy, however small or short-lived it was, should be a cause for concern because it indicates a considerable deceleration of previous improvements (Jasilionis 2018). Moreover, in the United States, life expectancy has declined for three consecutive years after 2014, and behavioral-related mortality at young ages seems to drive these declines (Barbieri 2019, Woolf and Schoomaker 2019).

The observed role of influenza- and drug-related mortality in the decline in life expectancy between 2014 and 2015 stresses the need of analyzing the temporal dynamics of the extrinsic causes of death, and their implications at the population level. Understanding the temporal pattern in these causes is crucial for understanding the ongoing mortality crisis, including how it can be mitigated, and what actions can be taken to prevent new crises in other populations. The evidence suggests that the observed recent increases in mortality from influenza and drug abuse do not respond to occasional fluctuations with transitory impacts. On the contrary, influenza and drug abuse appear to be risk factors with potentially important implications for mortality in the near future.

For instance, new, highly virulent influenza strains are slowly spreading worldwide and are threatening to become pandemics (CDC 2018a; Peiris et al. 2007; Pu et al. 2018; Quan et al. 2018; Shan et al. 2019; WHO 2018, 2019). Ho and Hendi (2018) found that in most of the high income countries that experienced a deterioration of life expectancy, influenza-related mortality was the leading negative contributor to the life expectancy change between 2014 and 2015. Nevertheless, since influenza incidence fluctuates from one year to the next, depending on the virulence of the virus subtype (H1N1, H3N2,…), the interactions host-pathogen, the pool of susceptible, and so on, these changes may very well be temporary and reversed in the coming years. The role played by influenza mortality in the observed decline in life expectancy will be further developed in the Discussion section of this dissertation (Chapter 7).

With respect to drug-related mortality, several signs indicate that worse outcomes are to be expected. The ongoing opioid crisis, which for now appears to be confined to a few countries (the United States, Canada, and Australia), could spread to other countries in Europe (Boseley 2018; Ho 2019; Ho and Hendi 2018; Paun 2019), Latin America, and Africa (Ryan et al. 2016; Staff and agencies

2019). In the United States, where the largest increases in overdose deaths to date are found, a smooth exponential trend of drug overdoses since 1990 suggests that the opioid epidemic is just a manifestation of a long-term process with apparently no signs of deceleration in the near future (Jalal et al. 2018). The deaths related to chronic substance abuse – such as overdoses, alcoholic cirrhosis, HIV/AIDS, and hepatitis C – have a considerable impact at the population level, and the exponential shape of the overdose mortality trend suggests that the future implications of drug abuse will be even greater.

As mentioned by Vallin and Meslé, "it is possible to enter into a new stage [of the health transition] without having completed the previous one" (Vallin and Meslé 2004, p. 38). Canada and the United States are clear examples of this divergence from the sequence of health progresses proposed within the health transition theoretical framework. Both countries made significant advancements into the third stage – i.e., the fight against aging – but are still struggling to reduce the fatal outcomes from human-made diseases, which were supposed to be addressed a long time ago, during the second stage. The delay of these countries for controlling extrinsic mortality seems to be rooted in education and wealth stratification and could be the main contributor for lifespan inequality within these populations (Ho 2018; Sasson 2016a, 2016b; van Raalte et al. 2012, 2014, 2018). Compared to behavioral-related mortality, social factors also seem to determine the risk of influenza-related mortality, but to a lesser degree (Cordoba and Aiello 2016; Lowcock et al. 2012; Nagata et al. 2013). Because lifespan inequality is considered the most fundamental of all inequalities (van Raalte et al. 2018), the analysis of extrinsic mortality should be considered an urgent issue in demographic research.

2.3.2. Cohort effects on extrinsic mortality

Regarding temporal patterns, as we argued earlier, it is not surprising that period effects are typically linked to extrinsic mortality, while cohort effects are usually linked to intrinsic mortality. It seems more intuitive to link extrinsic mortality to environmental exposures that kill instantaneously, than to events experienced earlier in life. Therefore, most studies on extrinsic mortality have privileged the period perspective, while overlooking the contributions of cohort effects to these causes of death. But as Koopman and colleagues (2015, p. 51) observed, "death can be better explained by the interaction of intrinsic and extrinsic stressors." As extrinsic mortality implies the interplay between

the individual and the environment, it may be expected that the intrinsic attributes of individuals influence their risk of mortality from extrinsic causes. Even with substantial variations over periods, acute or infectious causes of death are not exempt from cohort patterns. Indeed, intrinsic differences across cohorts, such as differences in immune or behavioral characteristics, may translate into susceptibility differentials to extrinsic risk factors in some segments of the population.

From the elements presented in this chapter, we argue that the partition of mortality between intrinsic and extrinsic causes is essential for a better understanding of how cohort effects on mortality operate. There are substantial differences between intrinsic and extrinsic mortality in the manner in which cohort effects originate and are enacted later in life. The *fetal origins*, the *technophysio evolution*, and the *cohort morbidity phenotype* hypotheses, which currently dominate the study and understanding of cohort effects on mortality, are well suited for the analysis of intrinsic causes. However, these theoretical frameworks are not appropriate to analyze cohort effects on extrinsic mortality; cohort effects on mortality from infectious diseases operate through immune-related mechanisms, and cohort effects on human-made causes usually relate to social exposures.

With the aim of analyzing the manifestation of cohort effects on extrinsic mortality patterns, we present in this dissertation two analyses of cohort effects on extrinsic mortality. The first analysis, which is on influenza mortality, focuses on the effects of the *antigenic imprinting* mechanisms. The second analysis is conducted in order to identify the main causes of death that led to a divergence from the secular trend of mortality among the boomers. These findings will help us evaluate whether the attributes of the mortality experiences of the boomer cohorts are compatible with the hypotheses that have been proposed to explain their disadvantage in mortality. In addition, to improve the analysis of nonlinear effects by elucidating the temporal pattern of cohort effects, we proposed a methodological contribution for the visual analysis of the changes over time of nonlinear APC effects.

Chapter 3 - Data and Methods

This chapter presents the different sources of data used in the three articles of this dissertation. We also describe the approach used to exploit these data and the methods of analysis that led to the estimation of influenza mortality, the visual methods for the depiction of the temporal dynamics of nonlinear APC effects, the statistical methods for the analysis of linear and nonlinear APC effects, and the decomposition of mortality change over cohorts by cause. Table 3.1 shows an outline of the data and methods employed in each article of this dissertation with the purpose of facilitating the comprehension of this section. More information of these components is detailed in the rest of the chapter.

Table 3.1: Objectives, data and methods by article

Article	Objective	Data	Methods
Determinants of Influenza Mortality Trends: Age-Period-Cohort analysis of influenza mortality in the United States, 1959-2016 (Chapter 4)	- Estimate monthly influenza-related mortality by virus subtype in the United States during the period 1959-2016 - Study the roles of age, period, and cohort factors as drivers of influenza mortality change in the United States over the years 1959-2016 - Address the changes in mortality risk over cohorts	- Monthly death counts by cause of death, sex, and single years of age in the United States between 1959 and 2016 (NVSS[a]) - Annual counts of population at risk by single years of age in the United States from 1959 to 2016 (HMD[b]) - Annual percentages of respiratory specimens testing positive by influenza subtype in the United States between 1976 and 1996 (FluView[c]) - Weekly indicators of ILI[d] and percentages of respiratory specimens testing positive for influenza in the United States between 1997 and 2016	- Classic Serfling model - Surveillance Serfling model - Lexis surfaces of mortality - Detrended APC models (Drift APC models) - Intrinsic estimator model - APC contrasts analysis
Baby Boomers' Excess Mortality in Canada and the United States (Chapter 5)	- Identify the disadvantaged cohorts by country and sex - Identify the leading causes of baby boomers' excess mortality - Estimate coefficients of nonlinear cohort effects by sex, country, and leading cause of death - Plot nonlinear cohort effects by sex, country, and	- Annual death counts for all-cause mortality for Canada and the United States by sex and single years of age between 1968 and 2016 (CHMD[e] and HMD) - Annual exposures to risk for Canada and the United States by sex and single years of age between 1968 and 2016 (CHMD and HMD) - Annual death records by cause of	- Lexis surfaces of mortality change - Cohort partial mortality rate - Detrended APC models - P-splines smoothing and interpolation - APC curvature plots

Article	Objective	Data	Methods
	leading cause of death for the period 1974-2016 - Plot nonlinear cohort effects by sex, race/ethnicity in the United States for the period 1990-2016	death, sex, and single years of age in the United States between 1968 and 2016 (NVSS) - Annual death records by cause of death, sex, and single years of age in Canada between 1974 and 2014 (CVSD[f]) - Annual death records by sex, race, ethnicity, cause of death, and single years of age in the United States between 1990 and 2016 (NVSS) - Annual population estimates by sex, race, ethnicity, and single year of age for the United States between 1990 and 2016 (NVSS)	
APC Curvature Plots: Displaying Nonlinear Age-Period-Cohort Patterns on Lexis Plots (Chapter 6)	- Plot mortality curvatures for drug-related causes among boomers by race/ethnicity in the United States for the period 1990-2016 - Plot young adult mortality hump for Spain, Russia, Taiwan, and the United States during the period 1965-2016 - Cohort fertility rate curvatures for Spain, Sweden, and the United States	- Annual death records by sex, race, ethnicity, cause of death, and single years of age in the United States between 1990 and 2016 (NVSS) - Population estimates by calendar year, single years of age, sex, race, ethnic group, and cause of death from 1990 to 2016 (NVSS) - Annual all-cause mortality data and exposures to risk for Spain, Russia, Taiwan, and the United States during the period 1965-2016 (HMD) - Age specific fertility rates for Spain, Sweden, and the United States for the cohorts born between 1905 and 1985 (HFD[g])	- Lexis surfaces of mortality - Lexis surfaces of mortality change - P-splines smoothing and interpolation - Detrended APC models - APC curvature plots

[a] U.S. National Vital Statistics System
[b] Human Mortality Database
[c] Web application containing weekly U.S. influenza surveillance reports
[d] Influenza-like Illness
[e] Canadian Human Mortality Database
[f] Canadian Vital Statistics Database
[g] Human Fertility Database

3.1. Data

This section presents a summary of the data used for the analyses presented in this dissertation. A detailed description can be found within each article. For the analysis of influenza mortality (article 1) and of the contributions of the leading causes of the baby boomers' excess mortality (article 2),

we required death counts and population estimates with high resolution in age and period dimensions. For the construction of the visual tool for the analysis of nonlinear APC effects (article 3), we required additional vital rates, because we were seeking to extend the application of this tool to other demographic phenomena. As we mentioned in the introduction, most of the data we used are openly available from official websites and previous scientific publications. The only exception is the set of micro-data on Canadian mortality, which is not publishable because of confidentiality restrictions. However, for reproducibility purposes, smoothed Canadian mortality rates by the causes of death included in the analyses are openly available in the respective OSF repository (Acosta 2019c).

3.1.1. Death counts

Death counts data by sex, single year of age (0-100), and calendar year (1959-2016) for Canada and the United States were obtained from the Canadian Human Mortality Database (CHMD) (2019) and the Human Mortality Database (HMD) (2019), respectively. The CHMD obtained the Canadian death counts from Statistics Canada, and the HMD obtained the U.S. death counts from the National Center for Health Statistics. For both countries, the death counts were available by age, but not by single year birth cohort, which is an important limitation that will be discussed later. Mortality counts were adjusted in the CHMD and in the HMD when information about age or sex was missing by distributing missing cases proportionally according to observed distributions by sex or age (Wilmoth et al. 2019).

For the analysis of influenza mortality in the United States (article 1) and the baby boomers' excess mortality in Canada and the United States (article 2), mortality data by cause of death were needed. For the United States, death counts by sex, age, calendar year, race, ethnicity, and cause were retrieved from the mortality micro-data files for the period 1959-2016. These mortality micro-data files were collected and coded from individual death certificates that were published by the National Vital Statistics System (NVSS), and are openly available through the National Bureau of Economic Research website (NBER 2019). These death counts are considered complete and of good quality from 1933 onward because of the legal requirements for death registration. As mortality counts in the United States are confined to those that occurred within the country, deaths of U.S. residents that occurred outside the country are not included (Andreeva et al. 2019).

For Canada, mortality data by age (0-100), cause, and sex between 1974 and 2014 were aggregated from the Vital Statistics - Death Database (CVSD) (Statistics Canada 2018). As we mentioned earlier, Canadian mortality micro-data are not openly available due to confidentiality restrictions. This database is compiled by Statistics Canada from death certificates received from all provinces and territorial vital statistics registries. It is considered virtually complete because the registration of deaths is a legal requirement in each Canadian province and territory. The potential for undercoverage is considered minimal, and it is constantly monitored. The database includes all deaths of residents in Canada and of Canadian residents that occur in the United States. For any missing province or territory of residence, sex, age, and date of birth of the decedent, Statistics Canada, the provinces, and the territories carry out imputations that are based on standard edit specifications (Statistics Canada 2018).

The U.S. mortality data cover four successive revisions of the International Statistical Classification of Diseases (ICD) (from the 7th to the 10th ICD revisions), whereas the Canadian mortality data cover three of these revisions (from the 8th to the 10th ICD revisions). An important discontinuity in the trend was noted for influenza and pneumonia mortality when the revisions were implemented, but not for behavioral causes (Anderson et al. 2001). Therefore, the death counts classified in the influenza and pneumonia category using ICD codes from the 7th to the 9th revisions (1959-1999) were adjusted to ensure comparability with the 10th ICD revision (1999-2016). These adjustments were made by using the comparability ratios computed from the bridge-coding studies between the following ICD revisions: 7th and 8th (Klebba and Dolman 1975), 8th and 9th (Klebba and Scott 1980), and 9th and 10th (Anderson et al. 2001). Since the 6th ICD revision in 1949, the method for computing the comparability ratios has been based on a dual classification of a single year's mortality data; that is, a classification of the underlying cause of death according to both the previous and the new revision. Based on this dual coding, it is possible to measure discontinuities in mortality data resulting from the introduction of each new revision, and to compute comparability ratios (Anderson et al. 2001; Klebba and Scott 1980). The cause-specific comparability ratios are estimated by dividing the death counts classified in the new revision by the death counts classified in the previous revision. The comparability ratios may be applied to adjust the mortality counts in order to ensure that the causes of death classified by a previous revision are comparable to the same causes classified by the new revision. For our analyses, we adjusted pneumonia and influenza deaths by dual-coding the mortality data referring to the years 1969, 1976, and 1996 in order to measure the

discontinuities resulting from the introduction of the 8th, 9th, and 10th revisions, respectively (Anderson et al. 2001; Klebba and Dolman 1975; Klebba and Scott 1980).

Table 1 presents the ICD codes (from the 7th to the 10th ICD revisions) that we used to identify the pneumonia and influenza (P&I) mortality for the analysis of influenza mortality in the United States between 1959 and 2016 (article 1). Table 1 also includes the ICD codes (from the 8th to the 10th ICD revisions) we used to identify deaths from drugs, alcohol, HIV/AIDS, hepatitis C, suicide, and chronic obstructive pulmonary disease (COPD) for the analysis of the baby boomers' excess mortality in Canada and the United States (article 2). Note that codes identifying deaths from HIV/AIDS and from hepatitis C were first used starting in 1987.

Table 3.2: ICD codes (from ICD-7 to ICD-10 revisions) for selected causes of death

ICD revision	**7th**	**8th**	**9th**	**10th**
ICD periods for Canada	**1958-1968**	**1969-1978**	**1979-1999**	**2000-2016**
ICD periods for the United States	**1959-1967**	**1968-1978**	**1979-1998**	**1999-2016**
Pneumonia and Influenza (P&I)	480-483, 490-493	470-474, 480-486	480-487	J10-J18
HIV		NA	0420-0449	B20-B24
Hepatitis C		NA	0704-0705	B171, B182
COPD		4900-4928	4900-4928	J40-J44
Suicides		9500-9599	9500-9599	X60-X84
Drug-related causes (accidental overdoses + drug dependence + mental and behavioral disorders due to use of drugs)		2943, 3040-3049, 3091, 8500-8599, 9800-9803	2920-2929, 3040-3049, 3052-3059, 8490-8589, 9800-9805	F11-19, F55, X40-X44, Y10-Y14
Alcohol-related causes (accidental alcohol intoxication + long-term harm from liver cirrhosis + mental and behavioral disorders due to use of alcohol + other diseases due to consumption of alcohol)		2910-2919, 3030-3039, 5353, 5710, 8600-8609	2910-2919, 3030-3039, 3050, 3575, 4255, 5353, 5710-5713, 7903, 8600-8609	E244, F10, G312, G621, G721, I426, K292, K700-K709, K860, X45, Y15, Y90, Y91

3.1.2. Population estimates

For the estimation of mortality rates by age, calendar year, and sex in Canada and the United States, we employed population estimates from the CHMD (2019) and the HMD (2019), respectively. For both countries, the exposure-to-risk estimates were adjusted in the HMD to reflect the timing of

deaths during the calendar year (Wilmoth et al. 2019). The Canadian annual population estimates were provided to the CHMD by Statistics Canada (2017). The primary sources for the Canadian population estimates are the decennial and quinquennial censuses, as well as the intercensal and postcensal population estimates produced by Statistics Canada. The undercount errors of the population estimates vary between 1% and 3% from census to census, and Statistics Canada has corrected these errors since 1971 (Andreev et al. 2019). The only problem that has been detected in Canadian population estimates is the number of centenarians, which appears to be large relative to the numbers reported in other high-income countries (Bourbeau and Lebel 2000); fortunately, these figures have recently been adjusted by Statistics Canada (Andreev et al. 2019). Be that as it may, this potential problem does not affect our analyses because we used population estimates below age 100.

For the United States, the HMD obtained the annual population estimates from the U.S. Census Bureau. For consistency, the HMD adjusted the data between 1959 and 1969 to exclude members of the Armed Forces serving overseas. The data on population counts since 1970 were obtained directly from the U.S. Census Bureau intercensal population estimates for the U.S. resident population, without applying additional corrections (Andreeva et al. 2019).

For the analysis of influenza mortality, monthly exposures were required. We interpolated the annual exposures to risk to obtain the monthly exposures, assuming that changes in the exposures were distributed uniformly during the year. The seasonality of fertility, mortality, and migration is not expected to bias the estimates when aggregated by epidemic season.

For the analysis of the baby boomers' excess mortality by race and ethnicity, annual population estimates by sex, single year of age, race, and ethnicity between 1990 and 2016 were obtained from the Bridged-Race Population Estimates, which were published online by the NCHS (2019). The bridged-race estimates were elaborated by an agreement between the NCHS and the U.S. Census Bureau. These data resulted from bridging the 31 race categories used in Censuses 2000 and 2010 to the four race categories that are used in the U.S. Vital Statistics System. These estimates provide a way to compare racial and ethnic categories registered in the Vital Statistics System and in the census, and, thus, to obtain an accurate estimate of vital rates by race and ethnicity (Ingram et al. 2003).

In addition to the above data, we used aggregated vital data in the third article (chapter 6). Data on exposures and mortality counts from Spain, Russia, Taiwan, and the United States between 1965 and

2016 were obtained from the HMD (2019). Age-standardized fertility rates (ASFR) from Spain, Sweden, and the United States were obtained from the Human Fertility Database (HFD) (2019).

3.1.3. Measures of Influenza Virus Circulation

For the estimation of monthly influenza mortality in the United States in the first article, we estimated monthly indicators of influenza-like illness (ILI) and percentages of respiratory specimens testing positive for influenza between 1997 and 2016 from weekly indicators registered in the FluView Interactive database (CDC 2018), as we had done in previous work (Gagnon et al. 2018a).

Information on ILI in the United States is collected from near 50 million patient visits per year to more than 3,500 healthcare providers in all states and territories. The health care providers report the total number of patients seen for any reason and those with ILI symptoms, which are defined as those who presented "fever and cough and/or sore throat without a known cause other than influenza" (CDC 2019). Virologic surveillance data of laboratory-confirmed influenza cases are routinely obtained from 100 public health providers and 300 clinical laboratories that perform tests for surveillance and diagnosis purposes, respectively. These laboratories are located in all 50 states and territories of the United States. Virologic surveillance data are published weekly, and include information on age group, tested virus subtype, and geographical location (CDC 2019).

In addition, to estimate the influenza-related mortality by virus subtype between 1959 and 2016, we retrieved information from complementary sources on virologic surveillance before 1997. Because there was no information available in the FluView Interactive database before October 1997, the annual percentages of respiratory specimens testing positive by influenza virus subtype between 1976 and 1996 were obtained from Thompson et al. (2003). In contrast to the FluView Interactive database, the information provided by Thompson et al. (2003) is aggregated for all ages and the whole epidemic year, which prevented the estimation of influenza mortality before 1997 in models that required surveillance data.

3.2. Methods

The analyses presented in this dissertation are entirely reproducible, except for some steps applied to Canadian data, due to confidentiality. We published all the scripts required in Open Science Framework (OSF) repositories (Acosta 2019a, 2019b, 2019c).

3.2.1. Estimation of influenza-related mortality

Before analyzing influenza-related mortality in the first article (chapter 4), it was required to identify these deaths, which is challenging for at least two reasons. First, flu infections are not typically confirmed by laboratory tests. Second, a considerable number of deaths, to which influenza is likely a contributor, result from secondary complications, such as bacterial pneumonia or the exacerbation of underlying chronic diseases. Therefore, we can assume that the number death records with influenza as a standalone cause of death is much smaller than the number of deaths related to influenza (Noymer and Nguyen 2013; Simonsen et al. 2006).

Various methods have thus been developed for estimating influenza mortality (Thompson et al. 2009). For the analyses performed here, we applied two kinds of Negative Binomial Serfling regression models. We summarize these methods in this section, but a more detailed explanation about their application is provided in the first article (chapter 4). To estimate influenza mortality between 1959 and 2016, we applied a classical Serfling model, which is based exclusively on seasonal variations. This model assumes that there is no circulation of influenza during summer periods in temperate regions. Hence, a mortality baseline was estimated by fitting P&I deaths that occurred exclusively within summer seasons. Then, influenza-related mortality was defined as the difference between the observed P&I death counts and the estimated mortality baseline.

A surveillance Serfling model that includes influenza measures was applied to improve the accuracy of the estimates. This model takes into account influenza-like illness measures (ILI) and laboratory test data. To estimate influenza mortality, deaths recorded in the P&I categories were fitted to obtain a "predicted" mortality count. Next, all influenza activity terms were set to zero in order to estimate a mortality baseline without influenza activity. The difference between the predicted mortality and the baseline then reflected the mortality caused by influenza. Although this method generates more accurate estimates than the classical Serfling model, its use is restricted to periods in which influenza

circulation measures are available on a monthly basis. As there is no measure of influenza circulation by month and age prior to 1997 in the United States, the Surveillance-Serfling method could not be applied to earlier periods. Additional details of the Serfling models are included in the supplementary material of the first paper (S1), such as information on the parameterization, the criteria for the selection of the best models, the fitting measures, and the sensitivity analyses that were performed.

3.2.2. Estimation of mortality by cohort and the decomposition of changes by cause of death

For the analysis of the leading causes of death contributing to the relative excess mortality among baby boomers in the second article (Chapter 5), we propose the *cohort's partial mortality rate* to measure the mortality level within a cohort, and to decompose its change by cause of death. This measure is defined as:

$$CPMR^{c(k,l)} = \sum_{x=k}^{l} m_x^c \,, \tag{1}$$

where m_x is the age-specific mortality rate, for the age interval k, l, over the cohort c.

Being the sum of the age-specific mortality rates between two ages in a cohort, this measure is the mortality analogous of the cohort's total fertility rate (TFR^C) (Preston et al. 2000). A similar index (*indice synthétique de mortalité*) was previously suggested by Termote (1998) as a measure of changes in mortality over periods.

An advantage of the $CPMR^{c(k,l)}$ is that it attributes the same weight to all deaths, independent of age, and thus avoids the distortion of the contributions of causes of death that are highly correlated with age.

The *change in the cohort's partial mortality rate* between cohort (a) and a disadvantaged cohort (d) for the age interval(k, l) is defined as:

$$\Delta CPMR^{d-a(k,l)} = CPMR^{d(k,l)} - CPMR^{a(k,l)}. \tag{2}$$

The decomposition of the $\Delta CPMR^{d-a(k,l)}$ by cause of death is straightforward because the sum of all the *changes in the cohort's partial mortality rate by cause of death* i ($\Delta CPMR_i^{d-a(k,l)}$) equals the observed total *change in the cohort's partial mortality rate*:

$$\Delta CPMR^{d-a(k,l)} = \sum_i \Delta CPMR_i^{d-a(k,l)}. \tag{3}$$

3.2.3. Smoothing of mortality rates

To identify trends and avoid the "noise" introduced by random variations, we smoothed the mortality rates in numerous instances. For this smoothing process, we used the P-spline method, which is a very flexible method of smoothing that combines B-splines and a penalized likelihood function. The B-spline consists of an aggregate of consecutive polynomial pieces that are joined at certain values, denoted as knots (Eilers and Marx 1996). Such polynomial pieces are bell-shaped curves that add an excellent local control to the data smoothing (Ouellette 2011). The number of knots and smoothing values is critical: too many leads to overfitting, while too few leads to underfitting (Eilers and Marx 1996). Eilers and Marx (1996) proposed using a relatively large number of knots and penalizing the flexibility of the fitted curve to find an optimal smoothing value. This penalization is applied to the regression coefficients. In the P-spline approach, the selection of the optimal smoothing parameters for the B-splines is done by finding a balance between parsimony and accuracy. For this purpose, Eilers and Marx (1996) proposed the use of the Akaike Information Criterion (AIC) (Burnham and Anderson 2002; Camarda 2012; Hilbe 2011; Raftery 1995). Later, Currie and colleagues (2004) extended the P-splines method for smoothing and forecasting two-dimensional mortality tables to allow for the fitting of mortality surfaces. They pointed out that the use of the Bayesian Information Criterion (BIC) was preferable to the use of the AIC in the selection of optimal parameters, because this measure penalizes model complexity more heavily, avoiding the undersmoothing of data (Camarda 2012; Currie et al. 2004). Another advantage of the P-spline method is that it allows for the fitting of Poisson distribution data that account for overdispersion (negative binomial model). These attributes are suitable for the smoothing of mortality data because death counts are positive integer values, some having low to very low frequencies, with overdispersion. We used the R package *MortalitySmooth* (Camarda 2012) to estimate one- and two-dimensional P-Splines of mortality data.

3.2.4. Age-Period-Cohort analyses of vital rates

Graphical and statistical methods for APC analyses are abundant in the literature. This section presents a summary of the developments of the APC methodology that justify its use in this dissertation. The section begins with a general presentation of the *classical APC model,* in which we

describe the identification problem and other attributes that are specific to APC models. Then, we distinguish between methods that are suitable for the analysis of linear effects and nonlinear effects.

As we mentioned in the introduction, several statistical methodological attempts have been made since the end of the 19th century to analyze the APC effects on mortality. However, the model proposed by Mason and colleagues (1973) – denoted as the multiple-classification model – was the first that accounted simultaneously for APC variations (Glenn 1976; O'Brien 2014; Yang et al. 2004). For more than 40 years, most of the proposed APC statistical models have been adaptations of the multiple-classification model developed by Mason (1973). For this reason, this model is also referred to in the APC literature as the *Classical APC model* (CAPC) (Fosse and Winship 2019a, 2019b; O'Brien 2014; Yang and Land 2013a). The multiple-classification model is defined as:

$$log(deaths_{a,t}) = \theta_0 + \alpha_a + \beta_t + \gamma_c + log(exposure_{a,t}), \quad (4)$$

where $deaths_{a,t}$ is the death counts at age a at time t, θ_0 is a constant, α_a is the effect of age a, β_t is the effect of period t, γ_c is the effect of cohort c, and $exposure_{a,t}$ is the population of age a at risk at time t. Single or multiple years may be employed.

Subsequent studies have acknowledged that the APC effects could be decomposed into linear and nonlinear components (Fienberg and Mason 1979; Holford 1983; Rodgers 1982). In this partitioning approach, the linear effects refer to the overall linear trend, and the nonlinear effects refer to the divergences from this linear trend. Rodgers (1982) proposed the concept of a *curvilinear* component – later referred to and popularized as *curvature* by Holford (1983) – to refer to the divergences from the linear effects. Other methods for the analysis of nonlinear components were further developed (Clayton and Schifflers 1987; Holford 1991, 2005; O'Brien 2014a, 2014b; Tango and Kurashina 1987; Tarone and Chu 1996). According to this approach, instead of using the dummy variables in Equation 4, each temporal dimension of the APC model can be decomposed into linear and curvature terms (Holford 1983; Rodgers 1982). As an example, for age, we have:

$$\alpha_a = \alpha_a^d + \delta_a(a - a_0), \quad (5)$$

where α_a is the effect of age a, α_a^d is the age curvature for age a, δ_a is the age linear effect, and a_0 is the reference age. Similarly, period and cohort effects have nonlinear (β_p^d, γ_c^d) and linear (δ_p, δ_c) components. Being independent of the partitioning of the linear effects, the nonlinear components or curvatures remain the same whatever the constraint used and are identifiable.

Although the partitioning of linear effects among APC components has an infinite number of solutions, these solutions are restricted to the linear dependence between the three temporal dimensions. Then, taking into account the perfect multicollinearity between APC variables ($cohort = period - age$), and the decomposition between the linear and curvature components presented in Equation 5, Equation 4 can be reformulated as (Holford 2006):

$$log(deaths_{a,t}) = \theta_0 + x\,\alpha_a^d + \delta_a(a - a_0) + y\,\beta_p^d + \delta_p(p - p_0) + (y - x)\,\gamma_c^d + \delta_c(c - c_0)\beta_t + log(exposure_{a,t}), \quad (6)$$

where x and y are arbitrary constants; i.e., are determined by one of infinite solutions of the decomposition of the linear trend among the APC dimensions. From Equation 6, two essential implications from APC models can be noted. First, although the solutions for the partitioning of the linear component are infinite, the slopes of the age, period, and cohort linear effects cannot vary freely from each other. Second, if any of the slopes is fixed, the other two are determined (Rodgers 1982).

In this sense, the possible values that x and y can take in Equation 6 are constrained to a solution line, which represents all the possible slope values that give an identical fit to the data in terms of likelihood ratios, AICs, BICs, and the like (Fosse and Winship 2019a; Holford 1991; Mason et al. 1973). As proposed by Rodgers (1982), the linear effects of any APC model can be expressed as:

$$\delta_a^* = \delta_a + v, \quad (7)$$

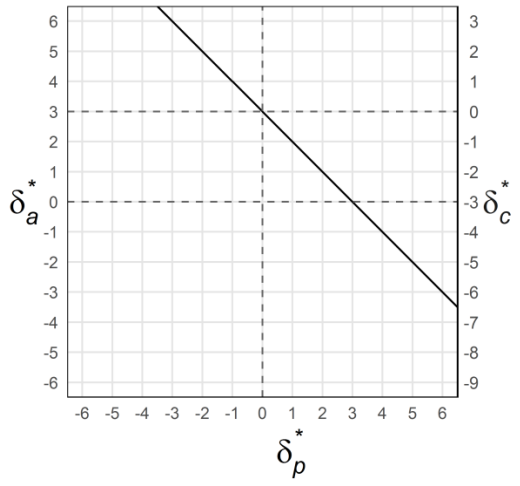
$$\delta_p^* = \delta_p - v, \quad (8)$$

$$\delta_c^* = \delta_c + v, \quad (9)$$

where δ_a^*, δ_p^*, and δ_c^* are arbitrary age, period, and cohort slopes, respectively, from an APC model under particular constraints; and v is an arbitrary constant, fixed to some value, which is the bias of the APC slopes estimates from the true linear effects (Rodgers 1982).

Fosse and Winship (2019a, 2019b) have proposed the visualization tool *2D-APC graph*, which helps visually depict the solution line and the interrelationship among age, period, and cohort linear effects. Figure 1 presents a *2D-APC graph* with arbitrary dependence of the linear effects as an example. In this plot, the vertical axis on the left indicates the set of possible values for the slope of the age effects (δ_a^*), the horizontal axis indicates the set of possible values for the slope of the period effects (δ_p^*), and the vertical axis on the right indicates the set of possible values for the slope of the cohort effects (δ_c^*). The vertical and horizontal dashed lines indicate when the slope of the linear age, period, or cohort effects take the value of zero (i.e., when the effects are detrended in each dimension). And, finally, the diagonal solid line indicates a solution line of the APC model in which all points (i.e., all the possible partitions of the linear effects among the APC factors) offer the exact same fit. This plot offers an intuitive way of visualizing several properties of the APC model: the identification problem (i.e., there is not a unique solution), the interdependence of APC linear effects contained in the solution line described in Equations 6 to 9 (i.e., the APC slopes are not independent of each other), and the fact that arbitrarily defining one of the slopes in any of the three temporal dimensions implies the identification of the other two.

Figure 3.1: **Example of a *2D-APC graph* of the partitioning of the linear effects.**



Note: The vertical axis on the left indicates the slope of the age effects (δ_a^*), the horizontal axis indicates the slope of the period effects (δ_p^*), and the vertical axis on the right indicates the slope of the cohort effects (δ_c^*). The vertical and the horizontal dashed lines indicate when the slope of the linear age, period, or cohort effects takes the value of zero. The diagonal solid line indicates the solution line of the APC model.

Analysis of linear effects

Unique solution approaches

Since the formulation of the multiple-classification model, several methods have been proposed that attempt to overcome the identification problem by imposing mathematical constraints with a unique solution for the partitioning of the linear effects. The nature of these constraints can be divided into two main groups: *explicit* and *mechanical* constraints (Fosse and Winship 2019a).

Most of the models that impose explicit constraints were developed during the 1970s and the 1980s. The most common approach used for the selection of explicit constraints is the constraint-based model (Mason et al. 1973). This approach consists of restricting two of the age, period, or cohort categories so that they have the same effect on the outcome variable under theoretical assumptions (e.g., that the effects of two age groups are identical, independent of period and cohort variations). However, as has been noted by others, these assumptions are difficult if not impossible to justify from a theoretical standpoint, and the resulting slope of each estimated linear effect is highly sensitive to minor differences in the specification of the model (Clayton and Schifflers 1987; Fosse and Winship 2019a; Rodgers 1982; Tarone and Chu 1996; Yang et al. 2004; Yang and Land 2013).

The most recent type of statistical model aiming to decompose the linear trend on the basis of mechanical constraints was proposed during the first decade of the 21st century. In this approach, the constraint is not imposed by the researcher, but is generated by the design matrix itself. The logic behind this approach is to select, among the infinite possible solutions, the solution for which the estimators reach the minimum variance. One way to select such a solution is to apply a Moore-Penrose (MP) inverse estimation, which produces a solution that is orthogonal to the null vector of a particular design matrix (Fosse and Winship 2018; Fu 2000; O'Brien 2014a; Yang et al. 2004). However, there is no a unique MP solution, and different estimators can be obtained when applying this approach depending on the parameterization of the model (Fosse and Winship 2018; O'Brien 2014a). Among the possible MP estimators are the ridge estimator (Fu 2000), the intrinsic estimator (Yang et al. 2004; Yang and Land 2013a), and the orthogonal estimator (Fosse and Winship 2018).

The validity of this "general purpose" approach has been debated (Bell and Jones 2013, 2014; Fienberg 2013; Fosse and Winship 2018; Fu 2016; Held and Riebler 2013; Land et al. 2016; Luo 2013; Masters et al. 2016; O'Brien 2013; Reither et al. 2015; Tolnay 2013; Yang and Land 2013b).

The main reason for the broad skepticism surrounding this mechanical approach is that it is impossible to prove that the actual process under observation – in this case, mortality– behaves according to the implicit assumptions of the MP estimators, which are based on statistical properties, rather than being grounded in social, cultural, or biological theory (Fosse and Winship 2018; Luo 2013).

Interval solution approaches

Beyond the approaches we discussed above, other methods that attempt to overcome the identification problem have been proposed. These methods offer a range of possible solutions for the partitioning of the linear effects (i.e., a segment of the solution line) instead of a "true unique solution" (i.e., a point of the solution line). These models rely on weaker and less arbitrary assumptions, which are more tenable from a theoretical standpoint.

Within the *drift* approach proposed by Clayton and Schifflers (1987), for instance, they state that the linear component can be decomposed into two dimensions: one linear component pertaining to age effects, and a second component that is impossible to separate into period and cohort effects, which is the *drift*. Equations 7 to 9 imply that the sum of the period and cohort linear effects (i.e., the *drift*) is the same and unbiased, independently of the constraint imposed on the model. Thus, the *drift* of the model is defined as:

$$\delta = \delta_p + \delta_c \ . \tag{10}$$

where δ_p and δ_c are the period and cohort linear effects. Again, note that given the identification problem presented earlier, the model yields the same fit for an infinite number of different partitions of the drift (δ) among the period (δ_p^*) and cohort (δ_c^*) components.

From this approach, two opposite scenarios can be proposed: one in which the whole drift is attributed to period changes (i.e., the cohort effects are detrended, $\delta_c^* = 0$), and a second one in which it is completely attributed to cohort changes (i.e., the period effects are detrended, $\delta_p^* = 0$). According to this approach, it is highly plausible that the true partition of the linear effects is located somewhere in between these two scenarios, and the common aspects that are invariant in both could be considered valid in the unknown "true" scenario.

An alternative interval approach, which has been denoted as *restricted ranges* (Holford 1991; Wickramaratne et al. 1989), and has been further developed as the *bounding analysis of APC effects*

(Fosse and Winship 2019b, 2019a), is based in prior theoretical knowledge that is applied to constrain the possible values of the slope in each temporal dimension (e.g., mortality cannot decrease between two specific ages, or mortality necessarily increases between two periods because of an epidemic that affects all age groups). After restricting the model to theoretical constraints, the output of this approach is a range of solutions, which can, in some cases, approximate a unique solution.

Analysis of nonlinear effects

Statistical approaches

As we pointed out in chapter 2, an advantage of the analysis of the nonlinear effects is that these effects do not vary depending on the constraint imposed on the model specification, and are thus identifiable (Carstensen 2007; Clayton and Schifflers 1987; Holford 1991). For this reason, some approaches focus exclusively on the identification and measurement of the curvature components α_a^d, β_p^d, and γ_c^d, which are the only components that can be identified; leaving aside the linear effect, whose "true" value remains unknown.

When reducing the linear trends to zero (the so-called detrended APC effects), it is possible to isolate and plot the curvatures and to estimate the relative risk of each category of age, period, and cohort; compared to the expected risk for the overall trend (Holford 1991).

In addition, Tango and Kurashina (1987) have proposed the analysis of *contrasts*, which are the second derivatives (also known in the APC literature as *local curvatures* or *second-order effects*) of the mortality changes that are specific to each temporal dimension. Contrast measures follow the form:

$$C_h = (\pi_{h+1} - \pi_h) - (\pi_h - \pi_{h-1}), \tag{11}$$

where π_h is the h-th age, period, or cohort effect estimate. The resultant local curvature C_h is invariant to the parameterization used to obtain the effects. This measure essentially compares the h-th category with the categories on either side (Holford 1991).

Based on the contrast idea, Tarone and Chu (1996) developed a simple but useful extension of Equation 12 to measure the change in slope between two disjoint segments of effects, each of which is composed of several age, period, or cohort categories. The utility of Tarone and Chu (1996)'s

contrast approach is that it is able to quantify the changes in risk between two blocks composed of several APC categories, plus a statistical measure of significance. Therefore, it can be used to identify "breakpoints" or "rupture points" at which the direction of the risk trend changes significantly (i.e., the risk increases or decreases significantly). Further details about the formulation of the contrasts can be found in the supplementary material of chapter 4 (S1).

It is important to highlight that, although they are identifiable, a limitation of these nonlinear effects is that they refer to fixed average effects, and do not allow the size of the nonlinear effects to vary over time/age (Chauvel 2013). In other words, these averages hide variations of the nonlinear effects over age, period, or cohort. For instance, as described in chapter 2, a selection mechanism could manifest initially with a higher relative risk of death for one cohort and later reverse to relative advantage because of the gradual exclusion of the frailest individuals. This variation in time of the cohort mortality risk would be not reflected in the resulting cohort effect, and even might cancel out when averaged. A partial solution to this problem was proposed by Chauvel (2013): namely, the *Age-Period-Cohort hysteresis model*, which can be used to measure increases or decreases in the magnitude of the curvature over age/time. However, this estimate is still a fixed measure of change that only allows for continuous increases or decreases over time. Thus, it does not identify non-constant changes or temporary nonlinear effects, which is crucial information when analyzing APC effects on mortality. For instance, when analyzing cohort effects on mortality, the lack of information about the actual pattern of nonlinear effects over age/time makes it impossible to detect the difference between a short-term age-period interaction and a real, sustained cohort effect, or the changes in the location of the most advantaged or disadvantaged cohorts over age/time.

Visual approaches

Graphical methods for the analysis of nonlinear variations over age, period, and cohort have been widely used in mortality research since the 19th century (Caselli and Vallin 2005; Keiding 2011; Vaupel et al. 1987). Given the identification problem of statistical analyses, several authors have argued that graphical analyses are more transparent (Murphy 2010; Preston and Wang 2006; Willets 2004). Although using graphical analyses does not overcome the identification problem, it offers some advantages over using the available statistical methods for the analysis of nonlinear APC effects.

In particular, the Lexis surfaces of mortality change are widely recognized in the demographic literature as being very powerful, yet simple methods for detecting age, period, and cohort effects in the mortality dynamic (Barbi and Camarda 2011; Ouellette et al. 2012; Rau et al. 2013; Schöley and Willekens 2017; Vaupel et al. 1987). Unlike statistical analyses, the visualization of mortality changes makes it possible to identify the temporal dynamics of nonlinear effects, such as their changes in location and intensity over age/time.

Changes in mortality rates over age/cohort (i.e., vertical changes along the same period in the Lexis diagram) reflect the confounded linear and nonlinear age/cohort effects operating within the same period. Analogously, changes in vital rates over period/cohort (i.e., horizontal changes along the same age in the Lexis diagram) reflect the confounding age/cohort effects within the same period, and changes in vital rates over age/period (i.e., diagonal changes along the same cohort in the Lexis diagram) reflect the confounding age/period effects within the same cohort.

To construct mortality surfaces of mortality change, we first estimate two-dimensional smoothed mortality rates with the P-splines methods described above in order to eliminate the noise of random fluctuations. Then, for each single-year age x and period t, we estimate single-year rates of mortality change (Kannisto 1994; Rau et al. 2013) over age/cohort

$$\Delta ac_{x,t} = \log\left(m^s_{x,t}\right) - \log\left(m^s_{x-1,t}\right), \tag{12}$$

over period/cohort

$$\Delta pc_{x,t} = \log\left(m^s_{x,t}\right) - \log\left(m^s_{x,t-1}\right), \tag{13}$$

and over age/period

$$\Delta ap_{x,t} = \log\left(m^s_{x,t}\right) - \log\left(m^s_{x-1,t-1}\right), \tag{14}$$

where $m^s_{x,t}$ is the smoothed death rate for the single-year age x in period t.

Then, we plot $\Delta ac_{x,t}$, $\Delta pc_{x,t}$, and $\Delta ap_{x,t}$ values on separate Lexis surfaces using two different color scales, with one scale depicting the slope of the mortality improvement, and the second scale displaying the slope of the mortality deterioration over age/period/cohort. Invariance of color in the Lexis surfaces is indicative of monotonic changes in mortality rates (linear changes), whereas changes in color are indicative of changes in the slope of the mortality change (nonlinear changes or curvatures). The presence of systematic changes in the color scale that follows horizontal, vertical, and diagonal traces are symptomatic of age, period, and nonlinear cohort effects, respectively. The

changes between scales indicate that mortality change reaches a local valley or a local peak in mortality change; i.e., maximum improvement or maximum deterioration, respectively.

The advantage of using these surfaces rather than the statistical methods described above is that whereas the former allow us to identify all nonlinear variations present in the Lexis surface, the latter only estimate averages of the nonlinear changes, as discussed earlier. The use of Lexis surfaces of mortality change allows the shapes of curvatures to move freely through the Lexis diagrams, and depicts the pattern with higher fidelity to the observed data. Thus, using this approach, it is possible to identify the differences between short-term interactions and sustained effects, as well as effects that are reversed over time. A rich summary of several options for using Lexis surfaces to depict mortality dynamics can be found in the works of Vaupel et al. (1987) and Rau et al. (2018).

On the other hand, when we compare the Lexis surfaces of mortality change with the statistical estimates obtained from APC models, we can see that the former are more difficult to use for the comparison of several curvature features, populations, or demographic phenomena in the same plot. For these comparisons, we need as many surfaces as the populations or phenomena we are interested in comparing. Thus, this approach has been inadequate in some cases, as it not only uses space inefficiently; it makes it difficult to compare the patterns even when the surfaces are facetted.

Being aware of these limitations, we identified the need to design a new visual tool that allows us to take advantage of the flexibility that the Lexis surfaces offer, while also enabling us to extract and depict the information required for comparisons across populations or demographic phenomena. In the third article of this dissertation (Chapter 6), we propose the *APC curvature plots*, which represent a methodological contribution to improving the analysis of nonlinear APC effects of any population change process.

Chapter 4 - Determinants of Influenza Mortality Trends: Age-Period-Cohort analysis of influenza mortality in the United States, 1959-2016[3]

Abstract

This study examines the roles of age, period, and cohort in influenza mortality trends over the years 1959–2016 in the United States. First, we use Lexis surfaces based on Serfling models to highlight influenza mortality patterns as well as to identify lingering effects of early-life exposure to specific influenza virus subtypes (e.g., H1N1, H3N2). Second, we use age-period-cohort (APC) methods to explore APC linear trends and identify changes in the slope of these trends (contrasts). Our analyses reveal a series of breakpoints where the magnitude and direction of birth cohort trends significantly change, mostly corresponding to years in which important antigenic drifts or shifts took place (i.e., 1947, 1957, 1968, and 1978). Whereas child, youth, and adult influenza mortality appear to be influenced by a combination of cohort- and period-specific factors, reflecting the interaction between the antigenic experience of the population and the evolution of the influenza virus itself, mortality patterns of the elderly appear to be molded by broader cohort factors. The latter would reflect the processes of physiological capital improvement in successive birth cohorts through secular changes in early-life conditions. *Antigenic imprinting*, *cohort morbidity phenotype*, and other mechanisms that can generate the observed cohort effects, including the baby boom, are discussed.

4.1. Introduction

At the beginning of the twentieth century, pneumonia and influenza (P&I) were the leading causes of death in the United States (Deaton 2015), and today, they remain the most important causes of

[3] Article published in the journal *Demography* as: Enrique Acosta, Stacey A. Hallman, Lisa Dillon, Nadine Ouellette, Robert Bourbeau, D. Ann Herring, Kris Inwood, David J.D. Earn, Joaquin Madrenas, Matthew S. Miller, and Alain Gagnon (2019a), Determinants of influenza mortality trends: age-period-cohort analysis of influenza mortality in the United States, 1959–2016. *Demography* 56:5, 1723-1746. https://doi.org/10.1007/s13524-019-00809-y

death among infectious diseases (Armstrong et al. 1999). The Spanish Flu (1918-1920), also known as the "mother of all pandemics" (Taubenberger and Morens 2006), caused more deaths than the First World War and killed more people in 24 weeks than AIDS did over a span of 24 years (Barry 2005). The following three influenza pandemics (in 1957, 1968 and 2009) and the appearance of new subtypes such as the highly-pathogenic avian H5N1 and H7N9 influenza viruses (Haque et al. 2007) demonstrate that influenza remains a significant threat to public health. Population aging makes it likely that casualties will increase (Simonsen et al. 2011), given that about 90% of all influenza deaths occur among people aged 65 and over (Thompson et al. 2003).

As is true for most infectious diseases, mortality from influenza diminished appreciably during the twentieth century (Armstrong et al. 1999). However, there is still much uncertainty regarding the mechanisms responsible for this reduction. The emphasis has been on monitoring disease and mortality from specific strains from year to year, with indicators of virulence, basic reproductive number (the number of people infected by one index case) or attack rates (the percentage of people infected) broken down by geographic areas and broadly defined age groups (Reichert et al. 2004; Thompson et al. 2010; Thompson et al. 2003). The generalized nature of these investigations has fostered interpretations of change over time almost exclusively in terms of secular or period change, modulated by biological age, with few alternative explanations of time trends. More recently, some investigators have focused on age-specific mortality from influenza during pandemics (Lemaitre et al. 2012; Nguyen and Noymer 2013), while others have analyzed the consequences of early life exposure to pandemic influenza on health and mortality in general (Almond 2006; Kelly 2009; Mazumder et al. 2010) or on mortality during subsequent influenza pandemics (Gagnon et al. 2013; Hallman 2015; Hallman and Gagnon 2014; Ma et al. 2011; Oeppen and Wilson 2006; Viboud et al. 2010). To our knowledge, only a few studies (see, e.g., Azambuja (2009, 2015) and Cohen et al. (2010)) have undertaken an analysis of influenza mortality variation over time in an age-period-cohort (APC) framework.

In most previous analyses, information on age was analysed using five-year (or larger) age groups, allowing for broad distinctions in mortality patterns among infants, children, adolescents, adults and seniors, but affording few chances to identify cohort effects defined on a yearly basis, as pertaining to cohorts born during a pandemic year. There is also non-negligible heterogeneity within broadly defined age categories, especially when referring to individuals in a terminal age category as broad as 65+ years. Some studies have shown an important change in influenza mortality risk after age 60,

with an 11-fold higher risk for a senior aged over 80 compared to persons aged between 65 and 69 (Simonsen et al. 2005, 2011; Thompson et al. 2009).

The present study examines the roles of age, period, and cohort factors as drivers of influenza mortality change over the years 1959-2016 in the U.S. It also addresses the effect of early-life exposure to the different influenza A virus (IAV) subtypes that have circulated over the past decades on later life mortality in the U.S. for single-year ages, periods, and cohorts, focusing on both seasonal epidemic and pandemic periods. To this end, we first estimated influenza mortality from death records by single years of age in the U.S. from 1959 to 2016 using Serfling models based on mortality data (Serfling 1965). Second, we used Surveillance-Serfling models (Thompson et al. 2009) accounting for influenza-like illness (ILI) incidence between 1997 and 2016 to estimate the proportion of deaths during the month of infection by age. Then we constructed Lexis surfaces from influenza death rates and applied detrended APC models (Carstensen 2007; Clayton and Schifflers 1987; Holford 1991) and the Intrinsic Estimator model (W. J. Fu 2000; Yang et al. 2004) to explore period and cohort effects on mortality variation. We also estimated "contrasts," proposed by Tarone and Chu (Tarone and Chu 1996), to identify statistically significant changes in mortality risk along birth cohorts trends. We interpret our results in light of the *antigenic imprinting* (Davenport et al. 1953; Ma et al. 2011) and the *cohort morbidity phenotype* hypotheses (Finch and Crimmins 2004), described in the next section.

4.2. Age-Period-Cohort Effects on Influenza Mortality

Susceptibility to infection and mortality from influenza chiefly depends on virus-host interaction factors and on the evolution of the virus itself (Thompson et al. 2003). As the immune response generated against a given strain of the influenza A virus (IAV) is not fully cross-protective, the virus can evade the host's immunity from one season to the next by accumulating mutations that change its antigenicity. This process, called *antigenic drift,* is differentiated from the appearance of a novel IAV by reassortment of the HA and NA surface proteins of IAV, called *antigenic shift*, which can lead to pandemics (Nelson and Holmes 2007).

Whereas typical IAV seasonal outbreaks most seriously affect the elderly (M. W. Thompson et al. 2010), epidemiological analyses of influenza pandemics have revealed a shift of mortality toward

younger ages, as was the case during the 1918, 1968, and 2009 pandemics in the US (Nguyen and Noymer 2013; Oeppen and Wilson 2006; Simonsen et al. 1998). During these outbreaks, older individuals often benefited from immunity acquired from previous exposures to virus strains similar to the current pandemic strain, while younger adults and children were at higher risk because of a lack of cross-protection from previous infections by similar IAVs. Risk can also be compounded in younger individuals, whose strong immune response to the virus can quickly turn overreactive and dysregulated, leading to immunopathology and organ damage (Kobasa et al. 2007; Loo and Gale 2007; Shanks and Brundage 2012).

The *antigenic imprinting* hypothesis additionally postulates that mortality from influenza not only depends on the virulence of the circulating strain but also on the strain to which a specific cohort was primed (Davenport et al. 1953; Ma et al. 2011; Rajendran et al. 2017). This original strain would indeed keep its senior position in the immune repertoire over successive episodes of infection, with each novel strain taking a more junior position (Henry et al. 2018; Miller et al. 2013). Based on studies showing the variable efficacy of repeated annual influenza vaccination (Smith et al. 1999), protection is expected when the original strain is similar to the circulating strain, but if the two are very dissimilar, susceptibility to severe outcome may increase (Cobey and Hensley 2017). According to this hypothesis, infection in the first years of life with a H3N8 virus, as was presumably the case for those born during the 1890 Russian IAV pandemic (Worobey et al. 2014), increased the risk of death upon encounter with the doubly heterosubtypic H1N1 virus that was responsible for the Spanish flu pandemic in 1918 (Gagnon et al. 2013; Hallman and Gagnon 2014; Shanks and Brundage 2012). Corroborating this, fifty years later, during the 1968 H3N2 Honk Kong flu pandemic, the largest excess mortality was for those aged 50 or a little older (Gagnon et al. 2015). Similarly, a peak in excess mortality during the 2009 H1N1 pandemic was observed at age 52, i.e., for those born in 1957, at the time of the H2N2 Asian flu pandemic (Gagnon et al. 2018a).

Hence, whereas mortality at all ages during a given year should reflect the virulence of the circulating strain that year, mortality levels of a specific cohort are expected to reflect the antigenic distance between this strain and the first strain this cohort encountered in early life. The priming of specific cohorts to specific viral strains is expected to produce punctual cohort-specific influences, independently of period trends, that is, turning points in the longer-term ascending or descending mortality trends that persist over time.

Patterns of influenza mortality may also be interpreted in the light of broader theoretical perspectives such as Finch and Crimmins' *cohort morbidity phenotype* hypothesis (2004), which attributes the vast reductions in later life mortality from chronic conditions over the last 200 years to the secular reduction in infections during early life. Together, improvements in nutrition and the declining incidence of infectious diseases have been almost continuous since the Industrial Revolution (Floud et al. 2011). Both are believed to have played a salient role in boosting *physiological capital*, an initial health advantage resulting from improved conditions during infancy and early childhood, leading to large increases in life expectancy (Fogel and Costa 1997; Meslé and Vallin 2000). Improvements gained at the individual level in successive cohorts could also have benefited the progeny, with further health improvements reverberating down the generations, as implied by the theory of technophysio evolution (Fogel and Costa 1997). Finding firm evidence for such a mechanism, however, requires linking a wealth of socioeconomic and environmental data over many generations. Such data are, especially at the individual level, rarely, if ever, available.

The *cohort morbidity phenotype* hypothesis specifically addresses secular changes in mortality from chronic or non-transmissible diseases in old age. Yet, much research has also documented strong comorbidities between chronic diseases and influenza-related mortality for people aged over 65 (Plans-Rubió 2007; Reichert et al. 2004; Simonsen et al. 2005). This provides a rationale to address past reductions in mortality from influenza from a cohort perspective – and more generally from an APC perspective – and not only as the result of secular (period) changes. In other words, improved survival from IAV infections in successive cohorts of elderly could have resulted not only from enhanced responses to infection and to medical treatments but also from delayed onset of comorbid conditions involving influenza and chronic diseases. In this respect, other cohort processes may also shape influenza mortality via these comorbidities or its relationship with mortality in general. For instance, increases in all-cause mortality (or at least slowdown in life expectancy improvements) have been documented for the boomer generation in recent years (Canudas-Romo and Guillot 2015; Rau et al. 2013), and it is possible that what drives these cohort processes also partly drives influenza mortality. Thus, our study also briefly addresses the baby boom as a possible contributor to APC trends in influenza mortality.

4.3. Data and Methods

4.3.1. Data

Aggregate U.S. death counts by month, single years of age, cause, and sex between January 1959 and December 2016 were obtained from the *National Center for Health Statistics* (2018). These data cover four successive revisions of the International Statistical Classification of Diseases (from ICD-7 to ICD-10) to classify the deaths. Concordance tables bridged the 7^{th}, 8^{th}, and 9^{th} to the 10^{th} ICD revisions to ensure consistency of definitions for disease categories under study and their comparability over time (Anderson et al. 2001; Klebba and Dolman 1975; Klebba and Scott 1980). Annual counts of population at risk from 1959 to 2016 by single years of age were taken from the *Human Mortality Database* (2019); monthly counts were estimated through interpolation. Monthly indicators of influenza-like illness (ILI) and percentages of respiratory specimens testing positive for influenza between 1997 and 2016 were estimated from weekly indicators registered in the CDC FluView Interactive database (2018). All these data are openly available in the referenced websites. Annual percentages of respiratory specimens testing positive for influenza between 1976 and 1996 were obtained from Thompson et al. (2003).

4.3.2. Influenza Mortality

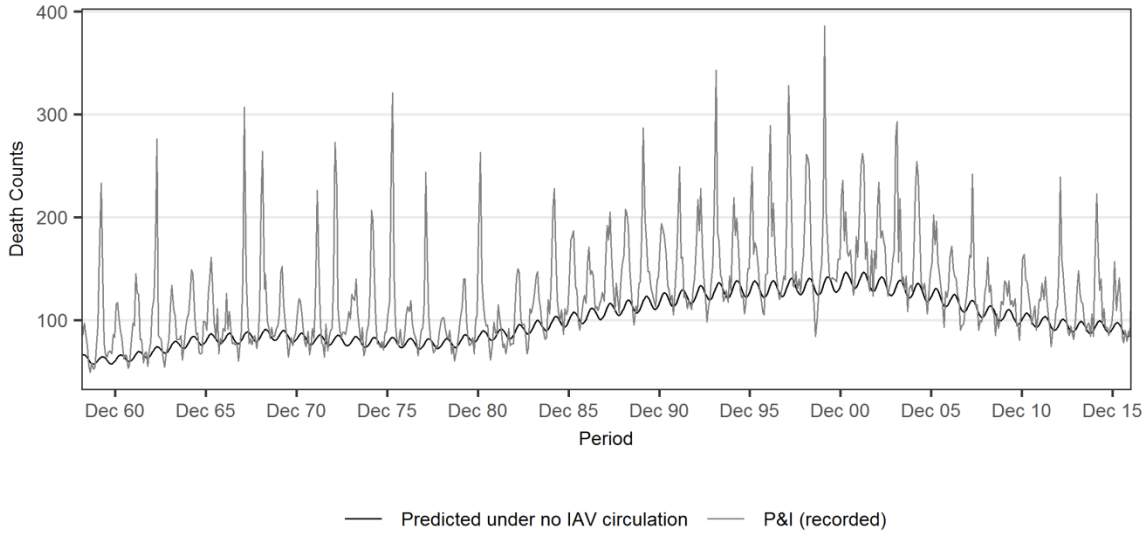
Measuring and estimating cause-specific mortality is challenging. Mortality from influenza is no exception (Thompson et al. 2009). On one hand, death records do not contain information from laboratory tests to confirm influenza as the "true" underlying cause of death. Therefore, many deaths recorded as "deaths from influenza" may, in fact, result from morbid events initiated by a disease other than influenza. On the other hand, an influenza infection could trigger a wide spectrum of secondary complications, such as bacterial infections, heart disease, or kidney and diabetes complications, among others (Simonsen et al. 2011), and many deaths primarily due to influenza infections may be wrongly attributed to another cause. Previous analyses of U.S. death certificates confirm that reports of influenza as a standalone cause-of-death are not to be trusted and should be regrouped first with other causes of death prior its estimation and analysis (Noymer and Nguyen 2013). Given that our purpose is to specifically account for APC effects on influenza mortality, and not to precisely estimate general influenza mortality levels, we estimated the Serfling models based on the restricted "Pneumonia & Influenza" (P&I) cause of death category.

4.3.3. The Serfling Regression Model

Serfling models estimate a mortality baseline by fitting death counts of the summer season, during which influenza virus does not circulate widely, while taking into account seasonal and secular mortality trends (Serfling 1963; Thompson et al. 2009). Influenza-related mortality is then estimated for each month as the difference between the observed P&I death counts and the estimated baseline (see Fig. 4.1). Note that the amplitude of the baseline (and thus the estimated number of deaths) depend on the months chosen to define the summer period. According to our estimates, the best fit was obtained when using a summer period from June to September (details of the Serfling model and the sensitivity tests of alternative summer period definitions are provided in the Supplementary Material).

