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Socioeconomic Determinants and Evolution of Health over the Later Life Course: Longitudinal Evidence from China, the U.S., and Europe

Cheng Mengling

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FACULTÉ DES SCIENCES SOCIALES ET POLITIQUES

INSTITUT DES SCIENCES SOCIALES

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THÈSE DE DOCTORAT

présentée à la

Faculté des sciences sociales et politiques
de l'Université de Lausanne

pour l'obtention du grade de

Docteure en sciences sociales

par

Mengling Cheng

Directeur de thèse
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"Socioeconomic Determinants and Evolution of Health over the Later Life Course : Longitudinal Evidence from China, the U.S. and Europe."

Nicky LE FEUVRE
Doyenne

Lausanne, le 26 mars 2024

Abstract

This thesis adopts a life course perspective to investigate how socioeconomic determinants impact later-life health. It pursues two lines of inquiry. The first line of inquiry revolves around the role of early-life exposure to famine in predicting health trajectories. The second line of inquiry revolves around the role of income also in predicting health trajectories. Empirical analyses rely on advanced analytical tools and various datasets, namely, the China Health and Retirement Longitudinal Study, the Health and Retirement Study from the U.S., the Survey of Health, Ageing and Retirement in Europe, and the Dutch Hunger Winter Families Study. Results from the first line of inquiry showed that individuals exposed to famine had a higher risk of non-communicable diseases and a faster pace of biological aging six decades later. Underlying mechanisms involve developmental time windows, cumulative advantage/disadvantage, and gender differences. Results from the second line of inquiry showed that for physical health the income–health gradient weakened as individuals age, whereas for cognitive health the income–health gradient strengthened with aging. Possible explanations are that physical health may be more biologically grounded and cognitive health may be more socially grounded. Taken together, these two lines of inquiry provide a comprehensive picture of how historical context and personal life history shape health trajectories. This thesis concludes by reflecting on the lifelong process of aging and health, the multidimensional nature of health, and cross-cultural similarities and differences in shaping individual health trajectories.

Résumé

Cette thèse adopte la perspective de parcours de vie pour étudier l'impact de déterminants socio-économiques sur la santé des adultes âgés. Elle poursuit deux axes de recherche. Le premier axe de recherche concerne le rôle de l'exposition à la famine au début de la vie pour prédire les trajectoires de santé. Le second axe de recherche concerne le rôle du revenu, également pour prédire dans la prédiction des trajectoires de santé. Les analyses empiriques s'appuient sur des outils analytiques avancés et diverses bases de données, à savoir le China Health and Retirement Longitudinal Study, le Health and Retirement Study, le Survey of Health, Ageing and Retirement in Europe, et le Dutch Hunger Winter Families Study. Les résultats de la première ligne de recherche ont montré que les individus exposés à la famine présentaient un risque plus élevé de maladies non transmissibles et un rythme de vieillissement biologique plus rapide six décennies plus tard. Les mécanismes sous-jacents renvoient aux questions des fenêtres temporelles de développement, des avantages/désavantages cumulatifs et des différences entre les sexes. Les résultats de la deuxième ligne de recherche ont montré que pour la santé physique, le gradient revenu-santé s'affaiblissait avec l'âge, alors que pour la santé cognitive, le gradient revenu-santé se renforçait avec l'âge. Une explication possible résident dans le fait que la santé physique est peut-être plus biologiquement ancrée alors que la santé cognitive est peut-être plus socialement ancrée. Ces deux lignes de recherche sont reliées fournissent une illustration de la façon dont le contexte historique et l'histoire de la vie personnelle façonnent les trajectoires de santé. Cette thèse se termine par un ensemble de réflexions sur le processus de vieillissement et de santé tout au long de la vie, la nature multidimensionnelle de la santé, ainsi que les similitudes et les différences interculturelles dans la formation des trajectoires de santé individuelles.

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1. Introduction

We live in a world where population is aging rapidly (Lancet Healthy Longevity, 2021). This trend is not limited to high-income countries. Many low-income and middle-income countries are also experiencing rapid shifts toward an older population (Goodman-Palmer et al., 2023). By 2050, about 80% of individuals aged 60 years and above are projected to live in low-income and middle-income countries (United Nations, 2020). Such a large proportion of older adults present a global challenge to health systems and social services (Sleeman et al., 2019), particularly for low-income and middle-income countries where resources are limited (Cheng et al., 2020).

We also live in a world where economic disparities are widening (Chancel et al., 2022) and food insecurity is rising (Xia et al., 2022). The top 10% income share was about 50% in 2018 in the U.S. (Saez, 2020) and OCED countries (Organisation for Economic Cooperation and Development, 2019); and the Gini coefficient reached 0.55 in 2012 in China (Xie & Zhou, 2014). Globally, more than 345 million individuals are facing acute food insecurity and as many as 783 million individuals are facing chronic hunger in 2023 (World Food Programme, 2023). The widening economic inequalities and rising food crisis present a great challenge to health (Kuo & Kawachi, 2023; Lancet Gastroenterology & Hepatology, 2023).

In this context, the overall aim of this thesis is to investigate the socioeconomic determinants of health in later life. In contrast to many existing studies that lack a life course perspective, this thesis examines how historical contexts early in life and socioeconomic status over the life course predict health among older adults. Such an approach is essential for advancing our understanding of the complex nature of aging and health, as it focuses on individual trajectories of aging and health within both historical and social contexts (Ben-Shlomo et al., 2016; Bernardi et al., 2019; Elder et al., 2003). Based on this, the current thesis pursues two lines of inquiry.

Introduction

The first line of inquiry revolves around the role of early-life adversity shaped by specific historical and collective events in predicting later-life health. Despite famines have been prevalent throughout history and still threaten millions of individuals in contemporary times, the long-term health effects of famines remain poorly understood (Ekamper et al., 2015; Li et al., 2023; Short & Baram, 2019). Does famine exposure link to later-life health? Does the timing of famine exposure matter for later-life health? Is there a dose response effect? Do the effects of famine vary between women and men? The first and second empirical chapters of this thesis seek to answer these questions by focusing on the Chinese famine of 1959-1961 and the Dutch Hunger Winter of 1944-1945.

The second line of inquiry revolves around the role of individual-level socioeconomic status (SES) in later life in predicting health trajectories over time. Although the association between income and health—known as the income–health gradient—is well established (Adler et al., 1994; Chetty et al., 2016; Sareen et al., 2011), its evolution over the later life course remains poorly understood. Does the association between income and health weaken, widen, or remain stable with older age? Do patterns in the evolution of such association vary between physical health and cognitive health? Are these patterns gendered? Can these findings be generalized to different cultural settings? The third and fourth empirical chapters of this thesis seek to answer these questions by focusing on the U.S., Europe, and China.

Together, these two lines of inquiry provide a comprehensive picture of how later-life health evolves in the context of the broader history of a society and the personal life history of an individual. Histories, be they collective or individual, play a key role in shaping health outcomes in later life. The life course perspective provides a useful approach for placing individuals in a specific historical context and life history (Bengtson et al., 2005). Guided by the life course perspective, this thesis focuses not only on the fundamental importance of historical conditions but also on the role of the evolution of an individual's life course for

understanding human development and health. On the one hand, historical events or contexts can influence various outcomes such as attitudes, behaviors, and health outcomes over time. Collective history leaves a lasting mark on individuals who share the social, cultural, and historical circumstances. On the other hand, individual life history can play a role in shaping socioeconomic environments, transitions in life stage, and human agency. Personal life history presents variability in individuals' life trajectories over time. Taken together, this thesis advances our understanding of aging and health in context.

1.1 Evolution of Later-Life Health

1.1.1 Conceptualization of Later-Life Health

The concept of health was long confined to just the physical dimension. However, in 1948, the World Health Organization proposed a paradigm shift in understanding the concept of health. According to the organization, health should be viewed as a multidimensional concept involving physical, mental, and social well-being aspect (World Health Organization, 1948), a perspective that has since been widely accepted (Hjelm, 2010). Physical health usually concerns disability, impairments, chronic condition, symptoms, and energy level (Breslow, 1972). Mental health concerns the internal equilibrium which enables individuals to use their abilities in harmony with universal values of society (Galderisi et al., 2015). Social health concerns social integration, social contribution, social coherence, social actualization, and social acceptance (Keyes, 1998). Importantly, the physical, mental, and social dimensions of health are connected in a way that one dimension can influence another dimension. For example, loneliness is a risk factor for both physical health and mental health (Mann et al., 2022; F. Wang et al., 2023). In both lines of inquiry, I use the multidimensional concept of health, with a primary focus on biological aging and physical and cognitive aspects.

Moreover, health is not a static state, but is a dynamic process (Huber et al., 2011) that responds to age-specific, culture-specific, individual demands and challenges (Bircher, 2005). This is because health is shaped by not only biological factors (Bortz, 2005), but also socioeconomic factors (Braveman et al., 2011). Socioeconomic environment in which individuals are nested can have a significant impact on their health. For example, social policies that enhance educational attainment, provide equal access to health services, and income redistribution improve health outcomes (Mechanic, 2002). Lower-level socioeconomic factors, which are fundamentally shaped by socioeconomic environment, can also affect the health of an individual. For example, higher income is a protective factor for health of an individual (Chetty et al., 2016). In both lines of inquiry, I adopt the dynamic perspective on health and study the health trajectories over the later life course.

Older age is characterized by progressive changes in physical, mental, and social health. Prevalent health conditions in later life include non-communicable diseases (Makovski et al., 2019), disability (GBD 2019 Ageing Collaborators, 2022), and loneliness (Blazer, 2020). During the aging process, individuals tend to experience biological damage that occurs at molecular and cellular levels (Kirkwood, 2014). Such biological damage does not only lead to an accelerated rate of biological aging (Ferrucci et al., 2020) but also cause a gradual decrease in physical health (Rivero-Segura et al., 2020). In addition, as individuals age, they tend to experience a reduction in their social network and an increase in feelings of social disconnectedness or isolation; these changes can lead to a decline in mental health, manifesting as heightened anxiety and depression (Santini et al., 2020). Moreover, as individuals age, they are more likely to experience bereavement of loved ones, which can have detrimental effects on their social health (Donovan & Blazer, 2020). In both lines of inquiry, I not only consider the multidimensional nature of later-life health but also treat it as a dynamic construct.

Lastly, there might be sex or gender differences in health trajectories. Sex refers to the biological attributes that distinguish male and female individuals, which reflect genetic, hormonal, and morphological heterogeneity between male and female individuals (Mauvais-Jarvis et al., 2020). Gender refers to the socially constructed norms that determine roles, relationships, and positional power for individuals over the life course (Shannon et al., 2019). Sex or gender differences in health can be explained by male vulnerability and differential levels of exposure to risks and/or protective factors among women and men. In terms of male vulnerability, there is evidence that males are more vulnerable to environmental conditions (Wells, 2000) and variation in survival between males and females can be substantial (Iannuzzi et al., 2023). As a result, males who survived adverse environmental conditions and survived into older age tend to be particularly robust compared with their female counterparts. In terms of differential levels of exposure to risks and/or protective factors, women are more likely to have a higher level of exposure to risks but limited access to protective factors than men (Gu et al., 2009; Read & Gorman, 2010). As a result, women accumulate disadvantages more easily than men in the inequality accumulation process (Ferraro et al., 2009). In both lines of inquiry, in addition to considering the multidimensional and dynamic nature of later-life health, I also consider sex/gender difference in health trajectories. The choice between sex and gender is made based on the variable of interest and possible mechanisms involved (Colineaux et al., 2022). In the first line of inquiry, I am interested in famine exposure and therefore interpreting differences in the famine effects between women and men as reflecting differences between the sexes. In the second line of inquiry, I am interested in income and therefore interpreting differences in the role of income between women and men as reflecting differences between genders.

1.1.2 Life Course Perspective in Studying Later-Life Health

1.1.2.1 Life Course Perspective

Introduction

Life course perspective originated from sociology, and can be traced back to Cain's (1964) work on life course and social structure. Later on, Elder (1974) conducted a study on children who grew up during the Great Depression in the 1930s. In this longitudinal study, Elder followed a cohort of 167 participants born in 1920 or 1921 through the 1960s. This extended period of follow-up enabled him to investigate the long-term effects of the Great Depression. This study inspired subsequent sociological research to focus more on inequalities over the life course (e.g., Macmillan, 2005; Mayer & Schoepflin, 1989). Today, life course perspective is both multidisciplinary and interdisciplinary, with applications in various disciplines, like gerontology (Lampraki et al., 2023), public health (Black et al., 2017), epidemiology (Ben-Shlomo et al., 2016), geroscience (Ferrucci et al., 2016), and psychology (Spini et al., 2017), among others.

Definitions of the life course have evolved over time. Elder and O'Rand (1995) defined the life course as interlocking trajectories or pathways across the lifespan that are marked by sequences of events and social transitions. This definition positions the individual life events within broader social contexts. Later on, Giele and Elder (1998) defined the life course as a sequence of socially defined events and roles that an individual enacts over time. This definition extends the previous definition by highlighting the role of an individual in coping with socially structured life events. More recently, Bernardi et al. (2019) defined the life course as a multifaceted process of individual behavior that evolves from the steady flow of individuals' actions and experiences, which in turn modify their biographical states. This definition recognizes the multifaceted nature of the life course and emphasizes the interplay between life events and individual agency.

The foundational elements of these definitions are the five principles of the life course: life-span development; agency; time and place; timing; and linked lives (Elder & Johnson, 2003).

(1) The first principle, life-span development, posits that human development and aging are lifelong processes. This is because individual development interacts with social change in settings like family, school, workplace, and community. As a result, human development and aging occur in various life course periods from formative years throughout later life.

(2) The second principle, agency, posits that individuals construct their life course through choices and actions in situations that vary in terms of constraints and opportunities. This principle highlights the importance of initiative: Individuals are not passively influenced by social structure and change; instead, individuals make plans and choices and take actions based on historical and social circumstances.

(3) The third principle, time and place, posits that the life course of an individual is embedded and shaped by historical context and place. This principle highlights the influence of historical event and place for a given cohort. Historical circumstances exert an impact on groups of individuals during specific periods, and such impact may differ in magnitude or meaning across regions or nations.

(4) The fourth principle, timing, posits that the same exposures may affect individuals differently depending on when it occurs in the life course. This principle highlights the importance of temporal aspect of an exposure. This is because the very meaning of an exposure can change for individuals at different life course periods.

(5) The fifth and last principle, linked lives, posits that lives of individuals are lived interdependently and social changes affect individuals through shared relationships. This principle highlights the importance of interpersonal contexts and relationships, reminding us to consider the life course of an individual in relation to other people in the shared network.

1.1.2.2 Life Course Perspective in Studying Later-life Health

The life course perspective holds significant importance and offers three key insights into aging research. First, the life course perspective emphasizes the historical time that shape

individual experiences of aging and health (Elder et al., 2003). Comparisons in a historical lens bring sharper focus to the here and now. An example is a recent study on wartime experiences and frailty in later life in Vietnam (Zimmer et al., 2021). This study showed that exposure to war in early life had lasting effects and individuals exposed to war had a higher risk of frailty in later life five decades later.

Second, the life course perspective emphasizes the social and cultural contexts in which individuals age (Fry, 2018). That is to say, individual lives are to be understood in a broader context of society and culture. A closer look into social and cultural characteristics can provide better insights into the individual life course. An example is a recent study on life course socioeconomic status and health in later life across welfare regimes (Sieber et al., 2020). This study revealed that the education-related gap in self-rated health narrows with increasing age in Bismarckian welfare states such as Germany, Austria, and the Netherlands, whereas the occupation-related gap in self-rated health narrows with increasing age in Scandinavian welfare states such as Denmark and Sweden.

Third, the life course perspective emphasizes the timing of exposures that impact human development and aging across different periods of life (Ben-Shlomo & Kuh, 2002). An example is a recent study on exposure to the Great Depression in the 1930s and health in later life among U.S. residents (Schmitz & Duque, 2022). This study showed that individuals exposed to the Great Depression in utero, as opposed to the preconception, postnatal, childhood, or early adolescent periods, experienced accelerated epigenetic aging in later life.

Fourth and finally, the life course perspective emphasizes a long-term approach to capture changes in socioeconomic status and health (Kuh et al., 2003). An example is a recent study on socioeconomic status mobility and health in later life among Chinese residents (Payne & Xu, 2022). This study showed that individuals with persistently low SES throughout life

were most disadvantaged in terms of life expectancy and disability-free life expectancy. The subsequent section delves into a review of four life course models in aging research.

1.1.3 Life Course Models on the Evolution of Later-Life Health

Various life course models have been proposed to account for the long-term effects of an exposure on later-life health (Kuh et al., 2003). Herein, this section provides an overview of four life course models that have been supported by empirical evidence: (i) the critical period model (Mishra et al., 2008), (ii) the sensitive period model (Darin-Mattsson et al., 2018), (iii) the pathway model (Haas, 2008), and (iv) the accumulation model (Singh-Manoux et al., 2004). A summary of these life course models can be found in **Table 1.1**.

The *critical period model* and *sensitive period model* are related yet distinct. Both models suggest that an exposure during a specific developmental phase of life can have long-term health consequences (Dunn et al., 2018; Hallqvist et al., 2004). However, these two models diverge when it comes to the possibility of reversing or modifying the long-term health consequences. The critical period model posits that health consequences cannot be reversed or modified by subsequent exposures (Mishra et al., 2008). In contrast, the sensitive period model posits that, to some extent, it is possible to modify or even reverse these consequences beyond that specific developmental phase of life (Darin-Mattsson et al., 2018). One study that illustrates the sensitive period model is the research on early-life socioeconomic status and later-life health by Cheval et al. (2018). In this study, the authors followed a total of 24,179 older adults aged 50–96 in 14 European countries from 2004 to 2015. They found that early-life socioeconomic disadvantages at age 10 were associated with increased risk of low muscle strength in later life. This association weakened after adjusting for adulthood socioeconomic status, meaning that the effect of early-life exposure could be mitigated by adulthood exposure.

The *pathway model* suggests that an exposure in early life is linked to health consequences in later life through chains of risk or protective factor (Lyu & Burr, 2016). The

pathway model emphasizes the sequence of exposures, particularly life events during developmental transitions and turning points (Halfon & Hochstein, 2002). The pathway model suggests that an exposure in early life not only directly links to health consequences in later life, but also can act as a catalyst for risk/protective factors at a later life period that lead to health consequence in later life (Haas, 2008; Lee et al., 2021). One study that illustrates the pathway model is the research on life course socioeconomic status and later-life cognition by Künzi et al. (2021). In this study, the authors followed a total of 993 older adults aged 70–103 in Switzerland from 2011 to 2017. They found that childhood socioeconomic disadvantages were associated with worse memory in later life, through the pathway of adulthood socioeconomic status. Lower childhood socioeconomic status significantly led to lower adulthood socioeconomic status, and lower adulthood socioeconomic status subsequently led to worse later-life memory.

The *accumulation model* suggests that an exposure in early life can have cumulative effects which lead to health consequences in later life (Otero-Rodríguez et al., 2011). This model focuses on the total amount or duration of exposures (Lynch & Smith, 2005). The accumulation model suggests that a higher number/longer duration of exposures at different life course periods creates the accumulation of advantages and/or disadvantages over the life course that contribute to health consequences in later life (Singh-Manoux et al., 2004). One study that illustrates the accumulation model is the research on life course socioeconomic status and later-life health by Ramsay et al. (2018). In this study, the authors followed a total of 2,147 older men aged 71–92 in England from 1978 to 2012. They found that socioeconomic disadvantages across multiple periods of life, i.e., childhood, middle age, and later life, reflected an accumulation of risk. The accumulation of disadvantages were associated with poor self-rated oral health in later life.

Introduction

This thesis pursues two distinct lines of inquiry related to the socioeconomic determinants of later-life health. The first line of inquiry examines how early-life adversity, shaped by a specific historical and collective events (i.e., exposure to famine), predicts later-life health decades later. This first line of inquiry is linked to the critical period model, sensitive period model, pathway model, and accumulation model to investigate the link between early-life famine exposure and later-life health. The second line of inquiry examines how the associations between individual-level socioeconomic status in later life and health evolves over time. This second line of inquiry is linked to the pathway model and accumulation model to investigate changes in the impacts of socioeconomic status on later-life health.

Table 1.1. Summary of Life Course Models and Implications for the Thesis

Life course models	Definition	Connection to the thesis
Critical period model	An exposure during a specific developmental phase of life has long-term, irreversible/unmodifiable health consequences.	First line of inquiry
Sensitive period model	An exposure during a specific developmental phase of life has long-term, reversible/modifiable health consequences.	First line of inquiry
Pathway model	An exposure in early life is linked to health consequences in later life through chains of risk or protective factor.	Second line of inquiry
Accumulation model	An exposure in early life has cumulative effects on health consequences in later life.	First line of inquiry; Second line of inquiry

1.2 First Line of Inquiry: Developmental Origins and Later-Life Health

1.2.1 The Long Arm of Early-Life Adversity

Early life is a pivotal life stage in the life course of an individual. Adversity—defined as negative experiences or life events (Oh et al., 2018)—during this period can exert long-term effects on health in later life, a phenomenon that has been explored through the lens of various disciplines, like developmental psychology (Amir et al., 2018), public health (Duffy et al., 2018), epidemiology (Turner et al., 2020), sociology (Almquist & Brännström, 2018), and gerontology (Williams et al., 2018). One landmark study on early-life adversity is the work by Kessler et al. (2010). In this study, the authors examined joint associations between 12 childhood adversities and mental health over the life course among 51,945 participants in 21 countries. This study found that childhood adversity in the form of family dysfunction was the strongest predictor of lifetime mental health. Altogether, childhood adversities account for 29.8% of mental disorders across countries. Another notable study is the work by Shi and Dong (2022), who investigated the associations between early-life chronic poverty and two later-life health outcomes: Self-rated health and depression. This research, which includes more than 6,000 participants aged 45–90 years living in rural China, found that those who experienced early-life chronic poverty were more likely to have worse self-rated health and higher risk of depression in later life. A third study worth mentioning is by Noghanibehambari (2022), who investigated the associations between in-utero exposure to earthquakes and later-life mortality. The study encompassed 1,467,750 U.S. participants aged 34–105 years and found that compared with individuals unexposed to earthquakes, individuals exposed during the first trimester had 1.8 months reduction in longevity.

Early-life adversity is typically measured using a multifaceted approach that categorizes exposures into four key domains (Flaherty et al., 2009; Lopez et al., 2021). The first category is *abuse*, which encompasses various forms of physical, mental, or emotional

maltreatment that an individual may experience in early life. A recent study by Y.-X. Wang et al. (2023) showed that physical abuse in childhood (before age 12 years) or adolescence (12–17 years) was associated with a higher risk of premature mortality. The second category is *neglect*, which refers to the lack of attention, proper care, or nurturing during formative years. A recent study by Jakubowski et al. (2023) showed that neglect was associated with a higher risk of dysregulation of metabolic, cardiovascular, and inflammatory systems in later life. The third category is *household dysfunction*, which includes domestic violence, parental mental health issues, or substance abuse encountered in a family setting in early life. A recent study by Zhao et al. (2023) showed that experience of domestic violence in early life was associated a higher risk of multimorbidity in later life. The last category is *stressor*, which covers major life events, environmental strains, or financial hardship experienced in early life. A recent study by Zimmer et al. (2021) showed that exposure to war in early life was associated with a higher risk of frailty in later life.

1.2.2 Developmental Origins of Health and Disease Hypothesis

The Developmental Origins of Health and Disease (DOHaD) hypothesis is useful to understand the long-term effects of early-life adversity on health in adulthood and later life (Lucas et al., 1999). A summary of the DOHaD hypothesis is shown in **Table 1.2**. DOHaD hypothesis represents a paradigm shift in the understanding development and health. The DOHaD hypothesis, which originated from the work of David Baker, posits that early life, particularly the fetal development phase, plays a key role in shaping the health trajectories of an individual. In a groundbreaking study, Barker (1995) showed that fetal undernutrition in middle to late gestation led to disproportionate fetal growth, thus essentially programing coronary heart disease later in life. This study advanced our understanding of health in adulthood and later life by highlighting the role of early-life exposures in developing later-life chronic diseases. The DOHaD hypothesis has been supported by later studies on the impact of

early-life adversity on cardiovascular and metabolic health. For instance, Gluckman and Hanson (2004), Gluckman et al. (2008), and Painter et al. (2006) have shown that exposure to adversity in early life can program physiological changes that are related to cardiovascular and metabolic diseases. As another example, Haapanen et al. (2024) have shown that exposure to early-life adversity was associated with a faster rate of chronic disease accumulation across older age.

Three underlying mechanisms have been proposed to explain the link between early-life adversity and later health outcomes. The first underlying mechanism is *metabolic imprinting*, which posits that early-life adversity can leave lasting marks on metabolism in various ways (Waterland & Garza, 1999). These can range from changes in organ structure, alterations in cell number within specific tissues, selective survival and proliferation of specific cell populations, apoptotic remodeling, to metabolic differentiation. The second underlying mechanism is *genomic imprinting*, which posits that early-life adversity can lead to changes in gene expression that can affect metabolic processes in various ways (Waterland & Michels, 2007). These include modifications in DNA methylation, histone proteins, and transcription factors. The third and last underlying mechanism is *thrifty phenotype*, which posits that early-life undernutrition can lead to permanent changes in glucose-insulin metabolism (Hales & Barker, 2001). When an individual experiences nutritional scarcity during a specific developmental phase, their metabolism may adapt to become more efficient at conserving energy and storing fat. This response, when faced with nutritional abundance later on, can higher the risk of metabolic diseases. While both metabolic imprinting and thrifty phenotype mechanisms explain how early-life conditions can have lasting effects on metabolism, the metabolic imprinting mechanism focuses on a broader range of potential lasting marks on metabolism, while the thrifty phenotype mechanism focuses on glucose-insulin metabolism.

Table 1.2. Summary of DOHaD Hypothesis and Underlying Mechanisms

	Description	Key studies
DOHaD hypothesis	Early life, particularly the fetal development phase, plays a key role in shaping the health trajectories of an individual later in life.	Barker, 1995; Gluckman & Hanson, 2004; Painter et al., 2006; Gluckman et al., 2008.
Mechanisms of DOHaD hypothesis	1. Metabolic imprinting: Early-life adversity can leave lasting marks on metabolism in various ways ranging from changes in organ structure to metabolic differentiation.	Waterland & Garza, 1999
	2. Genomic imprinting: Early-life adversity can lead to changes in gene expression that can affect metabolic processes in various ways including modifications in DNA methylation, histone proteins, and transcription factors.	Waterland & Michels, 2007
	3. Thrifty phenotype: Early-life undernutrition can lead to permanent changes in glucose-insulin metabolism.	Hales & Barker, 2001

The DOHaD hypothesis can be understood from the life course perspective. In line with the critical model and sensitive period model, the DOHaD hypothesis underlines the importance of exposures during specific developmental windows (Kuh et al., 2003). Specifically, the DOHaD hypothesis highlights the role of early life in shaping later health outcomes: Adversities experienced in early life can have lasting effects on health in later life. However, it is important to position the DOHaD hypothesis within the life course perspective with caution (Skogen & Øverland, 2012). Although early life is an important phase for development and health, it is just one of the developmental stages throughout the life course of an individual. Each of the life stages—be it early life, adolescence, adulthood, middle age, and older age—offers opportunities for prevention and intervention.

In the first line of inquiry, I use the DOHaD hypothesis as a framework to understand the influence of early-life adversity on later-life health outcomes several decades later, and test the associations between early-life adversity and later-life health from a life course perspective.

1.2.3 Exposure to Famine and Health in Later Life

As suggested by the DOHaD hypothesis, early-life adversity can have long-lasting effects that persist decades after in older age. Historical events like famines provide a valuable opportunity to study such effects (Short & Baram, 2019). Despite famines have been prevalent throughout history and still threaten millions of individuals in contemporary times, the long-term health implications of famines remain poorly understood. Survivors of major historical famines such as the Chinese famine in 1959-1961 and the Dutch Hunger Winter in 1944-1945 could still be influenced by the enduring effects of famine exposure more than six decades later.

China experienced the worst famine in human history from the spring of 1959 to the winter of 1961. Both natural disasters, like droughts, floods, and typhoons, and policies, in particular agricultural and industrialization policies, contributed to the Chinese famine of 1959-1961 (Yao, 1999). This nationwide famine hit the food availability and caused unprecedented

excess deaths (Chen & Zhou, 2007). During the three years of famine, grain production decreased by about 25% and approximately 30 million individuals died (Ashton et al., 1984). Compared to urban areas, rural areas were more severely affected by the famine (Lin & Yang, 2000). The Chinese famine ended in 1961 after adaptations to natural forces and policy adjustments (Lin & Yang, 2000). Food availability returned to the pre-famine level in four to nine years after the end of famine (Smil, 1999), suggesting a slow but steady recovery to the normal level of food intake.

Numerous studies have explored the long-term effects of the Chinese famine of 1959-1961 on health in later life (Chen et al., 2022; Li et al., 2023; Sun et al., 2018; Wang et al., 2016; Wang et al., 2010; Wang et al., 2017; Wang et al., 2019; Yu et al., 2017). For example, Wang et al. (2019) showed that individuals exposed to the Chinese famine in infancy had an 83% higher risk of metabolic syndrome at age 50-59 compared to unexposed individuals. Sun et al. (2018) showed that individuals exposed at age 7-13 to the Chinese famine had a 57% higher risk of hyperglycemia at age 52-62 than unexposed individuals. Wang et al. (2017) showed that individuals exposed during fetal and infancy stage to the Chinese famine had a 58% and 52% higher risk of dyslipidemia at age 50-56 than unexposed individuals, respectively.

Another major famine occurred in the Netherlands from November 1944 to May 1945. The German occupying forces blocked food supplies to the occupied West of the country, which caused the Dutch famine (Van Der Zee, 1998). Starvation was common in the cities of the western Netherlands during that period (Stein et al., 1975). Official rations fell below 1,000 kcal per day by 26 November 1944 and further fell to 500 kcal per day by April 1945 (Lumey et al., 2007). Among the 2.6 million people who were affected approximately 20,000 individuals died of famine in 1944–1945 (de Zwarte, 2020). The Dutch famine ended with German capitulation in 1945 (Susser & Lin, 1992). Soon after the liberation, food availability

returned to the pre-famine level and the average food intake rose to the normal level of 2000 kilocalories per day (Lumey & Van Poppel, 1994).

A number of studies have also explored the long-term effects of the Dutch Hunger Winter of 1944-1945 on health in later life (de Rooij et al., 2022; de Rooij et al., 2016; Ekamper et al., 2015; Ekamper et al., 2014; Lumey, Terry, et al., 2011; Portrait et al., 2011; Tobi et al., 2014; Wiegersma et al., 2022). For example, Wiegersma et al. (2022) showed that women exposed to the Dutch Hunger Winter during late gestation had 1.2 times higher probability of developing cognitive problems at age 72 than unexposed women. Ekamper et al. (2014) showed that individuals exposed in early gestation to the Dutch Hunger Winter faced a 12% increased risk of mortality at age 18-63 than unexposed individuals. Portrait et al. (2011) showed that individuals exposed at age 11-14 to the Dutch Hunger Winter had four times higher probability of having diabetes at age 60-76 than unexposed individuals.

1.2.4 Limitations in Studying the Early-life Adversity and Health over the Later Life Course

Existing studies on the effect of famine exposure and later-life health are limited in three ways: Measurement error bias, age confounder, and causal inference.

1.2.4.1 Limitation #1: Measurement Error Bias

The first limitation is that many existing studies have used birth year to measure famine exposure and/or region of residence to measure severity of famine exposure (Kim et al., 2017; Sun et al., 2018; Xie & Zhu, 2022), instead of a direct measure of famine exposure (for a few exceptions, see Ekamper et al., 2015; Li et al., 2018). The manner in which famine exposure is measured is critical to understand the nature of exposure and its impact on later-life health. Although it is a convenient way to measure famine exposure using birth year (i.e., categorizing those born during the famine as ‘exposed’ and those born after as ‘unexposed’) and/or severity of famine exposure using region of residence, it may overlook variations in famine situation

across regions and food arrangement across families during famine years. A review by Li and Lumey (2017) has highlighted the importance of measuring famine exposure more directly and accurately when assessing how it may affect health in older age. This review showed that indirect measures of famine exposure may not reflect individual dietary intake and that aggregated measures of severity of famine exposure may not reflect local conditions during the famine. In the first line of inquiry, I measure famine exposure and severity of famine exposure using more direct and accurate indicators, namely, self-reported famine experiences (for the Chinese famine) and the official threshold of calory intake (for the Dutch Hunger Winter) to improve the exposure measurement and reduce the risk of measurement error bias.

1.2.4.2 Limitation #2: Age Confounder

The second limitation is that many existing studies have not controlled for age difference between famine-exposed group and unexposed group (Chen et al., 2022; Wang et al., 2017; Yu et al., 2017; for a few exceptions, see Khalangot et al., 2017; Li et al., 2018). As older age is a risk factor for later-life health (Barnett et al., 2012), partialing out the variance in health accounted for by age is critical to understand the true effects of famine exposure on later-life health. A review by Grey et al. (2021) has highlighted the importance of controlling for age difference to assess the health effects of famine exposure in older age. Their review showed that the uncontrolled age difference between participants born during the famine (who were older) and participants born after the famine (who were younger) can bias the association between famine exposure and later-life health. Consequences of this issue are particularly severe for studies on famines that lasted for a long period of time like the Siege of Leningrad (1941-1944), in which the age difference between participants born during the famine and participants born after the famine can be as large as four years. In the first line of inquiry, I control for the age difference between famine-exposed participants and unexposed participants (for both the Chinese famine and the Dutch Hunger Winter) and compare famine-exposed

participants with their time controls who were born in the same months of the year 1943 and 1947 (for the Dutch Hunger Winter).

1.2.4.3 Limitation #3: Causal Inference

The last limitation is that many existing studies have not been able to make causal inference (Li et al., 2021; Shao et al., 2022; Tao et al., 2019; for a few exceptions, see Deng & Lindeboom, 2022; van den Berg et al., 2015). Approaching causality is critical to understand the causal pathway linking famine exposure to later-life health. A commentary by Kramer (2000) showed how the association between famine exposure and later-life health can be influenced by confounding factors from various sources like socioeconomic status and other limitations. The author has highlighted the need to improve the tests of the DOHaD hypothesis to better approach causality. In the first line of inquiry, I approach causality with advanced analytical tools. Specifically, I use longitudinal data and growth curve models to investigate the effect of famine exposure on health trajectories over the later life course (in the context of the Chinese famine), and a natural-experiment design with sibling-comparison analysis to investigate the effect of famine exposure on biological aging in older age (in the context of the Dutch Hunger Winter).

1.3 Second Line of Inquiry: Socioeconomic Status and Later-Life Health Trajectory

1.3.1 Socioeconomic Status and Health Gradient

1.3.1.1 Conceptualization and Operationalization of Socioeconomic Status

Socioeconomic status (SES) is a commonly studied concept in many disciplines such as gerontology (George, 2005), public health (Braveman et al., 2005), epidemiology (Goldman, 2001), and psychology (Kraus & Stephens, 2012). This concept entails political ideologies about existing and desired social structures and reflects an individual's access to collectively

desired resources (Oakes & Andrade, 2017). Differences in access to resources combined with segregation based on differential access structure the sociocultural contexts that individuals navigate in their daily life (Goudeau et al., in press). SES is defined by unequal access to economic, cultural, social, and/or symbolic resources (Batruch et al., 2021), and typically encompasses economic status, social status, and work status (Dutton & Levine, 1989). There are two predominant approaches to conceptualize SES: The "classical" approach and the "resource" approach (Antonoplis, 2023)[1]. The "classical" approach, rooted in the work of Marx (1967) and Weber (1968), views SES in terms of social stratification based on power and prestige. In contrast, the "resource" approach, rooted in the work of Duncan (1961) and Hollingshead (1957), views SES in terms of differences in income, education, and occupational status.

There are several ways to measure socioeconomic status. First, SES can be measured either using individual indicators (e.g., income, wealth, education, or occupation) or using composite indices combining individual elements. Studies that have measured SES using different indicators sometimes find that the effect size varies by indicators, suggesting that specific resources associated with income, education, or occupation may affect health via differential mechanisms (Adler & Ostrove, 1999). Second, SES can be measured either objectively or subjectively. Objective measures of SES reflect an individual's absolute position on the socio-economic ladder (Kraus et al., 2012), whereas subjective measures of SES reflect an individual's perceived position within a society (Diemer et al., 2013). Third, SES can be measured at the individual level or at the contextual level (e.g., neighborhood, region, or country). Commonly used contextual-level indicators of SES include income inequality (Subramanian & Kawachi, 2004), area-based deprivation (Martin et al., 2019), and the socio-

[i] Another notable approach to conceptualizing SES is the "capability" approach proposed by Sen, A. (2005). Human rights and capabilities. *Journal of Human Development*, *6*(2), 151–166. https://doi.org/10.1080/14649880500120491 .However, this approach goes beyond the scope of this thesis and is discussed here.

demographic index (Vos et al., 2020). Finally, SES can also be assessed from a life course perspective rather than as a static resource. For instance, some studies have measured SES at different periods of the life course like early life (Pudrovska & Anikputa, 2014), while other studies have measured changes in SES over the life course (Graf et al., 2022).

In the second line of inquiry, I view SES as an umbrella term and adopt the "resource" approach and conceptualize SES by focusing on differences in socioeconomic status. I measure SES in a comprehensive way, using multiple individual indicators of SES such as income, wealth, and education to capture the role of specific resources in predicting later-life health. I focus on objective measures of SES at the individual level to investigate the absolute socioeconomic position of an individual within a given society. Lastly and importantly, I measure SES from a life course perspective to capture the effects of changes in SES on health over time.

1.3.1.2 Socioeconomic Status and Health

The association between socioeconomic status and health—known as the SES–health gradient—is well-established. One of the most renowned pioneering studies on the SES–health gradient is the Whitehall study of mortality (Marmot et al., 1984), which followed 17,530 British civil servants over a 10-year period. This study revealed a clear gradient between occupation and health: For each step up the occupational grade, the health of an individual improved, and the risk of mortality decreased. The SES–health gradient has since been replicated using various measures of SES and health outcomes (e.g., Marmot & Wilkinson, 1999; Phelan et al., 2010; Riley, 2020). For instance, a study from the U.S. showed that compared with individuals whose income was at bottom 1%, individuals whose income was at top 1% had longer life expectancy of more than 10 years (Chetty et al., 2016). Similar findings have been observed among older adults. For instance, a recent study from China showed that compared with older adults with lower education, older adults with higher education tended to

report higher levels of self-rated health (Yao et al., 2022). Another study from the U.S. showed that compared with older adults whose household income below $20,000 per year, older adults whose household income above $70,000 per year were at lower risk of incident mood disorders (Sareen et al., 2011).

