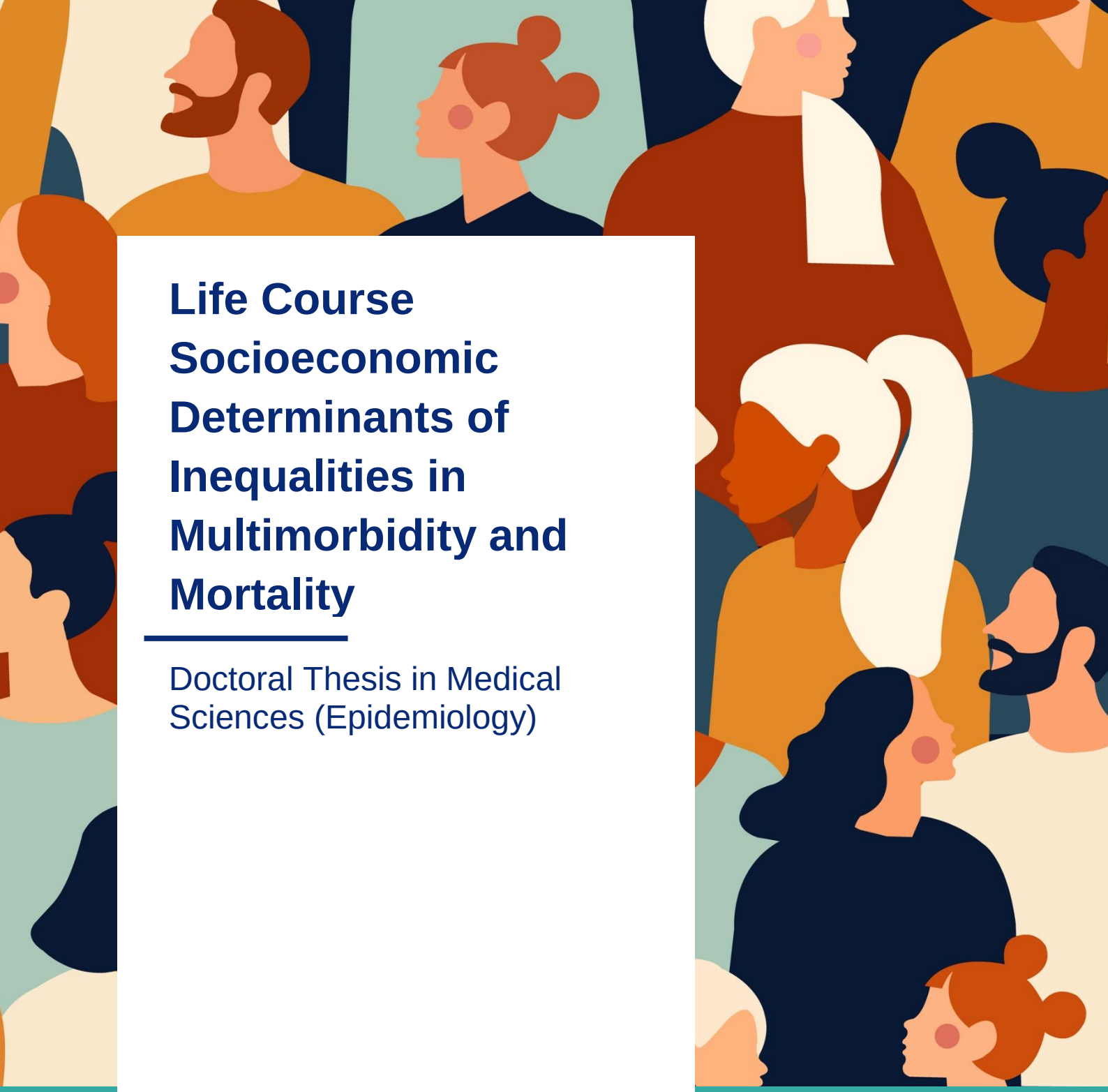

Life Course Socioeconomic Determinants of Inequalities in Multimorbidity and Mortality

Doctoral Thesis in Medical Sciences (Epidemiology)

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THESIS

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Fribourg, 29th February 2024

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Summaries

Abstract

Population health is the product of a dynamic interaction between individual, social, and environmental factors, spanning from the microcosm of the family to the macrocosm of the country, and evolving across the life course. Early-life exposures, like parental socioeconomic conditions and educational opportunities, set the stage for health trajectories across the life course. As one progresses through life, the impact of broader societal factors, such as socio-environmental conditions or healthcare policies, also play a role in shaping health trajectories. Understanding this multifaceted process is key for addressing and mitigating health inequalities, which typically take decades to develop and manifest as differential morbidity and mortality in later life. However, it is still not clear, first, in what way these different factors – parental influences, individual educational opportunities, and socio-environmental conditions – exactly interact to affect health in later life, and second, what the magnitude of this effect is. Therefore, this thesis aims to assess the interplay between socioeconomic trajectories, specifically intergenerational educational trajectories, and inequalities in multimorbidity and mortality from a life course perspective. This objective is divided over four aims, presented in four chapters.

In Chapter 4, we report a scoping review that investigates the association between life course socioeconomic conditions (SEC) and later-life multimorbidity. We assess to which extent this association supports different life course causal models: critical period, sensitive period, accumulation, pathway, or social mobility model. We find that SEC in early life could have an effect on multimorbidity, attenuated at least partly by SEC in adulthood, which is consistent with the sensitive period and the pathway models.

In Chapters 5 and 6, we assess the effect of intergenerational educational trajectories on inequalities in multimorbidity (Chapter 5) and longevity (Chapter 6). In both studies, we find that individuals with low educational attainment experience greater health inequalities, regardless of their parental education. In Chapter 5, we assess whether inequalities in multimorbidity are different between men and women and find that, when exposed to low individual education, women experienced larger inequalities, though supplementary analyses suggest that these differences could be due to higher health-seeking behaviors in women. In Chapter 6, we assess whether inequalities in longevity are mitigated by higher investments into social expenditures by the country of residence, and observe that inequalities are not diminished by higher spending.

Finally, in Chapter 7, we describe how life course epidemiology changes the way the etiology of chronic diseases is understood, taking the examples of hypertension, breast cancer, and dementia. For all three chronic diseases, life course research has identified risk factors across the life course, from fetal exposure to undernutrition, to health-detrimental behaviors, or socioeconomic

disadvantage. The origins of many chronic diseases can now be traced back to early life, opening the door to intervention strategies that target specific times during the life course in order to reduce (multi)morbidities, and increase life expectancy.

In conclusion, in this thesis we examine the interplay between socioeconomic trajectories and health in later life. Our findings suggest that early life sets the foundations for life-long health trajectories, but that these trajectories can be changed with the right interventions. Ultimately, this thesis underscores the importance of considering the entire life course when examining health inequalities in later life, which highlights the need for public health to target not only the individual but also the societal factors that perpetuate health inequalities, within and across generations.

Zusammenfassung

Die Gesundheit der Bevölkerung ist das Ergebnis einer dynamischen Wechselwirkung zwischen individuellen, sozialen und umweltbedingten Faktoren, die sich vom Mikrokosmos der Familie bis zum Makrokosmos des Landes erstreckt und sich über den gesamten Lebensverlauf hinweg entwickelt. Einflüsse am Lebensanfang, wie die sozioökonomischen Bedingungen der Eltern und die erfahrenen Bildungschancen, bilden die Grundlage für den Gesundheitsverlauf im Laufe des Lebens. Mit zunehmendem Lebensalter spielen auch die Auswirkungen weiterreichender gesellschaftlicher Faktoren, wie z. B. sozioökonomische Bedingungen oder gesundheitspolitische Massnahmen, eine Rolle bei der Entwicklung des Gesundheitsverlaufs. Das Verständnis dieses facettenreichen Prozesses ist von entscheidender Bedeutung, um gesundheitliche Ungleichheiten zu bekämpfen bzw. zu mildern, die sich in der Regel erst über Jahrzehnte entwickeln und sich in Form von ungleicher Morbidität und Mortalität im späteren Leben ausdrücken. Es ist jedoch immer noch nicht klar, erstens, auf welche Weise diese verschiedenen Faktoren - elterliche Einflüsse, individuelle Bildungschancen und sozioökonomische Bedingungen - exakt zusammenwirken, um die Gesundheit im späteren Leben zu beeinflussen, und zweitens, wie stark deren Auswirkungen sind. Ziel dieser Arbeit ist es daher, die Interaktion zwischen sozioökonomischen Lebensläufen, spezifisch generationsübergreifenden Bildungsverläufen, und Ungleichheiten bei Multimorbidität und Mortalität aus einer Lebensverlaufsperspektive zu untersuchen. Dieses Ziel ist in vier Unterziele unterteilt, die in vier Kapiteln vorgestellt werden.

In Kapitel 4 präsentieren wir eine Übersichtsstudie, die den Zusammenhang zwischen sozioökonomischen Bedingungen im Lebensverlauf («socioeconomic conditions», SEC) und Multimorbidität im späteren Leben untersucht. Wir prüfen, inwieweit dieser Zusammenhang verschiedene kausale Wirkungsmodelle im Hinblick auf den Lebensverlauf bestätigt: das Modell der kritischen Phase, der sensiblen Phase, der Akkumulierung, der Wirkungskette oder das Modell der sozialen Mobilität. Wir kamen zu dem Ergebnis, dass SEC im frühen Leben einen Einfluss auf die Multimorbidität haben könnten, der zumindest teilweise durch SEC im Erwachsenenalter abgeschwächt wird, was mit den Modellen der sensiblen Phase und der Wirkungskette übereinstimmt.

In den Kapiteln 5 und 6 untersuchen wir die Auswirkungen des generationsübergreifenden Bildungsverlaufs auf Ungleichheiten in der Multimorbidität (Kapitel 5) und der Lebenserwartung (Kapitel 6). In beiden Studien stellen wir fest, dass Personen mit niedrigem Bildungsniveau grössere gesundheitliche Ungleichheiten erfahren, unabhängig vom Bildungsgrad der Eltern. In Kapitel 5 prüfen wir, ob diese Ungleichheiten in der Multimorbidität zwischen Männern und Frauen variieren, und kommen zum Ergebnis, dass Frauen mit niedrigem Bildungsniveau grössere Ungleichheiten als Männer erfahren, obwohl Zusatzanalysen darauf hindeuten, dass diese Unterschiede auf ein anderes Gesundheitsverhalten bei Frauen zurückzuführen sein könnten. In Kapitel 6 untersuchen wir, ob Ungleichheiten in der Lebenserwartung durch höhere Investitionen in die Sozialausgaben des Heimatlandes abgemildert werden, und

können feststellen, dass die Ungleichheiten durch höhere Ausgaben nicht verringert werden.

In Kapitel 7 schliesslich beschreiben wir am Beispiel von Bluthochdruck, Brustkrebs und Demenz, wie die Lebensverlaufsepidemiologie das Wissen über die Entstehung chronischer Krankheiten beeinflusst hat. Für alle drei chronischen Krankheiten hat die Fachrichtung Risikofaktoren über den gesamten Lebensverlauf hinweg identifiziert, von der fetalen Unterernährung über gesundheitsschädliche Verhaltensmuster bis hin zur sozioökonomischen Benachteiligung. Die Ursprünge vieler chronischer Krankheiten lassen sich heute bis in die frühen Lebensjahre zurückverfolgen, was den Weg für Interventionsmassnahmen ebnet, die auf spezifische Zeiträume im Lebensverlauf zugeschnitten sind und so die (Multi)Morbidität verringern und die Lebenserwartung erhöhen können.

Zusammenfassend lässt sich sagen, dass wir in dieser Arbeit die Wechselwirkung zwischen sozioökonomischen Werdegängen und Gesundheit im späteren Leben untersucht haben. Unsere Ergebnisse deuten darauf hin, dass die Grundlagen für den lebenslangen Gesundheitsverlauf in der frühen Kindheit gelegt werden, und dass diese Entwicklung mit den richtigen Massnahmen verändert werden kann. Letztlich betont diese Arbeit, wie wichtig es ist, bei der Untersuchung gesundheitlicher Ungleichheiten im späteren Leben den gesamten Lebensverlauf zu berücksichtigen. Dies unterstreicht, dass die öffentliche Gesundheit nicht nur das Individuum ins Visier nehmen sollte, sondern auch die gesellschaftlichen Faktoren, die gesundheitliche Ungleichheiten innerhalb und zwischen den Generationen aufrechterhalten.

Chapter 1 | Introduction

Life course epidemiology

Life course epidemiology is the study of health and disease across the human life course, starting from gestation, to childhood, adolescence, and into adulthood and later life (Kuh & Shlomo, 2004). It is interested in the long-term biological, sociological, and behavioral processes that shape disease risk in later life (**Figure 1**) and draws from a range of disciplines, including genetics, psychology, sociology, public health, and different fields of epidemiology. Its origins stem from growing interest in the "long arm of childhood", i.e., the far-reaching effects of childhood exposures on later-life health, from an epidemiological as well as a sociological perspective (Elder, 2018; Hayward & Gorman, 2004). One example is the – sometimes contentious (Almond & Currie, 2011; Paneth & Susser, 1995) – Barker hypothesis that states that some adult chronic diseases, such as diabetes or hypertension, can partially be explained by fetal nutrition, as fetal exposure to limited nutrients changes the developing body's physiology and metabolism in a way that the effects can still be observed decades later, in mid and later life (Barker, 1997).

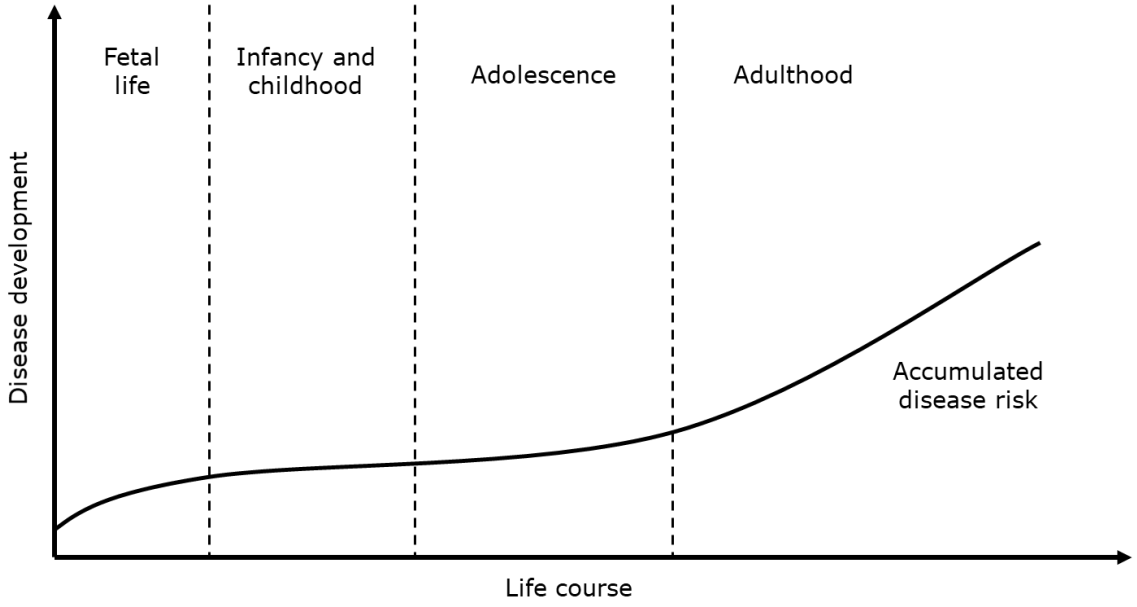

Figure 1 | *Conceptual framework for a life-course approach to health. This figure was adapted from Aboderin et al. (2002).*

A common way to conceptualize life course research is based on five basic principles (Elder Jr & Shanahan, 2006). First, life-span development: human development and ageing are lifelong processes not restricted to specific life stages. Second, agency: people have the capability to take actions and make choices that shape their lives, within the constraints of environmental, social, and historical contexts. Third, time and place: every individual life course is embedded within and influenced by its specific historical time and place. Fourth, timing: the same events, behaviors and policies can have different effects depending on when they happen in the life course. And fifth, linked lives: people do not experience life alone, but influence each other through shared interdependent relationships.

A fundamental aspect of life course epidemiological research is the utilization of longitudinal data (Ben-Shlomo et al., 2016). Data sources can include (birth) cohorts, population-based cross-sectional studies, health records, and databases, ideally collecting information on health, social, economic, and environmental factors. The advancement of life course epidemiology has also been facilitated by the collection of biomarkers, such as proteins and metabolites, that allow a better understanding of the biological mechanisms linking exposures and diseases across the life course (Kivimäki et al., 2021; Sudlow et al., 2015). Analyses in life course epidemiology often integrate statistical techniques like event history analysis (Wu, 2003), growth curve modeling (Macmillan & Furstenberg, 2016), sequence analysis (Aisenbrey & Fasang, 2010), and multi-study analysis (Zuber et al., 2023), allowing researchers to assess the independent and combined effects of early life and later life influences (Mayer, 2009). Ultimately, the goal is to identify underlying causal pathways as well as critical or sensitive periods for intervention to reduce the burden of disease in the population.

While life course epidemiology can offer many insights, it also presents its share of challenges and limitations. One notable challenge is the need for high-quality longitudinal data, which can be time-consuming and costly to collect. Retrospective recall bias can affect the accuracy of historical information, particularly in studies that rely on self-reported data (Berney & Blane, 1997). Additionally, attrition and loss to follow-up in long-term cohort studies can introduce selection bias and hinder the generalizability of findings (Ioannidis, 2005). Researchers also encounter difficulties in establishing causality when studying associations between life course exposures and outcomes due to the complexity of long-term causal pathways (Moore & Brand, 2016) and time-varying exposures (Power et al., 2023).

Despite these challenges, knowledge gained from life course epidemiology is increasingly implemented in public health. The life course is a fundamental idea in the World Health Organization's (WHO) world report on ageing and health (WHO, 2015), is featured in the United Nation's Sustainable Development Goal 3, to "ensure healthy lives and promote well-being for all at all ages" (UN, 2020), and is a key concept in the Lancet Commission on hypertension's call to action for a life course strategy to address the global burden of hypertension (Olsen et al., 2016). What these initiatives have in common is that they aim to identify

underlying and far-reaching risk factors for disease development in order to address the root causes of health disparities. Life course epidemiology has far-reaching implications for improving the well-being of populations, from enhancing maternal (Orchard et al., 2023) and child health (Cusick & Georgieff, 2016), most notably in the first 1,000 days of life (Darling et al., 2020), to tackling chronic diseases (Ben-Shlomo & Kuh, 2002) and promoting healthy ageing (Kuh et al., 2013). It underscores the importance of targeted interventions and offers a more comprehensive view of health that goes beyond singular life periods. As public health initiatives increasingly embrace a life course perspective, they should become better equipped to address the challenges of an ageing population affected by a high burden of chronic non-communicable diseases.

Social inequalities in health

The study of social inequalities in health centers on the examination of differential health outcomes among social groups, driven by disparities in factors such as income, education, race, and gender (Bartley, 2016). These inequalities manifest as differences in disease burdens, mortality rates, and access to healthcare services. For example, people with low educational attainment are more likely to become multimorbid (Pathirana & Jackson, 2018), have lower self-rated health (Furnée et al., 2008), and die earlier (Mackenbach et al., 2019) compared to those with higher education. Health inequalities have been described as "systematic, socially produced (and therefore modifiable) and unfair" by the WHO, recognizing that many health outcomes are not random but the product of a life-long exposure to unequal socioeconomic contexts (Matheson et al., 2020; Whitehead & Dahlgren, 2006).

The term "inequalities", also "disparities", therefore, is used to describe differences due to risk factors that can and should be modified, whereas health "variations" can be used to describe differences with less of a value judgment. Health inequality is also distinct from health inequity that describes whether health services reflect health needs, i.e., how fairly health services are distributed across different groups of people (Shaw et al., 2007). Health equity means paying special attention to those at greatest risk of poor health, based on the ethical viewpoint that health-sustaining resources are not a commodity but a human right, the "right to health", and should therefore be distributed in a way that everyone has the same chances at achieving good health (Braveman, 2014). Nevertheless, it is important to keep in mind that these definitions are not standardized and sometimes used interchangeably (Braveman, 2006).

There are different ways to measure social inequalities in health, both on the absolute and relative scale. Absolute measures, such as rate or risk differences, quantify the absolute gap in health outcomes between social groups. These

measures provide a more tangible assessment of inequalities that can be better indices of public health importance (Shaw et al., 2007). For example, one study assessing the absolute differences in male mortality from smoking between high and low social strata found a mean absolute difference of 19%, concluding that "widespread cessation of smoking could eventually halve the absolute differences between these social strata in the risk of premature death" (Jha et al., 2006). On the other hand, relative measures, including risk or hazard ratios, offer a relative perspective, focusing on proportionate disparities. These ratios express how many times higher or lower the health risk is for one group compared to another, allowing for a more nuanced interpretation of the magnitude of inequalities. For example, in a European comparison between high and low socioeconomic status (education, occupation) between 1990 and 2010, absolute inequalities in self-rated health remained stable, while relative inequalities increased (Hu et al., 2016).

The distinction between relative and absolute measures of social inequalities is important. It is often argued that relative risks are better indices of etiological effects, therefore more interesting to epidemiological studies, whereas absolute differences are more useful for public health interventions. This might explain why a review of 344 articles on health inequalities found that 88% reported a relative measure, 9% reported an absolute measure, and only 2% reported both (King et al., 2012). Experimental studies have shown that relative risk measures often lead to an overestimation of the efficacy of a particular treatment, thus affecting decision making (Forrow et al., 1992; Malenka et al., 1993). Absolute and relative inequalities sometimes also paint a different picture of whether health improvements have been made, as seen in the example above where absolute inequalities remained stable, but relative inequalities have increased. Thus, care should be taken when choosing how to report inequalities. For this thesis, as we are aiming to produce evidence useful for public health interventions, we are reporting absolute risk measurements (Chapters 5 and 6).

Intergenerational inequalities in health

Social inequalities in health are not limited to one lifetime, but can track intergenerationally (Hoke & McDade, 2014; Willson & Shuey, 2019). These inequalities are the result of a transmission of health advantages or disadvantages from one generation to the next, be it due to genetics, socioeconomic status, or shared environmental influences (Ahlburg, 1998; Bygren, 2013). For example, studies suggest that maternal economic disadvantage in the prenatal period leads to worse newborn health through poor health behaviors, exposure to harmful environmental factors, worse maternal health, and limited access to medical care (Aizer & Currie, 2014). A related but distinct concept is that of intergenerational social mobility which refers to the relationship between the socioeconomic status of parents and the status of their children (Causa & Johansson, 2009); this concept is discussed in more details in Chapters 4 to 7 and applied in Chapters 5 and 6.

There are multiple pathways that explain the intergenerational transmission of health. Firstly, there is a genetic component that makes individuals of the same family more likely to experience similar health outcomes (Thompson, 2014). Secondly, childhood and adolescence are time periods of strong social influence that establish health behaviors similar to that of the surrounding social network, i.e., family and peers (Perez-Felkner, 2013). Simply put, if parents smoke, consume alcohol, and never exercise, their offspring is likely to follow the same behaviors. Lastly, the social theory of cumulative dis/advantage states that advantages tend to lead to more advantages in the future, or "success breeds success", and this also holds true across generations (Dannefer, 2003). Highly educated parents tend to raise highly educated children (Schuck & Steiber, 2018), wealth can be directly transferred to the next generation via inheritance, and strong social networks make it easier to establish even more helpful connections (Cullati et al., 2018). This theory can also be applied to health outcomes; for example, poor childhood health makes poor health in mid-life more likely, which in turn raises the risk of subsequent health limitations and premature mortality (Blackwell et al., 2001; Hayward & Gorman, 2004).