One important advantage of the Serfling model is that it only requires death counts and populations at risk by month and age. In the present case, it permits the estimation of influenza mortality over a long period, i.e., from 1959 to 2016. However, since it relies strongly on seasonal variations, this model may capture unrelated mortality that follows a similar seasonal pattern leading to incoherent estimates, like a negative number of influenza deaths (Nguyen and Noymer 2013). Hence the interest of the "Surveillance-Serfling" model described next.

Figure 4.1: Monthly observed P&I death counts and baseline mortality (without influenza activity) predicted by the Serfling model at age 80, 1959-2016

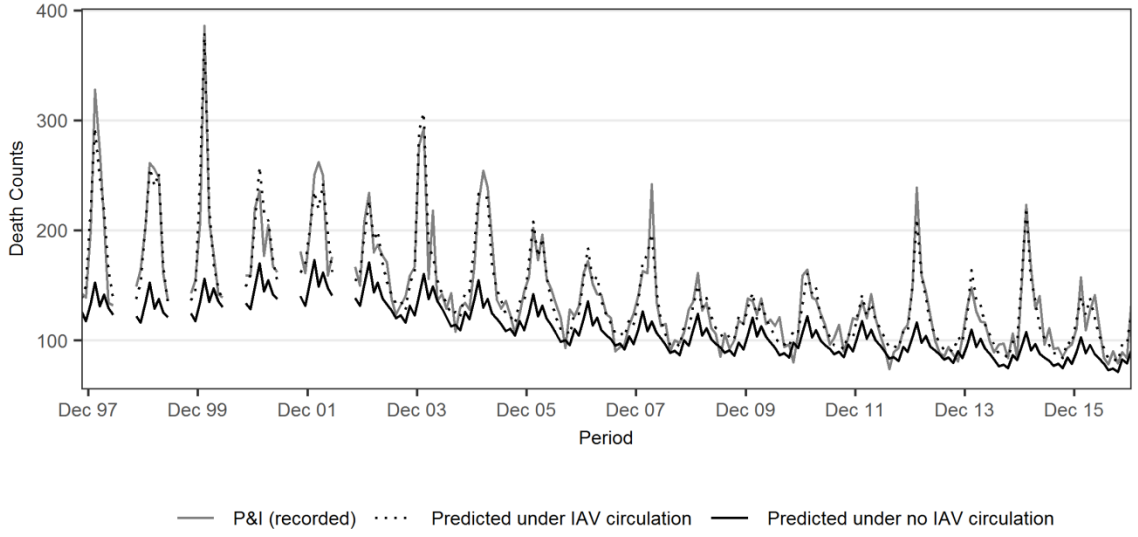


4.3.4. The Surveillance-Serfling Regression Model

Besides the three components of the Serfling regression model (time trend, seasonality, and population at risk), the Surveillance-Serfling model can also take into account influenza morbidity indicators, i.e., influenza-like illness (ILI) and other viral surveillance data, which may considerably improve the accuracy of the estimates (Lemaitre et al. 2012; Simonsen et al. 2011; Thompson et al. 2003, 2009). The Surveillance-Serfling model has the further advantage of fitting data from all seasons, and not exclusively from the summer seasons; it thus includes more observation points (i.e., throughout the year), which improves estimates for the single-year age data used in this study. We fitted this model for the P&I underlying causes of mortality in the US, from 1997 to 2016, i.e., for the periods during which measures of influenza circulation and mortality are both available on a monthly basis. We tested several models accounting for both ILI incidence (CDC 2018), its combination with subtype circulation (ILI decomposed by subtype according to the proportion of positive tests for H1N1, H2N2, etc.,), and including a 1-month lag term tracking influenza ILI incidence and subtype circulation the month preceding the index month. We selected the best fit for each age based on AIC (Burnham and Anderson 2002). A detailed description of the full model equation, the fitting procedure, and the chosen model parameterization by age are provided in the Supplementary Material.

In order to capture influenza mortality, we first fitted the model to deaths recorded in the P&I categories to obtain a predicted mortality count. Then we set the influenza activity terms (i.e., $flu_{a,t}$ and $flu_{a,t-1}$ in Eq. S2) to zero in order to obtain a mortality baseline, that is without influenza activity. The difference between predicted mortality and the baseline reflects mortality caused by influenza. For example, Fig. 4.2 shows the number of deaths recorded within the P&I category at age 80 between October 1997 and December 2016 (grey line), the number of deaths predicted by the Surveillance-Serfling model given the influenza incidence (dotted line), and the mortality baseline with the influenza terms set to zero (black line). The distance between the black and the dotted lines is defined as influenza-related mortality.

Figure 4.2: Observed and predicted influenza death counts at age 80, 1997-2016.



Note: Between 1998 and 2002, estimates for May – September are not included since there is no influenza circulation data during these periods

4.3.5. Lexis Surfaces

We estimated annual mortality rates over 101 single years of age (ages 0 to 100) and 57 epidemic years (from 1959-1960 through 2015-2016), comprising around 5,700 data points. The construction of Lexis surfaces (for more details, see Vaupel et al. (1987)) is done by binding together mortality rates estimated by the Serfling models. In order to identify differences in mortality levels, a color is assigned to each data point, with the lightest color-coding for the minimum mortality rate and the darkest for the maximum. Yearly mortality data was aggregated in our Lexis surfaces by epidemic seasons rather than calendar years, i.e., from October 1st to May 31st.

4.3.6. Age-Period-Cohort Analyses

Besides quantifying the influences of each temporal component, statistical age-period-cohort analyses avoid the subjectivity that may come from visual inspection of Lexis surfaces. Given perfect linear dependence (age = period - cohort), it is impossible, however, to estimate a unique solution describing long term APC trends without the imposition of additional constraints. Acknowledging this well-known identification problem, we propose two complementary approaches that provide tentative, yet heuristic insights on period and cohort trends over sizeable stretches of historical time.

More precisely, we first evaluate period and cohort effects according to two opposite scenarios: one in which all the linear trend in mortality change is attributed to period influences (i.e., the cohort effects slope is constrained to zero), and another in which this trend is solely attributed to cohort influences (i.e., the period effects slope is constrained to zero), respectively denoted as the APCd and ACPd scenarios.

Second, we used the intrinsic estimator (IE) method, which finds a solution of the partition of the linear trend between age, period, and cohort by using a constraint that minimizes the APC variance parameter (W. Fu 2016; Land et al. 2016; Xu and Powers 2016). Since the constraint is not explicitly chosen by the user, it may be seen as less subjective than other methods (Yang et al. 2004). Yet, the estimates may vary widely according to the constraints, whether it is chosen by the user or not, making the choice of any method ultimately arbitrary.

If there is no unique, statistically optimal solution to partitioning the long-term linear trend in APC models, changes in the slope of these trends are, on the other hand, unambiguously identifiable. These changes provide important information about increases or decreases in mortality risks. For this analysis, we use the *contrasts* approach (Tarone and Chu 1996) to identify the "breakpoints" or "rupture points" where the trends of the cohort effects significantly change in direction and to quantify these changes (contrasts). For this, we measured the difference between the slopes of two disjoint blocks composed of several consecutive cohorts and assessed their statistical significance according to two alternative approaches. First, we quantified the difference between the slopes formed by the first and last cohort of each block of cohorts. Alternatively, we compared the sum of all slopes formed by any pair of cohorts contained within each block.

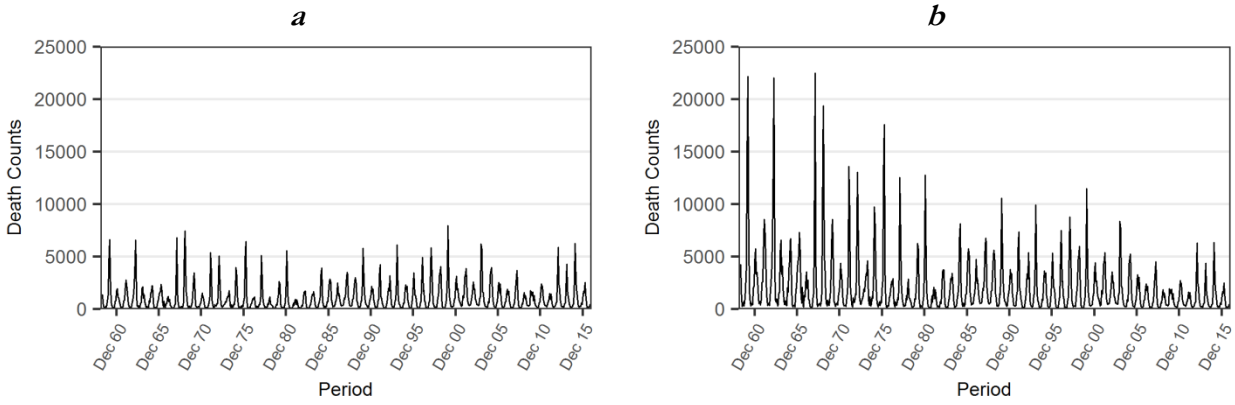
Finally, in order to reduce the influence of stochastic variation on the APC model estimates, we aggregated data on a 2-year basis. To avoid undue influences of seasonal infant and young child mortality that could be unrelated to influenza, such as from the Respiratory Syncytial Virus (RSV) (Simonsen et al. 2011), we also excluded ages 0-4 from the APC models. See the Supplementary Material for a broader discussion about the use of APC methods, details of the models, and sensitivity analyses. All of the data and code for reproducing results are openly available (Acosta 2019b).

4.4. Results

4.4.1. Influenza Mortality

We describe the dynamics of influenza mortality over time by first plotting the monthly influenza mortality counts estimated from the Serfling model over all available calendar months (Fig. 4.3a). In agreement with previous research, these estimates show substantial mortality variation by period that is related to the dominant virus subtype prevailing during each epidemic season (Reichert et al. 2004; Simonsen et al. 1997; M. W. Thompson et al. 2010). For instance, there are noticeable peaks in mortality for the epidemic seasons 1967-1968 and 1999-2000, dominated by the H2N2 and H3N2 influenza subtypes, respectively, whereas important mortality dips are apparent for the seasons 1976-1977, 1978-1979, and 2009-2010, respectively dominated by the B, H1N1, and pH1N1 strains. Yet, Fig. 4.3a shows no clear overall mortality trend over time.

Figure 4.3: Serfling estimates of monthly influenza death counts



Note: Serfling estimates of monthly influenza death counts (panel a) and of influenza death counts using the total U.S. population in 2015 as the standard population (panel b)

Second, we plotted in Fig. 4.3b the standardized influenza mortality counts using the July 2015 US total population size and age-structure as the standard population (so that results for each year are adjusted to 2015). As seen in this figure, once changes in the size and the age structure of the population are neutralized, a downward trend of influenza mortality appears. For instance, had the 1967 U.S. population shared the size and age structure of the 2015 U.S. population, the number of deaths due to influenza would have been more than three times higher (39,973 vs. 12,463), primarily

because older age groups experiencing the highest risk of influenza mortality would have accounted for a larger share of the population.

Table 4.1 indicates that influenza seasons dominated by the H2N2 subtype (which circulated in the earliest periods covered in this study and disappeared in 1968) were the deadliest, at least based on the U.S. population of 2015 as the standard. Compared to seasons in which the seasonal H1N1 was the dominant subtype, mortality was 2.2 times higher during seasons dominated by the H2N2 subtype, 1.5 times higher for those dominated by H3N2, and 38% lower in the seasons when the pH1N1 subtype, introduced during the 2009 pandemic, was dominant. If overall mortality was lower during that pandemic (Lemaitre et al. 2012; Nguyen and Noymer 2013; Simonsen et al. 2011), it is mostly due to an overall shift in increased susceptibility from older to younger ages. Young and middle-aged adults (up to age 50-60) indeed had increased risks of death during the 2009 outbreak relative to usual influenza seasons, while the opposite was true for the elderly (Gagnon, Acosta, Hallman, et al. 2018). Contrary to what may be observed during pandemics, as in 2009, influenza mortality is higher during normal influenza seasons for the very young or the very old (see upcoming Fig. 4.4).

Table 4.1: **Influenza-associated mortality by dominant viral strain using the size and the age distribution of the total US population in 2015 as the standard population, influenza seasons 1959-2016**

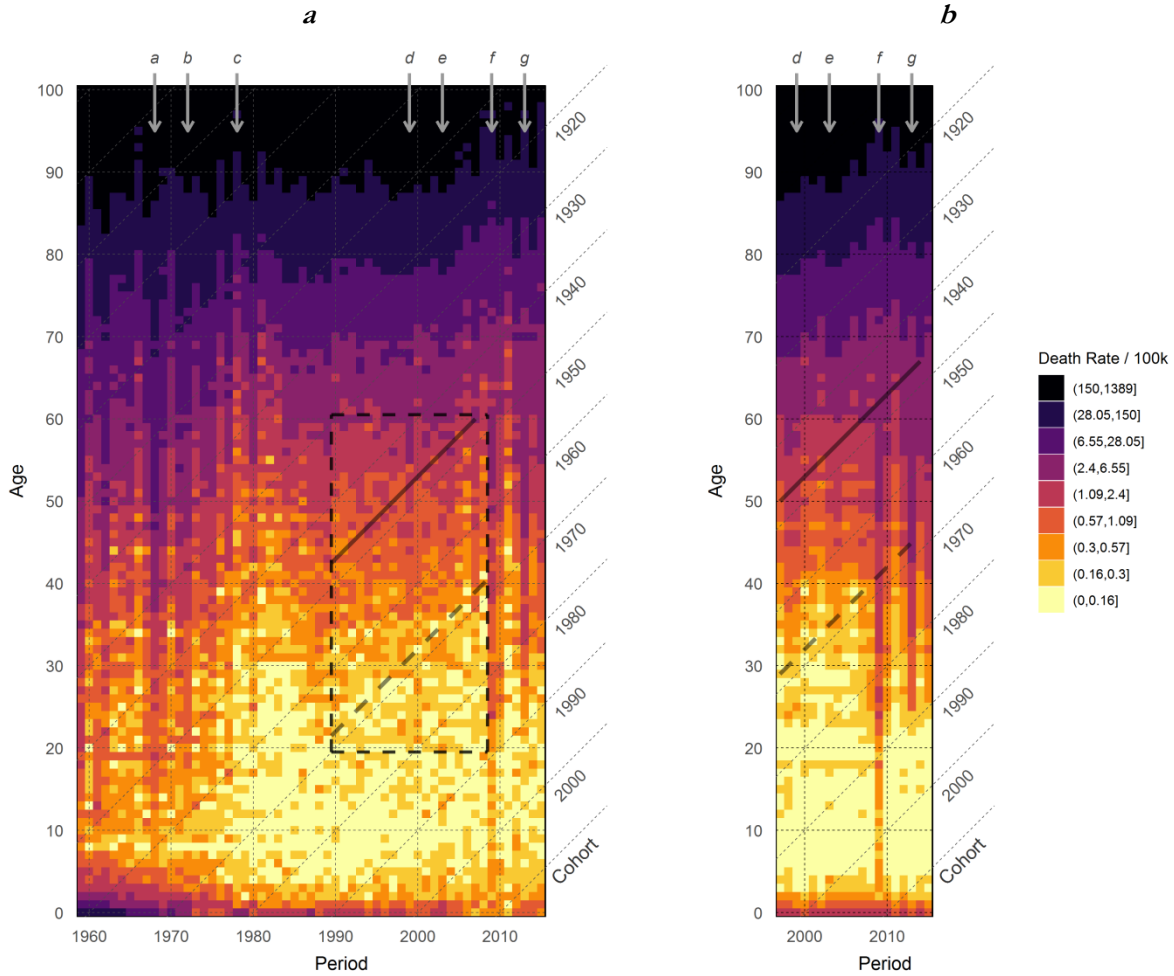
Dominant strain [a]	Average number of deaths per epidemic season [c]	Standardized average number of deaths per epidemic season [d]	Relative risk of deaths (with H1N1 as the reference) [d]
B	8,661	17,504	1.10
H1N1	9,075	15,967	Ref.
pH1N1	9,274	9,946	0.62
H2N2	11,311	34,947	2.19
H3N2	13,024	23,844	1.49
No dominant [b]	11,056	15,836	0.99

[a] The dominant strain for a specific season was defined as the strain that cumulated at least 50% of all isolates identified during that season. H2N2 was imputed as the dominant subtype between 1959 and 1975, where no data about subtype tests are available.
[b] Influenza seasons for which no subtype reached 50% of all isolates. Four seasons show no dominant subtype: 1988-1989, 2002-2003, 2006-2007, and 2010-2011.
[c] Influenza mortality was estimated from the Serfling model applied to P&I mortality data.
[d] Influenza mortality standardized using the total US population in 2015.

4.4.2. Lexis Surfaces

Figures 4.4a and 4.4b show Lexis surfaces of influenza mortality estimated with the Serfling and surveillance models. The estimated mortality levels and patterns from both models are highly consistent. Along the age dimension, the surfaces uncover high mortality for the newborn, very low mortality for children and young adults, and a considerable increase in the risk of death after age 50 or 60, as one would expect for this disease.

Figure 4.4: Lexis surfaces of influenza mortality rates estimated by the Serfling models

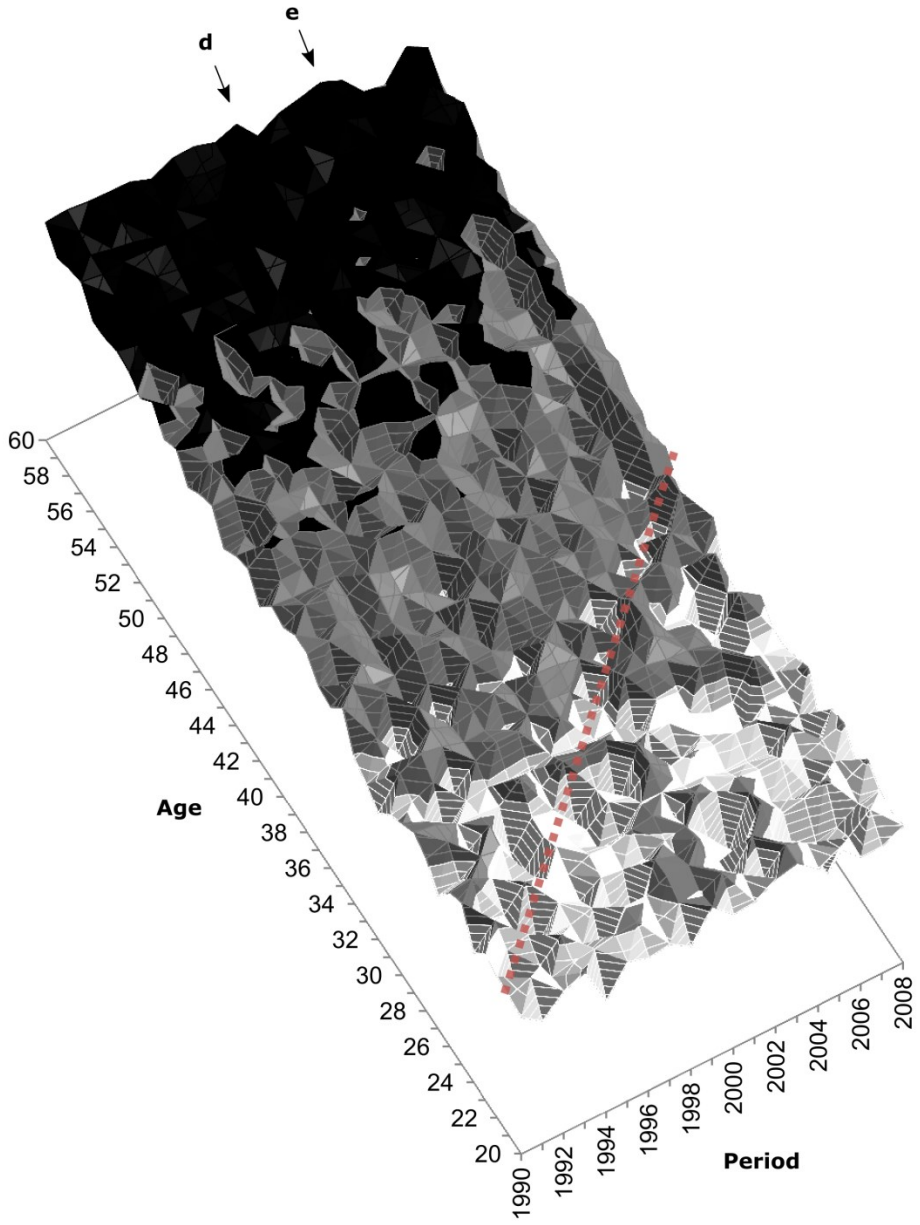


Note: Lexis surfaces of influenza mortality rates estimated by the Serfling model, 1959-2016 (panel a) and the Surveillance-Serfling model, 1997-2016 (panel b). The vertical arrows *a*, *b*, *d*, and e indicate periods of severe H3N2 epidemics. Arrow *c* marks the reappearance of H1N1 (1977-1978); arrows *f* and *g* indicate periods dominated by pH1N1. The solid and dashed black diagonal lines mark the 1947 and 1968 birth cohorts, respectively. The surface covered by the dashed square in Fig. 4.4a is shown in a three-dimensional perspective in Fig. 4.5

The surfaces also show high variations of mortality by period, with important mortality surges at all ages during the 1968-1969 pandemic, as well as during the flu seasons of 1972-1973 (Chin et al. 1974), 1999-2000 (CDC 2000), and 2003-2004 (Meadows 2004), all of which resulted from significant drift events of the H3N2 strain (see periods identified by arrows *a*, *b*, *d*, and *e* at the top of both panels in Fig. 4.4). Although the 2009 pandemic and the 2013-2014 season were not particularly lethal, they show – especially for 2009 – a mortality shift from older to younger ages (see periods identified with arrows *f* and *g*). As discussed above, mortality levels are highly dependent on the predominant virus subtype circulating during each epidemic season. In this sense, the 1960s and 1970s, the second half of the 1990s, as well as the first half of the 2000s, are considered as extended periods with high influenza mortality, coinciding with the circulation of the H2N2 and H3N2 subtypes. Conversely, lower mortality is observed after the re-appearance of the H1N1 at the end of the 1970s (see period identified with arrow *c*), especially during the first halves of the 1980s and 1990s, and during the second half of the 2000s, which were dominated by this milder seasonal subtype.

Diagonal patterns in Fig. 4.4 also suggest the presence of cohort effects. These are immediately perceptible during two main periods, i.e., from the 1960s to the beginning of the 1980s, and again from the late 1990s to the late 2000s. Some diagonal patterns are apparent during the milder H1N1 era that spans in between those two periods, but only at ages below 60. Of notice are the cohorts born around the 1968 pandemic (dashed diagonal lines in Figs. 4.4 and 4.5), which were presumably exposed early in life to the 1968 H3N2 influenza pandemic virus, and which thereafter experienced lower mortality relative to neighboring cohorts (see the light tone "valley" between 1996 and 2006, marked by a dashed diagonal line in Figs. 4.4 and 4.5). Fig. 4.4 also suggests the presence of a slight drop in mortality for the 1947 cohort (the tone is generally lighter for this cohort relative to its neighbours, as is clearly the case between 1993 and 1997) and of other "punctual" cohort effects, but further analyses are needed in order to provide firmer support for these observations. The results of our APC analyses presented next help providing such support.

Figure 4.5: Three-dimensional perspective of the influenza mortality estimated by the Serfling model applied to P&I mortality data



Note: This section frames ages 20-60 and period 1990-2008, covered by the dashed square in Fig. 4.4a. The dashed diagonal line locates the 1968 birth cohort. Arrows *d* and *e* mark severe H3N2 epidemics (see also Fig. 4.4)

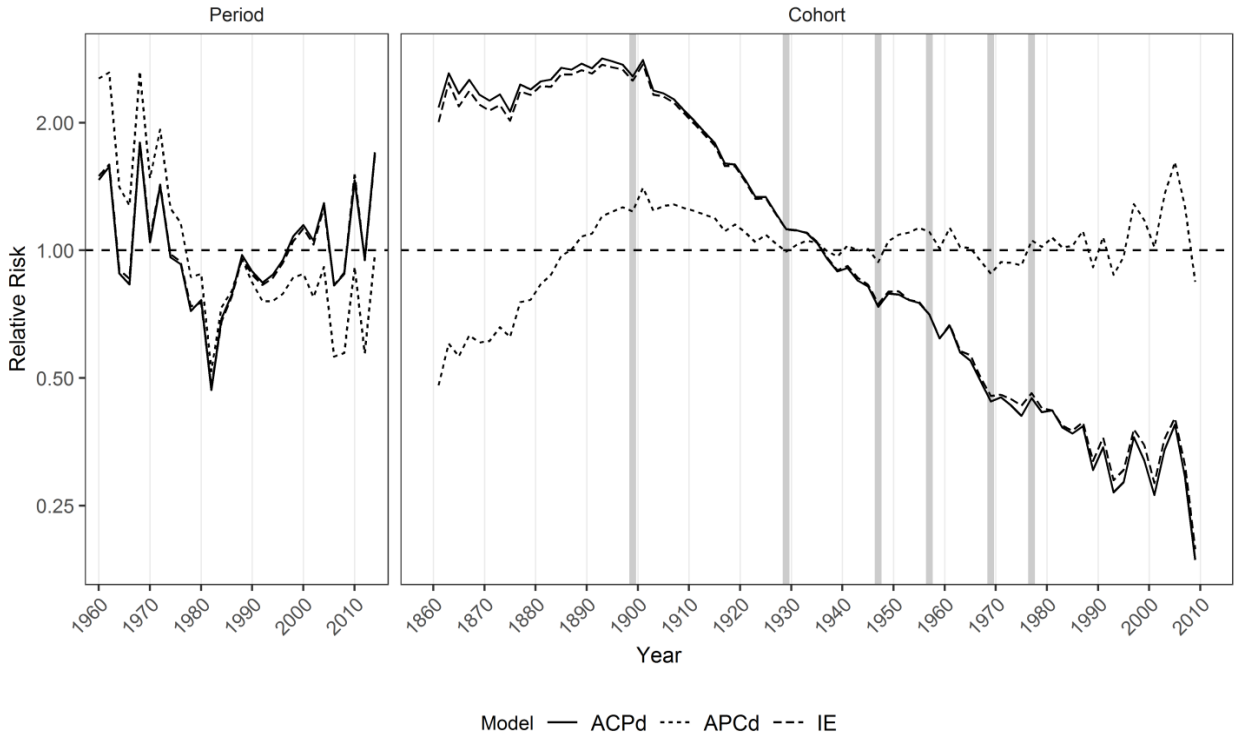
4.4.3. Linear APC Trends

Since age-specific effects are regular over time, we focus on period-specific and cohort-specific influences on mortality change. According to our APC detrended model, the long-term slope of mortality change is -0.02024 ($p<0.001$). In other words, controlling for age effects, influenza

mortality risk significantly decreased on average by 2.02% per year between 1959 and 2016. Figure 4.6 and Table S1.4 (Supplement Material) present APC estimates of influenza mortality derived from two scenarios in which this linear trend is completely attributed either to period influences (APCd, dotted line) or to cohort influences (ACPd, solid line), as well as from the IE model (dashed line).

As expected, the period effect estimates (Fig. 4.6, left panel; Table S1.4, upper part) reveal important fluctuations of mortality that closely follow the major antigenic drifts and shifts that took place in the last few decades. Independent of the model's parametrization, important peaks are immediately visible for the 1968 H3N2 pandemic, as well as for the 2003-2004 and 2014-2015 severe H3N2 epidemic seasons. Appreciable dips are also apparent for the 1981-1982, 1993-1994, and 2005-2006 epidemic seasons, during which the dominant subtype was the less virulent H1N1 seasonal virus.

Figure 4.6: Period and cohort relative (to average) risks of influenza-related mortality derived from the Serfling model, ages 5 to 100, 1959-2016.



Notes: The bold gray vertical lines highlight birth cohorts where statistically significant changes in slope occur, i.e., 1896-1901, 1928-1929, 1947-1948, 1956-1957, 1968-1969, and 1977-1980 (see Table 4.2)

Regarding the longer-term linear cohort effects (Fig. 4.6, right panel; Table S1.4, lower part), the IE estimates are very similar to those from the ACPd model, suggesting that broadly defined cohort

influences mainly account for improvements over time in influenza mortality. The ACPd and the IE estimates both depict a slight increase of mortality throughout cohorts born from 1860 to the late 1890s, followed by a sharp decline from one cohort to the next continuing to the last decades of the 20th century. This trend differs markedly from the flatter trend drawn from the APCd estimates, which instead first suggests a sizeable increase in mortality across cohorts born in the second half of the 19th century, followed by a monotonic reduction for cohorts born from around 1900 to the 1930s, and a leveling-off thereafter. Note that a method that attributes all the linear trends of mortality to period changes, such as the APCd method, naturally yield a cohort trend that neither increase nor decrease over the period of observation.

Despite substantial differences in the above scenarios and uncertainties regarding the "true" trends, some attributes of the cohort effects are common to the three sets of APC estimates: all suggest a decline in the cohort mortality trend for individuals born between 1900 and 1930 and between 1957 and 1968, as well as an increasing trend for years of birth ranging from 1947 to the mid-1950s, and from 1968 to the end of the 1970s. Afterwards, the cohort trend might have been either decreasing or levelling-off. Admittedly, recent cohorts, especially those born after 2000, were only followed-up in their youth and during a brief stretch of time. In contrast, the cohorts born in the last decades of the 19th century could only be observed at very old ages, also for a brief number of years, shortly after the onset of our study period in 1959. In between, a number of cohorts could be followed over a longer period of time and throughout a larger portion of the life course, even though none is observed over its entire life.

4.4.4. Changes in Trends

Based on visual inspection of Fig. 4.6, we first identified several ostensible turning points in the cohort effects trend and then investigated these further using the linear contrasts approach. Table 4.2 lists the six turning points where we identified changes in the direction of the cohort trend were statistically significant, along with the magnitude of these changes; the turning points are also marked by bold gray vertical lines in the right panel of Fig. 4.6. Two disjoint blocks composed of 8 to 16 single-year cohorts (i.e., 4 to 8 two-year cohorts) were defined for each breakpoint. We performed the two alternative contrast approaches, denoted *a* and *b*. For five breakpoints out of six,

the changes in slope were significant ($p < 0.01$ or $p < 0.05$), regardless of the estimated contrast (for one breakpoint, $p < 0.1$). For simplicity, we focus here on contrast *a*.

The first contrast in Table 4.2 indicates a change in slopes of magnitude -0.530 ($p < 0.001$) between two blocks composed of eight two-year cohorts each, indicating a -0.033 difference in the slope by single-year cohort. This contrast mortality flanks the cohorts born at the turn of the 20th century (~1896-1901), with the first block including cohorts born from 1882-1883 to 1896-1897, and the second block those born from 1900-1901 to 1914-1915. The negative contrast indicates a reduction in the slope of the trend of the second block relative to the slope of the first block (see how the curve depicting the cohort effects is concave down in Fig.4.6 for the cohorts born at the turn of the 20th century, regardless of the APC method used). It is worth noting that the crisp peak in Fig. 4.6 for the cohort 1900-1901 (i.e., a punctual peak flanked by a trough at each side) is the result of systematic misreporting of age (and year of birth) in the death certificates of people born around 1900. Such instance of age heaping, also visible in the form of a diagonal trace in Fig. 4.4 for the 1900 cohort, are described for influenza mortality during the 1918 influenza pandemic in Ontario in Hallman (2015).

The second contrast indicates an increase of 0.21 (0.013 per year, $p < 0.05$) in the slope of the cohort trend around 1926-1927. A third contrast indicates a significant upward change of 0.287 (0.036 per year, $p < 0.01$) in the slope of the trend after the 1946-1947 cohort. The forth contrast suggests a 0.45 downward change in slope (0.038 per year, $p < 0.001$) after the 1956-1957 birth cohorts. A fifth contrast reveals a significant 0.397 increase in slope (0.04 per year, $p < 0.05$) after 1968-1969, and a sixth identifies a decrease of 0.348 (0.035 per year, $p < 0.05$) in the slope after 1976-1981. The changes in slopes for more recent cohorts were not statistically significant (the small numbers of death make the estimates uncertain). To test the sensitivity of the contrast estimates, we reran the model using three-year instead of two-year cohorts. The results were highly consistent with those presented in Table 4.2 (see Table S1.3 in the Supplementary Material).

Table 4.2. Contrasts for comparing the linear trends between two disjoint blocks of 2-year birth cohorts

#	Cohorts where changes in slope occur	Block 1	Block 2	Contrast a	SE	Contrast b	SE
1	~ 1896-1901	1882-1897	1900-1915	-0.528***	0.085	-5.584***	0.774
2	~ 1928-1929	1914-1929	1928-1943	0.214*	0.093	1.802*	0.774
3	~ 1946-1947	1940-1947	1946-1953	0.246**	0.095	0.772**	0.295
4	~ 1956-1957	1946-1957	1956-1967	-0.430***	0.1	-0.982***	0.221
5	~ 1968-1969	1960-1969	1968-1977	0.393*	0.156	0.839*	0.337
6	~ 1976-1981	1968-1977	1980-1989	-0.335*	0.155	-0.585+	0.354

Note: Contrast a is defined as the difference between the slopes formed by the straight lines connecting the first and the last pair of consecutive birth cohorts within each block. Contrast b is defined as the sum of differences of all slopes formed by any pair of cohorts taken in each block.
+ $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$

4.5. Discussion

This study identifies several factors modulating influenza mortality in the US population between 1959 and 2016. Consistent with previous analyses (Reichert et al. 2004; Simonsen et al. 1997; M. W. Thompson et al. 2010), the particular IAV subtype circulating during a given season is an important determinant of all-age mortality during that season, with H2N2 being the most lethal subtype, followed by H3N2, H1N1, and pH1N1 (Fig. 4.3 and Table 4.1). Over time, the succession and alternation in virus subtypes from one season to the next leaves clear one-year vertical bars on the Lexis configuration that are genuine period effects affecting all age groups simultaneously (vertical arrows in Figs. 4.4 and 4.5).

Yet, year-to-year changes in virulence and virus subtype also prime successive cohorts to alternative strains which, through lingering effects on later life mortality, leave specific diagonal traces on the Lexis configuration typical of a cohort effect. Our analyses suggest up to three, perhaps four, such "imprinted cohort" effects, centered around the 1947, 1957, 1968, and ~1978-1980 cohorts; the other two significant contrasts identified for the ~1901 and ~1928 cohorts could also be interpreted as imprinted cohort effects, but we believe that they point to longer term changes in mortality at older ages, in line with the *cohort morbidity phenotype*. We discuss first the imprinted cohort effects.

The clearest one concerns the cohorts born at the time of the 1968-1969 "Hong Kong" flu pandemic. Mortality in these cohorts was lower relative to neighboring cohorts, as observed in Figs.

4.4, 4.5, and 4.6, and confirmed by a statistically significant change in slope documented in Table 4.2. We propose that individuals from the 1968-1969 birth cohorts developed a robust immune response to the H3N2 pandemic virus circulating around the time of their birth. They then benefited from having been primed to that variant when exposed again to subsequent (and numerous) epidemics dominated by the same H3N2 subtype, which has proved to be more lethal than the co-circulating H1N1 variant. However, APC analysis conducted on all-cause mortality and other causes of death (cardiovascular and respiratory) also produced a dip in mortality for cohorts born at the end of the baby boom (Table S1.4, Supplementary Material). This suggests that the 1968 cohort could also have benefitted from a reduction in influenza mortality unrelated to its early-life antigenic imprinting. Although we cannot fully discard this possibility, we note that the significant contrast identified for influenza mortality is precisely centered on the 1968 cohort in Table S1.4, whereas the signal for all-cause, cardiovascular, and respiratory mortality is dispersed among cohorts born up to six years before or after 1968.

If the 1968-1969 cohorts benefited from lower mortality relative to neighboring cohorts, the opposite is true for those born around 1978-1980. The increment of risk among the cohorts born from 1969 to 1976 most likely results from the gradual decrease in the proportion of cohort members primed to the H3N2 subtype. Indeed, with the B subtype, the H1N1 – reintroduced into the circulation in early 1978 – largely dominated the 1976-1977, 1979-1980, and 1981-1982 flu seasons and the relative gain in protection the H1N1-primed cohorts born those years might have had during subsequent outbreaks caused by the H1N1 subtype was more than offset by lack of protection during the more deadly H3N2 outbreaks. Accordingly, the risk could have decreased for cohorts born after 1980 because a higher proportion of individuals among these cohorts were primed to the co-circulating H3N2.

The picture is less clear for the cohorts born around 1957, who were primed to the H2N2 virus that appeared that year, i.e., during the "Asian flu pandemic." The drop in mortality following that cohort in Fig. 4.6 and the significant contrasts in Table 4.2 suggest that these cohorts benefitted from cross-protective immunity during the H3N2 seasons through sharing the neuraminidase component N2. Alternatively, the immune systems of the members of this cohorts might have been "refocused" on the H3N2 subtype upon early life exposure in 1968, adjusting its antigenic signature to this subtype "in time," at a relatively young age (see Gagnon et al. (2015)). Again, the baby boom could have had a role in this context: the 1957 cohort was among the largest of the era, with

potential for increased mortality, as described in Easterlin (1987). However, although we find significant contrasts for all-cause and respiratory disease mortality for the 1957 cohort, this signal appeared much more dispersed around that cohort than for influenza mortality (Table S1.4).

A decade before the Asian Flu pandemic, i.e., in 1947, a vaccine that was previously effective against the circulating H1N1 virus during the prior seasons totally failed to provide protection because of what turned out to be an important intrasubtypic antigenic drift, akin to a "pseudo-pandemic" (Kilbourne 2006). Yet, there is no simple immunologic explanation as to why the curve is concave up in Fig. 4.6 for the cohorts born at that time, quite the contrary since a "deep imprint" from H1N1 should instead have increased the risks of mortality in subsequent decades from the H3N2 subtype, as explained above for the 1978-1980 cohorts. Perhaps priming to H1N1 in 1947 was still protective relative to priming to H2N2 in 1957, which was associated with an increase in mortality during the 2009 H1N1 pandemic and the 2013-2014 resurgent outbreak (Gagnon, Acosta, Hallman, et al. 2018); that would explain an increase in risk in cohorts born after 1947. However, other mechanisms, unrelated to imprinting, might have been at play, such as selection. The year 1947 is not only notorious for a major antigenic shift. Demographers have also noted a record-breaking number of marriage licenses issued in May and June 1946 (Whelpton et al. 1948), the first spring season to follow the conclusion of WWII, and therefore a sudden surge of fertility in 1947. Since the healthiest couples had their first babies within a year following their marriage, the 1947 cohort could have been "graced" with greater than usual health via synchronization of the fertility of the healthiest parents. Such "selection-by-synchronization" phenomenon was proposed earlier to explain a surge in the frequency of twin births at the end of WWI in France (Pison et al. 2004).

Of note is the lack of a cohort effect for those born during the 1918 Spanish flu pandemic, which left no specific diagonal trace in the Lexis configuration and produced no significant second order cohort effects in the contrast analysis. It is possible that selection processes for this cohort offset the lingering effects of early life exposure to the H1N1 virus that caused the 1918 pandemic. However, its antigenic signature was apparently not fully erased. During the 1968 influenza pandemic, death rate ratios (relative to previous influenza seasons) peaked for the cohorts born around 1918 (Gagnon et al. 2015), while these same cohorts appeared protected during the 2009 flu pandemic (Gagnon, Acosta, Hallman, et al. 2018; Jacobs et al. 2012; Nguyen and Noymer 2013).

We hypothesize that the extent to which the lingering effects from early life imprinting is recognizable depends on the life stage at which mortality is observed. In this paper, we observe the cohorts primed to the 1918 virus mostly during seasonal outbreaks, at advanced ages, when influenza deaths would usually no longer directly result from the virus itself, but rather from comorbid conditions and poor health (Plans-Rubió 2007; Reichert et al. 2004; Simonsen et al. 2005), and thus, under the regime of the *cohort morbidity phenotype*. Accordingly, these differences by age are reflected in the parameterization of the surveillance model in this study. As shown in Table S1.1 in the Supplementary Material, for ages above 65 the model using a measure of ILI *with no subtype distinction* provided the best fit, whereas for ages 25 to 65, the inclusion of the information related to the virus subtype circulation significantly improved model fit.

This brings us to the contrasts identified for the cohorts born around 1900 and 1928 (see Table 4.2). The two years are often considered as years of significant antigenic drifts (Beveridge 1991; Collins 1931; Patterson 1986). Although the status of the first is debated (Hill et al. 2017), there is potential for long-term "imprinted cohort effects" for individuals born during those two years, as described above for more recent cohorts. However, we believe that the contrasts for these cohorts born in the first half of the 20th century (observed at older ages in this study) are rather mainly indicative of broader transition processes.

Researchers have extensively documented a context of deprived sanitary conditions in Northern America during the late nineteenth century due to the rapid growth of cities, reflected in high infant and child mortality (Burian et al. 2000; Haines 2000; Olson and Thornton 2011). Despite important discoveries in bacteriology in the 19th century, germ theory did not begin to guide public policies until the turn of the 20th century. As argued by Preston and Haines, "There is probably no area of public health where a majority of the progress between 1850 and 1950 occurred by 1900" (1991, p. 22). But between 1900 and 1930 the U.S. experienced the most rapid decline in mortality rates in documented history, as a result of sharp reductions in infant mortality from infectious diseases (Cutler and Miller 2005). This is consistent with the downward trend in cohort effects between these dates, as progressively lower levels of disease load early in life translated into lower and lower levels of influenza mortality later in life (recorded after 1959).

Congruently, a distinctive second-order linear contrast around 1900 clearly marks the beginning of this trend (Table 4.2). This is the only identified contrast that remains highly significant when

moving the rupture point forward or backward by a few years, suggesting that it is not associated to one specific antigenic drift year but to a smoother longer-term change. The contrast identified about thirty years later for the cohorts born around the years 1928-1929 could signal the end of the sharp decline in influenza mortality that began with the cohorts born at the turn of the 20th century. Had this contrast mainly resulted from the 1928 antigenic event, the changes in the slope would also have appeared more abrupt and more statistically significant. Nevertheless, it is not possible with the data at hand to provide firmer evidence regarding the nature of the contrasts identified. It is also possible that both *antigenic* imprinting and *cohort morbidity phenotypes* scenarios are at play in the earlier cohorts of this study.

This study has several limitations. We discuss three. First, Surveillance-Serfling models did not include information about other viruses that could be correlated with influenza seasonality, such as Respiratory Syncytial Virus (RSV). Consequently, our estimations of influenza mortality could be slightly overestimated. Nonetheless, this potential bias would be mostly concentrated in children aged less than five years (Simonsen et al. 2011), which were excluded from the APC analysis. In addition, RSV infections are unlikely to explain mortality trends that coincide with the circulation of specific strains of influenza virus in a given season.

Second, mortality data used here are useful for identifying age-related trends but are limited concerning other concomitant influences affecting disease burden and mortality risks, such as medical comorbidity, propensity for care-seeking, laboratory testing of viral strains, or even infection rates, which may break down differently by population subgroups. Our choice to focus on P&I deaths as a basis to estimate the number of influenza deaths most likely led to an underestimation of this number, especially at older ages (because of comorbidities). This means that the old-young difference is probably biased. Had we used a broader category such as "cardiorespiratory" instead, our model would have proportionally captured more deaths from the exacerbation of comorbidities at older than at younger ages. Other important differentials could affect mortality outcomes, notably differences based on race or sex. Haines notes for instance that African Americans were protected to some extent by their more rural residence in the first half of the 20th century, although their mortality remained higher than that of other Americans (Haines 2000, 2001). It is thus possible that the African Americans who were born during those years and who survived to the onset of this study in 1959 were less "deeply imprinted" to specific influenza strains than the general population because of lower incidence of influenza in early life, with potentially less clear antigenic imprinting

effects in these groups. Unfortunately, due to sample size issues, it was not possible in the context of this study to explore such possibility. Regarding sex differences, men are often said to declare more (and complain more) from flu symptoms than women, which is popularly encapsulated in the expression "man flu," perhaps erroneously (Sue 2017). Relative to women, they also appear to be less responsive to influenza vaccination and to be in general more susceptible to complications and death to many acute respiratory diseases, including influenza (Engler et al. 2008; Furman et al. 2014; Giefing-Kröll et al. 2015). However, the analyses conducted for this paper could not reveal fundamental sex-based differences with respect to APC patterns of influenza mortality (not shown here).

Third, and perhaps most importantly, the use of first-order APC statistical analysis has been criticized as unreliable because of the irresolvable issue of full dependency of the three age, period, and cohort components, which are sensitive to the restrictions arbitrarily imposed (Luo 2013; Luo et al. 2016; O'Brien 2013). Yet, although perfect collinearity will never be overcome, we believe it is still possible to gain useful knowledge about cohort trends, especially if several methods are used and if the analyses are supported and informed by external evidence from history and the social sciences in general (Luo 2013). For instance, based on Fig. 4.6, it is unclear whether mortality increased in cohorts born from 1850 to 1900 or whether it remained relatively stable. But the same figure shows that three models with widely different sets of constraints concur to show declining mortality in cohorts born from 1900 to 1930. This pattern can also be seen in the Lexis surfaces of Figs. 4.4 and, taking into consideration the historical sketch above, we feel it would be difficult to argue that period-based rather than cohort-based factors explain this trend. That said, results for long-term linear trends should always be seen as indicative or exploratory, not as confirmatory. For recent cohorts, it is no surprise that uncertainties persist about cohort versus period long-term trends on mortality; these cohorts were observed for only a short time at relatively young ages when mortality risks are relatively low.

4.6. Conclusion

The findings reported in this study have several key implications. On the one hand, they suggest that the mechanisms proposed by the *antigenic imprinting* and the *cohort morbidity phenotype* theories are not necessarily mutually exclusive as engines of influenza mortality variation; these two mechanisms

even seem to act simultaneously, triggering different mortality changes at distinct levels or scales. Yet, the irregular and sudden changes in influenza mortality at young ages are largely caused by the interactions between the population's *signature of antigenic imprinting* and the characteristics of the virus encountered in adulthood. The progressive decline in influenza mortality observed in cohorts born between 1900 and 1930 (and for virtually all cohorts born after 1900 if we accept the IE results), on the other hand, would result from continuous improvements of early life conditions (better hygiene, lower disease load in infancy, and so on), which manifest themselves at older ages.

We suggest that the contrasting mortality patterns reflect a difference in the pathways that lead from influenza infection to death at different ages and that this difference has major health policy implications. Interventions for younger patients should be focused on mitigating the immune response when this response is potentially harmful (e.g., during pandemics). On the other hand, in the case of the elderly, indirect pathways involving comorbid conditions should be targeted as priorities. It is also important that vaccination campaigns cease to identify susceptible groups of individuals based almost exclusively on their age group, and instead define susceptibility from a combination of APC influences. The yearly-defined cohort effects and contrasts are further evidence that surveillance and mortality data on influenza should be made available by single years of age to all stakeholders, as argued recently (Gagnon, Acosta, and Miller 2018). Knowing the strain to which a cohort has been primed and how "deep" this antigenic signature is would help to improve the efficiency of immunization campaigns and to inform medical professionals about priorities based on the age or the generation of patients.

The finding that cohort-specific influences may account for important changes in influenza mortality at older ages also tempers the common assumption that reductions in mortality from infectious diseases stemmed exclusively from period-based improvements in environmental and technological factors such as sanitation, hygienic practices, and medical technology. We argue that a considerable part of improvements, at least for the cohorts born between 1900 and 1930, was accomplished on a cohort basis. In this context, the general increase in overall mortality from influenza, which is expected in the coming years because of population aging (Simonsen et al. 2011), might be tempered by long-term beneficial effects of earlier improvements in early life conditions. Therefore, our results highlight the importance of these conditions not only for the reduction of chronic and degenerative mortality but also for the enhancement of survival from infectious diseases at old ages. It would be

interesting to perform similar analyses on other infectious diseases to assess the generalizability of the scenarios proposed here.

4.7. Acknowledgements

A Canadian Institutes of Health Research (CIHR) grant (PIs: Alain Gagnon and Matthew S. Miller) funded the project. Enrique Acosta was funded by a Social Sciences and Humanities Research Council of Canada scholarship and by the European Research Council Grant #716323. Matthew S. Miller was funded by a CIHR Operating Grant, a CIHR New Investigator Award, and an Early Researcher Award from the Government of Ontario. Robert Bourbeau was funded by a grant from the Social Sciences and Humanities Research Council of Canada. A version of this article was presented at the Population Association of America Annual Meeting, Washington, D.C., 28 March–2 April 2016.

Chapter 5 - Baby Boomers' Excess Mortality in Canada and the United States[4]

Abstract

Studies suggest that, relative to adjacent cohorts, baby boomers in Canada and the United States have experienced a slowdown in mortality improvements or even an increase in mortality in recent years. These findings are somewhat counterintuitive since the unprecedented improvements in early life conditions experienced by baby boomers were expected to lead, according to various theoretical approaches, to declines in morbidity and mortality in later life, as was the case for earlier generations.

The present study explores the mechanisms responsible for the "excess" mortality endured by the baby boom cohorts in Canada and in three racial/ethnic groups in the United States. Using micro-level mortality data from vital statistics systems, we analyzed the contributions of the causes of death that are likely driving this cohort's excess mortality and their dynamics over time. The analyses were done using methods of demographic decomposition, as well as visual, and other statistical methods.

We found evidence of a higher susceptibility in the "trailing edge boomer generations" (those born around 1960) to behavioral causes of death: namely, mortality from drugs, alcohol, HIV/AIDS, hepatitis C, COPD, and suicide. Most of these causes contributed to the mortality disadvantage of baby boomers through sustained cohort effects that followed the cohorts over time. This finding calls into question the assumption that secular improvements in early life conditions lead to a monotonic decline in later life cohort mortality rates. Instead, there may be important disruptions in the progress in health and mortality that have been recorded over the last two centuries or so, and it is possible that the baby boom generation represents one such disruption. Our results call for a renewed exploration of the mechanisms that drive current age-period-cohort mortality patterns. The mechanisms that can generate the observed cohort disadvantage of baby boomers (distress, frustration, riskier attitudes toward drug use and sexual practices) that are constituent of the boomer

[4] Article in preparation for submission as Enrique Acosta, Alain Gagnon, Nadine Ouellette, Robert Bourbeau, Marilia Nepomuceno, and Alyson A. van Raalte (2019b) Baby Boomers' Excess Mortality in Canada and the United States

generation identity, as well as the factors that could mitigate them, as seem to be the case of the Welfare State for Canadian females, are addressed and discussed.

5.1. Introduction

Previous research has established that all-cause mortality improvements slowed down or even reversed among baby boomers in Canada (Bourbeau and Ouellette 2016) and the United States (Canudas-Romo and Guillot 2015; Rau et al. 2013) in recent years[5]. These findings were unexpected.. According to the *cohort morbidity phenotype* and the *technophysio evolution* theories, the unprecedented gradual improvements in early life conditions experienced in recent history – such as better nutrition, reduction of infectious diseases, enhanced medical measures, and higher levels of education – have led to massive declines in mortality across birth cohorts (Floud et al. 2011; Fogel and Costa 1997). Other studies focusing on specific causes of death also identified mortality disadvantages for U.S. baby boomers with respect to overdoses (Chauvel et al. 2016) and other external causes (Remund et al. 2018; Zang et al. 2019). Moreover, U.S. boomers report being less satisfied with their health than adjacent birth cohorts, and tend to have a high prevalence of obesity, diabetes, hypertension, hypercholesterolemia, substance and alcohol abuse, as well as functional limitations (Duncan et al. 2010; D. E. King et al. 2013; Leveille et al. 2005; Martin et al. 2009).

There are at least four alternative mechanisms that may drive what could be termed the "boomer penalty" in mortality. First, the relatively low levels of mortality at early ages among baby boomers could have increased the health heterogeneity within the cohort, resulting in a decrease of the average physiological capital of its members (Canudas-Romo and Guillot 2015). Second, the large sizes of the boomer cohorts[6], compounded by the wide range of socioeconomic contexts they experienced in childhood and adulthood, may have increased the prevalence of stress and frustration

[5] In this analysis we refer to *excess mortality*, *disadvantage*, or *penalty* for the baby boomer cohorts, as divergences from the linear trend of mortality change. We avoid writing the term *relative* in all cases for better readability. These qualifiers should not be confused with absolute differences in mortality across cohorts.

[6] The most distinctive characteristic of the baby boomer cohorts is their large size in relative and absolute terms. Among the baby boomer cohorts, 1959 was the cohort with the largest amount of births (4'312.100 births in the United States and 479.275 in Canada) and 1961 was the cohort with the largest amount of exposure to risk at age 0 (4'166.678,6 person-years in the United States and 465.285.6 in Canada). Although the size of the cohorts could vary through the life course of their members due to mortality and migration, in the United States and Canada the relative differences in size across cohorts were virtually invariant. The person-years exposed to risk peaked for cohorts born between 1961 and 1963 in both countries during the period 1961-2018 among boomers.

among the members of this generation (Easterlin 1987). Third, the distinctive attitudes toward risk and the risk-taking behaviors associated with the boomers' generational identity could have increased mortality risks (Johnston 1991). Finally, the slowing or absence of mortality improvements observed among the boomers may have little to do with a usual cohort effects, and might instead result from a series of unrelated period crises that would have primarily targeted these cohorts but at increasing ages.

The boomer disadvantage in mortality is still poorly understood. The existing studies on this topic have tended to emphasize long-term cohort changes, while overlooking short-term relative differences across adjacent cohorts. Furthermore, there is still uncertainty about whether the composition and the temporal patterns of excess mortality in the boomer generation are similar across sexes, race, ethnicities, and countries.

This paper attempts to compare the cause-specific contributions to the excess mortality among baby boomers, and the temporal patterns of these contributions. This study has two primary objectives: 1) to examine the causes of death underlying the excess mortality among baby boomers in Canada and the United States; and 2) to determine whether this disadvantage is the result of a sequence of unrelated period crises that disproportionately affected the boomer cohorts at different ages, or of a tidy bundle of sustained, cause-specific disadvantages that has followed the boomers throughout their life course. In other words, we aim to determine whether the boomers' excess mortality resulted from a series of temporary "bruises" aligned diagonally in the Lexis configuration, or from lasting "scars" gained earlier in life but with lingering effects (Chauvel 2013; Ellwood 1982). The methodological approach taken in this study is based on decomposition techniques, age-period-cohort (APC) statistical models, and visual tools for analyzing the changes of cohort susceptibility over time. These methods were applied to mortality data retrieved from the Canadian and the U.S. vital statistics systems.

To our knowledge, this is the first comprehensive analysis of the composition and the temporal dynamics of the disadvantage in mortality among baby boomers in Canada and across races and ethnicities in the United States.

5.2. Data and Analytical Strategy

5.2.1. Data sources

Death counts for all-cause mortality for both countries between 1959 and 2016 were obtained from the Human Mortality Database (2019). Mortality data by cause were retrieved from available vital statistics. For Canada, death counts by sex, calendar year, single year of age (0-100), and cause of death between 1974 and 2014 were aggregated from the Vital Statistics - Death Database (CVSD) (Statistics Canada 2018). For the United States, death counts by cause, sex, race, ethnicity, calendar year, and single year of age between 1974 and 2016 were retrieved using mortality microdata from the National Center for Health Statistics (2018). Information about race and ethnicity has been included in U.S. death certificates since 1990, but is unavailable for Canada.

The period under analysis spans three International Classification of Diseases (ICD) revisions (8^{th}, 9^{th}, and 10^{th}). Table S1 (in the supplement material) shows the codes used to identify mortality by major causes of death in each ICD revision. For these broad categories, we found no important disruptions in the trend of mortality from these causes during the observed period of time.

Annual counts of the Canadian and the U.S. population at risk by sex and single year of age (0-100) between 1959 and 2016 were taken from the Human Mortality Database (2019). Estimates of the racial/ethnic proportions within the U.S. population between 1990 and 2016 were obtained from the Bridged-Race Population Estimates (NVSS 2019).

5.2.2. Analytical Strategy

We analyzed the excess mortality among baby boomers in four steps. We first located the cohorts with the smallest and the largest mortality deviations from the linear trend, and called them, respectively, the *advantaged* and the *disadvantaged* cohorts. Second, we identified the leading causes that contributed to these mortality deviations. Third, for each of these leading causes, we estimated the cohort effects on mortality when age and period variations are accounted for. Fourth, we analyzed the changes over time of these cohort penalties by cause. Because Canadian and U.S. populations are highly heterogeneous in terms of race and ethnicity, and mortality differs considerably between these groups (Masters 2012; Woolf et al. 2018; Zang et al. 2019), we also conducted the above analyses

separately for three racial/ethnic groups in the U.S. population: namely, Non-Hispanic blacks (NHB), Hispanics, and Non-Hispanic whites (NHW). For the sake of clarity, we present for each step of the analysis a detailed description of the methods used, immediately followed by a summary of the results obtained from the application of these methods. All of the data and code for reproducing results are openly available (Acosta 2019c).

5.3. Analysis of the Boomers' Excess Mortality

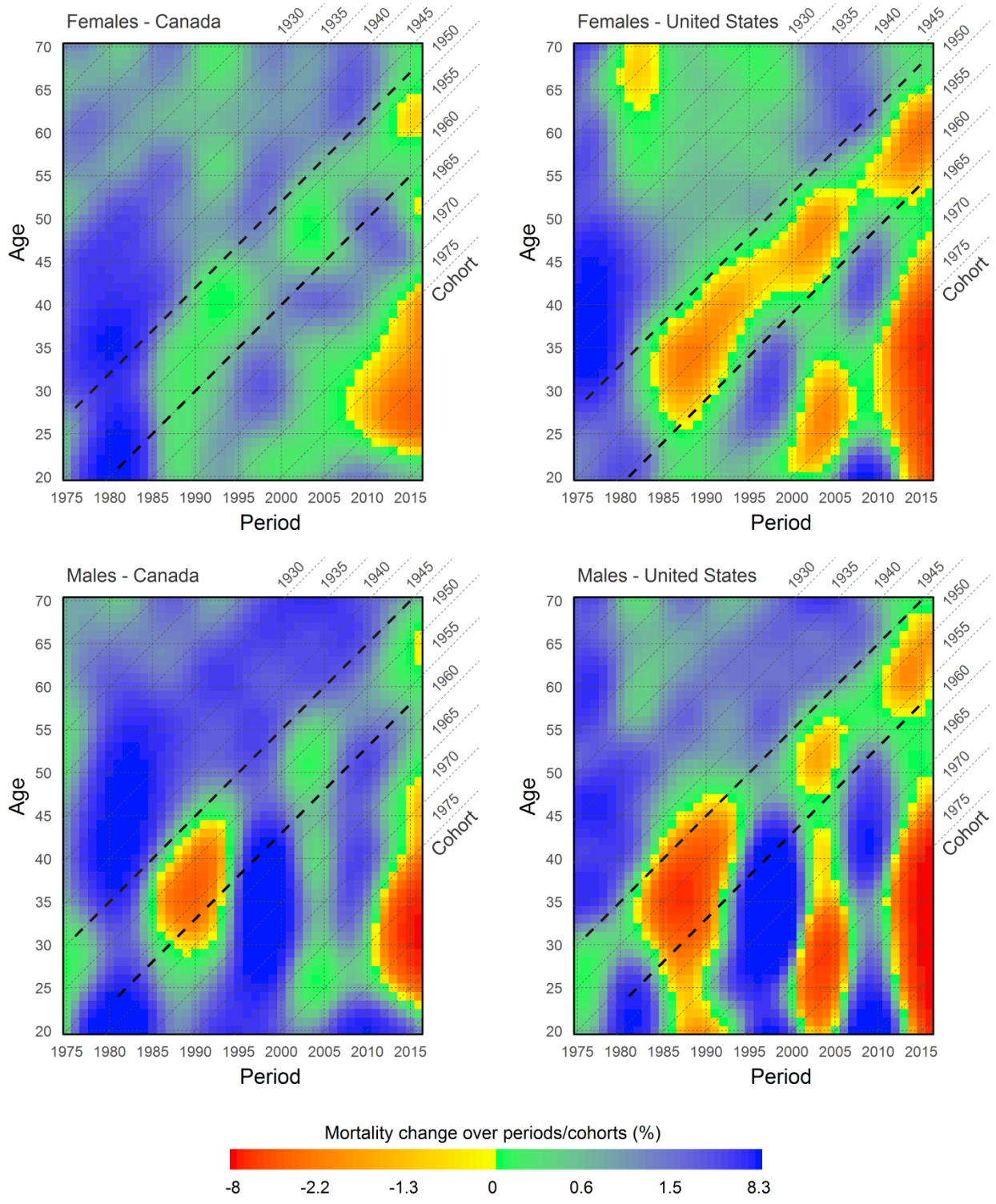
5.3.1. Cause-specific contributions to the boomers' excess mortality

To decompose the excess mortality among boomers by leading causes of death, we first identified those cohorts located at the beginning (advantaged) and the end (disadvantaged) of the relative deterioration in mortality. Second, we identified the leading causes of death responsible for this deterioration.