Several mechanisms have been proposed to explain the SES–health gradient (Marmot, 2002; Marmot & Wilkinson, 2001; Duffy et al., 2018). These encompass the material pathway, the psychosocial pathway, the behavioral pathway, and the biological pathway (**Figure 1.1**). According to the *material pathway*, SES impacts health via material factors and circumstances (Thomas Boyce & Hertzman, 2018). For instance, a recent study showed that individuals with lower childhood SES were more likely to experience financial hardship or unstable financial status, which exerts negative effects on their health (Stephens et al., 2022). Another study showed that individuals with lower SES were more likely to be exposed to occupational injuries, which exerts negative effects on their health (Evans & Kim, 2010).

According to the *psychosocial pathway*, SES impacts health via psychosocial factors such as emotions, social participation, and opportunities to control life circumstances (Matthews et al., 2010). A foundational concept here is allostatic load, which posits that exposure to chronic stressors can lead to "tear and wear" on the body and mind (McEwen & Stellar, 1993). Simply put, individuals with lower SES tend to live a more stressful life, which has detrimental effects on their health (Petrovic et al., 2016). In line with this explanation, a recent study showed that a low sense of control accounted for the detrimental effects of financial scarcity on health (Sommet & Spini, 2022).

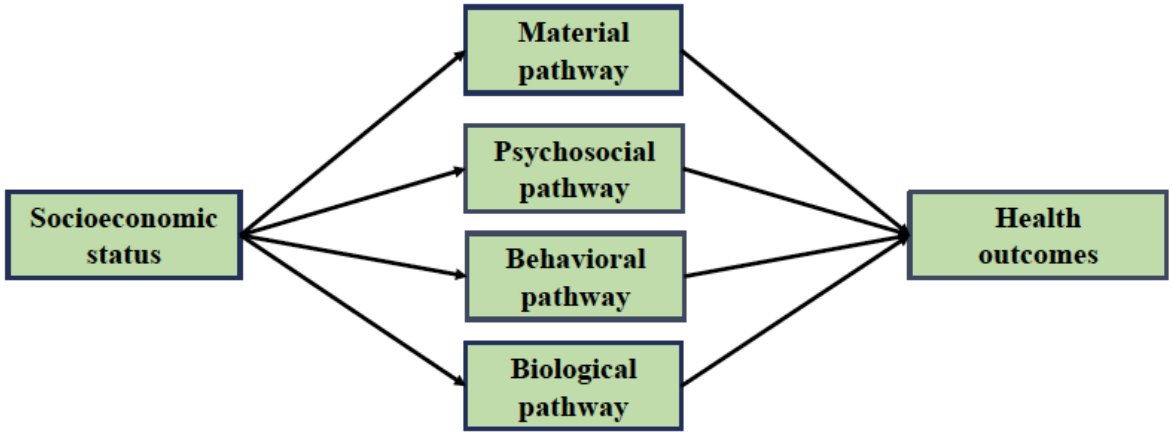
According to the *behavioral pathway*, SES impacts health via lifestyle factors and health-related behaviors (Tucker-Seeley & Thorpe, 2019). For instance, a study showed that compared with individuals with lower education, individuals with higher education were more likely to live a healthy lifestyle such as regular physical activity, which can affect individual

health (Laine et al., 2019). Another study showed that unhealthy lifestyles partially mediated the socioeconomic inequality in health (Zhang et al., 2021).

According to the *biological pathway*, SES impacts health via changes in physiological functioning (Kraft & Kraft, 2021). The biological pathway is at play in domains of inflammation, endocrinology, neurology, and so on. For instance, a study showed that lower SES was related to metabolic dysregulation, which can affect health (Yang et al., 2018). Another study showed that compared with individuals with lower parental education, individuals with higher parental education were more likely to better develop and engage key brain regions, which can affect individual health (Cascio et al., 2022).

These mechanisms underlying the SES–health gradient also apply when it comes to older age and explain the gradient observed in later life (Harari & Lee, 2021). However, within the second line of inquiry, my focus is not on distinguishing between the mechanisms underlying the SES–health gradient, but on elucidating how the income–health gradient evolves over the later life course.

Figure 1.1. A Framework of Mechanisms underlying the SES–Health Gradient



Note. The material pathway includes material factors such as financial history, material deprivation, etc.; the psychosocial pathway includes psychosocial factors such as emotion, social participation, sense of control, etc.; the behavioral pathway includes behavioral factors such as diet, smoking, physical activity, etc.; and the biological pathway includes biological factors such as metabolic regulation, neural adaptations, etc.

1.3.2 Evolution of the Income–Health Gradient over the Later Life Course

Scholars have proposed three patterns in how the income-health gradient evolves over the later life course: the age-as-leveler pattern, the cumulative advantage/disadvantage pattern, and the persistent inequality pattern. A summary of these patterns in the evolution of the income-health gradient over the later life course is shown in **Table 1.3**.

The *age-as-leveler pattern* suggests that the income–health gradient weakens as individuals age (O'Rand, 2009). According to this perspective, the income-related disparities in health tend to diminish in later life, leading to a less pronounced association between income and health in older ages. This phenomenon has spurred several theoretical explanations regarding the underlying mechanisms. The first proposed underlying mechanism is biological aging (Brown et al., 2016; Herd, 2006; Kirkwood, 2014; Hoffmann, 2011; Rehnberg, 2020). During the aging process, individuals from different socioeconomic backgrounds may experience physiological declines that have a leveling effect on the income-health gradient, thereby diminishing the income-related disparities in later-life health. The second underlying mechanism is selective mortality (Dupre, 2007). Over the life course, individuals with lower socioeconomic status are disproportionately affected by premature mortality. As a result, older adults with lower income in social surveys tend to be the "healthier survivors," making their health status more comparable to their higher-income counterparts, thereby diminishing the income-related disparities in later-life health. The third underlying mechanism is social policy (Sieber et al., 2020; Wallace et al., 2021). Social policies, such as healthcare provisions, social services, and pension systems can distribute resources more equitably and provide equal access to protective factors among older adults, thereby again diminishing the income-related disparities in later-life health.

The *cumulative advantage/disadvantage pattern* suggests that the income–health gradient strengthens as individuals age (Dannefer, 2020; DiPrete & Eirich, 2006). According

to this perspective, the income-related disparities in health tend to widen in later life, leading to a more pronounced association between income and health in older ages. There are two theoretical explanations regarding the underlying mechanisms. The first proposed underlying mechanism is risk accumulation (O'Rand, 2002; Lantz et al., 2005). Over the life course, when compared to individuals with higher income, individuals with lower income are more likely to be exposed to risk factors that are detrimental to health such as suboptimal life circumstances, limited access to healthcare, and increased stress. These risk factors can affect health as independent risks, clustered risks, or chains of risks (Kuh et al., 2003). As a result, the influences of differential exposure to risk factors accumulate over the life course, thereby widening the income-related disparities in later-life health. The second proposed underlying mechanism is reserves (Cullati et al., 2018). Over the life course, when compared to individuals with higher income, individuals with lower income tend to have fewer reserves that act as a buffer against health-related risks and stressors such as financial stability, social support networks, and coping strategies. As a result, the influences of differential reserves against risks and stressors accumulate over the life course, thereby again widening the income-related disparities in later-life health.

The *persistent inequality pattern* suggests that the income–health gradient remains stable as individuals age (Ferraro, 2011). According to this perspective, the theoretical explanation of underlying mechanisms primarily concerns the social structure (Mackenbach, 2017). The persistent inequality pattern is supposedly rooted in the persistent socioeconomic hierarchies. Compared to individuals with lower income, individuals with higher income find themselves consistently positioned in the higher hierarchy in a given society. Enduring socioeconomic stratification in income, education, and occupation can generate health inequalities in early life and perpetuate these disparities throughout the life course (Abramson, 2015; Brown et al., 2016; Lynch, 2020).

Table 1.3. Summary of Patterns in Evolution of the Income–Health Gradient with Older Age

Patterns	Description	Key studies
Age-as-leveler pattern	The income–health gradient weakens as individuals age.	O'Rand, 2009; Hoffmann, 2011; Rehnberg, 2020; Sieber et al., 2020.
Cumulative advantage/disadvantage pattern	The income–health gradient strengthens as individuals age.	DiPrete & O'Rand, 2002; Lantz et al., 2005; Eirich, 2006; Dannefer, 2020.
Persistent inequality pattern	The income–health gradient remains stable as individuals age.	Ferraro, 2011; Brown et al., 2016; Mackenbach, 2017; Lynch, 2020.

Does the income–health gradient weaken, widen, or remain stable over the later life course? There is no definite answer to this research question. Each of these patterns has received empirical support from existing studies: Some studies support the age-as-leveler pattern (Bonaccio et al., 2019; Brown et al., 2016; Doebler & Glasgow, 2017; Griffith et al., 2021; Li & Mutchler, 2019; Rehnberg et al., 2019; Sieber et al., 2020; Van Der Linden et al., 2020), others support the cumulative advantage/disadvantage pattern (Boen, 2016; Lahelma et al., 2015; Lai et al., 2022; Leopold, 2018; Leopold, 2019; Veenstra & Aartsen, 2022; Xu et al., 2017; Zeng et al., 2022), and some others support the persistent inequality pattern (Boen, 2016; Brown, 2018; Brown et al., 2016; Hoogendijk et al., 2017; Leopold, 2019; Wachtler et al., 2019; Zhu & Ye, 2020). Notably, there are several limitations in previous studies on the evolution of income–health gradient over the later life course.

1.3.3 Limitations in Studying the Income–Health Gradient over the Later Life Course

Existing studies on the income–health gradient over the later life course are limited in four ways: Conceptualization of health, cultural setting, and study design.

1.3.3.1 Limitation #1: Conceptualization of Health

The first limitation is that many existing studies have used a generic health outcome, most often self-rated health (Li & Mutchler, 2019; Veenstra & Aartsen, 2022; Zhu & Ye, 2020), without considering the multidimensional nature of health (for a few exceptions, see Brown et al., 2012; Xu et al., 2014). A generic health outcome captures an individual's overall assessment of their own health status and while it is a convenient way to measure health, it may mask important nuances across different health domains. As stated before, health is a multidimensional concept involving physical, mental, and social well-being aspects. Studies by Brown et al. (2012) and Xu et al. (2014) revealed variations in the evolution of the income–health gradient across different health domains. This variation exists because income may impact the onset and progression of a condition in different health domains through different

mechanisms (Cockerham et al., 2017), thereby highlighting the importance of conceptualizing health as a multidimensional construct to study the income–health gradient over the later life course. In the second line of inquiry, I conceptualize health as a multidimensional construct and focus on physical health and cognitive health. Specifically, I assess physical health using multimorbidity and cognitive health using memory, both of which are important indicators of later-life health (Makovski et al., 2019; Park & Festini, 2016).

1.3.3.2 Limitation #2: Cultural Setting

The second limitation is that many existing studies have focused on a single country, most often the U.S. (Boen, 2016; Brown, 2018; Zeng et al., 2022), without considering lower income and/or non-Western countries (for a few exceptions, see Rehnberg et al., 2019; Sieber et al., 2020). The cultural setting is critical to understand the extent to which the findings regarding the evolution of income–health gradient can be generalized across societies. Studies on the U.S. provide useful insights into health dynamics in this particular population, but it should be recognized that findings from a single country may not generalize to a broader context (Rai et al., 2013). It is important to interpret health-related estimates in a context-sensitive manner (Kessler & Bromet, 2013). This is because health-related estimates can vary from one society to another, especially when health, social, and economic policies are different. Such differences are distinct between Western, educated, industrialized, rich and democratic (WEIRD) societies and non-WEIRD societies (Henrich et al., 2010). In the second line of inquiry, I investigate the evolution of the income–health gradient among older adults in the largest Western economy, i.e., the U.S., but also in the largest Eastern economy, i.e., China, as well as in European countries including countries that are not typically studies such as Poland, Slovenia, Estonia, and others.

1.3.3.3 Limitation #3: Study Design

The last limitation is that many existing studies have used a cross-sectional design (Andel et al., 2017; Griffith et al., 2021; Li & Mutchler, 2019) rather than a longitudinal design (for a few exceptions, see Leopold, 2019; Van Der Linden et al., 2020). The choice of study design is crucial for capturing dynamics in the income–health gradient over time. A cross-sectional design uses socioeconomic and health information that were collected at a single time point, and it does not allow one to investigate the change in the income–health gradient over time. The main reason is that, compared to longitudinal data, cross-sectional data are more susceptible to potential biases introduced by selection effects (Jager et al., 2020). In particular, selective mortality may lead to a sample in which lower-income participants tend to be the "healthy survivors" of their cohort, making their health status comparable health status to that of their higher-income counterparts. In the second line of inquiry, I adopt a longitudinal design to investigate income and health trajectories over the later life course of an individual.

1.4 Overview of the Four Empirical Chapters

1.4.1 Research Questions

This thesis uses a life-course perspective to examine the socioeconomic determinants that shape the health of older adults in China, the U.S., and Europe. It has two overarching objectives. The first line of inquiry aims to examine how early-life exposure to historical famine predicts later-life health. The second line of inquiry aims to examine how individual income in later life predicts health trajectories over time.

Specifically, as shown in **Table 1.4**, Chapter 2 and Chapter 3 delve into the developmental origins in the context of historical and collective famine and later-life health (first line of inquiry). These two chapters aim to determine whether and how the Developmental Origins of Health and Disease hypothesis on famine exposure and later-life health is empirically supported by the data from China and the Netherlands. I answer this research

question while addressing issues pertaining to measurement error bias, age confounders, and causal inference.

Chapter 4 and Chapter 5 delve into the relationship between individual-level socioeconomic status in later life and health trajectories (second line of inquiry). These two chapters aim to determine which pattern in the evolution of the income–health gradient over the later life course—age-as-leveler, cumulative advantage/disadvantage, and persistent inequality patterns—is empirically supported by data from China, U.S., and Europe. I answer this research question while differentiating physical from cognitive health, working in various cultural settings, and using a longitudinal study design.

Table 1.4. Summary of Aims, Research Questions, and Methods in Each Empirical Chapter

	First line of inquiry		Second line of inquiry	
	Chapter 2	**Chapter 3**	**Chapter 4**	**Chapter 5**
Research question	How does exposure to the 1959-1961 Chinese famine link to risk of non-communicable diseases in later life?	How does exposure to the 1944-1945 Dutch famine link to biological aging in later life?	How does the income–health gradient evolve over the later life course in the U.S.?	How does the income–health gradient evolve over the later life course in Europe and China?
Study design	longitudinal	cross-sectional	longitudinal	longitudinal
Data	CHARLS (2011-2018)	DHWFS (2003-2005)	HRS (1992-2016)	SHARE (2004-2019) CHARLS (2011-2018)
Focal predictor	famine exposure, life stage, famine exposure–life stage	famine exposure, duration of exposure, gestational time window	income	income
Focal outcome	non-communicable diseases	epigenetic clocks	multimorbidity, memory	multimorbidity, memory
Modeling	multilevel growth curve models	generalized estimating equation models; sibling-fixed-effects models	multilevel growth curve models	multilevel growth curve models

1.4.2 Methods

This thesis uses data from various sources. Chapters 2, 4, and 5 use various longitudinal datasets, namely, the China Health and Retirement Longitudinal Study (CHARLS) from China, the Health and Retirement Study (HRS) from the U.S., and the Survey of Health, Ageing and Retirement in Europe (SHARE) from Europe. Chapter 3 uses a cross-sectional dataset, namely, the Dutch Hunger Winter Families Study (DHWFS) from the Netherlands. Specifically:

• CHARLS is a nationally representative longitudinal survey conducted biennially since 2011 that has collected socioeconomic and health data on approximately 17,500 individuals aged 45 or older in China.

• HRS is a nationally representative longitudinal survey conducted biennially since 1992 that has collected socioeconomic and health data on approximately 20,000 individuals aged 50 or older in the U.S.

• SHARE is a series of nationally representative longitudinal surveys conducted biennially since 2004 that has collected socioeconomic and health data on approximately 140,000 individuals aged 50 or older in 28 European countries and Israel.

• DHWFS is a cross-sectional survey conducted in 2003-2005, about six decades after the Dutch Hunger Winter, that has collected famine and health data on approximately 1,000 individuals aged 60 or older in famine-exposed cities in the Western Netherlands.

Moreover, this thesis uses different advanced analytic modeling strategies. Chapters 2, 4, and 5 use multilevel growth curve models (Sommet & Morselli, 2021), whereas Chapter 3 uses generalized estimating equation (GEE) regression models (Hanley et al., 2003) and sibling-fixed-effects (FE) regression models (Petersen & Lange, 2020). Specifically:

• For the CHARLS and HRS data, I build a series of multilevel growth curve models in which wave-specific observations (level-1 units) are nested in participants (level-2 units) to examine health trajectories over the later life course.

• For the SHARE data, I build a series of multilevel growth curve models in which wave-specific observations (level-1 units) are nested in participants (level-2 units) and countries (level-3 units) to examine health trajectories over the later life course.

• For the DHWFS data, I build a series of generalized estimating equation models and sibling-fixed-effects models to compare between-family and within-family famine effects on later-life health.

1.4.3 Summary of Empirical Chapters

Findings of this thesis are based on two series of empirical studies. Below is the summary of the findings for each empirical chapter.

The first empirical study in Chapter 2, "*Long Arm of Exposure to the 1959-1961 Chinese Famine into Later-Life Non-Communicable Diseases*," investigates the link between exposure to the Chinese famine and the risk of non-communicable diseases about 50 years later. In addition, this study examines whether this link depends on the life stage at famine exposure, famine severity, and sex. This study uses Poisson growth curve models and adjusts for age differences between exposed individuals and unexposed individuals. Findings suggest that famine survivors exposed before age 18 have an increased risk of later-life non-communicable diseases, with those exposed in-utero or under age two at double the risk. The famine effects do not differ between moderately exposed individuals and severely exposed individuals, nor between women and men. This study has been published in *PLOS Global Public Health* in August 2023 (Cheng, Sommet, Kerac, et al., 2023) and highlighted by the PLOS press team on *EurekAlert*.

The second empirical study in Chapter 3, "*Long Arm of Prenatal Exposure to the 1944-1945 Dutch Hunger Winter into Later-Life Biological Aging*," investigates the link between exposure to the Dutch famine and both biological age and aging approximately 60 years later. In addition, this study examines whether this link depends on the duration of exposure,

gestational timing at exposure, and sex. This study uses generalized estimating equation (GEE) regression models and sibling-fixed-effects (FE) regression models and disentangles the between-family and within-family estimates of famine effects on biological age and aging. Findings suggest that famine survivors age faster but have similar biological age as compared to unexposed individuals. Individuals with longer prenatal famine exposure age faster but have similar biological age compared to individuals with shorter exposure. There is no timing-specificity for famine exposure in predicting biological age and aging. The famine effects are larger among women than men. This study is not published yet but will soon be submitted to *PNAS*.

The third empirical study in Chapter 4, "*Evolution of the Income–Health Gradient over the Later Life Course: Longitudinal Evidence from the U.S. (1992-2016)*," investigates changes in the income–health gradient with older age in the U.S. This study tests which of the age-as-leveler, cumulative advantage/disadvantage, and persistent inequality patterns is best supported by the data. In addition, this study examines whether these patterns differ in physical and cognitive health domains, and whether these patterns differ between women and men. This study uses Poisson growth curve models and disentangles the within-participant effects from the between-participant effects. Findings suggest that the income–health gradient in multimorbidity weakens as individuals age, whereas the income–health gradient in memory strengthens as individuals age. The cumulative advantage of higher income and cumulative disadvantage of lower income on memory appear to be more pronounced among older women than men. These findings are observed both between participants and within participants. This study has been published in *Research on Aging* in June 2023 (Cheng, Sommet, et al., 2023b).

The fourth empirical study in Chapter 5, "*Evolution of the Income–Health Gradient over the Later Life Course: Longitudinal Evidence from 19 European Countries (2004-2019) and China (2011-2018)*," investigates changes in the income–health gradient with older age in

Europe and China. This study again tests which of the age-as-leveler and cumulative advantage/disadvantage patterns, and persistent inequality patterns is best supported by the data, but this time in non-U.S. contexts. This study also uses Poisson growth curve models and disentangles the within-participant from the between-participant effects and examines outcomes in both the physical and cognitive health domains. Findings from Europe and China are consistent and suggest that the income–health gradient in multimorbidity, functional disability, and mobility disability weakens as individuals age, whereas the income–health gradient in memory strengthens as individuals age. This study has been published in *European Journal of Ageing* in August 2023 (Cheng, Sommet, et al., 2023a).

2. Long Arm of Exposure to the 1959-1961 Chinese Famine into Later-Life Non-Communicable Diseases

Published as: Cheng, M., Sommet, N., Kerac, M., Jopp, D., & Spini, D. (2023). Exposure to the Chinese famine of 1959-1961 at different life stages and risk of later-life non-communicable diseases: A retrospective cohort study from a life course perspective. *PLOS Global Public Health*. *3*(8), e0002161. (Highlighted by the PLOS press team on EurekAlert)
DOI: 10.1371/journal.pgph.0002161 • PDF

2.1 Abstract

Child undernutrition and later-life non-communicable diseases (NCDs) are major global health issues. Literature suggests that undernutrition/famine exposure in childhood has immediate and long-term adverse health consequences. However, many studies have theoretical and methodological limitations. To add to the literature and overcome some of these limitations, we adopted a life course perspective and used more robust methods. We investigated the association between exposure to the 1959-1961 Chinese famine and later-life NCDs and if this association depends on: life stage at exposure, famine severity, and sex. We conducted a secondary data analysis of a large-scale, nationally representative, longitudinal study—the China Health and Retirement Longitudinal Study (2011-2018, 11,094 participants). We measured famine exposure/severity using self-reported experience, life stage using age at exposure, and health using the number of NCDs. We performed Poisson growth curve models. We obtained three findings. First, compared with unexposed participants, those exposed before age 18 had a higher risk of later-life NCDs, particularly if exposed in-utero (IRR=1.90, 95% CI [1.70, 2.12], $p < .001$) and in the "first 1,000 days" of life (IRR=1.86, 95% CI [1.73, 2.00], $p < .001$; for 0-6 months group, IRR=1.95, 95% CI [1.67, 2.29], $p < .001$). Second, the famine effects among participants moderately and severely exposed were similar (IRR=1.18, 95% CI [1.09, 1.28], $p < .001$ and IRR=1.24, 95% CI [1.17, 1.32], $p < .001$). Third, the famine effects

did not differ between females and males (IRR=0.98, 95% CI [0.90, 1.07], p = .703). In an individual's life course, in-utero and the "first 1,000 days" are a particularly sensitive time period with marked long-term implications for NCDs if undernutrition/famine is experienced in this period. However, this window remains open until young adulthood. This highlights the need to invest more in preventing and treating child/adolescent undernutrition to tackle later-life NCDs.

2.2 Introduction

Globally, 194 million children aged under five years suffer from undernutrition and undernutrition accounts for around 45% of deaths in the age group (Lancet, 2013; World Health Organization, 2021a). Conflict, climate crisis and COVID-19 further exacerbate the strain on undernutrition prevention and treatment services (Ghebreyesus, 2022). Non-communicable diseases (NCDs) are another major global issue accounting for 71% of all deaths (World Health Organization, 2021b).

Existing literature suggests that undernutrition in childhood has immediate detrimental and long-term adverse health consequences (Kirolos et al., 2022), including increasing the risk of NCDs in later life (Grey et al., 2021). Such long-term sequelae can be explained by both biological and socioeconomic pathways. Biological explanations include the "Developmental Origins of Health and Disease" hypothesis (Barker, 1995; Mandy & Nyirenda, 2018) and the "Capacity-load" model (Wells, 2018): individuals who experienced undernutrition in early years of life have impaired metabolic and organ capacity, which increases the risk of NCDs in later life. Socioeconomic explanations include life-long consequences of early-life poverty: a greater risk of undernutrition in childhood leads to impaired development, suboptimal educational achievement and earning, and loss of full human potential (Almond et al., 2010;

Victora et al., 2008). These consequences of early-life poverty are associated with poverty in adulthood, which independently increases the risk of NCDs in later life (Guerrant et al., 2013).

One body of the literature has explored the long-term consequences of famine exposure, and how that links to NCDs in later life. This includes studies of the Dutch Hunger Winter (1944-1945), the Siege of Leningrad (1941-1944), the Chinese Famine (1959-1961), and famines in other countries (Grey et al., 2021; Li & Lumey, 2017; Li & Lumey, 2022). However, many existing studies have theoretical and methodological limitations.

2.2.1 Theoretical Limitations: Lack of A Life Course Perspective

From a theoretical angle, many existing studies on the association between famine exposure and later-life health lack a life course perspective. First, they often focus on individuals exposed to famine during a narrow period of life, often on the "first 1,000 days" of life (Meng et al., 2017). This is problematic because other evidence suggests that the window of development and growth may extend beyond these "first 1,000 days" (Wang et al., 2016; Yu et al., 2017). Second, other studies do not always consider the age at which individuals were exposed to famine (Li & Lumey, 2017). Life course epidemiology suggests that the timing of exposure is critical and that the effect of exposure during a specific period may differ from the effect of the same exposure during another period (Ben-Shlomo & Kuh, 2002; Kuh et al., 2003). Thus, individuals exposed to famine at different life stages may be affected differently.

2.2.2 Methodological Limitations: Information Bias and Survivor Bias

From a methodological angle, the observed association between famine exposure and later-life health in many existing studies may be subject to information bias and survivor bias. A major source of information bias is the misclassification of famine exposure and/or severity of famine exposure (Grey et al., 2021). To determine famine exposure, with few exceptions (Woo et al., 2010), many studies classify participants by their birth year: participants born during the famine are classified as exposed, and those born after as unexposed. However, given

that older age is a risk factor for NCDs (Barnett et al., 2012), a consequence is that the uncontrolled age difference between participants born during the famine (i.e., older) and participants born after the famine (i.e., younger) potentially biases the health effects attributed to famine exposure. This issue is particularly severe for studies on famines that lasted for several years (i.e., entailing a nontrivial age difference between participants born during the famine and born after the famine), such as the Chinese famine of 1959-1961.

To determine severity of famine exposure, with few exceptions (Li et al., 2018), many studies classify participants by regional mortality: participants born in regions where excess mortality during famine was above a predefined threshold are classified as severely exposed, and those born in regions where excess mortality was below that threshold are classified as moderately exposed. Using this approach may lead to misclassification issues because there might be important within-region variations. For example, the food rationing system preferentially supplied urban residents at the time of the Chinese famine of 1959-1961; because they were not entitled to additional food through the rationing system, rural residents within the same region were therefore affected more by the famine than urban residents (Lin & Yang, 2000). This type of information bias highlights the need to avoid classification based on year of birth or region.

In addition, another potential source of bias is survivor bias among famine survivors (Li & Lumey, 2017). A recent review suggests that boys are biologically more vulnerable to undernutrition than girls (Thurstans et al., 2020). However, studies on the Chinese famine of 1959-1961 suggest that due to a culture of son preference, families may have preferentially allocated food to sons over daughters (Mu & Zhang, 2011). The implication is that the males exposed to famine might be less affected and thus more likely to survive than their female counterparts. In the context of the Chinese famine of 1959-1961, this type of survivor bias highlights the need to explore the possible moderating role of sex.

2.2.3 Overview of the Study

The current study of a large-scale, nationally representative, longitudinal study (≈ 26,000 participants) aimed to add to the literature and overcome some of the limitations found in previous research, that is, the lack of a life course perspective and information bias. Specifically, we adopted a life course perspective by focusing on a wide period of life ranging from the in-utero to adulthood (24-40 years) and considering the age at famine exposure. Moreover, we used more robust methods to adjust for age/cohort and used a more direct measure of famine exposure/severity. Our overall aim was to understand the link between exposure to the Chinese famine of 1959-1961 and NCDs 50 years later in 2011-2018. Our objectives were to determine if the link between famine exposure and NCDs in later life varied among individuals exposed at different life stages, individuals exposed to different levels of famine severity, and women and men.

2.3 Methods

We conducted a secondary analysis of a large-scale, nationally representative, longitudinal study, which provides both prospective data and retrospective data: the China Health and Retirement Longitudinal Study (CHARLS), which followed Chinese urban and rural residents aged 45 years old and above from 2011 to 2018. We measured famine exposure and severity of famine exposure using the individual self-reported famine experience, life stages using the age at famine exposure, and later-life health using the number of NCDs. We built a series of Poisson growth curve models to investigate the association between famine exposure and later-life NCDs. Specifically, to understand if this association depends on the life stage (age) at which individuals were exposed, we used two analytical approaches that have been used in the few existing studies on the topic: the factorial approach (i.e., the interaction between famine exposure and life stages) and a more parsimonious approach—the

concatenation approach (i.e., the famine exposure-life stages cohort). We also conducted two sets of sensitivity analysis to test the robustness of the association between famine exposure, life stage, and later-life NCDs. In addition, we tested the role of severity of famine exposure and sex.

2.3.1 Study Setting: The Chinese Famine of 1959-1961

More than half a century ago, China experienced the largest famine in human history, in terms of duration, nationwide geographic scope, and the number of individuals affected (Smil, 1999; St Clair et al., 2005). The famine lasted for three years from the spring of 1959 to the winter of 1961 throughout the country. During the famine years, grain production dropped dramatically by about 25% and nearly 30 million people died prematurely from famine (Ashton et al., 1984). Grain production and grain production per capita returned to the pre-famine level in 1965 and after 1970, respectively (Smil, 1999), indicating a slow and steady recovery to normal food intake.

2.3.2 Data and Participants

We used the data from the CHARLS, a large-scale, nationally representative, longitudinal study that provides both prospective data and retrospective data. CHARLS collects prospective health data from Chinese urban and rural residents aged 45 years old and above biennially since 2011. CHARLS applies a stratified, multistage probability sampling design (Zhao et al., 2012). First, CHARLS uses a probability proportion to size (PPS) sampling approach for all county-level unit except for Tibet after stratification by region, county characteristic (urban or rural), and per-capita gross domestic product. Primary sampling units (PSUs) are administrative villages in rural areas and neighborhoods in urban areas. Second, CHARLS uses CHARLS-GIS software to randomly sample households within each PSU. Last, within each sampled household, if occupants were aged above 40, one of them is randomly selected. If the selected person was aged 45 or above, they become the main respondent and

their spouse is also interviewed; if the selected person was aged between 40 and 44, they are reserved as a refreshment sample. If an age-eligible person was too frail to answer questions, a proxy respondent is identified to help them to answer questions. The sample is representative of participants aged 45 and above living in households. In our analyses, we merged the retrospective Life History data collected in 2014 with all four regular data waves collected in 2011, 2013, 2015, and 2018 (25,863 participants).

We included eligible participants based on two a-priori criteria: (i) participants with complete information on NCDs, famine exposure, sociodemographic variables, childhood family financial status, and childhood and adulthood health status; and (ii) participants born between 1 January 1919 and 30 September 1960 (i.e., in-utero to age of 40 at famine exposure).

2.3.4 Ethics

This study conformed to the principles laid down in the Declaration of Helsinki and was approved by the London School of Hygiene & Tropical Medicine Ethics Committee (Reference 28001).

2.3.5 Variables

2.3.5.1 Number of Non-Communicable Diseases (Outcome)

We used the responses to the questions asking participants whether they have been diagnosed by a doctor with any of the 14 following NCDs: hypertension, dyslipidemia, diabetes, cancer, lung disease, liver disease, heart disease, stroke, kidney disease, digestive disease, psychiatric problems, memory-related disease, arthritis, and asthma (0 = *no*; 1 = *yes*). We counted the number of concurrent NCDs for each participant in each wave Marengoni et al., 2011.

2.3.5.2 Famine Exposure (Predictor, Factorial Approach)

We used the responses to the question asking "Between 1958-1962 did you and your family experience starvation?" to build a binary variable differentiating participants who were unexposed to the famine (i.e., who answered "no") from participants who were exposed (i.e., who answered "yes").

2.3.5.3 Life Stages (Predictor, Factorial Approach)

We adopted a life course perspective and included participants ranging from in-utero to age of 40 at famine exposure. We used age at famine exposure on the 1 January 1959 to categorize participants into seven life stages adapted from definitions commonly used in major global policies and strategies World Health Organization, 2013 (**Figure 2.1**):

(1) **"In-utero"**—those born between 1 October 1959 and 30 September 1960;

(2) **"First 1,000 days" infants** (0-2 years) (reflecting the focus on this age group by the "Scaling Up Nutrition Movement" Scaling Up Nutrition, 2010)—those born between 1957 and 30 June 1959, among whom participants born between 1 January 1959 and 30 June 1959 were categorized as "0-6 months";

(3) **"Pre-school" children** (3-5 years)—those born between 1954 and 1956;

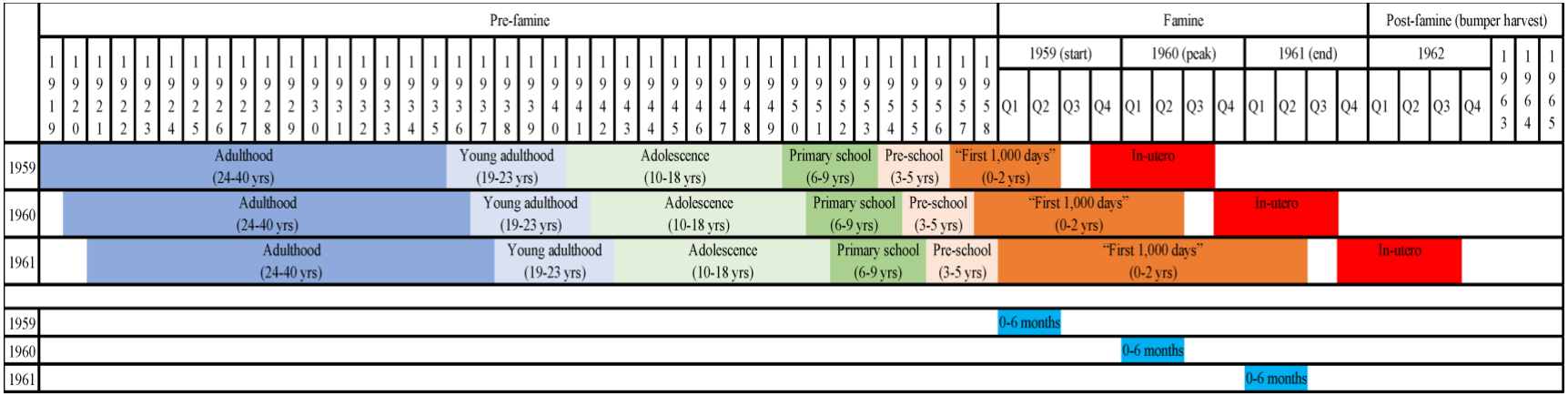
(4) **"Primary school" children** (6-9 years)—those born between 1950 and 1953;

(5) **"Adolescents"** (10-18 years)—participants born between 1941 and 1949;

(6) **"Young adults"** (19-23 years)—participants born between 1936 and 1940;

(7) **"Adults"** (24-40 years)—participants born between 1919 and 1935.

Figure 2.1. Categorization Scheme of the Seven Life Stages



Note. Columns refer to birth year/quarter, rows refer to reference year of 1959, 1960, and 1961.
Q1, Q2, Q3, and Q4 refer to the first, second, third, and fourth quarter of the year.
yrs refers to age in years.

2.3.5.4 Famine Exposure-Life Stages (Predictor, Concatenation Approach)

We used the variable "famine exposure" (i.e., no/yes) and the variable "life stages" (i.e., in-utero to adulthood) to build a superordinate categorical variable of famine exposure-life stages comparing unexposed participants with exposed participants from in-utero to in adulthood. Specifically, we concatenated the two variables to categorize participants into eight groups: (1) unexposed to the famine during their life course (i.e., control group), (2) exposed in-utero, (3) exposed in the "first 1,000 days" (0-2 years), (4) exposed in pre-school age (3-5 years), (5) exposed in primary school age (6-9 years), (6) exposed in adolescence (10-18 years), (7) exposed in young adulthood (19-23 years), and (8) exposed in adulthood (24-40 years).

2.3.5.5 Severity of Famine Exposure (Predictor)

We used the responses to the questions following up the famine exposure question to build a variable differentiating participants who were unexposed to famine from participants who were *moderately* exposed to famine (i.e., who answered "yes" to the question "Between 1958-1962 did you and your family move away from the famine-stricken area?"), and participants who were *severely* exposed to famine (i.e., who answered "yes" to either of the questions "Between 1958-1962 had any of your family starved to death?" or "Between 1958-1962 had your family lost any child?").

2.3.5.6 Potential Confounders

We controlled for the following potential confounders in our analysis: age, sex (-0.5 = *male*, +0.5 = *female*), residence in later life (0 = *rural*, 1 = *urban*), current marital status (0 = *not married*, 1 = *married*), current working status (0 = *not working*, 1 = *working*), family financial status in childhood (from 1 = *much better* to 5 = *much worse than families in the same community*), education levels (1 = *less than upper secondary*, 2 = *upper secondary and vocational*, 3 = *tertiary*), household income deciles (1 = *bottom 10%*, 10 = *top 10%*), number of diseases in childhood, and number of diseases in adulthood.

2.3.6 Analytical Strategy

2.3.6.1 Poisson Growth Curve Models

To estimate trajectories of the number of NCDs in the later life course, we built a series of two-level growth curve models in which wave-specific observations (N = 39,337 level-1 units) were nested in participants (K = 11,094 level-2 units). Specifically, we built Poisson growth curve models instead of linear growth curve models (King, 1988), because our outcome variable (the number of NCDs) was a count variable following a Poisson distribution. The overdispersion test revealed that the assumption of the equidispersion of the Poisson regression was not violated, χ^2 (2, N = 39,337) = 15,849, p = 1.00.

2.3.6.2 Associations between Famine Exposure, Life Stage, and Later-Life NCDs: Two Approaches

We used two approaches that have been used in previous studies to test the associations between famine exposure, life stage, and later-life NCDs: the factorial approach (Idris et al., 2013; van Abeelen et al., 2012a, 2012b) and the concatenation approach (Khalangot et al., 2017; Li et al., 2018).

The factorial approach. In the first approach, we tested whether the dichotomous variable "famine exposure" (unexposed vs. exposed) interacted with the variable "life stages" in predicting the number of NCDs. As life stage at famine exposure is partially dependent on the current age of the participant, we included the age variable in our model to estimate the effect of life stage at famine exposure independent of the current age (Yang & Land, 2013). We regressed the number of NCDs on three focal predictors: (i) famine exposure, (ii) life stages, (iii) famine exposure × life stages, and (iv) age (see Eq. 1), with and without control variables.

$$\log(\lambda_{ij}) = (\beta_{00} + u_{0j}) + \beta_{01} \times \text{Famine exposure}_j + \sum_{k=1}^{6}\left(\beta_{0(1+k)} \times \text{Life stage } k_j\right) + \sum_{k=1}^{6}\left(\beta_{0(7+k)} \times \text{Famine exposure}_j \times \text{Life stage } k_j\right) + \beta_{10} \times \text{Age}_{ij} + \beta_{ij} \times \text{Control}_{ij} \quad \text{(Eq.1)}$$

The outcome variable follows a Poisson distribution ($Y_{ij} \sim \text{Poisson}(\lambda_{ij})$); $i = 1, 2, \ldots, N$ (wave-specific observations), $j = 1, 2, \ldots, K$ [participants]; "Life stage" 1 to 6 correspond to in-utero, the "first 1,000 days", pre-school, primary school, adolescence, and young adulthood, respectively; $\beta_{ij} \times \text{Control}_{ij}$ represents a vector of control variables; and u_{0j} represents the participant-level residuals.