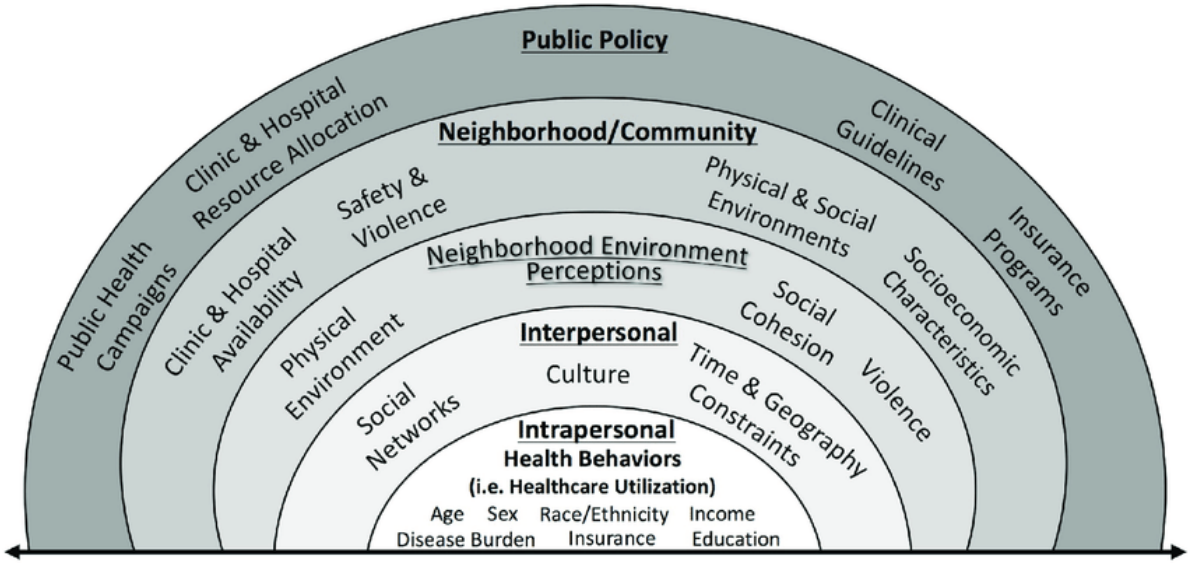

Figure 2 | *The eco-social perspective on health. This figure was reproduced from Ceasar et al. (2020).*

The intergenerational transmission of health inequalities can be stopped with the right public health interventions. To do so, it is crucial to recognize that these disparities are not solely a result of individual choices or behaviors but are deeply rooted in systemic, structural, and environmental factors (Krieger, 2001; Krieger & Davey Smith, 2004). The eco-social perspective on health (**Figure 2**) recognizes that individuals are embedded within multiple social circles, i.e., families, peers, neighborhoods, cities, countries, and each circle has an influence on health on a personal and population level (Krieger, 1994; Shultz et al., 2021). To break the intergenerational transmission of health inequalities, policies can target different eco-social levels across the life course. A helpful guideline here is the theory of

resource substitution which states that socioeconomic resources, like education, power, or wealth, can substitute for one another should one be lacking (Ross & Mirowsky, 2011). This means that the right interventions, like promoting high individual education in those with poorly educated parents, can help overcome health disadvantages due to family backgrounds. Such interventions can have long-lasting benefits that extend towards younger and older family members and can ensure that health advantages, rather than disadvantages, are passed on to future generations.

Mortality

Mortality is a fundamental measure of population health. Life expectancy at birth, i.e., the number of years a person can expect to live, has risen almost universally across the globe over the last decades, mostly due to a reduction in child mortality and mortality due to infectious diseases (Wang et al., 2016). The leading cause of death worldwide are now non-communicable diseases, mainly driven by cardiovascular diseases and cancer (**Figure 3**) (Roser, 2021). What makes mortality interesting as a public health target is that death cannot be prevented. Instead, interventions may focus on delaying death, improving quality of life leading up to death, or reducing inequalities in death.

While life expectancies have continuously improved, from 61.7 years in 1980 to 71.8 years in 2015, inequalities in life expectancies persist (Dugravot et al., 2020; Marmot et al., 1991; Wang et al., 2016). Individuals with high educational attainment (Mackenbach et al., 2019), higher occupational class (Stringhini et al., 2017), and higher wealth (Demakakos et al., 2016) regularly outlive their less advantaged peers. For example, Mackenbach et al. (2019) found that the gap between life expectancies of low and high educated individuals was 2.3 (95% confidence intervals (CI): 2.2 to 2.6) to 8.2 (95% CI: 8.0 to 8.4) years among men and 0.6 (95% CI: 0.5 to 0.6) to 4.5 (95% CI: 4.2 to 4.7) years among women, depending on the country of residence. Not only that, but some countries, like England or the United States, experience a worsening of social inequalities in life expectancies (Bennett et al., 2018; Bosworth, 2018). Aiming to explain how social inequalities raise mortality risk, one study in the UK reported that low socioeconomic status increases the risk of multimorbidity, frailty, and disability, but does not affect mortality risk after the onset of these adverse health conditions (Dugravot et al., 2020). This indicates that socioeconomic factors might not have a direct effect on mortality, but work indirectly through intermediary health outcomes across the life course.

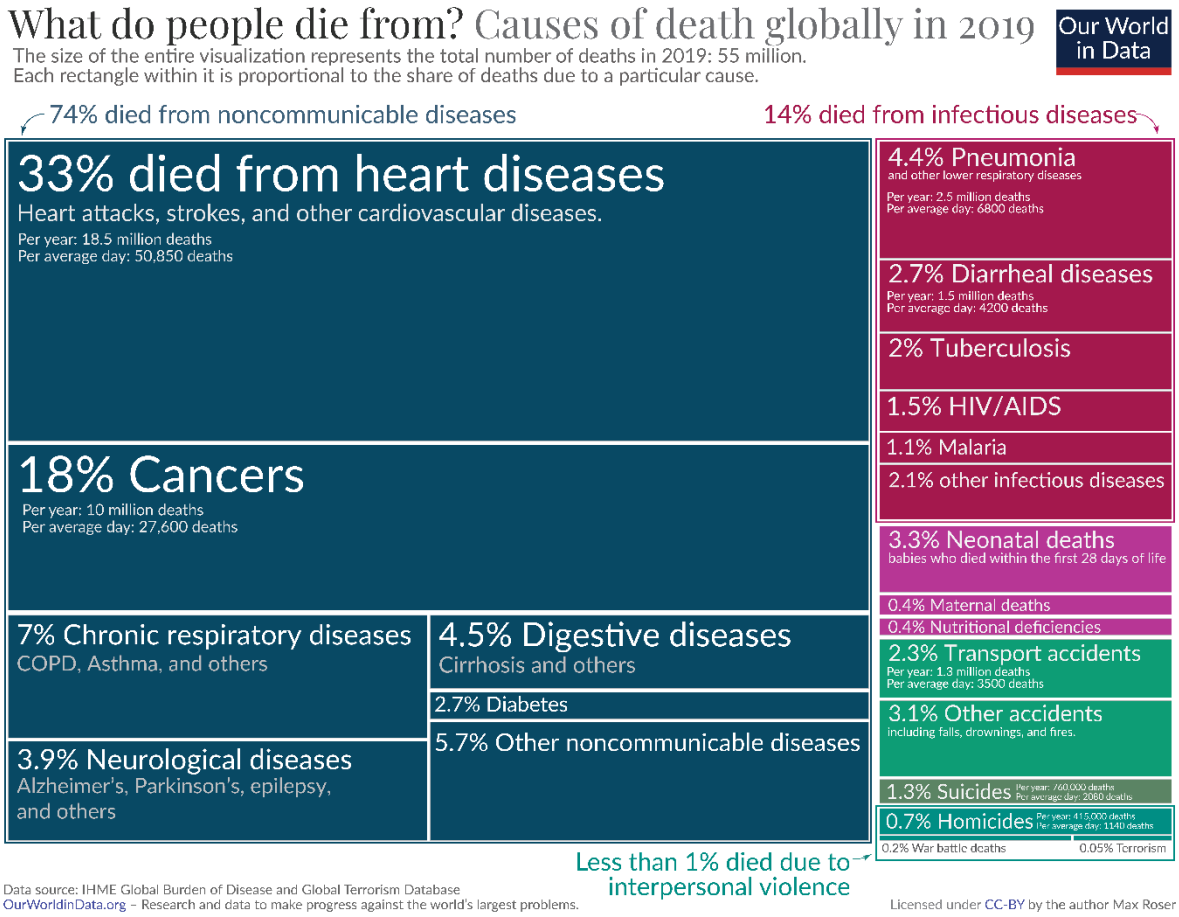

Figure 3 *| Causes of death globally in 2019. This figure was reproduced from Roser (2021).*

In Europe, the situation is complex. Mackenbach et al. (2016) assessed changes in social inequalities in mortality, comparing low and high socioeconomic groups (education, occupational class), between 1990 and 2010 in 11 European countries. They found that all-cause mortality declined among both low and high socioeconomic groups in most European countries. Relative inequalities (rate ratios) in mortality, however, widened in almost all countries, due to a smaller percentage decline in mortality in lower socioeconomic groups. Conversely, absolute inequalities (rate differences) narrowed by up to 35%, due to a smaller absolute decline in mortality in higher socioeconomic groups. The same result was observed for premature mortality (Mackenbach et al., 2015). Interestingly, the improvements in absolute inequalities did not differ depending on whether countries had employed national strategies targeting health inequalities, suggesting these improvements were most likely a byproduct of population-wide behavioral changes and improvements in disease prevention and treatment overall.

Taking these findings together, they suggest that while mortality trends have generally improved over the last decades, social inequalities in mortality persist, but potentially with differing patterns depending on whether one assesses them on the relative or absolute scale. One possible way for public health to address and

reduce social inequalities in mortality is wide-scale primary prevention, i.e., the prevention of the development of diseases in the first place (Gillman, 2015; Kaplan & Lynch, 1999). Individual risk factors need to be contextualized within socioeconomic structures that give differential access to health-protective resources, such as knowledge, money, or beneficial social connections, and thus determine which people are put "at risk of risks" (Link & Phelan, 1995; Phelan et al., 2010). Possible ways to achieve that could be a reduction of resource inequalities in the first place, or the development of interventions that benefit individuals irrespective of their own resources or behaviors, for example mandating salt (NaCl) reductions in food production rather than advising consumers to reduce their salt intake (Phelan et al., 2010). Ultimately, the aim should be to continuously improve mortality trends, while also distributing that health more equally.

Multimorbidity

Multimorbidity, also sometimes referred to as comorbidity, is the co-occurrence of two or more chronic diseases in the same person. It poses a challenge to individuals and health care systems alike since multimorbid patients are more likely to be admitted to hospitals, have a lower health-related quality of life, and die prematurely compared to those with singular or no chronic diseases (Menotti et al., 2001; Vogeli et al., 2007). Multimorbidity becomes more prevalent as people age (**Figure 4**) which poses a problem for societies facing an ageing population (Barnett et al., 2012). The findings of the most recent Global Burden of Disease Study (GBD) show that people are living longer, but with more diseases and increased disability, making multimorbidity a major public health challenge of the future (Atun, 2015; Vos et al., 2020).

While the definition of the co-occurrence of minimum two chronic diseases in the same person is the most common definition of multimorbidity, much discourse around this topic exists. For one, the terms "multimorbidity" and "comorbidity" are sometimes used interchangeably, despite the latter more correctly referring to the co-occurrence of multiple diseases with one main index disease at the center (Valderas et al., 2009). Some studies define multimorbidity as three or more diseases, most often in the form of "complex multimorbidity", the co-occurrence of three or more chronic conditions affecting three or more different body systems within one person (Harrison et al., 2014). There have also been suggestions to make multimorbidity more relevant for clinical work, namely by adding disease severity and symptoms into the definition (Willadsen et al., 2016). Other concepts often mentioned in this context are the Charlson Comorbidities Index (CCI), which considers 17 comorbidities and weighs them from 1 to 6 on their mortality risk and disease severity (Roffman et al., 2016), or the Index of Coexisting Disease (ICED)

that measures the severity of 14 chronic diseases and the resulting functional limitations (Diederichs et al., 2011).

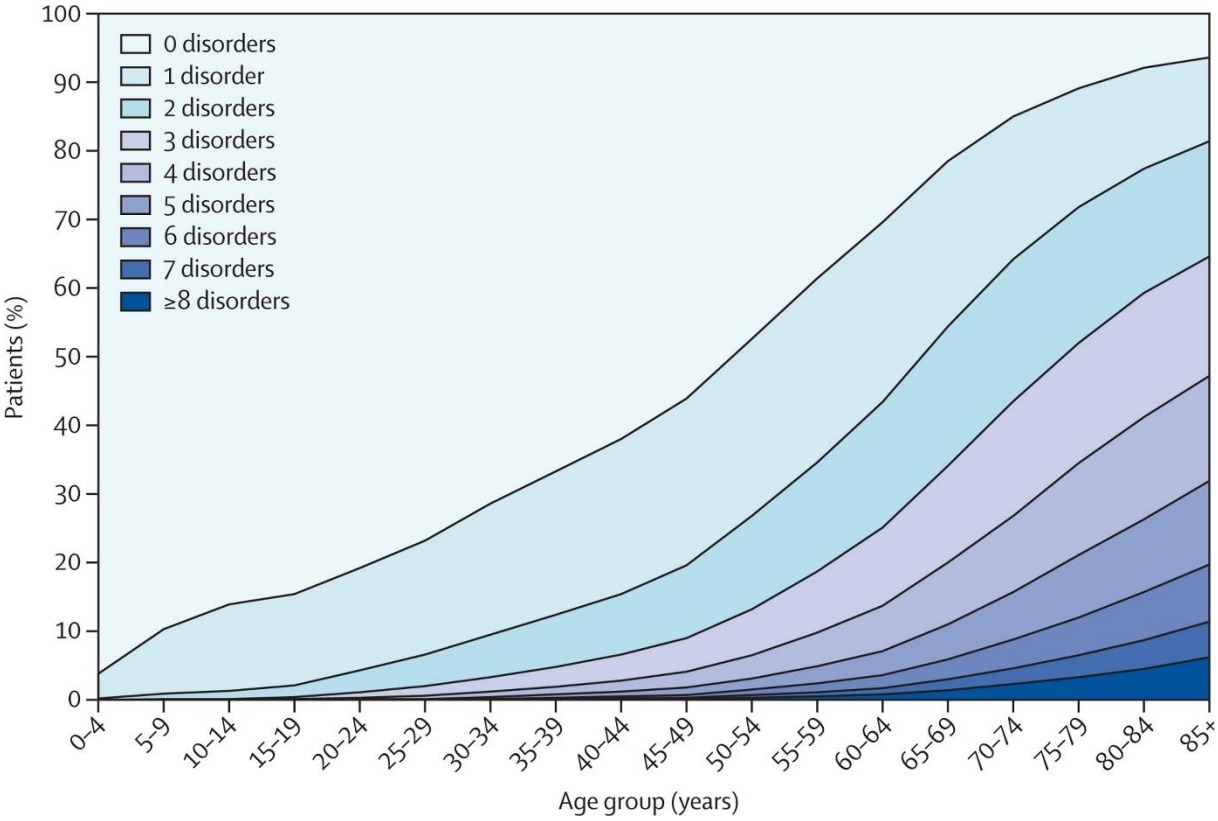

Figure 4 | *Number of chronic disorders by age group in a Scottish patient population of 1,751,841 individuals. This figure was reproduced from Barnett et al. (2012).*

The biggest challenge in homogenously defining multimorbidity, however, lies in the question of which and how many chronic diseases to consider. A systematic review including 163 articles on multimorbidity definitions has found a range of 4 to 147 different conditions considered (Willadsen et al., 2016). Most studies used diseases, i.e., diagnosed conditions, but others also included risk factors, e.g., hypertension or obesity (Agborsangaya et al., 2012), or symptoms, e.g., back pain or dizziness (Aarts et al., 2011). Unsurprisingly, multimorbidity prevalence can vary widely between studies, making it unclear whether these differences are due to actual differences between populations and study settings, or whether they are due to different definitions and conditions considered (Fortin et al., 2012).

As a result, capturing the global burden of multimorbidity is challenging. One meta-analysis of 70 observational studies across 49 countries gives a pooled multimorbidity prevalence of 33.1% (95% confidence intervals (CI): 30.0 to 36.3) in the general population (Nguyen et al., 2019). Within those studies, prevalence ranged in high-income countries from 3.5% (Hong Kong) to 70% (Russia), and in low- and middle-income countries from 1% (India) to 90% (China). Another meta-analysis, based on 126 studies and including nearly 15.4 million people, finds similar results with a global multimorbidity prevalence of 37.2% (95% CI: 34.9 to

39.4) (Chowdhury et al., 2023). Other consistent findings are that multimorbidity risk is higher in socioeconomically disadvantaged (low education, low income) (Barnett et al., 2012; Salisbury et al., 2011) as well as older individuals (Barnett et al., 2012; Fortin et al., 2012). However, even though age is the strongest driver of multimorbidity, more people under the age of 65 are afflicted with multimorbidity than those over 65 in absolute numbers, partially because more people in the general population are in that age group (Skou et al., 2022). This highlights that multimorbidity is not an exclusively geriatric disease, but a public health burden that affects all age groups.

In order to tackle this burden, two key aims emerge: one, shifting treatment paradigms from a singular-disease to a multi-disease perspective, and two, preventing the development of chronic diseases and thus multimorbidity in the first place. Regarding the treatment of multimorbid patients, many health care systems still employ a singular-disease perspective, often leading to a fragmentation of care over different medical specializations as well as to polypharmacy, the simultaneous and prolonged prescription of multiple drugs in one patient (Calderón-Larrañaga et al., 2012). A health care system recognizing the needs of multimorbid patients could coordinate treatments, be mindful of how different diseases interact, and focus on patients' overall well-being (Salisbury, 2012). Regarding prevention, life course epidemiology has made it clear that the origin of many chronic diseases can be traced back to early life. It is most effective, thus, to prevent the emergence of risk factors in the first place, such as health-detrimental behaviors, hypertension, or obesity, by acting early in life (Skou et al., 2022). Ideally, prevention and improved treatment should go hand-in-hand in order to reduce the burden of multimorbidity in the population and improve the quality of life of those afflicted by it.

Summary

At the heart of this thesis is a life course epidemiological perspective which is interested in the long-term processes that determine health in later life. Early life plays a key role in establishing patterns and setting trajectories that can, at least partially, explain health outcomes later in life. These trajectories are influenced by many factors, including socioeconomic factors like education or occupation, that result in social gradients in health where more advantaged individuals regularly experience better health outcomes than their less advantaged peers. Most importantly, many of these factors are modifiable, meaning if their link to health is better understood, they can be intervened on to improve population health.

What is still unclear is how life-course socioeconomic trajectories exactly interact to affect health in later life and what the magnitude of the effect of this interaction on inequalities in mortality and multimorbidity is. Therefore, we aim to examine

how these social inequalities in health are linked to the life course at a population level, focusing particularly on the intergenerational transmission of health via educational attainment, since this exposure is a widely used indicator of socioeconomic position and can potentially be modified via social policies. For that, we have chosen the outcomes of mortality and multimorbidity, since they are comprehensive markers of overall population health. Throughout this work we aim to keep the link between life course epidemiological research and public health and hope that by doing so, we can not only deepen our understanding of social inequalities in health, but also create actionable evidence for a healthier and more equitable society.

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Chapter 2 | Objectives

The overarching objective of the research presented in this thesis is to assess the link between socioeconomic trajectories and inequalities in multimorbidity and mortality from a life course perspective. This objective is divided into four aims, each with their own research questions. The fourth aim is a more exploratory work that, besides answering the questions below, aims to place the three preceding studies into a wider context and to discuss the implications of life course research for public health.

Aim 1 | Scoping review on the effect of life course socioeconomic trajectories on multimorbidity (Chapter 4)

- What is the available evidence on the association between socioeconomic trajectories throughout the life course and multimorbidity in later life?
- Which life course models and frameworks are supported by the empirical studies included in the scoping review?

Aim 2 | Assessment of the effect of intergenerational educational trajectories on multimorbidity in later life (Chapter 5)

- What is the role of parental and individual education in shaping intergenerational inequalities in multimorbidity?
- Do these inequalities differ by sex?

Aim 3 | Assessment of the effect of intergenerational educational trajectories on mortality in later life (Chapter 6)

- What is the role of parental and individual education in shaping intergenerational inequalities in longevity?
- Does country-level social net expenditure of the country of residence mitigate these inequalities?

Aim 4 | Review on the implications of life course epidemiology for public health (Chapter 7)

- How does life course epidemiology change the way the etiology of chronic diseases is understood?
- How can life course epidemiology inform population-based, high-risk, and vulnerable-population preventive strategies?

Chapter 3 | Methodology

This chapter gives a general overview of methods and data sources relevant to the research presented in this thesis. More detailed methods are described in each study. The SHARE cohort has been chosen as the data source for Chapters 5 and 6 since it offers the necessary information needed to answer the research questions introduced in Chapter 2. It is a multi-country cohort with data on childhood (e.g., childhood health, used as a confounder in Chapter 5), parental education (part of the exposure in Chapters 5 and 6), as well as multimorbidity and mortality in later life (outcomes of Chapters 5 and 6, respectively). Since the underlying research questions are causal in nature, we performed causal inference using this observational data. Finally, the framework of scoping reviews provided the best way to collect and synthesize the studies presented in Chapters 4 and 7 due to the open-ended nature of their research questions.

SHARE cohort

The Survey of Health, Ageing, and Retirement in Europe (SHARE) is a longitudinal cohort study with a participant population of community-based Europeans aged 50 and above (Börsch-Supan et al., 2013; Börsch-Supan et al., 2015). It collects both prospective and retrospective data across financial, behavioral, social, and health dimensions, in order to study the well-being of an ageing population. SHARE is conducted across 28 European countries and Israel, allowing for cross-national comparisons. It was launched in 2004 and has been conducted biennially, with a total of 8 waves and over 140,000 participants available currently (**Figure 5**). Respondents are a representative sample of all people aged 50 years and older at the time of sampling who have their regular domicile in the respective SHARE country and are not living in nursing homes (Bethmann et al., 2019).

Interviews are conducted using computer-assisted personal interviewing (CAPI) (Martin & Manners, 2014), as well as self-administered questionnaires. While most answers are self-reported, and therefore dependent on respondents' knowledge and interpretation of a question, some physical measurements are taken as well, including grip strength or walking speed, though their application can vary between waves and countries (Börsch-Supan et al., 2013). Wave 3 was a retrospective life history survey called SHARELIFE, making use of life history calendars to collect data across the life course from childhood health and living conditions, to adulthood employment, accommodations, partnerships, and children (Freedman et al., 1988; Schröder, 2011). This retrospective life history survey was repeated

in Wave 7 for non-respondents in Wave 3 and for the new participants of countries included after Wave 3. Overall, SHARE aims to make their data easily interpretable and comparable, thus making use of generated variables, like multimorbidity status, and standardized measurements like the International Standard Classification of Education (ISCED) for educational attainment.