Identification of the advantaged and disadvantaged cohorts

We first plotted Lexis surfaces of smoothed mortality changes from one period to the next within the same age (see Figure 5.1), and then pinpointed the cohorts located at the onset and at the end of the deterioration in mortality – i.e., the *advantaged* and the *disadvantaged* cohorts, respectively. The smoothing of mortality rates was performed using two-dimensional P-splines. Additional information about the smoothing process, the estimation of the relative changes in mortality, and the construction of the Lexis surfaces is presented in the supplementary material S2 at the end of this manuscript.

Figure 5.1. Lexis surfaces of mortality changes over periods/cohorts.



Notes: Read horizontally from earlier to more recent calendar years/cohorts. The green-to-blue scale indicates the mortality rate decline for year *t* compared to year *t*-1 (or cohort *c* compared to cohort *c*-1) at the same age, and the yellow-to-red scale indicates a relative mortality increase between consecutive calendar years/cohorts. For example, if we examine age 50 for U.S. females, we see that the death rate decreased over

time, reaching its minimum value in 2000 (i.e., cohort 1950). We can also see that from 2000 to 2006, the death rate increased over time, reaching its maximum value in 2007 (i.e., cohort 1956). The diagonal black dashed lines indicate the proximate location of the advantaged and the disadvantaged cohorts for each subpopulation.

The diagonal patterns shown in Figure 5.1 indicate that the *advantaged* and the *disadvantaged* birth cohorts were centered in 1940 and 1960, respectively (black dashed lines). To identify the precise locations of these cohorts in the Lexis configuration, we needed to compare the mortality rates across cohorts. For this purpose, we proposed an index of the cohort's partial mortality rate ($\mathrm{CPMR}^{c(k,l)}$). This index was the sum of the age-specific death rates along the cohort c, between ages *k* and *l*. This measure offers the advantages of controlling for variations in the age structure of the population and allows us to decompose the cause-specific contributions to mortality changes across cohorts. See the supplementary material S2 at the end of the dissertation for more details about the formulation and attributes of the $\mathrm{CPMR}^{c(k,l)}$.

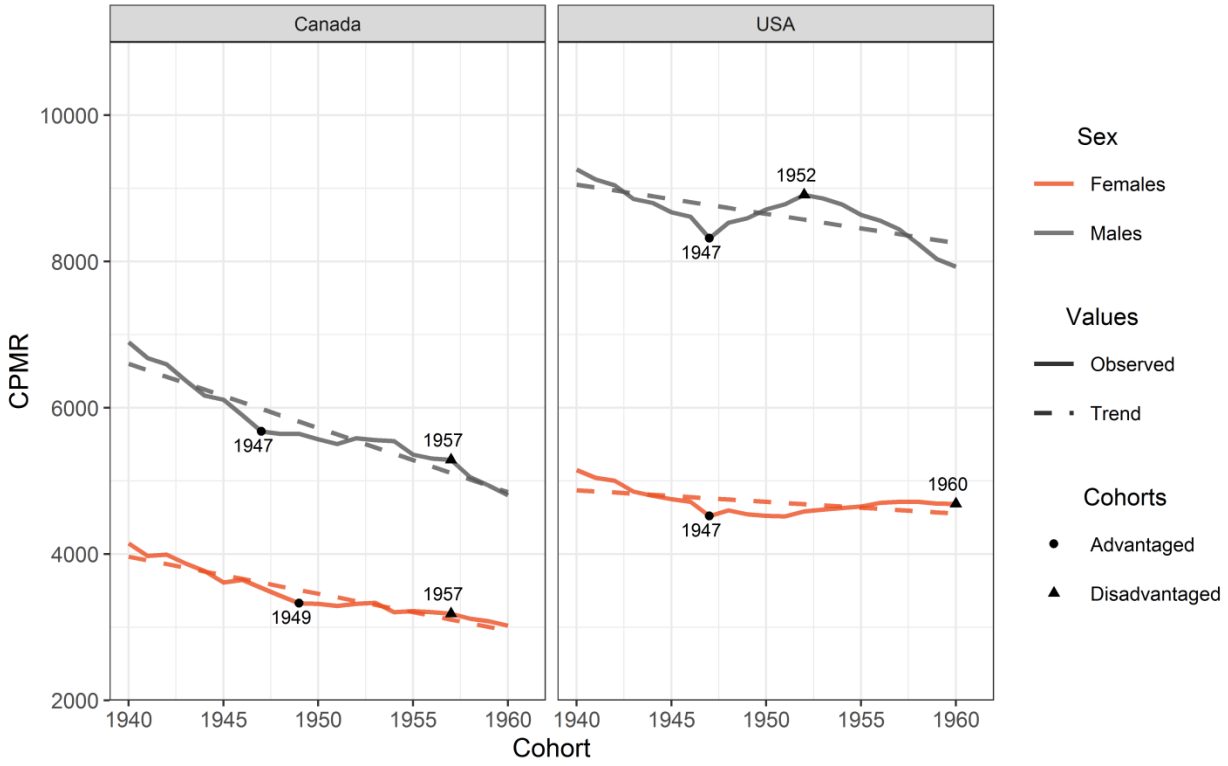
Since our goal was to identify relative and not absolute mortality changes, we based our analysis on the deviation from the linear trend in mortality. We obtained the linear trend by applying a linear regression over the $CPMR^{c(k,l)}$ estimates between the cohorts 1940 and 1960. The cohorts with the largest negative and positive differences relative to the linear trend were labeled, respectively, as the *advantaged* and the *disadvantaged* cohorts. To compare mortality rates across cohorts over the longest possible lifespan, we estimated the $CPMR^{c(k,l)}$ for the age interval 35-54 between the cohorts 1940 and 1960. These estimates cover the period 1975-2014, as 2014 was the last year for which information about causes of death was available for Canada.

Figure 5.2 displays the estimates of $CPMR^{1940(35,54)}$ to $CPMR^{1960(35,54)}$ (solid lines), as well as the respective linear trends (dashed lines). As expected, males had higher levels of mortality than females within each country. Mortality was also higher in the United States than in Canada (~40% higher for females and ~70% higher for males). Indeed, for the cohorts born at the end of the 1950s, the mortality levels of U.S. females and Canadian males were quite similar. In absolute terms, the male and female $CPMR^{c(35,54)}$ deteriorated in the United States, whereas in Canada, mortality improvement stagnated, but mortality did not increase.

Figure 5.2 identifies the cohorts with the largest negative and positive deviations from the $CPMR^{c(35,54)}$ linear trend. These cohorts are labeled, respectively, the *advantaged* (circles) and the

disadvantaged (triangles) cohorts. Whereas the advantaged cohorts were born around the same times in all the subpopulations (between 1947 and 1949), the disadvantaged cohorts of U.S. males were born considerably earlier (1952) than the disadvantaged cohorts in the other groups under observation (between 1957 and 1960). The difference between the advantaged and the disadvantaged cohort was also quite sizeable for U.S. males in comparison of the other groups. The selection of the disadvantaged cohorts for Canadian males and U.S. females, and especially for Canadian females, was not as straightforward, to the point that we can reasonably call into question the notion of advantaged versus disadvantaged cohorts in Canada. To assess the consistency of our estimates, we performed sensitivity tests in which we changed the location of the disadvantaged cohorts and the cohort intervals under observation. These estimates are presented in the supplemental materials (Figures S5.3 to S5.5).

Figure 5.2. Cohort's partial mortality rate within the age interval 35-54



Notes: $CPMR^{c(35,54)}$ by country and sex (solid lines), and their respective linear trends (in dashed lines). The points and labels indicate the year of birth of the *advantaged* (circles) and the *disadvantaged* (triangles) cohorts.

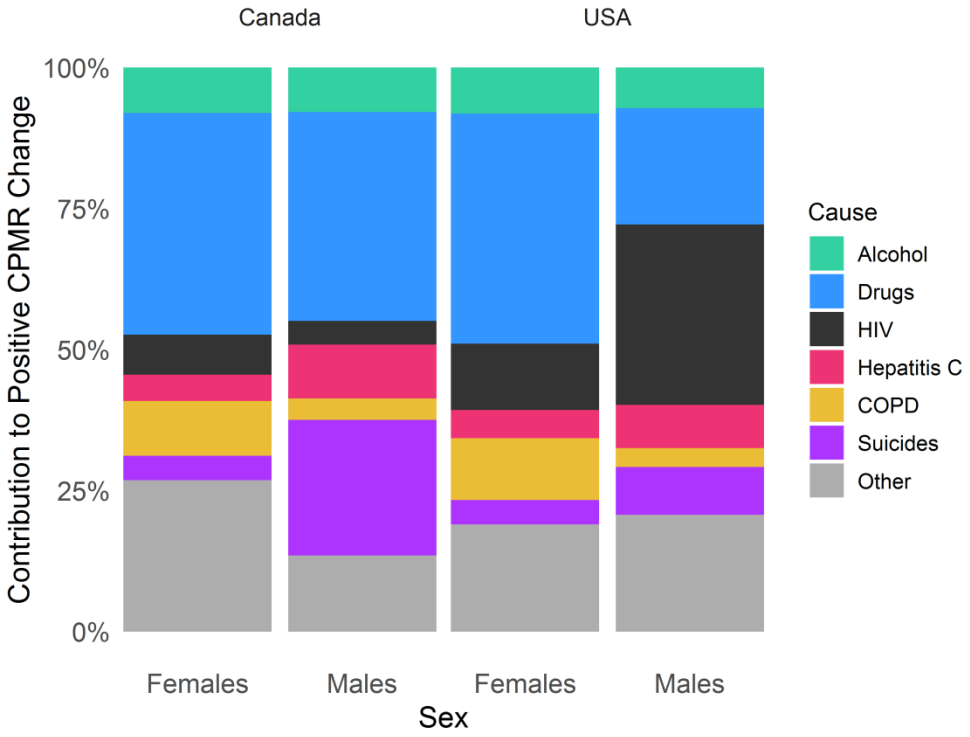
Decomposition of the cohorts' excess mortality by cause of death

After we established the precise locations of the *advantaged* and the *disadvantaged* cohorts in Figure 5.2 using the $CPMR^{c(35,54)}$, we proceeded to decompose the mortality changes between the two cohorts ($\Delta CPMR^{d-a(35,54)}$) by causes of death. See the supplementary material S2 for additional information about this decomposition.

The decomposition of $\Delta CPMR^{d-a(35,54)}$ into broad categories of causes of death showed that the largest contributions to the deterioration in mortality across cohorts, regardless of country and sex, were from external causes, infectious and parasitic diseases, diseases of the digestive system, mental and behavioral disorders, and diseases of the respiratory system. In all subpopulations, the contributions of external causes and infectious diseases were the most important (see Figure S5.1 in the supplemental materials).

Next, we disaggregated these broad causes into more detailed causes of death and re-estimated their contributions to mortality changes. The ICD codes used to identify deaths from these causes are detailed in Table S2 in the supplemental materials. The six causes with the largest positive contributions to mortality changes (i.e., mortality deterioration) across cohorts were those related to alcohol, drugs, HIV/AIDS, hepatitis C, chronic obstructive pulmonary disease (COPD), and suicide (see Figure S5.2 in the supplementary material S2). These six leading causes of together contributed ~75% - 80% of the total positive changes in mortality from the advantaged to the disadvantaged cohorts in all groups (Figure 5.3). The relative cause-specific contributions were consistent across subpopulations, with two exceptions. First, for U.S. males, HIV/AIDS was the cause that made the largest positive contribution, whereas for the other groups, the cause that made the largest positive contribution was drugs. Second, for Canadian males, the relative contribution of suicide (~25%) to the total positive changes in mortality was noticeably larger than in any other group (~5-10%). In the next steps of the analysis, we focus on these six leading causes of death as we attempt to determine the magnitude of the cause-specific cohort disadvantages and their temporal dynamics.

Figure 5. 3. Cumulative contribution to positive $\Delta CPMR^{d-a(35,54)}$ (i.e., mortality deterioration) by cause between the *advantaged* and the *disadvantaged* cohorts



5.3.2. The magnitude and the temporal dynamics of the boomer cohorts' disadvantage

Detrended cohort effects on mortality by cause of death

The estimates from the $\Delta CPMR_i^{d-a(35,54)}$ reported in Figure 5.3 were useful for identifying the causes of death that made the largest contributions to the relative deterioration in mortality from the *advantaged* to the *disadvantaged* cohorts. However, to properly assess the "cohort penalty" by cause of death, we need to account simultaneously for variations over the three APC dimensions (a further discussion on this topic is presented in the supplementary material S2). We should, however, note that the use of APC models is challenging because of the well-known *identification problem*, in which the perfect multicollinearity between the variables (*cohort* = *period* – *age*) results in an infinite number of solutions with an identical fit. Despite the several attempts to solve this problem by imposing arbitrary restrictions on the APC models (e.g., constrained generalized linear (Fienberg and Mason

1985) and intrinsic estimator (Yang et al. 2004) models), the problem remains entirely (Bell and Jones 2013; Fienberg 2013; Fosse and Winship 2018, 2019; Luo 2013).

In the present study, we were not interested in decomposing the linear effects, but were instead concerned with analyzing the deviation of the mortality of the boomer cohorts from the linear trend. As these divergences from the linear trend – which are also referred in the APC literature as nonlinear effects, curvatures (Holford 1983), or humps (Chauvel et al. 2016; Remund et al. 2018) – are unaffected by the constraints chosen for the model identification, they are unambiguously identifiable (Clayton and Schifflers 1987; Holford 1983; Rodgers 1982).

For the analysis of the cohort effects on mortality by cause, we estimated the relative mortality risks across cohorts (i.e., the nonlinear cohort effects) using a cohort-detrended APC model (APCd) (Carstensen 2007; Chauvel 2013). In this approach, the linear trend is attributed entirely to variations over the age and period dimensions, which results in a series of cohort components with zero slope. Under this parameterization, the logarithm of the cohort effects can be interpreted as relative risks with respect to the overall linear trend (Carstensen 2007; Holford 1991). To estimate the APCd model, we grouped ages, periods, and cohorts into two-year categories, and fitted splines to a Poisson model, using the R package Epi (Carstensen et al. 2018).

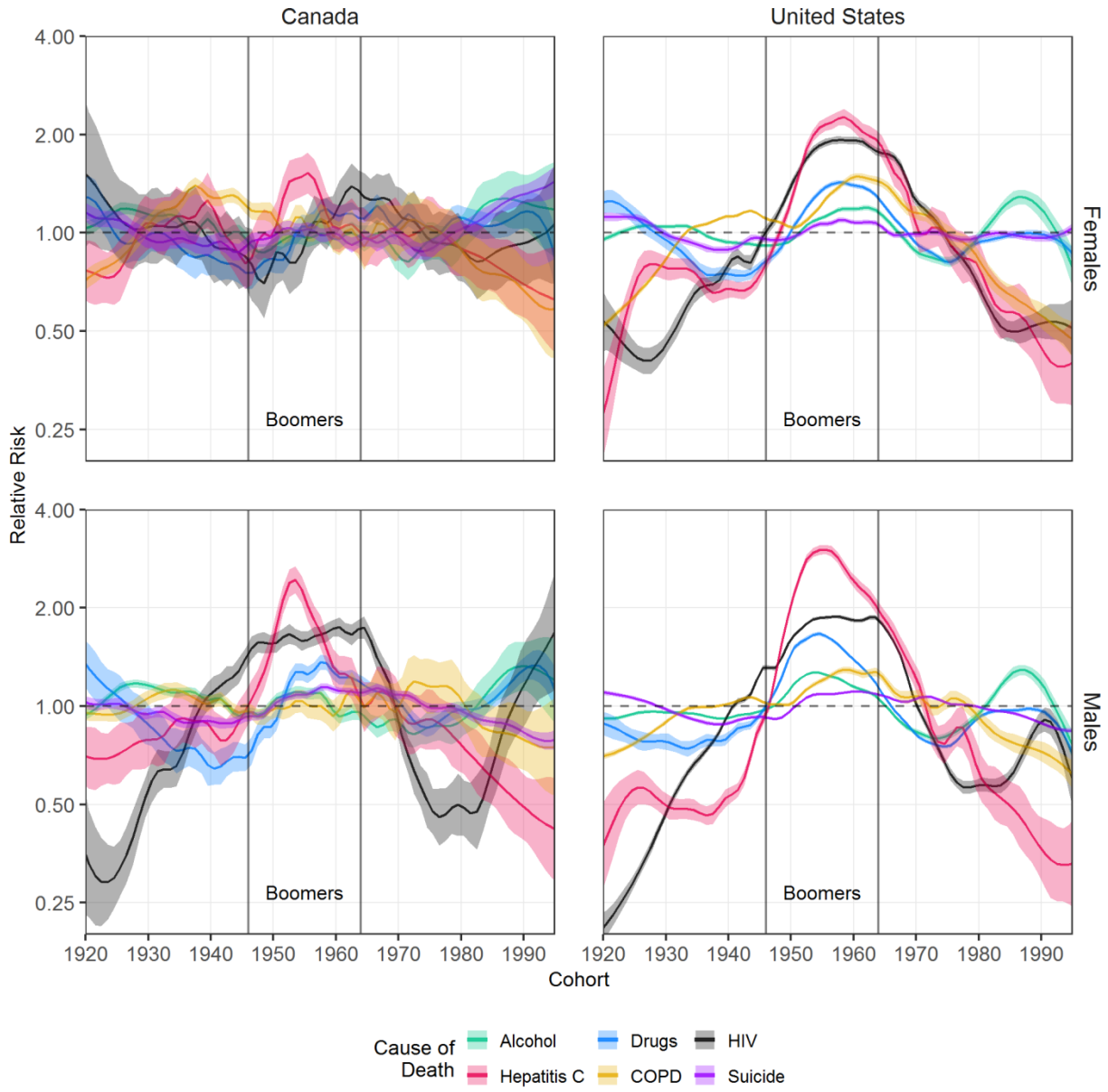
Comparisons between Canada and the United States

Figure 5.4 and Table S3 show the relative risks and confidence intervals obtained from the APCd model by country, sex, and cause of death (see Figure S5.6 in the supplemental materials for a facetted version of Figure 5.4). In all boomer groups, the largest relative cohort disadvantages were observed for hepatitis C, HIV/AIDS, and drug abuse mortality (with relative risks between 1.7 and 3.0), while the smallest cohort disadvantages were found for alcohol abuse, suicide, and COPD (with relative risks between 1.2 and 1.5). The main difference detected between the two countries was in the pattern of mortality due to COPD, for which only the U.S. boomers had a risk that was higher than the overall cohort average.

The mortality patterns of Canadian females differed considerably from those of their male counterparts and from those of U.S. males and females. For all causes of death, the Canadian female boomers had little to no disadvantage. For alcohol, suicide, and COPD, the mortality risks of this group were not significantly higher than the overall cohort average. In contrast, boomer males in Canada and boomer males and females in the United States had similarly high relative risks of dying

from hepatitis C, HIV/AIDS, drugs, and suicide. More precisely, these three subpopulations of boomers had the largest disadvantages in mortality for causes related to drugs, HIV/AIDS, and hepatitis C; moderate disadvantages for causes related alcohol; and considerably smaller disadvantages for death from suicide.

Figure 5. 4. Cohort relative risks by country, sex, and cause of death



Notes: The width of the ribbon indicates the confidence interval at the 95% level. Estimates were obtained from a cohort-detrended model (APCd). The reference category is the overall cohort average, depicted in the plot with a horizontal dashed line. The beginning and end of the baby boom (i.e., 1946 and 1964, respectively) are marked with vertical gray bars.

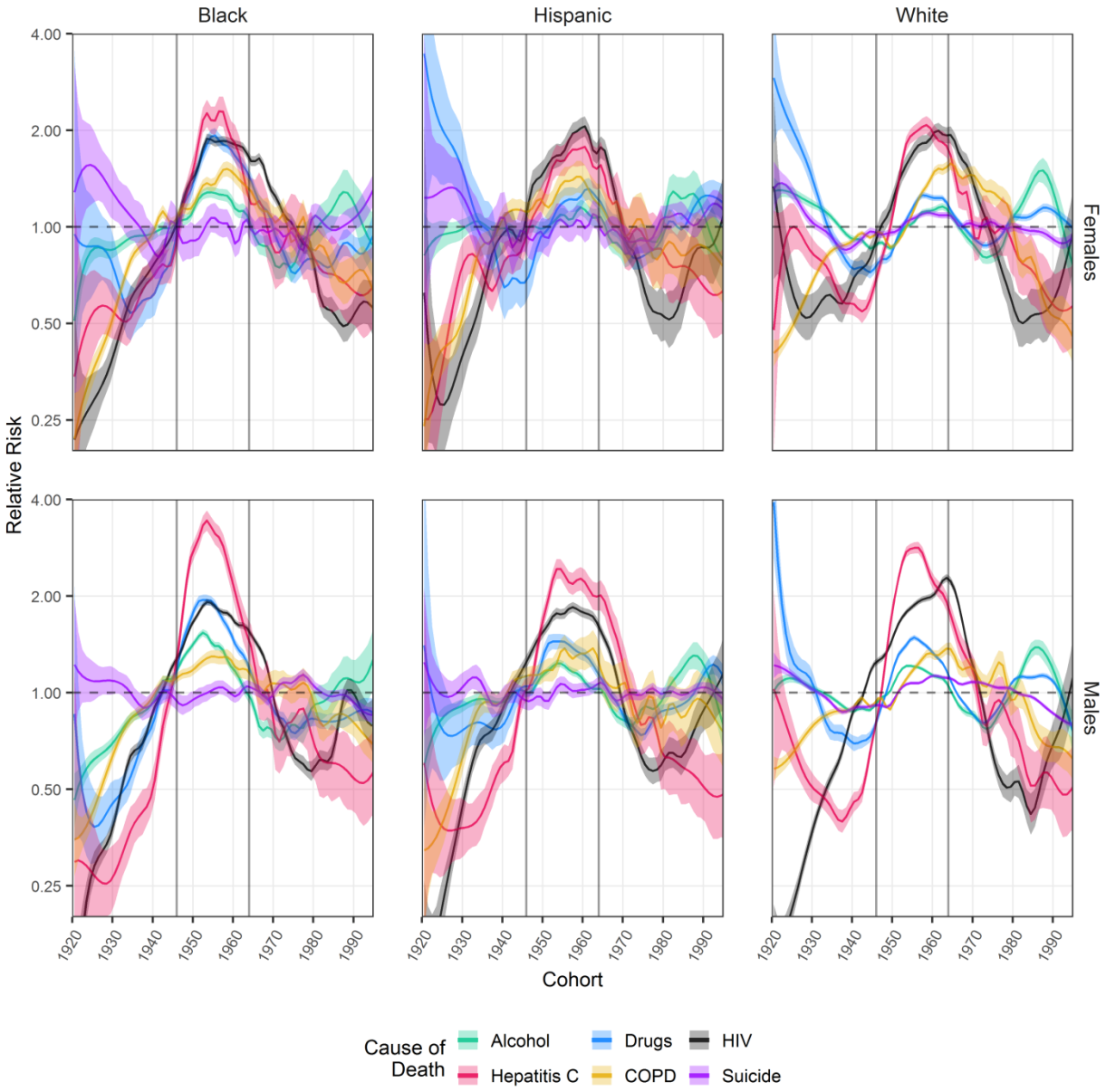
Comparisons across races and ethnicities in the United States

In order to explore the disparities across racial and ethnic groups in the United States, we estimated detrended cohort effects as cohort relative risks for the NHB, Hispanic, and NHW populations (Figure 5.5; see also separate plots in Figure S5.7 in the supplemental materials). Except for a few cases, the female and male boomers in the United States had similar cause-specific cohort disadvantages within each race or ethnicity. The causes that contributed the most to the boomers' disadvantages relative to their respective cohort average in all subpopulations were hepatitis C and HIV/AIDS, and the cause that contributed the least was suicide.

The main difference between the sexes in the causes that contributed to the boomers' mortality disadvantage was that hepatitis C, which posed a much greater risk for males (reaching a maximum of a 2.5-fold risk on average) than for females (2.1-fold risk on average), regardless of race/ethnicity.

When analyzing the cause-specific contributions to the boomers' mortality disadvantage by race and ethnicity, two results stand out. First, the NHW boomers of both sexes were the only groups with a significantly higher relative risk of suicide mortality. Second, although boomers of all groups had a large drug-related mortality disadvantage, the relative risks for NHB (1.9 for females and 2.0 for males) were substantially higher than those for Hispanics (1.32 and 1.45) and NHW (1.3 and 1.5).

Figure 5.5: **Cohort relative risks by race/ethnicity within the U.S., sex, and cause of death**



Notes: The width of the ribbon indicates the confidence interval at the 95% level. Estimates were obtained from a cohort-detrended model (APCd). The reference category is the overall cohort average, depicted in the plot with a horizontal dashed line. The beginning and the end of the baby boom (i.e., 1946 and 1964, respectively) are marked with vertical gray bars.

In summary, these results show that boomer cohorts had higher relative risks of dying from most of the causes that were making the largest contributions to the deterioration in mortality from the advantaged to the disadvantaged cohorts, regardless of national context, sex, and race/ethnicity. Three exceptions are, however, noteworthy. First, among Canadian female boomers, the relative

risks of mortality were significantly higher than the cohort average only for causes related to drugs, HIV, and hepatitis C. Second, only boomers in the U.S. had a significant disadvantage in COPD mortality. Third, only Canadian males and U.S. NHW males and females had a significantly higher relative risk of mortality from suicide. In the next section, we analyze the temporal pattern of these cause-specific cohort disadvantages.

Dynamics of the cohorts' excess mortality over time

The APCd estimates presented above were useful for the estimation of the average cohort disadvantage. However, these estimates were of limited use for the analysis of the temporal dynamics of nonlinear effects because, as averages, they did not allow us to observe variations in relative risks over time (Chauvel 2013). The changes in the magnitude or the location of the largest curvatures by cause over time, however, can help us determine whether the boomer penalty resulted from a sequence of temporary age-period interactions, or, conversely, from a process that operated continuously throughout the life course of the boomers. To analyze these temporal dynamics, we constructed *APC curvature plots*. This graphical tool allowed us to display the changes in the nonlinear APC components over time on a Lexis diagram by focusing on the ridges; i.e., the series of Lexis coordinates in which the relative risk reaches a maximum. These plots helped provide synthetic information on nonlinear APC effects simultaneously across several populations or for several causes of death. In Chapter 6 (article 3), we provide a detailed description of the construction and interpretation of the *APC curvature plots*.

To construct the *APC curvature plots*, we needed to extract the boomer curvatures – in this case, the excess mortality by cause of death. To do this, we first estimated a mortality baseline by excluding the cohorts that diverged from the secular trend in mortality and by interpolating the mortality rates. The excess mortality was defined as the difference between the observed and the interpolated surface. The interpolation of the mortality rates was estimated with two-dimensional P-splines, and performed with the R package *MortalitySmooth* (Camarda 2012). The measured excess mortality was then translated into visual attributes: the locations of the ridge over time (i.e., the age/cohort for which the positive divergence in mortality reached its maximum level in each period) were indicated through the coordinates position in the Lexis diagram; and the magnitude (i.e., the relative risk in the ridge compared to in the base of the hump) was indicated by the point size. We constructed *APC curvature plots* to compare the cohorts' excess mortality across causes of death, countries, and races/ethnicities simultaneously in the same figure.

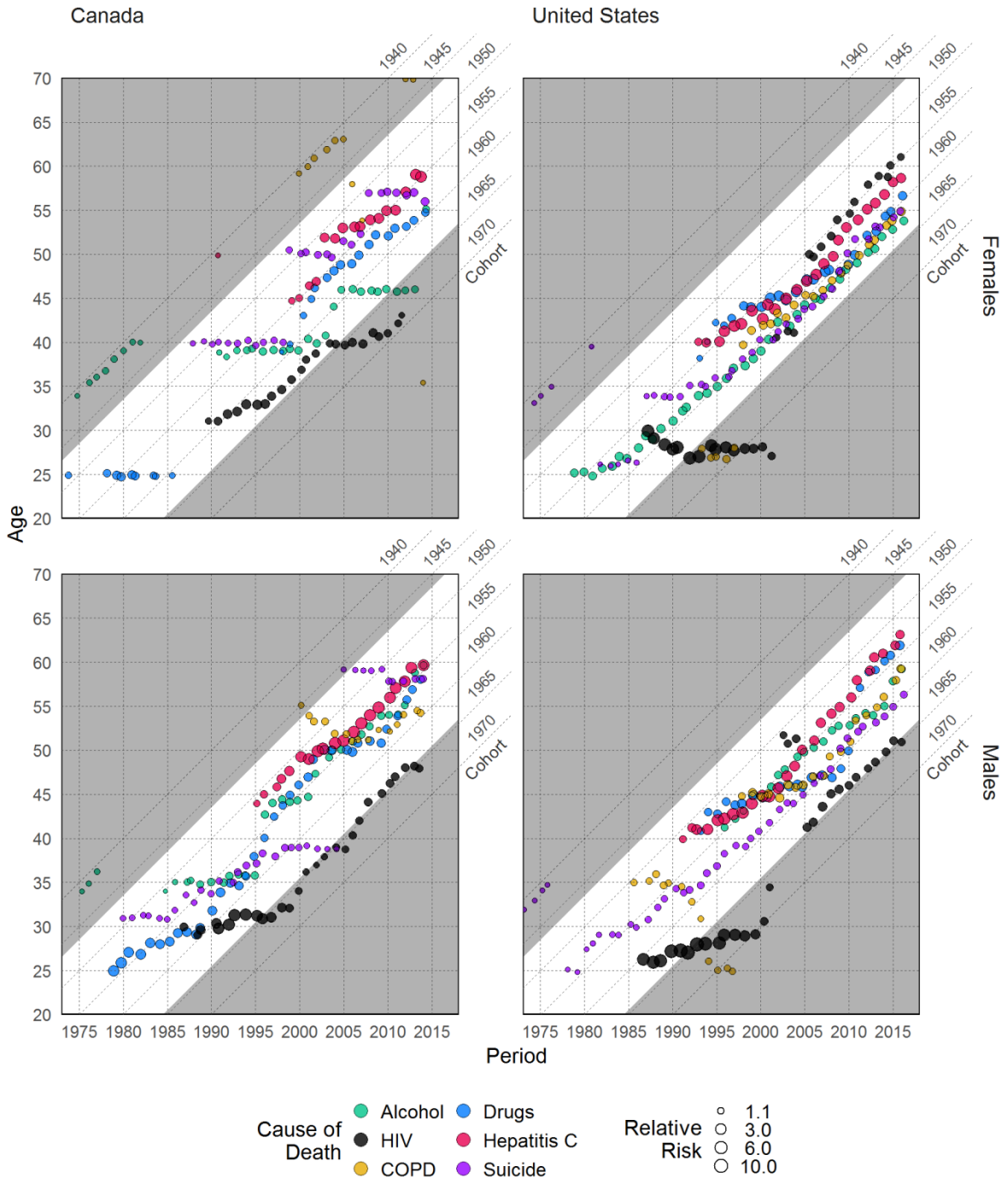
Comparisons between Canada and the United States

The APC curvature plots presented in Figure 5.6 show the temporal dynamics of excess mortality (i.e., the age/cohort with the greatest excess mortality in each period) by cause of death, country, and sex (see also Figure S5.8 in the supplementary material). We first describe the results for HIV/AIDS-related mortality. The patterns for HIV/AIDS were similar across subpopulations, but differed considerably from the patterns for the other causes. Between the mid-1980s and the mid-1990s, the ridge for HIV/AIDS-related excess mortality largely surfaced in the diagram as an age effect for both sexes in Canada and the United States, with young adults (ages 25-35) being disproportionately targeted. However, after the turn of the 21st century, the ridges for HIV/AIDS shifted and began to align diagonally toward a cohort pattern for all groups under observation, with some noticeable differences. Whereas Canadians of both sexes and U.S. males born around 1965 were most susceptible, the largest disadvantage for U.S. females was observed for those born around 1955. For Canadian females, this cohort effect was interrupted in the second part of the 2000s, when it returned to an age effect, but this time targeting those aged ~40.

The locations of the ridges of excess mortality from hepatitis C, drugs, and alcohol were similarly centered on the cohorts born around 1955-1960, with the relative risks of dying from drugs and alcohol being considerably lower. The main exception was for Canadian females, who did not have a sustained cohort mortality disadvantage related to alcohol, suicide, or COPD, which is consistent with previous results regarding this group. Whereas the COPD disadvantage did not follow any clear pattern, the horizontal traces of the alcohol and suicide ridges were more indicative of short-term age-period interaction effects.

Turning now to variations in the magnitude of the cohort disadvantage over time (see also Figure S5.8 in the supplemental materials), we can see that the relative risks of HIV/AIDS mortality were considerably higher at the turn of the 1990s for all groups (up to 10.7), and for U.S. males in particular. Nevertheless, at the turn of the century, the relative risks of HIV/AIDS mortality decreased sharply, and remained below 1.8 during the rest of the period. Apart from HIV/AIDS, the largest boomer disadvantages were observed for mortality from hepatitis C and drug abuse, which, respectively, hit their maximum relative risk levels of 4.9 and three at the turn of the century. Compared to the other causes, the relative risks of alcohol, COPD, and suicide mortality among boomers were substantially lower, never exceeding 1.7, 1.7, and 1.5, respectively.

Figure 5.6. APC curvature plots by country, sex, and cause of death



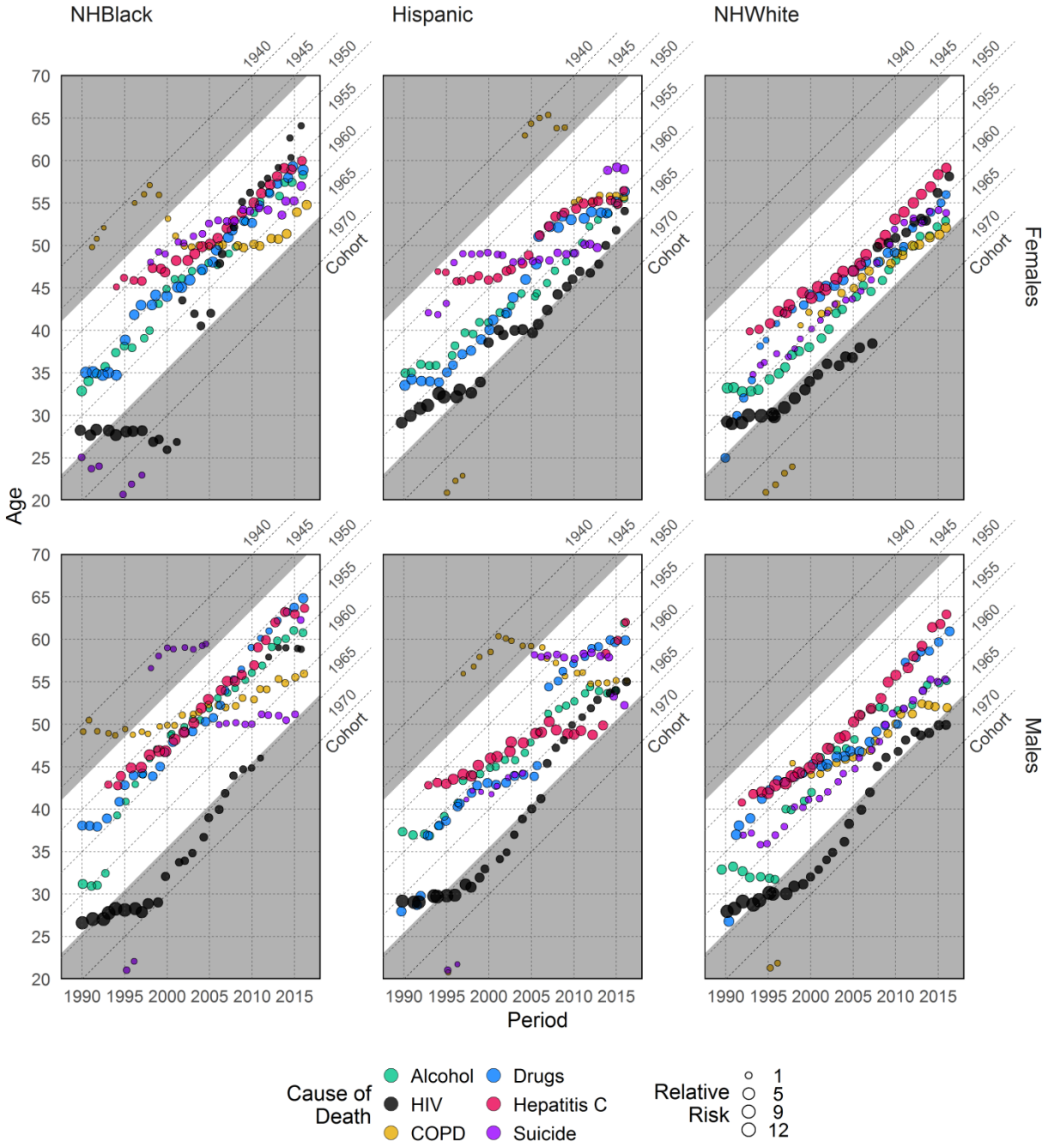
Notes: Location (age/cohort) and magnitude (in relative risks) of the largest excess mortality in each period. The color of the points indicates the cause of death and the size indicates the relative risk at the ridge, compared with the mortality baseline. The white diagonal band indicates the location of the baby boomer cohorts (i.e., 1946-1964).

Comparison across races and ethnicities within the United States

Figure 5.7 presents APC curvature plots of the cause-specific disadvantage in mortality by sex and race/ethnicity in the United States (see also Figure S5.9 in the supplementary material). The trends displayed in Figure 5.7 show that boomers of both sexes and of all race/ethnicities had clear and sustained cohort disadvantages for all causes of death except COPD and suicide. Systematic cohort disadvantages in COPD and suicide were only identified for NHW. For the other racial/ethnic groups, the ridges for these causes were more indicative of an age effect. Consistent with the estimates at the national level (presented in Figure 5.6), the ridges of HIV/AIDS-related mortality for all racial/ethnic groups showed an age pattern of disadvantage until the end of the 1990s, with the largest relative risks among all the causes (12.2). At the turn of the century, the relative risk of HIV/AIDS mortality among boomers decreased considerably and shifted into a sustained cohort effect. Moreover, consistent with the patterns at the national level, U.S. boomers of all race/ethnicities had the highest relative risks of hepatitis C and drug abuse mortality, reaching maximum levels of 4.7 and 3.8, respectively. The smallest relative disadvantages among boomers were for mortality from alcohol, COPD, and suicide (2.8, 2, and 1.9, respectively).

Turning finally to variations in relative risks over time, we can see that for most racial/ethnic groups, the relative risks of hepatitis C mortality peaked at the turn of the century and decreased thereafter. However, for Hispanic and NHB females, the relative risks of hepatitis C mortality did not start to decrease until 2010. The ridge of the drug-related mortality disadvantage peaked three times: first at the turn of the 1990s, then at the turn of the 2000s, and, finally, during in the last year of observation (i.e., 2016). The relative risks of alcohol-related mortality were especially high in 1990 (2.1- to 2.8) and decreased progressively over time for Hispanics and NHW. However, for NHB female and male boomers, this declining trend was reversed in 2010, as the relative risks of alcohol mortality increased markedly. For COPD and suicide, the relative risks among boomers increased monotonically during the observation period, reaching an average of 1.5.

Figure 5. 7. APC curvature plots by race/ethnicity within the U.S., sex, and cause of death



Notes: Location (age/cohort) and magnitude (in relative risk) of the largest excess mortality in each period, across causes of death, sexes, and races/ethnicities within the United States. The color of the points indicates the cause of death and the size indicates the relative risk at the excess ridge, compared with the mortality baseline. The white diagonal band indicates the location of the baby boomer cohorts (i.e., 1946-1964).

Taken together, these results suggest that what could be called "the boomer penalty" is the result of several cause-specific disadvantages that accompanied boomers throughout their life course, regardless of their country, sex, or race/ethnicity. However, the absence of a cohort disadvantage for several causes among Canadian female boomers should be noted.

5.4. Discussion

This study was designed to identify the leading causes of death that have contributed to the baby boomers experiencing a mortality disadvantage relative to their adjacent cohorts, and to explore the changes over time of these contributions in Canada and the United States. Relative to previous cohorts, Canadian boomers experienced a deceleration in mortality improvements, while American boomers experienced an increase, in absolute terms, in all-cause mortality.

In summary, six behavioral causes of death – namely, drug and alcohol abuse, HIV/AIDS, hepatitis C, suicide, and COPD – contributed at least 75% of the positive changes in mortality – i.e., the deterioration in mortality – across cohorts. The disadvantages observed among the boomers were substantially larger among males than among females for most causes, regardless of national context or race/ethnicity. The highest relative risks of mortality were from hepatitis C and drug-related causes, and the lowest relative risks of mortality were from COPD and suicide. These results should, however, be interpreted with caution, given that higher relative risks do not necessarily indicate greater excess mortality in absolute terms. For instance, even though boomers had considerably higher relative risks of mortality from hepatitis C than from alcohol, because the baseline for mortality from alcohol was much higher, alcohol contributed more than hepatitis C to the mortality disadvantage among boomers.

Our findings also revealed that excess mortality among baby-boomers was sustained over the life course for most of the main causes that we identified as constitutive of the boomer penalty, both in Canada and the United States, and regardless of race or ethnicity in the latter . The mortality disadvantages of Canadian female boomers were, however, much smaller and less indicative of any sustained cohort effects.

In the rest of this section, we discuss the mechanisms that may explain our results. In particular, we focus on the factors that could have contributed to an increased boomer susceptibility to mortality

from behavioral causes, and on the differences across population groups. We close this section by pointing out the advantages and limitations of our analysis and recommend further investigations on the current topic for future research.

5.4.1. Temporal dynamics of the cause-specific excess mortality among boomers

First, it could be argued that the boomers' excess mortality does not stem from sustained cohort effects, but from successive period crises that targeted the boomers at different life stages – that is, a sequence of age-period interaction effects that disproportionately affected these cohorts. The temporal patterns of mortality from HIV/AIDS are indicative of age-period interaction effects during the most critical stage of the epidemic (i.e., between the late 1980s and the early 1990s), which disproportionately affected those in their thirties. Although HIV/AIDS mortality decreased substantially after the introduction of the antiretroviral therapy in 1996 (Murphy et al. 2001; Palella et al. 2006; Vittinghoff et al. 1999), we found evidence that the effects of the epidemic lingered throughout the later adult lives of the late boomers (Figures 5.6, 5.7, S5.5, and S5.6). This higher susceptibility among boomers to HIV/AIDS may be the reason for the recent increases in HIV prevalence among people aged 50 and older, who account for nearly the half of those living with diagnosed HIV in the United States (CDC 2018a).

In the case of drug overdoses, our findings indicated that although the absolute changes in severity were largely driven by period-based factors that affected most ages, the boomer cohorts faced higher risks of drug-related mortality than the adjacent cohorts during the whole observation period. The magnitude of this cohort susceptibility was not, however, constant over time (Figures 5.6, 5.7, S5.8, and S5.9). The disadvantage in drug-related mortality among boomers peaked twice: at the turn of the 1990s, which marks the beginning of the crack epidemic, and at the turn of the 2000s, which corresponds to the start of the opioid epidemic. These increases in relative risks at the beginning of each crisis and their posterior attenuation may be attributable to the vanguard role of boomers in abusing these drugs before the epidemics spread to other cohorts. This "inter-cohort contagion" of substance abuse is particularly notable for the case of the millennial cohorts. While the boomer cohorts had the largest relative risks of alcohol- and drug-related mortality during the 1990s and 2000s, the millennial cohorts have started experiencing relative increases in mortality from these

causes, to the point that the millennials' risks of alcohol- and drug-related mortality have exceeded those of boomers in recent years (Huang et al. 2017; Miech et al. 2013; Sauer et al. 2018; Zang et al. 2019). For both HIV/AIDS and drug mortality, punctual and strong period crises affecting most age groups (i.e., period effects) have been detected. However, lagged effects from these disturbances along the cohorts have been observed among the boomers (i.e., cohort effects).

Figures 5.6 and 5.7 suggest that the mechanism outlined above underlies multiple outcomes. Our results are consistent with previous findings indicating that behavioral risks related to opioid abuse, HIV/AIDS, and hepatitis C interacted with each other in these cohorts. In most groups, the cohorts with the largest disadvantages for these causes of death had similar locations and synchronic variations in magnitude since the mid-2000s. Some of these similarities may result from the ongoing opioid epidemic, which might have contributed to the spread of HIV/AIDS and hepatitis C infections among chronic intravenous drug users (IVDUs) (Strader 2005; Zibbell et al. 2017). In addition, while IVDUs who share contaminated needles face a higher risk of HIV infection, individuals who have been diagnosed with HIV have both higher rates of prescription opioid use to treat chronic pain symptoms and higher risks of developing drug use disorders (Becker et al. 2016). Similarly, our observation of the synchronicity between COPD and drug abuse mortality among NHB females and NHW of both sexes (Figure 5.7) was consistent with previous findings suggesting that the risk of COPD mortality is higher among opioid users (Levine 2017; Vozoris et al. 2016). However, the results for the other groups did not display this kind of synchronicity.

Taken together, our findings suggest that the mortality penalty endured by the boomers is not the result of a series of age-period interactions that coincidentally increased mortality at different life stages. Instead, the boomer disadvantage resulted from multiple and parallel long-term disadvantages that have accompanied these cohorts over time.

5.4.2. Factors contributing to the boomer penalty

Although our research design is exploratory, our findings are consistent with numerous mechanisms already proposed in the literature. Below, we present and discuss in more detail the mechanisms, mentioned in the introduction, that may be driving the survival disadvantage among boomer cohorts. These mechanisms pertain to selection processes, birth cohort effects, and generational identity effects.

According to the *frailty* hypothesis (Vaupel et al. 1979; Zheng 2014), low selection pressure during infancy and childhood would have resulted in a heterogeneous cohort, with a large proportion of frail individuals surviving to adult ages and being susceptible to mortality from *intrinsic* causes of death. It has been argued that the higher mortality experienced by the boomers during their young and adult ages could be the consequence of increased survival rates early in life due to a reduced infection burden and improved nutrition intakes (Canudas-Romo and Guillot 2015). However, our results do not corroborate this hypothesis. The leading causes of death contributing to the boomer penalty are not intrinsic, but are, rather, behavioral or extrinsic. The likelihood that frail individuals who were "saved" in early life through better nutrition and reduced infection loads would go on to develop risky behaviors later in life seems rather low. Moreover, the *frailty* hypothesis does not explain the substantial mortality improvements among young adults in the cohorts born after the boomers, who experienced lower initial mortality rates than the boomers.

Based on our results, two complementary mechanisms allow us to interpret the higher susceptibility of the boomers: namely, Ryder (1965)'s *birth cohort* influence and Mannheim (1952)'s historical *generational*[7] membership influence. In his seminal work, Ryder (1965) stated that some the characteristics of some birth cohorts have permanent effects through the life course. According to Ryder, cohort size was the most evident manifestation of inter-cohort differences, since it is a persisting feature of the cohort's lifetime, with cascading effects on education, family formation, and labor force participation. Following Ryder's approach, Easterlin extensively studied the implications of cohort size and other cohort-specific characteristics for the historical locations of the boomers during their life course (Easterlin 1976, 1987; Easterlin et al. 1993). Easterlin's central argument was focused on the mismatch between the early life and the later life conditions that the boomers were known to have experienced. Born amid a post-war economic boom, the development of the welfare state, and unprecedented enrollment rates in higher education, the boomers became adults in a social context characterized by competition for resources – because of the large size of the cohort – a progressive erosion of the welfare state, and a weaker and increasingly precarious labor market. According to Easterlin, this imbalance between expectations and reality had serious implications for the perceived well-being of the boomers, increasing the prevalence of mental distress and frustration

[7] Here, we use *generation* in a historical sense, so it should not be confused with the genealogical sense of kinship. See Alwin and McCammon (2007) for an extensive discussion about the three uses of the concept *generation* in the social sciences.

among these cohorts. Easterlin (1987) expected baby boomers to experience higher mortality from suicide, substance abuse, vehicle accidents, and homicide.

In contrast, *generational* membership, in the Mannheimian sense, implies a more complex social process in which individuals participate in the social movements of their time, and develop a shared identity with a unique worldview (Alwin and McCammon 2007; Eyerman and Turner 1998; Mannheim 1952). The enormous and unprecedented generational rift experienced by the boomers at sensitive life stages helped to consolidate their distinctive generational identity. The social importance and the inclusion of social movements in the popular culture and mass consumption – especially in rock music and literature – boosted and magnified the influence of these minorities on their contemporaries (Alwin et al. 2014; Alwin and McCammon 2007; Bristow 2015; Eyerman and Turner 1998; Stewart and Torges 2014). For the first time in history, a generational identity was simultaneously diffused to several western societies, including the United States, Canada, the United Kingdom, France, and Australia (Edmunds and Turner 2005).

The signatures of solidarity within this generation were the defiance of social norms and the rebellion against the older generations, which were expressed in drug use and a more explicit sexuality (Cross and Kleinhesselink 1985; Johnston 1991). An increasing number of studies have found that dispositions and attitudes toward riskier behaviors regarding drug use and sexuality tend to be drawn from formative experiences and peer influences during the early stages of life, rather than from successive period-based influences throughout the life course (Johnson and Gerstein 2000; Keyes et al. 2011; Rhodes 1997). Thus, the differential constructions of risk perception and habituation during the early stages of the boomers' life course have been linked to higher risks of mortality from HIV/AIDS and other infections (McBride 1990), from substance abuse (Colliver et al. 2006; Crome and Rao 2018; Duncan et al. 2010; Miech et al. 2011; Patterson and Jeste 1999; R. Rao and Roche 2017), and from road traffic accidents (Puac-Polanco et al. 2016; T. Rao 2019).

Although they refer to different phenomena, *birth cohort* and *generational identity* are not completely independent. Their increased exposure to peers might have made the boomers less apt to identify with the values and beliefs of previous generations (Easterlin 1987; Phillips 2014; Stewart and Torges 2014), and encouraged the rise and spread of the youth-based social movements of the 1960s and 1970s (Abrams 1970; Bristow 2015, 2016; Cross and Kleinhesselink 1985; Goertzel 1972).

It is, therefore, possible that the cohort attributes of boomers not only reinforced their rebellious and risky generational identity, but that these two mechanisms may have acted in parallel to increase their mortality risk along the life course. In light of the mechanisms presented above, we now discuss some of the similarities and differences in the magnitude and the temporal dynamics of the boomer penalty across countries, sexes, and races/ethnicities.

5.4.3. Comparison of findings across the population groups under study

The unprecedented transnational diffusion of the boomer identity that we discussed above, as well as some similarities in the socioeconomic contexts in Canada and the United States during the sensitive life stages of the boomers, could explain our findings to some extent. We found that the causes that made the largest contributions to the excess mortality among the boomers were the same in both countries, and that the temporal patterns of the cohort effects were quite similar in the United States and Canada.

However, we also uncovered substantial differences in the magnitude of the boomer penalty between the two countries. As Figures 5.1 and 5.2 show, the Canadian boomers mainly experienced a slowdown in mortality improvements (indicated by the green diagonal trace in Figure 5.1), while the U.S. boomers experienced a noticeable deterioration in mortality (indicated by the change of the scale sign from a negative to a positive change in mortality in Figure 5.1).

A possible explanation for this difference in the magnitude of the penalty may be the dissimilar experiences of the Canadian and the U.S. boomers during critical stages of their life course, which could have led to sizable differences in how the birth cohort and the generational identity mechanisms were embodied in these groups, and unfolded in their later lives. First, the levels of stress and frustration may have been substantially lower among Canadian boomers than among their counterparts in the United States. Although Canadian boomers are also part of a large cohort and grew up amid a post-war economic boom, the mismatch between the expectations they developed in childhood and the reality they encountered in young adulthood was not as extreme as it was in the United States. Compared to the United States, Canada has a stronger welfare system (Banting and Hoberg 1997; Myles 1998), much lower levels of inequality (Lemieux 1993; Ross et al. 2000; Rycroft 2013), and a less pronounced cultural orientation toward individualistic values (Adams 2004; Clark 1991; Lipset 2013; Steger et al. 1989).

Second, the generational rift experienced by Canadian boomers may have been less striking than that experienced by their counterparts in the United States. The dominant values in Canadian society – such as traditional views on the rights of women, racial/ethnic minorities, and non-heterosexual communities, as well as attitudes regarding religion, sexuality, and drug use – were also challenged by the counterculture movements (Palmer 2008). However, the scale of the political and social conflicts during the 1960s and 1970s was smaller in Canada than it was in the United States (Campbell et al. 2012). At that time, Canada had no Jim Crow laws and was not involved in the Vietnam War. Indeed, Canada has historically been perceived and has served as a refuge for U.S. citizens fleeing racism and the draft. Such was the case for the NHB who were escaping from slavery through the Underground Railroad to Canada during the 19th century, and for the draft-dodgers – mostly young boomers – who were seeking to avoid military service in the Vietnam War during the 1960s. Previous research has shown that the civil rights and the antiwar movements were the most important sources of the generational rift. Thus, the most influential and cohesive events for the U.S. boomers occurred around the counterculture movements during the 1960s and 1970s (Alwin et al. 2014; Alwin and McCammon 2007; Bristow 2015; Stewart and Torges 2014). Meanwhile, the Canadian boomers may have experienced milder birth cohort effects that translated into lower levels of anxiety, which led them to adopt a less rebellious generational identity associated with less risky attitudes and behaviors. These social and political differences between the two countries might have contributed to the boomer penalty being smaller among the Canadians.

With respect to differences by sex, there is a large amount of evidence pointing to a higher propensity among males than among females to engage in risk-taking behaviors that could lead to death (Ferrence 1988; Fingerhut and Cox 1998; Harris and Jenkins 2006; Pampel 2001; Veevers and Gee 1986; Waldron et al. 2005). Since most of the excess mortality among the boomers stemmed from behavioral causes, it is not surprising that the boomer penalty was larger among males in all groups under observation.

Regarding the temporal patterns, two male-female differences stand out. First, the ridges of excess mortality by cause of death follow horizontal, rather than diagonal lines for Canadian females. The differences in the welfare state policies of Canada and the United States discussed above could explain this smaller boomer penalty among Canadian females. There is evidence that welfare state and social policies buffer social gender inequalities to some extent (Karamessini and Rubery 2013; Kushi and McManus 2018; Rubery 2012). It is possible that because they benefited from public

policies that supported single and married mothers, and that incentivized women to enter and remain in the labor market, Canadian female boomers experienced less work-family conflict than their U.S. counterparts. Nevertheless, there is still evidence of a boomer penalty in mortality among Canadian female boomers (see Figures 5.1, 5.2, and 5.4) involving the same causes of death as those that affected mortality among the other boomer groups (see Figure 5.3). Hence, these results need to be interpreted with caution. The analytical strategy adopted here may not able to capture the actual temporal pattern of the boomer penalty among Canadian females because of its small magnitude.

A second male-female difference was in the location of the most disadvantaged cohorts. As Figures 5.1, 5.6, and 5.7 indicate, the cohorts with the largest excess mortality among females were the more recent boomer cohorts. No similar pattern was observed among male boomers. This difference in location could reflect the age differences within couples, which was 2.4 years on average for married couples between 1960 and 1985 (USCB 2018). Since males are more prone to risky behaviors and may have more success in influencing couple choices (de Palma et al. 2011), the negative outcomes in boomer couples may have disproportionately affected females of the more recent cohorts.

Interestingly, when we looked at the differences across races and ethnicities within the United States, we found that despite the significant differences in the socio-historical contexts experienced by the different racial and ethnic groups, the patterns of sustained disadvantages of boomers relative to their respective average cohorts were similar across these groups. This finding is somewhat surprising given the birth cohort effect proposed by Easterlin (1987). When describing the large mismatch between the high expectations in childhood and the harsher reality encountered in adulthood, Easterlin was referring to the life courses of NHW boomers in the United States. These experiences were in stark contrast with those lived by minorities. NHW were the main beneficiaries of the economic boom and social policies implemented during the post-war period, which led boomer children to develop outsized expectations. The unprecedented numbers of university admissions and the large numbers of mortgage loans offered during the post-war period were selectively addressed to the young NHW population – the parents of the NHW boomers. For racial/ethnic minorities, however, residential segregation (Luders-Manuel 2017; Massey and Denton 1993; Rothstein 2017; Sharp and Hall 2014; Steil et al. 2018) and educational segregation (Herbold 1994; Humes 2006; Turner and Bound 2002), among other discriminatory policies, hindered their access to the social and economic benefits of that period.

By contrast, the generational rift the boomer cohorts experienced and embraced, albeit in very different ways, had a substantial impact on most racial/ethnic groups within the United States. Young boomers from different social, racial, and ethnic backgrounds became involved in the diverse social movements of the time, such as the student, anti-war, feminist, gay liberation, civil rights, Black Power, Red Power, and Chicano movements (Reed 2019; Rollins 1986; Stewart et al. 1998). Hence, it may be expected that the generational identities the boomers developed influenced wider segments of the U.S. population, regardless of their socioeconomic status and race/ethnicity. Thus, the birth cohort effects proposed by Easterlin may have been less relevant to the boomer generation.

These differences across race/ethnicities in the birth cohort effects and the generational identity mechanisms could be the reason behind the observed disparities in the temporal dynamics of suicides ridges. NHW boomers of both sexes were the only groups within the United States that showed sustained cohort disadvantages in suicide mortality. Whereas suicide mortality may have been more associated with the higher prevalence of stress and frustration resulting from the birth cohort effects proposed by Easterlin (Chauvel et al. 2016; Easterlin 1987; Phillips 2014), the higher susceptibility to mortality from substance abuse, HIV/AIDS, and hepatitis C may have been more responsive to the risky attitudes and behaviors embodied in the boomer generational identities (Boeri et al. 2006; Jalal et al. 2018; Johnston 1991; Keyes et al. 2011; Miech et al. 2011).

Regarding the drug epidemics, the crack and the opioid crises have been respectively associated with NHB and NHW populations in the scientific literature and media coverage. It is possible that the stigma and the lower price of crack made the poor black neighborhoods in the inner city more vulnerable to the crack epidemic at the turn of the 1990s (Agar 2003; Johnston 1991; Palamar et al. 2015; Palamar and Ompad 2014). Likewise, the medical-legal origin of the opioid crisis, as well as racial discrimination in prescription practices (Barnett et al. 2017; Hwang et al. 2015; Jones et al. 2018; King et al. 2014; Manchikanti et al. 2017; Quinones and Hellegers 2016; Zang et al. 2019), appear to have put the NHW blue-collar population at greater risk during the early stages of the opioid crisis at the turn of the 21st century. However, there is evidence that these drug epidemics have ravaged all social groups, even though they disproportionately affected specific social status or racial/ethnic groups in certain periods (Agar 2003; Ho 2017; Jalal et al. 2018; Woolf et al. 2018).

We have attempted here to provide a summary of the mechanisms that could contribute to the mortality penalty among baby boomers in Canada and the United States, as well as to point out some similarities and disparities in these mechanisms by country, sex, and race/ethnicity. To do so, we adopted a more comprehensive approach to analyzing the excess mortality among boomers as a whole than was used by most previous research on the topic. Instead of exploring a single cause of death, as most of the previous studies on mortality among boomers did, our strategy began by exploring the penalty in all-cause mortality common to boomers in Canada and the United States, and to subsequently decompose this disadvantage by cause of death. The decomposition of the mortality changes using the Cohort Partial Mortality Rate measure ($CPMR^{c(k,l)}$) – proposed for the first time in this research – allowed us to identify a common set of causes underlying the excess mortality among boomers in Canada and the United States.

The analysis of the temporal dynamics of nonlinear cohort effects using *APC curvature plots* permitted us to show that the disadvantage in mortality among boomers resulted from multiple and simultaneous cause-specific cohort effects, instead of from a sequence of age-period interaction effects. As we noted above, we would have been unable to generate such findings if we had limited our analytical strategy to the more conventional APC statistical models. Using this approach, we were able to show that multiple disadvantages were experienced concurrently by the boomer cohorts, and that these disadvantages may be interrelated and modulated by common mechanisms, independent of national context, sex, and race/ethnicity. These findings offer additional clues that can be used to analyze causal mechanisms that were not exclusively related to one output, but that instead generated simultaneous and sustained disadvantages throughout the life course of the boomers.