Although the factorial approach enabled us to directly test whether the association between famine exposure and later-life NCDs varies across life stages, the fact that there are seven life stages consumes a lot of degrees of freedom (i.e., seven for the main effect, and seven others for the interaction) and represents a potential threat to statistical power. Thus, we additionally used an alternative, more parsimonious and focal approach.

The concatenation approach. In the second approach, we tested whether the superordinate categorical variable "famine exposure-life stages" predicted the number of NCDs, comparing unexposed participants with participants exposed in-utero, in the "first 1,000 days" (0-2 years), in pre-school age (3-5 years), in primary school age (6-9 years), adolescence (10-18 years), in young adulthood (19-23 years), and in adulthood (24-40 years). We included the age variable in our model for the same reason mentioned above. We regressed the number of NCDs on two focal predictors: (i) famine exposure-life stages, and (ii) age (see Eq. 2), with and without control variables.

$$\log(\lambda_{ij}) = (\beta_{00} + u_{0j}) + \sum_{k=1}^{7}\left(\beta_{0k} \times \text{Famine exposure} \frown \text{life stage } k_j\right) + \beta_{10} \times \text{Age}_{ij} + \beta_{ij} \times \text{Control}_{ij} \quad \text{(Eq.2)}$$

The outcome variable that follows a Poisson distribution ($Y_{ij} \sim \text{Poisson}(\lambda_{ij})$); $i = 1, 2, \ldots, N$ (wave-specific observations); $j = 1, 2, \ldots, K$ [participants]; "Famine exposure-life stage" 1 to 7 corresponds to exposed to famine in-utero, in the "first 1,000 days", in pre-school, in primary school, in adolescence, in young adulthood, and in adulthood, respectively; $\beta_{ij} \times \text{Control}_{ij}$ represents a vector of control variables; and u_{0j} represents the participant-level residuals.

2.3.6.3 Sensitivity Analyses

We conducted two sets of sensitivity analyses to test the robustness of the associations between famine exposure, life stage, and later-life NCDs. First, to test if these associations were robust across the famine years as the famine evolved, we used two alternative reference dates of 1 January 1960 and 1 January 1961 to categorize participants into the seven life stages mentioned above (**Figure 2.1**). Second, to test is these associations were robust to the conceptualisation of life stages, we used an alternative scheme of life stages based on Erikson's developmental stages (1982) (**Supplementary Materials, Text A.1**).

We ran the Poisson growth curve models using the glmer function from the lme4 package (version 1.1-26) (Bates et al., 2015) in R (version 4.0.2). The R scripts to reproduce our findings are available via the Open Science Framework (OSF): https://osf.io/6zy43/?view_only=bacb4fa4927d4019a0c298da00082d91.

2.4 Results

Our final sample comprised 39,337 observations from 11,094 older adults (for the flow diagram of study participants, see **Figure 2.2**). As expected from the scope of the Chinese famine of 1959-1961, the majority of the analytical sample (9,257 participants, 83%) was exposed to famine whereas a small proportion of the analytical sample (1,837 participants, 17%)

was unexposed to famine. **Table 2.1** details the number of participants by sex and famine exposure at each life stage, and **Table 2.2** describes the sample characteristics.

Figure 2.2. Flow Diagram of Study Participants

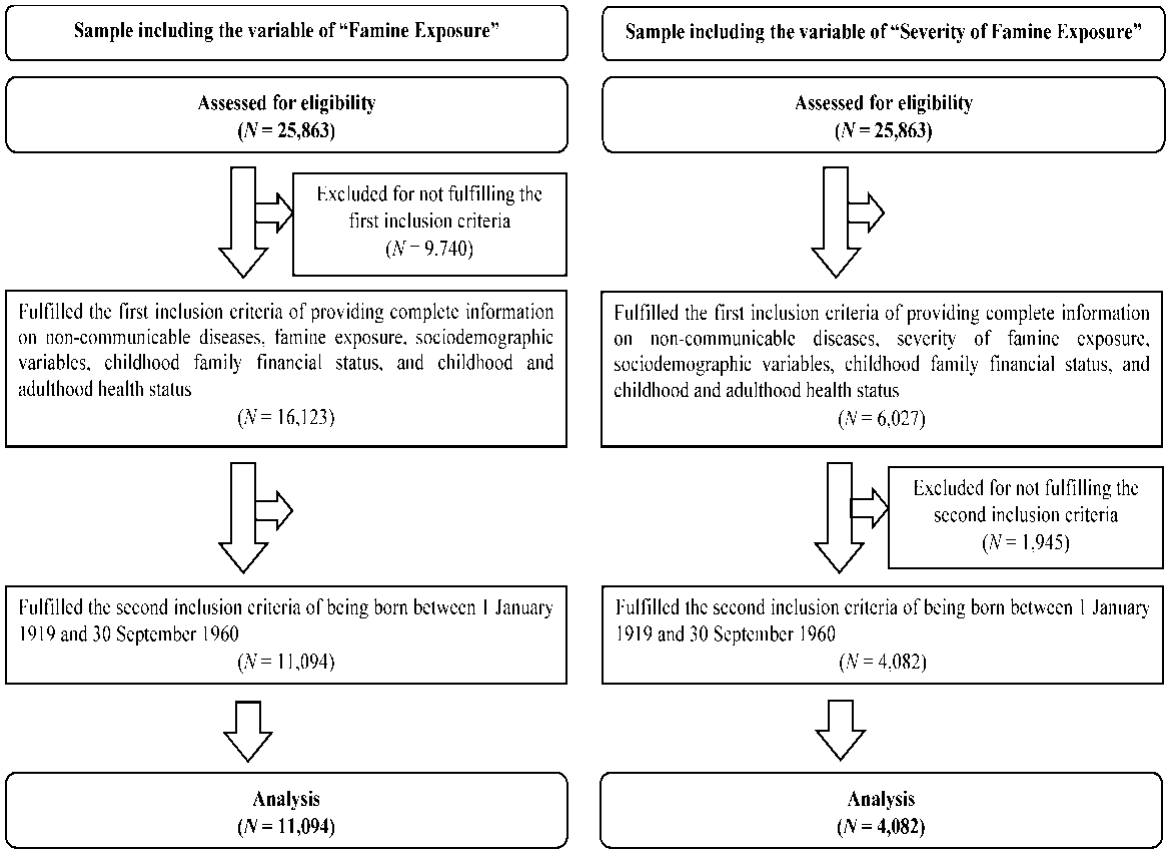


Table 2.1. Number of Study Participants, Stratified by Sex and Self-Reported Famine Exposure at Each Life Stage

	Overall (11,094 participants)		Male (5,446 participants)		Female (5,648 participants)	
	Exposed (9,257)	Unexposed (1,837)	Exposed (4,626)	Unexposed (820)	Exposed (4,631)	Unexposed (1,017)
In-utero	311	82	144	37	167	45
The "first 1,000 days" (0-2 years)[1]	914 (133)	225 (39)	448 (56)	102 (21)	466 (77)	123 (18)
Pre-school (3-5 years)	1,532	319	767	124	765	195
Primary school (6-9 years)	2,046	287	980	123	1,066	164
Adolescence (10-18 years)	3,001	489	1,554	217	1,447	272
Young adulthood (19-23 years)	813	239	437	116	376	123
Adulthood (24-40 years)	640	196	296	101	344	95

[1] Numbers in parentheses refer to the number of participants aged 0-6 months.

Table 2.2. Sample Characteristics, Stratified by Self-Reported Famine Exposure

	Overall (11,094 participants)	Exposed (9,257 participants)	Unexposed (1,837 participants)
Females (%)	50.9	50.0	55.4
Age (mean; in years)	65.6 (*SD* = 7.7)	65.5 (*SD* = 7.5)	66.3 (*SD* = 8.6)
Childhood family financial status (mean; 1 = *much better*, 5 = *much worse than other families*)	3.55 (*SD* = 0.99)	3.62 (*SD* = 0.98)	3.20 (*SD* = 0.96)
Equivalized Income (mean; in CNY)	13,705 (*SD* = 26,229)	13,148 (*SD* = 26,633)	16,514 (*SD* = 23,903)
Educational levels (%)			
less than lower secondary	91.0	91.4	88.7
upper secondary or vocational	7.7	7.4	8.9
tertiary	1.3	1.1	2.3
Number of non-communicable diseases (mean)	2.01 (*SD* = 1.56)	2.04 (*SD* = 1.57)	1.85 (*SD* = 1.50)
Number of childhood health conditions (mean)	0.08 (*SD* = 0.33)	0.08 (*SD* = 0.33)	0.07 (*SD* = 0.32)
Number of adulthood health conditions (mean)	0.38 (*SD* = 0.74)	0.39 (*SD* = 0.74)	0.34 (*SD* = 0.70)
Rural residence in later life (%)	62.3	63.1	58.0
Currently married (%)	84.9	85.4	82.3
Currently working (%)	57.8	59.1	51.4

2.4.1 Associations between Famine Exposure, Life Stage, and Later-Life NCDs

2.4.1.1 Factorial Approach

In our first set of models using the factorial approach (adjusted for confounders), we observed a main effect of famine exposure: compared with unexposed participants, participants exposed to famine had a 14% increased risk of NCDs in later life, IRR = 1.14, 95% CI [1.09, 1.19], $p < .001$. However, we did not observe an interaction between famine exposure and life stages: the overall detrimental effect of famine exposure did not vary across life stages when participants were exposed, χ^2 (6, N = 39,337) = 1.38, $p = .241$.

2.4.1.2 Concatenation Approach

In our second set of models using the concatenation approach (adjusted for confounders), we observed a main effect of the famine exposure-life stages: compared with participants unexposed to famine over their life course, participants exposed to famine at different life stages were affected differently, χ^2 (7, N = 39,337) = 1117.00, $p < .001$ (**Figure 2.3**; for the full results, see **Table 2.3**). Specifically, compared with participants unexposed to famine over their life course (control group): (i) participants exposed to famine in-utero and in the "first 1,000 days" of their life had an approximately 90% increased risk of NCDs in later life (for in-utero group, IRR = 1.90, 95% CI [1.70, 2.12], $p < .001$; for 0-2 years group, IRR = 1.86, 95% CI [1.73, 2.00], $p < .001$, among which for 0-6 months group, IRR = 1.95, 95% CI [1.67, 2.29], $p < .001$); (ii) participants exposed to famine in pre-school and primary school (i.e., before age 10) had an approximately 50% increased risk of NCDs in later life (for pre-school group (3-5 years), IRR = 1.56, 95% CI [1.47, 1.66], $p < .001$; for primary school group (6-9 years), IRR = 1.45, 95% CI [1.37, 1.54], $p < .001$); (iii) participants exposed to famine in adolescence (10-18 years) had a 8% increased risk of NCDs in later life, IRR = 1.08, 95% CI [1.03, 1.14], $p < .01$; whereas (iv) participants exposed to famine after age 18 had a decreased

risk of NCDs in later life (for young adulthood group (19-23 years), IRR = 0.66, 95% CI [0.61, 0.71], $p < .001$; for adulthood group (24-40 years), IRR = 0.40, 95% CI [0.37, 0.44], $p < .001$).

Figure 2.3. Associations between Exposure to the 1959-1961 Chinese Famine, Life Stage, and Non-Communicable Diseases in Later Life (the Concatenation Approach)

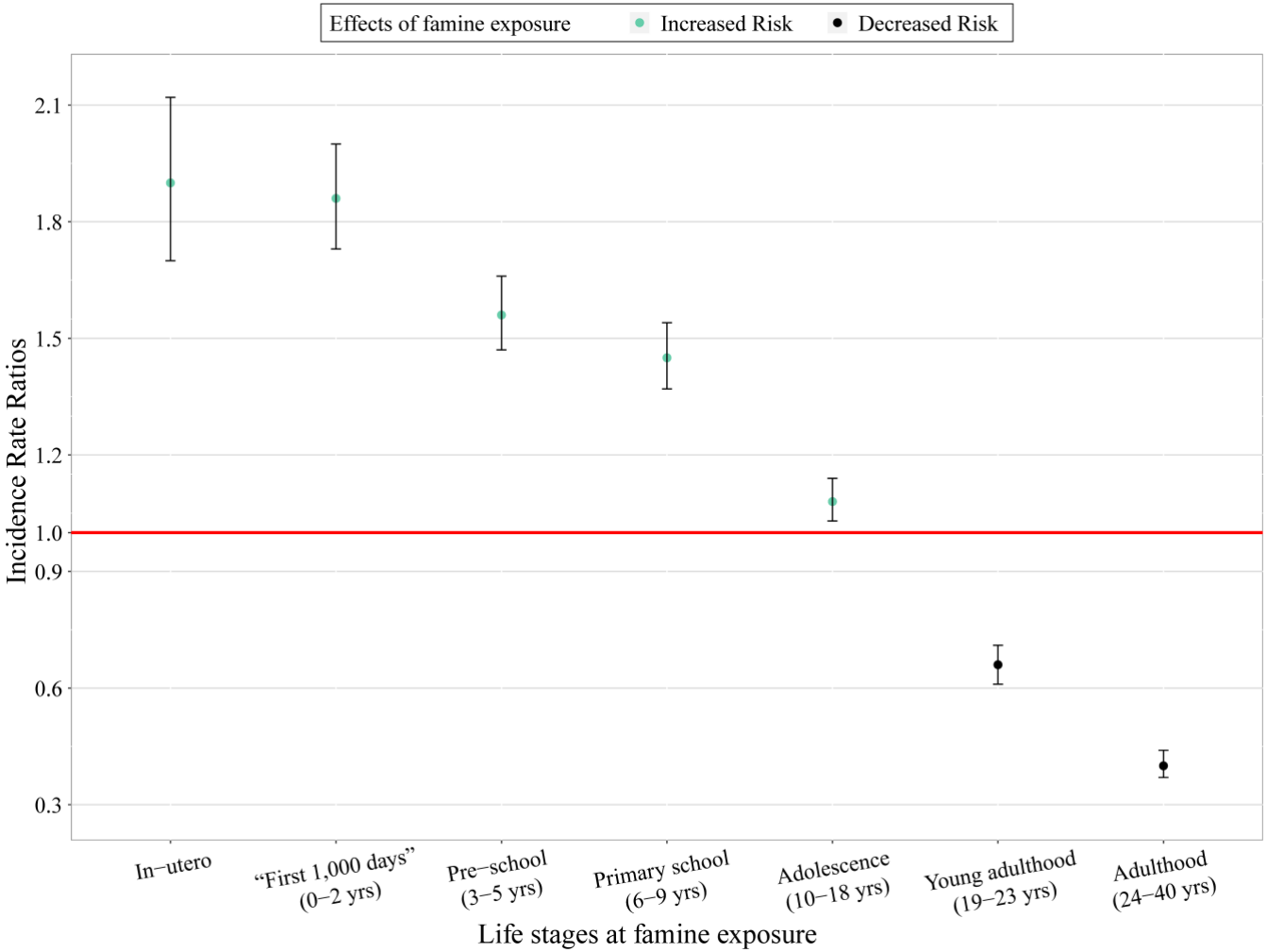


Table 2.3. Associations between Exposure to the 1959-1961 Chinese Famine, Life Stage, and Non-Communicable Diseases in Later Life (the Concatenation Approach)

	IRRs	95% CI
Unexposed (control group)	1.00	Reference
Exposed in-utero	1.90***	1.70–2.12
Exposed in the "first 1,000 days" (0-2 years)[1]	1.86*** (1.95***)	1.73–2.00 (1.67–2.29)
Exposed in pre-school age (3-5 years)	1.56***	1.47–1.66
Exposed in primary school age (6-9 years)	1.45***	1.37–1.54
Exposed in adolescence (10-18 years)	1.08**	1.03–1.14
Exposed in young adulthood (19-23 years)	0.66***	0.61–0.71
Exposed in adulthood (24-40 years)	0.40***	0.37–0.44

Note. IRRs = Incidence Rate Ratios. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Adjusted for age, sex, later-life residence, marital status, current working status, childhood family financial status, education, household income, number of diseases in childhood, and number of diseases in adulthood.

[1] Numbers in parentheses refer to the IRRs and 95% CI for participants exposed in the 0-6 months.

2.4.1.3 Sensitivity Analyses

We conducted two sets of sensitivity analyses to test the robustness of the associations between famine exposure, life stage, and later-life health. The results observed above were confirmed in the sensitivity analyses that used two alternative reference dates (**Supplementary Materials, Table A.1**) and an alternative scheme of life stages based on Erikson's developmental stages (1982) (**Supplementary Materials, Table A.2**).

2.4.2 Associations between Severity of Famine Exposure and Later-Life NCDs

We ran the same type of Poisson growth curve model as above, but this time we used severity of famine exposure (unexposed, moderately exposed, and severely exposed) as the focal predictor. Compared with unexposed participants, participants moderately or severely exposed to the famine had an increased risk of NCDs in later life, IRR = 1.18, 95% CI [1.09, 1.28], $p < .001$ and IRR = 1.24, 95% CI [1.17, 1.32], $p < .001$, respectively. However, the difference in the risk of NCDs in later life between moderately exposed participants and those severely exposed to famine was not statistically significant, $\beta = 0.05$, 95% CI [-0.05, 0.15], $p = .454$ (**Supplementary Materials, Table A.3**).

2.4.3 Sex-Specific Associations between Famine Exposure and Later-Life NCDs

We ran the same type of Poisson growth curve model as above and included the interaction between famine exposure and sex. The overall detrimental famine effects did not differ between females and males, IRR = 0.98, 95% CI [0.90, 1.07], $p = .703$ (**Supplementary Materials, Table A.4**).

2.5 Discussion

In this study, we adopted a life course perspective and analyzed whether exposure to the 1959-1961 Chinese famine was associated with NCDs in later life. We addressed the problem of information bias by using a more direct measure of famine exposure and the

severity of famine exposure. We also extended existing studies by testing whether this association depends on the life stage at exposure, the severity of famine exposure, and sex. We observed three main findings:

First, consistent with the few existing studies (Khalangot et al., 2017; Li et al., 2018), our analysis using the concatenation approach revealed that individuals exposed to famine at different life stages were affected differently—and the famine effects were independent of age/cohort differences (**Supplementary Materials, Table A.5**). Compared with individuals unexposed to famine over their life course, individuals exposed to famine before age 18 had a higher risk of NCDs in later life. The risk was particularly high for those exposed to famine in-utero and in the "first 1,000 days" of life, namely, between 0-2 years (particularly 0-6 months). The long-term detrimental health consequences of famine exposure before age 18 can be explained by the wide time window of development and growth (Ozanne & Constância, 2007). Development during the "first 1,000 days" is particularly rapid and critical, and individuals exposed during this period are most affected by adverse exposures. One widely acknowledged mechanism is the capacity-load model (Wells, 2018). Poor nutrition and slow/rapid growth during the critical developmental period constrain capacity for homeostasis and elevate metabolic load which increases the risk for NCDs in the long term.

In contrast, compared with those unexposed to famine over their life course, individuals exposed to famine in young adulthood (19-23 years) or adulthood (24-40 years) had a decreased risk of NCDs in later life. This may be explained by the combined effect of food allocation and mortality selection (survivor bias): during the famine adults prioritized food allocation to infants and children in the family (Fan et al., 2008). As a result, only the fittest adults survive the famine, which may explain why these adult survivors of famine are generally healthier than their unexposed counterparts.

Second, also consistent with the few existing studies (van Abeelen et al., 2012a), we found that although individuals moderately or severely exposed to the famine had a higher risk of NCDs in later life than unexposed individuals, the difference in the risk of NCDs between moderately and severely exposed individuals was not statistically significant. Future studies are warranted to investigate the possible dose-response effects of famine exposure severity on later-life health. We recognize that we had only retrospective and imperfect measures of famine exposure severity, and famine exposure severity might not be fully captured by the available data (e.g., we had no measure of an individual's nutritional/anthropometric status at the time of famine). Hence the true effects may have been underestimated. It is also possible that "healthy survivor" bias again applies and that those most affected were most likely to die in the short or medium term (**Supplementary Materials, Table A.6**).

Third, in contrast to some previous studies that reported a more pronounced detrimental impact of famine exposure among females than males (Wang et al., 2010; Yang et al., 2008), we found that the association between famine exposure and NCDs in later life did not differ between females and males. The more pronounced detrimental impact of famine exposure among females than males reported by some previous studies may be biased by the healthy survivor effect among males (Thurstans et al., 2020) and the food allocation priority given to sons in the family (Mu & Zhang, 2011). Future studies are warranted to investigate the possible sex-specific mechanisms underlying the famine exposure and later-life health (Thurstans et al., 2022). Many mechanisms are possible, but which are active and how they vary in different settings is poorly understood.

We acknowledge four main limitations. First, the retrospective measures of famine exposure and severity of famine exposure were self-reported and might be subject to recall bias and misclassification. However, a recent review points out that the information on major life events collected by interview-based procedures has acceptable levels of reliability (Monroe &

Slavich, 2019). Second, we could not control for birth weight or gestational age, which might be important confounders, because information on these is unavailable. However, several studies showed that the association between famine exposure and NCDs remained after controlling for birth weight (Head et al., 2008). Third, life stages were categorized based on the age at exposure. Future studies should consider the context and transitions into adulthood when categorizing life stages (e.g., experiencing famine during transitions to entering the labor market, starting a family, or having a child). Last, survivor bias might be part of the story. Future studies need to evaluate the effects of survivor bias by investigating the possible selection mechanisms and adjust the effect estimates of famine exposure (Banack et al., 2019).

2.5.1 Implications for Policy and Practice

Our findings have several implications for policy and practice in global health. First, our finding that famine exposure in childhood and adolescence is associated with later-life NCDs is an important argument for seeing undernutrition/famine prevention as a long-term investment rather than a short-term cost. Second, the particularly marked long-term effects if famine is experienced in-utero and in the "first 1,000 days" further justify the current focus of nutrition programmes on this period (Scaling Up Nutrition, 2010). Third, our observation that infants aged 0-6 months are also especially vulnerable justifies WHO's current focus on growth failure in this age group in upcoming wasting guidelines (Emergency Nutrition Network, 2021; Kerac & McGrath, 2017). Finally, the fact that older children and adolescents also experience long-term effects should remind policy-makers and practitioners that these groups also matter and that life course approaches are essential to future health and wellbeing.

2.6 Conclusion

Our research analyzed a large-scale, nationally representative, longitudinal study, which provides both prospective data and retrospective data: the China Health and Retirement

Longitudinal Study (CHARLS, approximately 26,000 participants, 2011-2018, aged 45 and above). Our findings show that famine exposure has long-term detrimental consequences for later-life NCDs and affects individuals exposed at different life stage ranging from in-utero until young adulthood. These findings suggest that in an individual's life course, in-utero and the "first 1,000 days" is a particularly sensitive time window of development and growth but that this time window remains open until young adulthood. This represents a powerful argument for actions to protect nutrition throughout this period: such actions should be viewed as an investment, with beneficial short-term as well as long-term health and socioeconomic consequences, not only for individual children and families, but also for nations and the world.

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3. Long Arm of Prenatal Exposure to the 1944-1945 Dutch Hunger Winter into Later-Life Biological Aging

Revised and resubmitted to *PNAS*: Cheng, M., Conley, D., Kuipers, T., Li, C., Ryan, C., Taeubert, J., Wang, S., Wang, T., Zhou, J., Schmitz, L., Tobi, E., Heijmans, B., Lumey, L.H., & Belsky, D. Accelerated biological aging six decades after prenatal famine exposure.

3.1 Abstract

To test the hypothesis that early-life adversity accelerates the pace of biological aging, we analyzed data from the Dutch Hunger Winter Families Study (DHWFS, N=951). DHWFS is a natural-experiment birth-cohort study of survivors of in-utero exposure to famine conditions caused by the German occupation of the Western Netherlands in Winter 1944-5, matched controls, and their siblings. We conducted DNA methylation analysis of blood samples collected when the survivors were aged 58 to quantify biological aging using the DunedinPACE, GrimAge, and PhenoAge epigenetic clocks. Famine survivors had faster DunedinPACE, as compared with controls. This effect was strongest among women. Results were similar for GrimAge, although effect-sizes were smaller. We observed no differences in PhenoAge between survivors and controls. Famine effects were not accounted for by blood-cell composition and were similar for individuals exposed early and later in gestation. Findings suggest in-utero undernutrition may accelerate biological aging in later life.

3.2 Introduction

Insults to early-life development are predicted by theory to impact trajectories of healthy aging (Barker, 1995; Brakefield et al., 2005; Gavrilov & Gavrilova, 2004; Gluckman et al., 2008). Consistent with this hypothesis, longitudinal observational studies have identified associations between early-life conditions and later-life health outcomes (Ben-Shlomo & Kuh,

2002). But establishing the causality of such associations is difficult due to potential confounding effects of family history and other factors that may affect both early-life development and later aging outcomes (Brakefield et al., 2005; De Stavola & Daniel, 2016). Natural experiments, which seek to overcome this obstacle to causal inference, are study designs that take advantage of historical events beyond the control of individuals or their families that impact a subset of otherwise comparable individuals in a population. An established natural-experiment design for investigating effects of early-life adversity on later-life health is in-utero exposure to famine (Vaiserman, 2011). In studies of the Dutch Hunger Winter (1944-5), Siege of Leningrad (1941-4), Holodomor famine in Ukraine (1932-3), and Great Chinese Famine (1959-61), survivors of in-utero famine exposure exhibit higher burdens of multiple aging-related diseases and have shorter lifespans as compared to unexposed individuals born before or after famine or in adjacent, unaffected regions (Cheng, Sommet, Kerac, et al., 2023; Ekamper et al., 2014; Grey et al., 2021; Li & Lumey, 2017; Li & Lumey, 2022; Lumey, Stein, et al., 2011). Within the Fetal Origins and Developmental Origins of Health and Disease literatures, these observations are often interpreted as reflecting in-utero programming of risk for cardiovascular and metabolic disease later in life (Gluckman & Hanson, 2004; Gluckman et al., 2008; Painter et al., 2006). However, an alternative hypothesis is that famine-induced insult in early life impairs the development of more general robustness and resilience capacities of the organism, resulting in accelerated systemic decline with aging.

To explore this alternative hypothesis, we analyzed blood DNA methylation (DNAm) data collected in a natural-experiment study of in-utero famine exposure to test differences in the pace and progress of biological aging between famine-survivors and matched controls. The Dutch Hunger Winter Families Study (DHWFS) enrolled a cohort of survivors of in-utero exposure to the Dutch Famine (1944-5), matched controls born before or after the famine in the same hospitals as the survivors, and their same-sex siblings (Lumey et al., 2007). We

compared famine survivors to unexposed controls on three DNAm measures of biological aging linked in prior studies with histories of early-life adversity, the DunedinPACE, GrimAge, and PhenoAge DNAm clocks (Graf et al., 2022; McCrory et al., 2022; Schmitz & Duque, 2022). Our analysis further explored differences in the effects of famine between women and men and by gestational timing of exposure, and tested consistency of findings in both between- and within-family comparisons.

3.3 Methods

3.3.1 Study Setting: The Dutch Hunger Winter of 1944-1945

The Dutch famine was initiated by a food supply embargo imposed by the German occupying forces in early October 1944. The severity and widespread nature of the famine are well documented (de Zwarte, 2020; Lumey et al., 2007; Stein et al., 1975). Prior to the embargo, nutrition in the Netherlands had generally been adequate. Official rations, which eventually consisted of little more than bread and potatoes, fell below 900 kcal/day in late November 1944, and were as low as 500 kcal/day by April 1945. The macronutrient composition of the ration remained relatively stable over this period, but the composition of non-ration foods changed, with a reduction in the intake of fat. The famine ceased with liberation in May 1945, after which Allied food supplies were distributed.

3.3.2 Participants

Famine-Exposed individuals were identified from review of archival obstetric records. We selected all the 2,417 singleton births between 1 February 1945 and 31 March 1946 at three institutions in famine-exposed cities in the western Netherlands whose mothers were exposed to the famine during or immediately preceding that pregnancy.

Time Controls were selected from births at the same hospitals and in the same months of the year as the famine-exposed group during 1943 and 1947 (two years before and two years

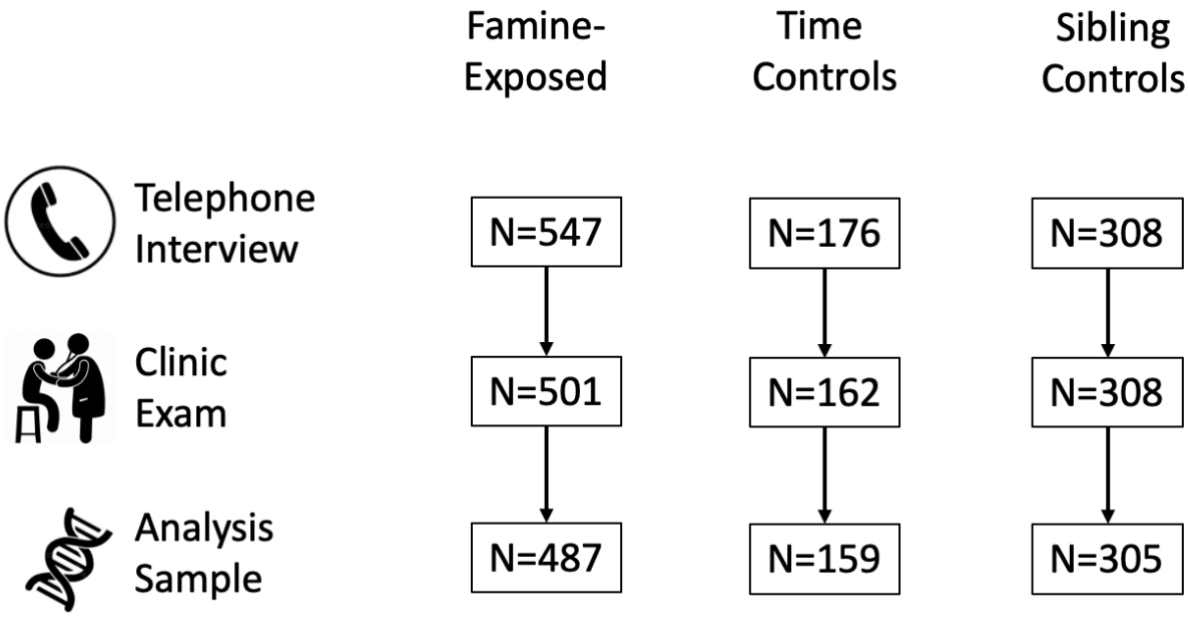
after the famine). We sampled an equal number of births in each month, allocated across the three institutions according to their size, to obtain 890 singleton births.

Of the total famine-exposed and time-control births, current addresses were able to be traced for 70%. These individuals were invited by mail to join the study and were additionally asked if a same-sex sibling born before or after the famine would be available to participate. A total of N=547 of the famine-exposed group, N=176 of the time-control group, and N=308 same-sex unexposed siblings consented to participate and underwent a computer-assisted structured interview by telephone.

Data Collection was conducted in 2003-2005, approximately six decades after the famine. Of the N=1,031 participants who were interviewed, N=971 also participated in a clinic exam (**Figure 3.1**). Following the Helsinki guidelines, we obtained ethical approval both from the Institutional Review Board of Columbia University Medical Center and from the Medical Ethical Committee of the Leiden University Medical Center (LUMC). The study participants provided verbal consent in a telephone interview, and in case of clinical examinations, a written informed consent was obtained and additional METC approval for epigenetic studies was later confirmed by the METC of the LUMC.

Figure 3.1. Flow Diagram of the Dutch Hunger Winter Families Study. The figure shows how the analysis sample size was arrived at in each step for survivors of in-utero famine exposure, time controls, and same-sex sibling controls. N=1,031 participants completed telephone interviews. Of this group, 971 participated in the clinic exam. DNA extracted from blood samples was analyzed to determine DNA methylation and data passed quality controls

for N=951 individuals. The figure illustrates the number of individuals in each exposure and control group included in the telephone interview, clinic examination, and analysis sample.



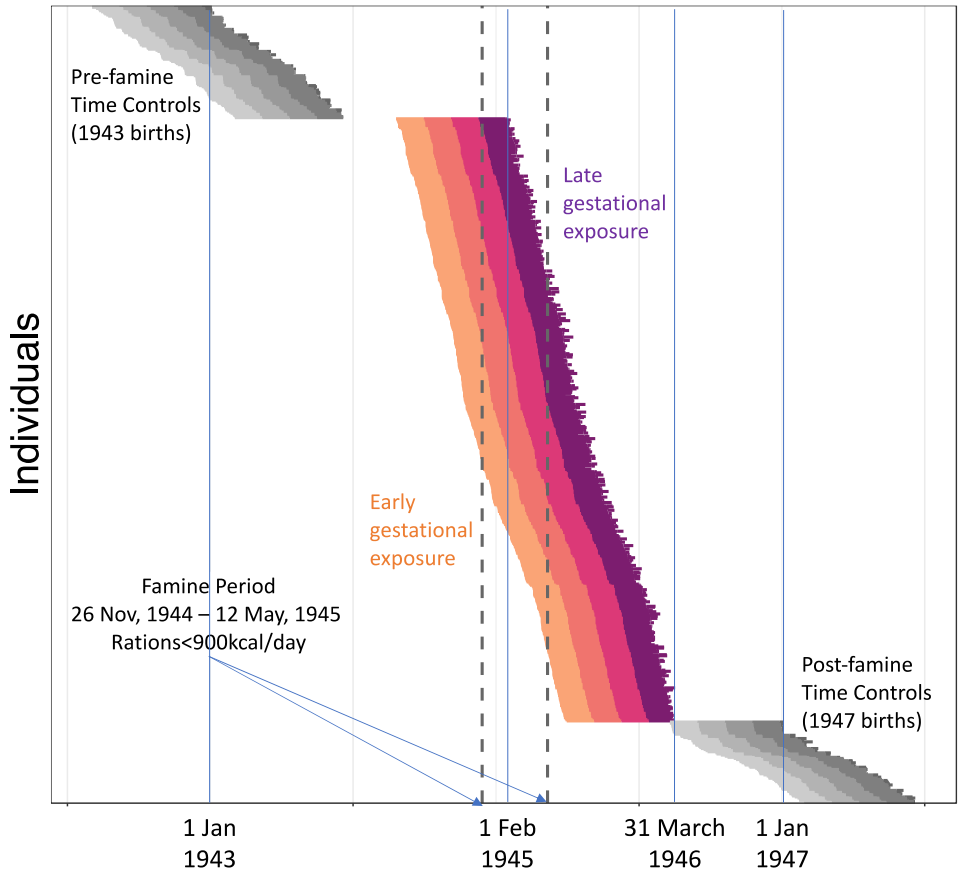
3.3.3 Measures

3.3.3.1 Famine Exposure

We defined the period of famine from archival records of weekly ration distributions, as described previously (Lumey et al., 2007). Briefly, the start of the famine-exposure period was defined as November 26, 1944, based on the threshold <900 kcal/day of distributed food rations. The end of the famine-exposure period was defined as May 12, 1945, one week following the German surrender. Participants' exposure during gestation was determined from the date of their mother's last menstrual period (LMP) and their date of birth. In cases where the LMP date was missing or implausible (12% of births), LMP was estimated from birth-record data on birth weight and date of birth using tables of gender, parity, and birth weight specific gestational ages from the combined birth records of the Amsterdam Midwives School (1948-57) and the University of Amsterdam Wilhelmina Gasthuis Hospital (1931-65).

Famine-exposed participants experienced an average of 17 weeks of gestation during which ration distributions were <900kcal/day. Following prior work with the cohort (Lumey et al., 2009; Stein et al., 2007), participants were classified as famine exposed during each of four 10-week gestational periods on the basis of ration distributions. For each individual, average rations were calculated for each 10-week period of gestation and periods with average rations <900 kcal/day were classified as famine-exposed. Among the N=547 participants recruited as famine exposed, N=403 met criteria for exposure in at least one 10-week gestational period. A further N=82 had LMP dates prior to the end of the famine, but fewer than 10 weeks of gestational exposure to ration distributions <900kcal/day. A final N=62 had LMP dates after the end of the famine. Gestational periods for famine-exposed participants and time-controls are shown in **Figure 3.2**.

Figure 3.2. Gestational Timing of Exposure to Famine in the Dutch Hunger Winter Families Study. The figure shows individual gestations of N=547 famine-exposed participants (colored lines) and N=176 time controls (gray lines). Each gestation is plotted as a single horizontal line. The start of the line is the date of the mother's last menstrual period (LMP). The end of the line is the participant's date of birth. Individual gestations are plotted from the top of the graph to the bottom, ordered by LMP date. For the famine-exposed participants, the segment of each line showing the first 10 weeks of gestation is colored gold. The segment showing the second 10 weeks is colored orange. The segment showing the third 10 weeks is colored red. The segment showing the last 10 weeks is colored purple. For the time controls, 10-week gestational periods are colored in gray, with lighter shades for the earlier gestational periods. The x-axis shows the date. The vertical dashed lines show the start and end of the famine exposure period (November 26, 1944 - May 12, 1945).



3.3.3.2 DNA Methylation Measures of Biological Aging

Biological aging is the progressive loss of system integrity with advancing chronological age (Kirkwood, 2005). Biological aging is thought to arise from an accumulation of cellular-level changes that progressively undermine the robustness and resilience capacity of cells, tissues, and organ systems (Campisi et al., 2019; López-Otín et al., 2013, 2023). While there is no gold-standard measure of biological aging in humans (Ferrucci et al., 2020), the current-state of the art are algorithms that combine information from dozens or hundreds of DNA methylation (DNAm) marks, chemical tags on the DNA sequence that regulate gene expression and are known to change with aging (Rutledge et al., 2022). These algorithms are often referred to as "epigenetic clocks" (Horvath & Raj, 2018). We measured biological aging using epigenetic clocks computed from the existing DNA methylation database for the DHWFS.

Briefly, DNA methylation (DNAm) was measured from blood collected at the clinic exam using the Illumina Infinium Human Methylation 450k BeadChip and preprocessed as previously described (Tobi et al., 2015). Further details are provided in the **Supplementary Materials, Text B.1**.

Our primary analysis focused on three epigenetic clocks for which validation data across multiple studies establish robust associations with healthspan and lifespan and sensitivity to exposures known to hasten aging-related health decline: the DunedinPACE clock, which measures pace of aging, and the GrimAge and PhenoAge clocks, which measure biological age. We calculated DunedinPACE using the R code available on GitHub (https://github.com/danbelsky/DunedinPACE). We calculated high-technical-reliability "PC" versions of the GrimAge and PhenoAge clocks developed by the Levine Lab (Higgins-Chen et al., 2022) using the code available from GitHub (https://github.com/MorganLevineLab/PC-Clocks). The clocks are described in detail in the **Supplementary Materials, Text B.1**.