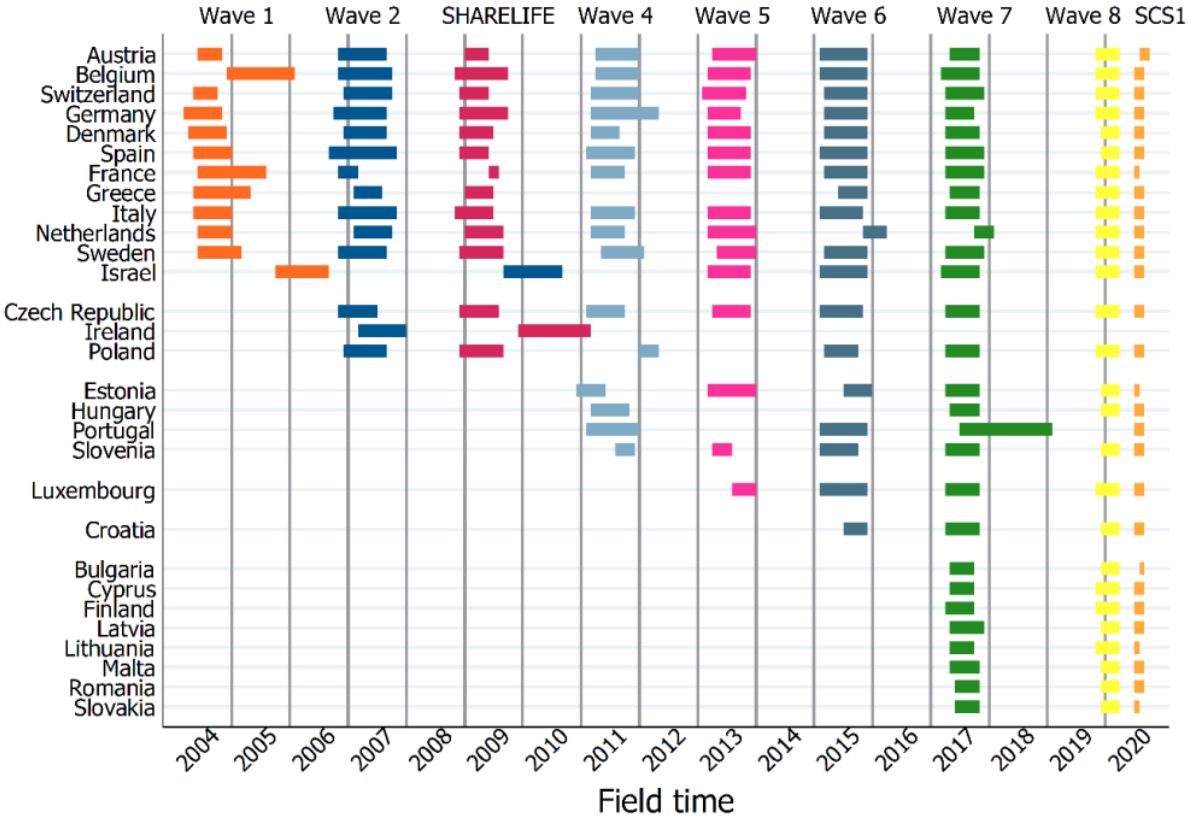

Figure 5 | *SHARE waves and field times. SCS1: first SHARE Corona Survey. This figure was reproduced from Bergmann et al. (2022).*

SHARE is part of a larger network of population-based cohort studies interested in healthy ageing (Lee et al., 2021). The 19 studies in 46 countries are often referred to as the Health and Retirement Study (HRS) family of surveys, named after the first study in this family launched in the United States in 1992 (Sonnega et al., 2014). The Gateway to Global Aging Data is a data and information platform that creates and releases harmonized data sets containing a subset of data with variables defined to be as comparable as possible between these surveys and over time (Lee et al., 2021). Thus, it is possible to compare the findings of SHARE not only within its participating European countries, but also across continents with comparable data from the United States, Mexico, India, Japan, China, and others.

Causal inference from observational data

Causal inference from observational data aims to determine cause-and-effect relationships based on non-experimental or observational data (Listl et al., 2016).

In the case of this thesis, we are aiming to determine the effect of intergenerational educational trajectories on multimorbidity and mortality based on the observational data collected in the SHARE cohort study. In contrast to experimental studies, where researchers can manipulate variables and control for any potential confounders already at study design, observational studies rely on existing data collected without experimental control. In epidemiology, causal inference often needs to be drawn from observational data since experimental research is either unfeasible and/or unethical (Nichols, 2007).

In order to perform causal inference from observational data, a causal model built from expert knowledge is needed. This means that as a first step to causal analysis, assumptions about the relationships between variables of interest need to be defined and described, often in the form of causal diagrams like directed acyclic graphs (DAGs) (Igelström et al., 2022). These assumptions need to be justified based on theory and/or existing evidence. This includes specification of exposure and outcome, potential confounders, mediators (if part of research question), as well as all assumed causal associations between these.

The key challenge for causal research is the fact that observational data are not only subject to selection and measurement bias, like experimental studies are, but also to bias from confounding, which can result in an underestimation or overestimation of the effects of interest (Hammerton & Munafò, 2021). Therefore, researchers aiming at causal inference need to make use of different methods to mitigate these biases. One approach is that of triangulation where multiple approaches, both design-based and statistical, are used to strengthen research findings by either reducing the impact of biases or at minimum identifying their size and direction (Hammerton & Munafò, 2021). Since design-based adjustments were not possible for the work in this thesis, we have relied on statistical methods to strengthen our research findings in Chapters 5 and 6, such as inverse probability weighting.

Inverse probability weighting (IPW) is based on knowledge gained from the causal model defined in the first analysis step, specifically which factors might be potential confounders. It assigns differential weights to each participant based on their probability of being selected as a participant, experiencing an exposure, or being lost to follow-up, depending on what the IPW is applied for (Mansournia & Altman, 2016). This is a two-part process where first the probability, or propensity, of being exposed to the risk factor of interest is calculated, and then weights are calculated as the inverse of this propensity score (Chesnaye et al., 2022). This technique creates a "pseudo-population" in which confounders are equally distributed across exposed and unexposed groups, thus balancing the study population and reducing the impact of measured confounding.

Scoping reviews

Scoping reviews are non-systematic reviews with the aim to synthesize and present research evidence on a chosen topic. They are similar to but distinct from other non-systematic reviews like mapping or narrative literature reviews (Grant & Booth, 2009). What differentiates scoping reviews from other formats is their focus on mapping the extent, range, and nature of research activities, whereas systematic reviews are generally aiming to sum up the best available research on a specific question, meaning they usually have to restrict the scope of this question to a single study design, exposure and outcome (Pham et al., 2014). Scoping reviews are especially useful when the topic of interest has not yet been extensively reviewed or is of a complex or heterogeneous nature, as is the case in the studies presented in Chapters 4 and 7. They can also serve as a pre-cursor to systematic reviews by identifying gaps in the literature and determining the potential scope of a systematic evaluation of the literature.

Scoping reviews follow systematic and transparent guidelines, best summarized in the PRISMA-ScR guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) (Tricco et al., 2018). Their checklist contains 22 reporting items aiming to increase methodological transparency. The full checklist can be found in Appendix B of Chapter 4.

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Chapter 4 | Life course socioeconomic conditions and multimorbidity in old age – A scoping review

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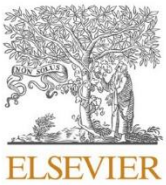

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Review

Life course socioeconomic conditions and multimorbidity in old age – A scoping review

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ABSTRACT

Multimorbidity disproportionally affects individuals exposed to socioeconomic disadvantage. It is, however, unclear how adverse socioeconomic conditions (SEC) at different periods of the life course predict the occurrence of multimorbidity in later life. In this scoping review, we investigate the association between life course SEC and later-life multimorbidity, and assess to which extent it supports different life course causal models (critical period, sensitive period, accumulation, pathway, or social mobility). We identified four studies (25,209 participants) with the first measure of SEC in childhood (before age 18). In these four studies, childhood SEC was associated with multimorbidity in old age, and the associations were partially or fully attenuated upon adjustment for later-life SEC. These results are consistent with the sensitive period and the pathway models. We identified five studies (91,236 participants) with the first measure of SEC in young adulthood (after age 18), and the associations with multimorbidity in old age as well as the effects of adjustment for later-life SEC differed from one study to the other. Among the nine included studies, none tested the social mobility or the accumulation models. In conclusion, SEC in early life could have an effect on multimorbidity, attenuated at least partly by SEC in adulthood.

1. Introduction

In ageing populations, the rise in the number of individuals suffering from multiple chronic health conditions is a major public health concern (Mathers and Loncar, 2005). Multimorbidity, the co-occurrence of two or more chronic diseases, decreases quality of life and increases risks for disability and mortality (Makovski et al., 2019; Nunes et al., 2016; Quiñones et al., 2016). Compared to frailty and disability, multimorbidity would have the strongest association with mortality, making it a central target for population health interventions (Dugravot et al., 2020; Nunes et al., 2016). Further, as life expectancy continues to rise globally, the burden of multimorbidity is expected to grow unless preventative measures are taken (Kingston et al., 2018).

Multimorbidity disproportionally affects groups exposed to disadvantaged socioeconomic conditions (SEC) (Ingram et al., 2021; Marengoni et al., 2011; Pathirana and Jackson, 2018). Hence, SEC at different periods of life has been shown to predict the risk of later-life multimorbidity. Most studies have however focused on either current SEC, i.e., at the time of multimorbidity assessment, like current education or current employment (Nagel et al., 2008; van den Akker et al., 2000), or SEC during one life period, either during childhood or young adulthood (Haas and Oi, 2018; Marengoni et al., 2008; Yang et al., 2021). However, this approach does not allow accounting for the change in SEC across the life course, i.e., along trajectories that could have differential effects on multimorbidity. There is also evidence that lifetime SEC is a stronger predictor for disease outcomes in later life than SEC at any singular life point (Tucker-Seeley et al., 2011).

What remains unclear is the causal relationship between life course SEC and multimorbidity. Different non-mutually exclusive life course causal models have been proposed to explain the link between exposures at different times across the life course and health and disease in later life. They are the critical period, sensitive period, accumulation, pathway, and social mobility models. Importantly, these theories have rarely been backed up and systematically evaluated with empirical data. Health outcomes that were reviewed through such a life course lens include quality of life or chronic diseases, among others, but not

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multimorbidity (Lynch and Smith, 2005; Niedzwiedz et al., 2012; Pudrovska and Anikputa, 2014). Thus, in this scoping review, we aimed to describe how SEC at different periods during the life course predict the risk of multimorbidity in later life. Further, we assessed to which extent the different life course causal models were supported by empirical studies.

2. Methods

2.1. Definition of life course models

In this review, we consider several life course models, that is, the (1) critical period, (2) sensitive period, (3) pathway, (4) accumulation, and (5) social mobility model.

The critical, or sensitive, period model (also called the "latency" model) refers to limited time windows during which exposures have an effect on an outcome occurring at a later point. It is an extension of the idea of biological or fetal programming that was proposed in the biological sciences to explain the "long arm of childhood", i.e., the long-lasting health effects of experiences in early life (Barker, 1997; Blane et al., 2007). The terms "critical" and "sensitive" are not homogenously defined in the literature. They can be used to distinguish between the permanence of an exposure: sensitive periods allow for a capacity to recover, whereas exposures during a critical period have a more irreversible impact, like the exposure of a fetus to tobacco or alcohol. However, some authors also use them to distinguish between the impact of an exposure, i.e., the same exposure has a greater effect if it occurs during a critical period compared to if it occurred during a sensitive period.

The pathway model views individual risk factors as interconnected. Also known as the "chain of risk" model or as the "social trajectory" model (Hendricks, 2012), the pathway model describes a sequence of exposures that are linked together: one bad experience tends to lead to another and so forth (Kuh et al., 2003). Thus, health inequalities in early life lead to further health problems, which over time widens the gap between the most advantaged and the most disadvantaged. One counter argument is the age-as-level-theory which states that, on average, discrepancies decrease over time, meaning that health inequalities in early life will eventually level out (Lynch, 2003).

The accumulation model states that it is not the timing of an exposure that matters, but its duration. Similar to a dose-response relationship, harmful exposures accumulate over the course of one's life to reach their full effect in later life. The underlying hypothesis is that stressors, like adverse health behaviors, injury, or illness, create cumulative damage that the body is eventually unable to compensate (Kuh et al., 2003).

Finally, the social mobility model focuses on how individuals move between different social groups across their life. The assumption is that this movement, whether upward or downward, has an effect on health outcomes later on (Lynch et al., 1994). This can take place on the individual, group, or intergenerational level and, depending on the field of research, may refer to movement between different social classes or income groups.

2.2. Search strategy and inclusion criteria

We conducted a scoping review following the PRISMA guidelines for scoping reviews (Tricco et al., 2018) (see Appendix B). We have chosen to conduct a non-systematic review since we have a broad research question and aim to identify a gap in current knowledge, not to estimate specific associations. We started with studies that we were familiar with due to our own expertize. To identify additional studies of interest, we scanned the reference list in those initial studies and searched for citing articles in Google Scholar. Finally, we conducted a search of online databases using PubMed and Google Scholar between April 1, 2021 and August 31, 2021. The search terms were "life course" AND "multimorbidity" OR "comorbidity" AND "socioeconomic"; the full electronic search strategy for PubMed is described in Appendix A. We only considered full-text articles published in English. There were no limitations regarding article publication date. The search was conducted by CW and SC; any disagreements regarding inclusion were resolved through discussion until consensus was established. We have not registered a research protocol prior to this work.

We considered cohort studies with prospective or retrospective data as well as cross-sectional studies with retrospective data, conducted in high-income countries. We chose to focus on high-income countries due to the rapid expansion of morbidity in these countries driven by increasing life expectancies (Hay et al., 2017; Spiers et al., 2021). Studies were considered if they examined multimorbidity at age 50 and above as an outcome, and measured SEC at different moments of the life course (at least twice). Multimorbidity could be assessed once or multiple times, self-reported or based on medical records or administrative data. Different definitions for multimorbidity were eligible, as long as they were explicitly defined.

We base our understanding of socioeconomic conditions (SEC) on previous studies in health research (Galobardes et al., 2007; Shaw et al., 2007). We define them as factors that grant individuals differential access to material, social, cultural, etc. resources within a socially stratified society. SEC could be assessed in different ways, including but not limited to income, wealth, education, etc., with a minimum of two measures across two different life periods (Shaw et al., 2007). For simplification, we have split the life course into two periods: childhood (between birth and age 18) and adulthood (ages 18 +). Periods of the life course could be uterine life, childhood, adolescence, young adulthood, middle age, or old age.

2.3. Data analysis

We summarized and described the included studies, focusing on key findings. First, we extracted information regarding SEC measurement, definition and measurement of multimorbidity, and how the association between the two was assessed. Second, we appraised if the results of the included studies support specific life course causal models (Fig. 1). We considered that:

(1) the **critical period model** was supported if an association between a SEC indicator in early life (developmental phase) and multimorbidity in later life was found, if this association was not attenuated after adjusting for later-life SEC indicators, and if the later-life SEC indicator was not associated with multimorbidity.

(2) the **sensitive period model** was supported if an association between a SEC indicator in the developmental phase of the life course and old age multimorbidity was found, if the association was attenuated but remained significant after adjusting for later-life SEC indicators, and if the later-life SEC indicator was associated with multimorbidity.

(3) the **pathway model** was supported if a SEC indicator in early life, or in later life course periods, was fully mediated by one or more later SEC indicators, suggesting an indirect effect of SEC over difference periods of the life course.

(4) the **accumulation model** was supported if any forms of an accumulation of multiple SEC exposures (in a minimum of two life course periods) was operationalized into one variable (e.g., as a score or latent variable) and found to be associated with later-life multimorbidity.

(5) the **social mobility model** was supported if an association between downward or upward social mobility and later-life multimorbidity was found. This mobility refers to the direction of an individual's change (over the life course) on the same social status indicator (e.g., starting in low social class in young adulthood and ending in high social class in late adulthood means upward social mobility).

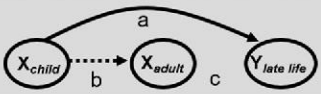
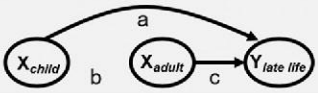
Life course models	Graphical representation
Critical period model Childhood (or any other developmental phase) is a critical period if c=0 and a≠0.	
Sensitive period model Childhood (or any other developmental phase) is a sensitive period if both c and a are ≠0.	
Pathway model Early-life exposures are fully mediated by one or more later exposures.	
Accumulation model Any form of duration of SEC exposures over the life course is operationalized.	*Not applicable*
Social mobility model The direction of intra-individual change (upward or downward mobility) is associated with the outcome.	*Not applicable*

Fig. 1. List and graphical representation of various life course causal models to understand how socioeconomic conditions (SEC) across the life course has an effect on multimorbidity later in life. X_{child} Exposure in childhood. X_{adult} Exposure in adulthood. $Y_{late\ life}$ Outcome in later life.

3. Results

3.1. Search results

We identified articles that measured the association between SEC and later-life multimorbidity (Table 1). After a full-text review, ten studies were excluded because they did not fit the eligibility criteria. Eight studies were excluded because SEC was assessed during one life period only, either during childhood or adulthood (Aminisani et al., 2020; Marengoni et al., 2008; Nagel et al., 2008; Pathirana and Jackson, 2018; Roberts et al., 2015; Schäfer et al., 2012; van den Akker et al., 2000; Yang et al., 2021). Two studies did not focus on individual life trajectories, but either on differences between birth cohorts (Canizares et al., 2018) or between individuals of different age groups (McLean et al., 2014). The final number of studies included in this review was nine, all published within the last ten years.

In these nine studies, multimorbidity was defined as the co-occurrence of min. 2 chronic conditions, with the exception of Schäfer et al. (2012) who defined it as min. 3 chronic conditions. The list of chronic conditions considered to define multimorbidity varied between studies, ranging from 5 to 46 conditions. The number of study participants ranged from 1673 (Aminisani et al., 2020) to 63,842 (Nielsen et al., 2017), with a total of 116,445 across the nine studies examined. These studies were conducted over twenty different countries, specifically New Zealand, South Korea, England, United States, and across 15 European countries included in the SHARE cohort study (Börsch-Supan et al., 2013).

3.2. Childhood as first SEC exposure

In four studies, the first SEC exposure was measured in childhood before the age of 18 (Dekhtyar et al., 2019; Henchoz et al., 2019; Pavela and Latham, 2016; Tucker-Seeley et al., 2011). Of these, two studies assessed childhood socioeconomic conditions via a composition of multiple variables: (a) child labor and parental unemployment or business failure (Henchoz et al., 2019), and (b) family's relative socioeconomic standing, whether the respondent's family has moved for financial reasons, and parental education (Pavela and Latham, 2016). One study assessed the occupation of the father during childhood (Dekhtyar et al., 2019). The fourth study assessed childhood SEC via the question "While you were growing up, before age 16, did financial difficulties ever cause you or your family to move to a different place?" (Tucker-Seeley et al., 2011). A majority of studies (n = 3) thus focused on financial variables to describe early-life SEC while one study focused on parental occupation exclusively.

Later-life SEC exposures were measured at study baseline, with the exception of Henchoz et al. (2019) who used exclusively retrospective exposures. Later-life SEC exposures included adolescence or young adulthood, with education featuring in three studies. Additional SEC exposure measurements were income and wealth in old age (Pavela and Latham, 2016) and lifetime earnings during young and middle adulthood (Tucker-Seeley et al., 2011).

In these four studies, there was an association between childhood SEC and later-life multimorbidity. Further, in these four studies, the association was partially or fully attenuated by later-life SEC exposures. Therefore, none of the studies supported childhood SEC as a critical period. They provided support for the pathway (Dekhtyar et al., 2019; Henchoz et al., 2019; Pavela and Latham, 2016) and sensitive period models (Pavela and Latham, 2016; Tucker-Seeley et al., 2011). Nothing can be said regarding the social mobility model nor the accumulation model since none of the included studies performed the necessary analyses.

3.3. Adulthood as first SEC exposure

Five studies measured respondents' first SEC in young adulthood, i.e., after the age of 18 (Aminisani et al., 2020; Nielsen et al., 2017; Schäfer et al., 2012; Singer et al., 2019; Yi et al., 2019). The SEC indicators were education and later-life income in all five studies.

Regarding the association between SEC and multimorbidity in later life, the findings were inconsistent. Aminisani et al. (2020) reported no association between old age income nor education and multimorbidity in a fully adjusted model. Singer et al. (2019), found an association for old age household wealth, but not for education; social status and occupation in middle age had minimal effects in their study. Both Nielsen et al. (2017) and Schäfer et al. (2012) found an association for education and household income, respectively household-size adjusted net income. For Yi et al. (2019), findings differed slightly depending on location, with a stronger impact of SEC in urban regions compared to rural ones. Education was only associated with multimorbidity in urban locations, not in rural ones. Higher income was associated with a lower multimorbidity risk regardless of location.

Table 1
Overview of included studies measuring associations between socioeconomic exposures and multimorbidity in later life.

Authors, Year	Country (cohort), sample size, age and sex distribution at baseline	Exposures[a] **Childhood (ages 0 – 18)**	**Adulthood (ages 18–50)**	Life course model(s) supported	Controlled for	Main results
Aminisani et al. (2020)	New Zealand (Health, Work and Retirement Study), n = 1673, age groups (percentage): 55–64 (76.7%), > 65 (23.3%), 51.9% female	Education	Education, income	No model supported	Sex, ethnicity, education, income, BMI	Higher education and income were protective factors against multimorbidity onset.
Dekhtyar et al. (2019)	Sweden (SNAC-K), n = 2589, age groups (percentage): 60–66 (44.7%), 72–78 (30.6%), 81–87 (17.0%), > 90 (7.8%), 62.0% female	Father's occupation, education	Education, occupation	Pathway	Sex, age, smoking, alcohol, dropout status, underweight, number of medications at baseline	Speed of disease accumulation was lower in individuals with more than elementary education and for active occupations compared with high-strain jobs. The association between childhood circumstances and speed of disease accumulation was attenuated by later-life experiences.
Henchoz et al. (2019)	Switzerland (Lc65 +), n = 4731, mean age 67.9 ± 1.5 years (SD), 58.0% female	Education, child labor, family economic environment, food restrictions	Education, Socioeconomic status, stressful live events in adulthood, supplemental retirement benefits	Pathway	Problematic alcohol consumption, smoking, BMI, physical activity, education, living arrangement, supplemental retirement benefits, stressful live events in adulthood	All childhood adversity indicators, including poor family economic environment, child labor, and food restrictions, were significantly associated with multimorbidity.
Nielsen et al. (2017)	15 European countries (SHARE), n = 63,842, age groups (percentage): 50–59 (28.3%), 60–69 (34.9%), 70–79 (24.4%), 80 + (12.4%), 55.4% female	Education	Household income	Sensitive period	Age, gender	Across all studied European regions, lower education and lower household income were independently and significantly associated with higher odds of multimorbidity.
Pavela and Latham (2016)	USA (HRS), n = 10,584, mean age 54.9 ± 5.76 years (SD), 55.0% female	Education, family's socioeconomic standing, moving due to financial reasons, mother's education, father's education, father's occupation	Education, income, wealth	Sensitive period, pathway	Demographics, baseline adult health, health behaviors	Lower childhood socioeconomic status (SES) was associated with increased number of chronic conditions; however, childhood SES was no longer associated with chronic conditions after adjustment for adult SES.
Schäfer et al. (2012)	Germany (MultiCare Cohort Study), n = 3189, mean age 74.4 ± 5.2 years (SD), 59.3% female	Education	Education, income, former occupation, home ownership	Sensitive period	Age, gender, marital status, household type, education, degree of autonomy at former occupation, household-size adjusted net income, home ownership	Multimorbidity was associated with education and income. Former occupation and home ownership were not associated with multimorbidity.
Singer et al. (2019)	England (English Longitudinal Study of Ageing), n = 15,046, median age 64 years (56–73 interquartile range), 53.7% female	Education	Education, household wealth, subjective social status, occupation	No model supported	Social engagement, social support and individual sense of control, physical activity, alcohol consumption, tobacco smoking, wave, age, sex	The likelihood of multimorbidity was consistently associated with household wealth. People with low subjective social status and in routine or semi-routine occupations had slightly increased odds of multimorbidity. Education was not associated with multimorbidity.
Tucker-Seeley et al. (2011)	USA (HRS), n = 7305, mean age 65 years, 53.6% female	Education, financial hardship	Education, lifetime earnings	Sensitive period	Education, gender, race, ethnicity, age	Childhood financial hardship was positively associated with a higher number of chronic conditions. Lifetime earnings was negatively associated with multimorbidity, although the noted association was relatively small.
Yi et al. (2019)	Korea (KLoSA), n = 7486, 66.8	Education	Education, income, working for pay	No model supported	Unclear	Lower education levels, lower income levels and not

(continued on next page)

Table 1 (*continued*)

	± 10.2 years (SD), 53.8% female		currently working for pay were associated with higher odds of having multimorbidity.