To our knowledge, this is the first analysis that has reported concurrent and sustained cohort effects for Canadian and U.S. boomers. Such findings provide valuable information for designing health policies. Currently, the populations of these countries are dealing with health crises involving the causes that made the largest contributions the boomers' excess mortality. Specifically, these populations are experiencing dramatic increases in mortality from drug overdoses (Helmerhorst et al. 2017; Ho 2017; Huang et al. 2017; Jalal et al. 2018), alcohol abuse (CIHI 2018; Tapper and Parikh 2018), and suicide (Curtin et al. 2016); increases in binge drinking (Bulloch et al. 2016; Dwyer-Lindgren et al. 2015; Manthey et al. 2019) and in the incidence of hepatitis C infections (CDC 2018b; PHAC 2019; Zibbell et al. 2017); as well as the stalling of the long-term decrease in deaths

from of HIV/AIDS (CDC 2019). Our research suggests that policy-makers should encourage prevention and diagnosis based not only on an individual's risk factors and age, as is usually done, but on the person's birth cohort. Canadian and U.S. health authorities have already proposed adopting such an approach for dealing with hepatitis C, and have recommended systematic testing for baby boomers (CATIE 2018; CDC - Division of Viral Hepatitis 2019; CDC 2012; Shah et al. 2018). Our findings also suggest that such an approach should be extended to other behavioral causes. In the rest of this section, we consider the limitations of this study, and offer some recommendations for further research.

5.4.4. Limits of the analytical strategy and suggestions for future work

We are aware that our research has several limitations. The first is related to the information recorded on the death certificates. On the one hand, deaths from some of the causes under analysis may be misreported on the death certificates. HIV/AIDS and hepatitis C mortality began to be recognized within the ICD codes in 1987, and thus long after actual deaths from these causes started to occur. It may have taken some time for medical authorities to accurately recognize and record such causes on death certificates. Hence, underreporting is expected for these two causes. In addition, the attribution of just one cause to each death can hide multiple interactions, which can be especially problematic when the causes are related to behavioral factors. Because risk behaviors tend to cluster (Ho 2017), several deaths classified in one specific cause may have multiple contributing factors. For example, a death may be caused by a combination of drug and alcohol abuse, or of HIV and hepatitis C infections. For suicide mortality, suicidal intent is difficult to assess, and the approaches used in assigning such an intent vary by geographical location. Moreover, some causes cannot be discerned from the classification when the intentions and the means are mutually exclusive, as is the case for suicides by drug overdose. In Table S2 in the supplemental materials, we classified such deaths as suicides, which could mean that drug-related death rates have been underestimated, while the number of suicides has been overestimated. This bias in drug-related mortality could also be magnified by other underreporting issues for this cause of death on death certificates (Ho 2017; Paulozzi et al. 2006).

Another limitation of the identification of causes of death is the discontinuity resulting from the ICD revisions implemented during the observation period (see Tables S1 and S2). Although we did

not find evidence of significant disruptions in the classification at an aggregated level, several specific codes that did not exist in previous ICD revisions were introduced during the period, including codes for several alcohol- and drug-related causes of death. For instance, death from drug abuse was introduced in the 9th ICD version, and poisoning from both drugs and alcohol with undetermined intent was introduced in the 10th revision.

An additional potential source of error in the data is related to the racial/ethnic classification within the United States. Discrepancies between the numerator and the denominator in the Hispanic ethnic classification have been detected. Whereas on the death certificates (i.e., the numerator) the information on ethnicity is provided by funeral directors – who may be asked to use a certain classification by relatives of the deceased, or who simply impute the deceased's ethnicity using their own judgment – in the census (i.e., the denominator) this information is self-reported (Arias et al. 2008; Zang et al. 2019). This divergence in data collection procedures may have resulted in an underestimation of mortality in the Hispanic population. In addition, the lack of racial and ethnic information in the Canadian death register limited our analyses of the heterogeneity of boomers within Canada, and made it impossible to compare similar groups in the two countries.

With regard to the methods used to analyze the temporal pattern of the disadvantage in mortality, there is more than one approach to detecting excess mortality (Acosta and van Raalte 2019). Because each approach is conceptually different, their application can lead to different estimations. Here, we used an interpolation approach because our aim was to analyze the excess mortality among the boomers relative to the mortality levels of the more advantaged cohorts surrounding the boomers. If the question is about the deviation from the overall cohort average, the estimation of the residual from an age-period model would be more appropriate. It is noteworthy that the main difference between the two approaches lies in the magnitude of the excess they report, but that their findings regarding the temporal pattern over time are consistent.

On the question of the explanatory power of this work, neither the analytical strategy nor the data for the analysis presented here allowed us to test or disentangle the role played by the birth cohort and the generational identity effects on the boomer penalty in mortality. Here, we proposed such mechanisms as underlying determinants of the boomer disadvantage in mortality in a speculative manner. Longitudinal data that include measures of drug use, alcohol consumption, sexual behavior,

mental health, mental stress, and/or expectations, among other factors, would allow for an inquiry that takes an explanatory approach.

We believe that our research will serve as a basis for future studies on the excess mortality among boomers. We propose that further research should be undertaken in the following areas. First, future studies should test the causal mechanisms identified here as being potentially responsible for the excess mortality among boomers, and measure to what extent each of these mechanisms has contributed to the boomer penalty. Second, an important question that future studies should address is why the pattern of the cohort disadvantage among Canadian female boomers, for which no sustained cohort effects were identified, differed from that among Canadian male boomers and U.S. boomers for all races/ethnicities under analysis. Third, more analysis of the impact of the boomer disadvantage on changes in life expectancy and lifespan inequality, and on years of life lost, would help to clarify the implications of this excess mortality among the boomers at the population level for future mortality trends. Fourth, it is not yet known whether strong generational differences are a common feature of all socioeconomic groups, or whether they are disproportionately concentrated among the socially disadvantaged. It is vital to assess the contributions of different dimensions of social position to the inter- and intra-cohort inequalities in mortality related to substance abuse and infections. Finally, the similarities in the mortality penalty among boomers found in Canada and the United States suggest that similar mechanisms could be involved in other national contexts with similar mortality patterns, such as in France, Australia, and England (Acosta et al. 2017; HMD 2019).

5.5. Conclusions

We found evidence that most of the relative excess mortality among baby boomers in Canada and the United States was driven by behavioral causes of death: namely, drug abuse, alcohol abuse, HIV/AIDS, hepatitis C, COPD, and suicide. The main exception to this general finding was that among Canadian female boomers, these causes of death did not translate into sustained cohort effects over time. We also found that the contributions of these behavioral causes of death to the excess mortality among boomers in Canada and the United States were the consequence of multiple and simultaneous long-term sustained disadvantages that have followed the members of this cohort since their twenties.

The behavioral nature of the excess mortality among the boomers, and the sustained cause-specific effects of this excess mortality throughout their young and adult lives, highlight the pertinence of a more comprehensive and structural analysis of the boomer mortality disadvantage. The observation that the causes that made the largest contributions to the excess mortality among boomers were linked to behavioral risks suggests that a common set of mechanisms underlie the boomer penalty in Canada and the United States. We propose that the relatively high levels of distress and frustration among boomers – the birth cohort effect proposed by Easterlin – and the riskier attitudes toward drug use and sexual behavior that are constituent of the boomer generation identity have together played a substantial role in their mortality disadvantage. Further analyses are needed to test how these mechanisms have affected the mortality penalty among boomers, and how the impact of these mechanisms has differed across socioeconomic groups.

If the cohort differences in mortality continue along the same trend, it is possible that people who are currently aged 65 or older will experience substantial increases in mortality in the upcoming years. Such increases might be even greater than those previously experienced by the boomer cohorts, because the mortality risks related to suicide and mental health disorders are considerably higher at older than at younger ages. Moreover, as the baby boomers age, they will become increasingly likely to experience chronic pain, which has been a fundamental factor in the ongoing opioid abuse epidemic (Jones et al. 2018).

5.6. Acknowledgements

Enrique Acosta was funded by a Social Sciences and Humanities Research Council of Canada scholarship and by the European Research Council Grant #716323. A version of this article was presented at the Population Association of America Annual Meeting, Austin, TX, 10–13 April 2019.

Chapter 6 - APC Curvature Plots: Displaying Nonlinear Age-Period-Cohort Patterns on Lexis Plots[8]

Abstract

The analysis of age-period-cohort (APC) patterns of vital rate changes over time is of great importance for understanding demographic phenomena. Given the limitations of statistical modeling, the use of graphical analyses is often regarded as a more transparent approach to identifying APC effects. The current paper proposes a Lexis plot for the depiction and analysis of *curvature*, which is defined as the estimable nonlinear component of age, period, and cohort effects. In a single visualization, we combine the dynamics of the location, the magnitude, and the spread of nonlinear temporal effects for multiple populations or demographic phenomena. Using vital rates, we provide three examples in which we analyze the APC nonlinear effects of different demographic phenomena. We construct several APC curvature plots to display the following patterns: the modal cohort of excess mortality from drug-related causes by racial/ethnic group in the U.S. among the baby boomer generations; the modal age of excess mortality in young adults; and the modal age of fertility over cohorts and across populations. The use of the APC curvature plot offers more flexibility when analyzing nonlinear APC effects than the use of mathematical models or other Lexis plots.

6.1. Introduction

It has long been recognized that populations change along the three dimensions of age, period (typically calendar year), and cohort (typically year of birth) (Caselli and Vallin 2005; Keiding 2011). The question of whether it is possible to independently isolate these age, period, and cohort (APC) effects on temporal changes in population phenomena has been vigorously debated since the first half of the 20th century (Keyes et al. 2010; Murphy 2010). Recently, discussions of this topic became

[8] Article published in the journal *Demographic Research* as: Enrique Acosta and Alyson van Raalte (2019) APC curvature plots: displaying nonlinear age-period-cohort patterns on Lexis plots. *Demographic Research* 41:42, 1205-1234. https://doi.org/10.4054/DemRes.2019.41.42

even more heated in reaction to the set of methods proposed by Yang and colleagues (Bell and Jones 2013; Fosse and Winship 2018, 2019a; Luo 2013; Masters et al. 2016; Reither et al. 2015; Yang and Land 2013). At the center of this latest debate is the identification problem that arises because of the perfect linear dependence between these three dimensions (age = period - cohort), as this dependence makes it impossible to estimate a unique solution without imposing additional constraints.

Given this limitation, the use of graphical analyses is often regarded as a more transparent approach to identify APC effects than the use of statistical modeling (Murphy 2010; Preston and Wang 2006; Willets 2004). Consistent with this idea, the hand-drawn contours indicating cohort mortality improvement patterns presented in the work of Kermack, McKendrick, and McKinlay (1934) have been recognized as a pioneering example of research demonstrating that long-term mortality change tends to follow the birth cohort dimension (Finch and Crimmins 2004; Hobcraft, Menken, and Preston 1982; Preston and Wang 2006). Nevertheless, the question of whether the identification of such visual patterns could also be interpreted as "cohort effects" (i.e., whether improvements in mortality could be the consequence of period-based improvements or the improved performance of newer birth cohorts) has yet to be resolved. This is, for example, the case for APC statistical models; see Murphy (2010) for an interesting review.

The analyses that focus instead on identifying divergence from secular trends (also known as *curvature*[9]) in each of the three temporal dimensions (Holford 1983; Rodgers 1982; Tango and Kurashina 1987) are more effective and less polemical than those focused on identifying the dominant patterns of change. For example, such analyses might seek to identify a systematic fluctuation that follows a cohort, and that is independent of changes over the age and the period dimensions. Such curvature would be indicative of divergence in the behavior of members of a particular set of cohorts from the behavior of the cohorts born before or after them.

Our aim here is to propose a visualization tool that allows for the depiction of such APC curvature and its attributes. In particular, we overcome a key limitation of the existing methods: comparing the

[9] Note that the term *curvature* used here refers to deviations from linear effects, as originally proposed by Holford and used in the APC literature (Clayton and Schifflers 1987; Holford 1983, 1991, 2005; Tango and Kurashina 1987). Other names used for this component are *nonlinear effects* and *nonlinear fluctuations*. This term should not be confused with *local curvature*, also referred to as *contrast* and *second-order difference* (Clayton and Schifflers 1987; Holford 1991; Pullum 1980; Tango and Kurashina 1987; Tarone and Chu 1996), which are used to measure the change in the slope of the effects.

change in curvature attributes over time across several demographic phenomena or populations in a single visualization.

The paper is structured as follows. In section 2, we present a short description of some of the existing statistical and graphical methods for the detection and analysis of nonlinear APC effects, while highlighting the advantages and the limitations of each of these methods. For the sake of clarity, we complement the description of each method by applying it to the analysis of excess mortality related to drug abuse among Hispanic baby boomers in the United States. These mortality rates are presented in a Lexis surface in Figure 6.1. In section 3, we present our proposed visualization technique. We describe its advantages, and explain how it can complement existing methodologies. Section 4 consists of a step-by-step description of the construction of the plot. Section 5 provides three empirical applications of the proposed visualization (Figures 6.5-6.7). In the final section, we draw some conclusions.

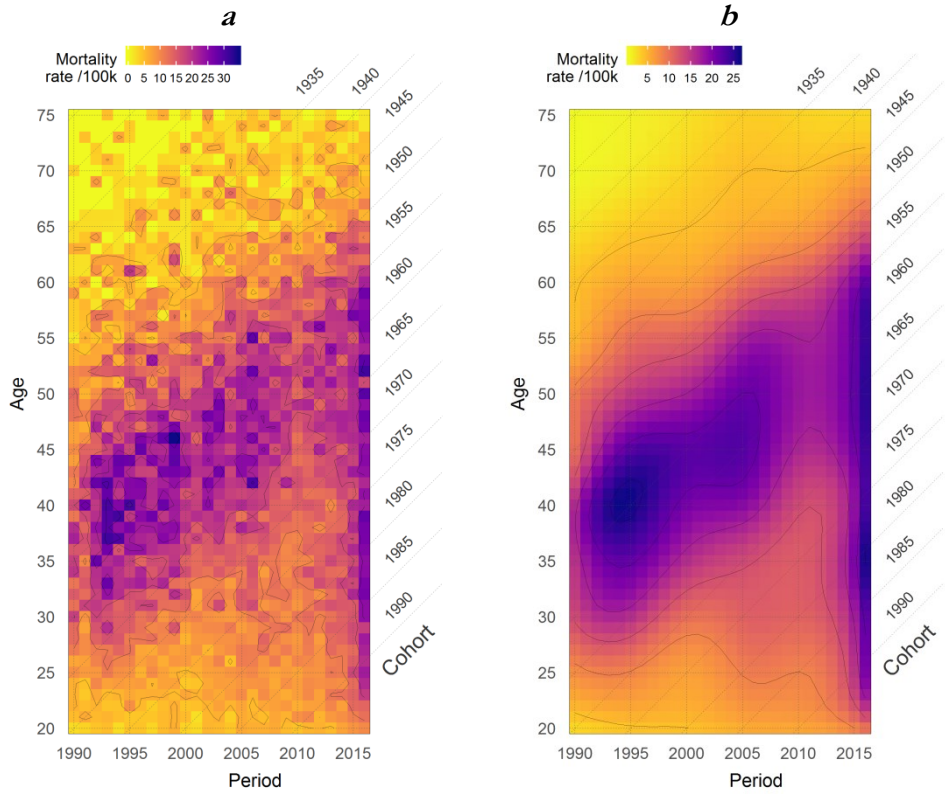
For the examples presented, we used the R programming language (R Core Team 2018) for the analysis and data visualization. In addition, we used the packages *ggplot2* (Wickham 2016), *Epi* (Carstensen et al. 2018), *MortalitySmooth* (Camarda 2012), and *HMDHFDplus* (Riffe 2015). All of the data and code for reproducing results are openly available (Acosta 2019a).

6.2. Existing methods for analyzing APC curvature

As discussed in the introduction, partitioning temporal variations into linear APC components is controversial due to the identification problem. Systematic divergence from this linearity, also known as curvature, is, however, unambiguously identifiable. Such curvature could have concave (humps) or convex (valleys) shapes, independent of linear trends. When looking at curvature graphically, it becomes clear that if a deviation follows horizontal, vertical, or diagonal trends on a Lexis surface, it is indicative of an age, period, or cohort effect, respectively. For instance, when looking at the Lexis surface of drug-related mortality rates for U.S. Hispanic males depicted in Figure 6.1, we can see that the diagonal pattern suggests that there is a cohort pattern of increased risk of death among the members of the baby boomer cohorts (i.e., conventionally defined as the cohorts born between 1946 and 1964). In this section, we review some existing statistical (*detrended Age-Period-Cohort models*) and visual (*Lexis surfaces of changes in vital rates,* and *Lexis surfaces of excess rates*)

tools for the detection and analysis of a curvature, and apply each one to the case of drug-related mortality among Hispanic baby boomers.

Figure 6.1: Lexis surface of observed and smoothed drug-related mortality rates for Hispanic males in the United States



Note: Panel (a) is a Lexis surface of observed drug-related mortality rates for Hispanic males in the United States between 1990 and 2016. **Panel (b)** is the corresponding Lexis surface of smoothed mortality rates. The smoothing was done using a two-dimensional non-parametric smoothing technique. Specifically, we assume that our events are Poisson-distributed, and smooth the data with P-splines, with the smoothing parameters optimized according to AIC. Smoothing was performed using the *MortalitySmooth* R package developed by Camarda (2012).

6.2.1. Statistical APC models for analyzing curvature

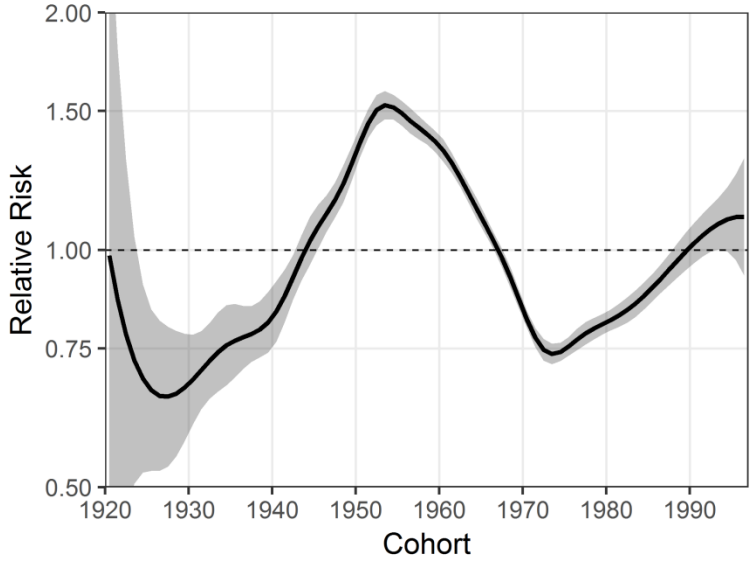
Several arithmetic and statistical models have been proposed to identify deviation from trends, such as the *Median Polish* technique (Keyes and Li 2010; Selvin 2001; Tukey 1977) and the *Detrended Age-Period-Cohort models* (dAPC) (Carstensen 2007; Clayton and Schifflers 1987; Holford 1983).

In general terms, the APC effects can be decomposed into linear trend and curvature components (Fosse and Winship 2019b; Holford 1983; Tango and Kurashina 1987). While there are infinitely

many ways to partition the linear effects into APC components, the curvature components have the same shape and magnitude regardless of the parameterization used to fit the model (Clayton and Schifflers 1987; Holford 1983, 1991). To obtain these nonlinear components, the effects (log of relative risks) in dAPC models are constrained to be zero on average, with a zero slope (detrended). In this parameterization, the reference category is the overall age, period, or cohort average; centered at its linear trend component. More details about the parameterization of the model can be found in Carstensen (2007).

As an example, Figure 6.2 shows the estimates of the nonlinear cohort effects in relative risk values that are obtained from a dAPC model applied to the drug-related mortality of Hispanic males. If we focus our attention on the concave shape of the curvature for the boomer cohorts (born between 1940 and 1970), we see that according to these estimates, the most disadvantaged cohort (the curvature peak) is the cohort born in 1953, for whom the risk of dying from a drug overdose is nearly 1.5 times higher than would be expected given the overall linear cohort trend.

Figure 6.2: Relative risks of drug-related mortality for cohorts of Hispanic males in the United States



Notes: The cohort relative risk estimates were obtained from a detrended APC model (dAPC) applied to drug-related mortality for Hispanic males aged 20-70 during the 1990-2016 period. Cohort effects (i.e., the log of the relative risks) are constrained to be zero (0) on average, with zero (0) slope. B-splines are used for fitting the APC effects. The reference category is the overall cohort average, indicated in the plot with a horizontal dashed line. The gray area indicates the 95% confidence interval. Estimates were obtained using the R package *Epi* (Carstensen et al. 2018).

Although identifiable, the curvature estimates are average effects that are fixed over the whole length of time (Chauvel 2013). The invariability of these estimates has two particularly undesirable consequences. First, the estimates do not allow the size of the effect to vary over time/age. Second, because of this lack of variability, the estimates attribute the highest or the lowest nonlinear effect to a fixed temporal dimension, permanently labeling it as advantaged or disadvantaged. For instance, from the estimates depicted in Figure 6.2, is not possible to establish variation in the magnitude of the relative risks over age/time; and, as a consequence, we are unable to determine whether those individuals born in 1953 actually had the highest risk during the entire period under observation.

An alternative model proposed by Chauvel (2013) allows for the estimation of a hysteresis value that indicates whether the magnitude of the curvature increases or decreases over time. This model is, however, a fixed measure of change that reflects only constant increases or decreases over time, and it does not allow for modifications in the curvature ridge/floor location over time/age.

6.2.2. Graphical tools for analyzing curvature

Several graphical tools have been proposed for uncovering patterns of systematic divergence from linear trends. The focus of most of these tools is the analysis of mortality. Plots of the change in smoothed rates over age/cohort, over period/cohort, and over age/period are effective tools for discerning the dynamics of demographic phenomena over time, and for uncovering patterns of systematic divergence from APC linear trends. Indicative Lexis diagrams (Willets 2004) and colored Lexis surfaces (Rau et al. 2008, 2018; Richards, Kirkby, and Currie 2006) of these derivatives have been proposed as visualization techniques that could be applied to identify the presence of such patterns in Lexis plots.

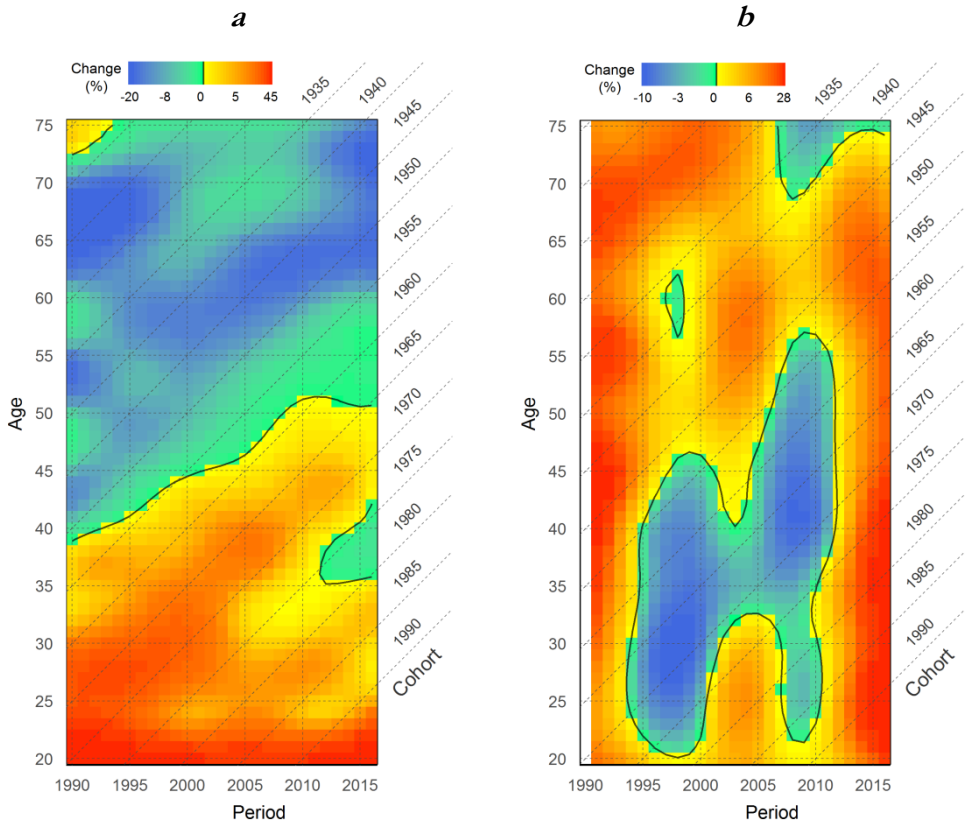
Variations over APC dimensions are complementary perspectives that can be used to visually detect curvature on Lexis surfaces. When looking at rate changes over age/cohort (i.e., vertical changes along the same period in the Lexis diagram), we can identify within-period divergence in rate changes, although we cannot unambiguously attribute such divergence to age or cohort because of the identification problem. Analogously, when looking at changes over age/period (i.e., diagonal

changes along the same cohort in the Lexis diagram) it is possible to determine age/period fluctuations that are independent from variations over cohorts.

Raw derivatives in vital rates are generally noisy, particularly when using high-resolution data or low-frequency events. Thus, it has been suggested that the underlying data should be smoothed over ages and years in order to reduce random fluctuations[10] (Rau et al. 2018); as shown in Figure 6.1.
Figure 6.3 depicts Lexis surfaces of rates of mortality change over age/cohort (Panel a) and over period/cohort (Panel b) from drug-related causes in Hispanic males in the United States. Note that for this empirical example, we do not depict the Lexis surface of rates of mortality change over age/period because our interest is on cohort effects, which are not identifiable in such surfaces.
Given the large variations in drug-related mortality over time, the plot of derivatives over age/cohort (vertical changes along the same period as in the Lexis diagram, Panel a) depicts the nonlinear cohort effect of the Hispanic boomers more clearly than the plot of derivatives over period/cohort (horizontal changes along the same age group as in the Lexis diagram, Panel b). The diagonal contour line following the cohorts born around 1955 in Figure 6.3a indicates that the peak in mortality rates followed those cohorts, even if the cohort curvature is camouflaged by the strong period fluctuations visible in Figure 6.3b.

[10] Note that smoothed rates are useful for identifying divergence from the trend that occur over large time scales (i.e., effects that appear gradually over several age, period, or cohort groups). However, when divergence is very exceptional and compromises only a few units of time in a given dimension (i.e., effects that appear in only a couple of age, period, or cohort groups) the smoothing process could weaken or remove the divergence of interest. In those cases, the use of observed rates is preferable to the use of smoothed rates.

Figure 6.3: Lexis surfaces of changes in drug-related mortality rates over age/cohort and over period/cohort for Hispanic males in the United States



Notes: Panel (a) is the Lexis surface of changes over age/cohort (read vertically from young to old ages, or from newer to earlier cohorts); with a yellow-to-red scale indicating the relative mortality rate increase for age *x* compared to age *x*-1 (or cohort *k* compared to cohort *k*+1) in the same year, and a green-to-blue scale indicating a relative mortality decline between consecutive ages/cohorts. The black contour line depicts zero changes in mortality, which indicates a local maximum or minimum death rate in a given calendar year/cohort (i.e., a curvature ridge or floor). For example, if we examine the year 2000, we see that death rates increased with age until hitting their maximum value at age 44 (curvature ridge). From ages 45 to 71, the death rates declined over age until reaching their minimum value at age 72 (curvature floor). **Panel (b)** is the corresponding Lexis surface of changes in drug-related mortality rates over period/cohort (read horizontally from earlier to more recent calendar years/cohorts) for Hispanic males in the United States; with a yellow-to-red scale indicating the relative mortality rate increase for year t compared to year *t*-1 (or cohort *k* compared to cohort *k*-1) in the same age, and a green-to-blue scale indicating a relative mortality decline between consecutive calendar years. Again, the black contour indicates a curvature ridge or floor in a given age/cohort. For example, if we examine age 50, we see that the death rates increased with time until hitting a maximum value in 2005 (curvature ridge). From 2006 to 2011, the death rates declined over time until reaching their minimum value in 2012 (curvature floor).

Alternatively, the use of Lexis surfaces to depict deviations from trends is an effective way to display variation in the magnitude and the spread of curvature over time/age. The first step in the extraction

of curvature (excesses or depths) is to estimate a baseline, which is a counterfactual scenario of vital rates in the absence of age, period, or cohort nonlinear effects.

Several methods are available to estimate a baseline from which it is possible to obtain curvature in vital rates. These approaches include applying interpolation techniques (Camarda 2012), extracting the irregularity using decomposition techniques (Remund, Camarda, and Riffe 2018), using detrended APC models (Chauvel, Leist, and Smith 2017), or simply detrending the smoothed vital rates over the selected perspective of change (i.e., over age, period, or cohort). There is no ideal generic method that can be applied because each demographic phenomenon and research question has specific underlying hypotheses that should be accounted for.

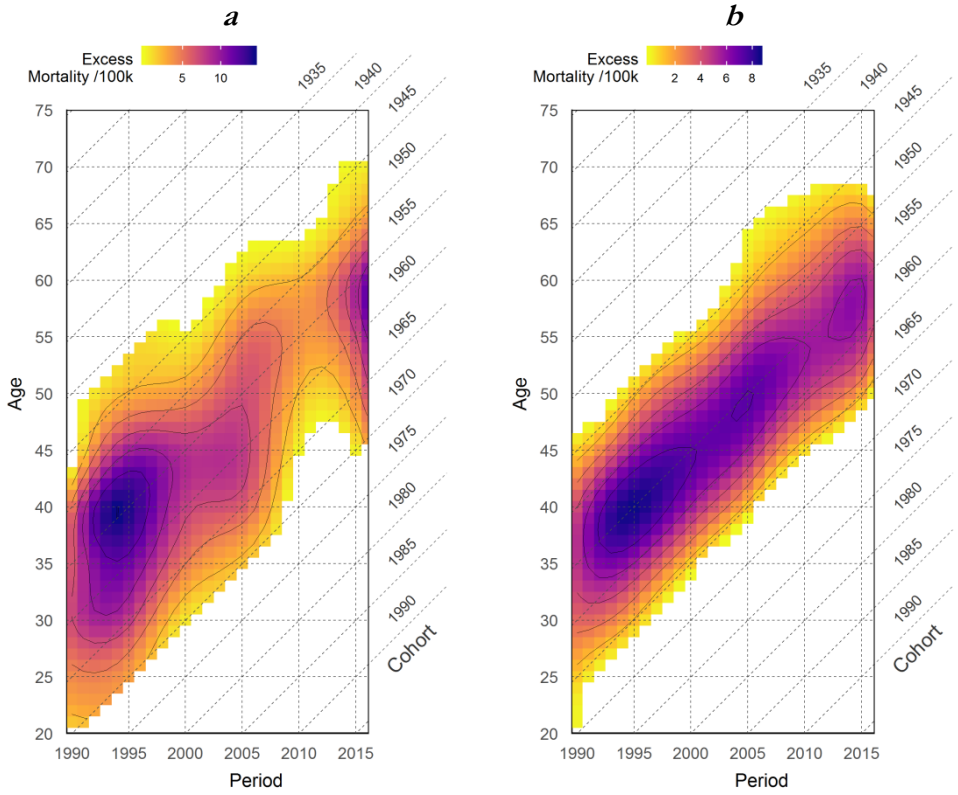
For the case of cohorts of Hispanic males in the United States who are disadvantaged in terms of drug-related mortality, we present two examples using the interpolation and dAPC approaches for the estimation of the mortality baseline. For the interpolation process, we excluded deaths pertaining to disadvantaged cohorts, who were previously estimated to be born between the advantaged 1940 and 1970 cohorts, and interpolated the surface with these 30 cohorts removed. The estimation of the mortality baseline was done through the two-dimensional interpolation option available in the R-package *MortalitySmooth*. Figure 6.4a depicts the excess mortality rates (per 100,000 population) among these cohorts over the interpolated baseline; i.e., the difference between the smoothed observed mortality rates and the hypothetical mortality that is predicted if mortality had developed according to a linear trend from the 1940 to the 1970 birth cohort.

Alternatively, to obtain a mortality baseline that accounts for all cohorts present in the observed data, we fitted a dAPC model with all linear trends attributed to age and period variations (cohort-detrended), and set all cohort terms to zero, while removing all cohort curvature components from the predicted baseline. Figure 6.4b presents the excess mortality among cohorts over a baseline that excludes cohort curvature; i.e., the difference between the smoothed observed mortality rates and the hypothetical mortality that is predicted if mortality had developed according to the overall linear trend for all of the cohorts.

Although they are similar in shape, the excess mortality estimates in Figures 6.4a and 6.4b are considerably different in magnitude and must be interpreted differently. As the magnitude and the shape of the excess mortality obtained from the interpolated baseline depend exclusively on the two cohorts selected for the interpolation, they are sensitive to the arbitrariness of the selection of these

cohorts. In contrast, the excess mortality that is obtained from the baseline without cohort curvature components is relative to the performance of all of the observed cohorts included in the observation window.

Figure 6.4: Lexis surfaces of the excess drug-related mortality rates for male Hispanic boomers in the United States during 1990-2016, ages 15-75



Note: Panel (a) is the excess mortality rates (/100k) estimated as the difference between the smoothed mortality rates and an interpolated baseline that omits the 1940-1970 cohorts from the Lexis mortality surface. **Panel (b)** is the excess mortality rates (/100k) estimated as the difference between the smoothed mortality rates and a baseline obtained from a dAPC model with the cohort terms set at zero; i.e., centered at the linear trend component of the cohort effects. In this case, the excess mortality is relative to the overall mortality trend across cohorts.

Compared to the curvature effects obtainable from statistical dAPC models, the plots of rate derivatives (Figure 6.3) and of trend divergence (Figure 6.4) are much more flexible in depicting the temporal dynamic of nonlinear fluctuations, as they allow the shape of curvature to move freely through the Lexis diagram, and depict patterns with a higher degree of fidelity to the observed data. Another important advantage of these plots is that they depict general patterns that modulate the changing phenomena over a wide age and time frame. In a single image, it is possible to identify

several irregularities potentially indicative of APC effects on the dynamics of a specific phenomenon of a population.

These plots are useful for the analysis of temporal patterns in a single phenomenon in a single population. However, when comparisons across several phenomena within a single population or of a single phenomenon across several populations are desired, it is necessary to construct a surface for each phenomenon/population analyzed. In addition to requiring considerable space, an important limitation of such comparisons is that displaying contrasting patterns across surfaces is visually difficult, even when surfaces are facetted.

6.3. The proposed visualization

In the current paper, we follow in the tradition of the aforementioned literature by attempting to visually depict and contrast the nonlinear changes in demographic phenomena over the APC dimensions. Specifically, we demonstrate the value of making a broad-picture comparison of how the location of a curvature feature of a demographic phenomenon is changing over time. This curvature feature could be anything from the location of the cohort with maximum excess mortality by cause of death to the mode of age-specific fertility in different populations. In the former case, the visualization enables the comparison of the temporal patterns for many phenomena (causes of death) in one population on one plot. In the latter case, the aim is to compare the temporal patterning of a single phenomenon (age-specific fertility schedules) across a variety of populations or subgroups. While the simplest visualization depicts the changing location of these demographic phenomena (i.e., a curvature ridge or floor), the use of visual attributes such as color, size, and opacity allows for more information about the densities to be depicted; including, for instance, the change in the magnitude and the spread of curvature.

It should be noted that if the emphasis is placed on the maximum/minimum point of the curvature over time (ridge/floor), other local maximums/minimums would be neglected in the case of multimodal distributions. This information could be of great importance, and alternative plots could depict the dynamics of multiple modes over time. Moreover, the depiction of several features in the same plot also offers the possibility of analyzing the interrelation among them, such as the correlation between magnitude and spread. Nevertheless, the choice of the amount of information

to display in the plots depends on the context of the research question, and should be made while strategically considering the tradeoff between visual complexity and the clarity of the visualization (Munzner 2014).

Although the APC curvature plots proposed here contribute additional information that is not available in APC statistical models, they should be seen as complementary. Some estimable functions from statistical APC models are of great value, and are not obtainable by graphical analysis, such as the statistical significance of a particular pattern (Holford 1991). In Table 1, we summarize some of the advantages and limitations of the statistical and visual methods we have discussed.

Table 6.1: Comparison of the properties of different methods for the analysis of nonlinear APC patterns

Type	Method	Detection of curvature	Temporal dynamic of curvature features			Comparability across populations / phenomena	Statistical measures [a]
			Location	Magnitude	Spread		
Statistical models	dAPC models	+	-	-	-	+	+
	dAPC hysteresis model	+	-	+/-	-	+	+
Graphical tools	Surface of derivatives	+	+	-	-	-	-
	Surface of excess	-	+/-	+	+	-	-
	APC curvature plots	-	+	+	+	+	-

Note: (+) indicates that the method is able to perform the property; (+/-) that it does so to some degree, albeit imprecisely; and (-) that it is not able to perform the property.

[a] Some examples of these statistical measures are tests of statistical significance and confidence intervals.

In the following, we describe the procedure for constructing APC curvature plots for demographic phenomena, and apply the procedure to three empirical examples: (1) the excess mortality of baby boomer cohorts in the United States from drug-related causes across racial/ethnic populations, (2) the stability of the age location of the young adult mortality hump, and (3) the temporal patterning of age-specific cohort fertility peaks across countries.

6.4. Construction of the plot

For this kind of analysis, we suggest the use of the finest possible resolution for the data. The smaller the grid in the Lexis surface, the clearer and more precise the depiction of the temporal dynamic of demographic curvature will be. The construction of the APC curvature plot involves three main steps:

6.4.1. Detection of curvature and the temporal section frame of interest

As mentioned in the introduction, there are statistical methods (e.g., dAPC models in Figure 6.2) and pre-existing visualization tools (e.g., Lexis surfaces of changes in vital rates over age/cohort and over period/cohort in Figure 6.3) that allow for the detection of curvature patterns.
After some features of curvature (e.g., curvature ridge and floor) have been identified, their temporal positions in the Lexis diagram determine the temporal frame of interest. This framing is important because other "irregularities" located outside of this temporal section represent a potential source of noise for the analysis.

6.4.2. Estimation of curvature features

Remund and colleagues (2017) proposed three attributes of interest that could be used in describing the young adult mortality hump, and provided examples of summary indices that could be used to measure them. These attributes are location (e.g., mode, mean, and median), magnitude (e.g., loss in life expectancy, years of life lost, and death counts), and spread (e.g., standard deviation and quantile). These dimensions and indices could be enriched so that they can be used to analyze other demographic phenomena.

The minimum requirement of a comparative APC curvature plot is the location measure (i.e., mode, mean, etc.). Other dimensions, such as magnitude and spread, are optional and complementary measures that could be used to enrich the comparative analysis, but that are not strictly necessary for the construction of a basic version of the plot.

In cases in which the deviance from the trend is also a local or an absolute maximum or minimum, the mode of the ridges and the valleys may be obtainable by extracting the age/period coordinates of the maximum or the minimum smoothed values within the temporal section frame. However, for cases in which these irregularities are not a local maximum or minimum, the estimation of their respective location, magnitude, and spread requires additional information pertaining to the divergence of vital rate estimates.

As discussed in section 2.2, several methods are available for estimating divergence in vital rates, and which method is appropriate depends on the underlying hypotheses regarding the demographic phenomenon and the research question to be addressed. The location, the magnitude, and the spread of curvature can be estimated from this divergence in vital rates. It is worth noting that all three features could be estimated using age, period, or cohort perspectives depending on the temporal dimension that is of interest.

6.4.3. Translation of curvature attributes into visual properties of the plot

The population or the demographic phenomenon to be compared in the Lexis surface is a categorical value that should be translated into color; preferably using a color-blind safe palette (as is done here), or into different point shapes for a black-and-white printout[11]. The location measures should be translated into the age and period coordinates in the Lexis diagram. To prevent unrelated curvatures from being fused, unifying these point coordinates by lines should be avoided.

The magnitude and the spread measures should be standardized, and can be translated into opacity level and shape size.

6.5. Empirical Application

For illustrative purposes, we applied the procedure described above to construct APC curvature plots for three demographic outcomes with different temporal perspectives: a) comparing excess mortality from drug-related causes across several racial/ethnic groups of boomers in the United

[11] When using different point shapes, equal areas must be given equal values of spread across the different point shapes employed. As this is usually not done by default in the plotting systems (e.g., *ggplot2*), a correction factor must be applied to adjust the proportionality of areas across the shapes.

States; b) examining excess mortality among young adults; and c) comparing cohort fertility rates across several countries. In this section, we describe how we estimated the location, the magnitude, and the spread features of curvature; and how we translated these features into an APC curvature plot that displays the attributes for each case. Although our main objective is to propose a visualization tool, we briefly comment on some of the determinants that might be driving the nonlinear APC patterns that are easily identifiable and comparable using this visualization technique.

6.5.1. Excess mortality from drug-related causes among boomers

Previous exploratory and descriptive analyses have suggested that baby boomers in the United States have a disproportionate susceptibility to drug-related mortality throughout their life course (Acosta et al. 2019; Miech, Koester, and Dorsey-Holliman 2011; Zang et al. 2019). Thus, for this specific case, we are interested in comparing the attributes (location, magnitude, and spread) of the cohort mortality curvature of drug-related mortality for several racial/ethnic groups of U.S. males in a single Lexis plot.

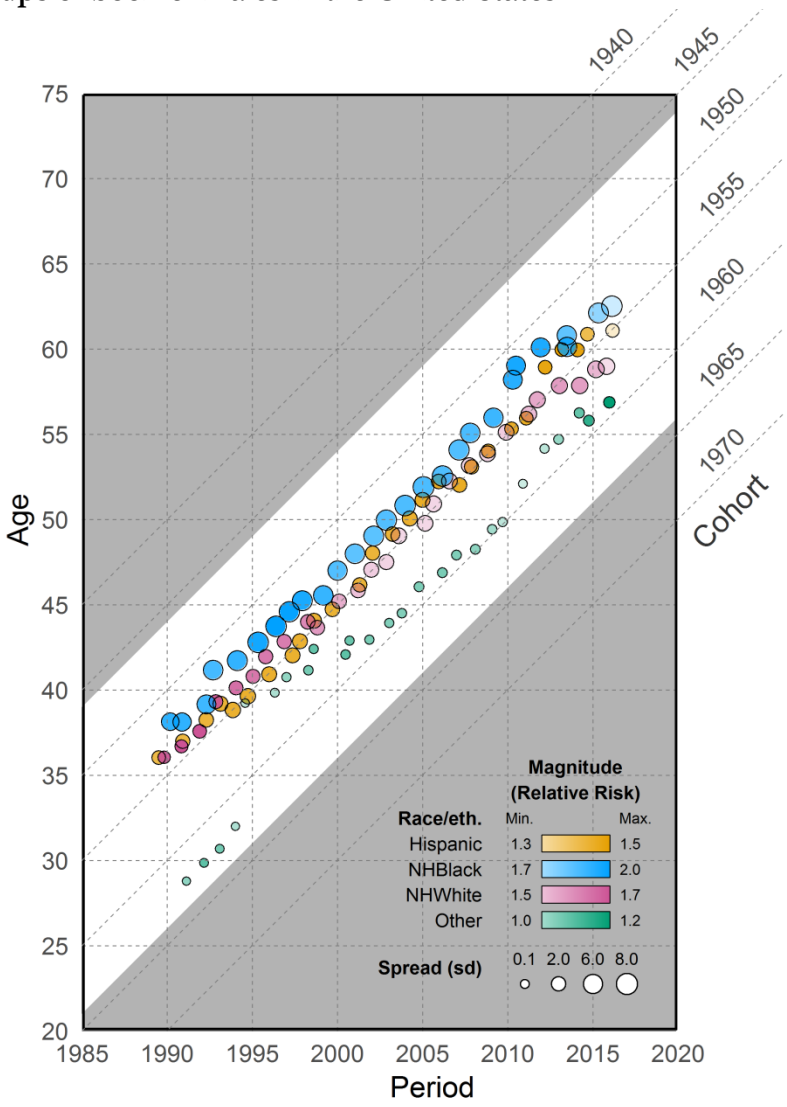
We use cause-specific mortality data and population estimates by single calendar year, single year of age, sex, race, ethnic group, and cause of death from 1990 to 2016 drawn from the U.S. National Vital Statistics System (NVSS 2019a, 2019b). This dataset allows us to use single-year resolution in the estimation and visualization of nonlinear cohort effects. Here, we define drug-related mortality as deaths involving drug use registered in the categories of accidental and undetermined intent overdoses, or in the categories of mental or behavioral causes (i.e., ICD 10 codes F11-19, F55, X40-44, Y10-14).

Detecting the mortality curvature and measuring its features (location, magnitude, and spread) involved three distinct steps. First, we smoothed the entire drug-related mortality surface over period and age using two-dimensional P-splines, with the smoothing parameters optimized by AIC, for all male racial/ethnic groups; as presented in Figure 6.1b for the Hispanic ethnic group. Second, from these smoothed rates, we calculated the change in mortality from age x to age x+1 (from cohort k to cohort k-1) for each year (Figure 6.3a), and the change in mortality from period t to period t+1 (from cohort k to cohort k+1) for each age (Figure 6.3b). The ridges and floors of curvature were identified with black lines used to indicate the ages at which the mortality change was zero. In the derivative over age/cohort (plotted in Figure 6.3b), the curvature ridge indicating the

maximum level of drug-related mortality is mostly diagonal, following the cohorts born between 1950 and 1960 throughout their life course. Third, using a dAPC model, we estimated the excess mortality relative to the overall cohort average risk for each racial/ethnic group; as the example presented in Figure 6.4b for U.S. Hispanic males shows. From these excess mortality estimates, we were able to extract information about the temporal dynamic of the location (age/cohort with the largest mortality relative risk), the magnitude (largest mortality relative risk compared at the curvature), and the spread (steepness of the excess mortality compared to the mortality of the surrounding ages) of the curvature during the 1990-2016 period. We can see that the curvature trajectory is not completely straight, and that its magnitude and spread are not constant over time. As discussed in the introduction, these changes in the location, the magnitude, and the spread over age/time cannot be identified from the dAPC estimates, such as those depicted in Figure 6.2. To compare the curvature ridge pattern differences across racial/ethnic groups, we plotted in Figure 6.5 the following attributes of the excess drug-related mortality among boomers on an APC curvature plot:

1. *Category*: Each observed racial/ethnic group was identified by a distinct color, or by a different point shape in the case of a black-and-white printout (see Figure S3.1).
2. *Location*: For each calendar year, we plotted the age/cohort location of the maximum relative risk of drug-related mortality.
3. *Magnitude*: The relative risk compared to the baseline value for each point was translated into opacity. Note that the opacity scale reflects the difference in relative risk within each racial/ethnic group. We use a relative scale because it allows us to better identify the variation in magnitude over time and for each group. The absolute differences in magnitude across racial/ethnic groups can be seen by comparing the minimum and maximum values reached by group. This range in magnitude is indicated in the legend for each group.
4. *Spread*: The standard deviation of the hump in relative risk for each period was translated into point size.

Figure 6.5: APC curvature plot of the features of excess drug-related mortality among four racial/ethnic groups of boomer males in the United States



Notes: The coordinates of the points indicate the location of the curvature ridge over time (i.e., the modal age/cohort with the excess mortality in each single-year period). The magnitude, indicated by the color opacity, is measured as the relative risk of the death rate in the modal age/cohort to the corresponding death rate in the baseline. The minimum and maximum levels of relative risk that the curvature ridge of each racial/ethnic group reached during the period under observation are indicated in the legend. The spread, indicated by the point size, is estimated as the standard deviation of the curvature in each single-year period. The white band indicates the baby boomer cohorts (i.e. born between 1946 and 1964).

In this case, we were not only able to extract and summarize the differences in location from four different plots in a single visualization; we were able to compare additional outputs to the rate of mortality change plots, such as the magnitude (relative risk) of the mortality curvature ridge compared to the expected values and the spread (standard deviation) of the curvature. Thus, we

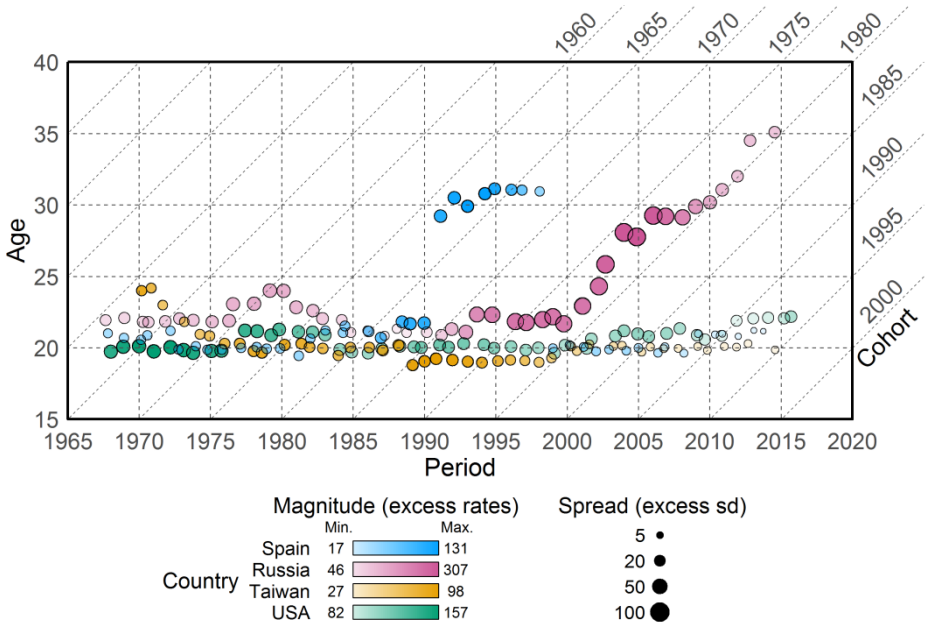
were able to clearly identify the disadvantaged cohorts for all of the racial/ethnic groups by observing the alignment of the points along a diagonal line. Our finding that the degree of cohort disadvantage, relative to the overall cohort average, was greater among non-Hispanic black boomers than among other race groups is reflected in the larger values of relative risk among the former group (i.e., 1.7 to 2.0). Note that we picked a cause of death with particularly strong cohort patterning. For other causes of death, such as cerebrovascular diseases, nonlinear excess mortality risks would not follow cohort patterns; thus, the depicted points would not fall along a diagonal line.

6.5.2. Young adult mortality hump

Excess mortality in young adults –also known as the accident or young adult mortality hump– is a well-known feature of the age structure of most mortality regimes, particularly among males. Goldstein (2011) presented a plot of the hump peaks over time for several countries, and Remund and colleagues (2018) decomposed and plotted the contributions by cause of death in order to analyze several features of the hump in the United States. Here, we used mortality data for certain countries drawn from the Human Mortality Database (HMD 2019) to compare not only the curvature ridges of the hump, but the additional features of their changes in magnitude and spread over time and across different countries. As in the method employed by Goldstein, we defined the hump as the difference between the cross-sectional period smoothed mortality rates and an interpolated mortality baseline between ages 10 and 40. We performed the smoothing and the baseline interpolation using the methods we previously applied to obtain Figure 6.4a. However, unlike the example presented in Figure 6.4a, we interpolated the hypothetical baseline with excess age-related mortality rather than cohort-related mortality.

We compared the young adult mortality hump in Spain, Russia, Taiwan, and the United States during the 1965-2016 period. Figure 6.6 (S3.2 for the black-and-white printout) shows the variation over time of the modal age of the hump, its magnitude measured by excess death rates (per 100,000 population), and the spread of the hump measured by standard deviation.

Figure 6.6: APC curvature plot of the features of excess mortality in young adult males in four countries



Notes: The coordinates of the points indicate the location of the curvature ridge over time (i.e., the modal age/cohort of the excess mortality by single-year period). The magnitude, indicated by the color opacity, is the excess death rates (/100k), calculated as the difference between the death rate in the modal age/cohort and the corresponding death rate in the baseline. The minimum and maximum excess mortality rates reached by the curvature ridge of each country during the period under observation are indicated in the legend. Finally, the curvature spread, indicated by the point size, is estimated as the standard deviation of the curvature in each period.

In contrast to the more regular location patterns we see for Taiwan and the United States, we observe in this plot an age-period interaction effect for Spain around age 30 during the first half of the 1990s and a cohort effect for Russia among the cohorts born between 1975 and 1980. In the case of Spain, this finding of an age-period interaction effect is consistent with evidence indicating that in this period, Spain was the western European country with the highest incidence of HIV infection, which was mainly driven by the sharing of contaminated needles during the "heroin boom" of the 1980s (Valdes and George 2013). In the case of Russia, the cohort pattern could be indicative of a long-term mortality disadvantage for those cohorts who entered adulthood in the early 1990s, when the country was undergoing a profound socio-historical transformation, as well as a severe alcohol abuse epidemic (Keenan et al. 2015). This pattern is consistent with a cohort pattern found in Belarus (not shown here), a country that experienced similarly far-reaching contextual changes during the same period. It is noteworthy that part of the age-period interaction effect depicted in the APC curvature plot for Spain would be attributed to a cohort effect if a statistical

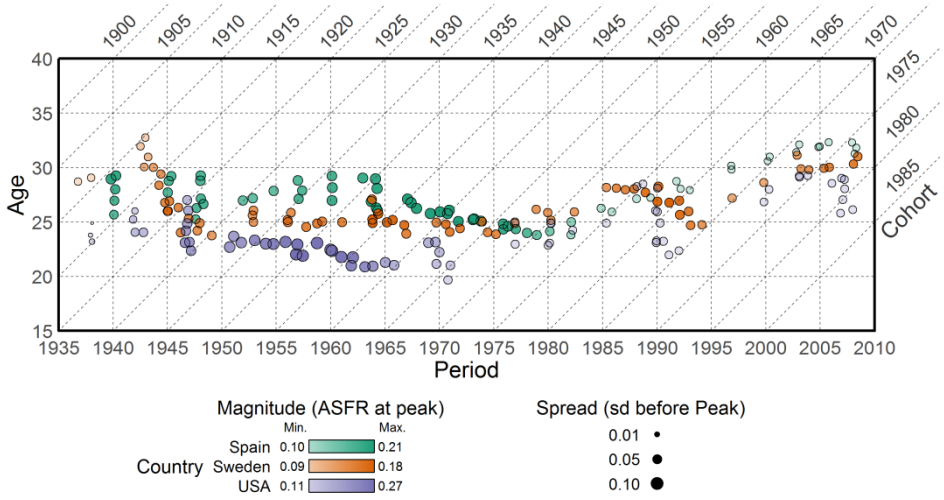
approach would have been used. This is because, unlike the visual tools, the existing APC statistical methods are unable to make the distinction between age-period interaction effects and sustained cohort effects.

6.5.3. Cohort fertility rate

As a final example to show the applications beyond mortality, we plotted some aspects of fertility behavior along cohorts. Figure 6.7 (S3.3 for the black-and-white printout) depicts the age-specific fertility outcomes of the cohorts born between 1905 and 1985 in Spain, Sweden, and the United States. Cohort age-specific fertility rates (ASFR) were obtained from the Human Fertility Database (HFD 2019) and extracted using the R package *HMDHFDplus* (Riffe 2015).

In this case, we plotted the modal age/period of fertility for each cohort (location), the ASFR pertaining to this mode (magnitude), and the standard deviation before that age/period (spread). The standard deviation before the mode was used to enable us to consider more recent cohorts who are likely to have reached the modal age in fertility, but have not yet completed their childbearing. As mentioned previously, any number of indices could be used to capture the three dimensions of location, magnitude, and spread.

Figure 6.7: APC curvature plot of cohort fertility rate peaks in three countries



Notes: The coordinates of the points indicate the location of the curvature ridge along the cohort (i.e., the modal age/period of the ASFR by single-year cohort). The magnitude, indicated by the color opacity, is measured as the ASFR mode by cohort. The minimum and maximum ASFR reached by the modal age/period of each country are indicated in the legend. The curvature spread, indicated by the point size, is estimated as the standard deviation of the curvature before the modal age/period.

This plot highlights a number of interesting features in the fertility dynamics of these three countries. We see strong evidence of period effects for many of the countries in which the fertility booms were synchronous for several cohorts (e.g., Sweden in 1943-1944; the U.S. in 1947, 1990, and 2007; and Spain in 1940, 1948, and 1964). The plot also illustrates the sustained differences in modal ages of fertility over time (e.g., the ages are consistently youngest for the U.S. and oldest for Spain; with an exceptional shift between Sweden and Spain during the 1980s). The overall decline in fertility in Spain and the United States is also illustrated by the fading peak ASFR over time, whereas this pattern is irregular in Sweden. Lastly, the concentration of fertility at more advanced ages is reflected in the decline in the standard deviation before the modal age at fertility in all three countries.

6.6. Conclusions

In this paper, we discussed the advantages of using visualization tools on Lexis diagrams for analyses of age-period-cohort nonlinear effects of vital rates rather than mathematical models, as well as some of the limitations of these tools. We proposed the APC curvature plot to enrich the analysis of irregularities in vital rates that are indicative of nonlinear age, period, or cohort effects. We argue that compared to mathematical models and other Lexis plots, this visual display provides a higher level of flexibility because it allows us not only to depict the dynamics of the location, the magnitude, and the spread of temporal effects over time together; but to contrast different populations or subtypes of demographic phenomena in a single visualization. We outlined the process that can be used to construct APC curvature plots for the analysis of nonlinear APC effects. Using vital rates, we provided some examples of how this approach can be applied by analyzing cohort effects on drug-related mortality by racial/ethnic groups within the United States; age effects on young adult mortality in Russia, Taiwan, Spain, and the United States; and age/period effects on fertility in Spain, Sweden, and the United States. Finally, we have provided R-code that can be used to reproduce these examples.

6.7. Acknowledgements

We thank the anonymous reviewers and the editors of this Special Collection on "Data Visualization" for their valuable comments and suggestions, which considerably improved the quality of this work. A version of this article was presented at the Population Association of America Annual Meeting, Austin, TX, 10–13 April 2019. This project was supported by a starting grant from the European Research Council awarded to A.vR. (grant no. 716323).

Chapter 7 - General Conclusions

The articles presented in this dissertation covered analyses of APC effects on mortality from influenza and behavioral causes, and provided a methodological contribution for the visual analysis of nonlinear APC effects. In this chapter, we first explore how the cohort effects on extrinsic mortality analyzed in this dissertation differ from the more conventional cohort effects on intrinsic mortality that have been conceptualized and analyzed in the existing literature. Next, we discuss the similarities and the differences between the cohort effects on influenza and behavioral mortality, such as the age-cohort and period-cohort interactions, and the interactions of these cohort effects with intrinsic factors. We also present two hypotheses regarding the greater relative susceptibility of baby boomers to mortality from influenza and behavioral causes[12], which allow us to explore possible interactions between these two set of causes. Then, we discuss the advantages of using the nonlinear effects approach for the analysis of mortality, highlighting the methodological contribution presented in chapter 6, and the contributions of our approach to the analyses presented in chapters 4 and 5. Finally, we outline a few of the potential implications of the mortality patterns we have detected for population health; discuss the potential usefulness of our findings for public health policies; describe the general limitations of our study; and offer some ideas for further research.

7.1. Cohort effects on influenza and behavioral mortality

7.1.1. Cohort mechanisms

The findings presented in this dissertation highlight the usefulness of analyzing cohort effects on extrinsic mortality at different stages of the life course. Our results indicate that even in the presence of large period disturbances affecting mortality at most ages, relative differences across cohorts were sustained over time. These findings invite us to rethink the dominant assumptions about how cohort

[12] As noted in Chapter 5, when we refer to differences in mortality across cohorts with the terms such as "advantage", "disadvantage", "greater susceptibility", "penalty", and "excess", etc., these are expressed relative to the linear trend of change – i.e., nonlinear effects or divergence from the linear trend –, and make no reference to absolute differences in mortality between cohorts. The identification problem that is inherent in APC data prevents us to attribute absolute variations over period or cohort dimensions.

effects on mortality arise, as well as about how these effects operate over the life course, and through which causes of death. As we pointed out in chapter 2, the cohort effects that are typically conceptualized and studied in mortality analyses are those that originate from exposures during critical stages of development, and have lingering effects on intrinsic mortality at older ages. Our findings suggest that other mechanisms also play important roles in shaping contemporary mortality. We identified cohort effects that stemmed from physical and social exposures, and that affected the extrinsic mortality of these cohorts starting at young ages.