There are many other epigenetic clocks, although none with comparable evidence of validity to DunedinPACE, GrimAge, and PhenoAge. Most other clocks were developed to predict differences between individuals in their chronological age (sometimes referred to as "first-generation clocks"). For comparison purposes, we report results in the **Supplementary Materials, Table B.3 and Table B.5** for three of the best-known first-generation clocks, the Horvath, Hannum, and Skin & Blood clocks (Hannum et al., 2013; Horvath, 2013; Horvath & Raj, 2018). We also report results for the original versions of three second-generation clocks, the Zhang, GrimAge, and PhenoAge clocks (Levine et al., 2018; Lu et al., 2019; Zhang et al., 2017). Original versions of the clocks were computed using the methylclock R package (Pelegí-Sisó et al., 2020) and Python code to calculate GrimAge provided by Ake Lu.

3.3.4 Analysis

The analysis sample for this study was formed from participants in the clinic examination who provided a blood sample from which DNA was extracted and stored at LUMC. For our analysis, DNA were available for N=960 individuals. After quality controls, DNA methylation datasets were available for N=951. These individuals formed our analysis sample.

We used regression analysis to test associations between in-utero famine exposure and DNAm measures of biological aging. First- and second-generation epigenetic clock values have high correlations with chronological age. For analysis and interpretation, the standard approach is to regress clock values on participants' chronological age values and predict residual values. These values, often referred to as "age acceleration residuals", aim to quantify the difference between how much aging a person has actually experienced relative to the expectation based on their chronological age. No residualization was performed for DunedinPACE, which is a rate measure and shows only moderate correlation with chronological age. To account for the non-independence of measurements taken from siblings,

we used generalized estimating equation (GEE) regressions (Hanley et al., 2003). Our models included covariates for participants' sex, age, and age-squared at the time of the clinic exam. We explored sex differences in famine effects by repeating analysis with inclusion of product term testing interaction between famine exposure and sex. We repeated our analysis with a control group restricted to the "time controls" born immediately before or after the famine. We tested consistency of results in within-family comparisons of siblings using sibling-fixed-effects (FE) regressions (Petersen & Lange, 2020). We tested the sensitivity of associations between famine exposure and biological aging to differences between participants in leukocyte composition of DNA samples by repeating analysis with additional covariates for DNAm estimates of leukocyte proportions estimated using the Houseman equations (Houseman et al., 2012).

3.4 Results

We analyzed data for N=951 cohort members with available DNAm data (N=487 famine survivors, N=159 time controls, N=305 sibling controls; **Table 3.1**). The characteristics of this analysis sample were similar to the Dutch Hunger Winter Families Study interview sample (**Supplementary Materials, Table B.1**).

Table 3.1. Characteristics of the Dutch Hunger Winter Families Study DNA Methylation Sample. The table shows characteristics of the analysis sample overall (left column) and the famine-exposed and control groups (middle and right columns).

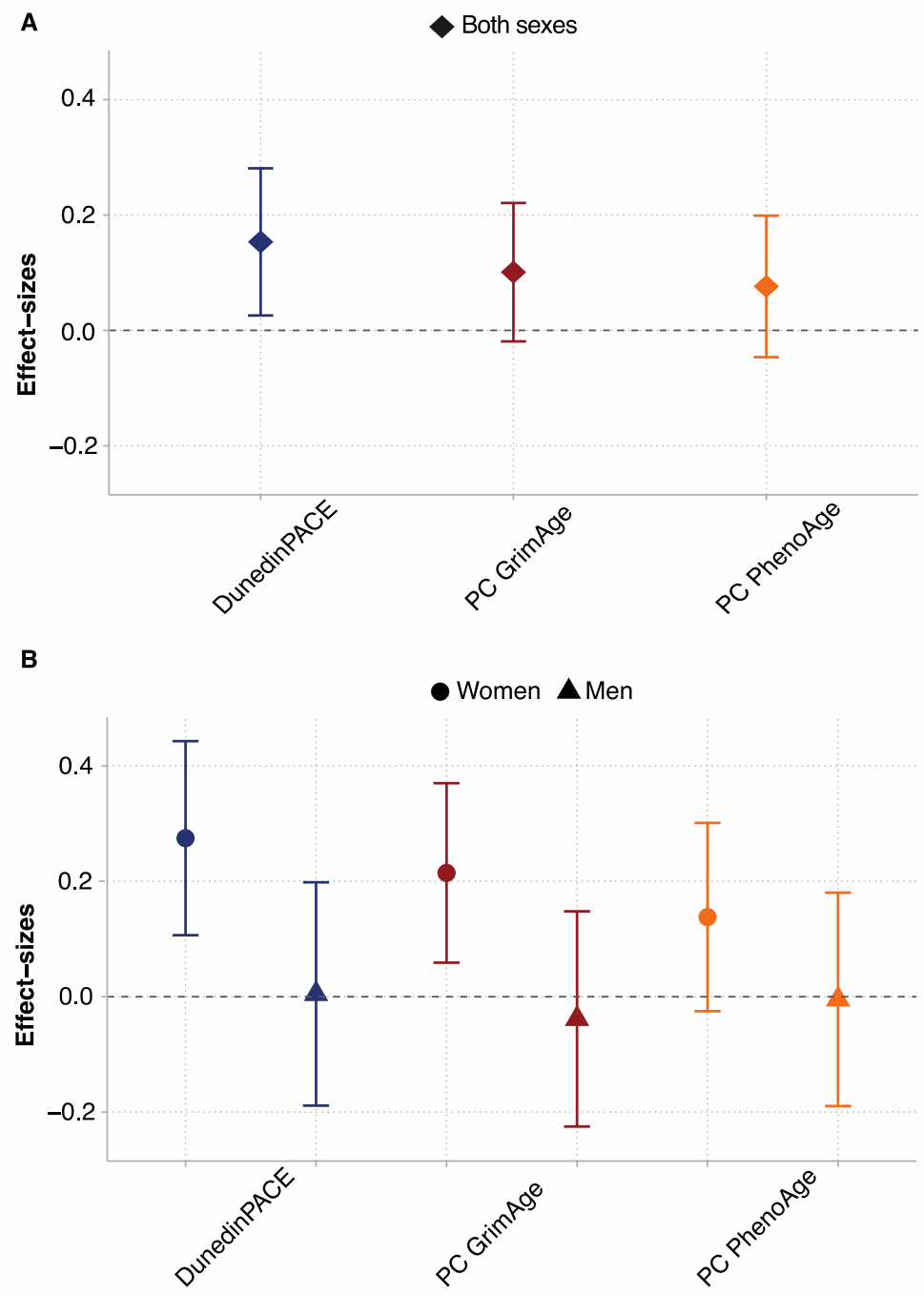
Panel I: DHWFS sample (N=951)								
	DHWFS		**Famine-exposed**		**Controls**			
					Time controls		**Sibling controls**	
	(N=951)		(N=487)		(N=159)		(N=305)	
	Mean/ %	(SD)	Mean/ %	(SD)	Mean/ %	(SD)	Mean/ %	(SD)
Age (years)	58	(4)	59	(1)	59	(2)	57	(6)
Men (%)	45%		47%		45%		42%	
Duration of exposure (weeks)			17	(7)				
DunedinPACE	0.97	(0.11)	0.97	(0.11)	0.95	(0.11)	0.97	(0.11)
PC GrimAge	69.92	(5.03)	70.42	(4.20)	70.18	(4.60)	68.98	(6.20)
PC PhenoAge	50.18	(5.87)	50.61	(5.18)	50.61	(5.10)	49.27	(7.07)

Our analysis proceeded in three steps. First, to test the hypothesis that in-utero famine exposure contributed to accelerated biological aging, we compared DNAm measures of pace of aging (DunedinPACE) and biological age (GrimAge and PhenoAge) between famine-survivors and controls. Second, we conducted dose-response analysis to test if participants who were exposed to the famine for more weeks of gestation exhibited larger famine effects as compared with those exposed for fewer weeks of gestation. Third, to explore specificity of famine effects to exposure during specific periods of gestation, we classified famine survivors according to when in gestation they were exposed, as described in the Methods section, and computed effect estimates for each window of exposure. In each step, we conducted analysis (a) in the full DHWFS; (b) using a between-families comparison of famine-survivors to unexposed time controls born immediately before or after the famine; and (c) using a within-family comparison of famine-survivors to their unexposed same-sex siblings. We also explored whether associations of famine exposure with biological aging differed between men and women.

3.4.1 In-Utero Famine Exposure Was Associated with Faster Biological Aging as Measured by DunedinPACE

Cohort members exposed to famine in utero had faster pace of aging compared with unexposed cohort members (DunedinPACE β=0.15, 95% CI [0.03, 0.28], p=.018). Differences between famine survivors and controls were of smaller magnitude for GrimAge and PhenoAge and not statistically different from zero at the alpha=0.05 level (βs<0.10, p>.099). Results were similar in analysis restricted to include only famine survivors and unrelated time controls. Results are shown in **Figure 3.3*A*** and reported in **Supplementary Materials, Table B.2**; full results for all biological aging measures are reported in **Supplementary Materials, Table B.3**; a correlation matrix is shown in **Supplementary Materials, Figure B.1**.

Figure 3.3. Differences in Biological Aging between Survivors of In-Utero Famine Exposure and Unexposed Control Participants in the Dutch Hunger Winter Families Study. The figure shows effect-sizes of in-utero famine exposure associations with three DNA methylation (DNAm) measures of biological aging, DunedinPACE, PC GrimAge, and PC PhenoAge (N=951). Panel A shows effect-sizes estimated in the full cohort. Panel B shows effect-sizes estimated for women and men separately. Effect-sizes were estimated from generalized estimating equation regressions and are denominated in standard-deviation units of the aging measures, interpretable as Cohen`s d values. Error bars show 95% confidence intervals.



3.4.2 Longer Prenatal Famine Exposure Was Associated with Faster Biological Aging as Measured by DunedinPACE

In dose-response analysis, cohort members who were exposed to the famine for more weeks of gestation had faster biological aging (per 10-weeks of exposure DunedinPACE β=0.08, 95% CI [0.02, 0.14], *p*=.013). There were no dose response effects for GrimAge and PhenoAge (βs=0.04, *p*>.160). Results are reported in **Supplementary Materials, Table B.4**; full results for all biological aging measures are reported in **Supplementary Materials, Table B.5**.

3.4.3 No Timing-Specificity for Famine Exposure in Predicting Biological Aging as Measured by DunedinPACE

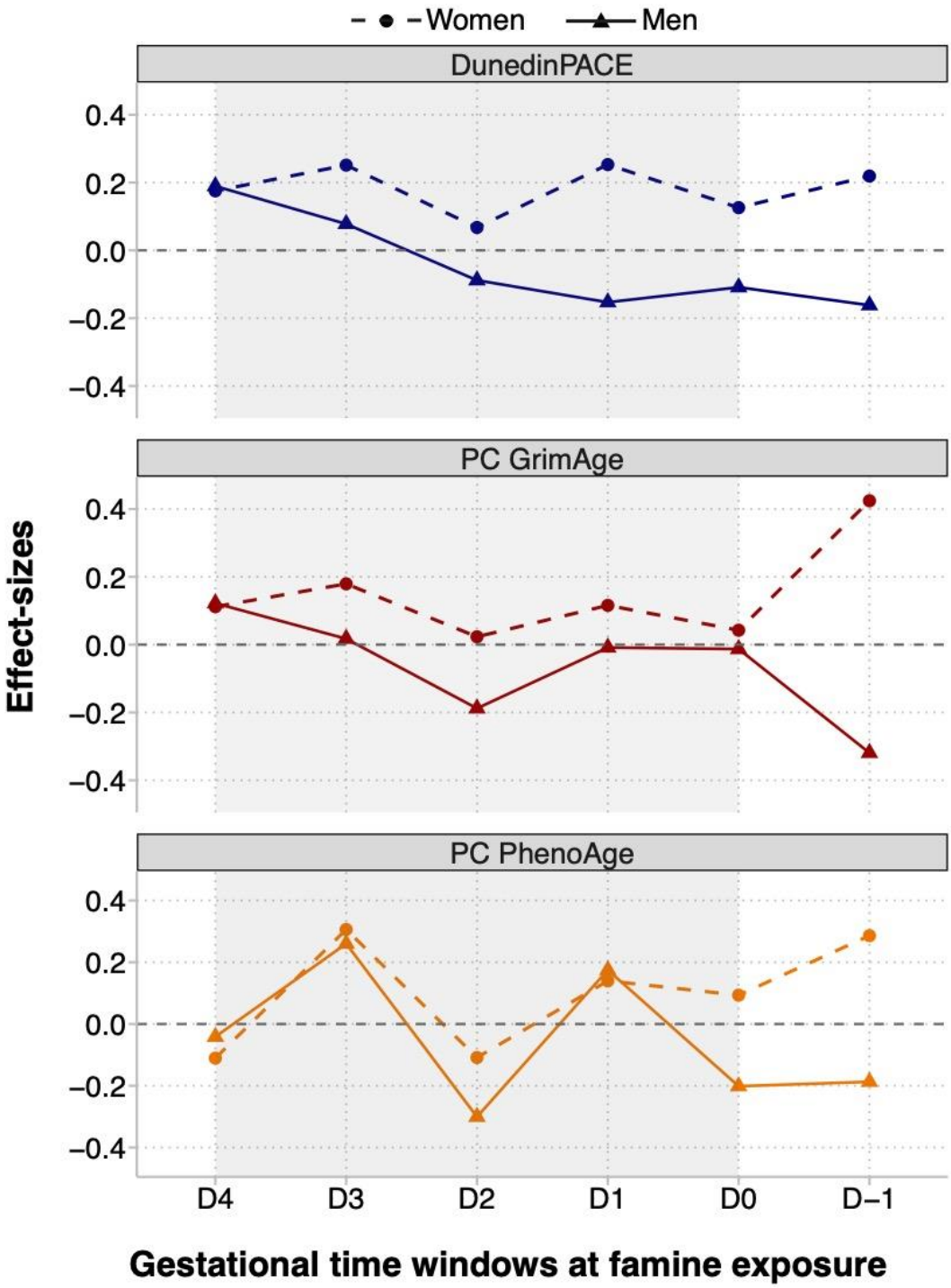
The effects of in-utero famine exposure may vary depending on when in gestation famine exposure occurs. We estimated associations of famine exposure with biological aging at each of six time windows from the preconception period through the end of gestation. Because cohort members could be exposed in multiple time windows, we included indicator variables for exposure in each time window in the same regression. Effect-sizes for DunedinPACE ranged from -0.01 to 0.18 and were somewhat larger for later gestational exposure windows. Effect-sizes for GrimAge ranged from -0.08 to 0.12. Effect-sizes for PhenoAge ranged from -0.19 to 0.28. For GrimAge and PhenoAge, there were no gestational timing patterns in effect-sizes. Effect-sizes are reported in **Supplementary Materials, Table B.6**.

3.4.4 Sex Differences in Associations of In-Utero Famine Exposure with Biological Aging

We conducted exploratory analysis of sex differences in famine effects using sex-stratified regressions and analysis of effect-measure modification. In stratified analysis, famine effects were consistently larger for women and were near zero for men (**Figure 3.3*B***; **Supplementary Materials, Table B.2**). Findings from sex-stratified dose-response analysis

showed similar results (**Supplementary Materials, Table B.4**). In sex-stratified analysis of gestational timing, results were different for women and men (**Supplementary Materials, Table B.6**). For women, DunedinPACE effect-sizes were similar across gestational time windows (effect-sizes ranged from β=0.07-0.25). In contrast, for men, DunedinPACE effect-sizes were largest for later-gestational exposures and smaller for exposure in early gestation (effect-sizes ranged from β=-0.16-0.19). This pattern was similar for GrimAge. There was no consistent pattern for PhenoAge. Results are shown in **Figure 3.4**. Formal tests of effect-measure modification found sex differences were statistically different from zero at the $p<0.05$ level for DunedinPACE and GrimAge, but not PhenoAge.

Figure 3.4. Differences in Biological Aging between Survivors of In-Utero Famine Exposure and Unexposed Control Participants in the Dutch Hunger Winter Families Study by Gestational Timing of Famine Exposure. The figure shows effect-sizes estimated for famine exposure during six gestational time windows. Famine-exposed participants were exposed during up to two periods. The developmental periods are ordered in the x-axis in chronological order relative to the famine. The left-most tick shows effect-sizes for late-gestational exposure (defined as exposure for the final 10 weeks of gestation; N=139 exposed). The second tick to the left shows effect-sizes for exposure during the penultimate 10 weeks of gestation (N=146 exposed). The third tick shows effect-sizes for exposure during the second 10 weeks of gestation (N=125 exposed). The fourth tick shows effect-sizes for exposure during the first 10 weeks of gestation (N=74 exposed). The fifth tick shows effect-sizes for early gestational exposure with duration <10 weeks (N=94 exposed). The right-most tick shows effect-sizes for preconceptual exposure, i.e., for exposure during the period preceding conception (N=52 exposed). Numbers exposed do not add up to the total exposed sample because many participants were exposed in two adjacent periods (N=143). Effect-sizes are reported for DunedinPACE, PC GrimAge, and PC PhenoAge. Effect-sizes were estimated from a multivariate regression in which indicator variables for each exposure window were included as predictor variables along with covariates for sex, age, and age-squared. Effect-sizes are denominated in standard-deviation units of the aging measures, interpretable as Cohen`s d values. Full results are reported in **Supplementary Materials, Table B.6**. Effect-sizes are plotted separately for women (circles) and men (triangles). The figure shows a consistent sex-specific pattern in DunedinPACE and PC GrimAge effect-sizes. Women who survived in-utero famine exposure, whether at early or later gestation, tended to have faster pace of biological aging, as measured by DunedinPACE, and older biological age, as measured by PC GrimAge DNAm clock. In contrast, men who survived later-gestational famine exposure tended to have faster pace of biological aging and older biological age; whereas men who survived early-gestational famine exposure tended to have slower pace of biological aging and younger biological age, as measured by DunedinPACE and PC GrimAge DNAm clock, respectively. There was no consistent pattern in PC PhenoAge effect-sizes.


Women
Men
DunedinPACE
PC GrimAge
PC PhenoAge
0.4
0.2
0.0
−0.2
−0.4
Effect-sizes
D4
D3
D2
D1
D0
D−1
Gestational time windows at famine exposure

3.4.5 Sibling-Comparison Analysis

Finally, we repeated our analysis using a sibling-comparison design. This design holds constant all factors that are shared by siblings in a family. In the context of the famine natural experiment, the sibling comparison design aims to rule out the possibility that differences between exposed and unexposed individuals reflect differences between families in their preferences and/or ability to conceive and carry to term a child under famine conditions. In full-sample sibling comparison analysis (n=227 pairs), famine survivors tended to be aging faster than their unexposed same-sex siblings; however, effect-sizes were attenuated by roughly half as compared with the full-sample analysis and were not statistically different from zero. In sex-stratified analysis, differences between sisters discordant for famine exposure (n=129 pairs) were nearly identical to famine-effect estimates from our original models whereas, among brothers (n=98 pairs), effect estimates were near zero or in the opposite direction of our original analysis. Results are reported in **Supplementary Materials, Table B.2 and Table B.3**.

3.4.6 Sensitivity Analysis

We repeated our analysis with additional covariates for estimated proportions of white blood cell types. In cell-count-adjusted analysis, effect-sizes were similar for DunedinPACE, GrimAge, and PhenoAge (**Supplementary Materials, Table B.7-3.9**).

3.5 Discussion

We analyzed blood DNA methylation data from participants in a natural-experiment study of the Dutch Famine to test the hypothesis that in-utero famine exposure would be associated with accelerated biological aging over six decades of follow-up. We found that survivors of in-utero famine exposure had faster pace of biological aging as measured by the DunedinPACE clock. However, differences in biological age measured by the GrimAge and PhenoAge clocks were smaller and less consistent. There were no differences between famine

survivors and controls in biological age measured by first-generation epigenetic clocks. We did not observe evidence for a timing specific effect of famine exposure on these measures. These findings were robust to covariate adjustment for cell counts and were similar in sibling-difference analysis, although estimates were less precise.

All three of the DNAm clocks we analyzed show evidence of association with morbidity and mortality in other studies (Bernabeu et al., 2023; Hillary et al., 2020). A prior quasi-experimental analysis of early-life economic adversity found evidence of in-utero-exposure effects on later-life biological aging measured by both an earlier version of the DunedinPACE clock and the GrimAge clock (Schmitz & Duque, 2022). However, only DunedinPACE showed consistent evidence of association with in-utero famine exposure in the full DHWFS sample. It could be that DunedinPACE is somewhat more sensitive to preclinical health changes occurring in famine survivors as compared with GrimAge. DunedinPACE was developed from analysis of the rate of physiological decline in midlife adults (Belsky et al., 2022). It is designed to measure the Pace of Aging phenotype (Belsky et al., 2015), defined as the rate of decline in system integrity. GrimAge, in contrast, was developed from analysis of mortality risk in mid-late life adults (Lu et al., 2019). It is designed to measure biological age, or the current level of system integrity. These design differences may have consequences for sensitivity in the context of midlife follow-up of in-utero famine exposure. Alternatively, the effect-size differences between DunedinPACE and GrimAge were small and could reflect statistical noise. Follow-up in other studies is needed to clarify the significance of the difference in results for the two measures.

Our analysis of gestational timing of famine exposure did not find evidence for earlier gestation as a sensitive period. Prior studies suggest that exposure during the early phase of gestation may be more impactful (Ekamper et al., 2015; Lumey, Stein, et al., 2011; Tobi et al., 2014; Tobi et al., 2015). For DunedinPACE, effect-sizes were somewhat larger for men

exposed later as compared to earlier in gestation; but this pattern was not seen for women. Results were similar for GrimAge, although differences by period of gestation were even smaller. Participants exposed to famine during later gestation were conceived prior to the famine period whereas those exposed in early gestation were conceived during the famine. Timing of gestational exposure may therefore be related to factors that affect fertility behaviors and outcomes under famine conditions, making interpretation of these small differences difficult. Overall, results suggest that any in-utero exposure is associated with a faster pace of biological aging six decades later.

Our analysis of sex differences in famine effects found larger effects of in-utero famine exposure on DNAm measures of biological aging in women as compared with men. This was observed for all three epigenetic clocks, but was most pronounced for the DunedinPACE and GrimAge clocks. In non-human animals, there is evidence that males are more vulnerable to early-life insults (Wells, 2000). However, prior studies of in-utero famine exposure often reported larger famine effects on cardiovascular and metabolic diseases among women as compared with men (Chen et al., 2014; Lumey et al., 2009; Wang et al., 2016; Yu et al., 2018). There is some evidence that selective fertility or fetal loss result in fewer male births during periods of famine (Song, 2012). A result could be that the subset of male babies born are especially robust. This would be consistent with our results. But a reduction in male births is not documented in the case of the Dutch Famine (Cramer & Lumey, 2010; Stein et al., 2004). There are not yet analyses of sex differences in mortality among survivors of in-utero exposure to the Dutch Famine; the most comprehensive study of mortality relied on data from military conscripts, who were all men (Ekamper et al., 2015). New models in population science suggest that environmental conditions, such as in-utero exposure to famine, can induce substantial variation in sex differences in survival (Iannuzzi et al., 2023). Replication of the observed sex difference in famine effects is needed.

We acknowledge limitations. There is no gold standard to measure biological aging (Ferrucci et al., 2020). We analyzed the DNAm measures of aging with the best available evidence for reliability and validity. As new measures are introduced, follow-up will be needed. However, agreement between different biological aging measures build confidence that our findings do capture aging processes. We were unable to conduct dose-response analysis of famine-exposure severity. Because of the lack of family-level nutrition data and the consistency of rations across the affected areas of the Netherlands, analysis of exposure severity will need to be conducted in different settings, such as where famine severity was graded across geographic locations or time (Li & Lumey, 2017). Survival bias could affect the population of famine survivors alive or in sufficiently good health to be surveyed at follow-up. However, characteristics at birth of the DHWFS participants are similar to those of famine-affected births identified in hospital records but not successfully enrolled in the cohort, including birth weight, length, placental weight, maternal age, and birth order (Lumey et al., 2007). Excess deaths among survivors of in-utero famine exposure by the time of our study were <10% (Ekamper et al., 2014). Therefore, any bias is likely to be modest. Moreover, it is expected that healthy-participants and survival biases would bias effect-estimates toward the null because non-participation due to ill health and death would remove the most affected from the population. Therefore, our estimates of famine effects are expected to be conservative. Finally, because the cohort so far lacks follow-up to determine survival differences between famine-exposed and control participants, the extent to which differences observed in measures of biological aging will translate into differences in healthspan and lifespan remains to be determined.

3.6 Conclusion

Within the context of these limitations, our findings provide evidence for long-term impacts of in-utero famine exposure that may extend to a wide range of aging-related health

outcomes. Now that survivors of in-utero famine exposure are approaching their ninth decade of life, further study of famine births in administrative record data are needed to clarify the scope of famine effects on healthspan and lifespan.

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4. Evolution of the Income–Health Gradient over the Later Life Course: Longitudinal Evidence from the U.S. (1992-2016)

Published as: Cheng, M., Sommet, N., Jopp, D., & Spini, D. (2023). Income-related inequalities in physical and cognitive health domains over the later life course: Longitudinal evidence from the U.S. (1992-2016). *Research on Aging*, *0*(0), 1-13. DOI: 10.1177/01640275231183438 • PDF

4.1 Abstract

This study aims to investigate changes in the income–health gradient over the later life course. We test the age-as-leveler, the cumulative advantage/disadvantage, and the persistent inequality pattern for physical and cognitive health domains, and analyze whether these patterns are gendered. We used HRS data (1992-2016) and Poisson growth curve models to predict multimorbidity (33,860 participants) as an indicator of physical health and memory (25,291 participants) as an indicator of cognitive health. We disentangled the within-participant from the between-participant effects. For multimorbidity, the income–health gradient weakened as individuals aged; whereas for memory, the income–health gradient strengthened as individuals aged. The cumulative advantage/disadvantage of higher/lower income on memory may be more pronounced among women than men. Findings were confirmed by sensitivity analyses. Findings suggest that the support for the age-as-leveler or cumulative advantage/disadvantage pattern may depend on health domains and the effect strength may depend on gender.

4.2 Introduction

It has been established that the income–health gradient (Marmot, 2005) begins in in-utero development and persists into later life (for a review, see Corna, 2013). However,

researchers are divided on the theoretical assumptions and empirical evidence regarding the evolution of the income–health gradient over the later life course. Some researchers argue that the link between income and health weakens in later life, as the impact of biological aging and selective mortality eclipses the impact of income and narrows the health gap between the rich and poor (the "age-as-leveler pattern"; O'Rand, 2009; for empirical evidence, see, e.g., Brown et al., 2016; Sieber et al., 2020). Other researchers argue that the link between income and health strengthens in later life, as the advantages of being rich and the disadvantages of being poor in a given cohort accumulate over the life course and widen the health gap between the rich and poor (the "cumulative advantage/disadvantage pattern"; Dannefer, 2020; DiPrete & Eirich, 2006; for empirical evidence, see, e.g., Boen, 2016; Veenstra & Aartsen, 2022). Finally, some other researchers argue that the link between income and health remains stable in later life, as the structures and/or processes of socioeconomic stratification persist over the life course and stabilize the health gap between the rich and poor (the "persistent inequality pattern"; Ferraro, 2011; for empirical evidence, see, e.g., Wachtler et al., 2019; Zhu & Ye, 2020). Arguably, many previous studies are limited in two ways. First, they often focus on a single generic health outcome (most often self-rated health). It is possible that the support for the age-as-leveler pattern or the cumulative advantage/disadvantage pattern varies across outcomes in different health domains (Brown et al., 2012; Xu et al., 2014). Second, they often focus on between-participant effects. Estimates of between-participant effects are more likely to be influence by selection effects than estimates of within-participants effects (Jager et al., 2020).

To address these limitations, (i) we adopted a multidimensional conceptualization of health (Hjelm, 2010) by using multiple specific outcomes from the physical and cognitive health domains and (ii) we disentangled within-participant effect of aging from between-participant effect of age over time by using longitudinal data from the Health and Retirement Study. Moreover, one remaining question is whether the age-as-leveler, the cumulative

advantage/disadvantage, or the persistent inequality pattern differs between women and men. As women and men experience different levels of exposure and have differential sensitivity/vulnerability to socioeconomic determinants of health over the life course (Denton et al., 2004), these patterns may differ between women and men. To extend previous studies, we therefore investigated the role of gender in predicting these patterns.

4.2.1 How the Income–Health Gradient Changes over the Later Life Course

Scholars are divided on how the income–health gradient changes with old age: proponents of the age-as-leveler pattern claim that the income–health gradient weakens with old age, whereas proponents of the cumulative advantage/disadvantage pattern claim that the income–health gradient strengthens with old age. Importantly, the empirical evidence is also divided, with some research supporting the age-as-leveler pattern and others supporting the cumulative advantage/disadvantage pattern.

4.2.1.1 Age-as-Leveler Pattern

Research supporting the age-as-leveler pattern suggests that the income–health gradient weakens with old age (O'Rand, 2009). However, age is a broad category for the observed process that needs to be revealed. Three complementary explanations are provided in the literature that can explain the age-as-leveler effect: The first explanation concerns biological aging, the second concerns selective mortality, and the third concerns social policies. According to the biological perspective, individuals from all socioeconomic backgrounds eventually experience a decline in health as they age because of the gradual accumulation of cellular defects through random molecular damage (Kirkwood, 2014). As a result, individuals with higher income lose their advantages as they age (Brown et al., 2016), experiencing a faster decline in health and eventually catching up with their lower-income counterparts (Herd, 2006). In addition, selective mortality (Dupre, 2007) may also impact on the income-health gradient in old age. This selective process is caused by mortality at younger age for the most

disadvantaged. This leaves in the older adult population a more homogenous surviving population that is healthier and with higher socioeconomic status compared with the baseline population. Moreover, social policies may serve to offset disadvantages and adversities and narrow the gap in health disparities in old age by facilitating access to healthcare (Sieber et al., 2020). For instance, Medicare insurance has been shown to exert a leveling effect on disparities between socioeconomically advantaged and disadvantaged individuals in access to care and health status at age 65 (Wallace et al., 2021).

A series of empirical studies support the age-as-leveler pattern—many of which have used a single generic health outcome (most often self-rated health). For instance, studies have shown that the protective effect of higher income on self-rated health was stronger for middle-aged adults than for older adults, and that this protective effect began to wane in old age (Brown et al., 2016; Doebler & Glasgow, 2017; Li & Mutchler, 2019; Sieber et al., 2020). It is worth noting that a few existing studies that used alternative health outcomes other than self-rated health also lent support to the age-as-leveler pattern (e.g., mortality, Rehnberg et al., 2019; frailty, Van Der Linden et al., 2020).

4.2.1.2 Cumulative Advantage/Disadvantage Pattern

Research supporting the cumulative advantage/disadvantage pattern suggests that the income–health gradient strengthens with old age (Dannefer, 2020; DiPrete & Eirich, 2006). The theoretical assumption is that advantages and disadvantages accumulate over the life course through person–environment interactions involving individual capacity, location, resources, and context (Dannefer, 2003). Because of differential exposure to risk factors and differential access to protective resources, income-related advantages and disadvantages tend to accumulate over the life course into old age (O'Rand, 2002). Individuals with higher income are faced with less difficult life conditions, which could impact health outcomes (Lantz et al., 2005). In addition, individuals with higher income have more reserves (e.g., economic, social,

or cognitive reserves) available to help overcome and recover from adverse life events or stressors, whereas individuals with lower income have fewer such reserves and are more vulnerable to such events or stressors (Cullati et al., 2018).

A series of empirical studies support the cumulative advantage/disadvantage pattern—many of which have used a single generic health outcome (again, self-rated health). For instance, studies have shown that the protective effect of higher income on self-rated health was stronger for older adults than for middle-aged adults, and that older adults with higher socioeconomic status experience a slower decline in self-rated health than those with lower socioeconomic status (Boen, 2016; Leopold, 2018; Leopold, 2019; Veenstra & Aartsen, 2022). Similarly, a few existing studies that used health outcomes other than self-rated health also lent support to the cumulative advantage/disadvantage pattern (e.g., disability, Lai et al., 2022; cognition, Zeng et al., 2022).

4.2.1.3 Persistent Inequality Pattern

Research in line with the persistent inequality pattern suggests that the income–health gradient remains stable across the later life course (Ferraro, 2011). The theoretical explanation for this phenomenon revolves around the structures and/or processes that generate and perpetuate health inequalities early in life and throughout the life course (Mackenbach, 2017). Socioeconomic stratification, which gives differential access to resources and opportunities for achieving and maintaining a more favorable socioeconomic position, plays a crucial role in perpetuating income-related inequalities into old age (Abramson, 2015). Individuals with higher income have access to a broader range of material and non-material resources, yielding enduring health benefits (Lynch, 2020). In contrast, individuals with lower income have limited access to these resources, resulting in persistent health inequalities (Brown et al., 2016).

A series of empirical studies are consistent with the persistent inequality pattern—many of which have used a single generic health outcome (again, self-rated health). For

instance, studies have shown that the protective effect of higher income on self-rated health did not differ between older adults and middle-aged adults, and that older adults with lower socioeconomic status experienced persistent inequality in self-rated health (Brown et al., 2016; Leopold, 2019; Wachtler et al., 2019; Zhu & Ye, 2020). Similarly, a few existing studies that used alternative health outcomes other than self-rated health also aligned with the persistent inequality pattern (e.g., body mass index, Boen, 2016; functional limitations, Brown, 2018).

4.2.2 Theoretical and Methodological Concerns in Existing Studies

4.2.2.1 Limitations of Previous Studies

As seen above, many existing empirical studies are limited in that (i) they have used a single generic health outcome (often self-rated health); and/or (ii) they have focused on between-participant effects.

First, self-rated health is an omnibus construct that encompasses various aspects of physical and/or cognitive health. It is possible that the support for the age-as-leveler pattern or the cumulative advantage/disadvantage pattern varies across outcomes in different health domains (Brown et al., 2012; Xu et al., 2014), because socioeconomic indicators affect different aspects of health via different mechanisms both in terms of the onset and progression of disease (Cockerham et al., 2017). This phenomenon is unlikely to be identified using a single generic health outcome, but using multiple specific outcomes from the physical and cognitive health domains should enable to investigate the patterns of change in income-related disparities across health domains in old age.

Second, estimates of between-participant effects are more likely to be influence by selection effects than estimates of within-participants effects (Jager et al., 2020). As a result of the income–health gradient, older adults with low income tend to be underrepresented in cross-sectional surveys, either because their health status hinders them from taking part in surveys or because they have died prematurely. Therefore, older adults with low income who participate

in cross-sectional surveys represent positively selected "survivors" of such selection processes, meaning that the health differences observed between older adults with high income and those with low income in these surveys may reflect this selection effect rather than the change in the income–health gradient over time per se. In contrast, in longitudinal data, the selection effect incurred by attrition could be reduced by including predictors of attrition in the main model (Henderson et al., 2000). With longitudinal data, it is possible to track how the health trajectories of older adults are shaped by income and disentangle the within-participant from the between-participant effects of income on health.

4.2.2.2 Remaining Question: The Role of Gender

It is known that health trajectories in later life differ between women and men (Gorman & Read, 2006). However, there is limited understanding of whether the age-as-leveler, the cumulative advantage/disadvantage, or the persistent inequality pattern differs between women and men, as many existing studies on the income–health gradient in later life have not investigated the moderating role of gender in shaping income-related health trajectories (Dannefer, 2020). It is possible that these patterns may be different between women and men, as women and men experience different levels of exposure and have differential sensitivity/vulnerability to socioeconomic determinants of health over the life course (Denton et al., 2004). In terms of different levels of exposure, women, throughout their life course, are more likely to endure a lower socioeconomic status, be subject to higher levels of exposure to risk factors, and have less access to protective factors than men (Gu et al., 2009; Read & Gorman, 2010). In terms of differential sensitivity/vulnerability, women benefit more from a higher socioeconomic status or protective factors, but are more vulnerable to risk factors like strains and stressors than men (Ferraro et al., 2009). By investigating the gender differences in the income-health gradient over time, we could better understand how gender shapes the income-related health trajectories in the later life course.

4.2.3 Research Questions and Overview of the Study

In the present study, we aim to address two research questions. First, do we observe an age-as-leveler pattern, a cumulative advantage/disadvantage pattern, or a persistent inequality pattern for physical and cognitive health domains? Second, are these patterns gendered?

To address the limitations of many existing studies, we (i) used multiple specific outcomes from physical and cognitive health domains rather than a single generic health outcome and (ii) used longitudinal data of 13 waves spanning nearly 25 years to disentangle within-participant from between-participant effects over time. In addition, to extend previous studies, we investigated the role of gender in the pattern of change in income-related disparities in health over the later life course, although here also we did not formulate directional hypothesis. In the present study, we used data from the Health and Retirement Study (HRS), a nationally representative panel survey conducted biennially since 1992 that collects health data on approximately 20,000 U.S. residents aged 50 or older. We used multimorbidity as an indicator of physical health and memory as an indicator of cognitive health, which are particularly relevant to old age in the U.S. (Makovski et al., 2019; Nyberg & Pudas, 2019). We used Poisson growth curve models and disentangled the within-participant effect of aging from the between-participant effect of age. We conducted three sets of sensitivity analyses using alternative measures of health and excluding participants who died over the study period or dropped out the survey.

4.3 Methods

4.3.1 Sample

We used 13 waves of HRS data (1992-2016). The initial sample included 42,030 participants for multimorbidity and 33,542 participants for memory. To account for the

longitudinal nature of the data, we treated wave-specific observations (level-1 units) as nested within participants (level-2 units). We included eligible within-participants observations based on three inclusion criteria: (i) nonmissing sociodemographic variables (multimorbidity: n = 41,766, 99.4%; memory: n = 30,043, 89.6%); (ii) age was 50 or older (multimorbidity: n = 40,667, 96.8%; memory sample: n = 29,143, 86.9%); and (iii) participation in at least two waves of observations (i.e., demonstrating within-participants variance; multimorbidity: n = 33,860, 80.6%; memory: n = 25,291, 75.4%). Our analytical sample comprises 230,101 observations from 33,860 participants for analyses using multimorbidity and 143,011 observations from 25,291 participants for analyses using memory.

4.3.2 Measures

4.3.2.1 *Equivalized Income Decile (Time-Varying)*

Participants reported the sum of their own and their spouse's income during the last calendar year (potential sources include earnings, pensions and annuities, social security, unemployment and workers' compensation, other government transfers, capital income, and other income). To account for inflation, we converted total household income into inflation-adjusted income using the World Bank annual consumer price index (the reference year is 2010; World Bank, 2021) for each year of the survey as an inflation multiplier (i.e., we divided household income by the year-specific consumer price index). To adjust for the difference between coupled and single participants, we converted the inflation-adjusted income of the participants and their spouses into equivalized income using the Organisation for Economic Cooperation and Development (2013) square root equivalence scale (i.e., we divided the inflation-adjusted income of participants and their spouses by the square root of two for coupled participants or by one for single participants). To consider the income dynamics of older adults and their spouses over the later life course in the U.S. (Dowd et al., 2010), we used

the income value for each participant in each wave to create a time-varying variable of equivalized income decile (1 = *bottom 10%*; 10 = *top 10%*).