[a] The listed exposures are not extensive but have been selected as the ones with most relevance for this study. For a full list of measured exposures please refer back to the original studies.

Two of the five studies provided results supporting the sensitive period model (with education as an indicator of the period encompassing late adolescence and young adulthood, hereafter "young adulthood"), although not convincingly (Nielsen et al., 2017; Schäfer et al., 2012). For Nielsen et al. (2017), the association between young adulthood SEC (education) and multimorbidity was partially attenuated in a multivariable model, but it was not specified whether this attenuation was due the adjustment for later-life SEC (household income) or due to another covariate (age, sex). For Schäfer et al. (2012), young adulthood SEC (education) and later-life (income) were both associated with multimorbidity in a multivariable model. However, it was not clear which exposures were included in the multivariable model. The remaining three studies performed their analyses in a way that did not allow for testing of the life course models as we have defined them.

4. Discussion

In this scoping review, we investigated the association between SEC across the life course and later-life multimorbidity, defined as two or more chronic conditions, and assess to which extent it supports different life course causal models. In four studies, childhood SEC was associated with multimorbidity, and the associations were partially or fully attenuated upon adjustment for later-life SEC, what is consistent with a sensitive period or a pathway model. In six studies with the first measure of SEC in young adulthood, the associations with multimorbidity as well as the effects of adjustment for later-life SEC differed from one study to the other. The critical period model was not supported and there was no study to test the social mobility or the accumulation model.

The examined associations between adulthood SEC and multimorbidity risk were mostly in line with previous findings. Notably, higher educational achievement and higher economic resources had an inverse relationship with multimorbidity risk in later life when they were found to be associated. However, we examined as well studies that did not find an association between education and multimorbidity risk (Aminisani et al., 2020; Singer et al., 2019; Yi et al., 2019); a previous meta-analysis has reported on the heterogeneous results of studies assessing the association between education and multimorbidity and named differing methods of multimorbidity ascertainment as one of the possible reasons (Pathirana and Jackson, 2018). On the other hand, with the exception of (Aminisani et al., 2020), all studies found an association between economic resources (personal income, household income, wealth, etc.) and multimorbidity risk.

Importantly, the critical period model was not supported in the four studies examining the impact of childhood SEC. In other words, the association between poor SEC exposures in early life and the risk of multimorbidity in later life was modified by mid-life exposures and the later-life SEC indicator was associated with multimorbidity. This highlights the importance of intervention strategies across different periods of the life course, as no single life period seems to entirely determine multimorbidity risk. The right interventions, targeting the right predictors at the right time (or period of the life course), can decrease the burden of multimorbidity in the population. A better understanding of the link between life course socioeconomic position and multimorbidity in later life is the first step in that direction.

There are multiple possibilities for mechanisms underlying the sensitive period and pathway models. Being born into a poor family increases (i) the risk of having a low birth weight or being premature (Kuh et al., 2004), (ii) the risk of exposure to adverse childhood experiences (Walsh et al., 2019) and psychosocial stress (Kraft and Kraft, 2021), or (iii) the risk of exposure to environmental pollution (Hajat et al., 2015; Miao et al., 2015). Growing up in a family with poor socioeconomic conditions may jeopardize the development of the child across biological (e.g., brain), cognitive (e.g., language skills, memory) and social (e.g., education) characteristics, resulting in a health gradient between the most and least disadvantaged (Cooper and Stewart, 2021; Herbaut and Geven, 2019; Kuh et al., 2004; Kulic et al., 2019; Rakesh and Whittle, 2021). Alternatively, one can view early-life "success" as a form of capital that can be used to receive more advantages and benefits later on (Ferraro et al., 2009). Thus, there are most likely both biological and social drivers underlying these life course models.

However, it is important to note that for the purpose of this review, we have developed an operationalization of the life course models in which they are mutually exclusive. This may not correspond to the reality of the bio-psycho-social mechanisms underlying the association between life course SEC and multimorbidity in later life, whereby a mixture of models may be at work.

4.1. Limitations

Our study has major limitations. Firstly, both the exposure and the outcome of interest were measured heterogeneously across studies. For the exposure, different socioeconomic variables were considered by the study authors, with their own operationalizations. Further, multimorbidity was most often self-reported, which leads to an underestimation of the prevalence of multimorbidity (Ofori-Asenso et al., 2019). Additionally, though almost all studies defined multimorbidity as the co-occurrence of a minimum of two chronic conditions, the list of eligible chronic conditions differed between studies. For example, Tucker-Seeley et al. (2011) investigated multimorbidity within six common chronic conditions, whereas Schäfer et al. (2012) used a list of 46 chronic conditions in their study. The heterogeneity in how multimorbidity is constructed and examined in public health research has already been described in the literature (Diederichs et al., 2011; Ho et al., 2021; Willadsen et al., 2016). Further, it is possible that the association between multimorbidity and SEC differs depending on the disease, hence explaining some of the different findings of the included studies. Lastly, there are methodological limitations to scoping reviews. Our search was not systematic, thus we might have missed studies that could change our conclusions. We have also not assessed the quality of the included studies, increasing the risk that our findings are biased.

5. Conclusion

In this study, we studied the association between life course SEC and multimorbidity in later life and assessed the support of different life course causal models underlying this association. We have found limited support for the pathway and sensitive period models, suggesting that (a) there are developmental periods of the life course (childhood and young adulthood) which can influence multimorbidity risk in later life and (b) socioeconomic exposures may follow a chain of risk pattern in determining this risk. Based on these results, we suggest that interventions and health promotion aimed at reducing the risk of multimorbidity in old age should consider the early-life socioeconomic conditions of the targeted population. We have identified an important gap in the

literature and urge future research on multimorbidity to consider potential interactions between exposures across multiple life periods.

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Author contributions

All authors designed the study. CW and SC made the literature search. All authors reviewed the study findings. CW drafted the manuscript. All co-authors revised the first draft of the manuscript. All authors approved the final version of the manuscript before submission.

Data sharing

Access to data requires contacting the last author.

Acknowledgment

Results of this work were presented at the Swiss Public Health Conference, 25th/26th August 2021, Bern, Switzerland.

Conflicts of interest

We declare no conflicts of interest.

Appendix A

PubMed search strategy

((("life change events"[MeSH Terms] OR ("life"[All Fields] AND "change"[All Fields] AND "events"[All Fields]) OR "life change events"[All Fields] OR ("life"[All Fields] AND "course"[All Fields]) OR "life course"[All Fields]) AND ("multimorbid"[All Fields] OR "multimorbidities"[All Fields] OR "multimorbidity"[MeSH Terms] OR "multimorbidity"[All Fields])) OR ("comorbid"[All Fields] OR "comorbidity"[MeSH Terms] OR "comorbidity"[All Fields] OR "comorbidities"[All Fields] OR "comorbids"[All Fields])) AND ("socioeconomic factors"[MeSH Terms] OR ("socioeconomic"[All Fields] AND "factors"[All Fields]) OR "socioeconomic factors"[All Fields] OR "socioeconomics"[All Fields] OR "socioeconomic"[All Fields] OR "socioeconomical"[All Fields] OR "socioeconomically"[All Fields]).

Appendix B

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.

Section	Item	Prisma-ScR Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5–6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	5
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	–
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	–
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5–6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7–8
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	–
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	7–8

(*continued on next page*)

(*continued*)

Section	Item	Prisma-ScR Checklist item	Reported on page #
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	7–8
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	9
Limitations	20	Discuss the limitations of the scoping review process.	9–10
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	10
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	11

JBI Joanna Briggs Institute; PRISMA-ScR Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

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Chapter 5 | Educational inequalities in multimorbidity at older ages: a multi-generational population-based study

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Abstract

Background: Social inequalities in multimorbidity may occur due to familial and/or individual factors and may differ between men and women. Using population-based multi-generational data, this study aimed to (1) assess the roles of parental and individual education in the risk of multimorbidity and (2) examine the potential effect modification by sex.

Methods: Data were analysed from 62,060 adults aged 50+ who participated in the Survey of Health, Ageing and Retirement in Europe, comprising 14 European countries. Intergenerational educational trajectories (exposure) were High-High (reference), Low-High, High-Low, and Low-Low, corresponding to parental-individual educational attainments. Multimorbidity (outcome) was ascertained between 2013 and 2020 as self-reported occurrence of ≥2 diagnosed chronic conditions. Inequalities were quantified as multimorbidity-free years lost (MFYL) between the ages of 50 and 90 and estimated via differences in the area under the standardized cumulative risk curves. Effect modification by sex was assessed via stratification.

Results: Higher multimorbidity risk was associated with low individual education regardless of parental education. Compared to the High-High trajectory, Low-High was associated with -0.2 MFYL (95% confidence intervals: -0.5 to 0.1), High-Low with 3.0 (2.4 to 3.5), and Low-Low with 2.6 (2.3 to 2.9) MFYL. This pattern was observed for both sexes, with a greater magnitude for women. This effect modification was not observed when only diseases diagnosed independently of healthcare-seeking behaviours were examined.

Conclusions: Individual education was the main contributor to intergenerational inequalities in multimorbidity risk among older European adults. These findings support the importance of achieving a high education to mitigate multimorbidity risk.

Key-words: Education, Europe, Intergenerational Inequality, Multimorbidity

Introduction

Multimorbidity – two chronic conditions or more in an individual – is a growing public health challenge within ageing populations in Western countries as it is associated with poor quality of life, high health care costs, and an increased mortality risk.[1, 2] The prevalence of multimorbidity is higher among adults living in disadvantaged socioeconomic conditions, particularly among those with a low level of education.[3, 4, 5] This educational gradient can be explained by differential access to material and non-material health-beneficial resources.[6] However, educational inequalities in multimorbidity are influenced not only by individual but also by familial factors such as parental education, potentially leading to a long shadow of inequalities.[7]

Parental education may contribute to the amount of cultural and social capital a person has access to, and eventually to social inequalities in offspring health.[8] Particularly, parental education can affect offspring health via transference of educational attainments, as children of highly educated parents tend to be higher educated themselves. Additionally, parental education can affect offspring health via the promotion of health-beneficial behaviours like preventive healthcare use during the sensitive period of adolescence.[9] One registry-based study of Danish individuals aged 32–56 years in 2010 reported that both low individual and parental educational levels increased the odds of multimorbidity observed during eight years of follow-up.[10] Therefore, how the interplay between individual and parental education might affect the occurrence of multimorbidity in other Western countries and at older ages remains to be examined. What is also unclear is whether educational inequalities in multimorbidity risk differ by sex, as gender-related vulnerability mechanisms could either amplify or diminish the effect of education.[11] Some sex-specific differences in multimorbidity risk and prevalence have been reported, though findings are inconclusive.[12, 13, 14]

Using population-based multi-generational multi-country data, we aimed (1) to assess the role of parental and individual education in shaping educational inequalities in the risk of multimorbidity and (2) to assess potential effect modification by sex. While this is an observational study, we explicitly aimed at estimating causal effects of intergenerational educational trajectories on multimorbidity, drawing on a contemporary approach to causal inference from observational data. Specifically, we built a causal model and defined targeted estimands via counterfactual contrasts.

Methods

Data source and study population

Our study population stemmed from the Survey of Health, Ageing and Retirement in Europe (SHARE), a longitudinal cohort study spanning more than 20 European countries.[15, 16, 17] The SHARE study started in 2004 and has been conducted biennially, resulting in a total of 8 waves until 2019/2020. Our study's baseline corresponded to wave 5 (2013) being the first wave to include an assessment of parental education. During that survey year, participants were from 15 countries: Austria, Belgium, the Czech Republic, Denmark, Estonia, France, Germany, Israel, Italy, Luxembourg, the Netherlands, Slovenia, Spain, Sweden, and Switzerland. In our analysis, we excluded participants from Israel (n = 2,561) because it is not part of the European continent, and individuals with missing year of birth (n = 4). Our target population were individuals in their youth (<20 years), since potential interventions would target educational attainment in that early life period. SHARE measures both parental and individual education retrospectively.

SHARE respondents are a representative sample of all people aged 50 years and older at the time of sampling who have their regular domicile in the respective SHARE country.[18] Additionally, current partners living in the same household are interviewed at each wave regardless of their age. The number of participants at wave 5 (baseline) was 66,188, including those partners. We excluded participants younger than 50 years (n = 1,181) at baseline to keep in line with SHARE eligibility rules.

The study population at baseline was composed of 62,442 respondents (**Figure S1**). The analytic sample included 62,060 respondents, as we excluded those with a missing date of death (n = 90) and missing covariates at baseline (n = 292). During follow-up, 11,027 participants became multimorbid (n = 24,700 were multimorbid at baseline; 35,727 total), 1,303 passed away, and 12,237 were lost during follow-up, resulting in 12,793 participants being non-multimorbid and present at wave 8.

Causal model, exposure, and outcome

Our study relied on the causal model reported in **Figure 1**, that focuses on the putative effect of intergenerational educational trajectories (exposure) on multimorbidity (outcome). Four measured potential confounding factors were identified from background knowledge: childhood disease/disability, sex, country groups, and birth cohort. Their operationalization is described in supplementary materials.

Educational trajectories were constructed through the combination of individual and parental education, both self-reported by study participants. Parental education was defined as the highest educational attainment reached by either mother or father; in case one was missing, the other's educational attainment was used. Both individual and parental education were classified as "Low" for any achieved education up to lower secondary level (as per the International Standard Classification of Education (ISCED) 1997, levels 0-2) and as "High" for upper secondary education and beyond (ISCED-1997 level 3 or higher). Using this classification, we obtained four educational trajectories: High-High, Low-High, High-Low, and Low-Low, where the first part denotes the parents' education level and the second part the individual's education level.

Multimorbidity was operationalized as the self-reported occurrence of minimum two diagnosed chronic conditions from a list of pre-defined conditions. Specifically, participants were asked, “Has a doctor ever told you that you had / Do you currently have any of the conditions on this card?”. The list of possible responses spanned 17 different conditions, including “other conditions, not yet mentioned”. For this study, we followed a definition of chronic conditions as being permanent in their effects and requiring surveillance, among others.[19, 20] Thus, we included 13 chronic conditions that met this definition from SHARE’s original list, described in supplementary materials. Conditions such as cataracts, hip fractures and other fractures were excluded.

Assessment of intergenerational inequalities in multimorbidity

Our estimand was the controlled direct effect of educational trajectories on multimorbidity, corresponding to the pathway unmediated by mortality in **Figure 1**. Specifically, we estimated three controlled direct effects by comparing the intergenerational trajectories High-Low, Low-High, and Low-Low with the High-High trajectory. Colloquially, the chosen estimand formalizes educational inequalities in multimorbidity when participants are set to be immortal, thus blocking the pathway through mortality.[21] The internal validity of these effect estimates relied on several statistical assumptions described in supplementary materials.

Effects were quantified as multimorbidity-free years lost (MFYL) between ages 50 and 90. Multimorbidity-free years lost were calculated as differences between educational trajectories in expected years living without multimorbidity between ages 50 and 90. For each level of the exposure, expected number of years living without multimorbidity was calculated as the area under the corresponding cumulative risk curve standardized by the measured confounders. We chose MFYL to measure the size of inequalities on the absolute scale, to be more relevant in the evaluation of potential policy and public health actions on the examined exposure. In practice, multimorbidity probabilities were estimated via a weighted Kaplan-Meier non-parametric estimator with age as time-scale. Since the exact time a participant became multimorbid was unknown, the event was treated as interval-censored between the interview at which multimorbidity was first reported and the last interview the participant reported not being multimorbid. For those multimorbid at study baseline, we considered the interval between age 20 and age at baseline. All participants who did not become multimorbid during follow-up were right-censored at the time of wave 8. Death was treated as a censoring event and those participants were included among those lost during follow-up. The Kaplan-Meier derived probabilities were computed using the icenReg R package.[22] Effect modification (Δ) by sex was implemented by stratifying the data, estimating MFYL for both men and women, and finally calculating the difference in these MFYL.

Weights were the product of two separate stabilized inverse probability weights (IPWs) to account for (1) measured confounding and (2) potential non-random loss during follow-up.[23, 24] These models’ specification is described in supplementary materials. Confidence intervals (CI) were generated via percentiles of 1,000 bootstrap draws with replacement.

Ethics approval was not required for this study. We analysed anonymized data and informed consent was obtained at the time of original data collection. All analyses were run in R 4.1.2.

Sensitivity analyses

To assess the sensitivity of our estimates to the way diseases were ascertained (self-report of diagnosis), we examined the occurrence of only those diseases for which a diagnosis should be independent of healthcare-seeking behaviours. Specifically, we considered as the outcome a self-reported diagnosis of either stroke, cancer (excluding breast, thyroid, and prostate cancer), or stomach or duodenal ulcer. Given the small number of diseases, we focused on the occurrence of these morbidities and not of multimorbidity. Additionally, we repeated this analysis including hypertension and diabetes in the outcome – two diseases for which diagnosis can be related to healthcare-seeking behaviours. We hypothesized that if inequalities were only present when hypertension and diabetes were included, then inequalities or their potential effect modification by sex could be attributed to differences in healthcare-seeking behaviours and not in morbidity occurrence.

To assess the sensitivity of our estimates to the way education was operationalized, we lowered the high-education threshold for parental education. Specifically, we re-classified parental education as "Low" for ISCED-1997 levels 0 and 1 and as "High" for levels 2 or higher. As a further analysis we applied the same operationalization to individual education as well, for those participants born in or before 1927. This analysis was meant to account for the fact that the meaning of a "high" education could have shifted between the parental and individual generations of this study due to the educational expansion taking place in Europe in the middle of the 20th century.[25] Finally, we assessed the potential bias from the IPW models misspecification by incrementally truncating weights.[24]

Results

Analytic sample characteristics

Characteristics of the analytic sample are reported in **Table 1**. Participants had a mean age of 67 years at baseline and 55% were women. Approximately 40% of participants were multimorbid at baseline, and an additional 18% became multimorbid during follow-up (2013-2020). Prevalence of the 13 chronic conditions from which multimorbidity was ascertained is reported in **Table S2**. Participants with High-High and Low-Low trajectories accounted altogether for 63% of the non-missing sample, meaning that more than half of the participants attained the same educational level as their parents. Approximately 30% of the participants experienced upward mobility and 6% downward mobility. Additionally, a high education was achieved by nearly eight out of ten participants with high educated parents, and by four out of ten participants with low educated parents. Compared to women, a Low-High trajectory was more prevalent for men (34% versus 28%). By contrast, a Low-Low trajectory was more prevalent among women (41%) compared to men (36%). Finally, men had a higher mortality rate than women.

Intergenerational educational inequalities in multimorbidity

Multimorbidity-free years and multimorbidity-free years lost (MFYL) between ages 50 and 90 are reported in **Table 2**. While a High-High trajectory was associated with 21.1 multimorbidity-free years (95% confidence intervals: 20.8 to 21.3), High-Low and Low-Low trajectories were associated with 3.0 (2.4 to 3.5) and 2.6 (2.3 to 2.9) fewer multimorbidity-free years, respectively. A Low-High trajectory was associated with 0.2 (-0.1 to 0.5) multimorbidity-free years gained. Taken together, these findings indicate that inequalities in multimorbidity were

associated with low individual education regardless of parental education. Multimorbidity-free years lost were higher for women than for men (**Table 2** and **Figure 2**). Specifically, inequalities associated with both Low-High and Low-Low trajectories were approximately 2 years longer for women than for men.

Sensitivity analyses

Restricting the outcome to diseases assumed to be independent of healthcare-seeking behaviour yielded the same pattern of magnitude of inequalities across educational trajectories as in the main analysis, although the effect modification by sex vanished (**Table S3**). However, including hypertension and diabetes as outcomes reproduced the effect modification by sex observed in the main analysis (**Table S4**). This indicates that the sex differences observed in the main analysis could be attributed to differences in healthcare-seeking behaviours and not due to true differences in disease occurrence in men versus women.

The re-classification of parental as well as individual education for participants born in or before 1927 resulted in similar patterns and magnitude of inequalities compared to the one reported in the main results (**Table S5** and **Table S6**). This indicates that the main findings are robust to potential misclassification of education because of potential bias in self-report or because of historical drifts in educational achievements. Lastly, when truncating weights, inequalities were similar to those reported in the main analysis (**Table S7**), suggesting negligible bias from the potential misspecification of the IPWs models.

Discussion

We assessed the educational inequalities in multimorbidity across parent-offspring generations among adults aged 50 and older from 14 European countries. Regardless of parental education, adults with low education experienced a loss of approximately 2.8 years free of multimorbidity compared to those with high education, indicating that these inequalities primarily stem from individual education. Additionally, inequalities were larger for women than for men, although a supplementary analysis indicated that this effect modification could potentially be attributed to differences in diagnosis occurrence and not true disease occurrence.

This is one of few studies to examine inequalities in risk of multimorbidity by intergenerational educational trajectories among older adults. One Danish study reported both individual and parental education to be associated with the risk of certain multimorbidity patterns.[10] By contrast, our findings from 14 European countries suggest that only individual education contributes to intergenerational inequalities in multimorbidity. However, it is important to highlight that our results point to an indirect effect of parental education whereby parental education affects multimorbidity only via individual education, as participants with highly educated parents were more likely to become highly educated themselves. Additionally, we acknowledge that our study and the Danish study differ in some relevant aspects. Specifically, Schramm et al. used register-based information on 47 chronic conditions, whereas we used self-reported information on 13 different conditions, potentially leading to an underestimation of multimorbidity in our study population. Furthermore, we did not assess inequalities in specific patterns or types of multimorbidity, due to limitations in the available data. Finally, the Danish study estimated odds ratios, which overestimate risk – particularly with a common outcome

such as multimorbidity – and suffer from bias related to non-collapsibility. Taken together, the comparability of these two studies is limited.