We suggest that the observed cohort differentials in influenza mortality resulted from two mechanisms that varied depending on age. Children and young adults may have excess influenza mortality during a specific season or during a pandemic if the circulating influenza strain is very different from the strain they encountered early in life, and to which they are said to be "primed." Because the influenza virus is highly mutable, successive cohorts are primed to different subtypes, leading to a succession of cohorts with varying degrees of susceptibility every epidemic season depending on the strain in circulation (i.e., *antigenic imprinting* hypothesis). At old ages, the early life imprint of influenza appears to fade away, while the health capital of the cohort members, which largely depends on their infection load in early life, becomes the main determinant of influenza mortality (i.e., *cohort morbidity phenotype* hypothesis). Hence, cohort effects on influenza mortality seem to operate at two different levels based on *antigenic* and *scarring*[13] imprints early in life.

Our findings regarding the relative baby boomers' excess mortality suggest that social exposures during sensitive life stages increased their risk of behavioral mortality beginning at young ages. Two mechanisms acting together seem to have been involved in this cohort effect. First, the large sizes of the boomer cohorts and the socioeconomic contexts in which they were living increased their levels of stress and frustration (*birth cohort* effect in Ryder (1965)'s sense). Second, the boomers' exposure to sudden socio-historical changes and their involvement in social movements at young ages forged a generational identity that was characterized by risky attitudes and behaviors (*generational* effect in Mannheim (1952)'s sense).

[13] Note that these scarring imprints do not necessarily manifest as punctual and distinctive cohort effects on mortality, because they do not refer exclusively to short-term shocks experienced in early life, such as famines or pandemics. For influenza mortality at old ages, changes in exposure to infection loads early in life (scarring imprints) occurred gradually and monotonically over cohorts, which resulted in the cohort effects on mortality having a similar pattern.

Having presented these mechanisms and the dominant approach of cohort effects on intrinsic mortality, we will now move on to discuss the differences in how these cohort effects manifested themselves over time, especially with regard to their interactions with period- and age-based factors.

7.1.2. Cohort interactions with age and period dimensions

The differences between the mechanisms underlying the cohort influences on influenza and behavioral mortality have implications for age and period effects. Because extrinsic mortality is mainly determined by environmental factors, the variation of these factors over time may interact with cohort effects. For both influenza and behavioral mortality among the boomers, period-based fluctuations had significant effects at most ages. For instance, the influenza, drug, and HIV epidemics undoubtedly influenced the mortality of boomers at most ages. However, our findings suggest that the cohort differential in mortality risk was sustained, despite variations over periods.

More precisely, we identified considerable differences between influenza and behavioral mortality in these period-cohort interactions. In the case of influenza, a cohort advantage or disadvantage could be reversed depending on the similarities or differences between the *antigenic signatures* of the cohort and the influenza virus strains in circulation. For instance, those individuals born around 1918 – who were mostly primed to H1N1 – were disadvantaged when they were exposed to the 1968 H3N2 pandemic, but were advantaged when they were exposed to H1N1 during the 2009-2010 pandemic and during the 2013-2014 influenza season in both Mexico and the United States (Gagnon et al. 2018a). In contrast, the baby boomers' disadvantage in mortality due to behavioral causes was preserved over the full period under observation, despite period-based mortality crises.

Turning to the interactions with age-based factors, we can see that for influenza mortality, the cohort effects varied considerably depending on the life stage. For the younger cohorts in our analysis (i.e., the cohorts born during the second half of the 20th century), we identified changes in risk levels among those born during the years surrounding major antigenic events (i.e., pandemics or significant antigenic events). In these instances, it appears that the cohort differential in mortality for the young and the adult populations was mainly determined by the interaction between the *antigenic cohort signature* and the virus strain encountered later in life. For the older cohorts in our analysis (i.e., the cohorts born during the end of the 19th century and the beginning of the 20th century), we found that the changes in risk levels over cohorts were smoother, with large monotonic segments, and

appeared to be less related to important antigenic events during early life. The variations in risk levels over cohorts at older ages were more likely linked to changes in the sanitary conditions these cohorts were exposed to in early life, in line with the *cohort morbidity phenotype* hypothesis (Crimmins and Finch 2006; Finch and Crimmins 2004).

In contrast, for the causes of death that underlie the boomer penalty, the most disadvantaged cohorts (i.e., those born at the end of the 1950s and the beginning of the 1960s) were exclusively observed during young and adult ages (<60y). For this reason, we were not able to determine whether the cohort effects we found for these cohorts at youth and adult ages will continue to operate as they reach older ages, or whether these effects will change into a different temporal pattern, as was observed for influenza mortality. The cohort effects on mortality among these boomers could change at older ages in several ways. First, selection could reverse the observed trends. The large extrinsic mortality rates experienced by baby boomers during their young and adult ages might have weeded out the frailest individuals, increasing the average robustness of these cohorts. As a consequence, the levels of intrinsic mortality at older ages could decline. In a second scenario, the boomer penalty could disappear. It is possible that when these boomers reach older ages, their extrinsic mortality will become proportionally negligible, and their intrinsic mortality will be no different from that of their neighboring cohorts. A third possibility is that the boomer penalty will become even more pronounced at older ages. This exacerbation of the boomer disadvantage with age could result from two different processes that underlie the adverse health behaviors of baby boomers. The low levels of perceived well-being and the high levels of frustration observed among the boomers could increase as they grow older, thereby exacerbating their disadvantage in extrinsic mortality. In addition, the cumulative damage from the extrinsic stressors the boomers were exposed to over their life course may have weakened their health capital, which could precipitate the onset of chronic and degenerative diseases, thereby increasing their risk of intrinsic mortality.

Most of the interactions we identified between age-based factors and cohort effects on extrinsic mortality operate through the interactions of extrinsic and intrinsic factors in causing death. Various mutual influences between these two types of stressors can be identified from the analyses presented in chapters 4 and 5.

7.1.3. Interactions between extrinsic and intrinsic causes of death

Although mortality from influenza and behavioral mortality are essentially external causes of death, they may interact with intrinsic causes of death and frailty. As we discussed in chapter 4, influenza infections can exacerbate degenerative diseases, such as respiratory and cardiovascular diseases. In addition, injures from influenza infections can precipitate the onset of intrinsic diseases (McElhaney et al. 2006). In terms of behavioral causes, substance intoxications can lead to instant death, but the cumulative damage of drug and alcohol abuse can also lead individuals to develop chronic and non-communicable diseases later in life, or aggravate the severity of these diseases. Moreover, the use of substances, as well as acute HIV and hepatitis C infections, may induce or exacerbate other chronic diseases, such as substance abuse disorders, alcoholic cirrhosis, acquired immunodeficiency syndrome (AIDS), and chronic hepatitis C (Cherubin 1972; Jaffe and Kimmel 2006; Laine et al. 2001; Shield et al. 2014). In these cases, the stressors are extrinsic, but the cumulative damage from these stressors may lead to progressive levels of physiological deterioration and dysfunction that can substantially increase the risk of intrinsic mortality. Thus, the aging process is influenced not only by genetically determined intrinsic stressors (Koopman et al. 2015), but by cumulative interactions between intrinsic and extrinsic stressors.

Just as extrinsic stressors have an influence on mortality risk from intrinsic causes, intrinsic stressors can similarly interact with mortality from extrinsic causes. Their physiological and health capital could make individuals more or less resistant to the effects of extrinsic factors, such as acute infections or harmful behaviors. This influence of intrinsic stressors on extrinsic mortality suggests that there are links between the *cohort morbidity phenotype* hypothesis and mortality from influenza and behavioral causes. The improvements in health capital over cohorts, which resulted from the gradual amelioration of early life conditions, may have translated into an increased resistance to the damage caused by influenza, HIV, and hepatitis C infections, as well as by substance abuse. As our findings suggest, cohort effects on influenza mortality at old ages operate through the individuals' intrinsic status, rather than through the extrinsic stressor itself; that is, the virulence or the toxicity of the influenza virus itself.

Taken together, the interactions described above highlight the problems associated with the partitioning of mortality into intrinsic and extrinsic causes (Carnes et al. 2006; Carnes and Olshansky 1997). As Koopman and colleagues argued (2015, p. 51), "aging and death are not explained by a

single case, but by intrinsic and extrinsic stressors that congregate over age and each constitute partial causes."

7.2. Baby boomers and increased mortality risk from influenza and behavioral mortality

A common finding from the analyses of influenza and behavioral mortality that needs to be addressed is that the second-order cohort curvatures on influenza and behavioral mortality detected for the baby boomers in the United States were similar. A common feature of the cohort differences in mortality found in both analyses and the all-cause mortality patterns was that the cohorts born at the end of the 1950s had a higher relative risk of death than the earlier cohorts born in the late 1940s (also denoted "leading-edge" boomers) and the more recent cohorts born in the late 1960s (also denoted "leading-edge" Xers[14]; see Figures 4.6 and 5.4). Here, we address two alternative hypotheses regarding the causal mechanisms that may have led to these similarities.

The first hypothesis is that a common factor would have increased both influenza and behavioral mortality among boomers, compared to the linear trend. The most distinctive characteristic of the boomer generation compared to other generations is its large size. This variation in size was, according to Ryder, "the most evident manifestation of inter-cohort differences" (1965, p. 845). As we discussed in chapter 5, the large sizes of the baby boomer cohorts and the economic contexts they experienced increased the frustration and distress levels of their members through *birth cohort* effects (Easterlin 1987) or through a *generational identity effect* (Mannheim 1952). The large sizes of these cohorts and their unprecedented levels of educational enrollment increased their exposure to and the influence of their peers, which increased their isolation from the influence of previous generations (Easterlin 1987; Phillips 2014). Such increases in *horizontal identification* at the expense of *vertical identification* would have made the boomers less apt to identify with the values and beliefs of previous generations (Stewart and Torges 2014), and encouraged the rise and spread of the social youth-based movements of the 1960s and 1970s (Abrams 1970; Bristow 2015, 2016; Cross and

[14] Note, however, that the pattern is not identical. For influenza, the cohort born in 1957 had the largest departure from the linear trend in relative risk of mortality among the boomers; but for behavioral causes, the pattern is less precise, and is dispersed within the "trailer edge" boomer cohorts (1956-1964).

Kleinhesselink 1985; Goertzel 1972). Because of this generational rift, rebellious attitudes and behaviors became distinctive characteristics of the baby boomers' generational identity, and may, in turn, have increased their mortality risk from behavioral causes.

The large size of the boomer generation may have also played an important role in the increased mortality observed among the cohorts born around 1957. It is, for example, possible that the large sizes of these cohorts amplified the incidence rate during the 1957 pandemic among infants and children, and thus increased the imprinting of the H2N2 pandemic strain on these cohorts. The higher risk of infection these cohorts faced later in life would have been compounded by their larger number of "horizontal" social interactions with their cohort peers in different social contexts (e.g., schools, universities, workplaces, nursing homes) (Gagnon et al. 2018a).

A second hypothesis linking both sets of causes of death with the boomer cohorts is that riskier behaviors may have mediated the increasing risk of influenza-related mortality. This mediation could have occurred in different ways. As we discussed earlier in this section, substance abuse and infections linked to risky behaviors can lead to a higher prevalence of chronic diseases (Cherubin 1972; Jaffe and Kimmel 2006; Laine et al. 2001; Shield et al. 2014). This deterioration in health capital may, in turn, increase an individual's mortality risk by exacerbating his or her comorbidities when he or she is exposed to influenza infections (Plans-Rubió 2007; Reichert et al. 2004; Simonsen et al. 2005, 2011). An alternative form of mediation involves several and intricate pathways linking opioid consumption, HIV/AIDS, influenza, and bacterial infections. There is growing evidence that opioid users are more susceptible to infectious diseases, not only because they share needles, but because opioids impair their innate and adaptive immune system defenses (Becker et al. 2016). Several studies have found that opioid users have higher risks of contracting viral and bacterial infections (Becker et al. 2016; Edelman et al. 2019; Roy et al. 2011). In addition, there appears to be an endogenous causal relationship between HIV infection and opioid abuse. As individuals infected with HIV are often prescribed opioids for the treatment of painful chronic conditions, they also have a probability of developing a substance abuse disorder (Becker et al. 2016). Thus, opioid use and HIV infection not only mutually reinforce each other, but increase the risk of influenza infection given their immunosuppressive effects. Moreover, because influenza infection alone is sufficient to increase the host's susceptibility to secondary bacterial infections, such as pneumonia and tuberculosis (Redford et al. 2014; Small et al. 2010), when the infection occurs in the presence of opioid abuse or HIV infection, the host's risk of developing severe influenza-related complications –

and of subsequent mortality – rises dramatically (CDC 2019; Cohen et al. 2012; Coussons-Read et al. 1998; Redford et al. 2014; Sheth et al. 2011). Given these intricate causal mechanisms, it is possible that the higher rates of HIV infection and opioid abuse among the boomers provide a partial explanation for their higher levels of influenza mortality. Analogously, the lower prevalence of these related behavioral risks among the "leading-edge" boomers and the "leading-edge" Xers may have reduced their susceptibility to death from influenza.

Up to this point, we have discussed the different characteristics of our findings regarding the cohort effects on mortality from influenza and behavioral causes. In particular, we examined the similarities and differences between the cohort mechanisms underlying these effects, as well as their mutual interactions and their interactions with intrinsic stressors. We will now discuss a methodological aspect that was at the core of this dissertation: namely, the APC analysis of mortality change.

7.3. Nonlinear effects approach

The main contribution of this thesis perhaps lies in our analysis of nonlinear APC cohort effects on influenza and behavioral mortality. To this end, different approaches were applied. For the analysis of influenza mortality, the contrast approach allowed us to identify the cohorts in which the direction of the risk changed significantly. From the turning points at which risk either increased or decreased, we could identify those cohorts who were either advantaged or disadvantaged when exposed to influenza infections during the observed period.

In the analysis of the boomers' mortality, the APC curvature plot tool, which we proposed and generalized in chapter 6, was pertinent for at least two purposes. First, the ridges depicted in the plots allowed us to conclude that the contribution by cause to the boomer penalty operated as a sustained cohort effect. This finding permitted us to discard alternative processes that would have produced a similar boomer disadvantage in all-cause mortality, but that were not related to a cohort effect. The same cohort disadvantage in all-cause mortality could be produced from a sequence of age-period interactions targeting boomers at different ages, and involving different causes of death – e.g., a HIV crisis during the young adult stage, followed by the opioid crisis during the mid-life stage. In such cases, it would be more appropriate to consider such excess mortality not as a cohort effect, but as an aggregate of several unrelated age-period interaction effects. Second, this visual analysis

allowed us to compare the temporal dynamics of the ridges across causes of death and across subpopulations. The similar patterns and synchronicity of these ridges suggested that they shared an underlying mechanism that unfolded through several causes of death (substance abuse, HIV, hepatitis C, suicide, and COPD) in most subpopulations (females and males in Canada and most racial/ethnic groups in the United States). These similarities across causes and populations offered useful hints about the unobserved factors responsible for these cohort differences in mortality.

As we mentioned in chapters 2 and 3, the use of APC analyses is controversial because of the limitations imposed by the identification problem on the analysis of linear effects. As Fosse and Winship stated, "the APC identification problem can be radically simplified as a problem of determining the value of the three linear effects" (2019a, p. 468). In contrast, there has been a consensus regarding the robustness and validity of the analysis of nonlinear effects since the beginning of the 1980s (Holford 1983; Rodgers 1982).

Our findings do not rely on the controversial aspects of APC methodology because most of our analyses focused on nonlinear effects. We demonstrated that it is possible to gain useful knowledge from mortality patterns – and, in general, from any population process – through the rigorous application and interpretation of APC analyses. For this reason, we are confident that our findings will remain relevant amid future developments in and controversies surrounding APC methods.

However, the observation that the use of APC analyses is limited does not imply that all analyses of linear APC effects must be avoided. Important findings could be obtained from such analyses, provided we keep in mind that identifying the true and exact decomposition of these linear effects is not possible, and that the underlying assumptions should be based on theoretical knowledge. For instance, for our analysis of influenza mortality (chapter 4), we proposed several scenarios for the partitioning of linear effects based on restricted ranges (Holford 1991; Wickramaratne et al. 1989), and our interpretations of the results were cautious and guided by theory. The decomposition of the linear trend provided by the intrinsic estimator approach (Figure 4.6) was used for comparison purposes only.

7.4. Implications

7.4.1. Contemporary and future trends of mortality

As we argued in chapter 2, the hypothesis of an "insignificant" influence of extrinsic mortality on current mortality trends (Bongaarts 2006) is not supported by the recent mortality trends in several high income countries that showed a leading role of extrinsic causes in the observed decline in life expectancy (Ho and Hendi 2018; Raleigh 2019). Therefore, extrinsic mortality should be considered in the analysis and the projection of mortality trends. Our findings even suggest that cohort effects on extrinsic mortality had an important role in the decline in life expectancy between 2014 and 2015, and that the influence of extrinsic causes on changes in all-cause mortality could increase in the future.

It is noteworthy that changes in life expectancy between two periods do not only dependent on the mortality levels in second, but also on those experienced during the first. In this regard, Luy and colleagues (2019) have suggested that the low levels of influenza mortality during the 2013-2014 epidemic season – dominated by H1N1 subtype – increased the frailty of the pool of susceptible boosting in turn the mortality levels during the more severe 2014-2015 epidemic season – dominated by the more severe H3N2 subtype. They conclude that both the low mortality in 2014 and the increased frailty of the population inflated the mortality levels in 2015.

We argue here that the largest difference in influenza mortality between 2014 and 2015 might not have mainly resulted from an increased frailty composition of the pool of susceptible, as proposed by Luy and colleagues. Instead, we propose that the cohort effects on influenza mortality played the main role in this mortality change, and in consequence, they were the main culprit of the decline in life expectancy in several European countries. The elderly population – mostly primed to the H1N1 subtype – was relatively protected against the pH1N1 subtype that dominated the 2013-2014 epidemic season (Gagnon et al. 2018a), but had a larger susceptibility when exposed to the H3N2 subtype during the 2014-2015 epidemic season. If there was an exceptional year of influenza mortality, it was not 2015 but 2014, due to the large protection of the elderly population, which contribute to the largest proportion of mortality during seasonal influenza epidemics – that is, ~95% (Simonsen 2006). If the described mechanisms were actually responsible for inflating the mortality increase in 2015, relative to 2014, this is clear evidence of the important role that cohort effects on extrinsic mortality could play in the contemporary changes of life expectancy. This unprecedented

large sensibility of life expectancy change to variations in influenza mortality is also indicative that the large contributions of other causes to the previous improvements in life expectancy are decelerating.

Other cohort effect on extrinsic mortality that could have a considerable influence in future changes in mortality is the higher susceptibility of baby boomers to influenza, drug-taking, HIV, and hepatitis C. This boomer penalty should be a matter of serious concern. If the boomers' disadvantage does not diminish over age/time, as currently seems to be the case, the influence of these extrinsic causes of death on life expectancy could become even larger for two reasons. First, if the boomers' relative disadvantage in influenza mortality is the consequence of a higher prevalence of HIV infection and opioid abuse, this disadvantage may persist and even grow as this generation reaches old ages. Thus, if the high prevalence of HIV infections and opioid abuse persists among boomers, it could, in conjunction with increased frailty with age, worsen future influenza mortality trends. Second, the already high risks of death from substance abuse, COPD, and HIV and hepatitis C infections among the boomers could interact with the physiological weakening that comes with aging. These interactions could, in turn, result in a further expansion of the mortality disadvantage of this generation from both extrinsic and extrinsic causes.

7.4.2. Public policy

Typically, preventive measures such as influenza vaccination and substance abuse prevention campaigns are implemented during periods of crisis, and target specific population subgroups based on age, specific behaviors, and socioeconomic status. But our findings highlight the need to address cohort effects in a full APC framework for targeting groups at risk. This approach could improve the effectiveness of policies aimed at preventing and mitigating epidemics related to infections and behavioral risks.

For instance, the acknowledgment of the influence of *antigenic signatures* on influenza mortality could be an incentive to design cohort-specific vaccines. This would encourage the collection and publication of influenza measures by single year of age, as previous studies have already called for (Gagnon et al. 2018b; Gagnon et al. 2019; Gostic et al. 2019). When the *antigenic imprint* of a cohort is incompatible with the viruses they encounter later in life, they face an increased risk of contracting superinfections – i.e., co-parasitic infections such as bacterial pneumonia – and thus of mortality

(Gagnon et al. 2013; Kobasa et al. 2007). Information on the *antigenic signatures* of different cohorts would also be useful for anticipating such threats and regulating immune overreactions.

7.5. Limitations

The specific limitations of each article were previously discussed. Here, we discuss some of the general limitations of our research related to the data and the methods we employed.

The mortality and population records in the United States and Canada, which are used in all articles, are considered to be of very good quality (HMD 2019). However, as we mentioned in chapter 3, because these data sources provide information on individuals' completed ages but not on their birth dates, their birth cohorts had to be imputed. Because of the fine resolution used for all analyses (single year of age and calendar year), significant biases in the findings are not anticipated. We also performed several tests using adjustments available in the literature (Carstensen 2007) to convert from period to cohort data, and found no significant differences in our findings.

The identification of causes of death is also problematic because of changes in the ICD classification over our study period – between the 7th and 10th revisions for the United States, and between the 8th and 10th revisions for Canada. Although we applied comparability ratios (described in the *data and methods* chapter) to make the classification of influenza and pneumonia more homogenous, some discontinuity may persist because the ratios were obtained from dual coding in a single year for each introduction of a new revision. Therefore, there is no guarantee that the comparability ratios estimated for selected years are representative of the differences in all periods in which the adjustments were applied. Nevertheless, because the discontinuities introduced by such potential biases correspond to period changes that affected all ages/cohorts equally, we do not expect these discontinuities to have significant implications for our findings regarding cohort effects on mortality.

An additional issue with the identification of causes of death is related to the registered ICD codes on death certificates, as has already been pointed out in literature. Because we restricted our analysis to the unique cause recorded as the main underlying cause on the death certificate, the multiple interactions driving mortality were not observable. In the case of behavioral causes of death, this could be problematic, because risky behaviors tend to cluster (Ho 2017). The imputation of intent – i.e., self-inflicted or accidental – on death certificates may also be problematic for measuring

extrinsic mortality. Notably, the distinction in drug overdoses between accidental and suicide may lead to some bias.

Regarding the racial and ethnic information used in Article 2 for the United States, two limitations should be pointed out. First, there were discrepancies between the numerator and the denominator in the calculation of our death rates for Hispanics, because ethnic origin is self-reported in the census, but is recorded by funeral directors on the death certificates. As was reported in other studies (Arias et al. 2008; Zang et al. 2019), this discrepancy may have led to an underestimation of the mortality of the Hispanic population in our analyses. Second, previous research has shown that the cause of death influences racial classification on the death certificates in the United States (Noymer et al. 2011), which may bias our findings regarding the baby boomers' excess mortality by race and ethnicity. This could, for instance, shift drug-related death counts from other groups toward the NHB population, and alcohol-related death counts toward American Indians. In addition to these potential sources of error in racial/ethnic classification, the lack of information regarding race and ethnic origin on Canadian death certificates prevented the analysis of ethnic differences in the boomers' penalty for the Canadian population.

Finally, our empirical studies of extrinsic causes of mortality could only be exploratory, since they did not provide confirmatory tests of the unobserved and underlying mechanisms responsible for the observed mortality patterns, for which age-period-cohort effects are just markers. Nevertheless, we have suggested several hypotheses regarding the potential causal mechanisms that are consistent with the observed patterns of mortality, and with the principles that were proposed in theoretical works on the role of cohorts and generations in social processes. Thus, following Billari (2015), we might argue that our analyses are part of an initial stage of *discovery* that generates novel evidence at the population level. This step is indispensable for formulating hypotheses, which are essential inputs for a second stage of *explanation*, in which the hypothesized causal mechanisms are tested. In this sense, the analyses presented in this dissertation take a first and necessary step toward deepening our understanding of cohort effects on extrinsic mortality.

7.6. Directions for future research

Further research is needed to enrich our understanding of the observed demographic phenomena, and to analyze and test some of the mechanisms that underlie the cohort patterns of extrinsic mortality that we have observed and highlighted in this dissertation. In the case of influenza mortality, further analyses are needed to test our hypotheses that second-order cohort effects at old ages are determined by *cohort morbidity phenotype* mechanisms, and that the cohort patterns observed for those born during the second half of the 20th century are related to early life exposures to influenza infections. Longitudinal data that include serologic and morbidity information would be adequate for performing these kinds of tests.

In addition, further research should be undertaken to investigate why lingering effects from early life exposures to important antigenic events, such as the 1890 Russian and the 1918 Spanish pandemics, are not evident at old ages. For this purpose, mortality data from the second half of the 19th century onward are needed, as these data can be used to compare the mortality experiences of neighboring cohorts during the full span of their life course.

Moreover, to improve our understanding of the mechanisms that underlie the baby boomers' excess mortality, we need to examine the role of within-cohort heterogeneity. Although we attempted to do so by analyzing differences in the cohort mortality pattern by racial/ethnic group, our groups were still too heterogeneous in their socioeconomic attributes. A mortality disadvantage among boomers has also been identified in other several other western societies, such as France, Australia, and the UK (Acosta et al. 2017). Thus, further analyses that decompose the excess within these national contexts are required to determine whether the same mechanisms are operating at a transnational level.

In addition to observing that the boomer cohorts are more susceptible to risky behaviors than adjacent cohorts, the analysis presented here, as well as some other studies (Huang et al. 2017; Miech et al. 2013; Sauer et al. 2018; Zang et al. 2019), have identified a similarly large risk of substance abuse-related mortality among millennial cohorts, the intensity of which has even surpassed that of the boomers in recent years. There is a need for studies that investigate the mechanisms that have led millennials to acquire this disadvantage, and the extent to which it is the consequence of intergenerational transmission of risky behaviors, as has been suggested here and in other works (Sauer et al. 2018).

Moreover, it is necessary to examine the contributions of various processes within the birth cohort and generational effects, such as frustration, stress, parity, and generational identity. This decomposition is essential for identifying the role played by each of these determinants in the relatively high susceptibility to behavior-related mortality risks observed among boomers, and for designing health interventions aimed at preventing and mitigating adverse outcomes.

Another question that deserves attention and further analyses is whether there are causal links between influenza and behavioral mortality. The causal links between those two sets of causes proposed here need to be analyzed from an explanatory perspective. Analyses using longitudinal datasets that include information about comorbidity and multiple causes of death would clearly advance such research.

Concerning the methodological aspects of the APC analysis, measures of statistical significance would be a valuable addition to existing visual methods and the approach proposed here. Better statistical models also need to be developed to quantify changes in the nonlinear APC effects over age/time. This approach would make it easier to distinguish between age-period interactions and cohort effects from a quantitative perspective. As we discussed in the third paper, the hysteresis APC model (Chauvel 2013) is an attempt in this direction, but its inflexibility – i.e., a fixed estimate of change, which only allows for constant increases or decreases – makes it ill-suited for studying non-monotonic variations, and the changes in the location of the most advantaged and disadvantaged categories in APC dimensions over age/time.

References

Abrams, P. (1970). Rites de Passage: The Conflict of Generations in Industrial Society. *Journal of Contemporary History*, 5, 175–190.

Acosta, E. (2019a). Reproducible Materials for 'APC Curvature Plots: Displaying Nonlinear Age-Period-Cohort Patterns on Lexis Plots.' Open Source Software. [electronic resource]. https://osf.io/5bmyz/

Acosta, E. (2019b). Reproducible Materials for 'Age-Period-Cohort Analysis of Influenza Mortality in the United States, 1959-2016.' Open Science Framework (OSF). [electronic resource]. https://osf.io/dv9pg/

Acosta, E. (2019c). Reproducible Materials for 'The Boomers' Excess Mortality in Canada and the United States.' Open Science Framework (OSF). [electronic resource]. https://osf.io/c3efa/

Acosta, E., & van Raalte, A. (2019). APC curvature plots: Displaying nonlinear age-period-cohort patterns on Lexis plots. *Demographic Research*, 41(42), 1205–1234. https://doi.org/10.4054/DemRes.2019.41.42.

Acosta, E., Hallman, S. A., Dillon, L. Y., Ouellette, N., Bourbeau, R., Herring, D. A., et al. (2019a). Determinants of Influenza Mortality Trends: Age-Period-Cohort Analysis of Influenza Mortality in the United States, 1959–2016. *Demography*. https://doi.org/10.1007/s13524-019-00809-y

Acosta, E., Gagnon, Alain, Ouellette, Nadine, & Bourbeau, Robert. (2017). Baby Boomers' Excess Mortality: An International Comparative Analysis. In IPC 2017. Presented at the IUSSP - 2017 International Population Conference, Cape Town. https://iussp.confex.com/iussp/ipc2017/meetingapp.cgi/Paper/7386

Acosta, E., Gagnon, A., Ouellette, N., van Raalte, A.A., Bourbeau, R.R., and Nepomuceno, M. (2019b). *Racial and Ethnic Diversity in the Boomers' Excess Mortality Due to Substance Abuse in the United States*. Paper presented at PAA 2019 Annual Meeting, Austin, US, 2019. http://paa2019.populationassociation.org/abstracts/193435

Acosta, E., Torres, C., Silva-Ramirez, R., & Bourbeau, R. (2018). Violence and mortality from external causes in Colombia: Analysis of demographic costs during the period 1979-2016. Presented at the ALAP 2018, Puebla, Mexico. http://www.alapop.org/Congreso2018/PDF/0021a.pdf

Adams, M. (2004). Fire and Ice: The United States, Canada and the Myth of Converging Values (First Printing edition.). Toronto: Penguin Canada.

Agar, M. (2003). The Story of Crack: Towards a Theory of Illicit Drug Trends. *Addiction Research & Theory*, 11(1), 3–29. https://doi.org/10.1080/1606635021000059042

Almond, D. (2006). Is the 1918 Influenza Pandemic Over? Long-Term Effects of In Utero Influenza Exposure in the Post-1940 U.S. Population. *Journal of Political Economy*, *114*(4), 672–712. doi:10.1086/jpe.2006.114.issue-4

Alwin, D. F., & McCammon, R. J. (2003). Generations, Cohorts, and Social Change. In *Handbook of the Life Course* (pp. 23–49). Springer, Boston, MA. https://doi.org/10.1007/978-0-306-48247-2_2

Alwin, D. F., & McCammon, R. J. (2007). Rethinking Generations. *Research in Human Development*, 4(3–4), 219–237. https://doi.org/10.1080/15427600701663072

Alwin, D. F., McCammon, R. J., & Hofer, S. M. (2014). Studying Baby Boom Cohorts Within a Demographic and Developmental Context: Conceptual and Methodological Issues. In *The Baby Boomers Grow Up: Contemporary Perspectives on Midlife* (pp. 45–71). New York: Psychology Press.

Anderson, R. N., Miniño, A. M., Hoyert, D. L., & Rosenberg, H. M. (2001). Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System*, *49*(2), 1–32.

Andreev, K., Bourbeau, R., Ouellette, N., & Dukhovnov, D. (2019). About Mortality Data for Canada (Background and documentation). Rostock, Germany: Max Planck Institute for Demographic Research. https://www.mortality.org/hmd/CAN/InputDB/CANcom.pdf

Andreeva, M., Winant, C., & Barbieri, M. (2019). About Mortality Data for the United States. Human Mortality Database. https://www.mortality.org/hmd/USA/InputDB/USAcom.pdf

Andvord, K. F. (1921). Is tuberculosis to be regarded from the aetiological standpoint as an acute disease of childhood? *Tubercle*, 3(1), 97–116.

Andvord, K. F., Wijsmuller, G., & Blomberg, B. (1930). What can we learn by following the development of tuberculosis from one generation to another? 1930. The International Journal of Tuberculosis and Lung Disease: *The Official Journal of the International Union Against Tuberculosis and Lung Disease*, 6(7), 562–568.

Arevalo, P., McLean, H. Q., Belongia, E. A., & Cobey, S. (2019). Earliest infections predict the age distribution of seasonal influenza A cases. *medRxiv*, 19001875. https://doi.org/10.1101/19001875

Arias, E., Schauman, W. S., Eschbach, K., Sorlie, P. D., & Backlund, E. (2008). The validity of race and Hispanic origin reporting on death certificates in the United States. Vital and Health Statistics. Series 2, *Data Evaluation and Methods Research*, (148), 1–23.

Armstrong, G., Conn, L., & Pinner, R. (1999). Trends in infectious disease mortality in the united states during the 20th century. *JAMA*, *281*(1), 61–66. doi:10.1001/jama.281.1.61

Azambuja, M. (2009). Influenza Recycling and Secular Trends in Mortality and Natality. *British Actuarial Journal*, 15, 123–150.

Azambuja, M. (2015). *Use of 1-year intervals in graphic plots of age-period-cohort trends suggests a role for Influenza in secular (period and cohort) variations of all-causes mortality*. Presented at the Conference: Workshop of the EAPS: Health, Morbidity and Mortality Working Group, Prague.

Banting, K. G., & Hoberg, G. (1997). *Degrees of Freedom: Canada and the United States in a Changing World* (First Soft-Cover Edition edition.). Montreal: McGill-Queen's University Press.

Barbi, E., & Camarda, C. G. (2011). Period and cohort effects on elderly mortality: a new relational model for smoothing mortality surfaces. *Statistica*, 71(1), 51–69. https://doi.org/10.6092/issn.1973-2201/3604

Barbi, E., & Vaupel, J. W. (2005). Comment on "Inflammatory Exposure and Historical Changes in Human Life-Spans." *Science*, 308(5729), 1743–1743. https://doi.org/10.1126/science.1108707

Barbieri, M. (2019). The decrease in life expectancy in the United States since 2014. *Population and Societies*, *570*, 4.

Barker, D. J., & Osmond, C. (1986). Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* (London, England), 1(8489), 1077–1081.

Barnett, M. L., Olenski, A. R., & Jena, A. B. (2017). Opioid-Prescribing Patterns of Emergency Physicians and Risk of Long-Term Use. *New England Journal of Medicine*, 376(7), 663–673. https://doi.org/10.1056/NEJMsa1610524

Barry, J. M. (2005). *The Great Influenza: The Epic Story of the Deadliest Plague in History*. Penguin.

Becker, W. C., Gordon, K., Jennifer Edelman, E., Kerns, R. D., Crystal, S., Dziura, J. D., et al. (2016). Trends in Any and High-Dose Opioid Analgesic Receipt Among Aging Patients With and Without HIV. *AIDS and Behavior*, 20(3), 679–686. https://doi.org/10.1007/s10461-015-1197-5

Bell, A., & Jones, K. (2013). The impossibility of separating age, period and cohort effects. *Social Science & Medicine*, 93(Supplement C), 163–165. https://doi.org/10.1016/j.socscimed.2013.04.029

Bell, A., & Jones, K. (2014). Don't birth cohorts matter? A commentary and simulation exercise on Reither, Hauser, and Yang's (2009) age–period–cohort study of obesity. *Social Science & Medicine*, 101, 176–180. https://doi.org/10.1016/j.socscimed.2013.09.004

Bengtsson, T., & Broström, G. (2009). Do conditions in early life affect old-age mortality directly and indirectly? Evidence from 19th-century rural Sweden. *Social Science & Medicine*, 68(9), 1583–1590. https://doi.org/10.1016/j.socscimed.2009.02.020

Bengtsson, T., & Lindström, M. (2000). Childhood misery and disease in later life: The effects on mortality in old age of hazards experienced in early life, southern Sweden, 1760-1894. *Population Studies*, 54(3), 263–277. https://doi.org/10.1080/713779096

Bengtsson, T., & Lindström, M. (2003). Airborne infectious diseases during infancy and mortality in later life in southern Sweden, 1766–1894. *International Journal of Epidemiology*, 32(2), 286–294. https://doi.org/10.1093/ije/dyg061

Ben-Shlomo, Y., & Smith, G. D. (1991). Deprivation in infancy or in adult life: which is more important for mortality risk? *The Lancet*, 337(8740), 530–534. https://doi.org/10.1016/0140-6736(91)91307-G

Ben-Shlomo, Y., & Kuh, D. (2002). A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *International Journal of Epidemiology*, 31(2), 285–293.

Berkman, L. F. (2009). Social epidemiology: social determinants of health in the United States: are we losing ground? *Annual Review of Public Health*, 30, 27–41. https://doi.org/10.1146/annurev.publhealth.031308.100310

Beveridge, W. I. B. (1991). The Chronicle of Influenza Epidemics. *History and Philosophy of the Life Sciences*, *13*(2), 223–234.

Billari, F. C. (2015). Integrating macro- and micro-level approaches in the explanation of population change. *Population Studies*, 69 Suppl 1, S11-20. https://doi.org/10.1080/00324728.2015.1009712

Bilodeau Bertrand, M. (2015, April 30). L'influence sur la longévité de l'exposition très tôt dans la vie à une épidémie au Québec à la fin du XIXe siècle. Université de Montréal, Montréal. Retrieved from https://papyrus.bib.umontreal.ca/xmlui/handle/1866/12033

Boeri, M. W., Sterk, C. E., & Elifson, K. W. (2006). Baby Boomer Drug Users: Career Phases, Social Control, and Social Learning Theory*. *Sociological Inquiry*, 76(2), 264–291. https://doi.org/10.1111/j.1475-682X.2006.00154.x

Bongaarts, J. (2005). Long-range trends in adult mortality: Models and projection methods. *Demography*, 42(1), 23–49. https://doi.org/10.1353/dem.2005.0003

Bongaarts, J. (2006). How Long Will We Live? *Population and Development Review*, 32(4), 605–628.

Boseley, S. (2018, February 13). Prescription of opioid drugs continues to rise in England. The Guardian. https://www.theguardian.com/society/2018/feb/13/prescription-of-opioid-drugs-continues-to-rise-in-england. Accessed 2 July 2019

Bourbeau, R., & Lebel, A. (2000). Mortality statistics for the oldest-old: an evaluation of Canadian data. *Demographic Research*, 2(2). https://doi.org/10.4054/DemRes.2000.2.2

Bourbeau, R., & Ouellette, N. (2016). Trends, patterns, and differentials in Canadian mortality over nearly a century, 1921-2011. *Canadian Studies in Population*, 43(1–2), 48–77.

Bristow, J. (2015). *Baby Boomers and Generational Conflict*. Palgrave Macmillan UK.

Bristow, J. (2016). *The Sociology of Generations: New Directions and Challenges*. Springer.

Bulloch, A. G. M., Williams, J. V. A., Lavorato, D. H., & Patten, S. B. (2016). Trends in binge drinking in Canada from 1996 to 2013: a repeated cross-sectional analysis. *CMAJ Open*, 4(4), E599–E604. https://doi.org/10.9778/cmajo.20150124

Burian, S. J., Nix, S. J., Pitt, R. E., & Durrans, S. R. (2000). Urban Wastewater Management in the United States: Past, Present, and Future. *Journal of Urban Technology*, *7*(3), 33–62. doi:10.1080/713684134

Burnham, K. P., & Anderson, D. R. (2002). *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach* (2nd ed.). New York: Springer-Verlag. https://www.springer.com/de/book/9780387953649

Camarda, C. G. (2012). MortalitySmooth: An R Package for Smoothing Poisson Counts with P-Splines. *Journal of Statistical Software*. https://doi.org/10.18637/jss.v050.i01

Campbell, L. A., Clement, D., & Kealey, G. S. (2012). *Debating Dissent: Canada and the 1960s* (1 edition.). Toronto: University of Toronto Press, Scholarly Publishing Division.

Canon, L. (2018). Analyse de la distribution des décès aux grands âges selon le niveau de scolarité à partir d'un suivi de la mortalité sur 20 ans au Canada (Master Thesis). Université de Montréal, Montreal, Canada. Retrieved from https://papyrus.bib.umontreal.ca/xmlui/handle/1866/20100

Canudas-Romo, V., & Guillot, M. (2015). Truncated cross-sectional average length of life: A measure for comparing the mortality history of cohorts. *Population Studies*, *69*(2), 147–159. doi:10.1080/00324728.2015.1019955

Carnes, B. A., & Olshansky, S. J. (1997). A biologically motivated partitioning of mortality. *Experimental Gerontology*, 32(6), 615–631. https://doi.org/10.1016/S0531-5565(97)00056-9

Carnes, B. A., Holden, L. R., Olshansky, S. J., Witten, M. T., & Siegel, J. S. (2006). Mortality Partitions and their Relevance to Research on Senescence. *Biogerontology*, 7(4), 183–198. https://doi.org/10.1007/s10522-006-9020-3

Carnes, B. A., Olshansky, S. J., & Grahn, D. (1996). Continuing the Search for a Law of Mortality. *Population and Development Review*, 22(2), 231–264. https://doi.org/10.2307/2137434

Carstensen, B. (2007). Age-period-cohort models for the Lexis diagram. *Statistics in Medicine*, *26*(15), 3018–3045. doi:10.1002/sim.2764

Carstensen, B., Plummer, M., Laara, E., & Hills, M. (2019). *Epi: A Package for Statistical Analysis in Epidemiology. R.* https://cran.r-project.org/web/packages/Epi/index.html

Caselli, G., & Vallin, J. (2005). Frequency Surfaces and Isofrequency Lines. In *Demography: Analysis and Synthesis*.

CATIE. (2018). Latest Canadian hepatitis C guidelines encourage offer of a test to baby boomers (CATIE News). Canada: CATIE - Canada's source for HIV and hepatitis C information. https://www.catie.ca/en/catienews/2018-06-12/latest-canadian-hepatitis-c-guidelines-encourage-offer-test-baby-boomers

CDC - Division of Viral Hepatitis. (2019). *CDC Recommendation: Adults Born from 1945-1965 (Baby Boomers) get Tested for Hepatitis C*. https://www.cdc.gov/hepatitis/populations/1945-1965.htm

CDC. (2000). *Update: Influenza Activity --- United States, 1999-2000 Season* (No. 49(9)). CDC. https://www.cdc.gov/MMWR/preview/mmwrhtml/mm4909a1.htm

CDC. (2012). *Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965* (Recommendations and Reports No. 61). CDC. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6104a1.htm

CDC. (2018a). *Highly Pathogenic Asian Avian Influenza A(H5N1) Virus | Avian Influenza (Flu)*. CDC. https://www.cdc.gov/flu/avianflu/h5n1-virus.htm

CDC. (2018b). *National, Regional, and State Level Outpatient Illness and Viral Surveillance*. Flu View. https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html

CDC. (2018c). *HIV Surveillance Report, 2017* (The HIV Surveillance Report No. 29) (p. 125). CDC. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2017-vol-29.pdf

CDC. (2018d). *Surveillance for Viral Hepatitis – United States, 2016*. CDC, Division of Viral Hepatitis. https://www.cdc.gov/hepatitis/statistics/2016surveillance/commentary.htm

CDC. (2019a). *Estimated HIV incidence and prevalence in the United States, 2010–2016 (HIV Surveillance Supplemental Report* No. 24 (1)). https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-24-1.pdf

CDC. (2019b, April 11). *People with HIV & Influenza (Flu)* | CDC. CDC. https://www.cdc.gov/flu/highrisk/hiv-flu.htm

CDC. (2019c, September 13). *Overview of Influenza Surveillance in the United States* | CDC. https://www.cdc.gov/flu/weekly/overview.htm

Chauvel, L. (2013). Spécificité et permanence des effets de cohorte : le modèle APCD appliqué aux inégalités de générations, France/États-Unis, 1985-2010. *Revue française de sociologie*, 54(4), 665–705. https://doi.org/10.3917/rfs.544.0665

Chauvel, L., Leist, A. K., & Ponomarenko, V. (2016). Testing Persistence of Cohort Effects in the Epidemiology of Suicide: an Age-Period-Cohort Hysteresis Model. *PLOS ONE*, 11(7), e0158538. https://doi.org/10.1371/journal.pone.0158538

Cherubin, C. E. (1972). Chronic Liver Disease in Asymptomatic Narcotic Addicts. *Annals of Internal Medicine*, 76(3), 391. https://doi.org/10.7326/0003-4819-76-3-391

Chin, J., Magoffin, R. L., & Lennette, E. H. (1974). The Epidemiology of Influenza in California, 1968-1973. *Western Journal of Medicine*, *121*(2), 94–99.

CIHI. (2018). Alcohol Harm in Canada. Examining Hospitalizations Entirely Caused by Alcohol and Strategies to Reduce Alcohol Harm. Canadian Institute for Health Information.

Clark, P. G. (1991). Ethical Dimensions of Quality of Life in Aging: Autonomy vs. Collectivism in the United States and Canada. *The Gerontologist*, 31(5), 631–639. https://doi.org/10.1093/geront/31.5.631

Clayton, D., & Schifflers, E. (1987a). Models for temporal variation in cancer rates. II: Age–period–cohort models. *Statistics in Medicine*, 6(4), 469–481. https://doi.org/10.1002/sim.4780060406

Clayton, D., & Schifflers, E. (1987b). Models for temporal variation in cancer rates. I: Age–period and age–cohort models. *Statistics in Medicine*, 6(4), 449–467. https://doi.org/10.1002/sim.4780060405

Coale, A. J., & Kisker, E. E. (1986). Mortality Crossovers: Reality or Bad Data? *Population Studies*, 40(3), 389–401.

Cohen, C., Simonsen, L., Sample, J., Kang, J.-W., Miller, M., Madhi, S. A., et al. (2012). Influenza-Related Mortality Among Adults Aged 25–54 Years With AIDS in South Africa and the United States of America. *Clinical Infectious Diseases*, 55(7), 996–1003. https://doi.org/10.1093/cid/cis549

Cohen, S. A., Klassen, A. C., Ahmed, S., Agree, E. M., Louis, T. A., & Naumova, E. N. (2010). Trends for influenza and pneumonia hospitalization in the older population: age, period, and cohort effects. *Epidemiology and Infection*, *138*(8), 1135–1145. doi:10.1017/S0950268809991506

Collins, S. (1931). *Age and Sex Incidence of Influenza and Pneumonia Morbidity and Mortality in the Epidemic of 1928-29 with Comparative Data for the Epidemic 1918-19* (No. 48) (p. 29). United States: United States Public Health Service.

Colliver, J. D., Compton, W. M., Gfroerer, J. C., & Condon, T. (2006). Projecting drug use among aging baby boomers in 2020. *Annals of Epidemiology*, 16(4), 257–265. https://doi.org/10.1016/j.annepidem.2005.08.003

Cordoba, E., & Aiello, A. E. (2016). Social Determinants of Influenza Illness and Outbreaks in the United States. *North Carolina Medical Journal*, 77(5), 341–345. https://doi.org/10.18043/ncm.77.5.341

Coussons-Read, M. E., Daniels, M., & Gilmour, M. I. (1998). Morphine Alters the Immune Response to Influenza Virus Infection in Lewis Rats. In H. Friedman, J. J. Madden, & T. W. Klein (Eds.), *Drugs of Abuse, Immunomodulation, and Aids* (pp. 73–82). Boston, MA: Springer US. https://doi.org/10.1007/978-1-4615-5347-2_9

Crimmins, E. M., & Finch, C. E. (2006). Infection, inflammation, height, and longevity. *Proceedings of the National Academy of Sciences*, 103(2), 498–503. https://doi.org/10.1073/pnas.0501470103

Crome, I., & Rao, R. (2018). Our Invisible Addicts (No. CR211). *Royal College of Psychiatrists.* https://www.rcpsych.ac.uk/usefulresources/publications/collegereports/cr/cr211.aspx

Cross, H. J., & Kleinhesselink, R. R. (1985). The Impact of the 1960s on Adolescence. *The Journal of Early Adolescence*, 5(4), 517–531. https://doi.org/10.1177/0272431685054009

Currie, I. D., Durban, M., & Eilers, P. H. (2004). Smoothing and forecasting mortality rates. *Statistical Modelling*, 4(4), 279–298. https://doi.org/10.1191/1471082X04st080oa

Curtin, S. C., Warner, M., & Hedegaard, H. (2016). *Increase in Suicide in the United States, 1999-2014*. NCHS data brief, (241), 1–8.

Cutler, D., & Miller, G. (2005). The role of public health improvements in health advances: The twentieth-century United States. *Demography*, *42*(1), 1–22. doi:10.1353/dem.2005.0002

Davenport, F. M., Hennessy, A. V., Francis, T., & Fabisch, W. the T. A. of P. (1953). Epidemiologic and Immunologic Significance of Age Distribution of Antibody to Antigenic Variants of Influenza Virus. *Journal of Experimental Medicine*, *98*(6), 641–656. doi:10.1084/jem.98.6.641

de Palma, A., Picard, N., & Ziegelmeyer, A. (2011). Individual and couple decision behavior under risk: evidence on the dynamics of power balance. *Theory and Decision*, 70(1), 45–64. https://doi.org/10.1007/s11238-009-9179-6

Deaton, A. (2015). *The Great Escape: Health, Wealth, and the Origins of Inequality* (Reprint edition.). Princeton University Press.

Doblhammer, G., & Vaupel, J. W. (2001). Lifespan depends on month of birth. Proceedings of the National Academy of Sciences, 98(5), 2934–2939. https://doi.org/10.1073/pnas.041431898

Draper, N. R., & Smith, H. (1998). *Applied Regression Analysis* (3. edition.). New York: Wiley-Interscience.

Duncan, D. F., Nicholson, T., White, J. B., Bradley, D. B., & Bonaguro, J. (2010). The baby boomer effect: changing patterns of substance abuse among adults ages 55 and older. *Journal of Aging & Social Policy*, 22(3), 237–248. https://doi.org/10.1080/08959420.2010.485511

Dunnell, K. (2008). Ageing and mortality in the UK--national statistician's annual article on the population. *Population Trends*, (134), 6–23.

Dushoff, J., Plotkin, J. B., Viboud, C., Earn, D. J. D., & Simonsen, L. (2006). Mortality due to influenza in the United States--an annualized regression approach using multiple-cause mortality data. *American Journal of Epidemiology*, *163*(2), 181–187. doi:10.1093/aje/kwj024

Dwyer-Lindgren, L., Flaxman, A. D., Ng, M., Hansen, G. M., Murray, C. J. L., & Mokdad, A. H. (2015). Drinking Patterns in US Counties From 2002 to 2012. *American Journal of Public Health*, 105(6), 1120–1127. https://doi.org/10.2105/AJPH.2014.302313

Easterlin, R. A. (1976). The Conflict between Aspirations and Resources. *Population and Development Review*, 2(3/4), 417–425. https://doi.org/10.2307/1971619

Easterlin, R. A. (1987). *Birth and Fortune: The Impact of Numbers on Personal Welfare* (2 edition.). Chicago: University Of Chicago Press.

Easterlin, R. A., Schaeffer, C. M., & Macunovich, D. J. (1993). Will the Baby Boomers be Less Well off Than Their Parents? Income, Wealth, and Family Circumstances over the Life Cycle in the United States. *Population and Development Review*, 19(3), 497–522. https://doi.org/10.2307/2938464

Edelman, E. J., Gordon, K. S., Crothers, K., Akgün, K., Bryant, K. J., Becker, W. C., et al. (2019). Association of Prescribed Opioids With Increased Risk of Community-Acquired Pneumonia Among Patients With and Without HIV. *JAMA Internal Medicine*, 179(3), 297–304. https://doi.org/10.1001/jamainternmed.2018.6101

Edmunds, J., & Turner, B. S. (2005). Global generations: social change in the twentieth century. *The British Journal of Sociology*, 56(4), 559–577. https://doi.org/10.1111/j.1468-4446.2005.00083.x

Eilers, P. H. C., & Marx, B. D. (1996). Flexible Smoothing with B-splines and Penalties. *Statistical Science*, 11(2), 89–102.

Eilers, P. H. C., Marx, B. D., & Durbán, M. (2015). Twenty years of P-splines. *SORT-Statistics and Operations Research Transactions*, 39(2), 149-186–186.

Ellwood, D. T. (1982). *Teenage Unemployment: Permanent Scars or Temporary Blemishes? In The Youth Labor Market Problem: Its Nature, Causes, and Consequences* (p. 608). University of Chicago Press. https://www.nber.org/books/free82-1. Accessed 29 March 2019

Elo, I. T., & Preston, S. H. (1992). Effects of Early-Life Conditions on Adult Mortality: A Review. *Population Index*, 58(2), 186–212. https://doi.org/10.2307/3644718

Engler, R. J. M., Nelson, M. R., Klote, M. M., VanRaden, M. J., Huang, C.-Y., Cox, N. J., et al. (2008). Half- vs Full-Dose Trivalent Inactivated Influenza Vaccine (2004-2005): Age, Dose, and Sex Effects on Immune Responses. *Archives of Internal Medicine*, *168*(22), 2405–2414. doi:10.1001/archinternmed.2008.513

Eyerman, R., & Turner, B. S. (1998). Outline of a Theory of Generations. European Journal of Social Theory, 1(1), 91–106. https://doi.org/10.1177/136843198001001007

Ferrence, R. G. (1988). Sex differences in cigarette smoking in Canada, 1900-1978: a reconstructed cohort study. *Canadian Journal of Public Health = Revue Canadienne De Sante Publique*, 79(3), 160–165.

Fienberg, S. E. (2013). Cohort Analysis' Unholy Quest: A Discussion. *Demography*, *50*(6), 1981–1984. doi:10.1007/s13524-013-0251-z

Fienberg, S. E., & Mason, W. M. (1979). Identification and Estimation of Age-Period-Cohort Models in the Analysis of Discrete Archival Data. Sociological Methodology, 10, 1–67. https://doi.org/10.2307/270764

Fienberg, S. E., & Mason, W. M. (1985). Specification and Implementation of Age, Period and Cohort Models. In *Cohort Analysis in Social Research* (pp. 45–88). Springer, New York, NY. doi:10.1007/978-1-4613-8536-3_3

Finch, C. E., & Crimmins, E. M. (2004). Inflammatory exposure and historical changes in human life-spans. *Science (New York, N.Y.)*, *305*(5691), 1736–1739. doi:10.1126/science.1092556

Fingerhut, L. A., & Cox, C. S. (1998). *Poisoning mortality, 1985-1995*. Public Health Reports, 113(3), 218–233.

Floud, R., Fogel, R. W., Harris, B., & Hong, S. C. (2011). *The Changing Body: Health, Nutrition, and Human Development in the Western World since 1700*. Cambridge ; New York: Cambridge University Press.

Fogel, R. W. (2003). Changes in the Process of Aging During the Twentieth Century: Findings and Procedures of the Early Indicators Project (Working Paper No. 9941). National Bureau of Economic Research. http://www.nber.org/papers/w9941. Accessed 24 September 2015

Fogel, R. W., & Costa, D. L. (1997). A theory of technophysio evolution, with some implications for forecasting population, health care costs, and pension costs. *Demography*, *34*(1), 49–66.

Fosse, E., & Winship, C. (2018). Moore–Penrose Estimators of Age–Period–Cohort Effects: Their Interrelationship and Properties. *Sociological Science*, *5*(14), 304--334. doi:10.15195/v5.a14

Fosse, E., & Winship, C. (2019a). Analyzing Age-Period-Cohort Data: A Review and Critique. *Annual Review of Sociology*, 45(1), 467–492. https://doi.org/10.1146/annurev-soc-073018-022616

Fosse, E., & Winship, C. (2019b). Bounding Analyses of Age-Period-Cohort Effects. *Demography*. https://doi.org/10.1007/s13524-019-00801-6.

Francis, T. (1960). On the Doctrine of Original Antigenic Sin. *Proceedings of the American Philosophical Society*, 104(6), 572–578.

Frenk, J., Bobadilla, J. L., Stern, C., Frejka, T., & Lozano, R. (1991). Elements for a theory of the health transition. *Health Transition Review: The Cultural, Social, and Behavioural Determinants of Health*, 1(1), 21–38.

Frost, W. H. (1939). The Age Selection of Mortality from Tuberculosis in Successive Decades. *The Milbank Memorial Fund Quarterly*, 18(1), 61–66. https://doi.org/10.2307/3347652

Fu, W. (2016). Constrained Estimators and Consistency of a Regression Model on a Lexis Diagram. *Journal of the American Statistical Association*, *111*(513), 180–199. doi:10.1080/01621459.2014.998761

Fu, W. J. (2000). Ridge estimator in singulah oesiun with application to age-period-cohort analysis of disease rates. *Communications in Statistics - Theory and Methods*, *29*(2), 263–278. doi:10.1080/03610920008832483

Furman, D., Hejblum, B. P., Simon, N., Jojic, V., Dekker, C. L., Thiébaut, R., et al. (2014). Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. *Proceedings of the National Academy of Sciences*, *111*(2), 869–874. doi:10.1073/pnas.1321060111

Gagnon, A. (2012). Effect of birth season on longevity: Thrifty and hopeful phenotypes in historical Quebec. *American Journal of Human Biology*, 24(5), 654–660. https://doi.org/10.1002/ajhb.22287

Gagnon, A., & Bohnert, N. (2012). Early life socioeconomic conditions in rural areas and old-age mortality in twentieth-century Quebec. Social Science & Medicine, 75(8), 1497–1504. https://doi.org/10.1016/j.socscimed.2012.06.007

Gagnon, A., & Mazan, R. (2009). Does exposure to infectious diseases in infancy affect old-age mortality? Evidence from a pre-industrial population. *Social Science & Medicine*, 68(9), 1609–1616. https://doi.org/10.1016/j.socscimed.2009.02.008

Gagnon, A., Acosta, E., & Miller, M. (2019). Age-specific incidence of influenza A responds to change in virus subtype dominance. *Clinical Infectious Diseases*, [Submitted].

Gagnon, A., Acosta, E., Hallman, S., Bourbeau, R., Dillon, L. Y., Ouellette, N., et al. (2018a). Pandemic Paradox: Early Life H2N2 Pandemic Influenza Infection Enhanced Susceptibility to Death during the 2009 H1N1 Pandemic. *mBio*, *9*(1), e02091-17. doi:10.1128/mBio.02091-17

Gagnon, A., Acosta, E., & Miller, M. S. (2018b). Reporting and evaluating influenza virus surveillance data: An argument for incidence by single year of age. *Vaccine*. doi:10.1016/j.vaccine.2018.08.077

Gagnon, A., Acosta, J. E., Madrenas, J., & Miller, M. S. (2015). Is Antigenic Sin Always "Original?" Re-examining the Evidence Regarding Circulation of a Human H1 Influenza Virus Immediately Prior to the 1918 Spanish Flu. *PLoS Pathogens*, *11*(3), e1004615. doi:10.1371/journal.ppat.1004615

Gagnon, A., Miller, M. S., Hallman, S. A., Bourbeau, R., Herring, D. A., Earn, D. J., & Madrenas, J. (2013). Age-Specific Mortality During the 1918 Influenza Pandemic: Unravelling the Mystery of High Young Adult Mortality. *PLoS ONE*, *8*(8), e69586. doi:10.1371/journal.pone.0069586

Garnier, S., Ross, N., Rudis, B., Sciaini, M., & Scherer, C. (2018). *viridis: Default Color Maps from "matplotlib."* https://CRAN.R-project.org/package=viridis. Accessed 23 August 2019

Gavrilov, L. A., & Gavrilova, N. S. (2011). Season of Birth and Exceptional Longevity: Comparative Study of American Centenarians, Their Siblings, and Spouses. *Journal of Aging Research. Research article*. https://doi.org/10.4061/2011/104616

Giefing-Kröll, C., Berger, P., Lepperdinger, G., & Grubeck-Loebenstein, B. (2015). How sex and age affect immune responses, susceptibility to infections, and response to vaccination. *Aging Cell*, *14*(3), 309–321. doi:10.1111/acel.12326

Glenn, N. D. (1976). Cohort Analysts' Futile Quest: Statistical Attempts to Separate Age, Period and Cohort Effects. *American Sociological Review*, 41(5), 900–904. https://doi.org/10.2307/2094738

Gluckman, P. D., Hanson, M. A., & Pinal, C. (2005). The developmental origins of adult disease. *Maternal & Child Nutrition*, 1(3), 130–141. https://doi.org/10.1111/j.1740-8709.2005.00020.x

Goertzel, T. (1972). *Generational Conflict and Social Change. Youth and Society*; Beverley Hills, Calif., 3(3), 327–352.

Goldring, S., Henretty, N., Mills, J., Johnson, K., & Smallwood, S. (2011). Mortality of the "Golden Generation": what can the ONS Longitudinal study tell us? *Population Trends*, (145), 199–228. https://doi.org/10.1057/pt.2011.24

Goldstein, J.R. (2011). A Secular Trend toward Earlier Male Sexual Maturity: Evidence from Shifting Ages of Male Young Adult Mortality. *PLOS ONE* 6(8):e14826. doi:10.1371/journal.pone.0014826.

Gompertz, B. (1825). On the Nature of the Function Expressive of the Law of Human Mortality, and on a New Mode of Determining the Value of Life Contingencies. *Philosophical Transactions of the Royal Society of London*, 115, 513–583.