4.3.2.2 *Multimorbidity (Time-Varying)*

Participants reported whether they had been diagnosed by a doctor with any of the following seven chronic diseases: high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, or arthritis (0 = *no*; 1 = *yes*). We adopted the definition of multimorbidity proposed by Marengoni et al. (2011) and counted the number of concurrent chronic diseases reported by each participant in each wave.

4.3.2.3 *Memory (Time-Varying)*

Memory was measured using immediate and delayed word recall (Park & Festini, 2016). Participants were randomly assigned one of four 10-word lists, with a different assignment over four interviews and no overlap with the word assigned to the spouse. Participants were then asked to recall these words (i) immediately (ranging from 0 to 10) and (ii) after a delay of approximately five minutes spent answering other questions (ranging from 0 to 10). We summed the total number of words that were recalled correctly, resulting in a combined score of immediate and delayed word recall in each wave (ranging from 0 to 20).

4.3.2.4 *Covariates*

We selected control variables based on those commonly used in previous studies examining the change in the income–health gradient over the later life course (e.g., Brown et al., 2016; Veenstra & Aartsen, 2022) as well as those known to be associated with health (e.g., marital status, see Hoffmann, 2011; race, see Li & Mutchler, 2019). We gathered the following sociodemographic variables to use them as control variables: wealth decile (from 1 = *bottom 10%* to 10 = *top 10%*), education level (1 = *less than upper secondary*, 2 = *upper secondary or vocational*, 3 = *tertiary*), gender (-0.5 = *men*, +0.5 = *women*), race (0 = *White/Caucasian*, 1 = *non-White/Caucasian*), current marital status (0 = *not married*, 1 = *married*), current working

status (0 = *not working*, 1 = *working*), and household size (i.e., the number of individuals living in the household).

4.3.2.5 *Alternative Measures of Health*

We gathered alternative measures of health to use them in sensitivity analyses. For physical health domain, we used mobility (time-varying); for cognitive health domain, we used verbal skills (time-varying). For generic health outcome, we used self-rated health (time-varying). Regarding the mobility, participants reported how many of the following activities were difficult: walking one block, walking across a room, climbing one flight of stairs, getting in or out of bed, and bathing. We counted the total number of activities that were reported to be difficult (ranging from 0 to 5). Regarding the verbal skills, participants completed the tasks of object naming, president/vice president naming, and date naming. We counted the total number of naming that were correct (ranging from 0 to 8). Regarding self-rated health, participants reported their general health status (from 1 = *excellent*, 5 = *poor*).

4.3.3 Analytic Strategy

4.3.3.1 *Poisson Growth Curve Models*

To estimate health trajectories over the later-life course and to consider the hierarchical structure of the HRS data, we built a series of two-level growth curve models in which wave-specific observations (level-1 units) were nested within participants (level-2 units). We built Poisson growth curve models instead of linear growth curve models (Alt et al., 2001) because each of the outcome variables (i.e., multimorbidity and memory) is a count variable that follows a Poisson distribution. We used Poisson regression rather than negative binomial regression because the overdispersion test did not reject the null hypothesis of equidispersion, for multimorbidity, χ^2 (2, N = 230,101) =86,153, p = 1.00; for memory, χ^2 (2, N = 143,011) =90,679, p = 1.00.

4.3.3.2 *Centering Strategy to Disentangle the Within-Participant from Between-Participant Effect*

To disentangle the within-participant effect of aging from the between-participant effect of age, we used the Fairbrother (2014) centering strategy and two age variables: (i) grand-mean centered mean age and (ii) person-mean centered age. To compute the *grand-mean centered mean age*, we centered each participant's mean age across all waves on the grand mean age of all participants. This variable enables us to capture the between-participant effect of age (i.e., the effect of differences in age between participants). To compute the *person-mean centered age*, we centered each participant's age in each wave of the survey on their individual mean age across all waves. This variable enables us to capture the within-participant effect of aging (i.e., the effect of age-related changes within a single participant over time).

4.3.3.3 *Focal Model Equations*

We regressed health outcomes on five focal predictors: (i) grand-mean centered mean age (Age_gmc_i), (ii) income decile ($\text{Income Decile}_{it}$), (iii) grand-mean centered mean age × income decile (to estimate whether the effect of income differs between younger and older participants), (iv) person-mean centered age (Age_cmc_{it}), and (v) person-mean centered age × income decile (to estimate whether the effect of income changes as participants age) (see Eq. 1).

$$\log(\lambda_{it}) = (\beta_{00} + u_{0i}) + \beta_{01} \times \text{Age\_gmc}_i + \beta_{10} \times \text{Income Decile}_{it} + \beta_{11} \times \text{Age\_gmc}_i \times \text{Income Decile}_{it} + (\beta_{12} + u_{1i}) \times \text{Age\_cmc}_{it} + \beta_{13} \times \text{Age\_cmc}_{it} \times \text{Income Decile}_{it} + \beta_{ij} \times \text{Control}_{ij} \quad \text{(Eq. 1)}$$

where $Y_{it} \sim \text{Poisson}(\lambda_{it})$; Y_{it} is the outcome, which follows a Poisson distribution; $i = 1, 2, \ldots, N$ (participants); $t = 1, 2, \ldots, 13$ (waves); $\beta_{ij} \times \text{Control}_{ij}$ represents the vector of control

variables; u_{0i} represents the participant-level residuals; and u_{1i} represents the random slope of age. Decomposition of the interaction term $\text{Age\_gmc}_i \times \text{Income Decile}_{it}$ enables to compare the effect of income decile between younger participants and older participants, and decomposition of the interaction term $\text{Age\_cmc}_{it} \times \text{Income Decile}_{it}$ enables to compare the effect of income decile as participants age over the later life course. The age-as-leveler pattern corresponds to a weakening effect of higher income with old age, the cumulative advantage/disadvantage pattern to a strengthening effect of higher income with old age, and the persistent inequality pattern to a main protective effect of higher income with a null interaction with old age.

To test the role of gender, we included two-way and three-way interactions with gender in our model (see Eq. 2).

$$\begin{aligned}\log(\lambda_{it}) = {} & (\beta_{00} + u_{0i}) + \beta_{01} \times \text{Age\_gmc}_i + \beta_{10} \times \text{Income Decile}_{it} \\ & + \beta_{11} \times \text{Age\_gmc}_i \times \text{Income Decile}_{it} + (\beta_{12} + u_{1i}) \times \text{Age\_cmc}_{it} \\ & + \beta_{13} \times \text{Age\_cmc}_{it} \times \text{Income Decile}_{it} + \beta_{02} \times \text{Age\_gmc}_i \times \text{Gender}_i + \beta_{14} \times \text{Age\_cmc}_{it} \\ & \times \text{Gender}_i + \beta_{15} \times \text{Income Decile}_{it} \times \text{Gender}_i + \beta_{16} \times \text{Age\_gmc}_i \times \text{Income Decile}_{it} \times \\ & \text{Gender}_i + \beta_{17} \times \text{Age\_cmc}_{it} \times \text{Income Decile}_{it} \times \text{Gender}_i \\ & + \beta_{ij} \times \text{Control}_{ij}\end{aligned} \quad \text{(Eq. 2)}$$

We ran the Poisson growth curve models described above using the glmer function from the lme4 package (version 1.1-26) (Bates et al., 2015) in R (version 4.0.2). The R script to reproduce our findings is available via the Open Science Framework (OSF): https://osf.io/8wcey/?view_only=f04a4c585bd3496db340b9399fce5517.

4.4 Results

Our final sample comprises 230,101 observations from 33,860 participants for analyses using multimorbidity. Our final sample comprises 143,011 observations from 25,291 participants for analyses using memory. The sample characteristics are reported in **Table 4.1**.

Table 4.1. Sample Characteristics

(%)/[mean (SD)]	Multimorbidity sample (33,860 participants)	Memory sample (25,291 participants)
Women	56.25	57.89
Age (years)	66.6 (10.2)	64.2 (9.2)
White	75.75	76.73
Currently married	67.42	68.68
Currently not working	47.10	43.04
Household size (persons)	2.5 (1.3)	2.5 (1.3)
Equivalized annual income (in 2010 USD)	52,715 (86,086)	54,749 (72,749)
Household wealth (in 2010 USD)	85,946 (394,375)	90,336 (383,950)
Educational levels		
less than upper secondary	26.00	22.96
upper secondary or vocational	33.67	34.39
tertiary	40.33	42.65
Multimorbidity	43.33	-
Memory score	-	9.5 (3.0)

4.4.1 Main Analyses

4.4.1.1 *Changes in the Income–Health Gradient over the Later Life Course*

Multimorbidity. Our analyses using multimorbidity suggested that although the effect of income decile remained significant even in old age, the income–health gradient weakened as individuals aged (both between- and within-participant; **Table 4.2**, left column).

Between-Participant Effect. Our between-participant analysis found a significant positive interaction effect between income decile and grand-mean centered mean age, IRR = 1.12, 95% CI [1.10, 1.14], $p < .001$. As seen in **Figure 4.1** (upper panel), a further decomposition of the interaction effect suggested that the between-participant protective effect of higher income against multimorbidity was stronger for individuals in their 50s than for individuals in their 60s. Importantly, although this protective effect decreased, it remained significant until age 75 (+1 SD).

Within-Participant Effect. Similarly, our within-participant analysis found a significant positive interaction effect between income decile and person-mean centered age, IRR = 1.17, 95% CI [1.14, 1.19], $p < .001$. As seen in **Figure 4.1** (lower panel), a further decomposition of the interaction effect suggested that the within-participant protective effect of higher income against multimorbidity weakened as the individual aged (from just joining the panel to later panel waves). Importantly, although this protective effect decreased, it remained significant until advanced age of the individual (+1 SD).

Memory. Our analyses using memory suggested that although the effect of income decile remained significant even in old age, the income–health gradient strengthened as individuals aged (both between- and within-participant; **Table 4.2**, right column).

Between-Participant Effect. Our between-participant analysis found a significant positive interaction effect between income decile and grand-mean centered mean age, IRR = 1.05, 95% CI [1.04, 1.06], $p < .001$. As seen in **Figure 4.2** (upper panel), a further

decomposition of the interaction effect suggested that the between-participant protective effect of higher income on memory was strongest for individuals in their 80s, followed by individuals in their 70s and 60s, and was weakest for individuals in their 50s. Importantly, this protective effect remained significant over the later life course.

Within-Participant Effect. Similarly, our within-participant analysis found a significant positive interaction effect between income decile and person-mean centered age, IRR = 1.13, 95% CI [1.11, 1.15], $p < .001$. As seen in **Figure 4.2** (lower panel), a further decomposition of the interaction effect suggested that the within-participant protective effect of higher income on memory strengthened as the individual aged (from just joining the panel to later panel waves). Importantly, this protective effect started when the individual entered old age and remained significant over the later life course of the individual.

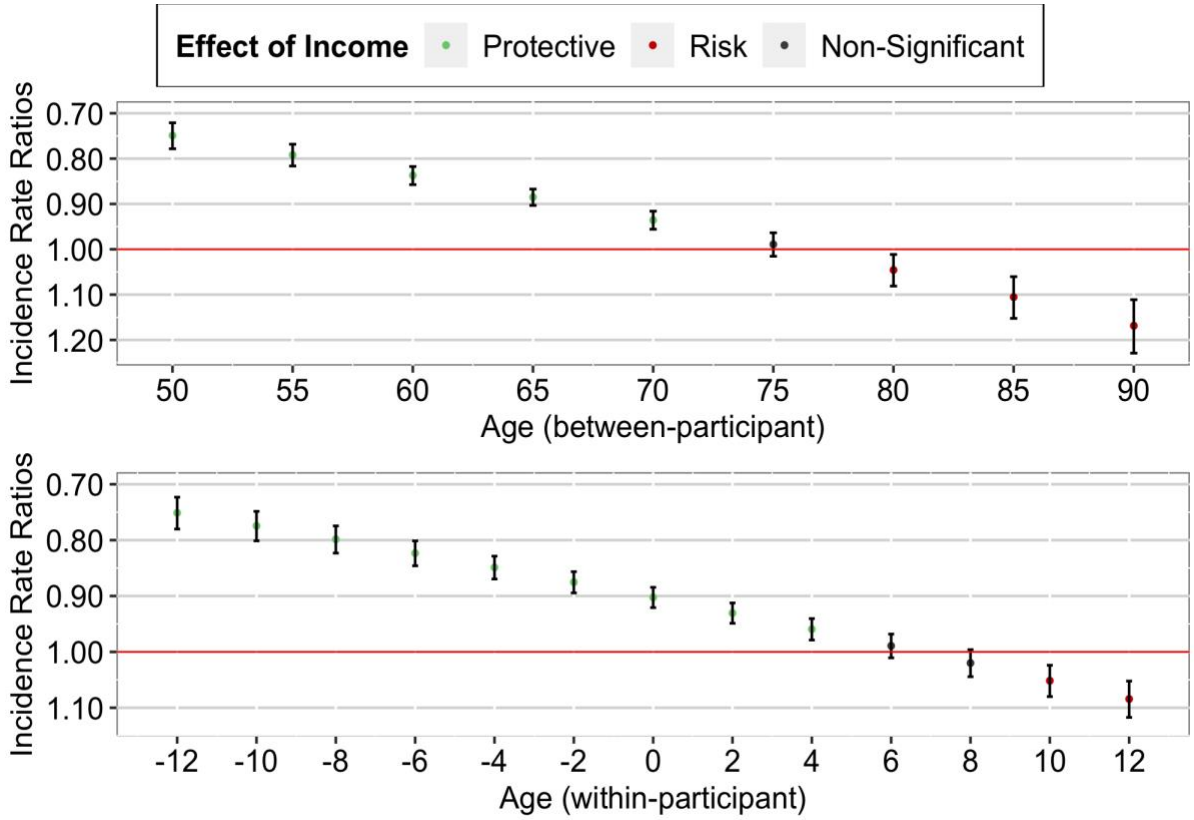
Table 4.2. Effect of Income on Multimorbidity and Memory as a Function of Age among Older Adults in the U.S.

	Multimorbidity		Memory	
	IRRs	95% CI	IRRs	95% CI
Grand-mean centered mean age	1.14***	1.13–1.15	0.86***	0.86–0.87
Person-mean centered age	1.87***	1.86–1.89	0.83***	0.83–0.83
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.89***	0.88–0.91	1.09***	1.08–1.10
Grand-mean centered mean age × income decile	1.12***	1.10–1.14	1.05***	1.04–1.06
Age (50 years old)	0.75***	0.72–0.78	1.02*	1.01–1.03
Age (-1 SD)	0.81***	0.79–0.83	1.05***	1.04–1.06
Age (+1 SD)	0.99	0.96–1.02	1.13***	1.12–1.15
Age (+2 SD)	1.09***	1.05–1.14	1.18***	1.16–1.20
Person-mean centered age × income decile	1.17***	1.14–1.19	1.13***	1.11–1.15
Panel waves (-2 SD)	0.77***	0.75–0.80	0.99	0.98–1.01
Panel waves (-1 SD)	0.84***	0.81–0.86	1.04***	1.03–1.05
Panel waves (+1 SD)	0.97*	0.95–0.99	1.15***	1.14–1.16
Panel waves (+2 SD)	1.05***	1.02–1.08	1.21***	1.19–1.23
Wealth decile (*1 = bottom 10%*, 10 = *top 10%*)	0.73***	0.71–0.76	1.12***	1.11–1.14
Upper secondary or vocational education	0.96***	0.94–0.98	1.16***	1.15–1.17
Tertiary education	0.90***	0.88–0.92	1.27***	1.25–1.28
Gender (-0.5 = *men*, +0.5 = *women*)	0.96***	0.95–0.98	1.13***	1.12–1.13
Race (0 = *White/Caucasian*, 1 = *non-White/Caucasian*)	1.04***	1.02–1.06	0.90***	0.90–0.91
Current marital status (0 = *not married*, 1 = *married*)	0.99	0.98–1.01	1.02***	1.02–1.03
Current working status (0 = *not working*, 1 = *working*)	0.87***	0.86–0.88	1.01***	1.01–1.02
Household size	1.00	0.99–1.00	0.99***	0.99–0.99
Number of participants	33,860		25,291	
Number of observations	230,101		143,011	

Note. IRRs = Incidence Rate Ratios.

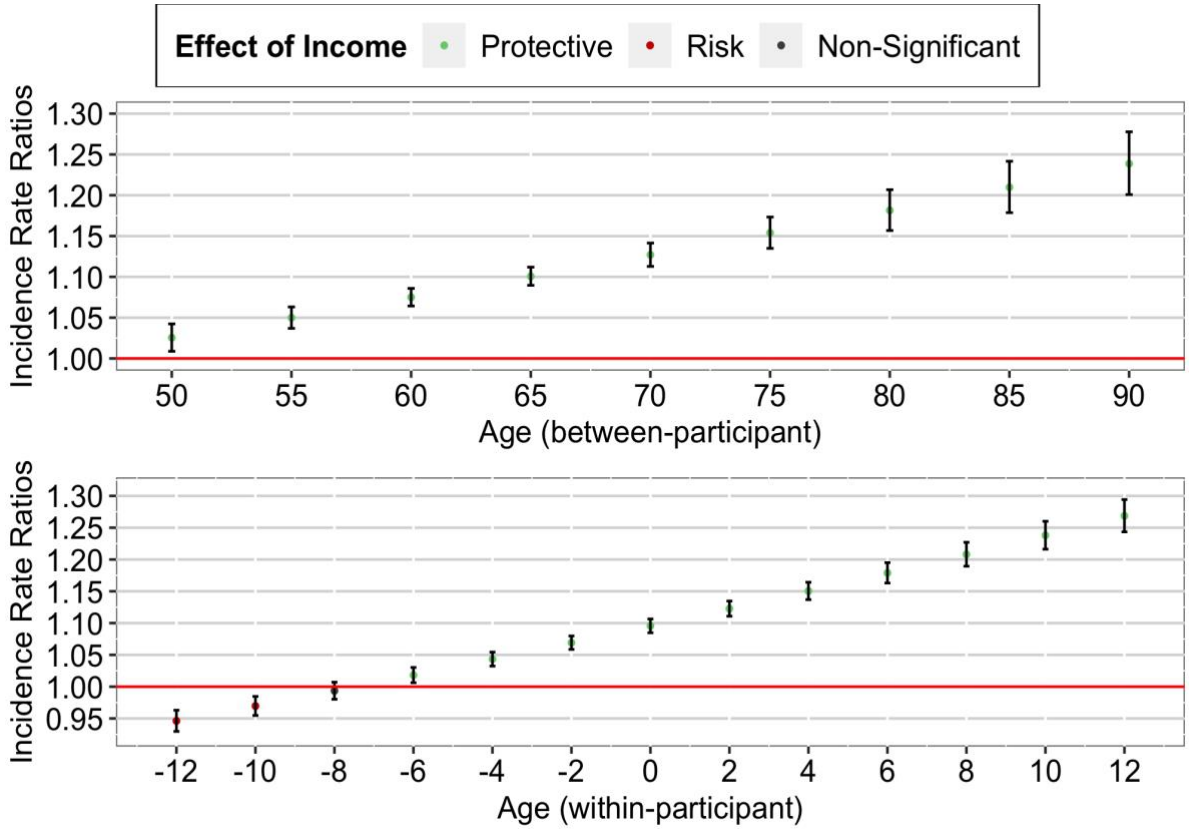
The effect of income and wealth refers to the comparison between the bottom 10% and the top 10%. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

Figure 4.1. Age-as-Leveler Effects of Income on Multimorbidity among Older Adults in the U.S.



Note. Red lines correspond to a null effect; error bars represent 95% CIs. The x-axis in the lower panel corresponds to the person-mean centered age, where zero refers to the mean age of the participant across all waves, negative numbers refer to the participant's age in earlier waves, and positive numbers refer to the participant's age in later waves.

Figure 4.2. Cumulative Advantage/Disadvantage Effects of Income on Memory among Older Adults in the U.S.

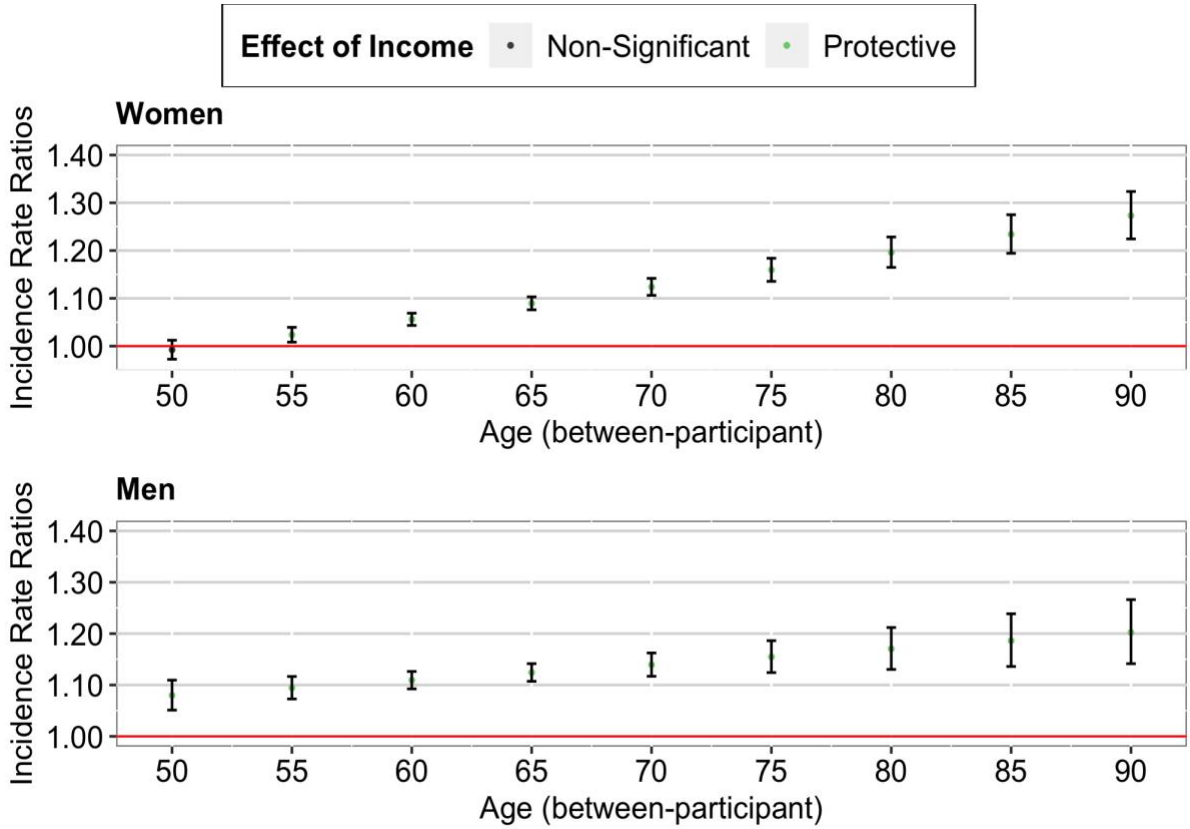


Note. Red lines correspond to a null effect; error bars represent 95% CIs. The x-axis in the lower panel corresponds to the person-mean centered age, where zero refers to the mean age of the participant across all waves, negative numbers refer to the participant's age in earlier waves, and positive numbers refer to the participant's age in later waves.

4.4.1.2 Gender as Moderator

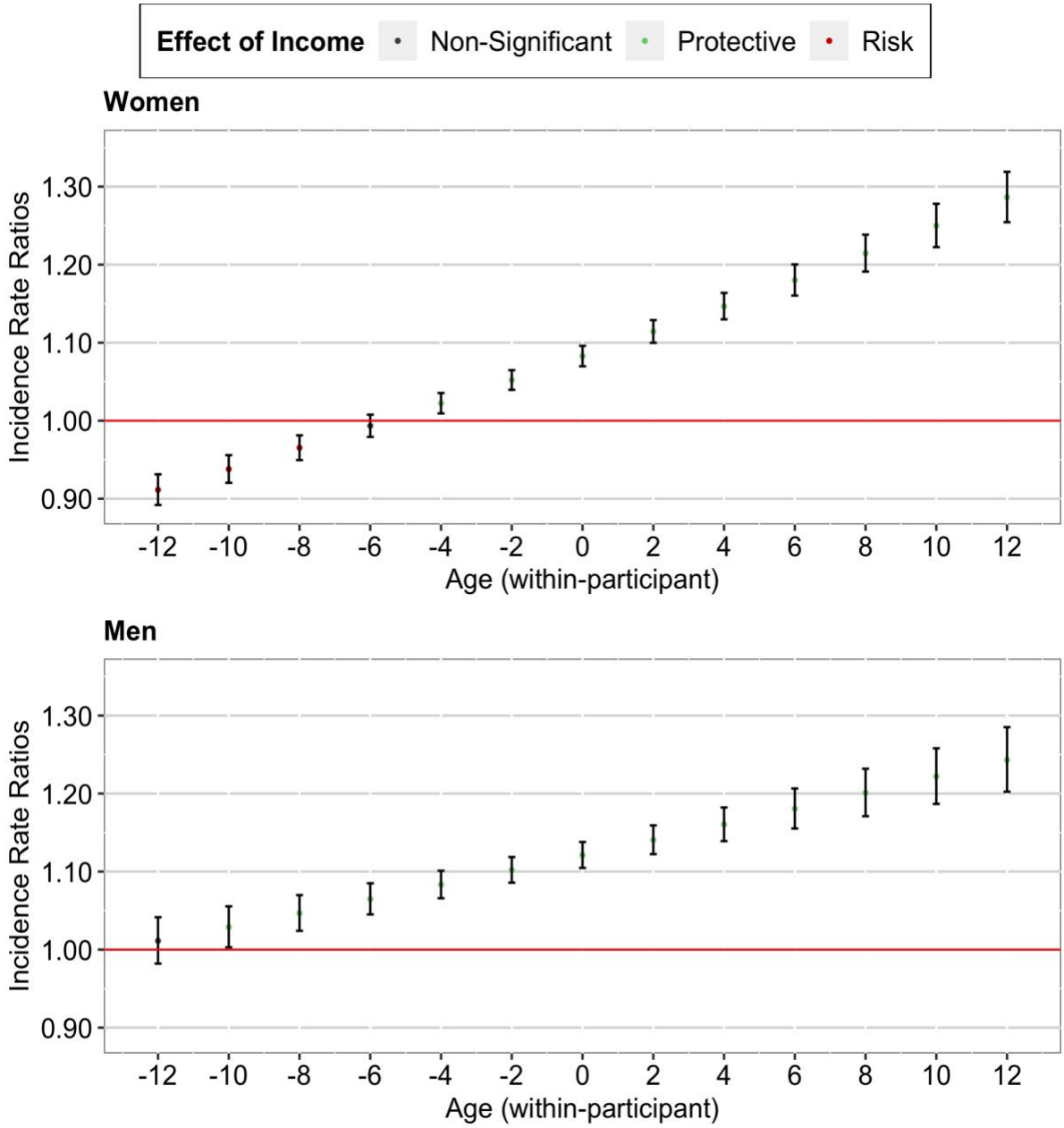
Our analyses including the gender interaction terms revealed three findings (**Supplementary Materials, Table C.1**). First, the observed effects on multimorbidity and memory remained significant (both between- and within-participant). Second, the observed effects on multimorbidity did not differ between women and men (both between- and within-participant). Third, the observed effects on memory tended to be more pronounced among women than men (between-participant, **Figure 4.3**; within-participant, **Figure 4.4**).

Figure 4.3. Between-Participant Cumulative Advantage/Disadvantage Effects of Income on Memory among Older Adults in the U.S. (by Gender)



Note. Red lines correspond to a null effect; error bars represent 95% CIs.

Figure 4.4. Within-Participant Cumulative Advantage/Disadvantage Effects of Income on Memory among Older Adults in the U.S. (by Gender)



Note. Red lines correspond to a null effect; error bars represent 95% CIs. The x-axis in both panels corresponds to the person-mean centered age, where zero refers to the mean age of the participant across all waves, negative numbers refer to the participant's age in earlier waves, and positive numbers refer to the participant's age in later waves.

4.4.2 Sensitivity Analyses

We conducted three sets of sensitivity analyses. The first set of sensitivity analyses used mobility (physical health domain) and verbal skills (cognitive health domain). We obtained generally consistent results with those of the main analyses. On the one hand, as shown in **Supplementary Materials, Table C.2**, we observed similar effects on mobility (compared to multimorbidity) and similar effects on verbal skills (compared to memory), both between- and within-participant. On the other hand, as shown in **Supplementary Materials, Table C.3**, the effects on mobility did not differ between women and men (both between- and within-participant), whereas the effects on verbal skills were significant only among women (between-participant). The second set of sensitivity analyses used self-rated health (a generic health outcome). We found that the effect of higher income on self-rated health weakened as individuals aged (both between- and within-participant; **Supplementary Materials, Table C.4**), and that this effect did not differ between women and men (both between- and within-participant; **Supplementary Materials, Table C.5**). The third set of sensitivity analyses excluded participants who either died over the study period or dropped out the survey. We obtained generally consistent results with those of the main analyses. The effects on multimorbidity and memory remained the same (**Supplementary Materials, Table C.6**) and the effects on memory were more pronounced among women than men (**Supplementary Materials, Table C.7**).

4.5 Discussion

In this study, we used multiple specific physical and cognitive health outcomes and longitudinal data of 13 waves spanning nearly 25 years to test the age-as-leveler pattern, the cumulative advantage/disadvantage pattern, and the persistent inequality pattern for physical and cognitive health domains, and analyze whether these patterns are gendered.

Our study yields two main findings. First, our between-participant and within-participant results suggest that the support for the age-as-leveler pattern or the cumulative advantage/disadvantage pattern tends to vary across physical and cognitive health domains. Regarding physical health, our between-participant and within-participant results support the age-as-leveler pattern. Our results are in line with the findings of previous cross-sectional studies (e.g., Li & Mutchler, 2019) and the few previous longitudinal studies that are available (e.g., Brown et al., 2016; Rehnberg et al., 2019; Van Der Linden et al., 2020). Given that the age-as-leveler pattern was observed not only between participants but also within participants, and that this pattern was robust to sensitivity analyses excluding participants who died or dropped out during follow-up, our study suggests that the selection-based explanations are less likely to account for this pattern. One possible explanation is the compression of morbidity in later life (Payne, 2022). A higher income helps older adults maintain good health, and the period of morbidity is compressed into advanced age, after which they experience a fast decline in physical health. Another possible explanation is age-related health deterioration (Hoffmann, 2011). In later life, the biological effects of aging become more predictive of physical health than socioeconomic indicators.

Regarding cognitive health, our between-participant and within-participant results support the cumulative advantage/disadvantage pattern. Our results are in line with the findings of previous cross-sectional studies (e.g., Andel et al., 2017) and the few previous longitudinal studies that are available (e.g., Leopold, 2019; Xu et al., 2017; Zeng et al., 2022). One possible explanation is that initial advantages lead to additional advantages and initial disadvantages lead to further disadvantages over time (Crystal et al., 2016). Individuals with higher income accumulate advantages over the life course, whereas individuals with lower income accumulate disadvantages in cognition, which widens the disparities in cognitive health. Another possible explanation is the cognitive reserves accumulated over the life course (Cullati et al., 2018).

Individuals with higher income are more exposed to cognitively stimulating activities in their life than individuals with lower income, which widens the disparities in cognitive health.

However, our between-participant and within-participant results suggest that neither the age-as-leveler nor the cumulative advantage/disadvantage pattern is mutually exclusive with the persistent inequality pattern. Although we found evidence of interactions, our between-participant and within-participant results show that the protective effect of higher income on physical and cognitive health remains significant over the later life course, which suggests a *partially* persistent inequality pattern. In other words, despite the age-as-leveler pattern in physical health and cumulative advantage/disadvantage pattern in cognitive health, income-related inequalities in physical and cognitive health neither fully emerge nor completely disappear in old age.

Second, we find that the cumulative advantage/disadvantage pattern may be gendered. The cumulative advantage/disadvantage effects of income on cognitive health tend to be more pronounced among women than men. Our results are in line with those of the few studies that stratify by gender (Hu et al., 2020; Lee & Park, 2019). Not only do individuals with lower income accumulate their disadvantage in cognitive health over time, but women do as well, meaning that as time passes, women with lower income are likely to find themselves less cognitively healthy than their men counterparts. One possible explanation for the stronger cumulative advantage/disadvantage effects of income on cognitive health among women is that in the inequality accumulation process, women tend to have more exposure to risk factors and fewer resources and accumulate disadvantage more easily than men (Ferraro et al., 2009).

4.5.1 Limitations and Future Research

Three limitations need to be acknowledged. First, our sample was from the U.S., a Western and industrialized country. We chose to work with the HRS data because it is the longest-running panel data on older adults in the U.S. However, this means that our results

cannot be generalized to other countries and that replication studies using samples from countries with different characteristics are needed. Second, multimorbidity was based on self-reported chronic diseases collected in interviews rather than based on clinical records. Despite the plausible measurement error, chronic disease data from health interview surveys have been proven to show acceptable reliability and validity (Beckett et al., 2000) and have been used in studies on the change in the income–health gradient over the later life course (e.g., Brown et al., 2012). Third, we did not specifically examine the role of race/ethnicity in predicting the changes in the income-health gradient over the later life course, as it was deemed beyond the scope of our study. Future research needs to consider the intersectionality of race/ethnicity, age, gender, and socioeconomic status to better understand how these factors shape the health trajectories over time.

4.6 Conclusion

Our findings suggest that in the U.S., as time passes whether the protective effect of higher income on health tapers off or burgeons tends to vary across physical and cognitive health domains, and that the strength of the effect may differ between women and men.

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5. Evolution of the Income–Health Gradient over the Later Life course: Longitudinal Evidence from 19 European Countries (2004-2019) and China (2011-2018)

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DOI: 10.1007/s10433-023-00781-y • PDF

5.1 Abstract

Some studies show that the protective effect of higher income on health *weakens* with old age (age-as-leveler pattern), whereas others show that it *strengthens* with old age (cumulative advantage/disadvantage pattern). Many existing studies are limited in that they use single-country and/or single-timepoint designs. To overcome these limitations and better understand how the income-health gradient evolves in older age, we used cross-national and longitudinal data of the Survey of Health, Ageing and Retirement in Europe (2004-2019, *N*=73,407) and the China Health and Retirement Longitudinal Study (2011-2018, *N*=10,067). We operationalized health using multimorbidity and three alternative indicators (functional disability, mobility disability, and memory). We performed Poisson growth curve modelling to capture the between-participant effects of age and the within-participant effects of aging. We obtained three consistent and robust findings for Europe (patterns were observed in most countries) and China. First, the protective effect of higher income on multimorbidity, functional disability, and mobility disability was weaker for older than for younger adults (between-participant age-as-leveler pattern). Second, only the protective effect of higher income on mobility disability weakened over the later life course (within-participant age-as-leveler pattern). Third, the protective effect of higher income on memory was stronger for older than

for younger adults and strengthened over the later life course (between-participant and within-participant cumulative advantage/disadvantage pattern). Longitudinal data, growth curve modelling distinguishing the between-participant from within-participant effect, and adjustments for potential confounders based on the hypothesized causal structure enabled us to better navigate the landscape of causal inference. Findings suggest that the income-related gap in physical health but not in cognitive health narrows in old age for both Europe and China.

5.2 Introduction

Existing studies testing how the link between income and health evolves with old age document two opposite patterns of findings (Holman & Walker, 2021): the age-as-leveler pattern and the cumulative advantage/disadvantage pattern. Studies in line with the age-as-leveler pattern report that the protective effect[ii] of higher income on health *weakens* with old age (Bonaccio et al., 2019; Brown et al., 2016; Crimmins et al., 2004; Griffith et al., 2021; House et al., 1990; Kim & Durden, 2007; Schöllgen et al., 2010; Sieber et al., 2020). Scholars believe that the fundamental reason for this trend is that the socioeconomic determinants of health are outweighed by biological determinants of health after a certain point in later life (Hoffmann, 2011; Rehnberg, 2020) and the selective mortality (Dupre, 2007), meaning that income becomes less and less predictive of health as people age. In contrast, studies in line with the cumulative advantage/disadvantage pattern report that the protective effect of higher income on health *strengthens* with old age (Chen et al., 2010; Crystal & Shea, 1990; Lahelma et al., 2015; Leopold, 2018; O'Rand, 2002; Veenstra & Aartsen, 2022; Willson et al., 2007). Scholars believe that the fundamental reason for this trend is that socioeconomic-related advantage/disadvantage accumulate over the life course (DiPrete & Eirich, 2006; Lynch, 2003), meaning that income becomes increasingly predictive of health as people age.

[ii] In this occurrence, the term "effect" is used to refer to a statistical effect and does not denote a causal effect.

Many existing studies are limited in that (i) they use single-country designs and (ii) they use single-timepoint designs. First, most of the existing studies were conducted in *a single country*, most of the time in the U.S. (for example, House et al., 1990; Kaplan et al., 2007; for an exception, see Sieber et al., 2020). Generalization of findings from such studies may be misleading (Rai et al., 2013) because health-related estimates are known to vary from one national setting to another and should always be interpreted in a context-sensitive manner (Kessler & Bromet, 2013). Studies using cross-national designs and replications in different countries are therefore needed to better understand how the link between income and health evolves with old age. Second, most of the existing studies used *single-timepoint designs*, that is, they focused on a particular year of data collection (for example, Lowry & Xie, 2009; Robert et al., 2009; for an exception, see Rehnberg et al., 2019). Findings from such studies may also be misleading (Galbraith et al., 2017) because their health-related estimates pertain to comparisons between participants of different ages and cannot be interpreted as corresponding to changes in health over time (Fitzmaurice et al., 2011). Studies using longitudinal designs to capture within-participant dynamics over time are therefore needed to better understand how the link between income and health evolves with old age.

In the present study, we investigated in two older adults panel datasets how the effect of income on health evolves with age from both a cross-national and a longitudinal perspective. In contrast to most existing studies that focused on the U.S., we chose to focus on two important economies where—in recent decades—population aging has put a strain on health systems and social services, namely, Europe and China (Rechel et al., 2013; Zhao et al., 2014). Moreover, in contrast to most existing studies that used cross-sectional data, we used longitudinal European and Chinese datasets on older adults, namely, the Survey of Health, Ageing and Retirement in Europe (SHARE) and the China Health and Retirement Longitudinal Study (CHARLS). We aimed to make causal inference of how the effect of income on health evolves

with age. We tested the following two hypotheses: (i) the effect of income on health weakens as people age (the age-as-leveler hypothesis) or (ii) the effect of income on health strengthens as people age (the cumulative advantage/disadvantage hypothesis). We operationalized health using an indicator particularly relevant to old age, namely, multimorbidity (Makovski et al., 2019). To gain further evidence, we also used three alternative measures of outcomes from physical and cognitive health domains, namely, functional disability, mobility disability, and memory.