The observed sex differences in educational inequalities are in line with other studies, whereby women experienced greater health-detrimental effects than men when exposed to low educational attainment.[26, 27] Ross and Mirowsky (2010) propose the theory of resource substitution as an explanation.[27] This theory states that socioeconomic resources can substitute for each other, meaning the less there is of one resource, the more important other resources become for compensation. The authors suggest that women may have fewer resources than men in society, including power, authority, and high earnings, making a high education more important for women. This could partially explain the observed findings, but it is important to not only consider sociological pathways (gender) but also the biological pathways (sex) at play. Research suggests that there are differences in health-relevant biomarkers according to sex at birth, with higher cardiometabolic biomarkers in men and higher inflammatory and neuroendocrine biomarkers in women, and that both sex and gender may lead to these differences.[28]

Sensitivity analyses indicated that the observed effect modification by sex could be due to differences in diagnoses occurrence. Some evidence suggests that women are more likely to visit primary care providers and are thus more likely to be diagnosed with chronic conditions than men.[29] Ultimately, this is a limitation stemming from how multimorbidity is ascertained in the SHARE dataset. Additional studies with multimorbidity ascertainment of higher validity are required to assess whether there are sex differences in educational inequalities that go beyond self-reported diagnoses.

This study's findings should be considered within the context of a few potential limitations. The findings may be subject to misclassification bias in the exposure and outcome since they were self-reported. For the outcome, misclassification could also be due to the operationalization of multimorbidity as diagnosed diseases, meaning undiagnosed diseases are missed, and because the list of diseases was limited. The potential direction of this bias is difficult to determine as it is very likely to be differential, and could have possibly masked a direct contribution of parental education to the inequalities. Future studies with more reliable ascertainment of both education and multimorbidity are warranted. Additionally, as this is an observational study, we may have bias from unmeasured confounding, and because we were unable to control for finer measured confounding factors due to positivity restrictions. Further, there could be selection bias as the study population comprises individuals that survived until age 50 or longer. This may have resulted in an underestimation of the inequalities.[30] For men, this could also explain the observed small reverse inequalities in upwardly mobile individuals compared to High-High. Thus, overall the findings may not be generalizable to the target population. Particularly, it is unclear whether the findings can be applied to more recent birth cohorts, i.e. those born after 1963. Research suggests that the burden of morbidity – and by extension multimorbidity – is evolving across demographic cohorts. More recent generations, i.e. those born after 1945, in some European countries experience greater life expectancy, but also an expansion of morbidity.[31, 32]

One key strength of our study is the utilization of a population-based multi-generational and multi-country data sample with multiple multimorbidity assessments. Further, we have adopted a causal framework to estimate marginal inequalities that, contrary to inequalities measured

via conditional hazard or odds ratios, are not affected by issues of non-collapsibility and implicit selection bias.[21]

Conclusion

Our analysis of educational inequalities in multimorbidity risk in later life provides some insights into the intergenerational transmission of social inequalities in health. The findings underscore the role of low individual education as a main contributor to higher multimorbidity risk, regardless of parental education. Additionally, inequalities were larger for women than for men, though whether this is a difference in disease diagnoses or in underlying health conditions warrants further investigation. Through a multi-generational, multi-country perspective, this study highlights the importance of achieving high education and of interventions facilitating it, in order to mitigate social inequalities in multimorbidity in later life.

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Conflicts of interest

We declare no conflicts of interest.

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Data sharing

Data is available via registration to the SHARE project website (see www.share-project.org).

Key Points

- Multimorbidity risk is higher among older adults with a low achieved education compared to those with high achieved education; growing up in a family with parents of low education, too, may increase the risk of multimorbidity at older ages independently of individual education, but empirical evidence is limited.
- Additionally, it is not well known whether intergenerational educational gradients in multimorbidity are different for women and men.
- Low individual education was the main contributor to higher multimorbidity risk, regardless of parental education.
- Educational inequalities in multimorbidity were approximately twice larger for women than for men, but it is unclear whether this is due to differences in multimorbidity occurrence or due to differences in disease diagnoses.
- These findings underscore the importance of achieving a high education and of policies facilitating it in order to mitigate multimorbidity risk at older ages.

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Tables and Figures

Table 1 *Characteristics of analytic sample. SD = standard deviation. Central and Southern Europe = Austria, Germany, Netherlands, France, Switzerland, Belgium, Luxembourg, Spain, Italy. Eastern Europe = Czech Republic, Slovenia, Estonia. Scandinavia = Sweden, Denmark.*

Characteristics	Total	Men	Women
Number of participants	62,060	27,695 (45%)	34,365 (55%)
Age at baseline (years), mean and SD	67.1 (± 10.0)	67.1 (9.7)	67.1 (10.3)
Birth cohorts			
1909 – 1927	2,773 (4.5%)	1,036 (3.7%)	1,737 (5.1%)
1928 – 1938	12,312 (19.8%)	5,482 (19.8%)	6,830 (19.9%)
1939 – 1945	12,721 (20.5%)	5,974 (21.6%)	6,747 (19.6%)
1946 – 1955	22,140 (35.7%)	10,113 (36.5%)	12,027 (35.0%)
1956 – 1963	12,114 (19.5%)	5,090 (18.4%)	7,024 (20.4%)
Childhood disease/disability			
Yes	15,629 (30.0%)	7,731 (27.9%)	10,957 (31.9%)
No	36,334 (70.0%)	19,964 (72.1%)	23,408 (68.1%)
Multimorbidity (min. 2 chronic conditions)			
At baseline	24,700 (39.8%)	10,509 (37.9%)	14,191 (41.3%)
During follow-up	11,027 (17.8%)	5,054 (18.2%)	5,973 (17.4%)
Limitations with activities of daily living (min. 1 limitation, at baseline)	7,284 (11.7%)	2,951 (10.7%)	4,333 (12.6%)
Number of deaths (2013-2020)	6,090 (9.8%)	3,259 (11.8%)	2,831 (8.2%)
Death rate, crude (deaths per 100,000 person-years)	2,343	2,865	1,936
Educational trajectories			
High-High	12,589 (20.3%)	5,932 (21.4%)	6,657 (19.4%)
Low-High	15,607 (25.1%)	7,712 (27.8%)	7,895 (23.0%)
High-Low	2,986 (4.8%)	1,034 (3.7%)	1,952 (5.7%)
Low-Low	19,583 (31.6%)	8,085 (29.2%)	11,498 (33.5%)
Missing	11,295 (18.2%)	4,932 (17.8%)	6,363 (18.5%)
Country groups			
Central and Southern Europe	39,508 (63.7%)	17,947 (64.8%)	21,561 (62.7%)
Eastern Europe	14,054 (22.6%)	5,790 (20.9%)	8,264 (24.0%)
Scandinavia	8,498 (13.7%)	3,958 (14.3%)	4,540 (13.2%)

Table 2 *Multimorbidity-free years between ages 50 – 90 years and multimorbidity-free years lost associated with different educational trajectories compared to High-High. Standardized by sex (in total sample), birth cohort, country group, and childhood disease/disability. ∆ represents effect modification.*

Educational trajectory	Multimorbidity-free years (95% CI)	Multimorbidity-free years lost (95% CI)
High-High	**21.1** (20.8 to 21.3)	-
Low-High	**21.3** (21.1 to 21.5)	**-0.2** (-0.5 to 0.1)
High-Low	**18.1** (17.6 to 18.7)	**3.0** (2.4 to 3.5)
Low-Low	**18.5** (18.3 to 18.7)	**2.6** (2.3 to 2.9)
Men		
High-High	**21.0** (20.6 to 21.4)	-
Low-High	**21.6** (21.3 to 21.8)	**-0.6** (-1.0 to -0.1)
High-Low	**19.2** (18.1 to 20.2)	**1.8** (0.6 to 2.9)
Low-Low	**19.6** (19.2 to 20.0)	**1.4** (0.9 to 1.9)
Women		
High-High	**21.1** (20.7 to 21.5)	-
Low-High	**21.1** (20.7 to 21.4)	**0** (-0.5 to 0.5) *∆ = 0.6 (-0.1 to 1.3)*
High-Low	**17.3** (16.7 to 18.0)	**3.8** (3.1 to 4.5) *∆ = 2.0 (0.6 to 3.2)*
Low-Low	**17.6** (17.3 to 17.9)	**3.5** (3.0 to 4.0) *∆ = 2.1 (1.4 to 2.8)*

Figure 1 *Causal model underlying our study. Solid arrows: putative effect of educational trajectories (exposure) on multimorbidity (outcome) via direct and indirect (all-cause mortality) pathways. Dotted arrows: measured time-invariant confounding factors. U: potential unmeasured confounding.*

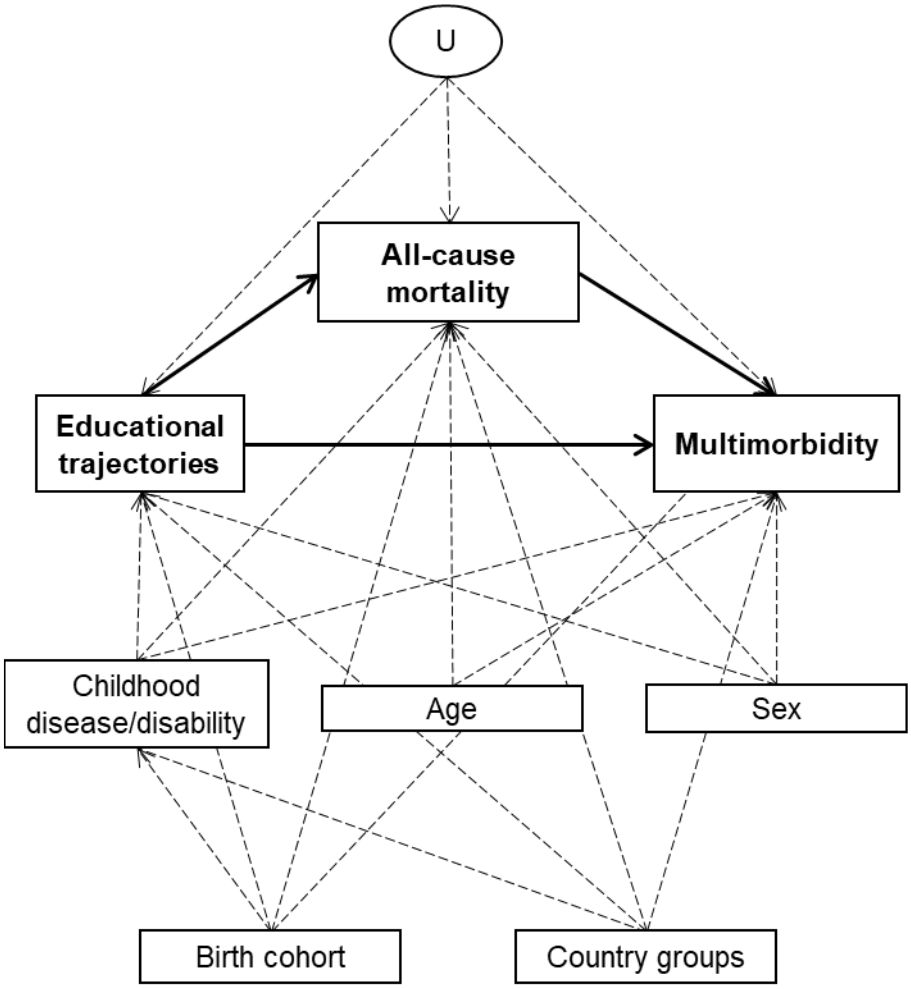
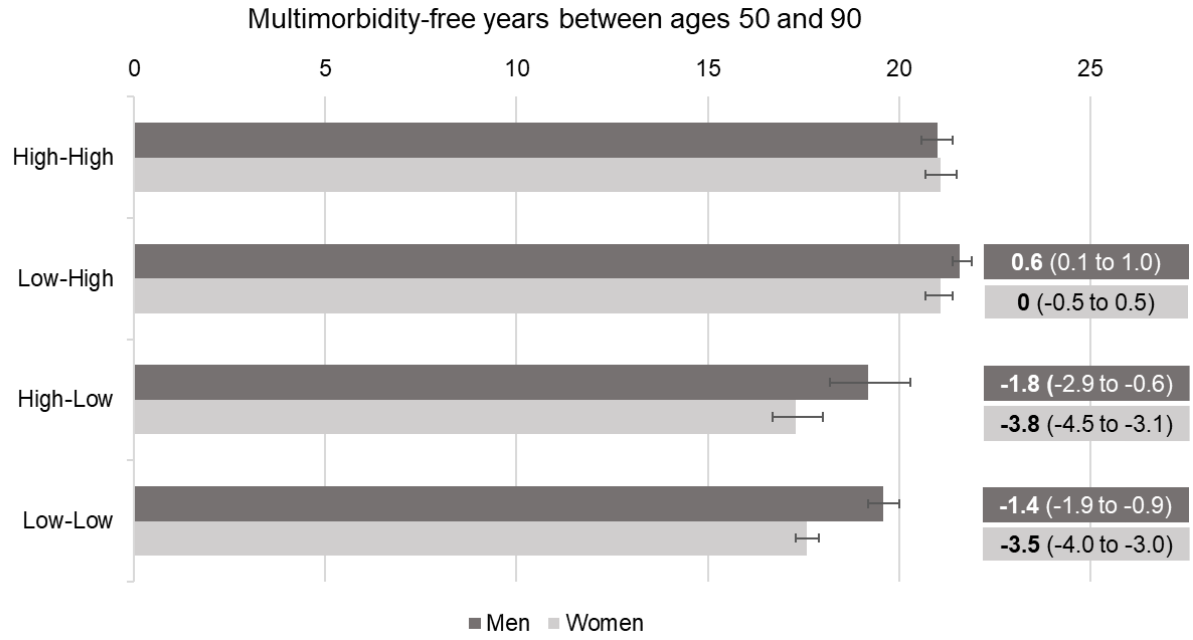
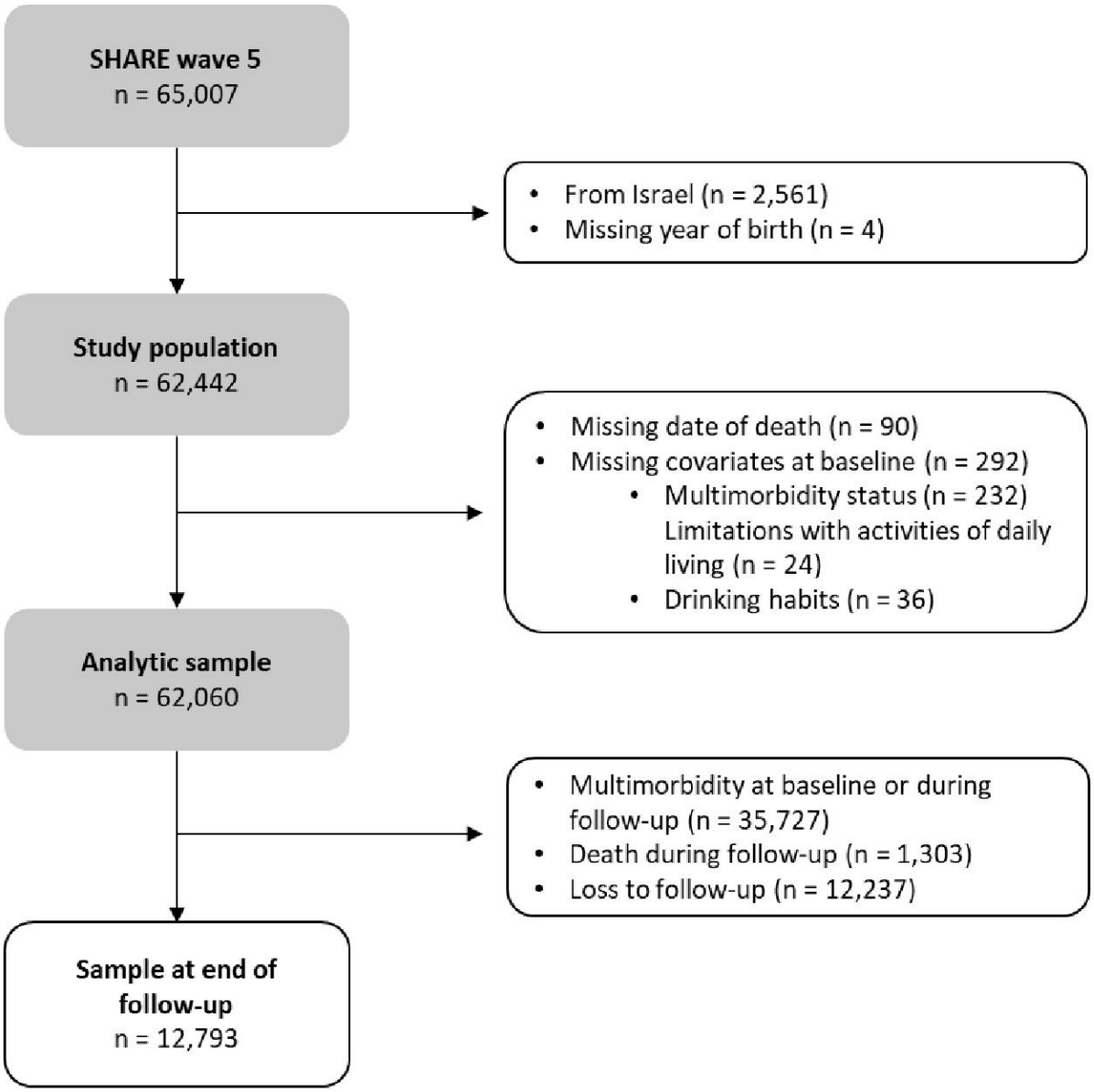


Figure 2 *Sex-specific multimorbidity-free years between ages 50 – 90 years and differences in multimorbidity-free years (95% confidence intervals) associated with different educational trajectories.*



Supplementary materials

Figure S1 *Flow chart of participants selection*



Causal model

The causal model underlying this study was designed to assess the effect of intergenerational educational trajectories (exposure) on multimorbidity (outcome), based on background knowledge. The total effect of the exposure on the outcome is composed of two pathways, one unmediated and one mediated by mortality, with deaths as events competing with the occurrence of multimorbidity. The pathway via all-cause mortality exists because individuals not yet multimorbid who died during follow-up cannot become multimorbid; death therefore has a deterministic effect on multimorbidity by making it impossible. Our inequalities of interest are those corresponding only to the pathway unrelated to mortality. The resulting estimand is the controlled direct effect of educational trajectories on multimorbidity, whereby participants cannot die during follow-up.[1] The assumption of immortal participants is unrealistic but necessary as the other estimand, the total effect, may result in a somewhat different direction and size of inequalities due to the strong effect of education on all-cause mortality.[2]

Mortality data was gathered through end-of-life surveys integrated into the routine SHARE waves. In the case of death of a participant, proxies, such as family members or partners, were invited to provide information regarding the participant's date (month and year) and cause of death. In this study, we considered deaths due to all causes occurring at any point within the follow-up period, i.e. between wave 5 (2013) and wave 8 (2019/20).

The internal validity of the effect estimates relied on the assumptions of positivity, consistency (of the hypothesized interventions on the exposure), no residual confounding, no measurement error of exposure/outcome/confounders, and correct specification of the statistical estimation model.[1, 3] Additionally, since we calculated the direct effect of educational trajectories on multimorbidity, unmediated by death, we relied on the assumption of immortal participants.[1]

Confounders

Measured potential confounders were participant's birth cohort (1909–1927, 1928–1938, 1939–1945, 1946–1955, 1956–1963), sex, country group of residence, and childhood disease/disability. All variables were self-reported and retrieved from the SHARE wave 5 baseline questionnaire. Childhood disease/disability (Yes/No) was defined as either (1) the occurrence of minimum one long-term health condition in childhood and/or (2) a positive response to the question, "Did you ever miss school for a month or more because of a health condition during childhood (that is, from when you were born up to and including age 15)?" (**Table S1**). Countries were categorized in three groups: Scandinavian countries (Sweden, Denmark), Central and Southern European countries (Austria, Germany, Netherlands, France,

Switzerland, Belgium, Luxembourg, Spain, Italy), and Eastern European countries (Czech Republic, Slovenia, Estonia). Countries were combined into groups to reduce the risk of positivity violations and following previous research describing differing intergenerational educational mobility patterns and mortality rates across these groups of countries.[4, 5, 6]

Table S1 *Operationalization of childhood disease/disability*

Childhood disease/disability was constructed from either (1) the report of one of the childhood conditions/disability below, or (2) a positive response to the question regarding school absence due to health reasons.

"Please look at this card. Did you have any of the diseases on this card during your childhood (that is, from when you were born up to and including age 15)?"	
1. Asthma 2. Respiratory problems other than asthma 3. Allergies (other than asthma) 4. Meningitis/encephalitis 5. Chronic ear problems 6. Speech impairment 7. Difficulty seeing even with eyeglasses 8. Severe headaches or migraines 9. Epilepsy, fits or seizures	10. Emotional, nervous, or psychiatric problem 11. Childhood diabetes or high blood sugar 12. Heart trouble 13. Leukaemia or lymphoma 14. Cancer or malignant tumour (excluding minor skin cancers) 15. Other serious health condition
"Did you ever miss school for a month or more because of a health condition during childhood (that is, from when you were born up to and including age 15)?"	

List of chronic conditions considered for multimorbidity

(1) Heart attack including myocardial infarction or coronary thrombosis or any other heart problem including congestive heart failure
(2) High blood pressure or hypertension
(3) High blood cholesterol
(4) Stroke or cerebral vascular disease
(5) Diabetes or high blood sugar
(6) Chronic lung disease such as chronic bronchitis or emphysema
(7) Cancer or malignant tumour, including leukaemia or lymphoma, but excluding minor skin cancers
(8) Stomach or duodenal ulcer, peptic ulcer
(9) Parkinson disease
(10) Alzheimer's disease
(11) Other affective or emotional disorders, including anxiety, nervous or psychiatric problems;
(12) Rheumatoid arthritis
(13) Osteoarthritis, or other rheumatism

Weights and confidence intervals

Weights were the product of two separate stabilized inverse probability weights (IPWs) to account for (1) measured confounding and (2) potential non-random loss during follow-up.[3, 7] The IPW models for confounding included sex (only for the total analytic sample), country group, birth cohort, and childhood disease/disability. The IPW models for follow-up losses included sex (only for the total analytic sample), country group, birth cohort, childhood disease/disability, educational trajectory, and time-varying limitations with activities of daily living (one limitation or more, no limitations).[8] Weight diagnostics encompassing the quality of the weights and the balance of measured confounders across exposure levels were examined. The standardized mean difference for these confounders was <0.01 after IPW, indicating the sample was well-balanced across different educational trajectories. Potential misspecification of the IPW model was ascertained in sensitivity analyses by estimating models using incrementally truncated weights.