Gostic, K. M., Bridge, R., Brady, S., Viboud, C., Worobey, M., & Lloyd-Smith, J. O. (2019). Childhood immune imprinting to influenza A shapes birth year-specific risk during seasonal H1N1 and H3N2 epidemics. *medRxiv*, 19001834. https://doi.org/10.1101/19001834

Grolemund, G., & Wickham, H. (2011). Dates and Times Made Easy with lubridate. *Journal of Statistical Software*, 40(1), 1–25. doi:10.18637/jss.v040.i03

Haines, M. (2000). The Population of the United States, 1790–1920. In *The Cambridge Economic History of the United States*. doi:10.1017/CHOL9780521553070.005

Haines, M. (2001). The urban mortality transition in the united states, 1800-1940. *Annales de demographie historique*, *no 101*(1), 33–64.

Hallman, S. (2015). The Demographic Links Between the 1890 and 1918 Influenza Pandemics in Ontario. *Electronic Thesis and Dissertation Repository*. http://ir.lib.uwo.ca/etd/3129

Hallman, S., & Gagnon, A. (2014). Does exposure to influenza very early in life affect mortality risk during a subsequent outbreak? The 1890 and 1918 pandemics in Canada. In *Are modern environments bad for human health? Revisiting the second epidemiological transition* (pp. 123–138). Wiley-Blackwell.

Haque, A., Hober, D., & Kasper, L. H. (2007). Confronting Potential Influenza A (H5N1) Pandemic with Better Vaccines. *Emerging Infectious Diseases*, *13*(10), 1512–1518. doi:10.3201/eid1310.061262

Harris, C. R., & Jenkins, M. (2006). Gender Differences in Risk Assessment: Why do Women Take Fewer Risks than Men? *Judgment and Decision Making*, 1(1), 16.

Hayward, M. D., & Gorman, B. K. (2004). The long arm of childhood: The influence of early-life social conditions on men's mortality. *Demography*, 41(1), 87–107. https://doi.org/10.1353/dem.2004.0005

Held, L., & Riebler, A. (2013). Comment on "Assessing Validity and Application Scope of the Intrinsic Estimator Approach to the Age-Period-Cohort (APC) Problem." *Demography*, 50(6), 1977–1979. https://doi.org/10.1007/s13524-013-0255-8

Helmerhorst, G. T. T., Teunis, T., Janssen, S. J., & Ring, D. (2017). An epidemic of the use, misuse and overdose of opioids and deaths due to overdose, in the United States and Canada. *The Bone & Joint Journal*, 99-B(7), 856–864. https://doi.org/10.1302/0301-620X.99B7.BJJ-2016-1350.R1

Henry, C., Palm, A.-K. E., Krammer, F., & Wilson, P. C. (2018). From Original Antigenic Sin to the Universal Influenza Virus Vaccine. *Trends in Immunology*, *39*(1), 70–79. doi:10.1016/j.it.2017.08.003

Herbold, H. (1994). Never a Level Playing Field: Blacks and the GI Bill. *The Journal of Blacks in Higher Education*, (6), 104–108. https://doi.org/10.2307/2962479

HFD. (2019). Human Fertility Database. Max Planck Institute for Demographic Research (Germany) and Vienna Institute of Demography (Austria). https://www.humanfertility.org/cgi-bin/main.php. Accessed 29 June 2018

Hilbe, J. M. (2011). *Negative Binomial Regression* (2 edition.). Cambridge, UK ; New York: Cambridge University Press.

Hill, E. M., Tildesley, M. J., & House, T. (2017). Evidence for history-dependence of influenza pandemic emergence. *Scientific Reports*, *7*, 43623. doi:10.1038/srep43623

HMD. (2019). Human Mortality Database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). http://www.mortality.org/. Accessed 15 March 2019

Ho, J. Y. (2017). The Contribution of Drug Overdose to Educational Gradients in Life Expectancy in the United States, 1992–2011. *Demography*, 54(3), 1175–1202. https://doi.org/10.1007/s13524-017-0565-3

Ho, J. Y. (2019). The Contemporary American Drug Overdose Epidemic in International Perspective. *Population and Development Review*, 45(1), 7–40. https://doi.org/10.1111/padr.12228

Ho, J. Y., & Hendi, A. S. (2018). Recent trends in life expectancy across high income countries: retrospective observational study. *BMJ*, 362, k2562. https://doi.org/10.1136/bmj.k2562

Hobcraft, J., Menken, J., & Preston, S. (1982). Age, Period, and Cohort Effects in Demography: A Review. *Population Index*, 48(1), 4–43. https://doi.org/10.2307/2736356

Holford, T. R. (1983). The Estimation of Age, Period and Cohort Effects for Vital Rates. *Biometrics*, 39(2), 311–324. https://doi.org/10.2307/2531004

Holford, T. R. (1991). Understanding the effects of age, period, and cohort on incidence and mortality rates. *Annual Review of Public Health*, *12*, 425–457. doi:10.1146/annurev.pu.12.050191.002233

Holford, T. R. (1991). Understanding the effects of age, period, and cohort on incidence and mortality rates. *Annual Review of Public Health*, *12*, 425–457. doi:10.1146/annurev.pu.12.050191.002233

Holford, T. R. (2005). Age-Period-Cohort Analysis. In *Encyclopedia of Biostatistics*. Wiley. https://onlinelibrary.wiley.com/doi/book/10.1002/0470011815

Holford, T. R. (2006). Approaches to fitting age-period-cohort models with unequal intervals. *Statistics in Medicine*, 25(6), 977–993. https://doi.org/10.1002/sim.2253

Horiuchi, S., & Wilmoth, J. R. (1998). Deceleration in the Age Pattern of Mortality at Older Ages. *Demography*, 35(4), 391–412. https://doi.org/10.2307/3004009

Huang, X., Keyes, K. M., & Li, G. (2017). Increasing Prescription Opioid and Heroin Overdose Mortality in the United States, 1999–2014: An Age–Period–Cohort Analysis. *American Journal of Public Health*, 108(1), 131–136. https://doi.org/10.2105/AJPH.2017.304142

Humes, E. (2006). How the GI Bill Shunted Blacks into Vocational Training. *The Journal of Blacks in Higher Education*, (53), 92–104.

Hwang, C. S., Chang, H.-Y., & Alexander, G. C. (2015). Impact of abuse-deterrent OxyContin on prescription opioid utilization. *Pharmacoepidemiology and Drug Safety*, 24(2), 197–204. https://doi.org/10.1002/pds.3723

Ingram, D. D., Parker, J. D., Schenker, N., Weed, J. A., Hamilton, B., Arias, E., & Madans, J. H. (2003). United States Census 2000 Population With Bridged Race Categories (*Data Evaluation and Methods Research* No. 2(135)). National Center for Health Statistics. https://www.cdc.gov/nchs/data/series/sr_02/sr02_135.pdf

Jacobs, J. H., Archer, B. N., Baker, M. G., Cowling, B. J., Heffernan, R. T., Mercer, G., et al. (2012). Searching for Sharp Drops in the Incidence of Pandemic A/H1N1 Influenza by Single Year of Age. *PLoS ONE*, *7*(8), e42328. doi:10.1371/journal.pone.0042328

Jaffe, J. A., & Kimmel, P. L. (2006). Chronic Nephropathies of Cocaine and Heroin Abuse: A Critical Review. *Clinical Journal of the American Society of Nephrology*, 1(4), 655–667. https://doi.org/10.2215/CJN.00300106

Jalal, H., Buchanich, J. M., Roberts, M. S., Balmert, L. C., Zhang, K., & Burke, D. S. (2018). Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science*, 361(6408), eaau1184. https://doi.org/10.1126/science.aau1184

Jarry, V., Gagnon, A., & Bourbeau, R. (2013). Survival advantage of siblings and spouses of centenarians in 20th-century Quebec. *Canadian Studies in Population*, 39(3–4), 67–78.

Jasilionis, D. (2018). Reversals in life expectancy in high income countries? *BMJ*, *362*. https://doi.org/10.1136/bmj.k3399

Johnson, R. A., & Gerstein, D. R. (2000). Age, period, and cohort effects in marijuana and alcohol incidence: United States females and males, 1961-1990. *Substance Use & Misuse*, 35(6–8), 925–948.

Johnston, L. (1991). Toward a theory of drug epidemics. In *Communication. Persuasive communication and drug abuse prevention* (pp. 93–131).

Jones, M. R., Viswanath, O., Peck, J., Kaye, A. D., Gill, J. S., & Simopoulos, T. T. (2018). A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. *Pain and Therapy*, 7(1), 13–21. https://doi.org/10.1007/s40122-018-0097-6

Kannisto, V. (1994). *Development of Oldest-Old Mortality, 1950-1990: Evidence from 28 Developed Countries* (1st ed.). Odense: University Press of Southern Denmark.

Kannisto, V., Christensen, K., & Vaupel, J. W. (1997). No increased mortality in later life for cohorts born during famine. *American Journal of Epidemiology*, 145(11), 987–994.

Karamessini, M., & Rubery, J. (2013). *Women and Austerity: The Economic Crisis and the Future for Gender Equality*. Routledge.

Keenan, K., Saburova, L., Bobrova, N., Elbourne, D., Ashwin, S., and Leon, D.A. (2015). Social Factors Influencing Russian Male Alcohol Use over the Life Course: A Qualitative Study Investigating Age Based Social Norms, Masculinity, and Workplace Context. *PLoS ONE* 10(11). doi:10.1371/journal.pone.0142993

Keiding, N. (2011). Age–period–cohort analysis in the 1870s: Diagrams, stereograms, and the basic differential equation. *Canadian Journal of Statistics*, 39(3), 405–420. https://doi.org/10.1002/cjs.10121

Kelly, E. (2009). The scourge of Asian Flu: In utero exposure to pandemic influenza and the development of a cohort of British children. *IFS Working Papers*, *09*(17).

Kelly, E. (2011). The Scourge of Asian Flu: In utero Exposure to Pandemic Influenza and the Development of a Cohort of British Children. *The Journal of Human Resources*, 46(4), 669–694.

Kermack, W. O., McKendrick, A. G., & Mckinlay, P. L. (1934). Death-Rates in Great Britain and Sweden some General Regularities and their Significance. *The Lancet*, 223(5770), 698–703. https://doi.org/10.1016/S0140-6736(00)92530-3

Keyes, K.M. and Li, G. (2010). A Multiphase Method for Estimating Cohort Effects in Age-Period Contingency Table Data. *Annals of Epidemiology* 20(10):779–785. doi:10.1016/j.annepidem.2010.03.006.

Keyes, K. M., Schulenberg, J. E., O'Malley, P. M., Johnston, L. D., Bachman, J. G., Li, G., & Hasin, D. (2011). The social norms of birth cohorts and adolescent marijuana use in the United States, 1976-2007. *Addiction* (Abingdon, England), 106(10), 1790–1800. https://doi.org/10.1111/j.1360-0443.2011.03485.x

Keyes, K. M., Utz, R. L., Robinson, W., & Li, G. (2010). What is a cohort effect? Comparison of three statistical methods for modeling cohort effects in obesity prevalence in the United

States, 1971–2006. *Social science & medicine (1982)*, *70*(7), 1100–1108. doi:10.1016/j.socscimed.2009.12.018

Kilbourne, E. D. (2006). Influenza Pandemics of the 20th Century. *Emerging Infectious Diseases*, *12*(1), 9–14. doi:10.3201/eid1201.051254

King, D. E., Matheson, E., Chirina, S., Shankar, A., & Broman-Fulks, J. (2013). The status of baby boomers' health in the United States: the healthiest generation? *JAMA internal medicine*, 173(5), 385–386. https://doi.org/10.1001/jamainternmed.2013.2006

King, N. B., Fraser, V., Boikos, C., Richardson, R., & Harper, S. (2014). Determinants of Increased Opioid-Related Mortality in the United States and Canada, 1990–2013: A Systematic Review. *American Journal of Public Health*, 104(8), e32–e42. https://doi.org/10.2105/AJPH.2014.301966

Klebba, A. J., & Dolman, A. B. (1975). *Comparability of mortality statistics for the seventh and eighth revisions of the International classification of diseases, United States*. Hyattsville: National Center for Health Statistics (U.S.).

Klebba, A. J., & Scott, J. (1980). Estimates of Selected Comparability Ratios Based on Dual Coding of 1976 Death Certificates by the Eighth and Ninth Revisions of the International Classification of Diseases. *Monthly Vital Statistics Report*, *28*(11), 1–19.

Kobasa, D., Jones, S. M., Shinya, K., Kash, J. C., Copps, J., Ebihara, H., et al. (2007). Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature*, *445*(7125), 319–323. doi:10.1038/nature05495

Koopman, J. J. E., Wensink, M. J., Rozing, M. P., van Bodegom, D., & Westendorp, R. G. J. (2015). Intrinsic and extrinsic mortality reunited. *Experimental Gerontology*, 67, 48–53. https://doi.org/10.1016/j.exger.2015.04.013

Kuh, D., Ben-Shlomo, Y., Lynch, J., Hallqvist, J., & Power, C. (2003). Life course epidemiology. *Journal of Epidemiology & Community Health*, 57(10), 778–783. https://doi.org/10.1136/jech.57.10.778

Kuh, Diana, & Ben-Shlomo, Y. (1997). *A Life Course Approach to Chronic Disease Epidemiology*. Oxford University Press. https://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780198578154.001.0001/acprof-9780198578154. Accessed 18 September 2019

Kushi, S., & McManus, I. P. (2018). Gender, crisis and the welfare state: Female labor market outcomes across OECD countries. *Comparative European Politics*, 16(3), 434–463. https://doi.org/10.1057/cep.2016.21

Laine, C., Hauck, W. W., Gourevitch, M. N., Rothman, J., Cohen, A., & Turner, B. J. (2001). Regular Outpatient Medical and Drug Abuse Care and Subsequent Hospitalization of Persons Who Use Illicit Drugs. *JAMA*, 285(18), 2355–2362. https://doi.org/10.1001/jama.285.18.2355

Land, K. C., Fu, Q., Guo, X., Jeon, S. Y., Reither, E. N., & Zang, E. (2016). Playing With the Rules and Making Misleading Statements: A Response to Luo, Hodges, Winship, and Powers. *American Journal of Sociology*, *122*(3), 962–973. doi:10.1086/689853

Lemaitre, M., Carrat, F., Rey, G., Miller, M., Simonsen, L., & Viboud, C. (2012). Mortality Burden of the 2009 A/H1N1 Influenza Pandemic in France: Comparison to Seasonal Influenza and the A/H3N2 Pandemic. *PLoS ONE*, *7*(9). doi:10.1371/journal.pone.0045051

Lemieux, T. (1993). Unions and Wage Inequality in Canada and the United States. Small Differences That Matter: Labor Markets and Income Maintenance in Canada and the United States, 69–108.

Leveille, S. G., Wee, C. C., & Iezzoni, L. I. (2005). Trends in obesity and arthritis among baby boomers and their predecessors, 1971-2002. *American Journal of Public Health*, 95(9), 1607–1613. https://doi.org/10.2105/AJPH.2004.060418

Levine, M. (2017). In older adults with COPD, new opioid use was linked to increased risk for respiratory and all-cause mortality. *Annals of Internal Medicine*, 166(2), JC11. https://doi.org/10.7326/ACPJC-2017-166-2-011

Lin, M.-J., & Liu, E. M. (2014). Does in utero exposure to Illness matter? The 1918 influenza epidemic in Taiwan as a natural experiment. *Journal of Health Economics*, 37, 152–163. https://doi.org/10.1016/j.jhealeco.2014.05.004

Lindeboom, M., Portrait, F., & van den Berg, G. J. (2010). Long-run effects on longevity of a nutritional shock early in life: The Dutch Potato famine of 1846–1847. *Journal of Health Economics*, 29(5), 617–629. https://doi.org/10.1016/j.jhealeco.2010.06.001

Lipset, S. M. (2013). Continental Divide : The Values and Institutions of the United States and Canada. Routledge. https://doi.org/10.4324/9781315021201

Loo, Y.-M., & Gale, M. (2007). Influenza: fatal immunity and the 1918 virus. *Nature*, *445*(7125), 267–268. doi:10.1038/445267a

Lowcock, E. C., Rosella, L. C., Foisy, J., McGeer, A., & Crowcroft, N. (2012). The Social Determinants of Health and Pandemic H1N1 2009 Influenza Severity. *American Journal of Public Health*, 102(8), e51–e58. https://doi.org/10.2105/AJPH.2012.300814

Luders-Manuel, S. (2017, September 18). The Inequality Hidden Within the Race-Neutral G.I. Bill. *JSTOR Daily*. https://daily.jstor.org/the-inequality-hidden-within-the-race-neutral-g-i-bill/. Accessed 3 September 2019

Luo, L. (2013). Assessing Validity and Application Scope of the Intrinsic Estimator Approach to the Age-Period-Cohort Problem. *Demography*, *50*(6), 1945–1967. doi:10.1007/s13524-013-0243-z

Luo, L., Hodges, J., Winship, C., & Powers, D. (2016). The Sensitivity of the Intrinsic Estimator to Coding Schemes: Comment on Yang, Schulhofer-Wohl, Fu, and Land. *American Journal of Sociology*, *122*(3), 930–961. doi:10.1086/689830

Lutz, W. (2013). Demographic Metabolism: A Predictive Theory of Socioeconomic Change. *Population and Development Review*, 38, 283–301. https://doi.org/10.1111/j.1728-4457.2013.00564.x

Luy, M., Di Giulio, P., Di Lego, V., Lazarevič, P., & Sauerberg, M. (2019). Life Expectancy: Frequently Used, but Hardly Understood. *Gerontology*, 1–10. https://doi.org/10.1159/000500955

Lynch, S. M., Brown, J. S., & Harmsen, K. G. (2003). Black-White Differences in Mortality Compression and Deceleration and the Mortality Crossover Reconsidered. *Research on Aging*, 25(5), 456–483. https://doi.org/10.1177/0164027503254675

Ma, J., Dushoff, J., & Earn, D. J. D. (2011). Age-specific mortality risk from pandemic influenza. *Journal of theoretical biology*, *288*, 29–34. doi:10.1016/j.jtbi.2011.08.003

MacMinn, R., & Weber, F. (2009, February). Select Birth Cohorts. Discussion Paper, Munich School of Management University of Munich. https://epub.ub.uni-muenchen.de/9207/. Accessed 21 June 2018

Makeham, W. M. (1860). On the Law of Mortality and the Construction of Annuity Tables. *The Assurance Magazine, and Journal of the Institute of Actuaries*, 8(6), 301–310.

Manchikanti, L., Kaye, A. M., Knezevic, N. N., McAnally, H., Slavin, K., Trescot, A. M., et al. (2017). Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*, 20(2S), S3–S92.

Mannheim, K. (1952). The problem of Generations. In *Essays on the Sociology of Knowledge* (Vol. 5, pp. 276–322). New York: Routledge.

Manthey, J., Shield, K. D., Rylett, M., Hasan, O. S. M., Probst, C., & Rehm, J. (2019). Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. *The Lancet*, 393(10190), 2493–2502. https://doi.org/10.1016/S0140-6736(18)32744-2

Manton, K. G., & Stallard, E. (1981). Methods for Evaluating the Heterogeneity of Aging Processes in Human Populations Using Vital Statistics Data: Explaining the Black/White Mortality Crossover by a Model of Mortality Selection. *Human Biology*, 53(1), 47–67.

Martin, L. G., Freedman, V. A., Schoeni, R. F., & Andreski, P. M. (2009). Health and Functioning Among Baby Boomers Approaching 60. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, 64B(3), 369–377. https://doi.org/10.1093/geronb/gbn040

Mason, K. O., Mason, W. M., Winsborough, H. H., & Poole, W. K. (1973). Some Methodological Issues in Cohort Analysis of Archival Data. *American Sociological Review*, 38(2), 242–258. https://doi.org/10.2307/2094398

Mason, W. M., & Fienberg, S. (Eds.). (1985). *Cohort Analysis in Social Research: Beyond the Identification Problem*. New York: Springer-Verlag. https://www.springer.com/de/book/9781461385387. Accessed 23 July 2018

Massey, D. S., & Denton, N. A. (1993). *American Apartheid: Segregation and the Making of the Underclass*. Harvard University Press.

Masters, R. K. (2012). Uncrossing the U.S. Black-White Mortality Crossover: The Role of Cohort Forces in Life Course Mortality Risk. *Demography*, 49(3), 773–796. https://doi.org/10.1007/s13524-012-0107-y

Masters, R. K., Hummer, R. A., Powers, D. A., Beck, A., Lin, S.-F., & Finch, B. K. (2014). Long-Term Trends in Adult Mortality for U.S. Blacks and Whites: An Examination of Period- and Cohort-Based Changes. *Demography*, *51*(6), 2047–2073. doi:10.1007/s13524-014-0343-4

Masters, R. K., Powers, D. A., Hummer, R. A., Beck, A., Lin, S.-F., & Finch, B. K. (2016). Fitting Age-Period-Cohort Models Using the Intrinsic Estimator: Assumptions and Misapplications. *Demography*, *53*(4), 1253–1259. doi:10.1007/s13524-016-0481-y

Masters, R. K., Tilstra, A. M., & Simon, D. H. (2018). Explaining recent mortality trends among younger and middle-aged White Americans. *International Journal of Epidemiology*, *47*(1), 81–88. doi:10.1093/ije/dyx127

Mayer, K. U. (2009). New Directions in Life Course Research. *Annual Review of Sociology*, 35(1), 413–433. https://doi.org/10.1146/annurev.soc.34.040507.134619

Mazumder, B., Almond, D., Park, K., Crimmins, E. M., & Finch, C. E. (2010). Lingering prenatal effects of the 1918 influenza pandemic on cardiovascular disease. *Journal of Developmental Origins of Health and Disease*, *1*(01), 26–34. doi:10.1017/S2040174409990031

McBride, D. C. (1990). Generational Differences in HIV Risk and AIDS. *American Behavioral Scientist*, 33(4), 491–502. https://doi.org/10.1177/0002764290033004009

McElhaney, J. E., Xie, D., Hager, W. D., Barry, M. B., Wang, Y., Kleppinger, A., et al. (2006). T Cell Responses Are Better Correlates of Vaccine Protection in the Elderly. *The Journal of Immunology*, 176(10), 6333–6339. https://doi.org/10.4049/jimmunol.176.10.6333

Meadows, M. (2004). A look at the 2003-2004 flu season. *FDA consumer*, *38*(2), 9–11.

Meslé, F., & Vallin, J. (2012). Transition sanitaire : tendances et perspectives. *médecine/sciences*, *16*(11), 1161. doi:10.4267/10608/1549

Miech, R., Bohnert, A., Heard, K., & Boardman, J. (2013). Increasing Use of Nonmedical Analgesics Among Younger Cohorts in the United States: A Birth Cohort Effect. *Journal of Adolescent Health*, 52(1), 35–41. https://doi.org/10.1016/j.jadohealth.2012.07.016

Miech, R., Koester, S., & Dorsey-Holliman, B. (2011). Increasing US mortality due to accidental poisoning: the role of the baby boom cohort. *Addiction* (Abingdon, England), 106(4), 806–815. https://doi.org/10.1111/j.1360-0443.2010.03332.x

Miller, M. S., Gardner, T. J., Krammer, F., Aguado, L. C., Tortorella, D., Basler, C. F., & Palese, P. (2013). Neutralizing Antibodies Against Previously Encountered Influenza Virus Strains Increase over Time: A Longitudinal Analysis. *Science Translational Medicine*, *5*(198), 198ra107-198ra107. doi:10.1126/scitranslmed.3006637

Montez, J. K., & Friedman, E. M. (2015). Educational attainment and adult health: Under what conditions is the association causal? *Social Science & Medicine*, 127, 1–7. https://doi.org/10.1016/j.socscimed.2014.12.029

Montez, J. K., & Hayward, M. D. (2011). Early Life Conditions and Later Life Mortality. In R. G. Rogers & E. M. Crimmins (Eds.), International Handbook of Adult Mortality (pp. 187–206). Springer Netherlands. http://link.springer.com/chapter/10.1007/978-90-481-9996-9_9. Accessed 6 January 2014

Montez, J. K., Hummer, R. A., & Hayward, M. D. (2012). Educational Attainment and Adult Mortality in the United States: A Systematic Analysis of Functional Form. *Demography*, 49(1), 315–336. https://doi.org/10.1007/s13524-011-0082-8

Mu, R., & Zhang, X. (2011). Why does the Great Chinese Famine affect the male and female survivors differently? Mortality selection versus son preference. *Economics & Human Biology*, 9(1), 92–105. https://doi.org/10.1016/j.ehb.2010.07.003

Munzner, T. (2014). *Visualization Analysis and Design*. 1 edition. Boca Raton: A K Peters/CRC Press.

Murphy, E. L., Collier, A. C., Kalish, L. A., Assmann, S. F., Para, M. F., Flanigan, T. P., et al. (2001). Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. *Annals of Internal Medicine*, 135(1), 17–26.

Murphy, M. (2009). The 'Golden Generations' in Historical Context. British Actuarial Journal, 15(S1), 151–184. https://doi.org/10.1017/S1357321700005559

Murphy, M. (2010). Reexamining the Dominance of Birth Cohort Effects on Mortality. Population and Development Review, 36(2), 365–390. https://doi.org/10.1111/j.1728-4457.2010.00334.x

Myles, J. (1998). How to Design a "Liberal" Welfare State: A Comparison of Canada and the United States. *Social Policy & Administration*, 32(4), 341–364. https://doi.org/10.1111/1467-9515.00120

Myrskylä, M. (2010a). The effects of shocks in early life mortality on later life expectancy and mortality compression: A cohort analysis. *Demographic Research*, 22(12), 289–320. https://doi.org/10.4054/DemRes.2010.22.12

Myrskylä, M. (2010b). The Relative Effects of Shocks in Early- and Later-Life Conditions on Mortality. *Population and Development Review*, 36(4), 803–829.

Myrskylä, M., Mehta, N. K., & Chang, V. W. (2013). Early Life Exposure to the 1918 Influenza Pandemic and Old-Age Mortality by Cause of Death. *American Journal of Public Health*, 103(7), e83–e90. https://doi.org/10.2105/AJPH.2012.301060

Nagata, J. M., Hernández-Ramos, I., Kurup, A. S., Albrecht, D., Vivas-Torrealba, C., & Franco-Paredes, C. (2013). Social determinants of health and seasonal influenza vaccination in adults ≥65 years: a systematic review of qualitative and quantitative data. *BMC Public Health*, 13(1), 388. https://doi.org/10.1186/1471-2458-13-388

Nam, C. B. (1995). Another look at mortality crossovers. Social Biology, 42(1–2), 133–142.

NBER, D. I. D. (2019). *Mortality Data*. http://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html. Accessed 14 January 2014

NCHS. (2018). *Data Access - Vital Statistics Online*. http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm. Accessed 5 December 2018

Nelson, M. I., & Holmes, E. C. (2007). The evolution of epidemic influenza. *Nature Reviews Genetics*, *8*(3), 196–205. doi:10.1038/nrg2053

Nguyen, A. M., & Noymer, A. (2013). Influenza Mortality in the United States, 2009 Pandemic: Burden, Timing and Age Distribution. *PLoS ONE*, *8*(5), e64198. doi:10.1371/journal.pone.0064198

Noymer, A., & Nguyen, A. M. (2013). Influenza as a Proportion of Pneumonia Mortality: United States, 1959–2009. *Biodemography and Social Biology*, *59*(2), 178–190. doi:10.1080/19485565.2013.833816

Noymer, A., Penner, A. M., & Saperstein, A. (2011). Cause of Death Affects Racial Classification on Death Certificates. PLOS ONE, 6(1), e15812. https://doi.org/10.1371/journal.pone.0015812

NVSS. (2019). *Bridged-Race Population Estimates - Data Files and Documentation*. Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/nvss/bridged_race/data_documentation.htm

NVSS (2019a). *Bridged-Race Population Estimates - Data Files and Documentation* [electronic resource]. https://www.cdc.gov/nchs/nvss/bridged_race/data_documentation.htm.

NVSS (2019b). *Vital Statistics Online Data Portal* [electronic resource]. https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm.

O'Brien, R. M. (2013). Comment of Liying Luo's Article, "Assessing Validity and Application Scope of the Intrinsic Estimator Approach to the Age-Period-Cohort Problem." *Demography*, *50*(6), 1973–1975. doi:10.1007/s13524-013-0250-0

O'Brien, R. M. (2014a). *Age-Period-Cohort Models: Approaches and Analyses with Aggregate Data* (1 edition.). Boca Raton: Taylor & Francis Inc.

O'Brien, R. M. (2014b). Estimable functions in age-period-cohort models: a unified approach. *Quality & Quantity,* 48(1), 457–474. https://doi.org/10.1007/s11135-012-9780-6

O'Brien, R. M., & Stockard, J. (2002). Variations in Age-Specific Homicide Death Rates: A Cohort Explanation for Changes in the Age Distribution of Homicide Deaths. *Social Science Research*, 31(1), 124–150. https://doi.org/10.1006/ssre.2001.0723

Oeppen, J., & Wilson, C. (2006). Epidemiological evidence for viral exposure in childhood as a risk-factor in subsequent influenza pandemics. Presented at the Population Association of America, Los Angeles, U.S.

Olshansky, S. J., & Ault, A. B. (1986). The Fourth Stage of the Epidemiologic Transition: The Age of Delayed Degenerative Diseases. *The Milbank Quarterly*, 64(3), 355–391. https://doi.org/10.2307/3350025

Olson, S., & Thornton, P. (2011). *Peopling the North American City: Montreal, 1840-1900*. Montreal ; Ithica: McGill-Queen's University Press.

Omran, A. R. (1971). The Epidemiologic Transition: A Theory of the Epidemiology of Population Change. *The Milbank Memorial Fund Quarterly*, 49(4), 509–538. https://doi.org/10.2307/3349375

Omran, A. R. (1983). The Epidemiologic Transition Theory. A Preliminary Update. *Journal of Tropical Pediatrics*, 29(6), 305–316. https://doi.org/10.1093/tropej/29.6.305

Ooms, J., & McNamara, J. (2018). *writexl: Export Data Frames to Excel "xlsx" Format*. https://CRAN.R-project.org/package=writexl. Accessed 23 August 2019

Ouellette, N. (2011). *Changements dans la répartition des décès selon l'âge : une approche non paramétrique pour l'étude de la mortalité adulte*. Université de Montréal, Montréal, canada.

Ouellette, N., Barbieri, M., & Wilmoth, J. R. (2014). Period-Based Mortality Change: Turning Points in Trends since 1950. *Population and Development Review*, 40(1), 77–106. https://doi.org/10.1111/j.1728-4457.2014.00651.x

Painter, R. C., Roseboom, T. J., Bossuyt, P. M. M., Osmond, C., Barker, D. J. P., & Bleker, O. P. (2005). Adult Mortality at Age 57 After Prenatal Exposure to the Dutch Famine. *European Journal of Epidemiology*, 20(8), 673–676. https://doi.org/10.1007/s10654-005-7921-0

Palamar, J. J., & Ompad, D. C. (2014). Demographic and socioeconomic correlates of powder cocaine and crack use among high school seniors in the United States. *The American Journal of Drug and Alcohol Abuse*, 40(1), 37–43. https://doi.org/10.3109/00952990.2013.838961

Palamar, J. J., Davies, S., Ompad, D. C., Cleland, C. M., & Weitzman, M. (2015). Powder Cocaine and Crack Use in the United States: An Examination of Risk for Arrest and Socioeconomic Disparities in Use. *Drug and alcohol dependence*, 149, 108–116. https://doi.org/10.1016/j.drugalcdep.2015.01.029

Palella, F. J. J., Baker, R. K., Moorman, A. C., Chmiel, J. S., Wood, K. C., Brooks, J. T., et al. (2006). Mortality in the Highly Active Antiretroviral Therapy Era: Changing Causes of Death and Disease in the HIV Outpatient Study. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 43(1), 27. https://doi.org/10.1097/01.qai.0000233310.90484.16

Palloni, A., Milesi, C., White, R. G., & Turner, A. (2009). Early childhood health, reproduction of economic inequalities and the persistence of health and mortality differentials. Social Science & Medicine, 68(9), 1574–1582. https://doi.org/10.1016/j.socscimed.2009.02.009

Palmer, B. (2008). *Canada's 1960s: The Ironies of Identity in a Rebellious Era* (First Edition edition.). Toronto ; Buffalo: University of Toronto Press, Scholarly Publishing Division.

Pampel, F. C. (2001). Gender equality and the sex differential in mortality from accidents in high income nations. *Population Research and Policy Review*, 20(5), 397–421. https://doi.org/10.1023/A:1013307620643

Patterson, K. D. (1986). *Pandemic Influenza, 1700-1900: A Study in Historical Epidemiology*. Rowan & Littlefield.

Patterson, T. L., & Jeste, D. V. (1999). The potential impact of the baby-boom generation on substance abuse among elderly persons. *Psychiatric Services* (Washington, D.C.), 50(9), 1184–1188. https://doi.org/10.1176/ps.50.9.1184

Paulozzi, L. J., Budnitz, D. S., & Xi, Y. (2006). Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*, 15(9), 618–627. https://doi.org/10.1002/pds.1276

Paun, C. (2019, June 6). Warnings over opioid use spook EU countries into action. *Politico*. https://www.politico.eu/article/warning-signs-over-opioid-use-spook-eu-countries-into-action/. Accessed 2 July 2019

Peiris, J. S. M., de Jong, M. D., & Guan, Y. (2007). Avian Influenza Virus (H5N1): a Threat to Human Health. *Clinical Microbiology Reviews*, 20(2), 243–267. https://doi.org/10.1128/CMR.00037-06

Pelzer, B., te Grotenhuis, M., Eisinga, R., & Schmidt-Catran, A. W. (2015). The Non-uniqueness Property of the Intrinsic Estimator in APC Models. *Demography*, *52*(1), 315–327. doi:10.1007/s13524-014-0360-3

PHAC. (2019). Reported cases from 1991 to 2016 in Canada - Notifiable diseases on-line. Public Health Agency of Canada. https://diseases.canada.ca/notifiable/charts?c=yl. Accessed 20 August 2019

Phillips, J. A. (2014). A changing epidemiology of suicide? The influence of birth cohorts on suicide rates in the United States. Social Science & Medicine, 114(Supplement C), 151–160. https://doi.org/10.1016/j.socscimed.2014.05.038

Pison, G., Couvert, N., & Wasserman, M. R. (2004). The Frequency of Twin Births in France. *Population*, *Vol. 59*(6), 765–794.

Plans-Rubió, P. (2007). Prevention and control of influenza in persons with chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease*, *2*(1), 41–53.

Preston, S. H., & Haines, M. R. (1991). Fatal Years: Child Mortality in Late Nineteenth-Century America. https://papers.nber.org/books/pres91-1. Accessed 20 October 2018

Preston, S. H., & Wang, H. (2006). Sex mortality differences in the United States: the role of cohort smoking patterns. *Demography*, 43(4), 631–646. https://doi.org/10.1353/dem.2006.0037

Preston, S. H., Elo, I. T., Rosenwaike, I., & Hill, M. (1996). African-American Mortality at Older Ages: Results of a Matching Study. *Demography*, 33(2), 193–209. https://doi.org/10.2307/2061872

Preston, S. H., Hill, M. E., & Drevenstedt, G. L. (1998). Childhood conditions that predict survival to advanced ages among African–Americans. *Social Science & Medicine*, 47(9), 1231–1246. https://doi.org/10.1016/S0277-9536(98)00180-4

Preston, S. H., Heuveline, P., & Guillot, M. (2000). *Demography: Measuring and Modeling Population Processes* (1 edition.). Malden, MA: Wiley-Blackwell.

Pu, Z., Xiang, D., Li, X., Luo, T., Shen, X., Murphy, R. W., et al. (2018). Potential Pandemic of H7N9 Avian Influenza A Virus in Human. *Frontiers in Cellular and Infection Microbiology*, 8. https://doi.org/10.3389/fcimb.2018.00414

Puac-Polanco, V., Keyes, K. M., & Li, G. (2016). Mortality from motorcycle crashes: the baby-boomer cohort effect. *Injury Epidemiology*, 3, 19. https://doi.org/10.1186/s40621-016-0083-6

Pullum, T.W. (1980). Separating age, period, and cohort effects in white U.S. fertility, 1920–1970. *Social Science Research* 9(3):225–244. doi:10.1016/0049-089X(80)90013-7.

Quan, C., Shi, W., Yang, Y., Yang, Y., Liu, X., Xu, W., et al. (2018). New Threats from H7N9 Influenza Virus: Spread and Evolution of High- and Low-Pathogenicity Variants with High Genomic Diversity in Wave Five. *Journal of Virology*, 92(11), e00301-18. https://doi.org/10.1128/JVI.00301-18

Quinones, S., & Hellegers, N. (2016). Dreamland: The True Tale of America's Opiate Epidemic (Unabridged edition.). Audible Studios on Brilliance Audio.

R Core Team (2018). R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing [electronic resource]. http://www.R-project.org.

Raftery, A. E. (1995). Bayesian Model Selection in Social Research. *Sociological Methodology*, 25, 111–163. https://doi.org/10.2307/271063

Rajendran, M., Nachbagauer, R., Ermler, M. E., Bunduc, P., Amanat, F., Izikson, R., et al. (2017). Analysis of Anti-Influenza Virus Neuraminidase Antibodies in Children, Adults, and the Elderly by ELISA and Enzyme Inhibition: Evidence for Original Antigenic Sin. *mBio*, *8*(2), e02281-16. doi:10.1128/mBio.02281-16

Raleigh, V. S. (2019). Trends in life expectancy in EU and other OECD countries. https://doi.org/10.1787/223159ab-en

Rao, R., & Roche, A. (2017). Substance misuse in older people. *BMJ*, 358, j3885. https://doi.org/10.1136/bmj.j3885

Rao, T. (2019). Baby boomers are increasingly more likely to risk drink-driving than millennials. The Conversation. http://theconversation.com/baby-boomers-are-increasingly-more-likely-to-risk-drink-driving-than-millennials-113130. Accessed 7 September 2019

Rau, R., Bohk, C., Muszynska, M. M., & Vaupel, J. W. (2013). Rates of Mortality Improvement on the Lexis Surface: Visualizing Age-, Period-, and Cohort-Effects. Presented at the PAA 2013, Washington, D.C. http://paa2013.princeton.edu/papers/130485

Rau, R., Bohk-Ewald, C., Muszyńska, M. M., & Vaupel, J. W. (2018). *Visualizing Mortality Dynamics in the Lexis Diagram*. Springer International Publishing. https://www.springer.com/de/book/9783319648187. Accessed 7 May 2018

Redford, P. S., Mayer-Barber, K. D., McNab, F. W., Stavropoulos, E., Wack, A., Sher, A., & O'Garra, A. (2014). Influenza A Virus Impairs Control of Mycobacterium tuberculosis Coinfection Through a Type I Interferon Receptor–Dependent Pathway. *The Journal of Infectious Diseases*, 209(2), 270–274. https://doi.org/10.1093/infdis/jit424

Reed, T. V. (2019). *The Art of Protest: Culture and Activism from the Civil Rights Movement to the Present*. U of Minnesota Press.

Reichert, T. A., Simonsen, L., Sharma, A., Pardo, S. A., Fedson, D. S., & Miller, M. A. (2004). Influenza and the Winter Increase in Mortality in the United States, 1959–1999. *American Journal of Epidemiology*, *160*(5), 492–502. doi:10.1093/aje/kwh227

Reither, E. N., Masters, R. K., Yang, Y. C., Powers, D. A., Zheng, H., & Land, K. C. (2015). Should age-period-cohort studies return to the methodologies of the 1970s? *Social Science & Medicine* (1982), 128, 356–365. https://doi.org/10.1016/j.socscimed.2015.01.011

Remund, A., Camarda, C.G., and Riffe, T. (2017). *Analyzing the Young Adult Mortality Hump in R with MortHump*. Rostock: Max Planck Institute for Demographic Research (MPIDR Technical Report TR-2018-003).

Remund, A., Camarda, C. G., & Riffe, T. (2018). A Cause-of-Death Decomposition of Young Adult Excess Mortality. *Demography*, 55(3), 957–978. https://doi.org/10.1007/s13524-018-0680-9

Rhodes, T. (1997). Risk theory in epidemic times: sex, drugs and the social organisation of 'risk behaviour.' *Sociology of Health & Illness*, 19(2), 208–227. https://doi.org/10.1111/1467-9566.ep10934410

Richards, S.J., Kirkby, J.G., and Currie, I.D. (2006). The Importance of Year of Birth in Two-Dimensional Mortality Data. *British Actuarial Journal* 12(1):5–61. doi:10.1017/S1357321700004682.

Richards, S. J. (2008). Detecting Year-of-Birth Mortality Patterns with Limited Data. Journal of the Royal Statistical Society. *Series A (Statistics in Society)*, 171(1), 279–298.

Riffe, T. (2015). *Reading Human Fertility Database and Human Mortality Database Data into* R. Rostock: Max Planck Institute for Demographic Research (MPIDR Technical Report TR-2015-004).

Rodgers, W. L. (1982). Estimable Functions of Age, Period, and Cohort Effects. *American Sociological Review*, 47(6), 774–787. https://doi.org/10.2307/2095213

Rollins, J. (1986). Part of a Whole: The Interdependence of the Civil Rights Movement and Other Social Movements. Phylon (1960-), 47(1), 61–70. https://doi.org/10.2307/274695

Ross, N. A., Wolfson, M. C., Dunn, J. R., Berthelot, J.-M., Kaplan, G. A., & Lynch, J. W. (2000). Relation between income inequality and mortality in Canada and in the United States: cross sectional assessment using census data and vital statistics. *BMJ*, 320(7239), 898–902. https://doi.org/10.1136/bmj.320.7239.898

Rothman, K. J., & Greenland, S. (2005). Causation and causal inference in epidemiology. *American Journal of Public Health*, 95 Suppl 1, S144-150. https://doi.org/10.2105/AJPH.2004.059204

Rothstein, R. (2017). *The Color of Law: A Forgotten History of How Our Government Segregated America* (1 edition.). New York ; London: Liveright.

Roy, S., Ninkovic, J., Banerjee, S., Charboneau, R. G., Das, S., Dutta, R., et al. (2011). Opioid Drug Abuse and Modulation of Immune Function: Consequences in the Susceptibility to Opportunistic Infections. *Journal of Neuroimmune Pharmacology*, 6(4), 442. https://doi.org/10.1007/s11481-011-9292-5

Rubery, J. (Ed.). (2012). *Women and Recession* (1 edition.). London: Routledge.

Ryan, H., Girion, L., & Glover, S. (2016, December 18). OxyContin goes global — "We're only just getting started." Los Angeles Times. http://www.latimes.com/projects/la-me-oxycontin-part3/. Accessed 1 July 2019

Rycroft, R. S. (2013). *The Economics of Inequality, Poverty, and Discrimination in the 21st Century* [2 volumes]. ABC-CLIO.

Ryder, N. B. (1965). The Cohort as a Concept in the Study of Social Change. *American Sociological Review*, 30(6), 843–861. https://doi.org/10.2307/2090964

Sasson, I. (2016a). Trends in Life Expectancy and Lifespan Variation by Educational Attainment: United States, 1990–2010. *Demography*, 53(2), 269–293. https://doi.org/10.1007/s13524-015-0453-7

Sasson, I. (2016b). Diverging Trends in Cause-Specific Mortality and Life Years Lost by Educational Attainment: Evidence from United States Vital Statistics Data, 1990-2010. *PLOS ONE*, 11(10), e0163412. https://doi.org/10.1371/journal.pone.0163412

Sauer, T., Ebeling, M., & Rau, R. (2018). The Fateful Cohorts. *American Journal of Public Health*, 108(10), e1–e2. https://doi.org/10.2105/AJPH.2018.304671

Schöley, J., & Willekens, F. (2017). Visualizing compositional data on the Lexis surface. *Demographic Research*, 36(21), 627–658. https://doi.org/10.4054/DemRes.2017.36.21

Selvin, S. (2001). *Epidemiologic Analysis: A Case-Oriented Approach*. Oxford University Press.

Serfling, R. E. (1963). Methods for current statistical analysis of excess pneumonia-influenza deaths. *Public Health Reports*, *78*(6), 494–506.

Schulhofer-Wohl, S., & Yang, Y. (2006). *APC: Stata module for estimating age-period-cohort effects*. Boston College Department of Economics. https://ideas.repec.org/c/boc/bocode/s456754.html

Shah, H., Bilodeau, M., Burak, K. W., Cooper, C., Klein, M., Ramji, A., et al. (2018). The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver. *CMAJ*, 190(22), E677–E687. https://doi.org/10.1503/cmaj.170453

Shahpar, C., & Li, G. (1999). Homicide Mortality in the United States, 1935–1994: Age, Period, and Cohort Effects. *American Journal of Epidemiology*, *150*(11), 1213–1222. doi:10.1093/oxfordjournals.aje.a009948

Shan, X., Lai, S., Liao, H., Li, Z., Lan, Y., & Yang, W. (2019). The epidemic potential of avian influenza A (H7N9) virus in humans in mainland China: A two-stage risk analysis. *PLOS ONE*, 14(4), e0215857. https://doi.org/10.1371/journal.pone.0215857

Shanks, G. D., & Brundage, J. F. (2012). Pathogenic Responses among Young Adults during the 1918 Influenza Pandemic. *Emerging Infectious Diseases*, *18*(2), 201–207. doi:10.3201/eid1802.102042

Sharp, G., & Hall, M. (2014). Emerging Forms of Racial Inequality in Homeownership Exit, 1968–2009. Social Problems, 61(3), 427–447. https://doi.org/10.1525/sp.2014.12161

Sheth, A. N., Althoff, K. N., & Brooks, J. T. (2011). Influenza Susceptibility, Severity, and Shedding in HIV-Infected Adults: A Review of the Literature. *Clinical Infectious Diseases*, 52(2), 219–227. https://doi.org/10.1093/cid/ciq110

Shield, K. D., Parry, C., & Rehm, J. (2014). Chronic Diseases and Conditions Related to Alcohol Use. *Alcohol Research : Current Reviews*, 35(2), 155–171.

Shryock, H. S., Siegel, J. S., & Larmon, E. A. (1973). *The Methods and Materials of Demography*. U.S. Bureau of the Census.

Simonsen, L., Clarke, M. J., Schonberger, L. B., Arden, N. H., Cox, N. J., & Fukuda, K. (1998). Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *The Journal of Infectious Diseases*, *178*(1), 53–60.

Simonsen, L., Clarke, Williamson, Stroup, Arden, & Schonberger, L. B. (1997). The impact of influenza epidemics on mortality: introducing a severity index. *American Journal of Public Health*, *87*(12), 1944–1950.

Simonsen, L., Reichert, T. A., Viboud, C., Blackwelder, W. C., Taylor, R. J., & Miller, M. A. (2005). Impact of influenza vaccination on seasonal mortality in the US elderly population. *Archives of Internal Medicine*, *165*(3), 265–272. doi:10.1001/archinte.165.3.265

Simonsen, L., Taylor, R., Viboud, C., Dushoff, J., & Miller, M. (2006). US flu mortality estimates are based on solid science. *BMJ (Clinical research ed.)*, 332(7534), 177–178. https://doi.org/10.1136/bmj.332.7534.177-a

Simonsen, L., Viboud, C., Taylor, R. J., & Miller, M. A. (2011). The Epidemiology of Influenza and Its Control. In R. Rappuoli & G. D. Giudice (Eds.), *Influenza Vaccines for the Future* (pp. 27–54). Springer Basel. doi:10.1007/978-3-0346-0279-2_2

Small, C.-L., Shaler, C. R., McCormick, S., Jeyanathan, M., Damjanovic, D., Brown, E. G., et al. (2010). Influenza Infection Leads to Increased Susceptibility to Subsequent Bacterial Superinfection by Impairing NK Cell Responses in the Lung. *The Journal of Immunology*, 184(4), 2048–2056. https://doi.org/10.4049/jimmunol.0902772

Smith, D. J., Forrest, S., Ackley, D. H., & Perelson, A. S. (1999). Variable efficacy of repeated annual influenza vaccination. *Proceedings of the National Academy of Sciences*, *96*(24), 14001–14006. doi:10.1073/pnas.96.24.14001

Smith, G. D., & Kuh, D. (2001). Commentary: William Ogilvy Kermack and the childhood origins of adult health and disease. *International Journal of Epidemiology*, 30(4), 696–703. https://doi.org/10.1093/ije/30.4.696

Staff, & agencies. (2019, June 26). Synthetic opioid use booms worldwide amid Africa "crisis", UN says. The Guardian. https://www.theguardian.com/politics/2019/jun/26/synthetic-opioid-use-booms-worldwide-amid-africa-crisis-un-says. Accessed 1 July 2019

StataCorp. (2017). *Stata Statistical Software: Release 15*. TX: StataCorp LLC. https://www.stata.com/

Statistics Canada. (2017, August 29). *CANSIM - Canadian socioeconomic database from Statistics Canada*. http://www5.statcan.gc.ca/cansim/home-accueil?lang=eng. Accessed 17 October 2017

Statistics Canada. (2018, November 8). *Vital Statistics - Death Database (CVSD)*. http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3233. Accessed 5 February 2019

Steger, M. A. E., Pierce, J. C., Steel, B. S., & Lovrich, N. P. (1989). Political culture, postmaterial values, and the new environmental paradigm: A comparative analysis of Canada and the United States. *Political Behavior*, 11(3), 233–254. https://doi.org/10.1007/BF00992298

Steil, J. P., Albright, L., Rugh, J. S., & Massey, D. S. (2018). The Social Structure of Mortgage Discrimination. *Housing studies*, 33(5), 759–776. https://doi.org/10.1080/02673037.2017.1390076

Stewart, A. J., & Torges, C. M. (2014). Social, Historical, and Developmental Influences on the Psychology of the Baby Boom at Midlife. In *The Baby Boomers Grow Up: Contemporary Perspectives on Midlife* (pp. 23–43). New York: Psychology Press.

Stewart, A. J., Settles, I. H., & Winter, N. J. G. (1998). Women and the Social Movements of the 1960s: Activists, Engaged Observers, and Nonparticipants. *Political Psychology*, 19(1), 63–94. https://doi.org/10.1111/0162-895X.00093

Strader, D. B. (2005). Coinfection with HIV and Hepatitis C Virus in Injection Drug Users and Minority Populations. *Clinical Infectious Diseases*, 41(Supplement_1), S7–S13. https://doi.org/10.1086/429489

Sue, K. (2017). The science behind "man flu." *BMJ*, *359*, j5560. doi:10.1136/bmj.j5560

Szreter, S. (1988). The Importance of Social Intervention in Britain's Mortality Decline c.1850–1914: a Re-interpretation of the Role of Public Health. *Social History of Medicine*, 1(1), 1–38. https://doi.org/10.1093/shm/1.1.1

Szreter, S. (2004). Author response: Debating mortality trends in 19th century Britain. *International Journal of Epidemiology*, 33(4), 705–709. https://doi.org/10.1093/ije/dyh143

Tango, T., & Kurashina, S. (1987). Age, period and cohort analysis of trends in mortality from major diseases in Japan, 1955 to 1979: Peculiarity of the cohort born in the early Showa Era. *Statistics in Medicine*, 6(6), 709–726. https://doi.org/10.1002/sim.4780060608

Tapper, E. B., & Parikh, N. D. (2018). Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. *BMJ*, k2817. https://doi.org/10.1136/bmj.k2817

Tarone, R., & Chu, K. C. (1996). Evaluation of birth cohort patterns in population disease rates. - PubMed - NCBI. *American Journal of Epidemiology*, *143*(1), 85–91.

Taubenberger, J. K., & Morens, D. M. (2006). 1918 Influenza: the Mother of All Pandemics. *Emerging Infectious Diseases*, *12*(1), 15–22. doi:10.3201/eid1209.050979

te Grotenhuis, M., Pelzer, B., Luo, L., & Schmidt-Catran, A. W. (2016). The Intrinsic Estimator, Alternative Estimates, and Predictions of Mortality Trends: A Comment on Masters, Hummer, Powers, Beck, Lin, and Finch. *Demography*, *53*(4), 1245–1252. doi:10.1007/s13524-016-0476-8

Termote, M. (1998). L'indice synthetique de mortalite. Un indicateur meconnu. In Morbidité, Mortalité : problèmes de mesure, facteurs d'évolution, essai de prospective (pp. 183–190). Presented at the Colloque international de Sinaia - AIDELF, Sinaia: Association Internationale des Demographes de Langue Francaise. https://www.ncbi.nlm.nih.gov/nlmcatalog/101079058. Accessed 17 October 2017

Thompson, W. W., & Shay, D. (2010). Estimates of Deaths Associated with Seasonal Influenza --- United States, 1976--2007. *Morbidity and Mortality Weekly Report*, *59*(33), 1058–1062.

Thompson, W. W., Shay, D. K., Weintraub, E., Brammer, L., Cox, N., Anderson, L. J., & Fukuda, K. (2003). Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*, *289*(2), 179–186.

Thompson, W. W., Weintraub, E., Dhankhar, P., Cheng, P.-Y., Brammer, L., Meltzer, M. I., et al. (2009). Estimates of US influenza-associated deaths made using four different methods. *Influenza and Other Respiratory Viruses*, *3*(1), 37–49. doi:10.1111/j.1750-2659.2009.00073.x

Tolnay, S. (2013). Editor's Note. *Demography*, 50(6), 1943–1944.

Turner, S. E., & Bound, J. (2002). *Closing the Gap or Widening the Divide: The Effects of the G.I. Bill and World War II on the Educational Outcomes of Black Americans* (Working Paper No. 9044). National Bureau of Economic Research. https://doi.org/10.3386/w9044

Tukey, J.W. (1977). *Exploratory Data Analysis*. 1 edition. Reading, Mass.: Pearson.

USCB. (2018). Historical Marital Status Tables. US Census Bureau. https://www.census.gov/data/tables/time-series/demo/families/marital.html

Valdes, B. and George, K. (2013). Demographic Analysis of AIDS Mortality in Spain. *Population* Vol. 68(3):473–485. doi:10.3917/popu.1303.0539.

van Raalte, A. A., Kunst, A. E., Lundberg, O., Leinsalu, M., Martikainen, P., Artnik, B., et al. (2012). The contribution of educational inequalities to lifespan variation. *Population Health Metrics*, 10(1), 3. https://doi.org/10.1186/1478-7954-10-3

van Raalte, A. A., Martikainen, P., & Myrskylä, M. (2014). Lifespan Variation by Occupational Class: Compression or Stagnation Over Time? *Demography*, 51(1), 73–95. https://doi.org/10.1007/s13524-013-0253-x

van Raalte, A. A., Sasson, I., & Martikainen, P. (2018). The case for monitoring life-span inequality. Science, 362(6418), 1002–1004. https://doi.org/10.1126/science.aau5811

Vaupel, J. W., Gambill, B. A., & Yashin, A. I. (1987, July). *Thousands of Data at a Glance: Shaded Contour Maps of Demographic Surfaces*. Monograph. http://pure.iiasa.ac.at/2905/

Vaupel, J. W., Zhenglian, W., Andreev, K. F., & Yashin, A. I. (1998). *Population Data at a Glance: Shaded Contour Maps of Demographic Surfaces Over Age and Time*. Odense Denmark: University Press of Southern Denmark.

Vaupel, J. W., Manton, K. G., & Stallard, E. (1979). The Impact of Heterogeneity in Individual Frailty on the Dynamics of Mortality. *Demography*, 16(3), 439–454. https://doi.org/10.2307/2061224

Veevers, J. E., & Gee, E. M. (1986). Playing It Safe: Accident Mortality and Gender Roles. *Sociological Focus*, 19(4), 349–360.

Venables, W. N., & Ripley, B. D. (2002). Modern Applied Statistics with S (4th ed.). New York: Springer-Verlag. https://www.springer.com/de/book/9780387954578. Accessed 23 August 2019

Viboud, C., Miller, M., Olson, D. R., Osterholm, M., & Simonsen, L. (2010). Preliminary Estimates of Mortality and Years of Life Lost Associated with the 2009 A/H1N1 Pandemic in the US

and Comparison with Past Influenza Seasons. *PLoS Currents*, *2*. doi:10.1371/currents.RRN1153

Vittinghoff, E., Scheer, S., O'Malley, P., Colfax, G., Holmberg, S. D., & Buchbinder, S. P. (1999). Combination Antiretroviral Therapy and Recent Declines in AIDS Incidence and Mortality. *The Journal of Infectious Diseases*, 179(3), 717–720. https://doi.org/10.1086/314623

Vozoris, N. T., Wang, X., Fischer, H. D., Bell, C. M., O'Donnell, D. E., Austin, P. C., et al. (2016). Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *European Respiratory Journal*, 48(3), 683–693. https://doi.org/10.1183/13993003.01967-2015

Waldron, I., McCloskey, C., & Earle, I. (2005). Trends in gender differences in accidents mortality: Relationships to changing gender roles and other societal trends. *Demographic Research*, S4(17), 415–454. https://doi.org/10.4054/DemRes.2005.13.17

Whelpton, P. K., Eldridge, H. T., Seigel, J. S., & Census, U. S. B. of the. (1948). *Forecasts of the population of the United States, 1945-1975*. U.S. Govt. Print. Off.

WHO. (2018). Human infection with avian influenza A(H7N9) virus – China: Update. WHO. http://www.who.int/csr/don/05-september-2018-ah7n9-china/en/

Wickham, H. (2016). *Ggplot2: Elegant Graphics for Data Analysis*. 2nd ed. Houston, TX: Springer International Publishing.

Wickham, H. (2017). *tidyverse: Easily Install and Load the "Tidyverse."* https://CRAN.R-project.org/package=tidyverse

Wickham, H., & Bryan, J. (2019). readxl: Read Excel Files. https://CRAN.R-project.org/package=readxl. Accessed 23 August 2019

Wickham, H., & Miller, E. (2019). *haven: Import and Export "SPSS", "Stata" and "SAS" Files*. https://CRAN.R-project.org/package=haven. Accessed 23 August 2019

Wickramaratne, P. J., Weissman, M. M., Leaf, P. J., & Holford, T. R. (1989). Age, period and cohort effects on the risk of major depression: results from five United States communities. *Journal of Clinical Epidemiology*, 42(4), 333–343. https://doi.org/10.1016/0895-4356(89)90038-3

Willets, R. C. (2004). The Cohort Effect: Insights and Explanations. *British Actuarial Journal*, 10(4), 833–898. https://doi.org/10.1017/S1357321700002762

Wilmoth, J. R., Andreev, D., Jdanov, D. A., Glei, T., & Riffe, T. (2019). *Methods Protocol for the Human Mortality Database*. Human Mortality Database. https://www.mortality.org/Public/Docs/MethodsProtocol.pdf

Woolf, S. H., Chapman, D. A., Buchanich, J. M., Bobby, K. J., Zimmerman, E. B., & Blackburn, S. M. (2018). Changes in midlife death rates across racial and ethnic groups in the United States: systematic analysis of vital statistics. *BMJ*, 362, k3096. https://doi.org/10.1136/bmj.k3096

Woolf, S. H., & Schoomaker, H. (2019). Life Expectancy and Mortality Rates in the United States, 1959-2017. *JAMA*, 322(20), 1996–2016. https://doi.org/10.1001/jama.2019.16932

Worobey, M., Han, G.-Z., & Rambaut, A. (2014). Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus. *Proceedings of the National Academy of Sciences*, *111*(22), 8107–8112. doi:10.1073/pnas.1324197111

Xu, M., & Powers, D. A. (2016). Bayesian Ridge Estimation of Age-Period-Cohort Models. In R. Schoen (Ed.), *Dynamic Demographic Analysis* (pp. 337–359). Springer International Publishing. doi:10.1007/978-3-319-26603-9_17

Yang, Y. C. (2008). Trends in U.S. adult chronic disease mortality, 1960-1999: age, period, and cohort variations. *Demography*, 45(2), 387–416.

Yang, Y. C., & Land, K. C. (2013a). *Age-Period-Cohort Analysis: New Models, Methods, and Empirical Applications*. Boca Raton, FL: Chapman and Hall/CRC.

Yang, Y. C., & Land, K. C. (2013b). Misunderstandings, Mischaracterizations, and the Problematic Choice of a Specific Instance in Which the IE Should Never Be Applied. *Demography*, 50(6), 1969–1971.