5.3 Methods

5.3.1 Study Design

Our study aimed to make causal inference, examining how the effect of income on health evolves with age. To approach causality, we used longitudinal data (VanderWeele et al., 2016), growth curve modelling distinguishing the between-participant effect from within-participant effect (Raymaekers et al., 2020), and adjustments for potential confounders based on the "hypothesised causal structure" (Wysocki et al., 2022).

5.3.2 Samples

We chose to work with longitudinal data because longitudinal data facilitates causal inference (VanderWeele et al., 2016). We used cross-national data from two different sources: SHARE and CHARLS. Both SHARE and CHARLS are longitudinal surveys that offer (i) prospective data (e.g., recurring health assessment, income), and (ii) retrospective data (e.g., childhood sociodemographic information). Specifically, SHARE is composed of a series of nationally representative panel surveys conducted biennially since 2004 that collected health data on approximately 140,000 people aged 50 or older from 28 European countries and Israel. CHARLS is a nationally representative panel survey conducted biennially since 2011 that

collected the same kind of health data on approximately 17,500 Chinese residents aged 45 or older.

We used all available waves of the SHARE data (i.e., six waves spanning 2004 to 2019) and the CHARLS data (i.e., four waves spanning 2011 to 2018). In SHARE, older adults are defined as people aged 50 or older, whereas in CHARLS they are defined as aged 45 or older. In both cases, we removed the few observations that were incorrectly included in the sample (i.e., in SHARE, people < 50 years old; in CHARLS, people < 45 years old). We included eligible observations based on two criteria: (i) complete cases for health and sociodemographic variables (a total of 277,633 observations in SHARE; a total of 37,451 observations in CHARLS) and (ii) at least two waves to be able to estimate within-participant effects over time (87.60% of observations in SHARE; 97.43% in CHARLS). Our final sample in SHARE comprised 243,207 observations from 73,407 older adults in 19 countries, and our final sample in CHARLS comprised 36,487 observations from 10,067 older adults (for the characteristics of both samples, see **Table 5.1**).

Table 5.1. Description of the SHARE (2004-2019) and CHARLS (2011-2018) Samples

	SHARE (2004-2019)	CHARLS (2011-2018)
Men (%)	44.31	48.25
Mean age (in years)	66.9 (*SD* = 9.5)	61.3 (*SD* = 9.4)
Urban residence (%)	69.25	33.57
Currently married (%)	73.14	87.35
Currently not working (%)	64.65	33.50
Mean household size (in persons)	2.3 (*SD* = 1.0)	3.5 (*SD* = 1.7)
Mean equivalized income (in 2010 USD)	38,405 (*SD* = 65,133)	2,094 (*SD* = 7,241)
Mean household wealth (in 2010 USD)	35,947 (*SD* = 140,283)	312 (*SD* = 65,022)
Educational level (%)		
Less than upper secondary education	42.48	90.86
Upper secondary or vocational education	36.61	8.12
Tertiary education	20.91	1.02
Multimorbidity (%)	45.43	43.78
Mean number of chronic diseases	1.9 (*SD* = 1.5)	1.8 (*SD* = 1.5)
Mean number of functional disabilities	0.1 (*SD* = 0.3)	0.5 (*SD* = 0.4)
Mean number of mobility disabilities	1.3 (*SD* = 1.5)	1.5 (*SD* = 1.4)
Mean number of immediate word recall	5.2 (*SD* = 1.5)	3.8 (*SD* = 1.3)

Note. Harmonized educational levels provided by the SHARE and CHARLS data are used in the study.

5.3.3 Measures

5.3.3.1 Equivalized Income Decile (Time-Constant)

Participants reported their total household income during the last year in both SHARE and CHARLS. Potential sources of income were earnings, capital, pension, government transfers, and other sources. To account for inflation, we converted the total household income into inflation-adjusted total household income. Specifically, we used the annual consumer price index available for each year of the survey as an inflation multiplier (i.e., we divided household income by the year-specific consumer price index included in the datasets). To adjust for the difference in household size, we converted inflation-adjusted total household income into equivalized income. Specifically, we used the square root equivalence scale of the Organization for Economic Co-operation and Development (Organisation for Economic Cooperation and Development, 2013), namely, we divided the inflation-adjusted total household income by the square root of household size (for descriptive statistics, see **Table 5.1**). As the income of older adults changes marginally over time in our datasets (for SHARE, 65%-68% of participants remain in the same income decile wave-to-wave; for CHARLS, 63%-68% of participants remain in the same income decile wave-to-wave)[iii], we treated equivalized income as a time-constant variable. To compare estimates across national contexts that use different currencies and/or have varying levels of economic development, we created a variable of equivalized income decile for each participant (1 = *bottom 10%*; 10 = *top 10%*).

5.3.3.2 Multimorbidity (Time-Varying)

We operationalised later-life health by counting the number of chronic diseases present within the individuals in each wave (Marengoni et al., 2011). Participants reported whether they had been diagnosed by a doctor with any of 12 chronic diseases in SHARE (i.e.,

[iii] For SHARE, 71%-74% of participants remain in the same income quintile wave-to-wave; for CHARLS, 69%-74% of participants remain in the same income quintile wave-to-wave.

high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, arthritis, high cholesterol, ulcer, Parkinson disease, cataracts, or hip fracture) and 12 chronic diseases in CHARLS (i.e., high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, arthritis, dyslipidemia, liver disease, kidney disease, stomach/digestive disease, or asthma).

5.3.3.3 Covariates

In our models, we controlled for variables based on the "hypothesized causal structure" (Wysocki et al., 2022). Specifically, we proposed a causal structure in which socioeconomic and demographic factors are plausible confounders of the causal effect of income on later-life health. The following variables have been evidenced to be confounders of income and later-life health: wealth, education, working status, gender, residence region, marital status, and household size (Brown et al., 2016; Chen et al., 2010; Hoffmann, 2011; Lahelma et al., 2015; Leopold, 2018; Sieber et al., 2020; Veenstra & Aartsen, 2022). We included these control variables in our models: wealth decile (from 1 = *bottom 10%* to 10 = *top 10%*), education level (1 = *less than upper secondary*, 2 = *upper secondary or vocational*, 3 = *tertiary*), gender (-0.5 = *men*, +0.5 = *women*), region of residence (0 = *urban*, 1 = *rural*), current marital status (0 = *not married*, 1 = *married*), current working status (0 = *not working*, 1 = *working*), and household size (i.e., the number of people living in the household).

5.3.3.4 Alternative Measures of Health Outcomes for Supplementary Analyses

In our supplementary analyses, we used three alternative measures of health outcomes from two health domains: for the physical health domain, we used functional disability and mobility disability; for the cognitive health domain, we used memory. Specifically, (i) we measured functional disability using the number of instrumental activities of daily living reported to be difficult out of the following: using the phone, managing money, and taking medications; (ii) we measured mobility disability using the number of activities reported to be difficult out of the following: walking 100 meters, climbing several flights of stairs, getting up

from a chair, stooping or kneeling or crouching, extending arms up, lifting 10 pounds (in SHARE) or 5 kilograms (in CHARLS), and picking up a small coin; and (iii) we measured memory using the number of words from a 10-word list that were correctly recalled immediately.

5.3.4 Analytic Strategy

5.3.4.1 Poisson Growth Curve Models

To take the hierarchical structure of the data into account and estimate health trajectories over the later life course, we built a series of multilevel growth curve models. Regarding SHARE, we treated wave-specific observations (N = 243,207 level-1 units) as nested in participants (K = 73,407 level-2 units) and countries (L = 19 level-3 units). Regarding CHARLS, we treated wave-specific observations (N = 36,487 level-1 units) as nested within participants (K = 10,067 level-2 units). We used Poisson regression rather than negative binomial regression because the overdispersion test did not reject the null hypothesis of equidispersion, χ^2 (3, N = 243,207) = 88,814, p = 1.00 in SHARE, χ^2 (2, N = 36,487) = 14,135, p = 1.00 in CHARLS. We built Poisson growth curve models rather than linear growth curve models because the outcome variables (i.e., multimorbidity, functional disability, mobility disability, and memory) are count variables that follow a Poisson distribution (King, 1988).

5.3.4.2 Centering Strategy to Disentangle the Between-Participant from the Within-Participant Effect

Between-participant estimates and within-participant estimates may lead to different results (Curran & Bauer, 2011) and have different implications in terms of directionality (Allison, 2009). To better assess causality, we used an analytical approach that enabled us to estimate both the between-participant effect and the within-participant effect (Raymaekers et al., 2020). Specifically, we used Fairbrother's (2014) centering strategy and computed two age variables: (i) grand-mean centered mean age and (ii) person-mean centered age. To compute

the *grand-mean centered mean age*, we centered each participant's mean age across all waves on the grand mean age of all participants. This variable enabled us to capture the between-participant effect of age (i.e., the effect of age-related differences between distinct participants). To compute the *person-mean centered age*, we centered each participant's age in each wave of the survey on their individual mean age across all waves. This variable enabled us to capture the within-participant effect of aging (i.e., the effect of age-related changes within a single participant over time).

5.3.4.3 Focal Model Equation

We regressed health outcome variables on five focal predictors: (i) grand-mean centered mean age (Age_gmc_i), (ii) income decile ($\text{Income Decile}_{i(k)}$), (iii) grand-mean centered mean age × income decile (to estimate whether the effect of income against multimorbidity differed between younger and older participants), (iv) person-mean centered age (Age_cmc_{ij}), and (v) person-mean centered age × income decile (to estimate whether the effect of income against multimorbidity changed as participants aged). We also included a set of seven control variables (see Eq. 1).

$$\begin{aligned}\log(\lambda_{ij[k]}) = {} & \beta_{00[0]} + \beta_{01[0]} \times \text{Age\_gmc}_j + \beta_{02[0]} \times \text{Income Decile}_{j[k]} \\ & + \beta_{03[0]} \times \text{Age\_gmc}_{j[k]} \times \text{Income Decile}_{j[k]} + (\beta_{10[0]} + u_{1i[k]}) \times \text{Age\_cmc}_{ij[k]} \\ & + \beta_{11[0]} \times \text{Age\_cmc}_{ij[k]} \times \text{Income Decile}_{j[k]} + \beta_{ij[k]} \times \text{Control}_{ij[k]} + u_{0j[k]} [+ u_{00k}]\end{aligned} \quad \text{(Eq. 1)}$$

where $Y_{ij[k]}$ is the outcome, which follows a Poisson distribution ($Y_{ij[k]} \sim \text{Poisson}(\lambda_{ij[k]})$); $i = 1, 2, \ldots, N$ (wave-specific observations); $j = 1, 2, \ldots, K$ (participants); $\beta_{ij[k]} \times \text{Control}_{ij[k]}$ represents the vector of the seven control variables (i.e., see the relevant subsection in "Measures"); $u_{0j[k]}$ represents the participant-level residuals; and $u_{1i[k]}$ represents the random slope of age. In SHARE, the equation involves three levels, including the terms and subscripts in brackets,

where k = 1, 2, …, L (countries), and u_{00k} represents the country-level residuals. We chose to assess the interaction between age and income decile on the multiplicative scale based on theoretical and methodological reasons. From a theoretical perspective, relative risk measures on the multiplicative scale may be more suitable to assess causality (Poole, 2010). From a methodological perspective, relative risk measures on the multiplicative scale have less heterogeneity in statistical significance (VanderWeele & Knol, 2014) and offer acceptable effectiveness (Sommet & Morselli, 2017).

An interaction term is significant on the multiplicative scale if the combined effect of two exposures is larger or smaller than the product of the individual effects of the two exposures (Knol et al., 2011). In our model, decomposition of the between-participant-based interaction term $\text{Age\_gmc}_{j[k]} \times \text{Income Decile}_{j[k]}$ enables to compare the effect of income decile between younger participants and older participants, whereas decomposition of the within-participant-based interaction term $\text{Age\_cmc}_{ij[k]} \times \text{Income Decile}_{j[k]}$ enables to compare the effect of income decile as participants age over the later life course.

We ran the Poisson growth curve models described above using the glmer function from the lme4 package (version 1.1-26) (Bates et al., 2015) in R (version 4.0.2). The instructions for retrieving the datasets and the R scripts to reproduce our findings are available via the Open Science Framework (OSF): https://osf.io/mb8nc/?view_only=b4d526e930594d66a7428db9fbefc4ba.

5.4 Results

5.4.1 Main Analyses

5.4.1.1 Results from Europe

We observed a significant between-participant age-as-leveler effect (i.e., interaction between grand-mean centered mean age and income decile on the multiplicative scale) for

Europe (12 out of 19 countries[iv]), IRR = 1.12, 95% CI [1.10, 1.14], $p < .001$ (for the full results, see **Table 5.2**, left column). Congruent with the age-as-leveler hypothesis, the protective effect of higher income against multimorbidity was weaker for older than for younger adults (for the simple effects of income for each decade of age, see **Figure 5.1**, upper panel). The relationship between income and multimorbidity *reversed* after age 75, meaning that a higher income was no longer protective against multimorbidity but became a risk factor in advanced age.

However, we did not observe a significant within-participant age-as-leveler pattern (i.e., interaction between person-mean centered age and income decile on the multiplicative scale) for Europe, IRR = 0.99, 95% CI [0.96, 1.02], $p = .554$. In other words, the within-participant protective effect of higher income against multimorbidity *did not* vary over the later life course, meaning that the protection of higher income against multimorbidity was present equally over the later life course of the individual.

5.4.1.2 Results from China

Replicating the results from Europe, we observed a significant between-participant age-as-leveler pattern (i.e., interaction between grand-mean centered mean age and income decile on the multiplicative scale) for China, IRR = 1.19, 95% CI [1.12, 1.27], $p < .001$ (for the full results, see **Table 5.2**, right column). Again, congruent with the age-as-leveler hypothesis, the protective effect of higher income against multimorbidity was weaker for older than for younger adults (for the simple effects of income for each decade of age, see **Figure 5.1**, lower panel). This time, the relationship between income and multimorbidity *reversed* after age 65, meaning that a higher income was no longer protective against multimorbidity but became a risk factor in old age.

[iv] The 12 countries for which the age-as-leveler effect was observed were Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Italy, Sweden, Switzerland; the 7 countries for which this effect was not statistically significant were Israel, Luxembourg, Netherlands, Poland, Portugal, Slovenia, Spain. We did not identify a clear pattern in the countries where the effect was observed or not. It is possible that the variations in the effect are due to insufficient power in the country-specific subsamples.

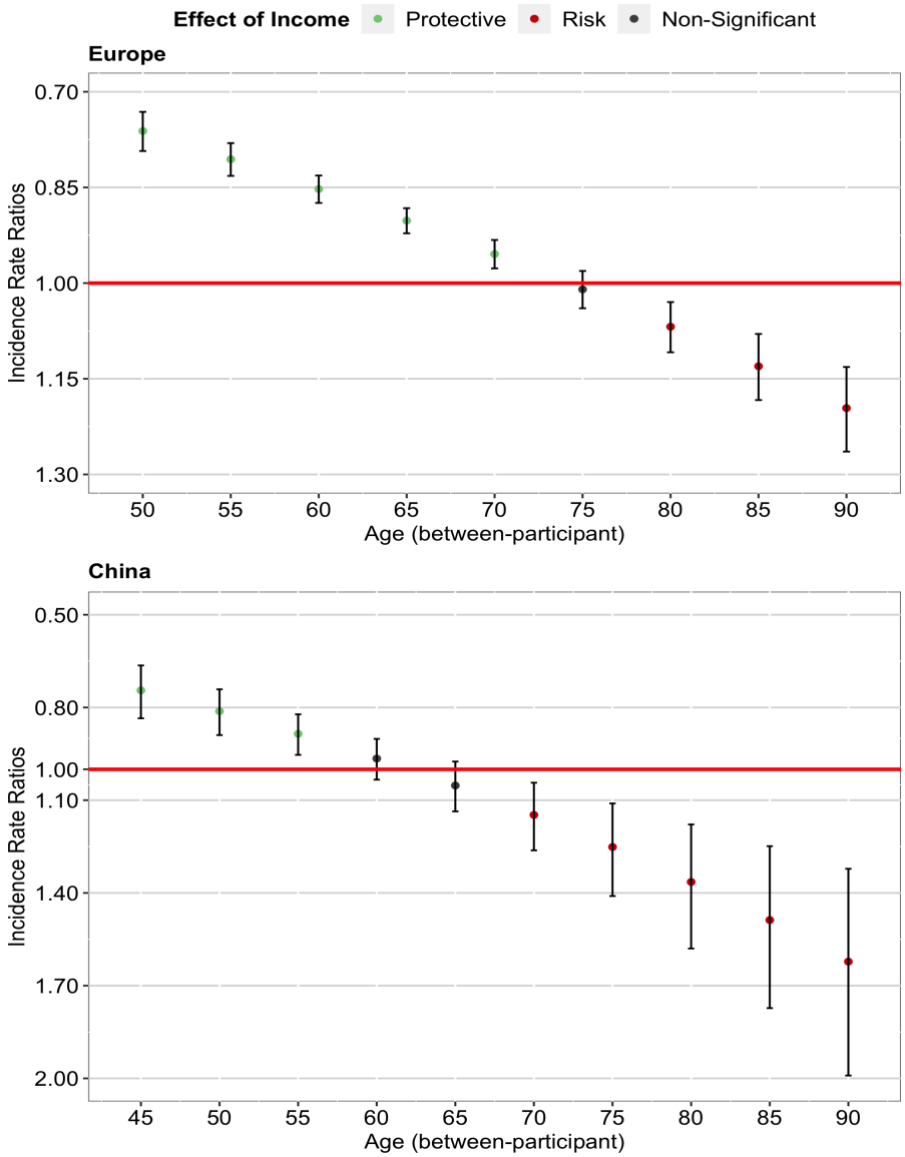
Similar to Europe, we did not observe a significant within-participant age-as-leveler pattern (i.e., interaction between person-mean centered age and income decile on the multiplicative scale) for China, IRR = 0.99, 95% CI [0.88, 1.11], p = .815. In other words, the within-participant protective effect of higher income against multimorbidity *did not* vary over the later life course, meaning that the protection of higher income against multimorbidity was present equally over the later life course of the individual.

Table 5.2. Effect of Income on Multimorbidity as a Function of Age among Older Adults in Europe and China

	Europe		China	
	IRRs	95% CI	IRRs	95% CI
Grand-mean centered mean age	1.30***	1.29–1.31	1.12***	1.10–1.14
Person-mean centered age	2.15***	2.03–2.27	2.86***	2.77–2.96
Equivalized income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.91***	0.89–0.93	0.97	0.90–1.03
Grand-mean centered mean age × equivalized income decile	1.12***	1.10–1.14	1.19***	1.12–1.27
Middle-aged adults (-2 SD)	0.74***	0.71–0.78	0.70***	0.62–0.80
Older middle-aged adults (-1 SD)	0.82***	0.80–0.85	0.82***	0.75–0.90
Older adults (+1 SD)	1.01	0.98–1.04	1.13**	1.03–1.24
Oldest old adults (+2 SD)	1.12***	1.07–1.17	1.33***	1.16–1.52
Person-mean centered age × equivalized income decile	0.99	0.96–1.02	0.99	0.88–1.11
Wealth decile (1 = *bottom 10%*, 10 = *top 10%*)	0.83***	0.81–0.84	0.82***	0.77–0.87
Upper secondary or vocational education	0.91***	0.90–0.93	1.03	0.97–1.10
Tertiary education	0.84***	0.83–0.85	1.07	0.90–1.27
Gender (-0.5 = *men*, +0.5 = *women*)	1.00	0.99–1.01	1.14***	1.10–1.18
Region of residence (0 = *urban*, 1 = *rural*)	0.99	0.98–1.00	0.95**	0.91–0.99
Current marital status (0 = *not married*, 1 = *married*)	1.00	0.99–1.02	1.04	1.00–1.08
Current working status (0 = *not working*, 1 = *working*)	0.82***	0.81–0.83	0.90***	0.88–0.92
Household size	0.98***	0.98–0.99	0.99**	0.98–0.99
$N_{countries}$	19			
$N_{participants}$	73,407		10,067	
Observations	243,207		36,487	

Note. IRRs = incidence rate ratios. Comparisons were made between the bottom 10% and the top 10% in terms of income and wealth. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

Figure 5.1. Between-Participant Age-as-Leveler Effect of Income on Multimorbidity in Europe and China



Note. Red lines correspond to a null effect; error bars represent 95% CIs.

5.4.2 Supplementary Analyses

We conducted three sets of supplementary analyses repeating the main analyses (i) using alternative health outcomes, (ii) using log-transformed equivalized income as our focal predictor, and (iii) assessing the interaction between age and equivalized income decile on the additive scale (i.e., relative excess risk due to interaction [RERI], attributable proportion [AP], synergy index [SI]).

First, we repeated the main analyses using three alternative measures of outcomes from two health domains: functional disability and mobility disability as indicators of the physical health domain and memory as indicator of the cognitive health domain. The supplementary analyses led to consistent findings for both Europe and China (for a summary and comparison with the findings from the main analyses, see **Table 5.3**; for the full results for Europe and China, see **Table D.1** and **Table D.2**, respectively). First, between-participant age-as-leveler pattern that was observed in the main analyses was observed in the analyses using functional disability and mobility disability as alternative measures of health outcomes. Second, within-participant age-as-leveler pattern that was *not* observed in the main analyses was observed in the analyses using mobility disability as an alternative measure of health outcome. Third, cumulative advantage/disadvantage pattern that was *not* observed between participants *or* within participants in the main analyses was observed both between participants and within participants in the analyses using memory as an alternative measure of health outcome.

Second, to ensure a comprehensive analysis, we repeated the main analyses using log-transformed equivalized income instead of income decile as the focal predictor. Similar to the main analyses, the findings in Europe and China exhibited comparable trends: we observed a between-participant age-as-leveler pattern, but did not observe a within-participant age-as-leveler pattern.

Third, in the main analysis, we chose to assess the interaction between age and income decile on the multiplicative scale. In order to gain a comprehensive understanding of the interaction effect between age and income, we also assessed this interaction on the additive scale. An interaction is significant on the additive scale if the combined effect of two exposures is larger or smaller than the sum of the individual effects of the two exposures (Knol et al., 2011). Consistent with the main analyses, the analyses using the additive scale revealed a between-participant age-as-leveler pattern and a within-participant age-as-leveler pattern in Europe and China (for the details of the analysis, see **Table D.3**).

Table 5.3. Patterns of Income Effects on Physical and Cognitive Health Outcomes as a Function of Age among Older Adults in Europe and China

	Physical Health						Cognitive Health	
	Multimorbidity		Functional Disability		Mobility Disability		Memory	
	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI
Europe								
Between-participant age × income	1.12***	1.10–1.14	1.15*	1.03–1.28	1.14***	1.10–1.18	1.04***	1.03–1.05
	(age-as-leveler)		(age-as-leveler)		(age-as-leveler)		(cumulative dis/advantage)	
Within-participant age × income	0.99	0.96–1.02	1.23	0.97–1.55	1.10***	1.05–1.15	1.04***	1.02–1.06
	(inconclusive)		(inconclusive)		(age-as-leveler)		(cumulative dis/advantage)	
China								
Between-participant age × income	1.19***	1.12–1.27	1.32***	1.17–1.49	1.08*	1.01–1.16	1.11***	1.08–1.14
	(age-as-leveler)		(age-as-leveler)		(age-as-leveler)		(cumulative dis/advantage)	
Within-participant age × income	0.99	0.88–1.11	1.41	0.80–2.47	1.17*	1.03–1.32	1.38***	1.27–1.51
	(inconclusive)		(inconclusive)		(age-as-leveler)		(cumulative dis/advantage)	

Note. IRRs = incidence rate ratios. Cells in blue are consistent with the age-as-leveler pattern, cells in orange are consistent with the cumulative advantage/disadvantage pattern, and cells in grey show inconsistent results. Comparisons were made between the bottom 10% and the top 10% in terms of income. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

5.5 Discussion

Existing studies testing how the link between income and health evolves with old age are limited in that most of them use single-country and/or single-timepoint designs. In our study, we investigated the evolution of the link between income and health with old age using a cross-national design (involving 20 countries) and a longitudinal design (using two large-scale panel datasets). Our study revealed three main findings that are consistent for Europe and China. These findings were robust to different model specifications.

First, we found between-participant age-as-leveler pattern in multimorbidity, functional disability, and mobility disability. In line with previous cross-sectional studies (e.g., Griffith et al., 2021; House et al., 1990; Robert et al., 2009), the between-participant protective effect of higher income on multimorbidity, functional disability, and mobility disability was weaker for older adults than for younger adults. This could be explained by the selection effect (Pearce & Richiardi, 2014), which suggests that lower-income older adults participating in the survey are healthy survivors of mortality selection whose health status is closer to that of higher-income older adults. Therefore, the narrowing health gap observed between higher-income and lower-income older adults may reflect distinct differences between individuals (Ferraro & Farmer, 1996) rather than a temporal change in the income–health link over the later life course. In addition, the reversal of the age-as-leveler pattern after age 75 in Europe and after age 65 in China could also be explained by a selection effect. It is plausible that most adults with higher income have a greater likelihood of surviving to an advanced age, while only the most resilient and healthier adults with lower income survive to such age. This is evidenced by the fact that the reversal of the effect was observed in the between-participant analysis (where selection is most potent) and not in the within-participant analysis (where selection is less potent). The earlier onset of the reversal of effect that happened in China, compared with Europe, may be accounted for by the particularly high mortality rates in 1960s

to 1980s (Banister & Hill, 2004). These high mortality rates were the consequences of the country's low level of economic and social development during that period (Banister & Zhang, 2005).

Second, we only found within-participant age-as-leveler pattern in mobility disability. In line with few longitudinal studies that are available (e.g., Beckett, 2000; Sieber et al., 2020), the within-participant protective effect of higher income on mobility disability weakened over the later life course of the individual. One possible explanation for the fact that the between-participant effects were not always replicated when focusing on the within-participant dynamics is that the number of waves in the datasets was somewhat limited (six waves in SHARE and four waves in CHARLS), meaning that statistical power may not have been sufficient to observe small-size longitudinal effects. This further warns us that between-participant results from the literature should be interpreted with caution.

Third, we found both between-participant and within-participant cumulative advantage/disadvantage pattern in memory. In line with previous studies focusing on cognitive health (Cheval et al., 2019; Landy et al., 2017; Lyu & Burr, 2016), we found that the protective effect of higher income on memory strengthened over the later life course of the individual. It is possible that the age-as-leveler pattern applies to physical health (i.e., multimorbidity, functional disability, and mobility disability) and that the cumulative advantage/disadvantage pattern applies to cognitive health (i.e., memory). This could be explained by the fact that physical health in later life is more biologically grounded (e.g., changes in aging phenotypes, Fabbri et al., 2015), whereas cognitive health in later life is more socially grounded (e.g., cognitively stimulating activities or experiences, Cullati et al., 2018). As suggested by the lifespan theory, the biological and cultural factors of a health outcome are interwind and the dynamics between biology and culture evolve across the life course (Baltes & Smith, 2004),

future studies are warranted to investigate the biocultural dynamics underlying a health outcome over the lifespan.

5.5.1 Limitations

One limitation of our study is that our samples were from Europe and China. We chose to work with SHARE and CHARLS because most existing studies were based on U.S. data, and we aimed to study two important economies outside of the U.S. where aging and age-related health issues pose a notable societal challenge. Although our findings were consistent between high-income countries in Europe and a low- and middle-income country, namely, China, replication studies from other countries are needed to determine how the age-as-leveler pattern and the cumulative advantage/disadvantage pattern generalize across different societies (e.g., the Japanese Study of Aging and Retirement [JSTAR] (four waves spanning 2007 to 2013), the Longitudinal Ageing Study in India [LASI] (one wave in 2017/2018), and the Mexican Health and Aging Study [MHAS] (five waves spanning 2001 to 2018)). Another limitation of our study is that the covariates included in our models were common socioeconomic and demographic variables to both the SHARE and CHARLS data. The inclusion of these variables helped to capture the causal effect of income on later-life health. However, to further mitigate the impact of confounding effects, future studies need to pay more attention to factors that are specific to a certain society, and sensitive to the culture and structure of that society.

5.6 Conclusion

Our use of longitudinal data, growth curve modelling distinguishing the between-participant effect from within-participant effect, and adjustments for potential confounders based on the hypothesized causal structure enabled us to better navigate the landscape of causal inference. We believe that causality should be assessed as a continuum of plausibility as

opposed to a dichotomy (for relevant discussion, see Grosz et al., 2020). Advanced analytical strategy increases the plausibility of causality. Our between-participant and within-participant results suggest that in Europe and China, the income-related gap in physical health—but not cognitive health—narrows in old age. Future studies need to revisit the age-as-leveler pattern and the cumulative advantage/disadvantage pattern by considering the multidimensional health outcomes in a more systematic way. In particular, future studies need to test, as suggested by this study, if the biologically-driven processes of health may correspond to the age-as-leveler pattern, whereas the culturally-driven dimensions of health may correspond to the cumulative advantage/disadvantage pattern in old age.

6. Discussion

This thesis pursued two lines of inquiry to examine the socioeconomic determinants and development of later-life health from a life course perspective. The first line of inquiry sought to understand how health in later life was shaped by historical contexts. The specific research question was how exposure to famine was related to the health of older adults in China and the Netherlands six decades later. The first two empirical studies addressed this research question. The second line of inquiry sought to understand how health in later life was shaped by the personal history of an individual. The specific research question was how the income–health gradient evolved over the later life course among older adults in the U.S., Europe, and China. The third and fourth empirical studies addressed this research question.

These two lines of inquiry in this thesis were connected by the life course perspective in that it aimed to understand aging and health in a specific historical context and a particular individual life history. Focusing on historical events and contexts provided insights into the lasting mark of collective history on individuals, while focusing on individual life history provided insights into the impact of changing lives that individuals experienced on health outcomes in later life. Taken together, this thesis presented a complete picture of how later-life health is shaped in the context of the broader history of a society and the personal life history of an individual and has advanced our understanding of human development and health in context.

6.1 Summary of Findings

The first two empirical studies focused on famine exposure and health in later life. The first empirical study, "*Long Arm of Exposure to the 1959-1961 Chinese Famine into Later-Life Non-Communicable Diseases*," investigated the link between exposure to the Chinese famine

of 1959-1961 and the risk of non-communicable diseases in older age. Findings revealed that individuals exposed before age 18 were at higher risk of non-communicable diseases 50 years later. Notably, those exposed in utero or in the first 1,000 days of life were at twice the risk. Moreover, the famine effects did not differ between individuals who were moderately exposed and those who were severely exposed, nor between women and men. The second empirical study, "*Long Arm of Prenatal Exposure to the 1944-1945 Dutch Hunger Winter into Later-Life Biological Aging*," investigated the link between in-utero exposure to the Dutch Hunger Winter of 1944-1945 and biological aging in older age. This study tested both the between-family and within-family effects of famine on biological aging, revealing that individuals exposed to famine for a longer period of time had a faster pace of biological aging (but not a different biological age) compared to those exposed for a shorter period of time. Moreover, the effects of famine were consistently larger for women, while being virtually negligible for men. Furthermore, there was no timing-specificity for famine exposure in predicting biological age and aging. Taken together, the findings of these two papers highlight the importance of studying the long-term effects of early-life exposure to famine on later-life health from a life course perspective.

The next two empirical studies, *"Evolution of the Income–Health Gradient over the Later Life Course: Longitudinal Evidence from the U.S. (1992-2016)"* and *"Evolution of the Income–Health Gradient over the Later Life Course: Longitudinal Evidence from 19 European Countries (2004-2019) and China (2011-2018),*" investigated changes in the income–health gradient in the later life course in the U.S., Europe, and China, respectively. Both studies used an advanced analytical technique to disentangle the within-participant effects of aging from the between-participant effects of age. Findings across the U.S., Europe, and China were generally consistent, showing that the income–health gradient in physical health (e.g., multimorbidity, disability) weakened as individuals age, whereas the income–health gradient in cognitive

health (e.g., memory) strengthened with aging. The within-participant age-as-leveler effects of income on physical health observed in the U.S. were not observed in Europe and China. In addition, the cumulative advantage/disadvantage of higher/lower income on cognitive health may be more pronounced among women than men in the U.S. (not tested in Europe and China). Taken together, the findings of these two papers highlight the importance of considering the multidimensional nature of health to understand how the gradient evolves over the later life course.

6.2 Research Contribution

6.2.1 Studying Health from a Life Course Perspective (Chapters 2, 3, 4 and 5)

Health is a dynamic process and evolves over time. Chapters 2, 3, 4 and 5 of this thesis contribute to the understanding of health from a life course perspective by conceptualizing health as an evolving process and focusing on the temporal aspect.

Chapters 2 and 3 focused on two historical events, namely, the Chinese famine of 1959-1961 and the Dutch Hunger Winter of 1944-1945, and how early-life exposure to these famines was associated with health six decades later. Chapters 4 and 5 focused on how income was associated with health trajectory over the later life course. Empirical findings in Chapters 2 and 3 consistently showed that early-life exposure to famine had long-term effects on health in later life. Empirical findings in Chapters 4 and 5 consistently showed that over the later-life course, the protective effects of higher income on physical health faded away, but that these effects on cognitive health strengthened.

These findings have advanced our understanding of health from a life course perspective. Health is a lifelong process, during which various life course periods play a role in shaping individual health (Halfon et al., 2014; Kuh et al., 2003). Early-life exposure to historical events exerts not only short-term impacts on the health of a given cohort during

specific periods, but also long-term impacts on health decades later (Valentina & Lauren, 2023). In addition to exposure in formative years, exposure in later life can also impact health over time (Marden et al., 2017). Furthermore, effects of an exposure can differ in magnitude across different countries and regions (Faul et al., 2021). Taken together, these findings highlight the importance of studying health from a life course perspective. More studies are needed to investigate socioeconomic determinants of health trajectories over the later life course.

6.2.2 Treating Health as a Multidimensional Construct (Chapters 3, 4 and 5)

Health is a complex construct, with different mechanisms underlying different aspects. Chapters 3, 4 and 5 of this thesis contribute to the understanding of health by conceptualizing it from a multidimensional perspective.

Chapter 3 focused on the epigenetic aspect of health, while Chapters 4 and 5 focused on the physical and cognitive aspects of health. Empirical findings in Chapter 3 showed that in-utero famine exposure was associated with an accelerated pace of biological aging, while empirical findings in Chapters 4 and 5 consistently showed that the protective role of higher income weakened with older age in physical health, whereas this protective role of higher income strengthened with older age in cognitive health.

These findings have advanced our evolving understanding of health as a multifaceted entity. Health has multiple dimension and each dimension is influenced by distinct mechanisms (Galobardes et al., 2007; Hjelm, 2010). On the one hand, epigenetic health and physical health are deeply rooted in biology (Rivero-Segura et al., 2020). As individuals age, changes in physiological structures and processes play a predominant role in determining biological aging and physical health. That is to say, older adults with differential SES backgrounds are likely to experience physiological deterioration in later life. Moreover, older adults with higher SES are able to maintain good health until a certain age and their period of morbidity is compressed into advanced age, after which they are likely to experience a decline in physiological health.

On the other hand, cognitive health is more socially grounded (Jefferson et al., 2011). Over the life course of an individual, social interactions and cognitively stimulating experiences become increasingly important for cognitive health. Individuals with higher SES are more likely to be exposed to cognitively stimulating environments and activities whereas individuals with lower SES are more likely to accumulate risks of poor cognitive environments and experiences in the form of multiple exposures or chains of risks. As a result, compared with their lower-SES counterparts, individuals with higher SES have more cognitive reserves over time. Taken together, these findings highlight the necessity to treat health as a multidimensional construct and to take a holistic approach to understanding health. More studies are needed to shed light on various aspects of health and explore pathways through which an exposure is linked to specific aspects of health.

6.2.3 Considering Cross-Cultural Similarities and Differences (Chapters 2, 3, 4 and 5)

The course of individual life trajectories is embedded in particular socioeconomic and cultural contexts and reflects cultural, economic, and social conditions. Chapters 2, 3, 4 and 5 of this thesis contribute to the understanding of health in cross-cultural settings by investigating cross-cultural similarities and differences in shaping individual health in later life.

Chapters 2 and 3 focused on two famines, one in China and the other in the Netherlands, and their impacts on later-life health. Chapters 4 and 5 focused on the evolution of the income–health gradient in the U.S., 19 European countries, and China. Findings from the first line of inquiry (i.e., Chapters 2 and 3) and the second line of inquiry (i.e., Chapters 4 and 5) were generally consistent. Specifically, Chapters 2 and 3 showed that exposure to famine was associated with poor health in later life among individuals exposed to the Chinese famine of 1959-1961 and the Dutch Hunger Winter of 1944-1945, respectively. Chapters 4 and 5 showed that the income health–gradient weakened for physical health, but strengthened for cognitive health among older adults in the U.S., Europe, and China. These consistent findings across

cultural contexts have advanced our understanding of cross-cultural similarities in aging and health. Despite different levels of socioeconomic development across societies, the role of socioeconomic determinants in predicting later-life health may generalize across Western and non-Western countries (Chi, 2011). One step further would be to move beyond a culturally-specific understanding of observed patterns and gain understandings that apply to a wide range of cultures and societies.

While the findings across the chapters were consistent, it is important to acknowledge important contextual differences among the populations and events studied when interpreting the findings. Some findings were different across different contexts. Specifically, Chapter 2 revealed an effect of timing of famine exposure but no difference in the famine effect between women and men, whereas Chapter 3 revealed no effect of timing-specificity but a larger famine effect among women than men. Chapters 4 and 5 revealed that the turning point at which the protective effect of higher income appears to diminish was at an older age in the U.S. and Europe than in China. To better understand such differences in findings across contexts, we need to pay attention to the specific contexts studied. Chapters 2 and 3 focused on different contexts: The Chinese famine occurred as a result of natural disasters and policies, affected the whole country, and food availability recovered only slowly after the famine; and the Dutch Hunger Winter occurred as a result of German occupation, affected only the Western part of the country, and food availability recovered immediately after the famine. Chapters 4 and 5 focused on developed countries like the U.S. and European countries and less developed countries like China. Differences among these countries could explain the different turning points observed in these two chapters that the protective effect of higher income appears to diminish at an older age in the U.S. and Europe, but at a younger age in China. These findings have advanced our understanding of cross-cultural differences in aging and health. National contexts like the level of socioeconomic development and policies play a role in shaping

individual trajectories of aging and health (Sieber et al., 2020). The way in which age, gender, race, SES, and sociocultural contexts interact with the life domains vary across societies (Heinz & Krüger, 2001). Therefore, later-life health should be interpreted in a context-sensitive way (Fung & Jiang, 2016).

Taken together, these findings highlight the importance of considering cross-cultural similarities and differences and taking a comparative approach to understand aging and health. More studies are needed to provide insights into the socioeconomic determinants and the evolution of health among older adults in different countries, particularly non-Western countries.

6.3 Societal Implications

6.3.1 Implication from the First Line of Inquiry

The first line of inquiry showed that early-life adversity in the context of historical events had not only an immediate impact but also a long-term impact on health. Individuals exposed to early-life adversity were at a higher risk of developing health conditions and experiencing an accelerated pace of aging, particularly those exposed during the developmental time window and exposed for a long duration.