Confidence intervals (CI) were generated via percentiles of 1,000 bootstrap draws with replacement. Within each bootstrapped sample, the effect estimates were the average of 30 multiple imputed datasets for parental or individual education (n = 11,295; 18.2%). Our data imputations were carried out through chained equations, operating under the assumption of missingness at random. The prediction variables in the imputation model were sex, country, birth cohort, childhood disease/disability, multimorbidity at baseline, limitations with activities of daily living at baseline, alcohol consumption at baseline, age at baseline, and the cumulative death hazard. Imputations were implemented with the mice R package.[9]

Table S2 *Disease prevalence at baseline (wave 5)*

Disease	Total (n = 62,060)	Men (n = 27,695)	Women (n = 34,365)
Heart attack including myocardial infarction or coronary thrombosis or any other heart problem including congestive heart failure	7,085 (11%)	3,891 (14%)	3,194 (9%)
High blood pressure or hypertension	24,477 (39%)	10,752 (39%)	13,725 (40%)
High blood cholesterol	14,293 (23%)	6,347 (23%)	7,946 (23%)
Stroke or cerebral vascular disease	2,490 (4%)	1,309 (5%)	1,181 (3%)
Diabetes or high blood sugar	7,742 (12%)	3,889 (14%)	3,853 (11%)
Chronic lung disease such as chronic bronchitis or emphysema	3,909 (6%)	1,865 (7%)	2,044 (6%)
Cancer or malignant tumour, including leukaemia or lymphoma, but excluding minor skin cancers	3,542 (6%)	1,600 (6%)	1,942 (6%)
Stomach or duodenal ulcer, peptic ulcer	2,490 (4%)	1,099 (4%)	1,391 (4%)
Parkinson disease	521 (1%)	268 (1%)	253 (1%)
Alzheimer's disease	1,076 (2%)	438 (2%)	638 (2%)
Other affective or emotional disorders, including anxiety, nervous or psychiatric problems	3,644 (6%)	1,057 (4%)	2,587 (8%)
Rheumatoid arthritis	5,684 (9%)	1,700 (6%)	3,984 (12%)
Osteoarthritis, or other rheumatism	11,691 (19%)	3,750 (14%)	7,941 (23%)

Table S3 *Morbidity defined as min. 1 condition out of 3 conditions less dependent on medical diagnoses (stroke, cancer (excluding breast, thyroid, and prostate cancer), stomach or duodenal ulcer). Morbidity-free years between ages 50 – 90 years and Morbidity-free years lost due to different educational trajectories compared to High-High. Standardized by birth cohort, country group, and childhood disease/disability.* Δ *represents effect modification.*

Educational trajectory	Morbidity-free years (95% CI)		Morbidity-free years lost (95% CI)	
	Men	Women	Men	Women
High-High	**32.5** (32.1 to 32.8)	**33.8** (33.5 to 34.1)	-	-
Low-High	**32.7** (32.4 to 33.0)	**33.6** (33.3 to 33.9)	**-0.2** (-0.7 to 0.2)	**0.2** (-0.2 to 0.6) Δ = *0.4 (-0.2 to 1.0)*
High-Low	**31.4** (30.4 to 32.3)	**32.4** (31.7 to 33.0)	**1.1** (0.1 to 2.1)	**1.4** (0.7 to 2.1) Δ = *0.3 (-1.0 to 1.5)*
Low-Low	**31.6** (31.3 to 31.9)	**32.6** (32.4 to 32.9)	**0.9** (0.4 to 1.4)	**1.1** (0.8 to 1.5) Δ = *0.2 (-0.3 to 0.9)*

Table S4 *Morbidity defined as min. 1 condition out of 5 conditions, three of those less dependent on medical diagnoses (stroke, cancer (excluding breast, thyroid, and prostate cancer), stomach or duodenal ulcer) and two more dependent on medical diagnoses (hypertension, diabetes). Morbidity-free years between ages 50 – 90 years and Morbidity-free years lost due to different educational trajectories compared to High-High. Standardized by birth cohort, country group, and childhood disease/disability. Δ represents effect modification.*

Educational trajectory	Morbidity-free years (95% CI)		Morbidity-free years lost (95% CI)	
	Men	**Women**	**Men**	**Women**
High-High	**17.0** (16.7 to 17.4)	**19.0** (18.6 to 19.4)	-	-
Low-High	**17.9** (17.6 to 18.2)	**19.4** (19.0 to 19.7)	**-0.9** (-1.4 to -0.4)	**-0.4** (-0.9 to 0.1) *Δ = 0.5 (-0.3 to 1.2)*
High-Low	**15.8** (14.6 to 16.7)	**15.9** (15.2 to 16.6)	**1.3** (0.3 to 2.4)	**3.1** (2.3 to 3.8) *Δ = 1.8 (0.4 to 3.0)*
Low-Low	**16.4** (16.1 to 16.7)	**16.2** (15.9 to 16.4)	**0.6** (0.1 to 1.1)	**2.8** (2.3 to 3.3) *Δ = 2.2 (1.5 to 2.9)*

Table S5 *Educational trajectories with parental education re-classified as "low" (ISCED-1997 0,1) and "high" (ISCED-1997 2+). Multimorbidity-free years between ages 50 – 90 years and multimorbidity-free years lost associated with different educational trajectories compared to High-High. Standardized by sex (in total sample), birth cohort, country group, and childhood disease/disability. Δ represents effect modification.*

Educational trajectory	Multimorbidity-free years (95% CI)	Multimorbidity-free years lost (95% CI)
High-High	**21.2** (21.0 to 21.4)	-
Low-High	**21.2** (21.0 to 21.5)	**-0.1** (-0.4 to 0.3)
High-Low	**18.5** (18.1 to 18.8)	**2.7** (2.3 to 3.2)
Low-Low	**18.7** (18.4 to 18.9)	**2.5** (2.2 to 2.9)
Men		
High-High	**21.0** (20.7 to 21.4)	-
Low-High	**21.8** (21.4 to 22.1)	**-0.7** (-1.2 to -0.2)
High-Low	**18.9** (18.4 to 19.6)	**2.1** (1.4 to 2.7)
Low-Low	**19.9** (19.6 to 20.3)	**1.1** (0.6 to 1.6)
Women		
High-High	**21.3** (21.0 to 21.6)	-
Low-High	**20.7** (20.4 to 21.1)	**0.6** (0 to 1.0) *Δ = 1.3 (0.5 to 1.9)*
High-Low	**18.0** (17.6 to 18.5)	**3.3** (2.7 to 3.8) *Δ = 1.2 (0.4 to 2.0)*
Low-Low	**17.6** (17.2 to 17.9)	**3.7** (3.3 to 4.2) *Δ = 2.6 (2.0 to 3.3)*

Table S6 *Educational trajectories with parental education and individual education of those born before or in 1927 re-classified as "low" (ISCED-1997 0,1) and "high" (ISCED-1997 2+). Multimorbidity-free years between ages 50 – 90 years and multimorbidity-free years lost associated with different educational trajectories compared to High-High. Standardized by sex (in total sample), birth cohort, country group, and childhood disease/disability.* Δ *represents effect modification.*

Educational trajectory	Multimorbidity-free years (95% CI)	Multimorbidity-free years lost (95% CI)
High-High	**21.1** (21.0 to 21.4)	-
Low-High	**21.3** (21.0 to 21.5)	**-0.1** (-0.4 to 0.2)
High-Low	**18.5** (18.1 to 18.9)	**2.6** (2.2 to 3.1)
Low-Low	**18.6** (18.4 to 18.9)	**2.5** (2.2 to 2.9)
Men		
High-High	**21.0** (20.7 to 21.3)	-
Low-High	**21.8** (21.4 to 22.1)	**-0.8** (-1.2 to .0.3)
High-Low	**19.1** (18.4 to 19.7)	**2.0** (1.3 to 2.7)
Low-Low	**19.9** (19.5 to 20.3)	**1.1** (0.6 to 1.6)
Women		
High-High	**21.2** (20.9 to 21.5)	-
Low-High	**20.8** (20.4 to 21.1)	**0.4** (-0.1 to 0.9) Δ = *1.2 (0.5 to 1.8)*
High-Low	**18.0** (17.6 to 18.5)	**3.2** (2.6 to 3.7) Δ = *1.2 (0.3 to 2.0)*
Low-Low	**17.5** (17.2 to 17.9)	**3.7** (3.2 to 4.2) Δ = *2.6 (1.9 to 3.2)*

Table S7 *Multimorbidity-free years between ages 50 – 90 years and multimorbidity-free years lost due to different educational trajectories compared to High-High when truncating IPWs to the 1st and 99th (Model A), and the 5th and 95th (Model B) percentiles. Standardized by sex, birth cohort, country group, and childhood disease/disability.*

Educational trajectory	Morbidity-free years (95% CI)		Morbidity-free years lost (95% CI)	
	Model A	**Model B**	**Model A**	**Model B**
High-High	**21.0** (20.8 to 21.3)	**20.8** (20.6 to 21.1)	-	-
Low-High	**21.3** (21.1 to 21.5)	**21.2** (21.0 to 21.4)	**-0.3** (-0.6 to 0.1)	**-0.4** (-0.7 to 0)
High-Low	**18.1** (17.5 to 18.7)	**18.0** (17.4 to 18.5)	**2.9** (2.3 to 3.5)	**2.8** (2.3 to 3.4)
Low-Low	**18.5** (18.3 to 18.7)	**18.6** (18.3 to 18.8)	**2.5** (2.2 to 2.9)	**2.3** (1.9 to 2.6)

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Chapter 6 | Intergenerational educational trajectories and inequalities in longevity: A population-based study of adults born before 1965 in 14 European countries

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Intergenerational educational trajectories and inequalities in longevity: A population-based study of adults born before 1965 in 14 European countries

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ABSTRACT

Background: While educational gradients in longevity have been observed consistently in adult Europeans, these inequalities have been understudied within the context of family- and country-level influences. We utilized population-based multi-generational multi-country data to assess the role (1) of parental and individual education in shaping intergenerational inequalities in longevity, and (2) of country-level social net expenditure in mitigating these inequalities.

Methods: We analyzed data from 52,271 adults born before 1965 who participated in the Survey of Health, Ageing and Retirement in Europe, comprising 14 countries. Mortality from all causes (outcome) was ascertained between 2013 and 2020. Educational trajectories (exposure) were High-High (reference), Low-High, High-Low, and Low-Low, corresponding to the sequence of parental-individual educational attainment. We quantified inequalities as years of life lost (YLL) between the ages of 50 and 90 estimated via differences in the area under standardized survival curves. We assessed the association between country-level social net expenditure and YLL via meta-regression.

Results: Inequalities in longevity due to educational trajectories were associated with low individual education regardless of parental education. Compared to High-High, having High-Low and Low-Low led to 2.2 (95% confidence intervals: 1.0 to 3.5) and 2.9 (2.2 to 3.6) YLL, while YLL for Low-High were 0.4 (0.2 to 0.9). A 1% increase in social net expenditure led to an increase of 0.01 (0.3 to 0.3) YLL for Low-High, 0.007 (0.1 to 0.2) YLL for High-Low, and a decrease of 0.02 (0.1 to 0.2) YLL for Low-Low.

Conclusion: In European countries, individual education could be the main driver of inequalities in longevity for adults older than 50 years of age and born before 1965. Further, higher social expenditure is not associated with smaller educational inequalities in longevity.

1. Introduction

Educational gradients in longevity have been observed consistently in adult Europeans (Mackenbach et al., 2019), whereby a higher education is associated with a longer life expectancy. According to the fundamental cause theory (Masters et al., 2015), higher educational attainment grants access to resources such as social connections, higher income, higher labor market returns, or health-related knowledge, which all serve to improve health outcomes and eventually increase longevity. The putative causal effect of education has found empirical

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evidence via quasi-experiments in populations from the U.S., Sweden, and the United Kingdom (Davies et al., 2018; Lager & Torssander, 2012; Lleras-Muney, 2005). However, the extent to which educational attainment affects longevity may depend on contextual factors. Key contextual influences that are worth being studied are related to the familial environment and country of residence (Bambra et al., 2010).

The familial environment may contribute to the amount of cultural and social capital a person has access to, and eventually to social inequalities in offspring health. This can be explained via various pathways. Taking parental education as a proxy of the family/household socioeconomic status, one pathway is via differential access to material and social resources within society (Galobardes et al., 2007). Another pathway is via socialization of individuals into health behaviors typical of their social surroundings (Schuck & Steiber, 2018). Additionally, parental education is also an important cause of offspring education (Conley et al., 2015). Overall, parental education may set the stage for health inequalities that persist throughout the offspring life course, from childhood until death. What remains less clear is the interplay between parental and individual education. More specifically, which educational exposure – parental or individual – is the main driver of putative intergenerational inequalities in longevity?

Social theories predict different possible answers: cumulative advantage theory indicates that both parental and individual education drive inequalities (Willson et al., 2007). Resource substitution theory predicts that individual education is the main driver of health inequalities and parental education may either mitigate or amplify the effects of individual education (Ross & Mirowsky, 2011). Finally, social mobility theory indicates that the inter-generational movement across social strata, either upward or downward, is the main driver of inequalities (Hallqvist et al., 2004). Disentangling these alternative models with empirical data is relevant for public health, as each theory may inform specific actions to reduce educational inequalities in longevity, from the identification of groups at higher risk to the prioritization of family and/or institution related educational exposure.

Multi-generational educational trajectories have already been shown to affect all-cause mortality in different populations (Acacio-Claro et al., 2017; De Grande et al., 2015; Elo et al., 2014; Giesinger et al., 2014; Hayward & Gorman, 2004; Martikainen et al., 2020; Pudrovska & Anikputa, 2014; Wolfe et al., 2018). These studies were conducted in Finland, the United States, the United Kingdom and Belgium. Five studies (Belgium, Finland, USA) supported individual education as the main driver, while three supported that both parental and individual education affect longevity (Finland, United Kingdom, USA) (Elo et al., 2014; Giesinger et al., 2014; Martikainen et al., 2020). No study has yet examined the effect of intergenerational educational trajectories on longevity in other European countries.

Health inequalities have been observed to differ across country-related factors linked to social welfare (de Breij et al., 2020; Sieber et al., 2020). These macro-level factors are thought to impact health by moderating the effect of individual-level social determinants of health (Bambra, 2011). The most common operationalizations of these macro-determinants are based on welfare regimes, social policy institutions, and social expenditure (de Breij et al., 2020). While each approach has its own strengths and limitations, the first two can be particularly described as static, since they create broad non-changing clusters of countries. Also, they do not allow for comparison within their country clusters. The social expenditure approach involves a more dynamic country-by-country comparison, and is therefore the best suited to draw a cross-European comparison of inequalities in longevity.

It remains unclear whether country-level social expenditure modifies educational inequalities in longevity, potentially attenuating it. The empirical evidence in support of this hypothesis is still inconclusive in part due to contradicting findings across Europe (Brennenstuhl et al., 2012). For instance, while the Scandinavian welfare regime is widely regarded as the most generous in terms of social transfers, relative inequalities in mortality are higher there compared to Southern European states (Bambra, 2011; Mackenbach et al., 2008). At the same time, other research indicates that inequalities in self-reported health due to educational attainment are lower in countries with higher social expenditure (Álvarez-Gálvez & Jaime-Castillo, 2018). The effect of intergenerational educational trajectories on longevity may also vary cross-nationally, and this has not been examined yet. Thus, by using an intergenerational perspective on education we hope to shed more light on the contrasting findings from earlier research.

In this study, we aimed to utilize population-based multi-generational data to assess the role of parental and individual educational attainment in driving intergenerational inequalities in longevity among adults from 14 European countries. Further, we aimed to assess whether country-level social expenditure mitigates these inequalities.

2. Methods

2.1. Data source and study population

Our target population is adults born before 1965 and residing in European countries. The study population comprised community-dwelling adults participating in the Survey of Health, Ageing and Retirement in Europe (SHARE), a longitudinal cohort study across more than 20 European nations (Börsch-Supan et al., 2013, 2015; Börsch-Supan & Malter, 2015). The survey aims to examine the health of an ageing European population by collecting a multitude of socioeconomic, behavioral, and health-related data across the life course. Respondents are a representative sample of the whole population in each participating country. The SHARE study started in 2004 and has been conducted biennially, with a total of 8 waves until 2019/2020. Our study baseline was wave 5 (2013), since that was the first wave including an assessment of parental education. At that survey year there were 15 participating countries: Austria, Belgium, the Czech Republic, Denmark, Estonia, France, Germany, Israel, Italy, Luxembourg, the Netherlands, Slovenia, Spain, Sweden, and Switzerland.

The study population, i.e. total number of respondents, was 66,188. The analytic sample included 52,271 participants, corresponding to 83% of the study population, as we excluded participants from Israel (n = 2561; Israel is not part of the European continent), born after 1965 (n = 535), with a negative time under investigation due to an incorrectly reported date of death (n = 98), with missing multimorbidity status or limitations with activities of daily living (n = 294), and lost at baseline (n = 10,429) (Fig. 1).

2.2. Causal model, exposure, outcome, and covariates

The causal model underlying our study is represented in Fig. 2. We

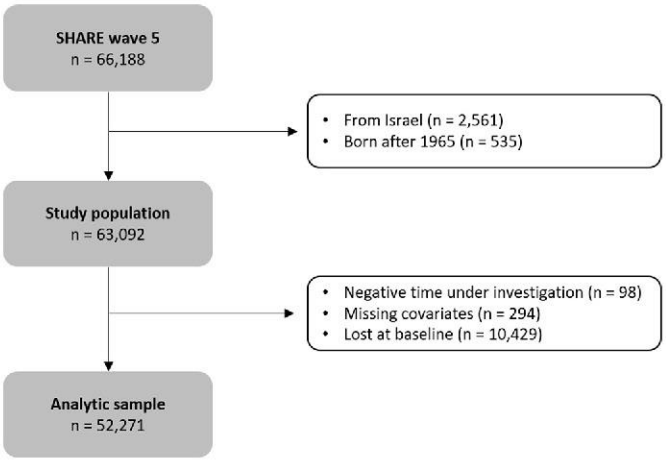

Fig. 1. Flow chart of participants selection.

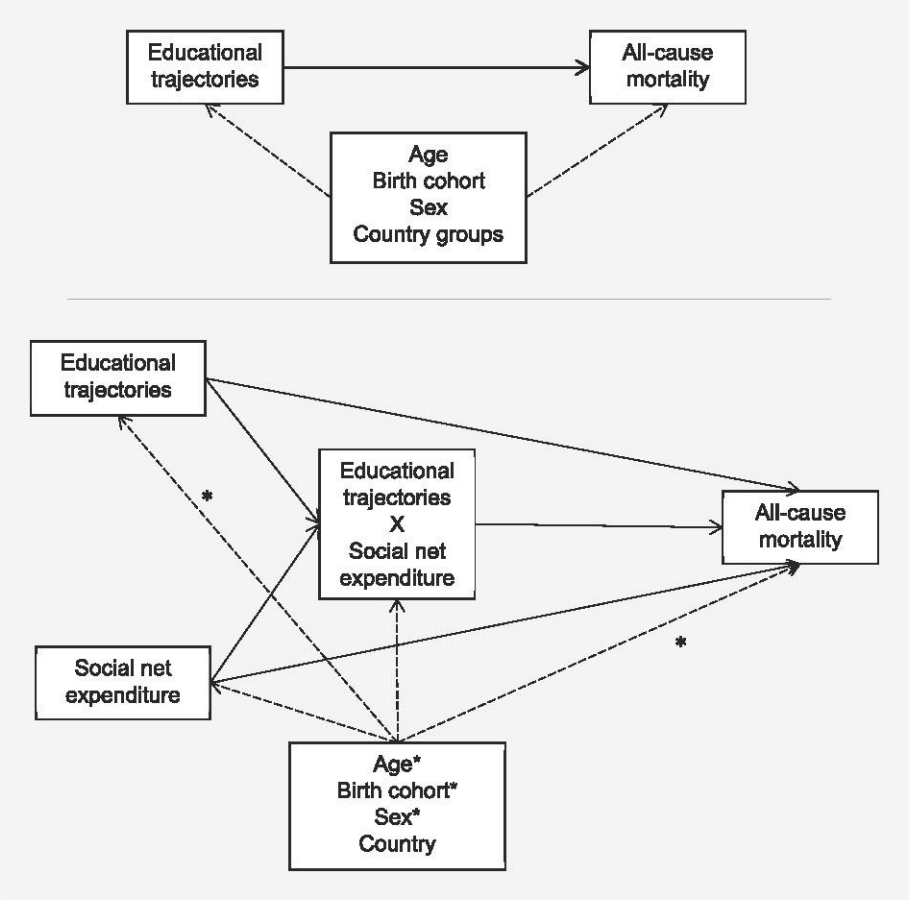

Fig. 2. Directed acyclic graph (DAG) underlying our study, split by aim one (top) and aim two (bottom). Normal arrow: putative effect of interest. Dashed arrow: confounding factors. Confounding factors with asterisks only apply to the arrows with asterisks; "country" applies to all confounding arrows.

designed it to focus on inequalities in all-cause mortality (outcome) driven by intergenerational educational trajectories (exposure) and modified by social net expenditure. In the model, the inequalities are represented by the total effect of the exposure on the outcome.

The design of the directed acyclic graph (DAG) for our second aim (bottom of Fig. 2) follows the recommendations of Attia et al. (2022) on how to represent effect modifications via DAGs. Here, the "Educational trajectories X Social net expenditure" node represents an additional effect on all-cause mortality due to the interaction between educational trajectories and social net expenditure.

Educational trajectories were constructed through the combination of individual and parental education. Both were self-reported by study participants. Parental education was operationalized as the highest achieved education between mother and father; in case one was missing, the other's educational attainment was used. Both individual and parental educational attainment were categorized as "Low" for any achieved degree up to lower secondary education (International Standard Classification of Education (ISCED) 1997 levels 0–2) and "High" for upper secondary education and above (ISCED-1997 level 3 or above). Using this categorization, we obtained four educational trajectories: High-High, Low-High, High-Low, and Low-Low, where the first part denotes the parents' education level and the second part the individual's education level. This categorization follows previous research as well as documentation by Eurostat, where we combined "medium" (ISCED-1997 levels 3 and 4) and "high" (ISCED 1997 levels 5 and 6) education into a singular "High" category of educational attainment (Eurostat, 2011). In a sensitivity analysis, we also categorized individual educational attainment into "Low" (ISCED-1997 levels 0 and 1), "Medium" (ISCED-1997 levels 2 and 3), and "High" (ISCED-1997 levels 4 and above), to ascertain whether increased social expenditure may be more beneficial for the middle educated. This analysis focused on individual education only given the trade-off between the complexity of numerous trajectories and the available sample size.

Mortality data were collected during end-of-life surveys conducted every two years as part of the regular SHARE waves. In the case of death of a participant, proxies, e.g. family members or partners, were invited to participate and provided information on the date (month and year) and cause of death of the participant. For this study, we considered deaths due to all causes occurring at any time during follow-up, that is between wave 5 (2013) and wave 8 (2019/20).

Potential measured confounders were participant's age at baseline, birth cohort (1909–1938, 1939–1945, 1946–1964), sex, and country of residence. These variables were self-reported and retrieved from the SHARE wave 5 baseline questionnaire. For analyses pertaining to our first aim, countries were categorized in four groups: Scandinavian countries (Sweden, Denmark), Central European countries (Austria, Germany, Netherlands, France, Switzerland, Belgium, Luxembourg), Southern European countries (Spain, Italy), and Eastern European countries (Czech Republic, Slovenia, Estonia). Countries were combined to reduce the risk of positivity violations. The choice of groups followed previous research describing differing intergenerational educational mobility patterns and mortality rates across these groups of countries (Schuck & Steiber, 2018; Torul & Oztunali, 2017).

Social expenditure was considered a country-level potential effect modifier and exposure (bottom of Fig. 2). Data on social expenditure came from the statistical office of the European Union Eurostat (Eurostat, 2022). Social expenditure was defined as public spending on social protection against risks such as unemployment, homelessness, sickness,

or disability. We computed the net social protection as the percentage of social expenditure with respect to a country's gross domestic product (GDP); Eurostat data is available from 2007 until 2018, and the net expenditure was approximately constant across this period. We considered the average social net protection spending between 2013 and 2018.

2.3. Statistical and sensitivity analyses

2.3.1. Assessment of intergenerational inequalities in longevity and role of parental/individual education

We examined estimates of three effects comparing the intergenerational trajectories High-Low, Low-High, and Low-Low with the High-High trajectory, since we hypothesized participants in this group to have the lowest mortality rates. By doing so, we are able to disentangle among the three competing social theories and identify the role of parental and individual education in driving inequalities (Howe et al., 2016). We considered the following scenarios:

1. Similar effect estimates between the three trajectories indicate that both parental and individual education drive inequalities (cumulative advantage).
2. Similar effect estimates of having High-Low and Low-Low while the effect of having Low-High is negligible, indicate that individual education is the main driver (resource substitution).
3. Similar effect estimates of having Low-High and/or High-Low while Low-Low is negligible indicates that change, i.e. upward or downward social mobility, is the main driver (social mobility).