Yang, Y. C., Fu, W. J., & Land, K. C. (2004). A Methodological Comparison of Age-Period-Cohort Models: The Intrinsic Estimator and Conventional Generalized Linear Models. *Sociological Methodology*, 34(1), 75–110. https://doi.org/10.1111/j.0081-1750.2004.00148.x

Zang, E., Zheng, H., Yang, Y. C., & Land, K. C. (2019). Recent trends in US mortality in early and middle adulthood: racial/ethnic disparities in inter-cohort patterns. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyy255

Zheng, H. (2014). Aging in the Context of Cohort Evolution and Mortality Selection. *Demography*, 51(4), 1295–1317. https://doi.org/10.1007/s13524-014-0306-9

Zibbell, J. E., Asher, A. K., Patel, R. C., Kupronis, B., Iqbal, K., Ward, J. W., & Holtzman, D. (2017). Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. *American Journal of Public Health*, 108(2), 175–181. https://doi.org/10.2105/AJPH.2017.304132

Supplementary Material S1: Determinants of Influenza Mortality Trends: Age-Period-Cohort analysis of influenza mortality in the United States, 1959-2016

Influenza Mortality Models

The Serfling Regression Model

We used a Serfling regression model in order to estimate mortality from influenza from 1959 to 2016 and to explore its age, period, and cohort components. We first estimated a mortality baseline without influenza by fitting Pneumonia and Influenza (P&I) death counts during the summer season, during which the influenza virus does not circulate widely in North America. Influenza-related mortality was estimated for each month as the difference between the observed P&I death count and the estimated baseline. Since previous analyses have used different combinations of summer months to define the baseline (Dushoff et al. 2006; Lemaitre et al. 2012; Nguyen and Noymer 2013; Simonsen et al. 2005), we tested four summer periods to fit the Serfling model (i.e., May to September, May to October, June to September, and June to October). The comparison of these estimates with those obtained from the Surveillance-Serfling model, which are estimated over the whole year (see below), guided us in selecting the summer period for the Serfling model (see Fig. S1.1).

The formulation of our Serfling model is:

$$log(deaths_{a,t}) = \sum_{i=0}^{10} \beta_i t^i + \beta_{11} sin\left(\frac{2\pi t}{12}\right) + \beta_{12} cos\left(\frac{2\pi t}{12}\right) + log(exposure_{a,t}), \qquad \text{(S1)}$$

where a is age (a = 0, 1, 2, …, 100), t the epidemic period (here from January 1959 to December 2016), $deaths_{a,t}$ the death count, and $exposure_{a,t}$ the population at risk. The model thus includes three key components: ($\sum_{i=0}^{10} \beta_i t^i$) controls for secular trends in mortality, while ($\beta_{11} sin\left(\frac{2\pi t}{12}\right) + \beta_{12} cos\left(\frac{2\pi t}{12}\right)$) captures influenza seasonality over time, and $log(exposure_{a,t})$ controls for changes in the age structure of the population over time.

In contrast to the original formulation and common uses of the Serfling method, which is based on linear regression models (Serfling 1963) or Poisson distributions (Thompson et al. 2009), we used a negative binomial distribution to estimate this model, which accounts for overdispersion. This distribution is also better-suited for low-frequency-count data (Hilbe 2011; Nguyen and Noymer 2013), which may indeed occur given the single-year age classification used here.

To estimate the mortality baseline for each age and summer period definition, we tested nine different polynomial degrees for the secular trend (from the 2nd to the 10th) and two seasonal terms (*sin* and *sin* + *cos*). Based on the Akaike information criteria (AIC) we selected the model providing the best fit among the 18 alternative parameterizations. The threshold values proposed by Hilbe (2011) were used to assist in deciding if the improvement of the model fit was statistically significant.

The Surveillance-Serfling Model

In order to estimate influenza mortality, we also use a "Surveillance-Serfling" regression model, which includes parameters tracking influenza-like illness (ILI) incidence and influenza circulation by subtype between 1997 and 2016. The model is written as:

$$\begin{aligned} log(deaths_{a,t}) = {} & \sum_{i=0}^{10} \beta_i t^i + \beta_{11} sin\left(\frac{2\pi t}{12}\right) + \beta_{12} cos\left(\frac{2\pi t}{12}\right) + \beta_{13} sin\left(\frac{3\pi t}{12}\right) + \\ & \beta_{14} cos\left(\frac{3\pi t}{12}\right) + \beta_{15} sin\left(\frac{4\pi t}{12}\right) + \beta_{16} cos\left(\frac{4\pi t}{12}\right) + \beta_{17} sin\left(\frac{6\pi t}{12}\right) + \beta_{18} cos\left(\frac{6\pi t}{12}\right) + \\ & \beta_{19} sin\left(\frac{8\pi t}{12}\right) + \beta_{20} cos\left(\frac{8\pi t}{12}\right) + \beta_{21} sin\left(\frac{10\pi t}{12}\right) + \beta_{22} cos\left(\frac{10\pi t}{12}\right) + \beta_{23} flu_{g,t} + \\ & \beta_{24} flu_{g,t-1} + log(exposure_{a,t}), \end{aligned} \tag{S2}$$

where a is age (a = 0, 1, 2, …, 100), t the monthly period (over 211 months, from October 1997 to December 2016, excluding periods from May through September between 1998 and 2002, for which influenza circulation data is not available), $deaths_{a,t}$ the death counts, and $exposure_{a,t}$ the population at risk. Like the traditional Serfling model, this model controls for secular trends in mortality ($\sum_{i=0}^{10} \beta_i t^i$) and seasonality (with the *sin*/*cos* terms), while $log(exposure_{a,t})$ tracks changes in the age structure of the population over time.

In addition, $flu_{i,g,t}$ and $flu_{i,g,t-1}$ account for influenza virus circulation during the current (t) and the previous (t-1) month, respectively. To define the measure of virus circulation, we tested

several options, with models that included influenza-like illness (ILI) incidence terms by age group *g* (*g* = 0, 1-4, 5-24, 25-64, 65+), combined with influenza surveillance data by subtype.

The measure accounting for ILI incidence by age group is defined for the current month *t* as:

$$flu_{g,t} = ILI_t * \frac{op_{g,t}}{Top_t}. \quad \text{(S3)}$$

For each month *t*, ILI_t is the percentage of outpatients with ILI symptoms, $op_{g,t}$ the numbers of outpatients of age group *g* with ILI symptoms, and Top_t the numbers of outpatients of all ages with ILI symptoms.

Alternatively, the measure combining information from ILI incidence by age group and influenza surveillance data by subtype is defined, for age group *g* and current month *t*, as:

$$flu_{i,g,t} = ILI_t * \frac{op_{g,t}}{Top_t} * \frac{pt_{i,g,t}}{Tpt_{g,t}}, \quad \text{(S4)}$$

where $pt_{i,t}$ is the numbers of specimens that tested positive for influenza subtype *i* (*i* = A-H1N1, A-H3N2, A-pH1N1, and B) in month *t*, and $Tpt_{g,t}$ the numbers of positive tests for all subtypes in age group *g* and month *t*.

For each age, we tried 216 models by combining nine different polynomial degrees (from the 2nd to the 10th), six orders of cyclical forms ($\frac{2\pi t}{12}$, …, $\frac{10\pi t}{12}$), and the two alternative influenza measures described above with and without their respective one-month lag term. We chose the model that provided the best fit according to AIC values, as we did for the Serfling model. Table S1.1 presents by single years of age the minimum AIC value obtained from each parametrization of influenza measures, the AIC change once the virus subtype information and the one-month lag variable are included, the statistical significance of this change, and the model providing the best fit. Alternatively, we applied a "*backward stepwise"* selection approach for each age (not shown here), starting with all flu activity terms in the model, removing at each step the least significant terms among the non-significant terms at the 5% level, and reintroducing, through re-estimation, the most significant term among those that reach a significance level of 4% (for a more detailed description of

the *backward stepwise* procedure, see Draper and Smith (1998)); the results obtained from this model selection strategy were not fundamentally different from those obtained from model selection based on AIC.

As shown in Table S1.1, there is considerable age variation with regard to the parameters that provided best AIC statistics. For example, neither the addition of one-month lag ILI terms nor the specification of virus subtype circulation (as in Eq. S4) provided significant improvement in model fit. We thus retained the default ILI model for that age, as we did generally until about age 20. From age 20 to age 65 approximately, the best models generally included terms specifying subtype circulation, usually without one-month lag terms for the younger portion of this age group (i.e., from age 20 to age 40), and then including these lag terms for the older portion (from age 40 to age 65). Interestingly, regarding the elderly (65+), models including lag terms systematically provided the best fit, while terms specifying subtype circulation were no longer kept in this age group.

Table S1.1: Fitting measures for alternative Surveillance-Serfling model parameterization and the model providing the best fit

Age	**Models with minimum AIC** for alternative influenza measures				**AIC Change**		**Model with Best Fit**
	ILI	**ILI + Lag**	**ILI by Subtype**	**ILI by Subtype + Lag**	**Subtype**	**Lag**	
0	1253.18	1249.56	1265.5	1265.92	12.32	-3.62	ILI
1	919.61	915.5	923.43	922.84	3.82	-4.11	ILI
2	725.45	723.27	731.26	738.15	5.81	-2.18	ILI
3	646.39	645.79	650.16	650.75	3.77	-0.6	ILI
4	573.62	574.81	579.92	583.57	6.3	1.19	ILI
5	559.41	561.4	558.08	564.56	-1.33	1.99	ILI
6	501.87	503.59	507.62	513.37	5.75	1.72	ILI
7	489.08	487.43	490.92	486.73	1.84	-1.65	ILI
8	455.09	454.21	458.14	463.76	3.05	-0.88	ILI
9	491.21	489.77	494.59	493.63	3.38	-1.44	ILI
10	466.71	470.62	470.56	478.43	3.85	3.91	ILI
11	453.68	450.11	458.19	455.83	4.51	-3.57	ILI
12	494.51	495.09	497.39	503.53	2.88	0.58	ILI
13	501.45	503.43	506.76	506.02	5.31	1.98	ILI
14	561.41	559.46	564.3	564.6	2.89	-1.95	ILI
15	517.14	510.13	519.99	516.18	2.85	-7.01*	ILI + Lag
16	513.91	515.85	519.42	526.81	5.51	1.94	ILI

Age	**Models with minimum AIC** for alternative influenza measures				**AIC Change**		**Model with Best Fit**
	ILI	**ILI + Lag**	**ILI by Subtype**	**ILI by Subtype + Lag**	**Subtype**	**Lag**	
17	581.24	569.74	584.72	579.01	3.48	-11.5*	ILI + Lag
18	634.97	627.68	637.26	635.55	2.29	-7.29*	ILI + Lag
19	620.07	622.02	621.99	624.73	1.92	1.95	ILI
20	709.84	708.75	710.87	711.1	1.03	-1.09	ILI
21	737.76	736.37	739.47	737.37	1.71	-1.39	ILI
22	756.61	753.29	756.38	746.25	-0.23	-3.32	ILI by Subtype + Lag
23	783.69	776.83	788.22	781.54	4.53	-6.86*	ILI + Lag
24	773.6	764.65	771.15	762.11	-2.45	-8.95*	ILI + Lag
25	772.79	763.86	761.31	752.58	-11.48*	-8.73*	ILI by Subtype + Lag
26	828.39	829.37	818.03	820.89	-10.36*	2.86	ILI by Subtype
27	822.74	823.57	816.73	819.48	-6.01*	2.75	ILI by Subtype
28	852.38	853.82	833.85	828.98	-18.53*	-4.87	ILI by Subtype
29	868.88	868.56	858.39	861.99	-10.49*	3.6	ILI by Subtype
30	868.75	864.05	840.67	838.92	-28.08*	-1.75	ILI by Subtype
31	898.65	897.54	888.72	892.16	-9.93*	3.44	ILI by Subtype
32	895.02	888.72	879.16	870.55	-15.86*	-8.61*	ILI by Subtype + Lag
33	902.35	902.82	879.92	885.36	-22.43*	5.44	ILI by Subtype
34	928.21	930.96	904.47	906.11	-23.74*	1.64	ILI by Subtype
35	957.63	950.01	930.15	920.91	-27.48*	-9.24*	ILI by Subtype + Lag
36	993.31	990.27	970.91	965.65	-22.4*	-5.26	ILI by Subtype
37	1003.80	1005.54	974.54	976.54	-29.26*	2.00	ILI by Subtype
38	1019.02	1019.71	994.78	997.54	-24.24*	2.76	ILI by Subtype
39	1039.89	1040.3	980.94	982.96	-58.95*	2.02	ILI by Subtype
40	1096.56	1096.6	1070.03	1071.26	-26.53*	1.23	ILI by Subtype
41	1117.01	1113.46	1070.26	1064.97	-46.75*	-5.29	ILI by Subtype
42	1139.82	1134.15	1098.46	1091.88	-41.36*	-6.58*	ILI by Subtype + Lag
43	1182.14	1178.64	1139.25	1129.00	-42.89*	-10.25*	ILI by Subtype + Lag
44	1174.09	1172.45	1139.65	1132.74	-34.44*	-6.91*	ILI by Subtype + Lag
45	1189.94	1173.68	1158.7	1137.30	-31.24*	-21.4*	ILI by Subtype + Lag
46	1193.53	1188.18	1162.46	1155.31	-31.07*	-7.15*	ILI by Subtype + Lag
47	1224.04	1220.95	1182.04	1176.25	-42.00*	-5.79	ILI by Subtype
48	1253.2	1241.69	1219.45	1200.79	-33.75*	-18.66*	ILI by Subtype + Lag
49	1230.24	1222.48	1195.82	1187.28	-34.42*	-8.54*	ILI by Subtype + Lag
50	1256.68	1239.82	1206.42	1178.99	-50.26*	-27.43*	ILI by Subtype + Lag
51	1278.99	1265.01	1257.43	1242.06	-21.56*	-15.37*	ILI by Subtype + Lag
52	1315.05	1310.33	1270.05	1264.2	-45.00*	-5.85	ILI by Subtype

Age	**Models with minimum AIC** for alternative influenza measures				**AIC Change**		**Model with Best Fit**
	ILI	**ILI + Lag**	**ILI by Subtype**	**ILI by Subtype + Lag**	**Subtype**	**Lag**	
53	1294.50	1291.12	1248.83	1241.36	-45.67*	-7.47*	ILI by Subtype + Lag
54	1348.10	1338.71	1322.77	1314.32	-25.33*	-8.45*	ILI by Subtype + Lag
55	1375.52	1365.52	1330.37	1310.74	-45.15*	-19.63*	ILI by Subtype + Lag
56	1340.04	1334.59	1305.5	1298.79	-34.54*	-6.71*	ILI by Subtype + Lag
57	1377.11	1360.76	1349.13	1320.86	-27.98*	-28.27*	ILI by Subtype + Lag
58	1393.18	1379.07	1363.76	1342.33	-29.42*	-21.43*	ILI by Subtype + Lag
59	1366.61	1358.58	1350.46	1343.21	-16.15*	-7.25*	ILI by Subtype + Lag
60	1400.24	1385.01	1385.27	1363.20	-14.97*	-22.07*	ILI by Subtype + Lag
61	1398.81	1382.72	1386.15	1364.82	-12.66*	-21.33*	ILI by Subtype + Lag
62	1406.38	1389.39	1401.95	1383.40	-4.43	-16.99*	ILI + Lag
63	1413.11	1387.61	1398.26	1371.30	-14.85*	-26.96*	ILI by Subtype + Lag
64	1411.28	1401.58	1407.53	1405.00	-3.75	-9.7*	ILI + Lag
65	1446.69	1439.4	1439.53	1434.19	-7.16*	-5.34	ILI + Lag
66	1420.72	1412.92	1422.14	1420.16	1.42	-7.80*	ILI + Lag
67	1478.71	1477.89	1469.73	1472.63	-8.98*	2.90	ILI by Subtype
68	1452.67	1443.32	1459.12	1451.76	6.45	-9.35*	ILI + Lag
69	1481.45	1470.96	1478.79	1465.77	-2.66	-10.49*	ILI + Lag
70	1514	1498.86	1520.66	1511.50	6.66	-15.14*	ILI + Lag
71	1528.38	1516.05	1520.66	1511.10	-7.72*	-9.56*	ILI + Lag
72	1542.65	1531.88	1550.73	1544.48	8.08	-10.77*	ILI + Lag
73	1581.03	1545.63	1593.46	1569.16	12.43	-35.4*	ILI + Lag
74	1625.8	1601.78	1630.62	1614.63	4.82	-24.02*	ILI + Lag
75	1610.39	1589.52	1612.54	1589.19	2.15	-20.87*	ILI + Lag
76	1669.03	1646.30	1688.18	1678.24	19.15	-22.73*	ILI + Lag
77	1655.57	1634.70	1672.49	1660.45	16.92	-20.87*	ILI + Lag
78	1687.91	1665.14	1698.20	1685.00	10.29	-22.77*	ILI + Lag
79	1671.13	1632.57	1686.63	1648.95	15.50	-38.56*	ILI + Lag
80	1741.59	1702.51	1751.36	1723.60	9.77	-39.08*	ILI + Lag
81	1756.79	1735.71	1762.31	1749.88	5.52	-21.08*	ILI + Lag
82	1796.94	1743.86	1808.05	1765.94	11.11	-53.08*	ILI + Lag
83	1818.83	1754.24	1817.96	1761.74	-0.87	-64.59*	ILI + Lag
84	1836.27	1791.06	1828.33	1798.58	-7.94*	-29.75*	ILI + Lag
85	1830.59	1766.90	1841.48	1798.47	10.89	-63.69*	ILI + Lag
86	1887.33	1830.52	1897.01	1858.01	9.68	-56.81*	ILI + Lag
87	1884.98	1845.15	1884.34	1863.21	-0.64	-39.83*	ILI + Lag
88	1868.12	1807.10	1878.52	1837.84	10.40	-61.02*	ILI + Lag

Age	**Models with minimum AIC** for alternative influenza measures				**AIC Change**		**Model with Best Fit**
	ILI	**ILI + Lag**	**ILI by Subtype**	**ILI by Subtype + Lag**	**Subtype**	**Lag**	
89	1895.92	1839.37	1890.94	1849.60	-4.98	-56.55*	ILI + Lag
90	1885.84	1833.45	1897.95	1872.23	12.11	-52.39*	ILI + Lag
91	1861.53	1818.42	1851.95	1821.22	-9.58*	-30.73*	ILI + Lag
92	1854.97	1819.36	1866.54	1851.63	11.57	-35.61*	ILI + Lag
93	1808.29	1756.82	1812.80	1784.57	4.51	-51.47*	ILI + Lag
94	1794.13	1759.20	1780.75	1759.90	-13.38*	-20.85*	ILI + Lag
95	1709.93	1682.89	1709.38	1698.82	-0.55	-27.04*	ILI + Lag
96	1655.25	1614.18	1657.18	1629.80	1.93	-41.07*	ILI + Lag
97	1582.43	1545.28	1593.54	1570.11	11.11	-37.15*	ILI + Lag
98	1538.01	1520.43	1541.58	1537.46	3.57	-17.58*	ILI + Lag
99	1468.42	1444.55	1465.76	1445.61	-2.66	-23.87*	ILI + Lag
100	1392.47	1373.31	1395.84	1388.01	3.37	-19.16*	ILI + Lag

* Statistically significant reduction in AIC values.

Note: The AIC is estimated to be -2LL+2k, where LL is the maximum log-likelihood and k is the number of parameters. A threshold value of 6 units is used to define whether the difference between two AIC statistic values is statistically significant, according to the selection criteria proposed by Hilbe (2011).

Specifying the Summer Season in the Serfling Model

Figure S1.1 presents estimates from the Serfling model using four different definitions of the summer period (i.e., May to September, May to October, June to September, and June to October) along with estimates from the Surveillance-Serfling model, while Fig. S1.2 shows the Lexis surfaces obtained from these models. Serfling estimates of death counts are generally sensitive to the definition of the summer period, with numbers yielded by those based on May to October or June to October being considerably lower compared to the others. For ages younger than 40, estimates obtained from the Surveillance-Serfling model are considerably lower and more erratic than those from any of the Serfling models (see Fig. S1.1). After that age, the surveillance model and the Serfling model based on the June to September summer period provides highly consistent estimates. Figures S1.1 and S1.2 show that estimates from the Serfling model using June – September as baseline months fluctuate less over age, compared to other Serfling models. Figure S1.3 plots the color version of the Lexis surfaces of influenza mortality rates estimated by the Serfling model and the Surveillance-Serfling model, also presented in black-and-white in Fig. 4 of the published version of this paper.

Figure S1.1: Serfling and Surveillance-Serfling influenza death count estimates by age, between 1997 and 2016, according to alternative summer periods as baseline months

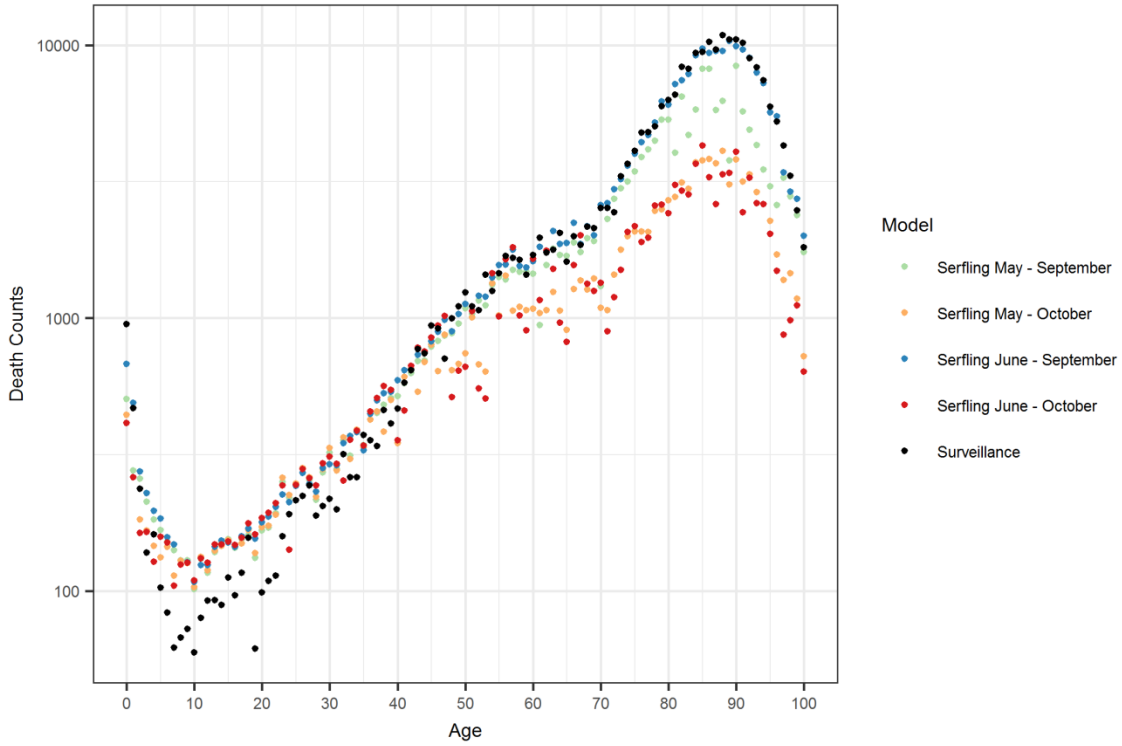


Figure S1.2: Lexis surfaces from Serfling estimates, between 1997 and 2016, according to different definitions of the summer period

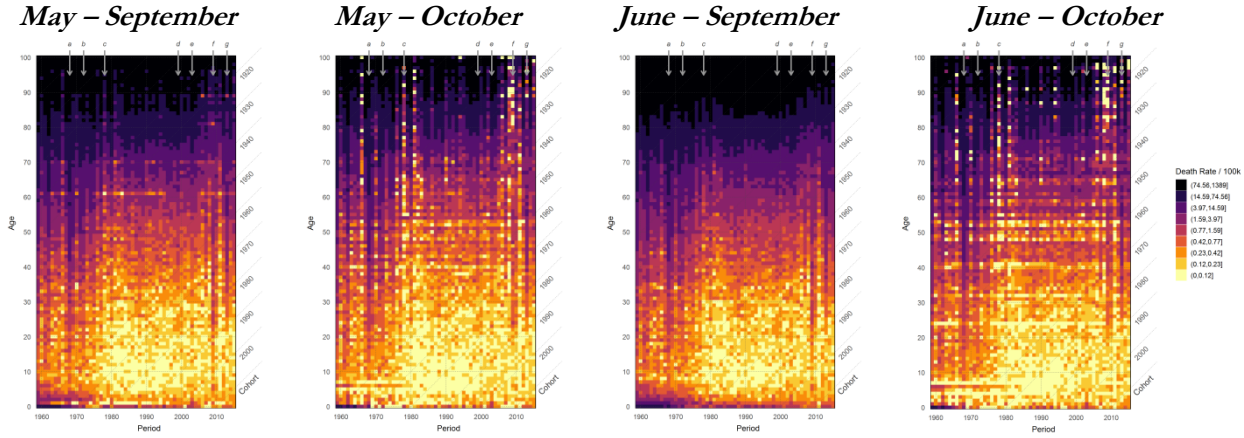
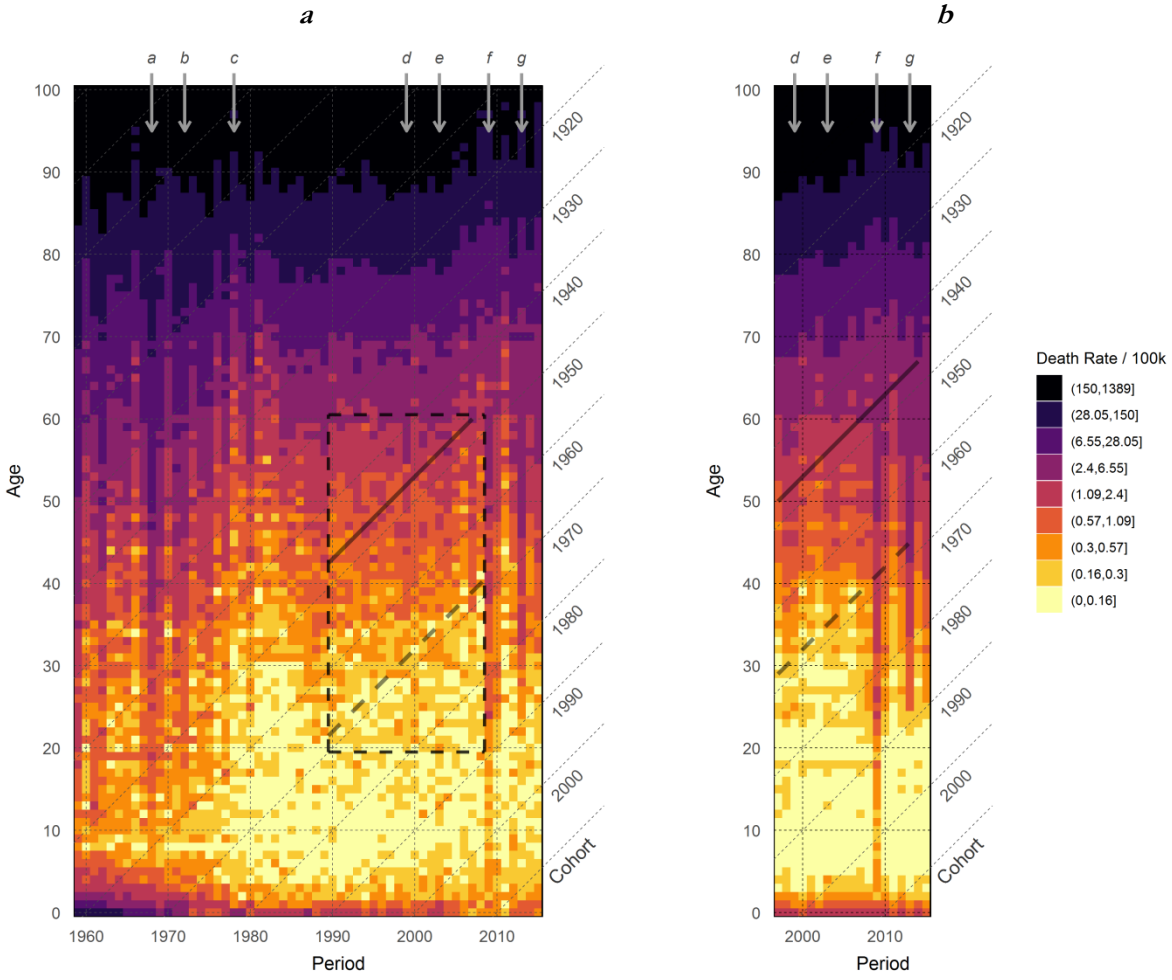


Figure S1.3: Lexis surfaces of influenza mortality rates estimated by the Serfling model, 1959-2016



Notes: Lexis surfaces of influenza mortality rates estimated by the Serfling model, 1959-2016 (a) and the Surveillance-Serfling model, 1997-2016 (b). The vertical arrows *a*, *b*, *d*, and e indicate periods of severe H3N2 epidemics. Arrow *c* marks the reappearance of H1N1 (1977-1978); arrows *f* and *g* indicate periods dominated by pH1N1. The solid and dashed black diagonal lines mark the 1947 and 1968 birth cohorts, respectively. The surface covered by the dashed square in Fig. 4.4a is shown in a three-dimensional perspective in Fig. 4.5

Age-Period-Cohort Analysis

In this section, we present several descriptive steps and sensitivity analyses made to evaluate period- and cohort-based trends in influenza mortality estimates, obtained from the application of the Serfling model to the 1959-2016 period.

Before fitting any APC models, it is suggested to ascertain first whether the three-factor model describes data better than any simpler two-factor age-period (AP) or age-cohort (AC) model

(Carstensen 2007; Clayton and Schifflers 1987; Holford 1991; Yang and Land 2013). Along with this evaluation, we also compared Poisson and Negative Binomial models to select the one that provides the best fit to our data. SE for our APC estimates were computed using a variance formula that accounts for autocorrelation (Hilbe 2011). The AICs presented in Table S1.2 suggest that the full APC model with Negative Binomial distribution for our response variable provides the best description of the data in terms of parsimony and goodness of fit.

Table S1.2: Akaike information criteria (AIC) values for APC models according to Poisson and negative binomial distributions

	k	Poisson		Negative Binomial	
		LL	AIC	LL	AIC
A	48	-98934	197964	-25736	51568
AP	75	-54503	109156	-23817	47784
AC	122	-67604	135452	-24609	49462
APC	148	-50074	100444	-23555	47406

Note: The AIC is estimated to be -2LL+2k, where LL is the maximum log-likelihood and k is the number of parameters.

Since the results in Table S1.2 indicate that the (three-factor) APC model accounts for significantly more variation than the simpler two-factor models, we proceeded to fit such a model, in which the number of influenza-related deaths at age *a* and time *t*, i.e., $deaths_{a,t}$, which are expressed as follows:

$$log(deaths_{a,t}) = \theta_0 + \alpha_a + \beta_t + \gamma_c + log(exposure_{a,t}), \quad \text{(S5)}$$

where θ_0 is a constant, α_a the effect of age group *a*, β_t the effect of period *t*, γ_c the effect of cohort *c*, and $exposure_{a,t}$ the population of age a at risk at time *t*.

Given the perfect linear dependency among the age, period, and cohort components (Period – Age = Cohort), this model has an infinite number of solutions if no additional constraints are specified. Several alternatives have been proposed to address this so-called "identification problem," essentially by imposing external constraints that are either explicitly chosen by the researcher (e.g., the constraint-based models of Fienberg and Mason (1985)), or implicitly defined by the design matrix, which depends on the number of age groups and periods (and thus cohorts) included in the model itself (e.g., the ridge and intrinsic estimators of Fu (2000) and Yang et al., (2004)). Yet, these

solutions are contentious because of the sensitivity of the outcomes to the constraint chosen, which validity can never be known with certainty (Clayton and Schifflers 1987; Fienberg 2013; Fosse and Winship 2018; Luo 2013; Tarone and Chu 1996). The main issue with all these models is indeed that they apportion the linear trend of change over time between period and cohort influences without providing a means to assess the validity of this decomposition using conventional statistical criteria (all solutions will yield the same goodness of fit statistics, e.g., the same AIC, BIC, Likelihood Ratio Test estimates, etc.). Hence, results obtained from this method should always be interpreted with caution and be seen as tentative or indicative rather than confirmatory.

The "long term slope" or "linear trend" that can be partitioned among period and cohort influences is known in the APC literature as the "drift parameter" (Carstensen 2007; Clayton and Schifflers 1987; Holford 1991). To avoid confusion with *antigenic drift*, we prefer to use the terms *long-term slope* or *linear trend*. To analyze the contribution of period and cohort variations to the linear trend of influenza mortality over time, we chose to use the *APC-detrended* and the *Intrinsic Estimator* (IE) approaches to model mortality rates, which are described below.

Period- and Cohort-Detrended Models

According to Clayton and Schifflers (1987) Eq. S5 can be rewritten as a factor model:

$$log\big(deaths_{a,t}\big) = \theta_0 + \alpha_a + \beta_p^d + \delta_P(p - p_0) + \gamma_c^d + \delta_C(c - c_0) + log\big(exposure_{a,t}\big), \qquad \text{(S6)}$$

where β_p^d and γ_c^d are the detrended period and cohort effects, δ_P and δ_C the linear trends of the period and cohort effects, p_0 and c_0 the reference period and cohort, respectively, and the remaining equation terms are defined as above. Thus, the overall linear trend of the model is

$$\delta = \delta_p + \delta_c \, . \qquad \text{(S7)}$$

Note that, given the identification problem discussed above, the model yields the same fit for an infinite number of different partitions of the linear trend (δ) among the period (δ_p) and cohort (δ_c) linear trends.

Under the assumption that the long-term slope of mortality change can be entirely attributed to either period- or cohort-based factors, it is possible to estimate both period-detrended ($\delta_p = 0$) and

cohort-detrended ($\delta_c = 0$) as alternative models, denoted here as APCd and ACPd, respectively. Different parameterization can be defined to extract the linear trend, either by using equal weight on all units in the dataset (Holford (1991)'s approach) or by using the death counts or exposures as weights (Carstensen (2007)'s approach). Yet, the slopes of the linear trends obtained from these three approaches are very similar (-2.024%, -1.967%, and -1.978%, respectively) and the difference between them is not statistically significant at the 95% confidence level.

The Intrinsic Estimator

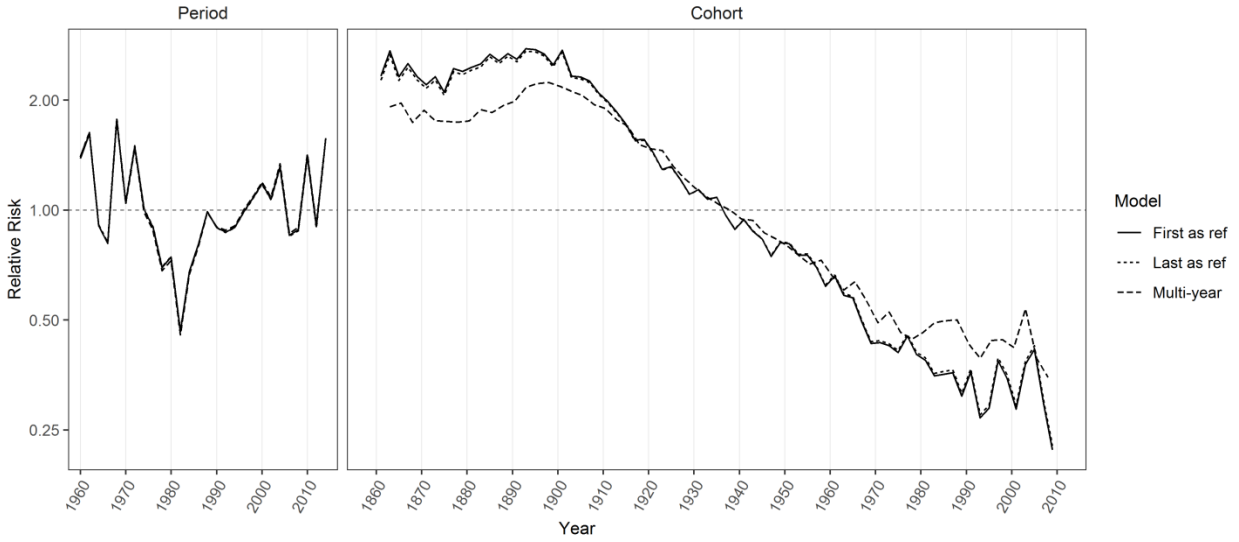
In order to address the identification problem arising from the perfect collinearity of the APC models, the Intrinsic Estimator (IE) method implicitly identifies a constraint that minimizes the APC parameter variance. The IE method can thus be seen in this regard as less arbitrary than other methods (Yang et al. 2004) since it does not leave the choice of the constraint to the researcher (note that in the case of the detrended method, one still has to choose to assign all the long-term slope to either cohort or period influences, which also amounts to the arbitrary addition of an external constraint). Yet, there remains controversy as to whether the IE method provides results that are truly less arbitrary (Luo 2013; Luo et al. 2016; Masters et al. 2014, 2016, 2018; Pelzer et al. 2015; te Grotenhuis et al. 2016; Xu and Powers 2016). In addition, a recent contribution by Fosse and Winship (2018) shows how the IE can be regrouped within a larger class of Moore-Penrose models and calls into question its applicability, at least based on extreme examples involving strongly "imbalanced" Lexis configurations, with as few as 5 age groups and up to 1,000 periods. That being said, we decided to include the IE estimates along the detrended estimates discussed above for comparison purposes, being aware of the limitations of all these methods. The results obtained from the APCd, APCd, and IE models are presented in Fig. 4.5, while the coefficients that were used to build this figure are presented at the end of this supplement (Table S1.5).

To demonstrate the applicability of the IE method to our data, we added sensitivity tests proposed in other studies (Luo et al. 2016; Masters et al. 2016, 2018; Yang and Land 2013). Note, however, that these tests, when successful, do not provide definitive support that the IE method could identify the "true" age, period, and cohort effects; as underlined above, there exists no unique, "best fit" solution to APC models.

We applied two different sensitivity tests for the IE. To test the robustness of the estimates and their sensitivity to model specification, we first changed the reference category from first to last of

each of the age, period, and cohort terms of the model. Second, we used alternative numbers of years to define the cohorts and periods. Figure S1.4 shows that the three estimates are consistent, and do not substantively differ when changing the category of reference or the width of the age, period, and cohort intervals. Note that the purpose of the multi-year model (dashed line in Fig. S1.4) is uniquely to assess the sensitivity of the IE's partition of first-order effects to alternative measurements of age, period, and cohort. Since cohort categories were generated as linearly dependent on the two-year age group and three-year time period (recall that Cohort = Period – Age), they do not correspond to actual cohorts, and thus, second-order cohort effects, discussed below, are not accurately obtained using this partition.

Figure S1.4: Intrinsic estimates of period and cohort relative risks of influenza-related mortality



Notes: Period and cohort effects derived from the estimates of the Serfling model. The solid and dotted lines indicate, respectively, estimates from using the first and the last age, period, and cohort as reference, while the dashed line provides estimates obtained when using two-year periods and three-year age groups (hence labeled as "multi-year")

Changes in Trends

Unlike the above age, period and cohort trend estimates (first-order effects), which are dependent on the constraint imposed on the model, the changes in the direction of these trends (second-order effects) are invariant, whatever the constraint imposed, and thus unambiguously identifiable (Holford 1991; Keyes et al. 2010). Among these second-order effects, a *contrasts* approach allow us to identify "breakpoints" where period or cohort trends significantly change direction and to quantify

the extent of these changes (O'Brien 2014b; Shahpar and Li 1999; Tarone and Chu 1996). Thus, we are able to measure the difference between the slopes of two disjoint blocks composed of several consecutive periods or cohorts.

A contrast comparing slopes between two disjoint blocks of *n* consecutive period or cohort groups is defined as:

$$C = \pi_{k+n} - \pi_k - (\pi_{h+n} - \pi_h), \tag{S8}$$

where π_h and π_k are respectively the *h*-th and *k*-th period or cohort parameter estimates from any constraint-based model, with $h + n \leq k$.

Alternatively, by estimating the difference between the linear contrasts defined over the two blocks being compared, it is possible to account for the contribution of all periods or cohorts included within each block. For two disjoints blocks of four, five, six, and eight consecutive period or cohort groupings, the differences in the linear contrasts respectively follow the forms:

$$C_4 = 3\pi_{k+3} + \pi_{k+2} - \pi_{k+1} - 3\pi_k - (3\pi_{h+3} + \pi_{h+2} - \pi_{h+1} - 3\pi_h), \tag{S9}$$

$$C_5 = 2\pi_{k+4} + \pi_{k+3} - \pi_{k+1} - 2\pi_k - (2\pi_{h+4} + \pi_{h+3} - \pi_{h+1} - 2\pi_h), \tag{S10}$$

$$C_6 = 5\pi_{k+5} + 3\pi_{k+4} + \pi_{k+3} - \pi_{k+2} - 3\pi_{k+1} - 5\pi_k - (5\pi_{h+5} + 3\pi_{h+4} + \pi_{h+3} - \pi_{h+2} - 3\pi_{h+1} - 5\pi_h), \tag{S11}$$

$$C_8 = 7\pi_{k+7} + 5\pi_{k+6} + 3\pi_{k+5} + \pi_{k+4} - \pi_{k+3} - 3\pi_{k+2} - 5\pi_{k+1} - 7\pi_{k+7} - (7\pi_{h+7} + 5\pi_{h+6} + 3\pi_{h+5} + \pi_{h+4} - \pi_{h+3} - 3\pi_{h+2} - 5\pi_{h+1} - 7\pi_{h+7}). \tag{S12}$$

The SE of the contrast estimate is:

$$se = \sqrt{s' V_\pi s}, \tag{S13}$$

where s is the vector of coefficients defining the contrast (in Eqs. S8 to S12) and V_π is the variance-covariance matrix for the maximum likelihood estimates of the period or cohort effects.

In Fig. 4.8 and Table 4.2, the units of analysis correspond to two-year age, period, and cohort groupings (analyses using one-year groupings resulted in estimates that were merely unstable). To test the sensitivity of the contrasts presented in Table 4.2, we re-estimated the models using three-year instead of two-year APC groupings and the new contrast estimates are displayed in Table S1.3. Note that due to the change in the number of years in the age, period, and cohort groupings, some breakpoints are shifted right or left relative to those reported in Table 4.2. Overall, however, the results in Table S1.3 are remarkably similar to the results in Table 4.2.

Table S1.3: Contrasts in the linear trends between two disjoint blocks of three-year birth cohorts

#	Cohorts where changes in slope occur	Block 1	Block 2	Contrast a	Contrast b
1	~ 1896-1898	1881-1898	1896-1913	-0.402***	-0.979***
2	~ 1929-1931	1917-1931	1929-1943	0.166*	0.352*
3	~ 1944-1946	1932-1946	1944-1958	0.233**	0.524**
4	~ 1956-1958	1944-1958	1956-1970	-0.395***	-0.909***
5	~ 1968-1970	1956-1970	1968-1982	0.431**	0.943**
6	~ 1977-1985	1968-1979	1983-1994	-0.423**	-1.178*

Notes: Contrasts a is defined as the difference between the slopes formed by the straight lines connecting the first and the last trio of consecutive birth cohorts within each block. Contrast b is defined as the sum of differences of all slopes formed by any pair of cohorts taken in each block.
$^+ p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$.

Finally, in order to provide a broader comparative perspective on influenza mortality, we also conducted additional contrast analyses for all-cause mortality and for cardiovascular and respiratory diseases mortality, which are the major causes associated with death from influenza complications (Reichert et al. 2004; Simonsen et al. 2011). We used data from the *Human Mortality Database* (2019) and from the *National Center for Health Statistics* (2018) over the period 1959-2016 to browse over the same years for which we have already identified significant contrasts (turning points) in influenza mortality. Changes in cohort mortality trends were also estimated two and four years *before and after* the identified turning points to assess the smoothness (or abruptness) of these changes.

For example, the first estimated contrast on the first line of Table S1.4, i.e., -0.458, is the change in slope occurring in cohorts born in 1892-1897, i.e., four years before the cohorts born in 1896-1901, where the contrast for the cohort trend in influenza mortality is maximum (i.e., -0.528). The fact that all the contrasts located on this first line are all significant and of similar magnitude indicates that the change in slope for cohort born at the turn of the 20th century is rather smooth and not focussed on a specific year. Also, as seen in Table S1.4, changes in slope in influenza mortality are "centered" in years with significant antigenic events, with much smaller contrasts in the previous or following four years, except for the cohorts born at the turn of the 20th century, as expected. The largest changes for all-cause, respiratory-, and cardiovascular-related mortality, on the other hand, are usually spread out with respect to the turning points identified for influenza.

Table S1.4: Contrasts in the linear trends between two disjoint blocks of two-year birth cohorts for deaths related to influenza, cardiovascular, and respiratory diseases, and for all-cause mortality

Cause	id	Cohorts	Contrast a					Contrast b				
			4 years before	2 years before	Centered	2 years after	4 years after	4 years before	2 years before	Centered	2 years after	4 years after
Influenza	1	~ 1896-1901	-0.458***	-0.393***	**-0.528*** **	-0.358***	-0.444***	-5.322***	-5.301***	**-5.583*** **	-4.620***	-5.208***
	2	~ 1928-1929	0.036	0.172*	**0.214***	0.071	-0.012	1.320+	1.760*	**1.801***	1.108	0.464
	3	~ 1946-1947	0.044	0.041	**0.246****	0.032	-0.067	0.008	0.252	**0.774****	0.178	-0.286
	4	~ 1956-1957	-0.173*	-0.157+	**-0.428*** **	-0.137	0.006	-0.384*	-0.576**	**-0.976*** **	-0.440+	-0.005
	5	~ 1968-1969	0.019	0.038	**0.392***	0.171	0.179	0.024	0.253	**0.837***	0.558	0.477
	6	~ 1976-1981	0.05	0.091	**-0.334***	-0.06	-0.278	0.109	0.070	**-0.587+**	-0.342	-0.697+
CVD[1]	1	~ 1896-1901	-0.142***	-0.127***	-0.152***	-0.128***	**-0.163*** **	-1.713***	-1.624***	-1.718***	-1.557***	**-1.760*** **
	2	~ 1928-1929	-0.024	-0.008	0.011	0.022	0.003	-0.127	-0.021	0.087	0.127	0.069
	3	~ 1946-1947	0.014	0.024	0.066***	**0.093*** **	0.074***	0.039	0.071	0.227***	**0.317*** **	0.247***
	4	~ 1956-1957	**0.102*** **	0.064***	0.029	0.008	0.030	**0.269*** **	0.159***	0.058	0.015	0.067+
	5	~ 1968-1969	0.033	0.064*	0.122***	**0.114*** **	0.075**	0.074	0.169**	0.300***	**0.309*** **	0.208***
	6	~ 1976-1981	0.000	-0.064*	-0.157***	**-0.223*** **	-0.201***	0.020	-0.158*	-0.399***	**-0.572*** **	-0.541***
RD[2]	1	~ 1896-1901	-0.058+	-0.089**	-0.155***	-0.155***	**-0.167*** **	-0.731*	-1.294***	-1.892***	-1.983***	**-2.071*** **
	2	~ 1928-1929	-0.158***	**-0.195*** **	-0.167***	-0.161***	-0.179***	-1.921***	**-2.265*** **	-2.225***	-2.117***	-2.071***
	3	~ 1946-1947	-0.023	-0.004	0.087**	**0.123*** **	0.067*	-0.096	-0.017	0.292***	**0.432*** **	0.230*
	4	~ 1956-1957	-0.135***	-0.157***	**-0.262*** **	-0.254***	-0.163***	-0.291***	-0.431***	-0.66***	**-0.654*** **	-0.444***
	5	~ 1968-1969	0.007	0.011	0.127**	**0.136*** **	0.091+	-0.017	0.066	0.297***	**0.356*** **	0.275**
	6	~ 1976-1981	0.106*	0.073	0.017	-0.106+	**-0.175*** **	0.274*	0.204+	0.043	-0.254+	**-0.467*** **
All-Cause	1	~ 1896-1901	-0.015	-0.006	-0.041*	-0.029+	**-0.079*** **	-0.182	-0.172	-0.359*	-0.332*	**-0.725*** **
	2	~ 1928-1929	**-0.061*** **	-0.051**	-0.025	-0.002	0.016	**-0.621*** **	-0.533***	-0.373*	-0.195	0.083
	3	~ 1946-1947	0.066***	0.083***	**0.102*** **	0.081***	0.015	0.21***	0.279***	**0.348*** **	0.274***	0.054
	4	~ 1956-1957	-0.079***	-0.151***	**-0.207*** **	**-0.207*** **	-0.149***	-0.185***	-0.382***	-0.539***	**-0.541*** **	-0.38***
	5	~ 1968-1969	-0.051*	0.017	0.083***	**0.099*** **	0.076**	-0.138**	0.050	0.219***	**0.264*** **	0.198***
	6	~ 1976-1981	0.032	-0.031	-0.110***	-0.167***	**-0.212*** **	0.086	-0.100	-0.272***	-0.406***	**-0.537*** **

[1] Cardiovascular diseases.
[2] Respiratory diseases.
Notes: Contrast a is defined as the difference between the slopes formed by the straight lines connecting the first and the last pair of consecutive birth cohorts within each block. Contrast b is defined as the sum of differences of all slopes formed by any pair of cohorts taken in each block. The grey columns highlight the contrasts centered on cohorts listed in the third column (also in grey), i.e., for cohorts with the largest changes in slope in influenza mortality; values in red indicate the largest among the five contiguous contrasts, separately for contrasts a and b.
$+p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$.

Table S1.5: APCd, ACPd, and IE period and cohort effects on influenza-related mortality derived from the Serfling model, ages 5 to 100, 1959-1960 through 2014-2015 influenza seasons

Effect	Index	Years	APCd		ACPd		IE	
			Coefficient	SE	Coefficient	SE	Coefficient	SE
Period	1	1959-1960	0.933	0.037	0.382	0.037	0.404	0.037
	2	1961-1962	0.965	0.025	0.456	0.025	0.466	0.025
	3	1963-1964	0.344	0.025	-0.125	0.025	-0.105	0.025
	4	1965-1966	0.243	0.034	-0.185	0.034	-0.153	0.034
	5	1967-1968	0.972	0.031	0.585	0.031	0.587	0.031
	6	1969-1970	0.392	0.034	0.045	0.034	0.073	0.034
	7	1971-1972	0.656	0.021	0.350	0.021	0.357	0.021
	8	1973-1974	0.227	0.025	-0.038	0.025	-0.021	0.025
	9	1975-1976	0.150	0.035	-0.074	0.035	-0.062	0.035
	10	1977-1978	-0.146	0.037	-0.330	0.037	-0.303	0.037
	11	1979-1980	-0.127	0.028	-0.270	0.028	-0.285	0.028
	12	1981-1982	-0.657	0.030	-0.759	0.030	-0.743	0.03
	13	1983-1984	-0.31	0.028	-0.371	0.028	-0.387	0.028
	14	1985-1986	-0.218	0.023	-0.239	0.023	-0.248	0.023
	15	1987-1988	-0.046	0.021	-0.025	0.021	-0.045	0.021
	16	1989-1990	-0.175	0.025	-0.114	0.025	-0.131	0.025
	17	1991-1992	-0.276	0.020	-0.174	0.020	-0.188	0.020
	18	1993-1994	-0.275	0.022	-0.132	0.022	-0.150	0.022
	19	1995-1996	-0.235	0.021	-0.052	0.021	-0.068	0.021
	20	1997-1998	-0.147	0.024	0.077	0.024	0.050	0.024
	21	1999-2000	-0.128	0.023	0.137	0.023	0.119	0.023
	22	2001-2002	-0.253	0.024	0.052	0.024	0.032	0.024
	23	2003-2004	-0.090	0.021	0.257	0.021	0.231	0.021
	24	2005-2006	-0.578	0.026	-0.190	0.026	-0.190	0.026
	25	2007-2008	-0.557	0.031	-0.129	0.031	-0.120	0.031
	26	2009-2010	-0.089	0.046	0.380	0.046	0.412	0.046
	27	2011-2012	-0.558	0.037	-0.048	0.037	-0.053	0.037
	28	2013-2014	-0.017	0.044	0.533	0.044	0.520	0.044
Cohort	1	1860-1861	-0.733	0.121	0.776	0.121	0.697	0.121
	2	1862-1863	-0.506	0.085	0.962	0.085	0.909	0.085
	3	1864-1865	-0.576	0.085	0.851	0.085	0.782	0.085
	4	1866-1867	-0.461	0.079	0.926	0.079	0.865	0.079
	5	1868-1869	-0.500	0.074	0.846	0.074	0.792	0.074
	6	1870-1871	-0.492	0.071	0.814	0.071	0.76	0.071
	7	1872-1873	-0.417	0.054	0.847	0.054	0.789	0.054
	8	1874-1875	-0.470	0.055	0.753	0.055	0.704	0.055
	9	1876-1877	-0.282	0.062	0.901	0.062	0.864	0.062

Effect	Index	Years	APCd		ACPd		IE	
			Coefficient	SE	Coefficient	SE	Coefficient	SE
	10	1878-1879	-0.268	0.06	0.874	0.06	0.844	0.06
	11	1880-1881	-0.183	0.062	0.918	0.062	0.894	0.062
	12	1882-1883	-0.132	0.053	0.928	0.053	0.889	0.053
	13	1884-1885	-0.029	0.052	0.991	0.052	0.958	0.052
	14	1886-1887	0.003	0.059	0.982	0.059	0.955	0.059
	15	1888-1889	0.076	0.05	1.014	0.05	0.979	0.050
	16	1890-1891	0.091	0.05	0.989	0.05	0.961	0.050
	17	1892-1893	0.185	0.042	1.042	0.042	1.009	0.042
	18	1894-1895	0.211	0.039	1.026	0.039	0.994	0.039
	19	1896-1897	0.234	0.039	1.009	0.039	0.982	0.039
	20	1898-1899	0.211	0.039	0.945	0.039	0.923	0.039
	21	1900-1901	0.341	0.038	1.034	0.038	1.009	0.038
	22	1902-1903	0.216	0.036	0.868	0.036	0.846	0.036
	23	1904-1905	0.241	0.034	0.853	0.034	0.836	0.034
	24	1906-1907	0.250	0.033	0.821	0.033	0.803	0.033
	25	1908-1909	0.231	0.035	0.761	0.035	0.745	0.035
	26	1910-1911	0.215	0.034	0.704	0.034	0.688	0.034
	27	1912-1913	0.195	0.036	0.644	0.036	0.629	0.036
	28	1914-1915	0.176	0.039	0.584	0.039	0.569	0.039
	29	1916-1917	0.104	0.038	0.472	0.038	0.458	0.038
	30	1918-1919	0.141	0.037	0.467	0.037	0.456	0.037
	31	1920-1921	0.098	0.037	0.383	0.037	0.374	0.037
	32	1922-1923	0.045	0.039	0.289	0.039	0.280	0.039
	33	1924-1925	0.086	0.037	0.29	0.037	0.284	0.037
	34	1926-1927	0.037	0.037	0.200	0.037	0.195	0.037
	35	1928-1929	-0.007	0.041	0.116	0.041	0.114	0.041
	36	1930-1931	0.028	0.035	0.110	0.035	0.108	0.035
	37	1932-1933	0.053	0.042	0.094	0.042	0.098	0.042
	38	1934-1935	0.041	0.032	0.041	0.032	0.047	0.032
	39	1936-1937	-0.004	0.038	-0.045	0.038	-0.037	0.038
	40	1938-1939	-0.033	0.041	-0.115	0.041	-0.109	0.041
	41	1940-1941	0.027	0.035	-0.096	0.035	-0.084	0.035
	42	1942-1943	0.000	0.039	-0.163	0.039	-0.148	0.039
	43	1944-1945	0.008	0.038	-0.196	0.038	-0.186	0.038
	44	1946-1947	-0.062	0.043	-0.307	0.043	-0.291	0.043
	45	1948-1949	0.051	0.038	-0.235	0.038	-0.225	0.038
	46	1950-1951	0.086	0.038	-0.240	0.038	-0.222	0.038
	47	1952-1953	0.097	0.039	-0.270	0.039	-0.268	0.039
	48	1954-1955	0.123	0.041	-0.285	0.041	-0.28	0.041

Effect	Index	Years	APCd		ACPd		IE	
			Coefficient	SE	Coefficient	SE	Coefficient	SE
	49	1956-1957	0.099	0.043	-0.349	0.043	-0.348	0.043
	50	1958-1959	0.011	0.045	-0.478	0.045	-0.478	0.045
	51	1960-1961	0.122	0.045	-0.408	0.045	-0.403	0.045
	52	1962-1963	0.017	0.042	-0.554	0.042	-0.546	0.042
	53	1964-1965	0.013	0.045	-0.599	0.045	-0.569	0.045
	54	1966-1967	-0.056	0.052	-0.709	0.052	-0.688	0.052
	55	1968-1969	-0.126	0.062	-0.820	0.062	-0.790	0.062
	56	1970-1971	-0.063	0.062	-0.797	0.062	-0.783	0.062
	57	1972-1973	-0.067	0.063	-0.842	0.063	-0.807	0.063
	58	1974-1975	-0.082	0.061	-0.898	0.061	-0.843	0.061
	59	1976-1977	0.054	0.056	-0.802	0.056	-0.775	0.056
	60	1978-1979	0.019	0.067	-0.879	0.067	-0.856	0.067
	61	1980-1981	0.069	0.080	-0.869	0.08	-0.869	0.08
	62	1982-1983	0.016	0.077	-0.962	0.077	-0.952	0.077
	63	1984-1985	0.025	0.082	-0.995	0.082	-0.978	0.082
	64	1986-1987	0.106	0.094	-0.955	0.094	-0.933	0.094
	65	1988-1989	-0.092	0.076	-1.193	0.076	-1.143	0.076
	66	1990-1991	0.073	0.070	-1.069	0.070	-1.017	0.070
	67	1992-1993	-0.132	0.089	-1.315	0.089	-1.248	0.089
	68	1994-1995	-0.035	0.092	-1.258	0.092	-1.193	0.092
	69	1996-1997	0.251	0.078	-1.014	0.078	-0.971	0.078
	70	1998-1999	0.165	0.104	-1.14	0.104	-1.057	0.104
	71	2000-2001	0.018	0.112	-1.328	0.112	-1.263	0.112
	72	2002-2003	0.303	0.135	-1.084	0.135	-1.025	0.135
	73	2004-2005	0.481	0.138	-0.946	0.138	-0.911	0.138
	74	2006-2007	0.235	0.172	-1.233	0.172	-1.168	0.172
	75	2008-2009	-0.171	0.138	-1.680	0.138	-1.622	0.138

Guide to Reproduce the Analyses and Results Presented in the Paper and Supplementary Material

This guide presents the material required to fully reproduce the analyses and results presented in the paper. All the scripts were elaborated by Enrique Acosta (acosta@mpg.demogr.de) and performed using Stata/MP version 15.1. (StataCorp 2017) and R version: 3.5.1 (R Core Team 2018). Data inputs (except micro-data files of US mortality), scripts, derived, and this document, are all available in the OSF link: https://osf.io/dv9pg/

Table S1.6 presents the data and the sources where they can be obtained. All datasets are openly available online or presented in previous scientific publications.

Table S1.6: Data

Datasets	Description	Source
mort1959.dta – mort2016.dta	Micro data of US mortality classified as pneumonia or influenza, by single year of age, between 1959 and 2016 (58 files, approximately 35 Gb in total). In order to use our scripts, download the "Stata (.zip)" versions of the files. Then unzip them into .dta files and place them all in the USmort folder.	Mortality Data - Vital Statistics NCHS' Multiple Cause of Death Data, 1959-2017. The files are available in several formats in the NBER website: https://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html
Exposures_1x1.csv	Annual exposure to risk in the US by single year of age between 1933 and 2016	Human Mortality Database, USA Exposure-to-risk (1x1) https://www.mortality.org/cgi-bin/hmd/country.php?cntr=USA&level=1
ILINET.xlsx	Influenza-Like-Illness (ILI). Weekly Percentage of visits for Influenza-Like-Illness reported by sentinel providers, by age-group, between 1997 and 2018	CDC – FluView https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html
virologic_surveillance.xlsx	Weekly values of Influenza positive specimens by subtype, by age-group, between 1997 and 2018	CDC – FluView https://gis.cdc.gov/grasp/fluview/flu_by_age_virus.html
Isolates_subtype_1976_1999_Thompson_etal_(2003).xlsx	Annual Influenza positive specimens by subtype in the US for the seasonal years 1976-77 to 1998-99	*Thompson, W. W. et al., (2003). Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA, 289(2), 179–186.*

Table S1.7 lists the procedures for the data standardization and transformation that are required before the analyses, whereas Tables S1.8 and S1.9 show processing steps and analyses to obtain all the results that are presented in the main text and Supplementary Material of our paper.