The implication is that just as the timing of exposure to early-life famine conditions matters, so should the timing of intervention. Early life is a vital phase of life for development and growth later in life (Hallqvist et al., 2004; Lynch & Smith, 2005). The current focus of nutrition intervention policies and programs on early life has been justified by improvements in health outcomes in the short term. For instance, investments and intervention in nutrition has contributed to a global decline in stunting (low height-for-age ratio) in the past three decades, during which the prevalence of stunting in children aged under 5 years declined from 39.2% in 1990 to 21.9% in 2018 (World Health Organization, 2019b). However, it is important

to recognize that the developmental time window can remain open beyond early life (Safi-Stibler & Gabory, 2020). Optimal nutrition in early life is also beneficial for health outcomes in the long term. For example, randomized controlled trials have shown that nutrition intervention in the form of dietary counseling was associated with lower glucose and cholesterol and reduced risk of metabolic syndrome in the long term (He & Stein, 2021). Health intervention policies and programs need to pay attention to the period of life in which the time window for development and growth is still open. A life course approach can contribute to ensuring optimal nutrition at these stages of an individual's life and improve health and well-being in the long run (World Health Organization, 2019a). As suggested by findings in this thesis, nutrition interventions focused on early life can have not only immediate positive impacts but also long-term effects.

6.3.2 Implication from the Second Line of Inquiry

The second line of inquiry showed that income-related disparities in health persisted over the later life course. Health disparities between the rich and the poor narrowed (but remained significant) in the physical health domain, but widened in the cognitive health domain over time.

The implication is that income is an important determinant of later-life health. Individuals with lower income are at an increased risk of health conditions in later life (Carr, 2019). Economic policies focused on poverty reduction and a more equal distribution of income can help to improve the health and well-being of individuals. Recently, several countries and cities within Europe and North America, such as the Netherlands and Canada have started experiments on universal basic income. These experiments have shown potential for providing income security and addressing health inequalities in later life (Haagh & Rohregger, 2019). In addition, social policies like equal access to healthcare, quality educational resources, and social cohesion can build a safety net for individuals with lower

income. For example, in 2022 Finland has finalized its largest-ever social and healthcare reform, aiming to guarantee equal access to health and social services and to reduce inequalities in health and well-being (Kangas & Kalliomaa-Puha, 2022). Such economic and social policies may further benefit the evolution of later-life health among individuals.

6.4 Strengths, Limitations, and Future Directions

This thesis applied various advanced analytical tools to high-quality data to investigate how socioeconomic determinants impacted health in later life from a life course perspective. Herein, I discussed the theoretical and methodological strengths and limitations of the four empirical studies included in this thesis, and provided directions for future research.

6.4.1 Theoretical and Methodological Strengths

6.4.1.1 Theoretical Strengths

A key theoretical strength of this thesis is that it examined later-life health in the context of both the broader history of a society and the personal history of an individual. The first two empirical studies focused on two historical events, namely, the Chinese famine of 1959-1961 and the Dutch Hunger Winter of 1944-1945, and how they impacted on health in later life about six decades later. The next two empirical studies focused on how individual income was linked to health over the later life course of an individual. Historical circumstances and individual life trajectories combined to provide a complete picture of how the later-life health of an individual was shaped over time. Taken together, this thesis has advanced our understanding of later-life health through the lens of historical contexts and individual life course and provided insights into aging studies.

The second theoretical strength of this thesis is that it examined later-life health from a life course perspective. The four empirical studies treated aging and health as lifelong processes and investigated health trajectories in the context of time and place. The first two empirical

studies focused on early-life adversity, operationalized as famine exposure, and its impact on the later-life health trajectories of an individual in China and the Netherlands. The next two empirical studies focused on the evolution of the income–health gradient over the later life course of an individual in the U.S., Europe, and China. A life course perspective provided a comprehensive and dynamic framework for studying later-life health trajectories and understanding the complexity of aging process. Taken together, this thesis has advanced our understanding of the foundations of the life course perspective such as life-span development, time and place, and timing and extended its application in aging studies.

6.4.1.2 Methodological Strengths

The first methodological strength of this thesis is that it used large-scale longitudinal datasets. The sample size in the first three empirical studies ranged from 10,067 to 73,407 older adults. The follow-up span in the first, third, and fourth empirical studies ranged from 8 to 25 years and dated back to as early as 1992. Large sample sizes and long follow-up periods provided strong statistical power to capture the trajectories and dynamics of health over the later life course of an individual. For example, the within-participant age-as-leveler effect of income on multimorbidity observed in the first empirical study which had a longer follow-up period (U.S., 1992-2016) was not observed in the second empirical study which had a short follow-up period (Europe, 2004-2019; China, 2011-2018). This means that a large number of waves in the dataset can help to observe small-size longitudinal changes.

Another methodological strength of this thesis is that it used advanced analytical tools. The first, third, and fourth empirical studies used Poisson growth curve modeling. Among them, the third and fourth studies further disentangled the within-participant effects from the between-participant effects. The second empirical study used generalized estimating equation modeling and sibling-fixed-effects modeling. It further disentangled the within-family effects from the between-family effects. Advanced analytical tools enabled me to test life course

models and analyze the complex nature of the link between socioeconomic determinants and health trajectories. For example, the effects of exposure to the Dutch Hunger Winter were halved when comparing famine-exposed participants and their unexposed siblings within a family. This corroborates the findings that in-utero famine exposure accelerated biological aging.

Lastly, a further methodological strength of this thesis is that it used datasets from various countries. It used data from the U.S., European countries, and China. Data from different countries made it possible to position the findings on socioeconomic determinants and evolution of health with older age across countries and settings. For example, the last two empirical studies observed consistent patterns that age-as-leveler applied to physical health and cumulative advantage/disadvantage applied to cognitive health across the U.S., China, and 19 European countries. This helps to understand the protective role of income in health in later life across different cultures and societies.

6.4.2 Theoretical and Methodological Limitations and Future Directions

6.4.2.1 Theoretical Limitations and Future Directions

The first theoretical limitation of this thesis is that although it was conducted in cross-cultural settings such as China, the U.S., and European countries, it did not include low- and middle-income countries such as African countries. Context, level of socioeconomic development, and culture in a given society can significantly influence later-life health of an individual (Liang & Luo, 2012). Compared with high-income countries, low- and middle-income countries often face greater levels of poverty, provide limited access to healthcare and social service, and confront more environmental risks, which are detrimental for later-life health. Different cultural norms and practices can have distinct perspectives on aging, well-being of older adults, and the roles and expectations of older adults within family and society.

Therefore, it is important to enhance the diversity of cross-cultural settings and include low- and middle-income countries in future aging research.

Another theoretical limitation of this thesis is that it did not examine how the later-life health of an individual was shaped by contextual-level socioeconomic factors in a given society. Individual trajectories of aging and health are shaped by a complex interplay of individual-level socioeconomic factors and contextual-level socioeconomic factors such as income inequality, neighborhood characteristics, and educational opportunities. Contextual-level socioeconomic factors can either amplify or buffer the impact of individual-level socioeconomic factors on later-life health (Adler & Stewart, 2010). Individuals with lower socioeconomic status living in a society where economic disparities are wide, crime rates are high, and access to quality education and lifelong learning opportunities are limited, are more likely to have worse later-life health outcomes than their counterparts living in more favorable environments. On the contrary, a society that is more equal, safe, and enhances equal educational opportunities can help to mitigate the detrimental impact of lower socioeconomic status on later-life health of an individual. Therefore, exploring the moderating role of contextual-level socioeconomic factors could be an exciting avenue for future aging research, especially with a broad cross-national approach. With widening economic disparities worldwide, it is important to advance our understanding of how contextual-level socioeconomic factors like income inequality at regional/national level, poverty rates, and the socio-demographic index affect individual health trajectories over the later life course.

6.4.2.2 Methodological Limitations and Future Directions

The first methodological limitation of this thesis is that information on some variables in the datasets was collected retrospectively. Retrospective data can be useful and provide rich information for analysis, particularly information on early-life experiences. For example, the CHARLS life history data collected in 2014 provides a valuable opportunity to study the effects

of exposure to the Chinese famine of 1959-1961 on health six decades later. But we need to keep in mind that retrospective data is subject to recall bias. Recall bias can be a significant concern in surveys that rely on participants' ability to accurately recall what happened in the past (Talari & Goyal, 2020). When participants are asked to recall past events, they might not be able to provide accurate or complete information of an exposure/outcome, which can lead to distorted or inaccurate research results. However, studies have shown that interview-based procedures for collecting retrospective information have acceptable levels of test-retest reliability and validity (Monroe & Slavich, 2019).

The second methodological limitation of this thesis is that the number of waves in some of the datasets was limited. There were six waves of data in SHARE and four waves of data in CHARLS available when this thesis was conducted. A limited number of data waves presented a significant challenge in detecting subtle and small-size longitudinal changes (Garcia & Marder, 2017), as shown in the third and fourth empirical studies. It reminds us to interpret cross-sectional associations and longitudinal changes more cautiously in such contexts. When the number of data waves is limited, it is possible that the observed cross-sectional results cannot be replicated with relatively short longitudinal data.

The next methodological limitation of this thesis is that it was subject to selection effects. Both longitudinal and cross-sectional data face the challenge of selection effects (Munafò et al., 2017). Older participants in these surveys tended to be the healthy survivors of their cohort, compared with individuals who died prematurely or were unable to participate due to health conditions. This may result in a convergence of health status among older participants, which can affect the interpretation of estimates. We need to bear in mind that the existence of selection effects can lead to an underestimation of the strength of associations observed between exposure and outcome. In the case of the Chinese famine of 1959-1961, the birth rate declined from 29.22 births per 1,000 persons in 1958 to 18.02 births per 1,000 persons

in 1961 (National Bureau of Statistics of China, 1983). In the case of the Dutch famine of 1944-1945, the reduction in fertility was greater among individuals with manual occupation than those with non-manual occupation (Stein & Susser, 1975). The decrease in birth rate during the famine years indicates that famine had a fertility-inhibiting effect and could induce a certain level of selection bias. That is to say, only the most robust babies survived the in-utero famine conditions to be born and/or couples with higher SES were more likely to retain fertility during the famine. This reminds us that the observed famine effects on health in later life might be underestimated and that the actual health effects of famine may be larger than the estimates.

A further limitation of this thesis is that the interpretation of the interaction effect could be more nuanced. The interaction effect is of interest in three empirical chapters in this thesis which used Poisson growth curve modeling. Although it is a typical practice to evaluate the interaction effect in linear models using the product term coefficient, the interaction effect in generalized linear models for counts data does not equate to the product term between predictor variables (McCabe et al., 2022). As such, the interaction effect cannot always be reliably inferred from the direction, magnitude, or statistical significance of the coefficient on the product term in nonlinear models. This is because the sign of the coefficient on the product term can be different for different observations in the sample and the magnitude of the interaction effect depends on the covariates included in the model. Instead, a more nuanced interpretation of the interaction effect needs to evaluate the cross difference (Ai & Norton, 2003). The computation of the cross difference can be facilitated by a recently available R-based software package modglm (McCabe et al., 2021). For example, in the chapter on the Chinese famine of 1959-1961 and non-communicable diseases, using the cross difference to assess the interaction effect between famine exposure and life stage in the Poisson growth curve modeling revealed that the interaction effect was significant across the observed data (interaction point estimates=-0.05, ranging from -0.15 to -0.03) and that the effect of famine

exposure on the risk of non-communicable diseases in later life was mitigated by the age at exposure, in line with the results from the concatenation approach. This highlights the need to evaluate the cross difference when interpreting the interaction effect in nonlinear models.

The last methodological limitation of this thesis is that findings cannot be generalized to countries where high-quality data is unavailable. This thesis used data from countries that have an established infrastructure for collecting and sharing high-quality data like the U.S., European countries, and China. Regrettably, the availability of high-quality data marks a notable gap in the research landscape for developed countries and less developed countries (Kämpfen et al., 2018). Such data is not yet available from many low- and middle-income countries where resources are limited or data quality is limited in terms of accuracy, coverage, or representativeness. The growing recognition of the importance of data in research, policy, and intervention has been prompting more countries, even those with limited resources, to prioritize high-quality data collection. Future studies would benefit from including low- and middle-income countries. High-quality data from countries like India (the Longitudinal Ageing Study in India [LASI], one wave in 2017/2018), Mexico (the Mexican Health and Aging Study [MHAS], six waves spanning 2001-2021), and South Africa ([Health and Aging in Africa], three waves spanning 2015-2022) will make it possible to understand how different contexts influence later-life health and how life course models generalize across different cultural settings.

6.5 Conclusion

Aging and health is a lifelong process. Various life course periods, from early life to older age, can impact on later-life health. An exposure may affect health outcomes differently depending on when it occurs in the life course. In this lifelong process, historical contexts and individual life history combine to shape health trajectories over time. Socioeconomic

determinants can exert lasting and cumulative effects on later-life health of an individual. In addition, health is a multidimensional concept, with differential mechanisms underlying different dimensions. Physical health may be more biologically grounded whereas cognitive health may be more socioeconomically grounded. Lastly, aging and health is underpinned by socioeconomic and cultural contexts across countries and societies. Cross-cultural similarities and differences are essential to understand how the health trajectory of an individual is shaped in a given society. A life course perspective can help policies and intervention programs targeted on socioeconomically disadvantaged individuals to reduce the socioeconomic gap in health in older age.

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8. Supplementary Materials

Appendix A

Text A.1. Categorization of Life Stages based on Erikson's Developmental Stages

We assigned (1) participants born in 1959 to "the fetal stage (newborn)", (2) participants born in 1958 to "the infancy stage (1 year)", (3) participants born between 1956 and 1957 to "the early childhood stage (2-3 years)", (4) participants born between 1954 and 1955 to "the preschool stage (4-5 years)", (5) participants born between 1948 and 1953 to "the school age stage (6-11 years)", (6) participants born between 1941 and 1947 to "the adolescence stage (12-18 years)", and (7) participants born between 1919 and 1940 to "the young adulthood stage (19-40 years)".

Table A.1. Associations between Exposure to the 1959-1961 Chinese Famine, Life Stage, and Later-Life Non-Communicable Diseases (Based on Life Stages Commonly Used in Major Global Policies and Strategies)

	1959.01.01 as reference date		1960.01.01 as reference date		1961.01.01 as reference date	
	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI
Unexposed (control group)	1.00	Reference	1.00	Reference	1.00	Reference
Exposed in-utero	1.90***	1.70–2.12	2.00***	1.76–2.27	2.03***	1.83–2.25
Exposed in "first 1,000 days" (0-2 years)[1]	1.86*** (1.95***)	1.73–2.00 (1.67–2.29)	1.77*** (1.80***)	1.63–1.91 (1.56–2.07)	1.83*** (2.13***)	1.68–1.99 (1.79–2.54)
Exposed in pre-school age (3-5 years)	1.56***	1.47–1.66	1.61***	1.51–1.72	1.64***	1.54–1.76
Exposed in primary school age (6-9 years)	1.45***	1.37–1.54	1.44***	1.36–1.52	1.41***	1.34–1.49
Exposed in adolescence (10-18 years)	1.08**	1.03–1.14	1.12***	1.07–1.18	1.14***	1.09–1.20
Exposed in young adulthood (19-23 years)	0.66***	0.61–0.71	0.72***	0.67–0.77	0.75***	0.70–0.80
Exposed in adulthood (24-40 years)	0.40***	0.37–0.44	0.42***	0.38–0.45	0.43***	0.40–0.46
Number of participants	11,094		11,361		11,823	
Number of observations	39,337		40,297		41,926	

Note. IRRs = Incidence Rate Ratios. *p< .05, **p< .01, ***p< .001

Adjusted for age, sex, later-life residence, marital status, current working status, childhood family financial status, education, household income, number of diseases in childhood, and number of diseases in adulthood.

[1] Numbers in parentheses refer to the IRRs and 95% CI for participants exposed in the 0-6 months.

Table A.2. Associations between Exposure to the 1959-1961 Chinese Famine, Life stage, and Later-Life Non-Communicable Diseases (Based on Erikson's Developmental Stages)

	1959.01.01 as reference date		1960.01.01 as reference date		1961.01.01 as reference date	
	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI
Unexposed (control group)	1.00	Reference	1.00	Reference	1.00	Reference
Exposed at the fetal stage (newborn)	1.86***	1.64–2.12	1.77***	1.56–2.01	2.02***	1.76–2.31
Exposed at the infancy stage (1 year)	1.73***	1.56–1.92	1.78***	1.58–2.00	1.73***	1.55–1.94
Exposed at the early childhood stage (2-3 years)	1.72***	1.60–1.86	1.74***	1.61–1.88	1.65***	1.52–1.79
Exposed at the preschool stage (4-5 years)	1.51***	1.41–1.61	1.49***	1.39–1.60	1.60***	1.49–1.73
Exposed at the school age stage (6-11 years)	1.37***	1.30–1.45	1.38***	1.31–1.45	1.37***	1.30–1.44
Exposed at the adolescence stage (12-18 years)	1.03	0.97–1.09	1.06*	1.01–1.12	1.08**	1.03–1.14
Exposed at the young adulthood stage (19-40 years)	0.55***	0.51–0.58	0.58***	0.54–0.62	0.60***	0.57–0.64
Number of participants	10,855		11,193		11,532	
Number of observations	38,495		39,701		40,891	

Note. IRRs = Incidence Rate Ratios. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Adjusted for age, sex, later-life residence, marital status, current working status, childhood family financial status, education, household income, number of diseases in childhood, and number of diseases in adulthood.

Table A.3. Associations between Severity of Exposure to the 1959-1961 Chinese Famine and Later-Life Non-Communicable Diseases

	IRRs	95% CI
Moderate famine exposure	1.18***	1.09–1.28
Severe famine exposure	1.24***	1.17–1.32
Age	1.99***	1.91–2.08
Sex (-0.5 = *male*, +0.5 = *female*)	1.16***	1.10–1.22
Later-life residence	0.90***	0.85–0.95
Marital status	1.02	0.97–1.08
Current working status	0.91***	0.88–0.94
Childhood family financial status	1.01	0.99–1.04
Upper secondary or vocational education	1.05	0.94–1.17
Tertiary education	1.13	0.91–1.40
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	1.00	0.99–1.01
Number of diseases in childhood	1.12**	1.04–1.20
Number of diseases in adulthood	1.24***	1.19–1.28
Number of participants	4,082	
Number of observations	14,471	

Note. IRRs = Incidence Rate Ratios. *p< .05, **p< .01, ***p< .001

Table A.4. Sex-Specific Associations between Exposure to the 1959-1961 Chinese Famine and Later-Life Non-Communicable Diseases

	IRRs	95% CI
Famine exposure	1.14***	1.09–1.19
Sex (-0.5 = *male*, +0.5 = *female*)	1.17***	1.08–1.27
Famine exposure * Sex	0.98	0.90–1.07
Age	1.99***	1.94–2.04
Later-life residence	0.93***	0.90–0.97
Current marital status	1.03*	1.01–1.07
Current working status	0.91***	0.89–0.93
Childhood family financial status	1.04***	1.02–1.05
Upper secondary or vocational education	1.00	0.94–1.06
Tertiary education	1.12	0.97–1.29
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	1.00	0.99–1.00
Number of diseases in childhood	1.13***	1.08–1.19
Number of diseases in adulthood	1.23***	1.20–1.25
Number of participants	11,094	
Number of observations	39,337	

Note. IRRs = Incidence Rate Ratios. *$p < .05$, **$p < .01$, ***$p < .001$

Table A.5. Age of NCDs Onset among Participants Exposed to the 1959-1961 Chinese Famine at Different Life Stage

	Mean age of NCDs onset
In-utero	40.0 (*SD* = 12.5)
The "first 1,000 days" (0-2 years)	42.4 (*SD* = 13.0)
Pre-school (3-5 years)	44.0 (*SD* = 13.4)
Primary school (6-9 years)	45.7 (*SD* = 15.0)
Adolescence (10-18 years)	49.7 (*SD* = 16.5)
Young adulthood (19-23 years)	56.0 (*SD* = 18.1)
Adulthood (24-40 years)	62.2 (*SD* = 18.6)

Table A.6. Associations between Severity of the 1959-1961 Chinese Famine and Later-Life Non-Communicable Diseases

	IRRs	95% CI
Exposed in moderately affected areas	1.20***	1.14–1.26
Exposed in severely affected areas	1.11***	1.06–1.17
Age	1.99***	1.94–2.05
Sex (-0.5 = *male*, +0.5 = *female*)	1.16***	1.12–1.20
Later-life residence	0.93***	0.90–0.97
Marital status	1.03	1.00–1.07
Current working status	0.91***	0.89–0.93
Childhood family financial status	1.03***	1.02–1.05
Upper secondary or vocational education	1.00	0.94–1.07
Tertiary education	1.13	0.98–1.30
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	1.00	0.99–1.00
Number of diseases in childhood	1.14***	1.09–1.20
Number of diseases in adulthood	1.22***	1.20–1.25
Number of participants	10,840	
Number of observations	38,420	

Note. IRRs = Incidence Rate Ratios. *p< .05, **p< .01, ***p< .001

Appendix B

Text B.1. Supplementary Methods

DNA methylation data

DNA methylation (DNAm) was measured using the Illumina Infinium Human Methylation 450k BeadChip and preprocessed as previously described (Tobi et al., 2018; Tobi et al., 2015). Briefly, samples were randomly distributed, ensuring similar distributions of exposure periods, sex ratios, and mean ages per 96-well plate and 450k array, keeping sibling pairs together, but were randomly assigned to either the left or right column of the 450k array. We assessed data quality using both sample-dependent and sample- independent quality metrics using the R package MethylAid (van Iterson et al., 2014). Bisulfite conversion efficiency was assessed using the dedicated 450k probes and sequencing the IGF2 DMR0 of a random set of samples. We remeasured a subset of the genotypes measured on the 450k array with MassARRAY and checked the gender of samples using all X-chromosomal CpGs to exclude sample swaps. We used noob and Functional Normalization as implemented in the minfi package (Aryee et al., 2014) using six principal components to normalize for batch effects, dye-color intensity differences, and background signal. Individual measurements with detection P-values >0.01 or zero-intensity values in one of the used color channels were set as missing. The measurement success rate per sample was >99%. Next, we removed a-specific/polymorphic and non-autosomal probes, probes with <95% success rate, and those probes that were completely methylated or unmethylated in all major cell types in whole blood. Methylation percentages in text, figures, and tables reflect microarray b-value estimates (which range from close to zero to close to one or 0 to 100%, as denoted throughout).

DNAm clocks and pace-of-aging measures

DNAm clocks are algorithms that combine information from DNAm measurements across the genome to quantify variation in biological age (Horvath & Raj, 2018).

The first-generation DNAm clocks were developed from machine-learning analyses comparing samples from individuals of different chronological age. These clocks were highly accurate in predicting the chronological age of new samples and also showed some capacity for predicting differences in mortality risk, although effect-sizes tend to be small and inconsistent across studies (Chen et al., 2016; Hannum et al., 2013; Horvath, 2013). We include in the **Supplementary Materials, Table B.3 and Table B.5** results for the first-generation clocks proposed by Horvath et al. (Horvath clock; Skin & Blood clock) and Hannum et al. (Hannum clock) (Hannum et al., 2013; Horvath, 2013; Horvath & Raj, 2018).

The second-generation DNAm clocks were developed with the goal of improving quantification of biological aging by focusing on differences in mortality risk instead of on differences in chronological age (Levine et al., 2018; Lu et al., 2019; Zhang et al., 2017). These clocks also include an intermediate step in which DNAm data are fitted to physiological parameters. The second-generation clocks are more predictive of morbidity and mortality as compared with the first-generation clocks (Levine, 2020) and are proposed to have improved potential for testing impacts of interventions to slow aging (Fahy et al., 2019). We analyzed the second-generation clocks proposed by Zhang et al. (Zhang clock), Lu et al. (GrimAge clock), and Levine et al. (PhenoAge clock) (Levine et al., 2018; Lu et al., 2019; Zhang et al., 2017).

First- and second-generation epigenetic clock values have high correlations with chronological age. For analysis and interpretation, the standard approach is to regress clock values on participants' chronological age values and predict residual values. These values, often referred to as "age acceleration residuals", aim to quantify the difference between how much aging a person has actually experienced relative to the expectation based on their chronological age. A limitation of several DNAm clocks is that these age-acceleration residuals show only moderate test–retest reliability across technical replicates (Higgins-Chen et al.,

2022; Sugden et al., 2020). To improve technical reliability, Higgins-Chen and colleagues developed a new computational method that retrained DNAm clocks using principal components computed from the DNAm data (Higgins-Chen et al., 2022). The resulting 'PC clocks' demonstrate exceptional test–retest reliability across technical replicates. Main-text analysis reports results for the PC versions of the GrimAge and PhenoAge clocks. Results for original and PC versions of the clocks are reported in the **Supplementary Materials, Table B.3 and Table B.5**.

A third generation of DNAm clocks measure pace of aging. In contrast to first- and second-generation DNAm clocks, which aim to quantify how much aging has occurred up to the time of measurement, pace-of-aging clocks aim to quantity how fast the process of aging-related deterioration of system integrity is proceeding (Belsky et al., 2015). We analyzed the newest pace-of-aging measure, DunedinPACE, which is shorthand for "Pace of Aging Computed from the Epigenome" (Belsky et al., 2022). DunedinPACE was developed by modeling within-individual multi-system physiological change across four timepoints in the Dunedin Study 1972–1973 birth cohort. Measurements were taken when participants were aged 26, 32, 38 and 45 years. DunedinPACE was developed from analysis of a pace-of-aging composite of slopes of aging-related change measured across this four-timepoint interval in the following measurements: ApoB100/ApoA1 ratio, BMI, blood urea nitrogen, high-sensitivity C-reactive protein, cardiorespiratory fitness, dental caries experience, total cholesterol, forced expiratory volume in 1 second, forced expiratory volume in 1 second/fixed vital capacity ratio, estimated glomerular filtration rate, hemoglobin A1C, high-density lipoprotein cholesterol, leptin, lipoprotein(a), mean arterial pressure, mean periodontal attachment loss, triglycerides, waist-to-hip ratio and white blood cell count. The DunedinPACE DNAm algorithm was derived from elastic net regression of the pace-of-aging composite on Illumina EPIC array DNAm data derived from blood samples collected at the age 45 measurement occasion. The

set of CpG sites included in the DNAm dataset used to develop the DunedinPACE algorithm was restricted to those showing acceptable test–retest reliability as determined by Sugden et al. (Sugden et al., 2020).

Table B.1. Comparison of Characteristics between DHWFS Analysis Sample and Telephone Sample. The table compares characteristics of the analysis sample and telephone sample overall (left column) and the famine-exposed and control groups (middle and right columns).

Panel I: DHWFS sample (N=951)								
	DHWFS		**Famine-exposed**		**Controls**			
					Time controls		**Sibling controls**	
	(N=951)		(N=487)		(N=159)		(N=305)	
	Mean/ %	(SD)	Mean/ %	(SD)	Mean/ %	(SD)	Mean/ %	(SD)
Age (years)	58	(4)	59	(1)	59	(2)	57	(6)
Men (%)	45%		47%		45%		42%	
Duration of exposure (weeks)			17	(7)				
DunedinPACE	0.97	(0.11)	0.97	(0.11)	0.95	(0.11)	0.97	(0.11)
PC GrimAge	69.92	(5.03)	70.42	(4.20)	70.18	(4.60)	68.98	(6.20)
PC PhenoAge	50.18	(5.87)	50.61	(5.18)	50.61	(5.10)	49.27	(7.07)

Panel II: Telephone sample (N=1,031)								
	Telephone sample		**Famine-exposed**		**Controls**			
					Time controls		**Sibling controls**	
	(N=1,031)		(N=547)		(N=176)		(N=308)	
	Mean/ %	(SD)	Mean/ %	(SD)	Mean/ %	(SD)	Mean/ %	(SD)
Age (years)	58	(4)	59	(1)	59	(2)	57	(6)
Men (%)	45%		47%		46%		42%	
Duration of exposure (weeks)			17	(7)				

Table B.2. Effect-Sizes for Associations of In-Utero Famine Exposure with Epigenetic-Clock Measures of the Pace of Aging and Biological Age. Panel A of the table reports effect-sizes from generalized estimating equations (GEE) regressions testing associations in the full Dutch Hunger Winter Families Study (DHWFS; **N=951**). Panel B reports effect-sizes from linear regressions testing differences between famine-exposed participants and unexposed time controls (N=646). Panel C reports effect-sizes from sibling-fixed-effects regressions testing differences between famine-exposed participants and their unexposed siblings (N=227 sibling pairs discordant for famine exposure). Results are reported for analysis of three epigenetic clocks: the DunedinPACE clock measures pace of aging; the PC GrimAge and PC Phenoage clocks measure biological age. For PC GrimAge and PC PhenoAge, clock values were residualized on chronological age prior to analysis. Panel A models included covaraites for sex, age, and age-squared. Panel B models included covariate for sex. Panel C models included covariates for age and age-squared (all DHWFS sibling pairs are of the same sex). Coefficients (Beta) and 95% confidence intervals (95% CI) are denominated in standard-deviation units of the outcome variables. Coefficients in each row of the table show results from independent regressions. The first row shows effect-sizes for famine exposure estimated in analyses including all participants in the sample. The second and third rows show effect-sizes for famine exposure estimated in sex-stratified samples (N=521 women and 430 men in Panel A; N=345 women and 301 men in Panel B; N=258 pairs of sisters and 196 pairs of brothers in Panel C). The fourth row reports the p-value for a product term (famine-exposure*sex) in a regression testing the sex differences in famine effect-sizes.

	Panel A. Full DHWFS Analysis			**Panel B. Analysis Restricted to Time Controls**			**Panel C. Sibling Difference Analysis**		
	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
DunedinPACE									
All	0.15	0.03, 0.28	**0.018**	0.20	0.03, 0.37	**0.020**	0.07	-0.13, 0.26	0.509
Women	0.27	0.11, 0.44	**0.001**	0.40	0.18, 0.62	**<0.001**	0.24	-0.02, 0.49	0.072
Men	0.00	-0.19, 0.20	0.962	-0.04	-0.29, 0.21	0.739	-0.13	-0.42, 0.16	0.374
Test of sex difference			**0.031**			**0.009**			**0.002**
PC GrimAge									
All	0.10	-0.02, 0.22	0.099	0.13	-0.04, 0.29	0.131	0.04	-0.15, 0.22	0.708
Women	0.21	0.06, 0.37	**0.007**	0.19	-0.48, 0.86	0.577	0.10	-0.13, 0.34	0.388
Men	-0.04	-0.22, 0.15	0.685	-0.16	-0.41, 0.09	0.205	-0.02	-0.30, 0.25	0.863
Test of sex difference			**0.021**			**<0.001**			**0.038**
PC PhenoAge									
All	0.08	-0.05, 0.20	0.222	0.06	-0.10, 0.23	0.464	0.04	-0.14, 0.22	0.676
Women	0.14	-0.02, 0.30	0.097	0.17	-0.11, 0.44	0.232	0.09	-0.14, 0.32	0.450
Men	0.00	-0.19, 0.18	0.961	-0.06	-0.28, 0.15	0.572	-0.02	-0.31, 0.27	0.909
Test of sex difference			0.441			0.143			0.340

Table B.3. Effect-Sizes for Associations of In-Utero Famine Exposure with Epigenetic-Clock Measures of the Pace of Aging and Biological Age. Panel A of the table reports effect-sizes from generalized estimating equations (GEE) regressions testing associations in the full Dutch Hunger Winter Families Study (DHWFS, **N=951)**. Panel B reports effect-sizes from linear regressions testing differences between famine-exposed participants and unexposed time controls (N=646). Panel C reports effect-sizes from sibling-fixed-effects regressions testing differences between famine-exposed participants and their unexposed siblings (N=227 sibling pairs discordant for famine exposure). Results are reported for analysis of 12 epigenetic clocks: the DunedinPACE clock measures pace of aging; the Horvath, Hannum, Skin & Blood, Zhang, GrimAge, and Phenoage clocks and their PC versions of clocks (except for Zhang clock) measure biological age. For Horvath, Hannum, Skin & Blood, Zhang, GrimAge, and Phenoage clocks and their PC versions of clocks, clock values were residualized on chronological age prior to analysis. Panel A models included covariates for sex, age, and age-squared. Panel B models included covariate for sex. Panel C models included covariates for age and age-squared (all DHWFS sibling pairs are of the same sex). Coefficients (Beta) and 95% confidence intervals (95% CI) are denominated in standard-deviation units of the outcome variables. Coefficients in each row of the table show results from independent regressions. The first row shows effect-sizes for famine exposure estimated in analyses including all participants in the sample. The second and third rows show effect-sizes for famine exposure estimated in sex-stratified samples (N=521 women and 430 men in Panel A, N=345 women and 301 men in Panel B, N=129 pairs of sisters and 98 pairs of brothers in Panel C). The fourth row reports the p-value for a product term (famine-exposure*sex) in a regression testing the sex differences in famine effect-sizes.

	Panel A. Full DHWFS Analysis			Panel B. Analysis Restricted to Time Controls			Panel C. Sibling Difference Analysis		
	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
DunedinPACE									
All	0.15	0.03, 0.28	**0.018**	0.20	0.03, 0.37	**0.020**	0.07	-0.13, 0.26	0.509
Women	0.27	0.11, 0.44	**0.001**	0.40	0.18, 0.62	**<0.001**	0.24	-0.02, 0.49	0.072
Men	0.00	-0.19, 0.20	0.962	-0.04	-0.29, 0.21	0.739	-0.13	-0.42, 0.16	0.374
Test of sex difference			**0.031**			**0.009**			**0.002**
Horvath									
All	0.18	0.05, 0.30	**0.006**	0.16	0.00, 0.33	0.053	-0.02	-0.21, 0.17	0.809
Women	0.11	-0.05, 0.27	0.191	0.05	-0.15, 0.26	0.597	-0.11	-0.35, 0.12	0.349
Men	0.26	0.06, 0.47	**0.011**	0.27	0.03, 0.52	**0.028**	0.10	-0.21, 0.42	0.511
Test of sex difference			0.254			0.132			0.377
PC Horvath									
All	0.13	0.01, 0.26	**0.035**	0.10	-0.07, 0.27	0.235	0.07	-0.10, 0.25	0.409
Women	0.15	-0.01, 0.31	0.071	0.15	-0.09, 0.39	0.234	0.00	-0.23, 0.23	0.992
Men	0.10	-0.09, 0.29	0.290	-0.02	-0.27, 0.22	0.864	0.18	-0.10, 0.46	0.217
Test of sex difference			0.664			0.183			0.420
Hannum									
All	0.03	-0.09, 0.15	0.606	0.00	-0.16, 0.15	0.965	0.07	-0.12, 0.25	0.475
Women	0.04	-0.13, 0.20	0.670	0.06	-0.17, 0.29	0.602	0.05	-0.19, 0.29	0.672
Men	0.02	-0.16, 0.20	0.826	-0.08	-0.29, 0.14	0.476	0.08	-0.21, 0.38	0.569
Test of sex difference			0.996			0.408			0.805
PC Hannum									
All	0.12	0.00, 0.24	0.060	0.09	-0.11, 0.29	0.371	0.14	-0.04, 0.32	0.135
Women	0.18	0.01, 0.34	**0.034**	0.15	-0.11, 0.40	0.257	0.13	-0.10, 0.36	0.281
Men	0.03	-0.15, 0.22	0.708	-0.08	-0.32, 0.15	0.490	0.16	-0.12, 0.44	0.277
Test of sex difference			0.282			0.193			0.829
Skin & Blood									
All	0.00	-0.13, 0.14	0.957	-0.19	-0.73, 0.35	0.496	0.01	-0.18, 0.21	0.902
Women	0.00	-0.17, 0.18	0.957	0.22	-0.06, 0.50	0.124	-0.06	-0.32, 0.19	0.632
Men	0.01	-0.19, 0.21	0.906	0.04	-0.15, 0.24	0.658	0.11	-0.19, 0.41	0.492
Test of sex difference			0.977			0.595			0.183
PC Skin & Blood									
All	0.09	-0.04, 0.21	0.186	0.10	-0.06, 0.27	0.221	0.06	-0.12, 0.24	0.506
Women	0.14	-0.03, 0.30	0.101	0.17	-0.09, 0.43	0.208	0.07	-0.16, 0.29	0.572
Men	0.01	-0.19, 0.21	0.923	-0.03	-0.27, 0.22	0.840	0.06	-0.23, 0.35	0.682
Test of sex difference			0.331			0.149			0.919
Zhang									
All	0.05	-0.08, 0.17	0.440	0.05	-0.19, 0.29	0.675	0.02	-0.16, 0.21	0.799
Women	0.00	-0.16, 0.17	0.969	0.00	-0.23, 0.24	0.976	-0.08	-0.32, 0.17	0.535
Men	0.09	-0.09, 0.28	0.330	0.10	-0.14, 0.33	0.432	0.16	-0.14, 0.46	0.306
Test of sex difference			0.413			0.454			0.201
GrimAge									
All	0.07	-0.05, 0.19	0.274	0.07	-0.09, 0.24	0.385	0.05	-0.14, 0.24	0.589
Women	0.16	0.01, 0.32	**0.042**	0.32	0.09, 0.55	**0.006**	0.12	-0.12, 0.37	0.332
Men	-0.04	-0.24, 0.15	0.654	-0.15	-0.42, 0.12	0.269	0.00	-0.29, 0.28	0.977
Test of sex difference			**0.036**			**0.012**			**0.023**
PC GrimAge									
All	0.10	-0.02, 0.22	0.099	0.13	-0.04, 0.29	0.131	0.04	-0.15, 0.22	0.708
Women	0.21	0.06, 0.37	**0.007**	0.19	-0.48, 0.86	0.577	0.10	-0.13, 0.34	0.388
Men	-0.04	-0.22, 0.15	0.685	-0.16	-0.41, 0.09	0.205	-0.02	-0.30, 0.25	0.863
Test of sex difference			**0.021**			**<0.001**			**0.038**
PhenoAge									
All	0.14	0.02, 0.27	**0.023**	0.06	-0.11, 0.24	0.493	0.02	-0.16, 0.20	0.812
Women	0.17	0.01, 0.34	**0.043**	0.11	-0.13, 0.36	0.371	0.00	-0.24, 0.24	0.991
Men	0.11	-0.07, 0.29	0.237	0.00	-0.24, 0.24	0.980	0.07	-0.21, 0.35	0.633
Test of sex difference			0.817			0.519			0.953
PC PhenoAge									
All	0.08	-0.05, 0.20	0.222	0.06	-0.10, 0.23	0.464	0.04	-0.14, 0.22	0.676
Women	0.14	-0.02, 0.30	0.097	0.17	-0.11, 0.44	0.232	0.09	-0.14, 0.32	0.450
Men	0.00	-0.19, 0.18	0.961	-0.06	-0.28, 0.15	0.572	-0.02	-0.31, 0.27	0.909
Test of sex difference			0.441			0.143			0.340

Table B.4. Effect-Sizes for Dose Response to the Duration of In-Utero Famine Exposure in Epigenetic-Clock Measures of the Pace of Aging and Biological Age. The table reports effect-sizes for generalized estimating equations (GEE) regressions testing dose response in the full Dutch Hunger Winter Families Study (DHWFS; N=951). Results are reported for analysis of three epigenetic clocks: the DunedinPACE clock measures pace of aging; the PC GrimAge and PC Phenoage clocks measure biological age. For PC GrimAge and PC PhenoAge, clock values were residualized on chronological age prior to analysis. The duration of in-utero famine exposure was measured by the number of per-10 weeks that individuals were exposed during gestation. The duration of in-utero famine exposure ranged from 0 to 24 weeks. Models included covaraites for sex, age, and age-squared. Coefficients (Beta) and 95% confidence intervals (95% CI) are denominated in standard-deviation units of the outcome variables. Coefficients in each row of the table show results from independent regressions. The first row shows effect-sizes for duration of famine exposure estimated in analyses including all participants in the sample. The second and third rows show effect-sizes for duration of famine exposure estimated in sex-stratified samples (N=521 women and 430 men). The fourth row reports the p-value for a product term (duration-of-famine-exposure*sex) in a regression testing the sex differences in famine effect-sizes.