The internal validity of the effect estimates relies on the assumptions of positivity, consistency, no residual confounding, no measurement error of exposure/outcome/confounders, and correct specification of the statistical estimation model (Westreich, 2019).

Effects were measured as years of life lost (YLL) between ages 50 and 90. Years of life lost were calculated as differences of life expectancies between ages 50 and 90. We chose YLL as our effect measurement because it is based on years of life expectancy, therefore more directly related to longevity compared to traditional hazard differences or ratios. Further, it is a measure of inequalities on the absolute scale, thus more relevant in the evaluation of potential policy and public health actions on the examined exposure. Life expectancy for each level of exposure was computed as the area under the corresponding survival curve. The survival probability due to a certain educational trajectory was estimated as the predicted proportion of survivors based on the counterfactual scenario of every study participants having that educational trajectory and not being lost during follow-up. In practice, survival probabilities were estimated via the weighted Kaplan-Meier survival with age as time-scale.

Weights were the product of two separate stabilized inverse probability weights (IPWs) to account for (1) measured confounders and (2) potential non-random loss during follow-up (Cole & Hernán, 2008; Westreich, 2019). The IPW model for confounding included sex, birth period, and country groups. Age was indirectly adjusted for by using it as the scale of the time-to-event analysis. The IPW model for follow-up losses included sex, country, educational trajectory, birth period, baseline multimorbidity (min. 2 chronic diseases, self-reported), and limitations with activities of daily living (no limitations, 1 limitation, >2 limitations, self-reported). Finally, we ran sensitivity analyses to assess (1) the potential effect modification of sex and country groups and (2) the potential violation of the assumption of no IPWs model misspecification by incrementally truncating weights (Cole & Hernán, 2008).

Confidence intervals (CI) were generated via percentiles of 1000 bootstrap draws with replacement. Within each bootstrapped sample, the effect estimates were the average of 30 multiply imputed data sets for parental or individual education (n = 9278; 18%). We performed data imputations via chained equations under the hypothesis of missingness at random. The prediction variables in the imputation model were sex, multimorbidity, alcohol consumption (classified as high, moderate, and abstainer), limitations with activities of daily living, birth period, country, age at baseline and end of follow-up, censored age, and the cumulative hazard. Imputations were implemented with the mice R package (Van Buuren et al., 2019).

2.3.2. Assessment of effect modification by social net expenditure

To assess variation of YLL by country-level social expenditure, we first estimated YLL per country, then we ran a meta regression with social net expenditure as explanatory variable (Harrer et al., 2021). Southern European countries (Italy and Spain) were excluded due to potential violation of the positivity assumption when estimating YLL for these countries; thus, we compared twelve out of the available fourteen countries. We repeated this analysis for life expectancies.

All analyses were run in R 4.1.2.

3. Results

3.1. Analytic sample characteristics

Characteristics of the analytic sample are reported in Table 1. Participants had a mean age of 67 years at baseline and were slightly more female (56%) than male. More than half were born after 1945, while approximately 20% were born during the Second World War (1939–1945). Southern countries had fewer participants with High-High (2%) and High-Low (3%) trajectories compared to other countries. Over approximately 7 years of follow-up, 6044 deaths occurred. The crude death rate was 2317 deaths per 100,000 person-years. Participants with High-High and Low-Low trajectories accounted altogether for 52% of the sample, that is more than half of the participants attained the same educational level as their parents. Approximately 25% of the participants experienced upward mobility and 5% downward mobility. Additionally, a high education was achieved by nearly eight out of ten participants with high educated parents, and by four out of ten participants with low educated parents. The remaining 18% of participants have missing information.

Participants with a High-Low and Low-Low trajectory had a higher proportion of multimorbidity (58% and 56%) compared to participants with a Low-High and High-High trajectory (44% and 45%, respectively). The same pattern was observed for limitations with activities of daily living and number of deaths (17% versus 8%).

3.2. Intergenerational educational inequalities in longevity

Life expectancies and years of life lost between ages 50 and 90 are reported in Table 2. The life expectancy associated with a High-High trajectory was 33.8 years (95% CI: 33.3 to 34.2). Compared to having a High-High educational trajectory, Low-High led to 0.4 (95% CI: 0.2 to 0.9) YLL, High-Low to 2.2 (95% CI: 1.0 to 3.5) YLL, and Low-Low to 2.9 (95% CI: 2.2 to 3.6) YLL (Table 2 and Fig. 3). To assess whether the YLL associated with High-Low and Low-Low were different, we directly compared the life expectancies related to these two exposure levels. The Low-Low vs High-Low estimate resulted in 0.7 (95% CI: 0.6 to 2.0) YLL, which was inconclusive given the wide compatibility interval.

There were 78 participants from Southern countries with a high value of the weights (>10), signaling a potential violation of the positivity assumption. To assess this, we ran additional analyses by implementing different model specifications for the weights related to measured confounding and by removing the Southern European countries (Table S1). Inequalities in these additional analyses were similar to those in main analyses, indicating the main results are robust to potential violations of the positivity assumption.

Table 1
Characteristics of analytic sample by educational trajectories, e.g. High-High high parental education – high individual education. SD standard deviation.

Characteristics	n (% or SD)	High-High	Low-High	High-Low	Low-Low
Number of participants	52,271	10,841 (21%)	13,118 (25%)	2523 (5%)	16,439 (31%)
Sex					
Female	29,159 (56%)	5798 (54%)	6704 (51%)	1647 (65%)	9701 (59%)
Male	23,112 (44%)	5043 (47%)	6414 (49%)	876 (35%)	6738 (41%)
Age at baseline (years), mean and SD	67.2 (±10.0)	64.8 (±9.1)	65.7 (±9.3)	67.8 (±10.1)	70.5 (±10.4)
Birth cohorts					
1909–1938	12,850 (25%)	1736 (16%)	2493 (19%)	657 (26%)	6092 (37%)
1939–1945	10,890 (21%)	2202 (20%)	2635 (20%)	543 (22%)	3610 (22%)
1946–1964	28,531 (55%)	6903 (64%)	7990 (61%)	1323 (52%)	6737 (41%)
Multimorbidity (min. 2 chronic conditions)					
Yes	25,448 (49%)	4830 (45%)	5800 (44%)	1463 (58%)	9139 (56%)
No	26,823 (51%)	6011 (55%)	7318 (56%)	1060 (42%)	7300 (44%)
Limitations with activities of daily living					
No limitations	46,069 (88%)	9942 (92%)	11,898 (91%)	2156 (86%)	13,757 (84%)
1 limitation	3049 (6%)	525 (5%)	673 (5%)	179 (7%)	1167 (7%)
>2 limitations	3153 (6%)	374 (3%)	547 (4%)	188 (8%)	1515 (9%)
Alcohol consumption					
High	14,683 (28%)	3350 (31%)	3875 (30%)	578 (23%)	3923 (24%)
Moderate	21,478 (41%)	5346 (49%)	5961 (45%)	1067 (42%)	4952 (30%)
Abstainer	16,110 (31%)	2145 (20%)	3282 (25%)	878 (35%)	7564 (46%)
Number of deaths (2013–2020)	6044 (12%)	881 (8%)	1174 (9%)	332 (13%)	2752 (17%)
Death rate, crude (deaths per 100,000 person-years)	2317	1566	1755	2660	3548
Country groups					
Scandinavia	7385 (14%)	1605 (15%)	2483 (19%)	257 (10%)	1536 (9%)
Central Europe	22,150 (42%)	5721 (53%)	5621 (43%)	957 (38%)	4966 (30%)
Eastern Europe	12,741 (24%)	3330 (31%)	3212 (25%)	1240 (49%)	2653 (16%)
Southern Europe	9995 (19%)	185 (2%)	1802 (14%)	69 (3%)	7284 (44%)

Table 2
Life expectancy (years) between ages 50–90 years and years of life lost (YLL) due to different educational trajectories with respect to High-High (parental-individual education). Standardized by age at baseline, sex, birth period, country group.

Educational trajectory	Life expectancy (95% CI)	YLL (95% CI)
High-High	**33.8** (33.3 to 34.2)	–
Low-High	**33.4** (33.1 to 33.7)	**0.4** (−0.2 to 0.9)
High-Low	**31.6** (30.3 to 32.8)	**2.2** (1.0 to 3.5)
Low-Low	**30.9** (30.3 to 31.4)	**2.9** (2.2 to 3.6)

3.3. Country-level relationship between YLL and social net expenditure

The per-country social net expenditures as percentage of GDP were: 30% for France, 27% for Denmark, 26% for Belgium and Austria and Germany, 25% for Sweden and Italy, 23% for Spain and Slovenia, 22% for Netherlands, 21% for Switzerland, 19% for Luxembourg, 18% for the Czech Republic, and 15% for Estonia.

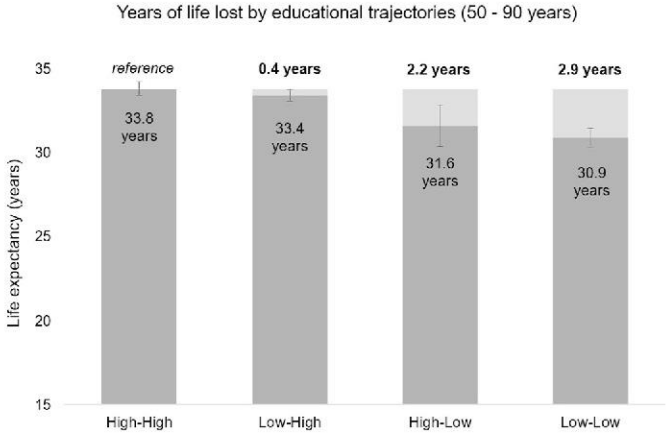

Fig. 3. Life expectancy between ages 50 and 90 years and years of life lost (bold) due to different educational trajectories (parental-individual education). Standardized by age at baseline, sex, birth period, country group.

A higher social net expenditure was associated with a longer life expectancy but not smaller YLL. Specifically, a 1% increase in social net expenditure was associated with additional 0.2 years of life expectancies for High-Low (95% CI: 0 to 0.5), and Low-Low (95% CI: 0 to 0.5) (Table 3 and Fig. S1). For the other two trajectories, the estimates were inconclusive as they were less precise, namely 0.2 (95% CI: 0.2 to 0.6) years and 0.2 (95% CI: 0.4 to 0.8) years for High-High and Low-High, respectively. Finally, a 1% increase in social net expenditure was associated with negligible changes in YLL for all levels of exposure (Table 3).

3.4. Sensitivity analyses

Years of life lost due to intergenerational educational trajectories were larger in men compared to women (Table 4). For men, parental education appeared to moderate intergenerational inequalities driven by low individual education, as having High-Low led to smaller YLL (2.7, 95% CI: 1.4 to 5.1) than having Low-Low (4.0, 95% CI: 2.6 to 4.6). This moderation was not observed for women: High-Low led to 1.7 (95% CI: 1.1 to 3.3) YLL while Low-Low led to 2.0 (95% CI: 1.3 to 2.7) YLL.

Pattern of years of life lost varied slightly across country groups (Table 4). Inequalities for Central Europe and Scandinavia were in line with the main analysis. Effect estimates for Eastern Europe indicated that low individual education drove intergenerational inequalities while parental education moderated them. Specifically, having a high parental education mitigated the inequalities, as having High-Low led to smaller YLL than having Low-Low. Finally, estimates for Southern European countries were inconclusive as their precision was low.

Participants lost at baseline (n = 10,429; 20%) were comparable to the analytic sample in their baseline characteristics (Table S2). This

Table 3
Country-level relationship between life expectancy between 50 and 90 years of age with social net expenditure (mean percentage of GDP between 2013 and 2018). LE: life expectancy between age 50 and 90; YLL years of life lost between age 50 and 90 with respect to reference educational trajectory High-High (parental-individual education). LE and YLL were standardized by age at baseline, sex, and birth period.

Educational trajectory	Change in LE per 1% increase in social expenditure (95% CI)	Change in YLL per 1% increase in social expenditure (95% CI)
High-High	**0.2** (−0.2 to 0.6)	-
Low-High	**0.2** (−0.4 to 0.8)	**0.01** (−0.3 to 0.3)
High-Low	**0.2** (0 to 0.5)	**0.007** (−0.1 to 0.2)
Low-Low	**0.2** (0 to 0.5)	**−0.02** (−0.2 to 0.1)

Table 4
Years of life lost (YLL) between ages 50–90 years due to the effect of educational trajectories, stratified by country groups and by sex. Reference High-High (parental-individual education). Standardized by age at baseline, sex, birth period, country groups.

	Low-High vs. High-High	High-Low vs. High-High	Low-Low vs. High-High
	YLL (95% CI)	**YLL** (95% CI)	**YLL** (95% CI)
Total	**0.4** (−0.2 to 0.9)	**2.2** (1.0 to 3.5)	**2.9** (2.2 to 3.6)
Sex			
Female (n = 29,159)	**0.2** (−0.4 to 0.7)	**1.7** (1.1 to 3.3)	**2.0** (1.3 to 2.7)
Male (n = 23,112)	**0.8** (−0.6 to 1.2)	**2.7** (1.4 to 5.1)	**4.0** (2.6 to 4.6)
Country			
Central Europe (n = 22,150)	**0.1** (−0.7 to 0.5)	**2.7** (0.8 to 4.9)	**2.9** (1.9 to 4.0)
Eastern Europe (n = 12,741)	**0.5** (−0.4 to 1.4)	**2.3** (0.8 to 3.9)	**3.7** (2.3 to 5.0)
Scandinavia (n = 7385)	**0.6** (−1.6 to 0.3)	**2.6** (−0.6 to 5.3)	**1.5** (−0.3 to 3.8)
Southern Europe (n = 9995)	**1.7** (−1.0 to 4.6)	**0.2** (−5.2 to 6.6)	**2.6** (−0.2 to 5.3)

indicates findings from the analytic sample can be generalized to the study population. Similarly, when truncating weights, inequalities were similar to those reported in main analyses (Table S3 and Table S4), suggesting negligible bias from the potential miss-specification of the IPWs models.

When categorizing individual education in three levels – low (27%), medium (51%), and high (21%) – for 1% increase in social net expenditure we observed an increase in life expectancy by 0.2 years (95% CI: 0 to 0.4) when having high education, 0.3 years (95% CI: 0 to 0.5) when having medium education, and 0.2 years (95% CI: 0.3 to 0.8) when having low education (Fig. S2). Finally, a 1% increase in social net expenditure was associated with negligible changes in YLL: 0.02 years (95% CI: 0.2 to 0.1) for medium education and 0.05 years (95% CI: 0.5 to 0.6) for low education. Overall, this indicates that our main findings are robust with respect to a different operationalization of the exposure.

4. Discussion

We assessed inequalities in longevity due to intergenerational educational trajectories among older adults from 14 European countries. There were approximately 2.5 years of life lost when having a low individual education regardless of parental education, indicating that inequalities were driven by individual education and that the resource substitution model held. To place the approximately 2.5 years of life lost into context, one multicohort study in seven high-income WHO member states estimated the years of life lost between ages 40 and 85 years to be around 0.5 years for high alcohol intake, 0.7 years for obesity, 1.6 years for hypertension, 2.4 years for physical inactivity, 3.9 years for diabetes, and 4.8 years for current smoking (Stringhini et al., 2017). Additionally, we assessed the potential mitigation of inequalities by increased social expenditure of the country of residence, and observed that the higher the social expenditure, the larger the life expectancy, but not smaller the inequalities.

Our work expands previous studies in European populations about the role of parent and offspring educations in shaping intergenerational inequalities in longevity for cohorts born before 1965. In Finnish birth cohorts from 1935 to 1971, childhood social conditions were observed to be a significant predictor of adult mortality, but adulthood socioeconomic conditions explained most of this association. This indicated that individual socioeconomic conditions during adulthood were the main drivers of inequalities in mortality (Elo et al., 2014; Martikainen et al., 2020). Conversely, in a study on British participants born in 1946, investigators observed that both early childhood and adulthood socioeconomic conditions contributed to inequalities in all-cause premature mortality (Giesinger et al., 2014). Our study adds to these findings by assessing them on a larger scale, i.e. across 14 other European countries, and by observing that individual education was the main driver of intergenerational inequalities in longevity.

Our results are in line with the resource substitution hypothesis of health and education. This theory states that higher parental education provides resources that increase the likelihood of their offspring also achieving a higher education, thus decreasing their mortality risk. The effect of parental education on longevity therefore seems to be indirect rather than direct (Ross & Mirowsky, 2011). Indeed, in our analytic population the likelihood of achieving a high education was twofold in individuals having high educated parents compared to those having low educated parents. Further, we observed a moderating effect of parental education for men and in Eastern Europe. Notably, a high parental education mitigated intergenerational inequalities driven by low individual education. In summary, it can be said that while individual education appears to be the main driver of inequalities in longevity, it functions within the context of parental education and should be understood as part of a larger web of socioeconomic determinants of health.

Increased social expenditure was associated with an increase in life expectancy, similar to what previous studies in multiple countries have reported (Bergqvist et al., 2013; Bradley et al., 2011). This finding may underlie the protection of high social expenditure from the adverse health effects of poverty, by allowing people to invest in human capital such as education (Reynolds & Avendano, 2018), and reducing exposure to health risk factors, such as chronic stress which has been linked to various cardio-metabolic disorders (Kivimäki et al., 2022). Social expenditure is theorized to strengthen human agency and support peoples' capacities to deal with stressful life events (Dahl & van der Wel, 2013). One study across 30 OECD countries, including non-European countries such as Japan, Mexico, or the United States, assessed the association of social expenditure with individual-level years of life lost between birth and age 69 and reported a positive effect of increased spending (Bradley et al., 2011). The authors conclude that social spending has beneficial effects on population health, beyond that of health spending alone.

Increased social net expenditure was not associated with reduced inequalities in longevity. This finding may have multiple explanations. First, only specific social expenditures, e.g. related to healthcare, might mitigate inequalities, as reported in at least one study (Vavken et al., 2012). As such, the use of total social expenditure may have blurred the examined relationship. Second, we were unable to assess social expenditure across the whole life course and therefore could not account for the fact that people benefit most from welfare at different life periods, e.g. educational expenditure before adulthood and pension benefits in older life (de Graaf & Maier, 2017).

Our study has limitations. Firstly, there is potential bias in both the exposure and outcome of interest. For the exposure, our findings may be subject to misclassification bias since education is self-reported. For educational attainment, the comparable results from classifying individual education into three instead of two levels indicate that the bias due to misclassification is likely to be small. Further, a study investigating the quality of retrospective childhood information provided in SHARE concluded that generally, respondents remembered their childhood living conditions with high accuracy (Havari & Mazzonna, 2015). For the outcome, mortality data is self-reported via proxies of the deceased, thus errors in the exact dates of death are possible. However, the ensuing bias is likely small (days) compared to the size of our estimated effects (years).

Secondly, residual confounding can be present. As this is an observational study, we may have unmeasured confounding, and we could not adjust for additional measured potential confounders due to positivity restriction. However, we note that the observed size of educational

inequalities in our study are consistent with social inequalities observed in another study of larger sample size and with different cohorts (Stringhini et al., 2017).

Third, our findings may not be generalizable to the target population. There could be selection bias as our study population comprised individuals that survived until approximately age 50. This may have resulted in an underestimation of the inequalities (Mayeda et al., 2018). Finally, there might be potential violations of the consistency assumption due to the chosen exposure. We measured education as the highest attained degree without capturing duration or quality of education, both of which may be differentially associated with mortality (Rehkopf et al., 2016). Thus, there remains a gap between our findings and specific targets for potential interventions.

One key strength of our study is the utilization of a population-based multi-generational and multi-country data sample. Further, we adopted a causal framework with transparent identifying assumptions to estimate marginal inequalities, rather than conditional hazard ratios as has been done in previous studies. The latter ones are known to provide potentially biased effect estimates due to both non-collapsibility and implicit selection bias of the hazard ratio (Daniel et al., 2021; Hernán, 2010).

5. Conclusions

We provide empirical evidence that low individual education drives intergenerational inequalities in longevity among adult Europeans and that these inequalities were not mitigated through increased social net expenditure during their older life. Thus, our study supports the importance of achieving a high education, and of interventions facilitating it. One example would be the various policies implemented in Ireland to reduce financial barriers to achieving higher education, such as the "free education scheme" of 1967 or the removal of higher education tuition fees in 1996 (McCoy & Smyth, 2011; O'Donoghue et al., 2016). The need for better educational outcomes for European citizens has also been acknowledged by the European Commission in its updated council recommendation on school success, calling on all member states to strengthen their educational systems to reduce early school leaving (Union, 2022). From a country-level perspective, further research could build upon our findings to examine more specific policies of social spending that may be able to diminish inequalities in longevity. Particularly, our study highlights the need to examine the effect of welfare systems earlier in life to truly understand how welfare may impact longevity in the long run. This would require younger cohorts that are followed up for longer periods of time, but could create valuable information for public health specialists and policy makers aiming to diminish social inequalities in longevity.

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Data sharing

Data is available via registration to the SHARE project website (see www.share-project.org).

Author contributions

Cornelia Wagner: Methodology, Formal analysis, Writing - Original Draft. Stéphane Cullati: Writing - Review & Editing. Stefan Sieber: Writing - Review & Editing. Tim Huijts: Writing - Review & Editing. Arnaud Chiolero: Writing - Review & Editing. Cristian Carmeli: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing, Supervision.