The values in the first column of the tables S1.7 to S1.9 indicate the logical order of the analyses. In the second column, we present a brief description of the dataset, the analysis, the table or the figure that is aimed to be accomplished. In the third column, we list the names of the scripts

corresponding to each step, in which the two first letters indicate whether its purpose is to create a dataset (db), to perform an analysis (an) or to plot a figure (fg), and the two following digits the order of the script within the group (i.e., data preparation, analyses or figure). Finally, the last column shows the values of the CPU time taken to complete each step (1:44:29.68 in total), which were performed using a 3.5 GHz Intel Core i5 processor with 4 cores and 8 GB of RAM.

Table S1.7: Data preparation

#	Data	Script	CPU time (h: m: s)
1	Monthly PI mortality by age 1959-2016	db_01_monthly_PI_by_age_1959-2016.do	00:02:15.0
2	Monthly measures of influenza circulation (ILI and influenza subtype) by age 1997-2016	db_02_monthly_flu_circulation_by_age.R	00:00:01.0
3	Master databases for Serfling (1959-2016) and surveillance (1997-2016) models, including monthly exposures to risk and influenza circulation measures	db_03_master_for_flu_estimation_1959-2016.do	00:00:03.6
4	Annual influenza subtype predominance 1959-2016	db_04_virus_prop_1959_2016.R	00:00:00.6
5	Annual mortality by All-cause, cardiovascular- and respiratory-related diseases	db_05_annual_deaths_broad_causes_1959-2016.R	01:30:46.2

Table S1.8: Analyses

#	Analysis	Script	CPU time (h: m: s)
Flu mortality estimates from the Serfling model (1959-2016)			
6	Analysis of parameterization for Serfling model using four summer periods	an_01_seasonal_AIC_analysis.do	00:27:19.1
7	Selection of parameters with best AIC for the Serfling model using four summer periods	an_02_best_serfling_AIC_selection.R	00:00:01.6
8	Estimation of flu mortality 1959-2016 with the Serfling model for each summer period	an_03_seasonal_best_AIC.do	00:02:06.2
9	Relative risk of mortality by influenza subtype (**Table 1**)	an_04_flu_by_subtype_1959_2016.R	00:00:00.6
Flu mortality estimates from the Surveillance model (1997-2016)			
10	Analysis of parameterization for Surveillance model	an_05_surveillance_AIC_analysis.do	01:10:58.6
11	Selection of parameters with best AIC for the Surveillance model (**Table S1**)	an_06_best_surveillance_AIC_selection.R	00:00:00.6
12	Estimation of flu mortality 1959-2016 with the Surveillance model	an_07_surveillance_best_AIC.do	00:00:35.5
Age-Period-Cohort Analyses of influenza mortality (1959-2016)			
13	Annual influenza mortality obtained from the Serfling model according to four summer periods (1959-2016) and from the Surveillance model (1997-2016)	an_08_seasonal_serfling_surveillance_estimates.R	00:00:01.1
14	Analysis of fit for APC models (**Table S2**)	an_09_APC_model_AIC_values.R	00:00:12.5
15	APC Intrinsic Estimator model using Yang method	an_10_APC_IE_Yang_method.do	00:00:05.9
16	APC Period and Cohort detrended models using Carstensen method (**Table S5**)	an_11_APC_detrended_Carstensen_method.R	00:00:04.5
17	Contrasts using Tarone method (**Tables 2 and S3**)	an_12_APC_flu_contrasts.R	00:00:06.5
18	Contrasts applied to broad causes of death (**Table S4**)	an_13_APC_broad_causes_contrasts.R	00:00:45.7
19	Sensitivity of Intrinsic Estimator estimates	an_14_IE_sensitivity_test.R	00:00:01.5

Table S1.9: Figures

#	Figure	Script	CPU time (h: m: s)
20	Monthly observed P&I death counts and baseline mortality (without influenza activity) predicted by the Serfling model at age 80, 1959-2016 (**Figure 1**)	fg_01.R	00:00:01.0
21	Observed and predicted influenza death counts at age 80, between October 1997 and December 2016 (**Figure 2**)	fg_02.R	00:00:00.8
22	Serfling estimates of monthly influenza death counts (a) and of influenza death counts using the US population of 2015 as standard (b), between January 1959 and December 2016 (**Figure 3**)	fg_03(a,b).R	00:00:01.5
23	Lexis surfaces of influenza mortality rates estimated by the Serfling model, 1959-2016 (a) and the Surveillance-Serfling model, 1997-2016 (b) (**Figure 4a-b**)	fg_04(a,b).R	00:00:06.6
24	Period and Cohort effects on influenza-related mortality derived from the Serfling model, age 5 to 100 years, 1959-2016 **(Figure 6)**	fg_06.R	00:00:01.6
25	Annual Serfling and Surveillance influenza death count estimates by age, between 1997 and 2016, according to different definitions of summer period (**Figure S1**)	fg_S01.R	00:00:03.0
26	Lexis surfaces from Serfling estimates, according to different parameterizations of summer period (**Figure S2a-d**)	fg_S02(a-d).R	00:00:18.7
27	Intrinsic estimates of period and cohort effects on influenza-related mortality derived from the estimates of the Serfling model, using the first and the last age, period, and cohort as reference, and using two-year periods and three-year age groups (**Figure S3**)	fg_S03.R	00:00:01.2

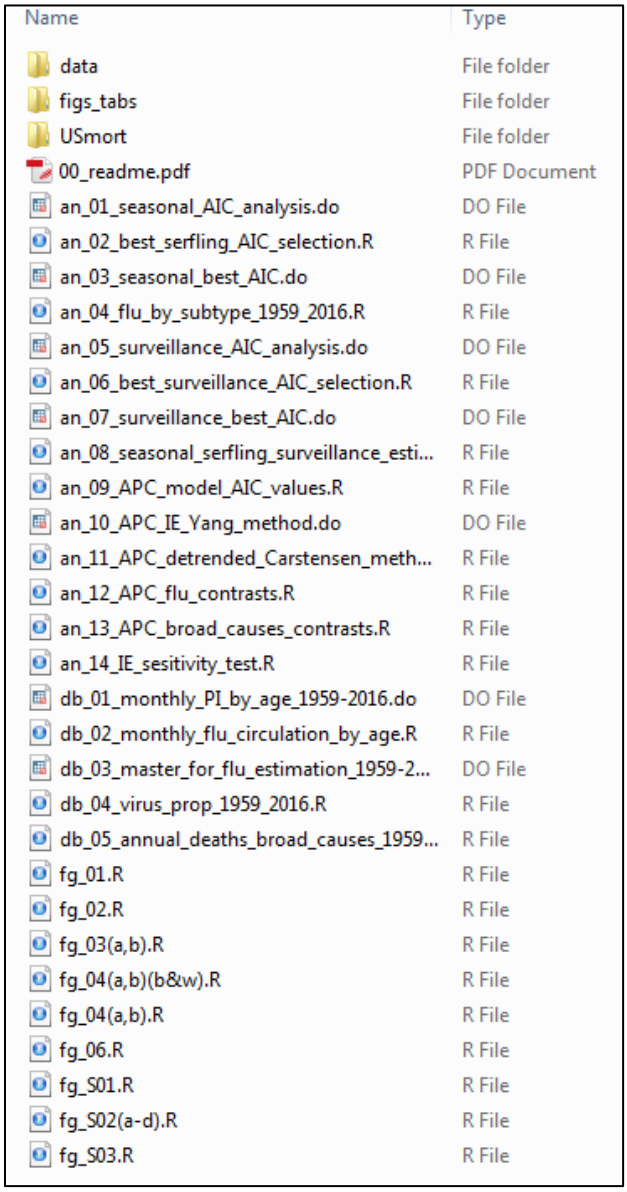
Technical Notes

File organization

Once the 27 scripts listed in Tables S1.7 to S1.9 are saved in a specific working directory (e.g., C:/Users/Jane/influenza_work), the 58 files correspondent to micro-data for the years 1959-2016 (i.e., mort1959.dta to mort2016.dta) should be placed in a subdirectory named USmort (*e.g.,* C:/Users/Jane/influenza_work/USmort), and the remaining four datasets in another subdirectory named *data* (i.e., C:/Users/Jane/influenza_work/data). An additional empty subdirectory named figs_tabs should be created for the storing of the figures and the tables (i.e., C:/Users/Jane/influenza_work/figs_tabs), as indicated in Fig. S1.5.

All 27 scripts are prepared to work under this configuration, but it is easily modifiable to adjust to the user convenience. We suggest executing the scripts in the order suggested to avoid conflicts of dependency.

Figure S1.5: *Suggested structure of files to execute the scripts db_01 to db_04, an_01 to an_13, and fg_01 to fg_S3*



Setting the working directory

Our scripts assume that the current working directory is the folder in which the scripts live. If you open a script file (.do or .R) by double-clicking on it then the current working directory *should* be set correctly. However, we have found that in some cases a different working directory is set by default. To avoid this nuisance we suggest:

1. To print the current working directory, type pwd in the Stata Command window, and getwd() in the R console .
   If the current working directory is the folder where the script files live, there is no problem and you can skip step 2.
2. Set the current working directory to the folder where the scripts files live by typing a cd command in the Stata Command window and a setwd()command in the R console. For example, on a Windows system you might type

   In Stata: cd "C:/Users/Jane/influenza_work"
   In R: setwd(C:/Users/Jane/influenza_work)

   whereas on a Mac you might type

   In Stata: cd "/Users/Jane/influenza_work"
   In R: setwd(/Users/Jane/influenza_work)

   and then confirm that you are where you think you are by repeating the step 1..

You should then be able to run our scripts. Note that in Stata for Mac, you should have to go through the above steps only once if you have "*Start in the last session's current working directory*" ticked in *Preferences -> General Preferences*. More details can be found in the Stata manuals Getting Started with Stata for Windows [GSW] (https://www.stata.com/manuals/gsw.pdf) and Getting Started with Stata for Mac [GSM] (https://www.stata.com/manuals/gsm.pdf).

Packages

The Stata module *apc* (Schulhofer-Wohl and Yang 2006) must be installed previous to the execution of the script an_10_APC_IE_Yang_method.do. To install it type ssc install apc in the Stata Command window.

The R packages *tidyverse* (Wickham 2017), *lubridate* (Grolemund and Wickham 2011), *viridis* (Garnier et al. 2018), *haven* (Wickham, code), et al. 2019), *writexl* (Ooms and details 2018), *readxl* (Wickham, Bryan, et al. 2019), *Epi* (Carstensen et al. 2019), *sandwich* (Zeileis 2004), and *MASS* (Venables and Ripley 2002) must be installed previous to the execution of the scripts. To install them use the install.packages() command in R. An easy way to install all of them is to assign all of them to a vector element, as indicated bellow

```
libs <- c("tidyverse", "lubridate", "viridis", "haven", "writexl", "readxl", "Epi", "sandwich", "MASS")
install.packages(libs)
```

Supplementary Material S2: The Boomers' Excess Mortality in Canada and the United States

Construction of Lexis surfaces of mortality change

Lexis surfaces of changes in mortality rates are widely recognized in the demographic literature as powerful, yet simple tools for identifying APC effects (Barbi and Camarda 2011; Rau et al. 2013; Schöley and Willekens 2017; J. W. Vaupel et al. 1987). Over periods (and, thus, cohorts) these changes reflect a combination of period and cohort effects, because age is controlled by estimating mortality changes within the same age group (i.e., horizontal mortality changes in the Lexis surfaces, from earlier to more recent calendar years/cohorts). To construct Lexis surfaces reflecting these changes, we first estimated two-dimensional smoothed mortality rates to eliminate random variations that are not part of the mortality trend. We applied the P-splines method (Eilers et al. 2015; Eilers and Marx 1996) for the two-dimensional smoothing, using the R package *MortalitySmooth* (Camarda 2012), which allowed us to select the best fitting parameters based on the Akaike Information Criteria (AIC) (Burnham and Anderson 2002). From the smoothed death rates, we estimated the rates of mortality change ($\Delta pc_{x,t}$), and then plotted them in a Lexis surface. According to the diagonal patterns shown in Figure 5.1, the advantaged and the disadvantaged birth cohorts were born during the mid-1940s and around 1960, respectively (black dashed lines).

From the smoothed death rates, we estimated, for each age *x,* the relative change in mortality from year *t-1* to year *t* (or from cohort *c-1* to cohort *c*) as:

$$\Delta pc_{x,t} = \log\left(m^s_{x,t}\right) - \log\left(m^s_{x,t-1}\right), \quad (1)$$

where $m^s_{x,t}$ is the smoothed death rate for age *x* in period *t*.

We then plotted $\Delta pc_{x,t}$ values in a Lexis surface in two color scales to depict the yearly changes in mortality over periods/cohorts (Figure 5.1). The relative mortality decrease for year *t-1* compared to that for year *t* (or cohort *c-1* compared to cohort *c*) in the same age *x* is indicated with a green-to-blue scale, while the relative mortality increase is indicated with a yellow-to-red scale. Vertical traces

on the Lexis surface are indicative of nonlinear period effects on mortality, and 45° diagonal traces are indicative of nonlinear cohort effects.

Cohort partial mortality rate measure

For the estimation and comparison of cohort mortality levels, we propose an index of the *cohort's partial mortality rate*, defined as:

$$CPMR^{c(k,l)} = \sum_{x=k}^{l} m_x^c \,, \tag{2}$$

where m_x is the age-specific mortality rate for the age interval $k - l$ for cohort *c*.

A similar index (*indice synthétique de mortalité*) was suggested by Termote (1998) as a complementary measure for analyzing mortality changes on a period basis. Being the sum of the age-specific mortality rates between two ages, this measure is the mortality analogous of the cohort's total fertility rate (TFR^c) (S. Preston et al. 2000), but framed within a specific age interval. This index is appropriate for our objective for at least three reasons. First, it is not influenced by variations in size across ages or cohorts. Second, contrary to other measures of mortality, such as life expectancy or life years lost, the $CPMR^{c(k,l)}$ is not weighted by age – that is, it does not overestimate the importance of the causes of death that are more prevalent in the younger age groups. Third, the index is fairly easy to decompose by causes of death.

The *change in the cohort's partial mortality rate* between the advantaged (a) and disadvantaged (d) cohorts for the age interval $k - l$ is defined as

$$\Delta CPMR^{d-a(k,l)} = CPMR^{d(k,l)} - CPMR^{a(k,l)}. \tag{3}$$

The decomposition of the $\Delta CPMR^{Cd-a(k,l)}$ by cause of death is straightforward, since this index satisfies a simple balance equation in which the sum of all *changes in the cohort's partial mortality rate by cause of death* i ($\Delta CPMR_i^{d-a(k,l)}$) equals the total *change in the cohort's partial mortality rate*:

$$\Delta CPMR^{d-a(k,l)} = \sum_i \Delta CPMR_i^{d-a(k,l)}. \tag{4}$$

Classification of causes of death and measurement of mortality change

The period under analysis spans three ICD revisions (8th through 10th). To facilitate an initial decomposition by cause of death of the mortality deterioration, we first constructed broad causes of death based on the ICD chapters (see Table S2.1). This broad categorization allowed us to analyze mortality changes across a few groups of causes, and guaranteed a low degree of variation across the three ICD revisions covered during the period of observation.

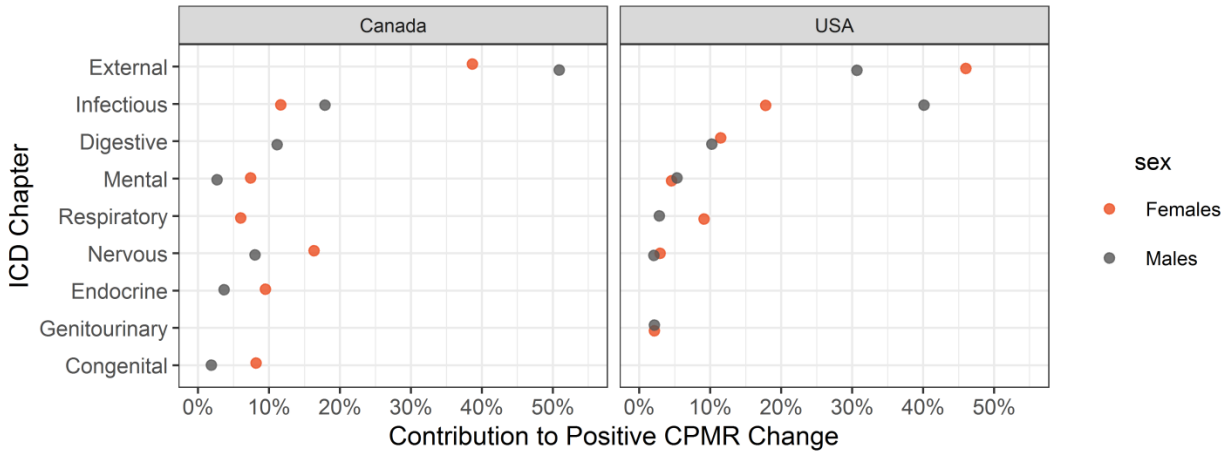
Table S2. 1. ICD Chapters revisions 8th to 10th

ICD	8	9	10
Period	**1968-1978**	**1979-1998**	**1999-2016**
Certain infectious and parasitic diseases	001-139	001-139	A00–B99
Neoplasms	140-239	140-239	C00–D48
Endocrine, nutritional, and metabolic diseases	240-279	240-279	E00–E90
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	280-289	280-289	D50–D89
Mental and behavioral disorders	290-319	290-319	F00–F99
Diseases of the nervous system	320-359	320-359	G00–G99
Diseases of the eye and adnexa	360-379	360-379	H00–H59
Diseases of the ear and mastoid process	380-389	380-389	H60–H95
Diseases of the circulatory system	390-459	390-459	I00–I99
Diseases of the respiratory system	460-519	460-519	J00–J99
Diseases of the digestive system	520-579	520-579	K00–K93
Diseases of the genitourinary system	580-629	580-629	N00–N99
Pregnancy, childbirth, and the puerperium	630-679	630-679	O00–O99
Diseases of the skin and subcutaneous tissue	680-709	680-709	L00–L99
Diseases of the musculoskeletal system and connective tissue	710-739	710-739	M00–M99
Congenital malformations, deformations, and chromosomal abnormalities	740-759	740-759	Q00–Q99
Certain conditions originating in the perinatal period	760-779	760-779	P00–P96
External causes of morbidity and mortality	800-999	800-999	V01–Y98
Other causes	780-799	780-799	R-U

Figure S2.1 shows the estimates of the cause-specific decomposition of the mortality deterioration from the advantaged to the disadvantaged cohorts. According to these results, most of the excess

mortality among boomers is composed of increases in deaths from causes within the ICD Chapters covering external, infectious, digestive, mental/behavioral, and respiratory diseases.

Figure S2. 1: Percentage contributions of broad causes to the mortality deterioration from the *advantaged* to the *disadvantaged* cohorts



Based on the leading broad causes of mortality deterioration identified in Figure S2.1, we constructed more detailed causes of death, and decomposed the mortality deterioration again. Table S2.2 presents the ICD codes used to classify deaths from HIV/AIDS, hepatitis C, COPD, suicide, alcohol, and drugs. Note that none of these causes of death was confined to the same broad category – that is, to the same ICD chapter. For instance, alcohol-related mortality included deaths from mental and behavioral disorders due to alcohol (which are covered by the mental and behavioral disorders chapter), from alcoholic liver disease (which are covered by the digestive system chapter), and from alcohol poisoning (which are covered by the external causes chapter).

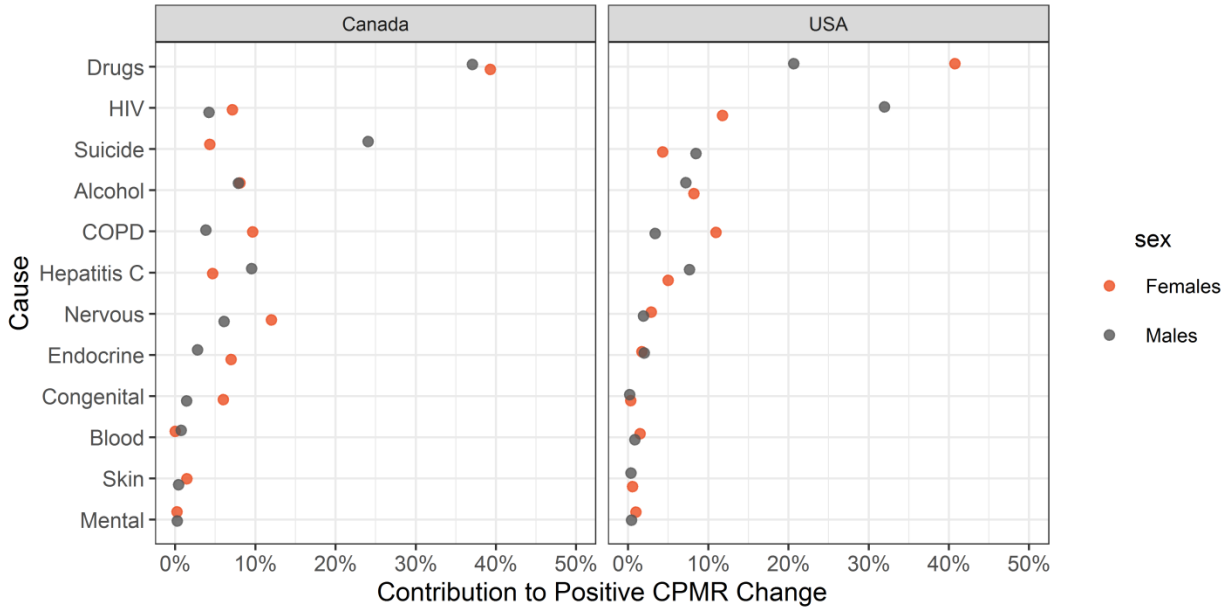
Table S2.2: ICD codes included in each category of causes of death, revisions 8th to 10th

ICD	8	9	10
Period	**1968-1978**	**1979-1998**	**1999-2016**
HIV/AIDS	NA	0420-0449	B20-B24
Hepatitis C	NA	0704-0705	B171, B182
Chronic lower respiratory diseases	4900-4939	4900-4939	J40-J47
Suicides	9500-9599	9500-9599	X60-84

ICD	8	9	10
Period	1968-1978	1979-1998	1999-2016
Drug-related causes (accidental overdoses + drug dependence)	2943, 3040-3049, 3091, 8500-8599, 9800-9803	2920-2929, 3040-3049, 3052-3059, 8490-8589, 9800-9805	F11-19, F55, X40-44, Y10-14
Alcohol-related causes (accidental alcohol intoxication + long-term harm from liver cirrhosis +)	2910-2919, 3030-3039, 5353, 5710, 8600-8609	2910-2919, 3030-3039, 3050, 3575, 4255, 5353, 5710-5713, 7903, 8600-8609	E244, F10, G312, G621, G721, I426, K292, K700-K709, K860, X45, Y15, Y90, Y91

Figure S2.2 depicts the contributions to the mortality deterioration of each cause of death. Increases in mortality from HIV/AIDS, hepatitis C, COPD, suicide, alcohol, and drugs contributed between 75% and 80% of the deterioration in mortality from the advantaged to the disadvantaged cohorts for both sexes in Canada and the United States.

Figure S2.2. Percentage contributions to the increase in $\Delta CPMR^{d-a(35,54)}$



Note: Only categories with positive contributions to $\Delta CPMR^{d-a(35,54)}$ of least 2% in the four subpopulations were included.

Estimates from the $\Delta CPMR_i^{d-a(35,54)}$ depicted in Figure 5.3 were useful for identifying the causes of death that made the largest contributions to the relative mortality deterioration between the *advantaged* and the *disadvantaged* cohorts within the age interval 35-54y.

However, this measure has two limitations. First, whereas the variable age is controlled when the mortality levels are compared within the same age interval, the variable period is not; consequently, changes in mortality over cohorts are confounded with changes over periods. For instance, the estimates of cohort differences in drug-related mortality levels could be the result of period variations. During the observed age interval, i.e., 35-54, the earliest cohorts were exposed for a shorter period of time and at incipient stages of the opioid epidemic (e.g., because the cohort 1945 was observed during the period 1980-1999, they had only been exposed to the initial years of the opioid crisis, which started in the late 1990s). The more recent cohorts, by contrast, had been exposed to the crisis for a more extended period, when it was in its more advanced stages (e.g., the cohort 1955 was observed during the period 1990-2009, when the opioid crisis was fully underway).

Second, while the decomposition of $\Delta CPMR^{d-a(35,54)}$ allows us to identify the causes of the relative mortality deterioration between the disadvantaged and the advantaged cohorts, because of how our window of observation was configured, we were not able to identify whether the causes of death that were responsible for the deterioration were also responsible for the subsequent improvements in mortality for the cohorts born after the boomers. If that was not the case (i.e., if the causes of the mortality deterioration were different from the causes of the subsequent improvements), the excess in all-cause mortality among the boomers would not be strictly related to the sum of multiple cause-specific excesses, but would instead be an artifact of more intricate processes involving increases in some causes and decreases in others.

To overcome these two limitations, and to properly assess the cohort's excess mortality by cause of death, we need to account simultaneously for variations over the three age-period-cohort (APC) dimensions.

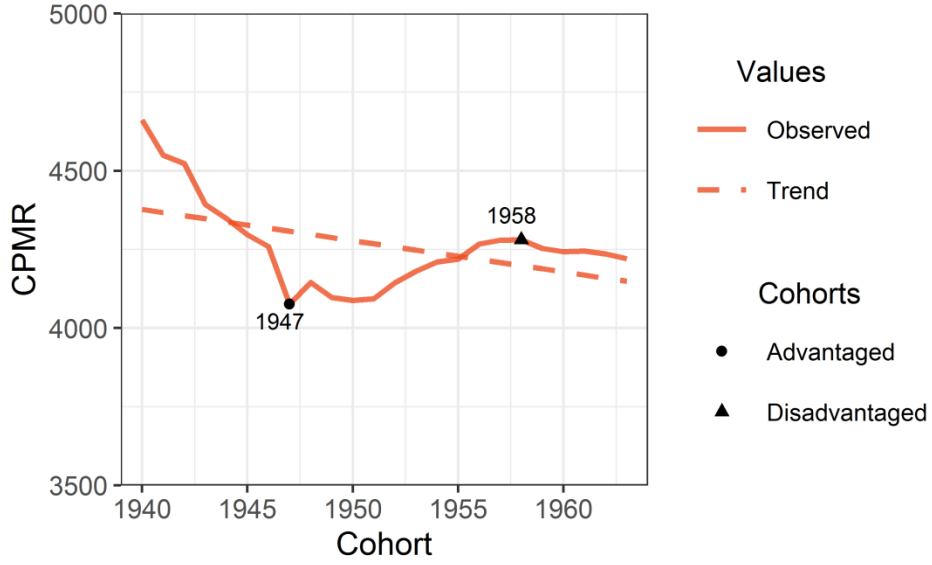
Alternative selection of disadvantaged cohorts

The selection criteria of the disadvantaged cohorts depicted in Figure 5.2 could be problematic for two reasons. First, for Canadian males, the cohorts 1954 and 1957 have similar degrees of deviance

from the linear trend of mortality (172 and 179, respectively), and it could be argued that $CPMR^{c(35,54)}$ is in absolute terms larger in 1954 than in 1957 (5,545 and 5,288, respectively). Second, since the highest degree of positive deviance from the mortality trend for U.S. females was reached by the cohort 1960 – i.e., the last cohort observed – we were not able to determine whether the deterioration in mortality continued among more recent cohorts. To address these points, we tested the consistency of our estimates by selecting 1954 as the disadvantaged cohort for Canadian males, and by extending the estimation of $CPMR^{c(35,54)}$ to more recent cohorts for U.S. females. These estimations are presented in the supplemental materials (see Figures S2.3 to S2.5).

The cause-specific contributions to the deterioration in mortality from the advantaged to the disadvantaged cohorts were sensitive to the locations imposed on these cohorts. In order to test the consistency of the estimates presented in Figure 5.3, we chose alternative locations for the disadvantaged cohorts in the cases in which the greatest divergence from the linear trend was not obvious. For Canadian males, the degree of deviation was roughly similar for the cohorts 1954 and 1957. Hence, we use 1954 as an alternative disadvantaged cohort. For U.S. females, the level of divergence did not stop increasing over the observed cohorts. We extended the estimation up to the cohort 1963, which was only possible by reducing the age interval to 35-53. These $CPMR^{c(35,53)}$ estimates between the cohorts 1940 and 1963 for U.S. females are depicted in Figure S2.3. According to these findings, the most disadvantaged cohort for this age interval is located in 1958.

Figure S2.3. Alternative estimates of the cohorts' partial mortality rates for U.S. females

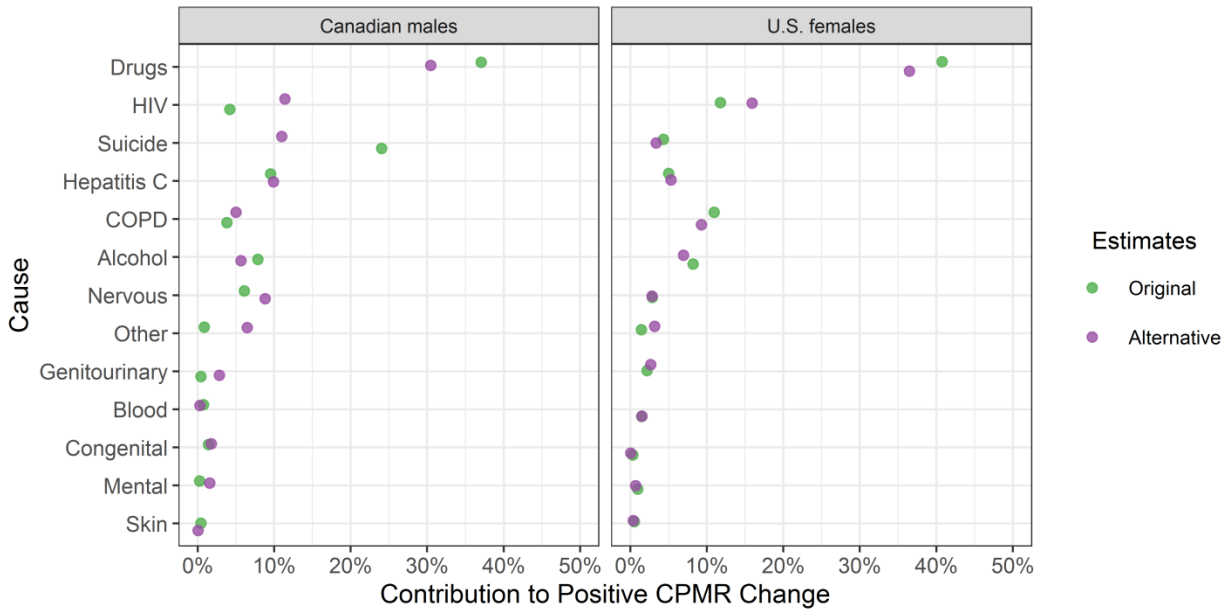


Notes: Cohorts' partial mortality rates (solid line) and the linear trend (dashed line) for U.S. females within the age interval 35-53 ($\mathbf{CPMR}^{c(35,53)}$), between the cohorts 1940 and 1963. The labels indicate the year of birth of the *advantaged* (circular shape) and the *disadvantaged* (triangular shape) cohorts.

In Figure S2.4, we compare the contributions by cause to the mortality deterioration of the *advantaged* and the *alternative disadvantaged* cohorts for Canadian males and U.S. females (in purple). To facilitate this comparison, the plot also presents the estimations of the cause-specific contributions obtained with the original disadvantaged cohorts (in green). Similarly, Figure S2.5 shows the cumulative contributions of the six leading causes of death to the mortality deterioration. As Figures S2.4 and S2.5 show, the contributions by cause of death to the mortality deterioration were highly similar between the estimates using the original location and those using the alternative location of the disadvantaged cohorts.

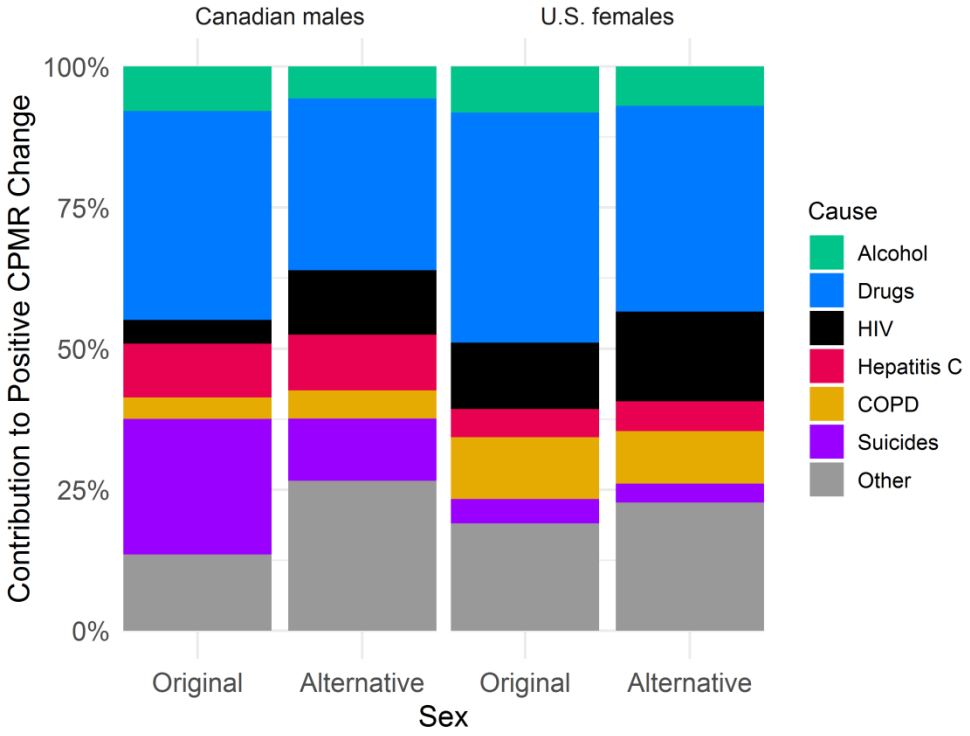
According to the estimates presented in Figures S2.3 to S2.5, the contributions of the leading causes to the mortality deterioration from the advantaged to the disadvantaged cohorts did not differ substantially when different disadvantaged cohorts were selected for Canadian males and U.S. females.

Figure S2.4. Alternative estimates of percentage contributions to the increase in $\Delta \boldsymbol{CPMR}^{\boldsymbol{d-a(k,l)}}$ for Canadian males and U.S. females



Notes: Percentage contributions to the increase in $\Delta CPMR^{d-a(k,l)}$ by cause of death for Canadian males ($\Delta CPMR^{d-a(35,54)}$) and U.S. females ($\Delta CPMR^{d-a(35,53)}$), according to the original (respectively, 1957 and 1960, in green) and the alternative (respectively, 1954 and 1958, in purple) disadvantaged cohorts. Only causes that contributed to mortality deterioration in all cases are shown.

Figure S2. 5. Alternative estimates of cumulative contributions by leading causes to the deterioration in mortality from the advantaged to the disadvantaged cohorts



Notes: Estimates according to the location of the disadvantaged cohort. For Canadian males, the disadvantaged cohort was originally placed in 1957, and alternatively in 1954. For U.S. females, the disadvantaged cohort was originally placed in 1960, and alternatively in 1958.

Detrended cohort effects from the APC model

Figure S2.6: APCd estimates by cause of death, sex, and country.

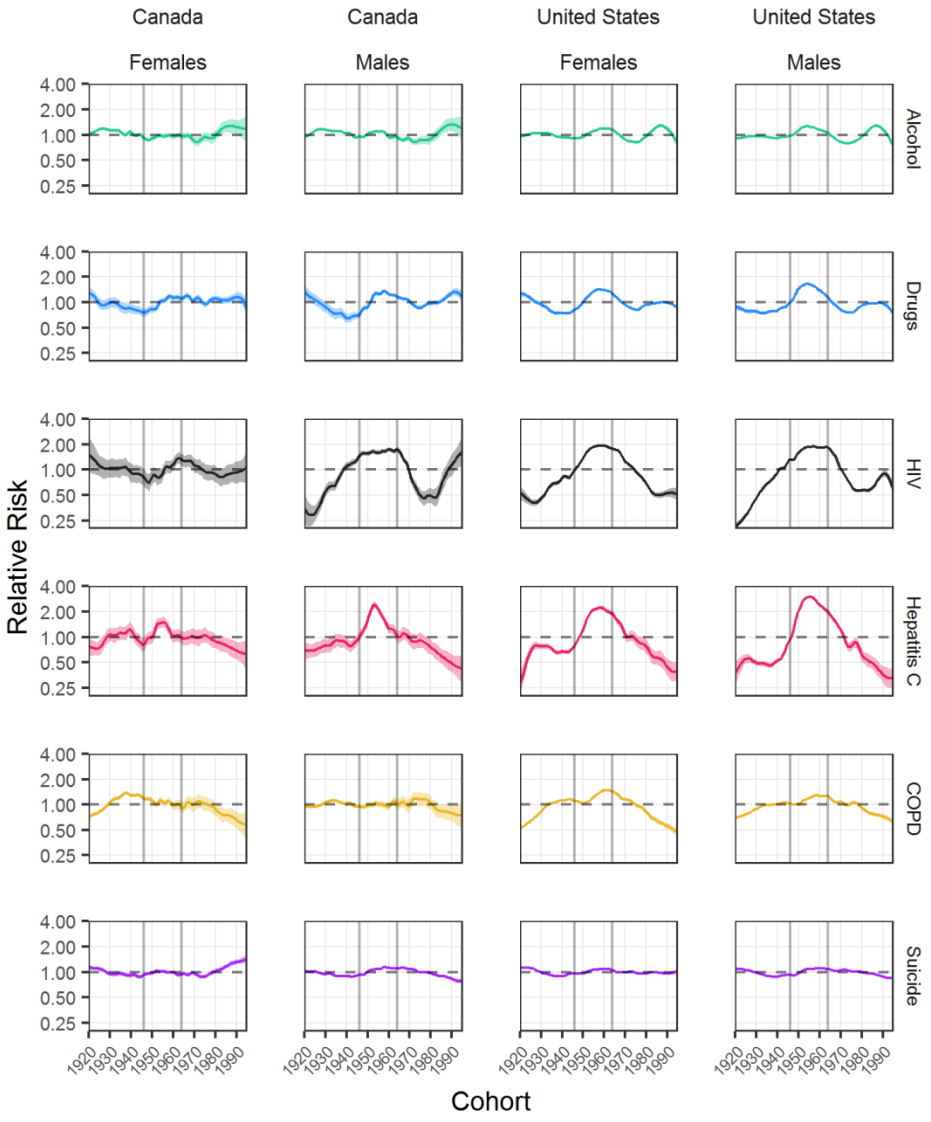
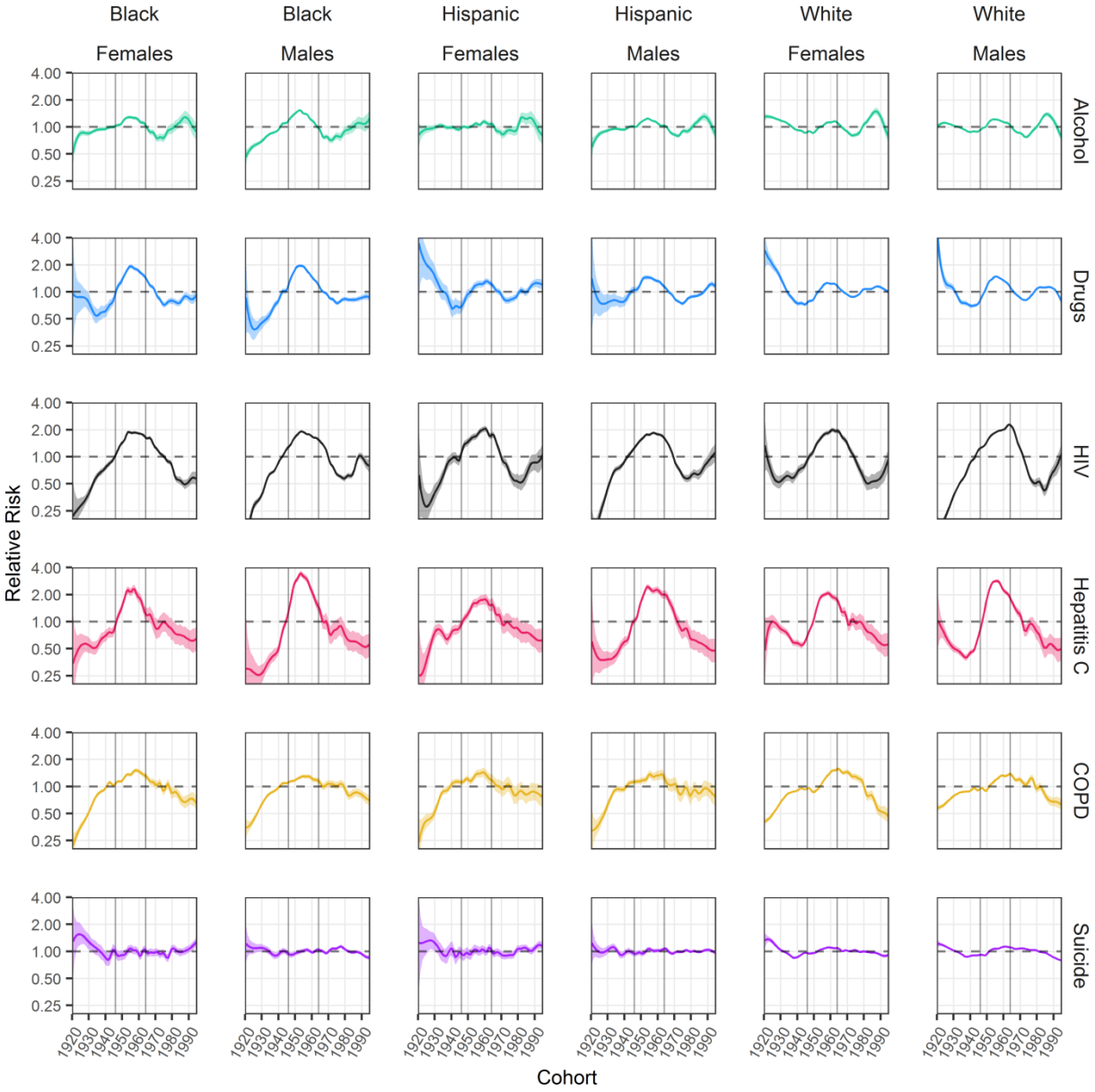


Figure S2.7: **APCd estimates for each sex and racial-ethnic group, comparing the leading causes of the boomers' excess mortality**



Temporal dynamic of the excess mortality among boomers by cause of death

Figure S2.8: Variation in relative risk at the ridge compared to the baseline over time by country

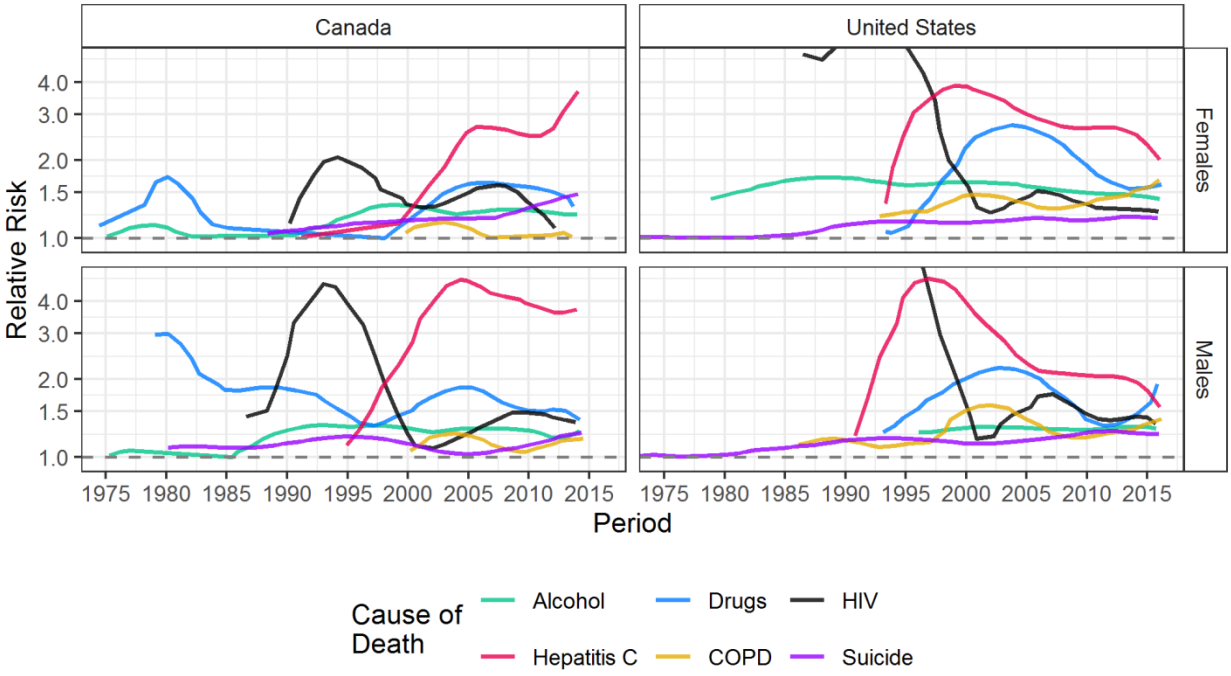
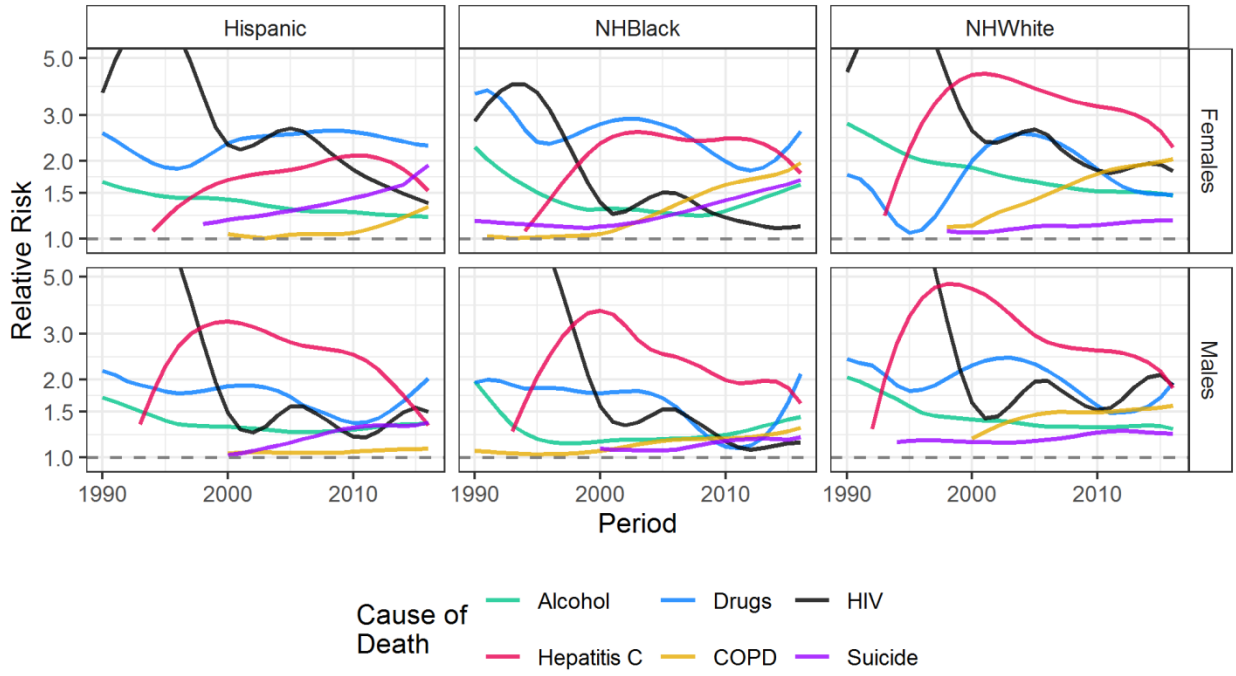


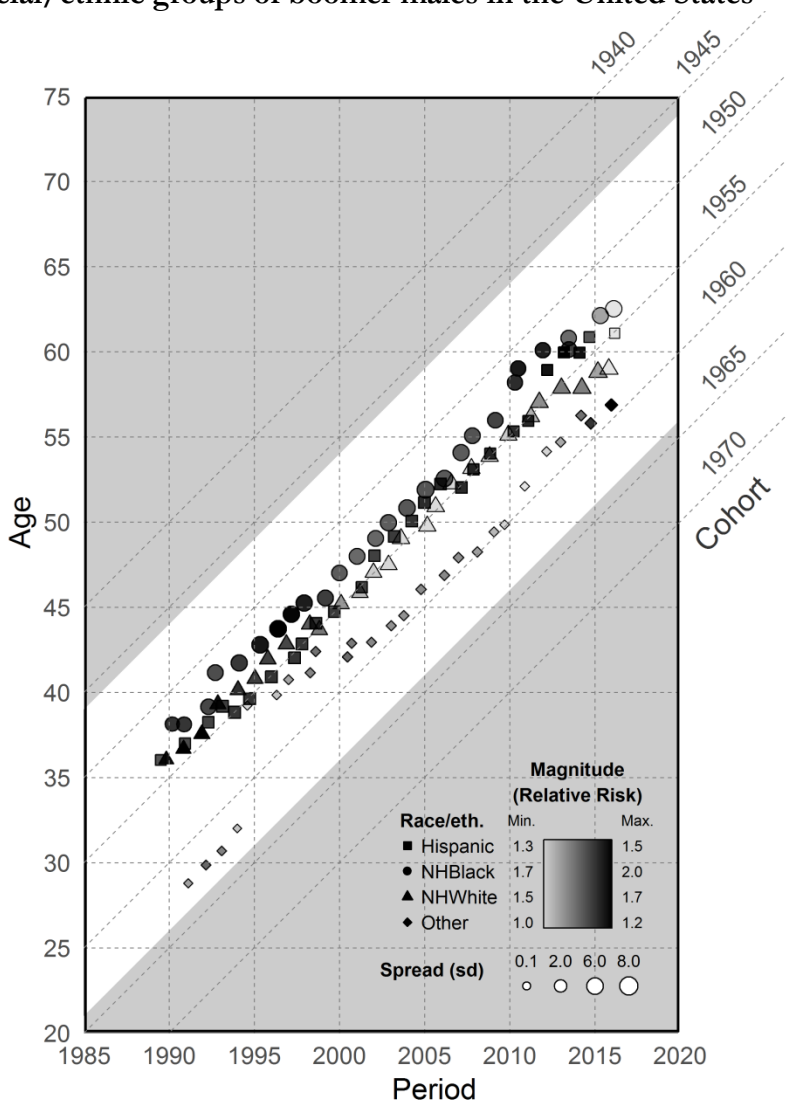
Figure S2.9: Variation in relative risk at the ridge compared to the baseline over time by race/ethnicity



Supplementary Material S3: Appendix APC Curvature Plots: Displaying Nonlinear Age-Period-Cohort Patterns on Lexis Plots

Black-and-white printout of the APC curvature plots

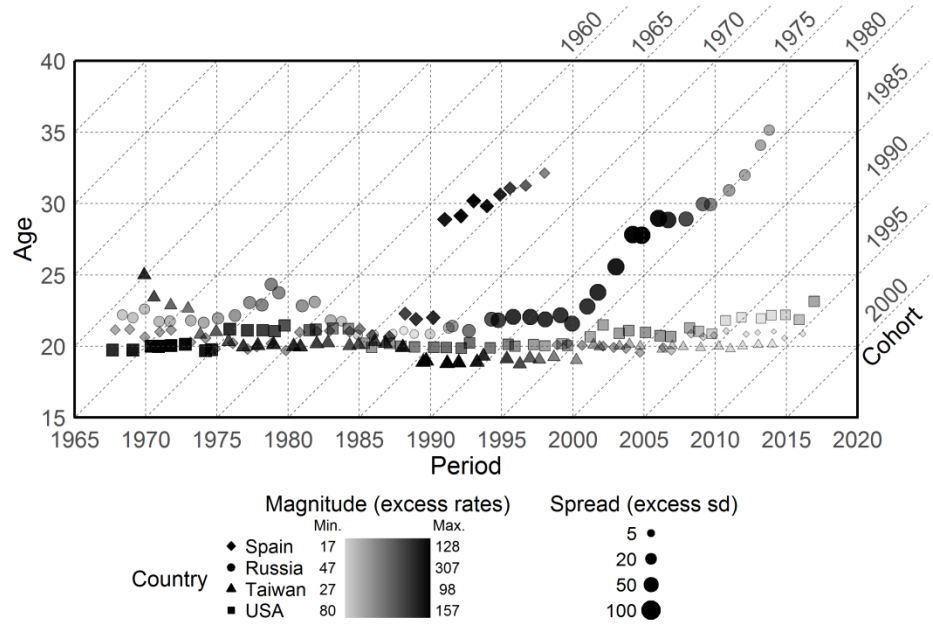
Figure S3.1: B&W APC curvature plot of the features of excess mortality from drug-related causes in four racial/ethnic groups of boomer males in the United States



Notes: The coordinates of the points indicate the location of the curvature ridge over time (i.e., the modal age/cohort with the excess mortality in each single-year period). The magnitude, indicated by the opacity, is measured as the relative risk of the death rate in the modal cohort to the corresponding death rate in the baseline. The minimum and maximum

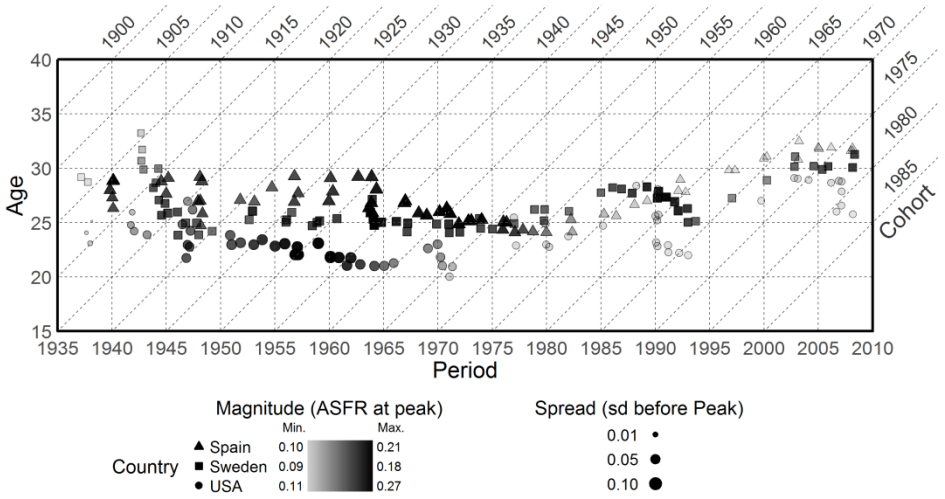
levels of relative risk that each racial/ethnic group reached during the period under observation are indicated in the legend. The spread, indicated by the point size, is estimated as the standard deviation of the curvature in each single-year period. The white band indicates the baby boomer cohorts (i.e. born between 1946 and 1964). A correction factor was applied to adjust the proportionality of areas across the shapes.

Figure S3.2: B&W APC curvature plot of the features of excess mortality in young adult males in four countries



Notes: The coordinates of the points indicate the location of the curvature ridge over time (i.e., the modal age/cohort of the excess mortality by single-year period/cohort). The magnitude, indicated by the opacity, is the excess death rates (/100k), calculated as the difference between the death rate in the modal age/cohort and the corresponding death rate in the baseline. The minimum and maximum excess mortality rates reached by country during the period under observation are indicated in the legend. Finally, the curvature spread, indicated by the point size, is estimated as the standard deviation of the curvature in each period. A correction factor was applied to adjust the proportionality of areas across the shapes.

Figure S3.3: B&W APC curvature plot of cohort fertility rate peaks in three countries



Notes: The coordinates of the points indicate the location of the curvature ridge along the cohort (i.e., the modal age/period of the ASFR by single-year cohort). The magnitude, indicated by the opacity, is measured as the ASFR mode by cohort. The minimum and maximum ASFR reached by the cohorts of each country are indicated in the legend. The curvature spread, indicated by the point size, is estimated as the standard deviation of the curvature before the modal age/period. A correction factor was applied to adjust the proportionality of areas across the shapes.

Guide to Reproduce the Analyses and Results Presented in the Paper

This guide presents the material required to fully reproduce the analyses and results presented in the paper. All the scripts were performed using R version: 3.6.1 (R Core Team 2019). Data inputs, scripts, and this document, are all available in the OSF link: https://osf.io/5bmyz/

Procedure for reproducing results

Open the master script (00_master.R) in a new R session. This script will execute all scripts required for reproducing the analyses and plots of the paper.

Before executing this master script, make sure to introduce within the quotation marks in lines 21-28 your username and password for the Human Mortality Database (HMD) and the Human Fertility Database (HFD). This information is required for constructing the APC curvature plots 6, 7, A2, and A3.

If you are not yet registered in these databases, you can do it in the respective websites https://www.mortality.org/ and https://www.humanfertility.org/.

Our scripts assume that the current working directory is the folder in which the master script (00_master.R) lives. If you open a new R session by double-clicking on the master file (00_master.R) then the current working directory should be set correctly.

You can also set the working directory to the folder where the master script (00_master.R) lives by typing a setwd() command in the R console. For example, on a Windows system you might type

setwd(C:/Users/Jane/apc_curvature_plots_rep_material/)

whereas on a Mac you might type

setwd(/Users/Jane/apc_curvature_plots_rep_material/)

Description of the files contained in the ZIP archive

The zip. file contains 1 data file and 12 scripts

Folder "data"

The file db_drugs_deaths_exposures_race.csv contains all drug-related male deaths and exposure-to-risk in the United States for the period 1990-2016, by single years of age, and race/ethnicity.

The mortality counts (456.776 deaths) were obtained from the micro-data files of the U.S. National Vital Statistics System. Here, we define drug-related mortality as deaths involving drug use registered in the categories of accidental and undetermined intent overdoses, or in the categories of mental or behavioral causes (i.e., ICD 10 codes F11-19, F55, X40-44, Y10-14).The raw files are available in http://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html

The exposure to death data come from the HMD and the proportion by race and ethnicity was estimated from the Bridged-Race Population Estimates. The raw files are available in https://www.cdc.gov/nchs/nvss/bridged_race/data_documentation.htm

Folder "scripts"

These are the R-files for generating the main results described in the paper. All these scripts are called from the master script.

- aa00_preparing_R_session.R: Script for preparing the R session: Installing and loading required packages for running the scripts.
- an01_smooth_US_mort_by_race_1990_2016.R: Estimation of smoothed, interpolated, and excess death rates of drug mortality in the US, by race.
- an02_excess_from_dAPC_Carstensen_function.R: Script for estimating of excess death rates of drug mortality in the US, by race, as the difference between the smoothed mortality rates and a baseline obtained from a dAPC model with the cohort terms set at zero.
- fg01_obs_&_smth_drugs.R: Script for plotting Figure 1: Lexis surface of observed and smoothed drug-related mortality rates for Hispanic males in the United States.
- fg02_drugs_cohort_effects.R: Script for plotting Figure 2: Relative risks of drug-related mortality for cohorts of Hispanic males in the United States.
- fg03_surfaces_change.R: Script for plotting Figure 3: Lexis surfaces of changes in drug-related mortality rates over age/cohort and over period/cohort for Hispanic males in the United States
- fg04a_excess_from_interpolation.R: Script for plotting Figure 4a: Lexis surfaces of the excess drug-related mortality rates for male Hispanic boomers in the United States during 1990-2016, ages 15-75. Excess mortality rates (/100k) estimated as the difference between the smoothed mortality rates and an interpolated baseline that omits the 1940-1970 cohorts from the Lexis mortality surface.
- fg04b_excess_from_dAPC_curvatures.R: Script for plotting Figure 4a: Lexis surfaces of the excess drug-related mortality rates for male Hispanic boomers in the United States during 1990-2016, ages 15-75. Excess mortality rates (/100k) estimated as the difference between the smoothed mortality rates and a baseline obtained from a dAPC model with the cohort terms set at zero; i.e., centered at the linear trend component of the cohort effects.
- fg05_APC_curvatures_plot_boomers.R: Script for plotting Figures 5 and A1: APC curvature plot of the features of excess drug-related mortality among four racial/ethnic groups of boomer males in the United States.
- fg06_APC_curvatures_plot_young_hump.R: Script for plotting Figures 6 and A2: APC curvature plot of the features of excess mortality in young adult males in four countries.

- fg07_APC_curvatures_plot_cohort_fertility.R: Script for plotting Figures 7 and A3: APC curvature plot of cohort fertility rate peaks in three countries.

Folder "figures"

All figures (1 to 7, and A1 to A3) will be stored in this folder.