	Beta	95% CI	p-value
DunedinPACE			
All	0.08	0.02, 0.14	**0.013**
Women	0.11	0.03, 0.19	**0.007**
Men	0.04	-0.06, 0.14	0.397
Test of sex difference			0.257
PC GrimAge			
All	0.04	-0.02, 0.22	0.242
Women	0.06	-0.02, 0.14	0.119
Men	0.00	-0.09, 0.10	0.953
Test of sex difference			0.231
PC PhenoAge			
All	0.04	-0.02, 0.10	0.160
Women	0.05	-0.03, 0.13	0.237
Men	0.04	-0.06, 0.13	0.449
Test of sex difference			0.957

Table B.5. Effect-Sizes for Dose Response to the Duration of In-Utero Famine Exposure in Epigenetic-Clock Measures of the Pace of Aging and Biological Age. The table reports effect-sizes for generalized estimating equations (GEE) regressions testing dose response in the full Dutch Hunger Winter Families Study (DHWFS, N=951). Results are reported for analysis of 12 epigenetic clocks: the DunedinPACE clock measures pace of aging; the Horvath, Hannum, Skin & Blood, Zhang, GrimAge, and Phenoage clocks and their PC versions of clocks measure biological age. For Horvath, Hannum, Skin & Blood, Zhang, GrimAge, and Phenoage clocks and their PC versions of clocks, clock values were residualized on chronological age prior to analysis. The duration of in-utero famine exposure was measured by the number of per-10 weeks that individuals were exposed during gestation. The duration of in-utero famine exposure ranged from 0 to 24 weeks. Models included covaraites for sex, age, and age-squared. Coefficients (Beta) and 95% confidence intervals (95% CI) are denominated in standard-deviation units of the outcome variables. Coefficients in each row of the table show results from independent regressions. The first row shows effect-sizes for duration of famine exposure estimated in analyses including all participants in the sample. The second and third rows show effect-sizes for duration of famine exposure estimated in sex-stratified samples (N=521 women and 430 men). The fourth row reports the p-value for a product term (duration-of-famine-exposure*sex) in a regression testing the sex differences in famine effect-sizes.

	Beta	95% CI	p-value
DunedinPACE			
All	0.08	0.02, 0.14	**0.013**
Women	0.11	0.03, 0.19	**0.007**
Men	0.04	-0.06, 0.14	0.397
Test of sex difference			0.257
Horvath			
All	0.09	0.03, 0.15	**0.005**
Women	0.04	-0.04, 0.12	0.295
Men	0.15	0.05, 0.25	**0.003**
Test of sex difference			0.101
PC Horvath			
All	0.06	0.00, 0.12	**0.050**
Women	0.06	-0.01, 0.14	0.109
Men	0.05	-0.04, 0.13	0.296
Test of sex difference			0.774
Hannum			
All	0.02	-0.04, 0.08	0.520
Women	0.02	-0.06, 0.09	0.610
Men	0.02	-0.07, 0.11	0.692
Test of sex difference			0.907
PC Hannum			
All	0.05	-0.01, 0.11	0.077
Women	0.07	-0.01, 0.15	0.080
Men	0.03	-0.06, 0.12	0.522
Test of sex difference			0.545
Skin & Blood			
All	0.00	-0.07, 0.06	0.884
Women	0.01	-0.07, 0.09	0.825
Men	-0.02	-0.11, 0.07	0.625
Test of sex difference			0.587
PC Skin & Blood			
All	0.05	0.00, 0.11	0.070
Women	0.07	0.00, 0.15	0.062
Men	0.03	-0.07, 0.12	0.585
Test of sex difference			0.424
Zhang			
All	0.01	-0.05, 0.07	0.776
Women	-0.01	-0.09, 0.07	0.801
Men	0.03	-0.05, 0.12	0.439
Test of sex difference			0.397
GrimAge			
All	0.00	-0.06, 0.06	0.894
Women	0.03	-0.05, 0.10	0.508
Men	-0.02	-0.12, 0.07	0.641
Test of sex difference			0.236
PC GrimAge			
All	0.04	-0.02, 0.10	0.242
Women	0.06	-0.02, 0.14	0.119
Men	0.00	-0.09, 0.10	0.953
Test of sex difference			0.231
PhenoAge			
All	0.08	0.01, 0.14	**0.016**
Women	0.07	-0.01, 0.15	0.108
Men	0.09	-0.01, 0.18	0.071
Test of sex difference			0.642
PC PhenoAge			
All	0.04	-0.02, 0.10	0.160
Women	0.05	-0.03, 0.13	0.237
Men	0.04	-0.06, 0.13	0.449
Test of sex difference			0.957

Table B.6. Effect-Sizes for Associations of Famine Exposure during Each of Six Developmental Time Periods with Epigenetic-Clock Measures of the Pace of Aging and Biological Age. The table reports effect-sizes estimated for famine exposure during six developmental periods. Famine-exposed participants were exposed during up to two periods. Effect-sizes were estimated from a multivariate regression in which indicator variables for each exposure window were included as predictor variables along with covariates for sex, age, and age-squared. The developmental periods are ordered in the table in chronological order relative to the famine. The left-most column shows effect-sizes for late-gestational exposure (defined as exposure for the final 10 weeks of gestation; N=139 exposed). The second column to the left shows effect-sizes for exposure during the penultimate 10 weeks of gestation (N=146 exposed). The third column shows effect-sizes for exposure during the second 10 weeks of gestation (N=125 exposed). The fourth column shows effect-sizes for exposure during the first 10 weeks of gestation (N=74 exposed). The fifth column shows effect-sizes for early gestational exposure with duration <10 weeks (N=94 exposed). The right-most column shows effect-sizes for preconceptual exposure, i.e., for exposure during the period preceding conception (N=52 exposed). Numbers exposed do not add up to the total exposed sample because many participants were exposed in two adjacent periods (N=143). Effect-sizes are reported for DunedinPACE, PC GrimAge, and PC PhenoAge. The first row shows effect-sizes estimated in the full DHWFS. The second and third rows show effect-sizes in sex-stratified samples. The final row reports the product-term coefficient from a regression testing sex differences in effects of exposure.

	D4			D3			D2			D1			D0			D-1		
	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
DunedinPACE																		
All	0.18	-0.02, 0.38	0.071	0.17	-0.03, 0.36	0.091	-0.01	-0.20, 0.18	0.902	0.07	-0.17, 0.30	0.589	0.01	-0.23, 0.25	0.948	0.06	-0.21, 0.33	0.661
Women	0.18	-0.08, 0.43	0.185	0.25	0.02, 0.49	**0.036**	0.07	-0.17, 0.30	0.570	0.25	-0.10, 0.60	0.158	0.13	-0.23, 0.48	0.491	0.22	-0.17, 0.61	0.269
Men	0.19	-0.12, 0.50	0.231	0.08	-0.25, 0.40	0.637	-0.09	-0.41, 0.24	0.594	-0.15	-0.45, 0.14	0.307	-0.11	-0.42, 0.21	0.497	-0.16	-0.50, 0.18	0.352
PC GrimAge																		
All	0.12	-0.07, 0.31	0.212	0.09	-0.09, 0.28	0.309	-0.08	-0.27, 0.11	0.405	0.06	-0.16, 0.28	0.597	0.02	-0.20, 0.24	0.858	0.12	-0.12, 0.35	0.338
Women	0.11	-0.15, 0.37	0.404	0.18	-0.07, 0.43	0.162	0.02	-0.20, 0.25	0.839	0.12	-0.20, 0.43	0.469	0.04	-0.30, 0.38	0.807	0.42	0.14, 0.71	**0.004**
Men	0.12	-0.16, 0.40	0.392	0.02	-0.24, 0.28	0.896	-0.19	-0.51, 0.13	0.251	-0.01	-0.31, 0.30	0.957	-0.01	-0.28, 0.25	0.924	-0.32	-0.66, 0.02	0.068
PC PhenoAge																		
All	-0.07	-0.26, 0.12	0.479	0.28	0.10, 0.46	**0.003**	-0.19	-0.38, 0.00	**0.048**	0.15	-0.09, 0.39	0.211	-0.05	-0.27, 0.18	0.681	0.10	-0.19, 0.38	0.506
Women	-0.11	-0.38, 0.16	0.427	0.31	0.08, 0.54	**0.009**	-0.11	-0.34, 0.13	0.365	0.14	-0.15, 0.43	0.347	0.09	-0.24, 0.42	0.579	0.29	-0.04, 0.61	0.086
Men	-0.04	-0.32, 0.23	0.768	0.26	-0.03, 0.55	0.082	-0.30	-0.62, 0.02	0.063	0.17	-0.21, 0.56	0.376	-0.20	-0.51, 0.10	0.194	-0.19	-0.68, 0.31	0.459

Table B.7. Effect-Sizes for Cell-Count-Adjusted Associations of In-Utero Famine Exposure with Epigenetic-Clock Measures of the Pace of Aging and Biological Age. The table reports effect-sizes for generalized estimating equations (GEE) regressions testing associations in the full Dutch Hunger Winter Families Study (DHWFS; N=951). Results are reported for analysis of three epigenetic clocks: the DunedinPACE clock measures pace of aging; the PC GrimAge and PC Phenoage clocks measure biological age. For PC GrimAge and PC PhenoAge, clock values were residualized on chronological age prior to analysis. Models included covaraites for sex, age, and age-squared. Models included additional covariates for DNAm estimates of leukocyte proportions. Coefficients (Beta) and 95% confidence intervals (95% CI) are denominated in standard-deviation units of the outcome variables. Coefficients in each row of the table show results from independent regressions. The first row shows cell-count-adjusted effect-sizes for famine exposure estimated in analyses including all participants in the sample. The second and third rows show cell-count-adjusted effect-sizes for famine exposure estimated in sex-stratified samples (N=521 women and 430 men). The fourth row reports the p-value for a product term (famine-exposure*sex) in a regression testing the sex differences in cell-count-adjusted famine effect-sizes.

	Beta	95% CI	p-value
DunedinPACE			
All	0.17	0.05, 0.29	**0.007**
Women	0.30	0.14, 0.45	**<0.001**
Men	0.00	-0.18, 0.19	0.970
Test of sex difference			**0.011**
PC GrimAge			
All	0.12	0.02, 0.23	**0.024**
Women	0.24	0.10, 0.37	**<0.001**
Men	-0.03	-0.19, 0.14	0.749
Test of sex difference			**0.003**
PC PhenoAge			
All	0.12	0.02, 0.21	**0.015**
Women	0.13	0.01, 0.26	**0.036**
Men	0.08	-0.07, 0.23	0.300
Test of sex difference			0.563

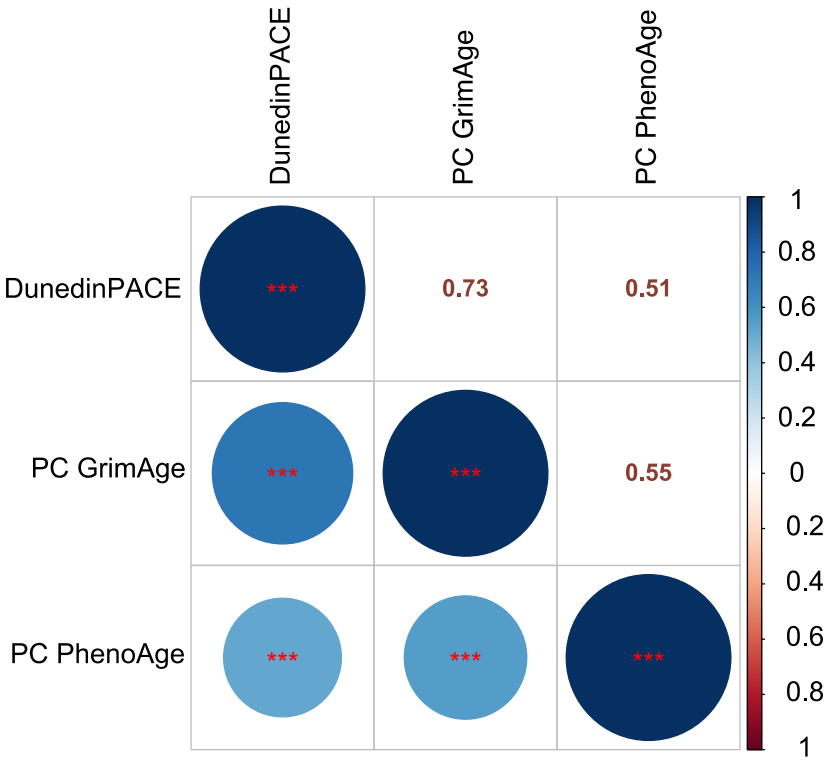
Table B.8. Effect-Sizes for Cell-Count-Adjusted Dose Response to the Duration of In-Utero Famine Exposure in Epigenetic-Clock Measures of the Pace of Aging and Biological Age. The table reports effect-sizes for generalized estimating equations (GEE) regressions testing dose response in the full Dutch Hunger Winter Families Study (DHWFS; **N=951)**. Results are reported for analysis of three epigenetic clocks: the DunedinPACE clock measures pace of aging; the PC GrimAge and PC Phenoage clocks measure biological age. For PC GrimAge and PC PhenoAge, clock values were residualized on chronological age prior to analysis. The duration of in-utero famine exposure was measured by the number of per-10 weeks that individuals were exposed during gestation. The duration of in-utero famine exposure ranged from 0 to 24 weeks. Models included covaraites for sex, age, and age-squared. Models included additional covariates for DNAm estimates of leukocyte proportions. Coefficients (Beta) and 95% confidence intervals (95% CI) are denominated in standard-deviation units of the outcome variables. Coefficients in each row of the table show results from independent regressions. The first row shows cell-count-adjusted effect-sizes for duration of famine exposure estimated in analyses including all participants in the sample. The second and third rows show cell-count-adjusted effect-sizes for duration of famine exposure estimated in sex-stratified samples (N=521 women and 430 men). The fourth row reports the p-value for a product term (duration-of-famine-exposure*sex) in a regression testing the sex differences in cell-count-adjusted famine effect-sizes.

	Beta	95% CI	p-value
DunedinPACE			
All	0.08	0.02, 0.14	**0.009**
Women	0.12	0.05, 0.20	**0.002**
Men	0.02	-0.07, 0.12	0.622
Test of sex difference			0.074
PC GrimAge			
All	0.03	-0.03, 0.08	0.333
Women	0.06	-0.01, 0.13	0.070
Men	-0.03	-0.11, 0.05	0.495
Test of sex difference			**0.025**
PC PhenoAge			
All	0.05	0.00, 0.10	**0.031**
Women	0.05	-0.01, 0.11	0.111
Men	0.04	-0.03, 0.12	0.235
Test of sex difference			0.890

Table B.9. Effect-Sizes for Cell-Count-Adjusted Associations of Famine Exposure during Each of Six Developmental Time Periods with Epigenetic-Clock Measures of the Pace of Aging and Biological Age. The table reports cell-count-adjusted effect-sizes estimated for famine exposure during six developmental periods. Famine-exposed participants were exposed during up to two periods. Effect-sizes were estimated from a multivariate regression in which indicator variables for each exposure window were included as predictor variables along with covariates for sex, age, and age-squared. Models included additional covariates for DNAm estimates of leukocyte proportions. The developmental periods are ordered in the table in chronological order relative to the famine. The left-most column shows cell-count-adjusted effect-sizes for late-gestational exposure (defined as exposure for the final 10 weeks of gestation; N=139 exposed). The second column to the left shows cell-count-adjusted effect-sizes for exposure during the penultimate 10 weeks of gestation (N=146 exposed). The third column shows cell-count-adjusted effect-sizes for exposure during the second 10 weeks of gestation (N=125 exposed). The fourth column shows cell-count-adjusted effect-sizes for exposure during the first 10 weeks of gestation (N=74 exposed). The fifth column shows cell-count-adjusted effect-sizes for early gestational exposure with duration <10 weeks (N=94 exposed). The right-most column shows cell-count-adjusted effect-sizes for preconceptual exposure, i.e., for exposure during the period preceding conception (N=52 exposed). Numbers exposed do not add up to the total exposed sample because many participants were exposed in two adjacent periods (N=143). Cell-count-adjusted effect-sizes are reported for DunedinPACE, PC GrimAge, and PC PhenoAge. The first row shows cell-count-adjusted effect-sizes estimated in the full DHWFS. The second and third rows show cell-count-adjusted effect-sizes in sex-stratified samples.

	D4			D3			D2			D1			D0			D-1		
	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
DunedinPACE																		
All	0.24	0.05, 0.42	**0.011**	0.12	-0.06, 0.30	0.178	0.02	-0.16, 0.20	0.802	0.08	-0.15, 0.31	0.505	0.09	-0.13, 0.31	0.416	0.03	-0.24, 0.29	0.835
Women	0.27	0.03, 0.50	**0.029**	0.19	-0.03, 0.42	0.096	0.13	-0.09, 0.35	0.261	0.30	-0.02, 0.62	0.068	0.21	-0.09, 0.52	0.168	0.13	-0.25, 0.52	0.497
Men	0.22	-0.07, 0.51	0.133	0.03	-0.26, 0.33	0.820	-0.08	-0.39, 0.23	0.615	-0.15	-0.44, 0.15	0.339	-0.06	-0.36, 0.24	0.700	-0.08	-0.40, 0.23	0.598
PC GrimAge																		
All	0.20	0.02, 0.37	**0.026**	0.03	-0.12, 0.19	0.681	-0.05	-0.22, 0.12	0.569	0.09	-0.10, 0.28	0.349	0.14	-0.03, 0.31	0.108	0.12	-0.07, 0.32	0.214
Women	0.21	-0.02, 0.44	0.070	0.11	-0.12, 0.33	0.348	0.07	-0.14, 0.28	0.496	0.16	-0.10, 0.41	0.221	0.18	-0.06, 0.43	0.138	0.33	0.07, 0.59	**0.012**
Men	0.17	-0.08, 0.42	0.184	-0.04	-0.27, 0.18	0.709	-0.19	-0.48, 0.11	0.213	0.02	-0.25, 0.30	0.859	0.07	-0.17, 0.31	0.561	-0.15	-0.42, 0.13	0.296
PC PhenoAge																		
All	0.04	-0.11, 0.19	0.612	0.16	0.02, 0.31	**0.029**	-0.05	-0.20, 0.10	0.524	0.18	-0.03, 0.39	0.093	0.11	-0.06, 0.28	0.191	0.03	-0.20, 0.25	0.819
Women	-0.02	-0.22, 0.19	0.877	0.16	-0.04, 0.37	0.112	0.01	-0.18, 0.20	0.929	0.21	-0.03, 0.44	0.081	0.17	-0.06, 0.40	0.150	0.11	-0.17, 0.38	0.444
Men	0.06	-0.15, 0.28	0.561	0.17	-0.05, 0.38	0.123	-0.15	-0.39, 0.10	0.248	0.14	-0.22, 0.51	0.443	0.02	-0.23, 0.27	0.874	-0.12	-0.49, 0.25	0.535

Figure B.1. Correlation Matrix of Epigenetic-Clock Measures of the Pace of Aging and Biological Age. The figure shows correlation of three DNA methylation (DNAm) measures of biological aging, DunedinPACE, PC GrimAge, and PC PhenoAge (N=951). Circles in blue represent positive correlation. Color intensity and the size of the circle are proportional to the correlation coefficients. Significance level is .05.



Appendix C

Table C.1. Effects of Income on Multimorbidity and Memory as a Function of Age among Older Adults in the U.S. (by Gender)

	Multimorbidity		Memory	
	IRRs	95% CI	IRRs	95% CI
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.90***	0.89–0.92	1.10***	1.09–1.11
Gender (-0.5 = *men*, +0.5 = *women*)	1.01	0.99–1.03	1.13***	1.13–1.14
Grand-mean centered mean age × income decile	1.11***	1.09–1.14	1.05***	1.03–1.06
Person-mean centered age × income decile	1.14***	1.11–1.17	1.12***	1.11–1.14
(Grand-mean centered mean age × income decile) × gender	1.02	0.98–1.06	1.04**	1.01–1.06
For men	/	/	1.03**	1.01–1.05
For women	/	/	1.06***	1.05–1.08
(Person-mean centered age × income decile) × gender	1.05	1.00–1.10	1.06***	1.03–1.09
For men	/	/	1.09***	1.06–1.12
For women	/	/	1.15***	1.14–1.17
Number of participants	33,860		25,291	
Number of observations	230,101		143,011	

Note. IRRs = Incidence Rate Ratios.

The effect of income refers to the comparison between the bottom 10% and the top 10%.

Adjusted for wealth, education, race, current marital status, current working status, and household size.

*$p < .05$. **$p < .01$. ***$p < .001$

Table C.2. Effect of Income on Mobility and Verbal Skills as a Function of Age among Older Adults in the U.S.

	Mobility		Verbal skills	
	IRRs	95% CI	IRRs	95% CI
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.68***	0.65–0.71	1.05***	1.04–1.07
Grand-mean centered mean age × income decile	1.16***	1.12–1.22	1.04***	1.02–1.05
Age (50 years old)	0.54***	0.49–0.58	1.01	0.99–1.02
Age (-1 SD)	0.59***	0.55–0.63	1.03***	1.02–1.04
Age (+1 SD)	0.78***	0.74–0.82	1.08***	1.06–1.09
Age (+2 SD)	0.89**	0.82–0.97	1.10***	1.08–1.13
Person-mean centered age × income decile	1.29***	1.20–1.39	1.11***	1.09–1.13
Panel waves (-2 SD)	0.53***	0.48–0.58	0.97**	0.96–0.99
Panel waves (-1 SD)	0.60***	0.56–0.64	1.01*	1.01–1.03
Panel waves (+1 SD)	0.78***	0.74–0.83	1.10***	1.09–1.12
Panel waves (+2 SD)	0.89**	0.83–0.97	1.15***	1.13–1.17
Number of participants	30,103		18,512	
Number of observations	187,945		103,228	

Note. IRRs = incidence rate ratios.
The effect of income refers to the comparison between the bottom 10% and the top 10%.
Adjusted for wealth, education, gender, race, current marital status, current working status, and household size.
$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

Table C.3. Effects of Income on Mobility and Verbal Skills as a Function of Age among Older Adults in the U.S. (by Gender)

	Mobility		Verbal skills	
	IRRs	95% CI	IRRs	95% CI
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.67***	0.64–0.70	1.05***	1.04–1.07
Gender (-0.5 = *men*, +0.5 = *women*)	1.45***	1.38–1.52	1.01**	1.01–1.01
Grand-mean centered mean age × income decile	1.18***	1.13–1.24	1.03***	1.01–1.04
Person-mean centered age × income decile	1.26***	1.16–1.36	1.11***	1.09–1.13
(Grand-mean centered mean age × income decile) × gender	0.93	0.85–1.03	1.04*	1.01–1.07
For men	/	/	1.01	0.99–1.03
For women	/	/	1.05***	1.03–1.07
(Person-mean centered age × income decile) × gender	0.94	0.80–1.09	1.03	0.99–1.07
For men	/	/	/	/
For women	/	/	/	/
Number of participants	30,103		18,512	
Number of observations	187,945		103,228	

Note. IRRs = Incidence Rate Ratios.

The effect of income refers to the comparison between the bottom 10% and the top 10%.

Adjusted for wealth, education, race, current marital status, current working status, and household size.

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

Table C.4. Effect of Income on Self-Rated Health as a Function of Age among Older Adults in the U.S.

	Self-rated health	
	IRRs	95% CI
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.83***	0.82–0.84
Grand-mean centered mean age × income decile	1.06***	1.04–1.07
Age (50 years old)	0.76***	0.75–0.78
Age (-1 SD)	0.79***	0.78–0.81
Age (+1 SD)	0.88***	0.86–0.89
Age (+2 SD)	0.92***	0.90–0.94
Person-mean centered age × income decile	1.08***	1.07–1.10
Panel waves (-2 SD)	0.77***	0.76–0.79
Panel waves (-1 SD)	0.80***	0.79–0.82
Panel waves (+1 SD)	0.87***	0.86–0.89
Panel waves (+2 SD)	0.91***	0.89–0.93
Number of participants	33,878	
Number of observations	230,239	

Note. IRRs = incidence rate ratios.
The effect of income refers to the comparison between the bottom 10% and the top 10%.
Adjusted for wealth, education, gender, race, current marital status, current working status, and household size.
$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

Table C.5. Effects of Income on Self-Rated Health as a Function of Age among Older Adults in the U.S. (by Gender)

	Self-rated health	
	IRRs	95% CI
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.84***	0.83–0.85
Gender (-0.5 = *men*, +0.5 = *women*)	0.98***	0.97–0.98
Grand-mean centered mean age × income decile	1.06***	1.05–1.07
Person-mean centered age × income decile	1.08***	1.07–1.10
(Grand-mean centered mean age × income decile) × gender	0.99	0.97–1.02
For men	/	/
For women	/	/
(Person-mean centered age × income decile) × gender	0.98	0.94–1.01
For men	/	/
For women	/	/
Number of participants	33,878	
Number of observations	230,239	

Note. IRRs = Incidence Rate Ratios.
The effect of income refers to the comparison between the bottom 10% and the top 10%.
Adjusted for wealth, education, race, current marital status, current working status, and household size.
*$p < .05$. **$p < .01$. ***$p < .001$

Table C.6. Effect of Income on Multimorbidity and Memory as a Function of Age in Samples Excluding Deaths and Dropout

	Sample excluding deaths				Sample excluding dropout			
	Multimorbidity		Memory		Multimorbidity		Memory	
	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI
Grand-mean centered mean age	1.13***	1.12–1.15	0.90***	0.90–0.91	1.13***	1.12–1.14	0.86***	0.86–0.87
Person-mean centered age	1.94***	1.92–1.95	0.86***	0.86–0.86	1.86***	1.85–1.87	0.83***	0.83–0.83
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.88***	0.86–0.90	1.08***	1.07–1.10	0.90***	0.88–0.92	1.09***	1.08–1.10
Grand-mean centered mean age × income decile	1.14***	1.10–1.17	1.04***	1.02–1.05	1.11***	1.09–1.14	1.05***	1.04–1.06
Age (50 years old)	0.76***	0.72–0.80	1.04***	1.02–1.05	0.75***	0.72–0.78	1.02*	1.00–1.03
Age (-1 SD)	0.80***	0.78–0.83	1.06***	1.05–1.08	0.81***	0.79–0.84	1.05***	1.04–1.06
Age (+1 SD)	0.96*	0.94–0.99	1.11***	1.10–1.12	0.99	0.97–1.02	1.13***	1.12–1.14
Age (+2 SD)	1.06*	1.01–1.11	1.14***	1.12–1.16	1.10***	1.05–1.14	1.18***	1.15–1.20
Person-mean centered age × income decile	1.18***	1.15–1.22	1.10***	1.08–1.11	1.16***	1.13–1.19	1.13***	1.11–1.15
Panel waves (-2 SD)	0.74***	0.71–0.78	0.99	0.98–1.01	0.77***	0.74–0.79	0.99	0.97–1.01
Panel waves (-1 SD)	0.82***	0.79–0.85	1.04***	1.03–1.06	0.83***	0.81–0.86	1.03***	1.02–1.04
Panel waves (+1 SD)	0.99	0.97–1.03	1.15***	1.13–1.16	0.98	0.96–1.01	1.16***	1.14–1.17
Panel waves (+2 SD)	1.10***	1.06–1.14	1.20***	1.18–1.23	1.07***	1.04–1.10	1.23***	1.21–1.25
Wealth decile (*1 = bottom 10%*, 10 = *top 10%*)	0.69***	0.66–0.72	1.10***	1.09–1.12	0.74***	0.72–0.76	1.12***	1.11–1.14
Upper secondary or vocational education	0.99	0.96–1.02	1.15***	1.14–1.16	0.96***	0.94–0.98	1.16***	1.15–1.17
Tertiary education	0.93***	0.90–0.96	1.25***	1.24–1.27	0.90***	0.88–0.92	1.27***	1.26–1.28
Gender (-0.5 = *men*, +0.5 = *women*)	0.97**	0.95–0.99	1.12***	1.11–1.13	0.96***	0.95–0.98	1.13***	1.12–1.14
Race (0 = *White/Caucasian*, 1 = *non-White/Caucasian*)	1.08***	1.05–1.10	0.91***	0.90–0.91	1.03***	1.01–1.05	0.90***	0.90–0.91
Current marital status (0 = *not married*, 1 = *married*)	1.00	0.99–1.02	1.02***	1.02–1.03	0.99	0.98–1.01	1.02***	1.02–1.03
Current working status (0 = *not working*, 1 = *working*)	0.90***	0.89–0.91	1.02***	1.01–1.02	0.87***	0.87–0.88	1.01***	1.01–1.02
Household size	0.99*	0.99–1.00	0.99***	0.99–0.99	1.00	0.99–1.00	0.99***	0.99–0.99
Number of participants	20,329		16,679		32,032		24,567	
Number of observations	150,785		101,039		222,711		140,186	

Note. IRRs = Incidence Rate Ratios.

The effect of income and wealth refers to the comparison between the bottom 10% and the top 10%.

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

Table C.7. Effect of Income on Multimorbidity and Memory as a Function of Age in Samples Excluding Deaths and Dropout (by Gender)

	Sample excluding deaths				Sample excluding dropout			
	Multimorbidity		Memory		Multimorbidity		Memory	
	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI
Income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.89***	0.87–0.92	1.09***	1.08–1.10	0.91***	0.89–0.93	1.10***	1.08–1.11
Gender (-0.5 = *men*, +0.5 = *women*)	1.04**	1.01–1.07	1.12***	1.12–1.13	1.01	0.99–1.03	1.14***	1.13–1.14
Grand-mean centered mean age × income decile	1.13***	1.09–1.16	1.04***	1.02–1.05	1.11***	1.09–1.14	1.05***	1.03–1.06
Person-mean centered age × income decile	1.16***	1.13–1.20	1.09***	1.07–1.11	1.14***	1.11–1.16	1.12***	1.11–1.14
(Grand-mean centered mean age × income decile) × gender	1.04	0.97–1.11	1.01	0.98–1.04	1.02	0.98–1.06	1.04***	1.01–1.06
For men	/	/	/	/	/	/	1.03***	1.01–1.05
For women	/	/	/	/	/	/	1.07***	1.06–1.09
(Person-mean centered age × income decile) × gender	1.04	0.99–1.11	1.05**	1.02–1.08	1.05	1.00–1.10	1.06***	1.03–1.09
For men	/	/	1.06***	1.04–1.09	/	/	1.09***	1.06–1.11
For women	/	/	1.12***	1.10–1.14	/	/	1.15***	1.14–1.17
Number of participants	20,329		16,679		32,032		24,567	
Number of observations	150,78		101,039		222,711		140,186	

Note. IRRs = Incidence Rate Ratios.
The effect of income and wealth refers to the comparison between the bottom 10% and the top 10%.
Adjusted for wealth, education, race, current marital status, current working status, and household size.
$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

Appendix D

Table D.1. Effects of Income on Alternative Health Outcomes as a Function of Age among Older Adults in Europe

	Functional Disability		Mobility Disability		Memory	
	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI
Grand-mean centered mean age	2.49***	2.40–2.58	1.56***	1.55–1.58	0.88***	0.88–0.89
Person-mean centered age	7.44***	6.07–9.13	1.60*	1.01–2.53	0.97***	0.95–0.98
Equivalized income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.59***	0.52–0.67	0.76***	0.73–0.79	1.08***	1.07–1.09
Grand-mean centered mean age × equivalized income decile	1.15*	1.03–1.28	1.14***	1.10–1.18	1.04***	1.03–1.05
Middle-aged adults (-2 SD)	0.46***	0.35–0.61	0.60***	0.56–0.64	1.00	0.99–1.02
Older middle-aged adults (-1 SD)	0.52***	0.43–0.63	0.68***	0.64–0.71	1.04***	1.03–1.05
Older adults (+1 SD)	0.67***	0.59–0.76	0.86***	0.82–0.90	1.12***	1.11–1.13
Oldest old adults (+2 SD)	0.76**	0.63–0.91	0.96	0.90–1.04	1.16***	1.14–1.18
Person-mean centered age × equivalized income decile	1.23	0.97–1.55	1.10***	1.05–1.15	1.04***	1.02–1.06
Earlier panel waves (-2 SD)	/	/	0.72***	0.69–0.76	1.05***	1.04–1.07
Early panel waves (-1 SD)	/	/	0.74***	0.71–0.77	1.07***	1.06–1.08
Late panel waves (+1 SD)	/	/	0.78***	0.76–0.81	1.09***	1.08–1.10
Later panel waves (+2 SD)	/	/	0.81***	0.77–0.84	1.10***	1.09–1.12
Wealth decile (1 = *bottom 10%*, 10 = *top 10%*)	0.49***	0.44–0.55	0.59***	0.57–0.61	1.07***	1.07–1.08
Upper secondary or vocational education	0.63***	0.59–0.68	0.83***	0.81–0.85	1.13***	1.12–1.13
Tertiary education	0.50***	0.46–0.55	0.66***	0.64–0.68	1.21***	1.20–1.22
Gender (-0.5 = *men*, +0.5 = *women*)	0.89***	0.84–0.94	1.51***	1.48–1.54	1.07***	1.06–1.07
Region of residence (0 = *urban*, 1 = *rural*)	1.02	0.96–1.07	1.01	1.00–1.03	1.00	0.99–1.00
Current marital status (0 = *not married*, 1 = *married*)	0.79***	0.74–0.84	0.94***	0.92–0.96	1.03***	1.03–1.04
Current working status (0 = *not working*, 1 = *working*)	0.50***	0.45–0.55	0.76***	0.75–0.78	1.02***	1.01–1.02
Household size	1.18***	1.15–1.21	1.02***	1.01–1.03	0.99***	0.99–0.99
$N_{participants}$	73,407		73,407		73,166	
Observations	242,753		242,948		237,317	

Note. IRRs = incidence rate ratios. Comparisons were made between the bottom 10% and the top 10% in terms of income and wealth.
$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$

Table D.2. Effects of Income on Alternative Health Outcomes as a Function of Age among Older Adults in China

	Functional Disability		Mobility Disability		Memory	
	IRRs	95% CI	IRRs	95% CI	IRRs	95% CI
Grand-mean centered mean age	1.63***	1.57–1.70	1.32***	1.29–1.35	0.87***	0.86–0.88
Person-mean centered age	2.39***	2.03–2.80	1.87***	1.80–1.94	0.58***	0.57–0.60
Equivalized income decile (1 = *bottom 10%*, 10 = *top 10%*)	0.46***	0.40–0.53	0.64***	0.60–0.69	1.21***	1.17–1.24
Grand-mean centered mean age × equivalized income decile	1.32***	1.17–1.49	1.08*	1.01–1.16	1.11***	1.08–1.14
Middle-aged adults (-2 SD)	0.27***	0.20–0.35	0.55***	0.48–0.64	1.00	0.95–1.05
Older middle-aged adults (-1 SD)	0.34***	0.28–0.41	0.60***	0.54–0.66	1.10***	1.06–1.13
Older adults (+1 SD)	0.57***	0.49–0.67	0.69***	0.63–0.76	1.32***	1.27–1.38
Oldest old adults (+2 SD)	0.74*	0.58–0.94	0.74***	0.64–0.85	1.46***	1.37–1.55
Person-mean centered age × equivalized income decile	1.41	0.80–2.47	1.17*	1.03–1.32	1.38***	1.27–1.51
Earlier panel waves (-2 SD)	/	/	0.59***	0.54–0.66	1.02	0.98–1.07
Early panel waves (-1 SD)	/	/	0.62***	0.57–0.67	1.11***	1.08–1.14
Late panel waves (+1 SD)	/	/	0.67***	0.62–0.72	1.30***	1.25–1.35
Later panel waves (+2 SD)	/	/	0.69***	0.63–0.76	1.41***	1.34–1.49
Wealth decile (1 = *bottom 10%*, 10 = *top 10%*)	0.55***	0.49–0.62	0.65***	0.60–0.69	1.08***	1.05–1.10
Upper secondary or vocational education	0.47***	0.39–0.56	0.76***	0.70–0.82	1.22***	1.19–1.25
Tertiary education	0.34***	0.19–0.62	0.64***	0.52–0.80	1.29***	1.22–1.37
Gender (-0.5 = *men*, +0.5 = *women*)	1.81***	1.69–1.93	1.66***	1.60–1.73	0.95***	0.93–0.96
Region of residence (0 = *urban*, 1 = *rural*)	1.37***	1.27–1.48	1.14***	1.09–1.18	0.92***	0.90–0.93
Current marital status (0 = *not married*, 1 = *married*)	1.09	1.00–1.18	1.01	0.96–1.05	1.07***	1.05–1.09
Current working status (0 = *not working*, 1 = *working*)	0.80***	0.75–0.85	0.80***	0.78–0.82	1.00	0.99–1.02
Household size	1.03***	1.01–1.05	1.01**	1.00–1.02	0.99*	0.99–0.99
$N_{participants}$	9,999		10,063		10,006	
Observations	26,106		36,307		33,045	

Note. IRRs = incidence rate ratios. Comparisons were made between the bottom 10% and the top 10% in terms of income and wealth.
*$p < .05$. **$p < .01$. ***$p < .001$

Table D.3. Effects of Income on Multimorbidity as a Function of Age among Older Adults in Europe and China (the Additive Scale)

	Europe	China
Between-participant effect		
RERI	0.11 [0.09, 0.12]	0.18 [0.15, 0.21]
AP	0.08 [0.07, 0.09]	0.15 [0.13, 0.17]
SI	1.69 [1.59, 1.78]	12.25 [2.16, 22.49]
Within-participant effect		
RERI	0.17 [0.10, 0.24]	0.12 [-0.14, 0.38]
AP	0.08 [0.05, 0.11]	0.05 [-0.05, 0.15]
SI	1.18 [1.11, 1.26]	1.09 [0.91, 1.30]

Note. RERI = relative excess risk due to interaction. AP = attributable proportion. SI = synergy index.