Declaration of competing interest

We declare no conflicts of interest.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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Supplementary materials

Table S1. *Results of sensitivity analyses to assess potential violations of positivity in main analyses. Inequalities in longevity due to intergenerational trajectories are measured via years of life lost (YLL) with respect to the reference High-High trajectory. Analysis 1 (reported as main results) included country groups among the confounders the survival curves were standardized to and included participants from Southern Europe. Analysis 2 included country groups as a potential confounding factor, but excluded participants from Southern Europe. Analysis 3 did not include country groups into the confounders and included participants from Southern Europe. Analysis 4 excluded country groups from the confounders and excluded participants from Southern Europe. SE countries = Southern European countries. Reference = High-High (parental-individual education). Standardized by age at baseline, sex, birth period.*

Educational trajectory	Analysis 1	Analysis 2	Analysis 3	Analysis 4
	YLL (95% CI)	**YLL** (95% CI)	**YLL** (95% CI)	**YLL** (95% CI)
Low-High vs High-High	**0.4** (-0.1 to 0.9)	**0.1** (-0.1 to 0.9)	**0.2** (-0.2 to 0.7)	**0.0** (-0.4 to 0.6)
High-Low vs High-High	**2.4** (1.1 to 3.6)	**2.2** (1.1 to 3.6)	**2.8** (1.7 to 3.9)	**3.0** (1.8 to 4.0)
Low-Low vs High-High	**2.9** (2.2 to 3.8)	**3.0** (2.2 to 3.8)	**2.7** (2.2 to 3.3)	**2.9** (2.1 to 3.7)

Table S2. *Sample characteristics for participants lost at baseline. Educational trajectories correspond to parental-individual educational attainments, e.g., High-High = high parental education – high individual education. SD = standard deviation.*

Characteristics	Analytic sample n (% or SD)	Lost at baseline n (% or SD)
Number of participants	52,271	10,429
Sex		
Female	29,159 (56%)	5,672 (54%)
Male	23,112 (44%)	4,757 (46%)
Age (years), mean and SD	67.2 (± 10.0)	65.9 (± 10.5)
Birth cohorts		
1909-1938	12,850 (25%)	2,306 (22%)
1939-1945	10,890 (21%)	1,836 (18%)
1946-1964	28,531 (55%)	6,287 (60%)
Multimorbidity (min. 2 chronic conditions)		
Yes	25,448 (49%)	4,668 (45%)
No	26,823 (51%)	5,761 (55%)
Limitations with activities of daily living		
No limitations	46,069 (88%)	9,290 (89%)
1 limitation	3,049 (6%)	541 (5%)
Min. 2 limitations	3,153 (6%)	598 (6%)
Number of deaths (2013-2020)	6,044 (12%)	-
Educational trajectories		
High-High (reference)	10,841 (21%)	1,888 (18%)
Low-High	13,118 (25%)	2,683 (26%)
High-Low	2,523 (5%)	496 (5%)
Low-Low	16,439 (31%)	3,333 (32%)
Missing	9,350 (18%)	2,029 (20%)

Table S3. *Life expectancies (years) between ages 50 – 90 years and years of life lost (YLL) due to different educational trajectories when truncating IPWs to the 1st and 99th percentiles. Reference = High-High (parental-individual education). Standardized by age at baseline, sex, birth period, country group.*

Educational trajectory	**Life expectancies** (95% CI)	**YLL** (95% CI)
High-High	**33.9** (33.5 to 34.2)	**-**
Low-High	**33.4** (33.0 to 33.7)	**0.5** (0.1 to 0.9)
High-Low	**31.6** (30.4 to 32.6)	**2.2** (1.1 to 3.5)
Low-Low	**30.8** (30.3 to 31.4)	**3.0** (2.4 to 3.7)

Table S4. *Life expectancies (years) between ages 50 – 90 years and years of life lost (YLL) due to different educational trajectories when truncating IPWs to the 1st and 95th percentiles. Reference = High-High (parental-individual education). Standardized by age at baseline, sex, birth period, country group.*

Educational trajectory	**Life expectancies** (95% CI)	**YLL** (95% CI)
High-High	**33.9** (33.5 to 34.2)	**-**
Low-High	**33.4** (33.1 to 33.8)	**0.4** (0.0 to 0.9)
High-Low	**31.5** (30.4 to 32.6)	**2.3** (1.2 to 3.5)
Low-Low	**31.0** (30.5 to 31.5)	**2.8** (2.2 to 3.5)

Figure S1. *Correlation between life expectancy (years, ages 50-90 years) and social net expenditure as percentage of GDP (mean, 2013-2018) by country. Split by educational trajectories, e.g., High-High = high parental education – high individual education. Bubbles correspond to individual countries; sizes correspond to precision of the estimate, i.e., the larger the circle the wider the 95% confidence interval.*

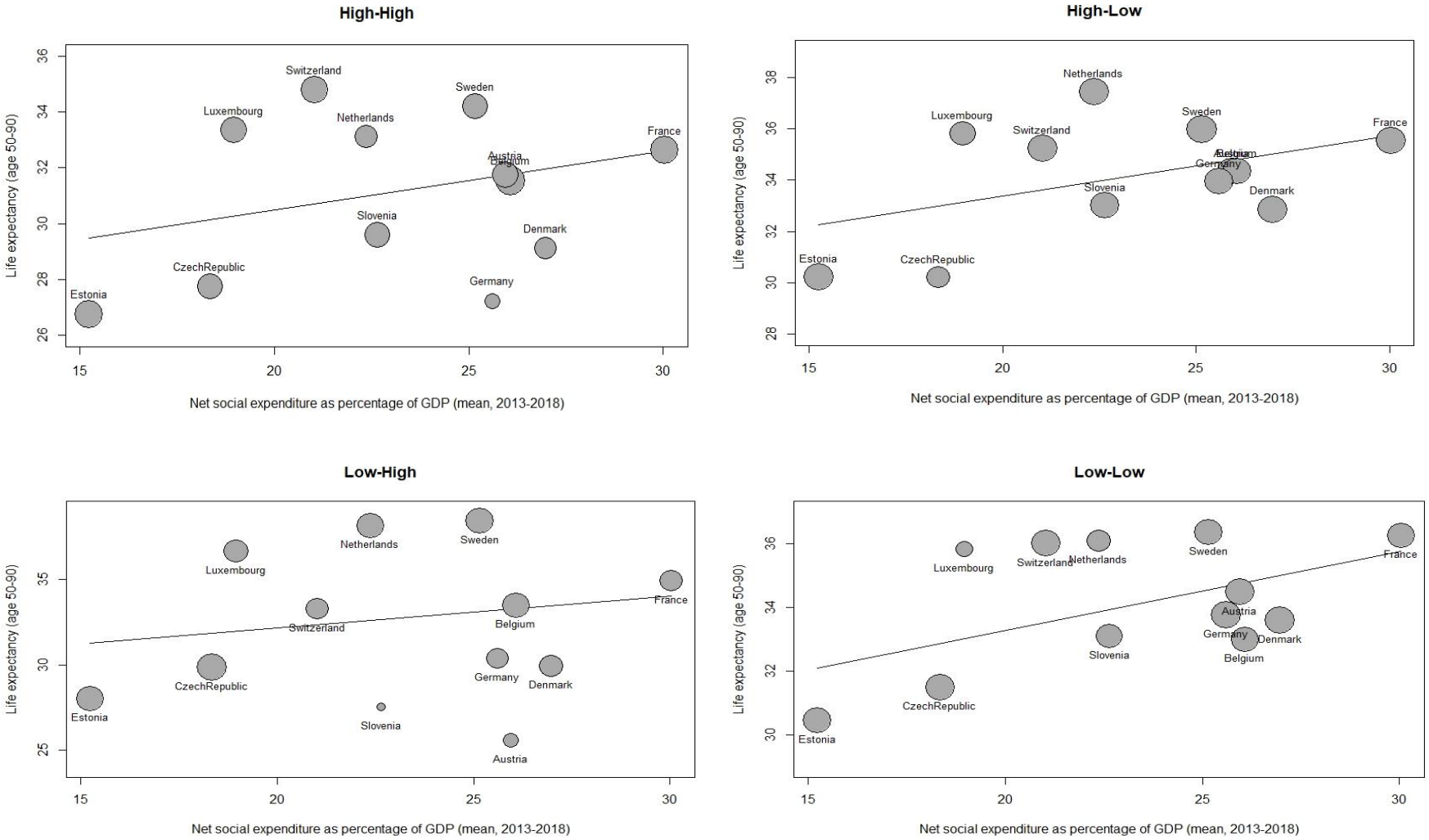
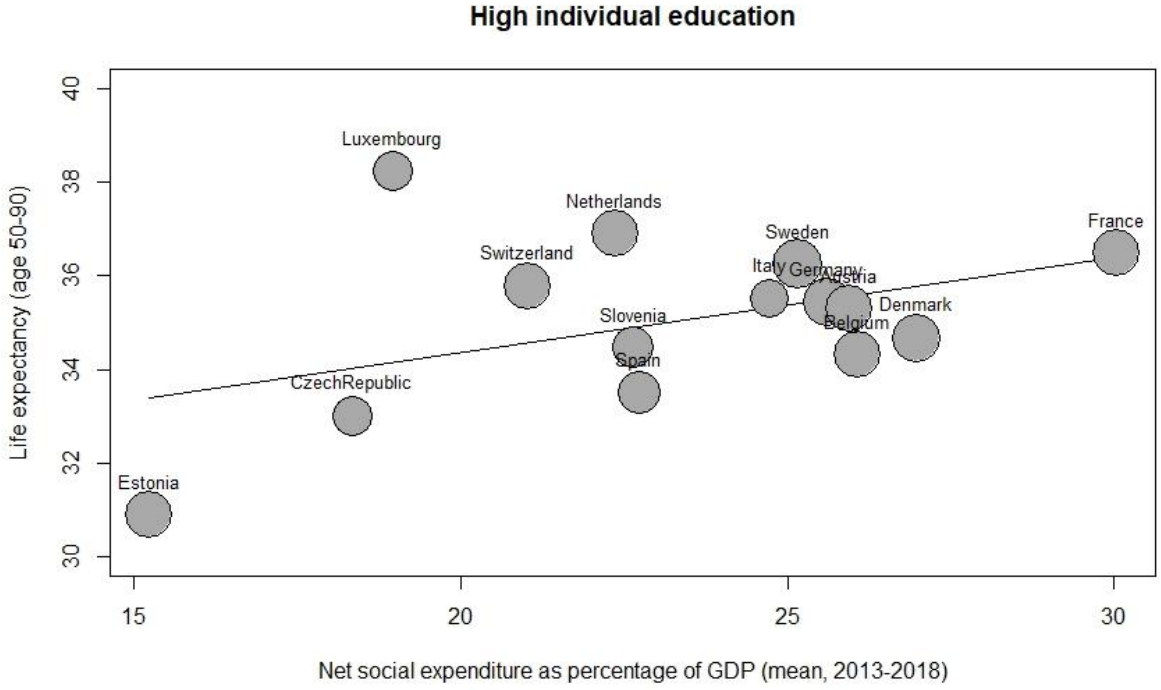
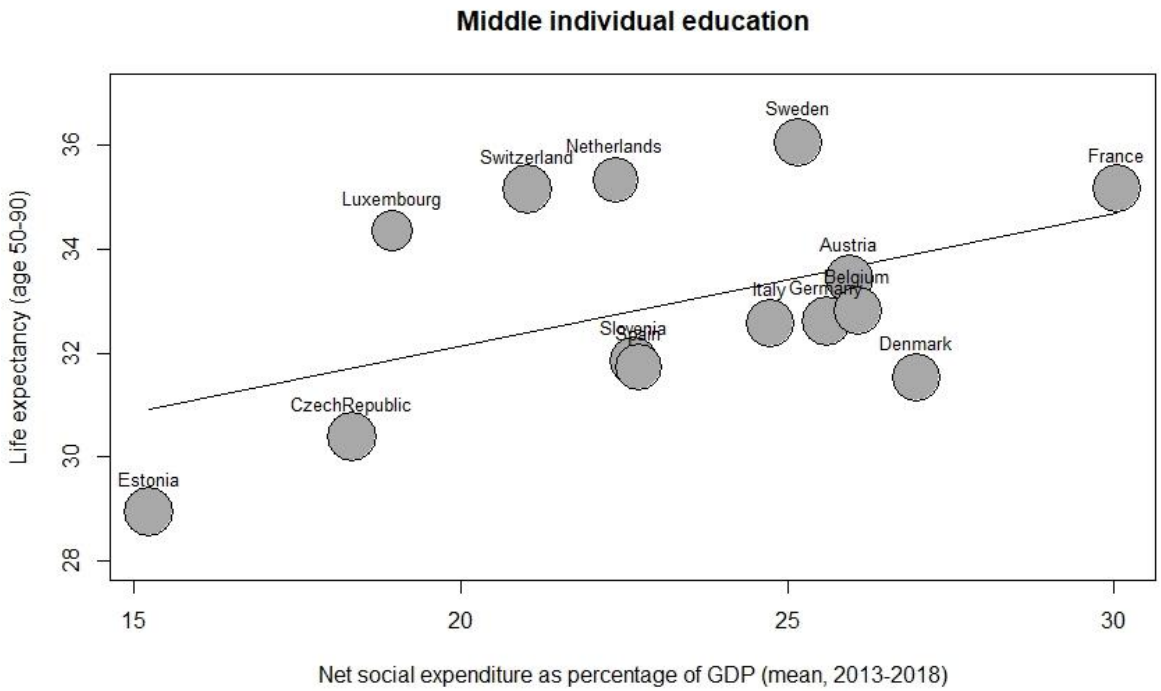
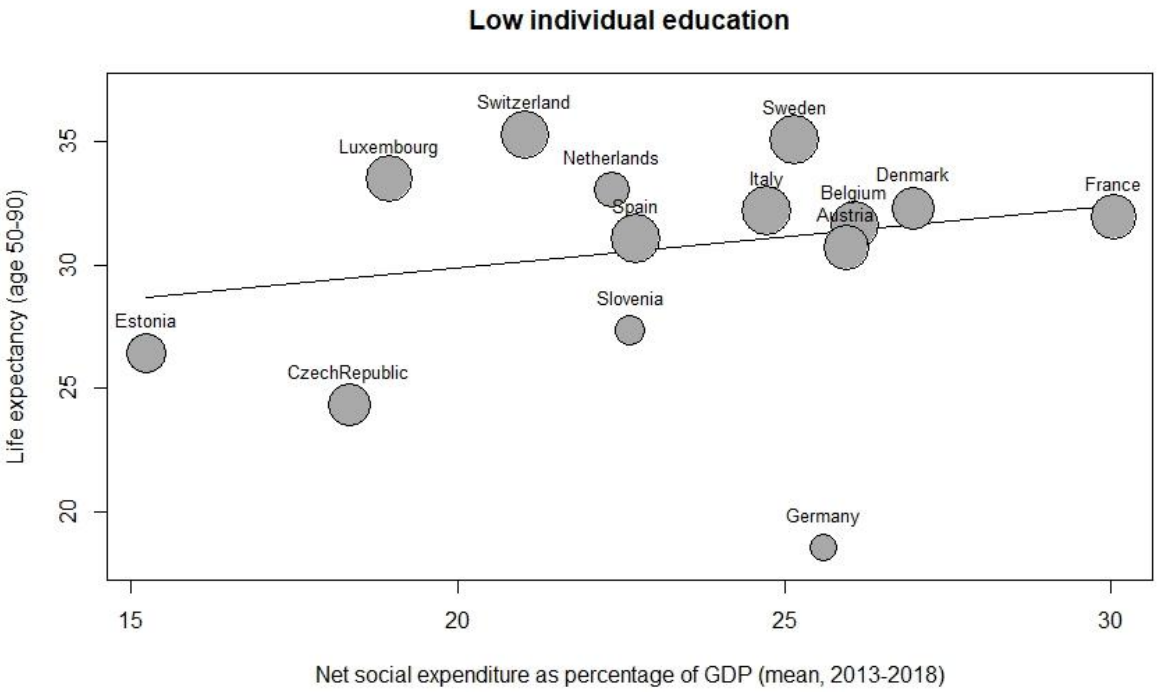


Figure S2. *Correlation between life expectancy (years, between 50-90 years of age) and social net expenditure as percentage of GDP (mean, 2013-2018) by country. Split by individual educational attainment. Bubbles correspond to individual countries; sizes correspond to precision of the estimate, i.e., the larger the circle the wider the 95% confidence interval.*






Low individual education
Switzerland
Sweden
Luxembourg
Netherlands
Italy
Denmark
Belgium
Austria
France
Spain
Slovenia
Estonia
CzechRepublic
Germany
Life expectancy (age 50-90)
35
30
25
20
15
20
25
30
Net social expenditure as percentage of GDP (mean, 2013-2018)

Chapter 7 | Life Course Epidemiology and Public Health

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Life course epidemiology and public health

Cornelia Wagner, Cristian Carmeli, Josephine Jackisch, Mika Kivimäki, Bernadette W A van der Linden, Stéphane Cullati, Arnaud Chiolero

Life course epidemiology aims to study the effect of exposures on health outcomes across the life course from a social, behavioural, and biological perspective. In this Review, we describe how life course epidemiology changes the way the causes of chronic diseases are understood, with the example of hypertension, breast cancer, and dementia, and how it guides prevention strategies. Life course epidemiology uses complex methods for the analysis of longitudinal, ideally population-based, observational data and takes advantage of new approaches for causal inference. It informs primordial prevention, the prevention of exposure to risk factors, from an eco-social and life course perspective in which health and disease are conceived as the results of complex interactions between biological endowment, health behaviours, social networks, family influences, and socioeconomic conditions across the life course. More broadly, life course epidemiology guides population-based and high-risk prevention strategies for chronic diseases from the prenatal period to old age, contributing to evidence-based and data-informed public health actions. In this Review, we assess the contribution of life course epidemiology to public health and reflect on current and future challenges for this field and its integration into policy making.

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Introduction

Life course epidemiology aims to study the effect of exposures across the life course (notably early in life) on health, looking as far back as exposures during gestation or in previous generations.[1,2] It draws on expertise from multiple scientific disciplines, ie, epidemiology, sociology, psychology, biomedical sciences, and other fields related to population health sciences. In the biomedical sciences, Barker's hypothesis of fetal programming[3] was crucial for the early development of life course epidemiology, stating that fetal nutrition can contribute to the risk of adult chronic diseases, such as diabetes or hypertension. In the social sciences, alongside social epidemiology, interest in long-term socio-environmental exposures was notably introduced by Elder in his study of Californian birth cohorts to understand the social and health impacts of the Great Depression.[4] The term life course epidemiology was coined in the 1990s to define a field of study interested in early-life and later-life determinants of chronic diseases.[5]

Since then, life course epidemiology has contributed substantially to the study of chronic diseases and has gained popularity across epidemiology and public health. Barker's fetal programming hypothesis has grown into the developmental origins of health and disease approach in medical research, which places emphasis on prenatal environmental exposures as determinants of later-life health.[6] This approach expands the classic epidemiological and biomedical perspective of the crucial role of risk factors during midlife as the causes of chronic diseases in later life to exposure to risk factors at other ages or other life stages.[7] Life course research has been made possible through the availability of prospective and retrospective birth cohort studies and other large, population-based, longitudinal studies (within and across generations) that collect a wide range of individual, biological, social, and environmental data over decades of life. Beyond the analysis of longitudinal data, life course epidemiology is a field in its own right with unique theories, methodologies, and public health implications.[1,5]

Although life course epidemiology is established in scientific research, its application to public health policy making is less advanced. Possible reasons are the high context specificity of some findings, the complexity of the mechanisms involved, and the challenge of establishing causality across the life course. Nevertheless, policy making already benefits from life course epidemiological concepts and findings, notably in the form of primordial prevention, the prevention of exposure to risk factors.[8,9] Reviewing how life course epidemiology helps design prevention strategies for chronic diseases, how it changes the way the cause of chronic diseases is understood, and how it informs population-based, high-risk, and vulnerable population preventive strategies is therefore important and timely.

From life course models to policy making

Life course models

Life course research is based on a set of five basic principles defined by Elder and Shanahan.[10] These are: lifespan development (human development and ageing are lifelong processes not restricted to specific life stages); agency (people have the capability to take actions and make choices that shape their lives within the constraints of environmental, social, and historical contexts); time and place (every individual life course is embedded within and influenced by its specific historical time and place); timing (the same events and behaviours can have different effects depending on when they happen in the life course); and linked lives (people do not experience life alone but influence each other through shared interdependent relationships).

These principles have contributed to the development of theoretical causal models that explain how exposures across the life course cause health outcomes in later life.[10] These models are simplistic by design to highlight potential causal mechanisms underlying the associations between exposures and health across the life course.[11,12] In the life course epidemiology of chronic diseases, four models are frequently used: the sensitive period model;

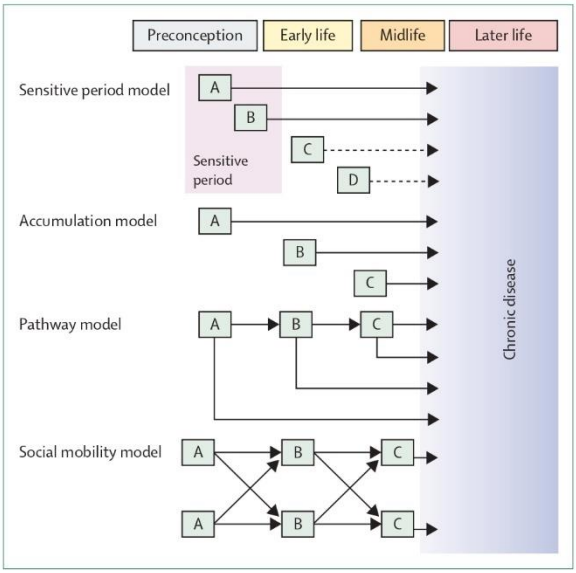

Figure 1: **Life course models for the causes of chronic diseases**
A, B, C, and D are exposure at different times during the life course. Arrows show causal effects; dotted arrows signify weaker causal effects.[11]

the accumulation model; the pathway model; and the social mobility model (figure 1).[11,13]

The sensitive period model focuses on the differential effect of an exposure depending on its timing. It posits that there are some periods across the life course, commonly in early life, during which an exposure has a stronger effect on health than if it were to happen outside of those periods. Gestation is a sensitive period for multiple exposures.[1] For instance, prenatal exposure to maternal starvation during the Dutch famine (1944–45) was associated with increased risk of later-life coronary heart disease, obstructive airways disease, and decreased glucose tolerance, depending on whether maternal starvation happened in early, mid, or late gestation, respectively.[14] Life transitions are also typical sensitive periods, such as the transition to motherhood, which is a major biosocial event.[15] Generally, there is the possibility of recovering from the effect of an exposure during a sensitive period. In contrast, an exposure during a critical period is considered to have a more permanent effect. For instance, lead exposure during early childhood, a critical period for brain development, can result in permanent cognitive impairments that persist into adulthood.[16] Identifying potential sensitive and critical periods for disease risk factors across the life course aids in the optimal timing of preventive interventions.

The accumulation model focuses on the accumulation and duration of exposures rather than their timing. It states that the accumulation of exposures across the life course determines later disease risk. This effect can be caused by an accumulation of different risk factors or by exposure to the same risk factor over an extended period. For instance, an accumulation across the life course of socioeconomic disadvantage,[17] low birthweight,[18] physical inactivity, and high salt intake during childhood and adolescence,[19] can result in hypertension in midlife.[20] The relationship takes the form of a dose–response association that incrementally builds towards a disease state. Accumulation of risks can be linear or exponential. Following this model, preventive interventions aim to stop the accumulation of risk before the disease threshold is attained.

The pathway model focuses on the sequential link between multiple exposures. It is also known as the chain-of-risk model since it states that each exposure to a risk factor increases the likelihood of being exposed to another risk factor.[21]

Finally, the social mobility model focuses on the direction of change of an exposure and is used almost exclusively for the study of the effects of socioeconomic exposures. According to this model, social exposures are states that individuals can transition in and out of: individuals can move between different social classes or income levels, and the direction of this change—upward, downward, or non-mobile—determines their later disease risk.[22,23] In a Swedish study, the direction of change between occupational classes between ages 25 years and 55 years was associated with myocardial infarction risk.[24] Specifically, moving from a non-manual to a manual occupation in later life—ie, downward mobility—was associated with an increased risk of myocardial infarction compared with no change in occupation class. Potential interventions could build upon this knowledge by promoting policies that favour upward social mobility in the population. One shortcoming of the social mobility model is the challenge of disentangling the effects of the final exposure, per se, from the effects of the trajectory leading up to this last exposure.[25]

These four models acknowledge the fundamental social causes of disease that contextualise individual-level determinants of health. Individual risk factors should be contextualised by "attempting to understand how people come to be exposed" or come to be put at the "risk of risks" to design more effective preventive interventions.[26] Furthermore, social factors such as socioeconomic status can be considered fundamental causes of diseases, since they determine people's access to health-protective resources, such as knowledge, money, power, prestige, and beneficial social connections.[26] If social conditions truly put people at risk of risks, life course-informed policies aiming to decrease health inequalities should target social causes in addition to more proximal causes. The vulnerable population preventive strategy is built partly on this concept.[26,27]

Testing the value of these models has been made possible by the availability of large, population-based cohort studies in, for example, the UK (eg, the 1958 National Child Development Study and Lothian birth cohort studies), Finland (eg, the Northern Finnish Birth Cohort Study), and New Zealand (eg, the Christchurch

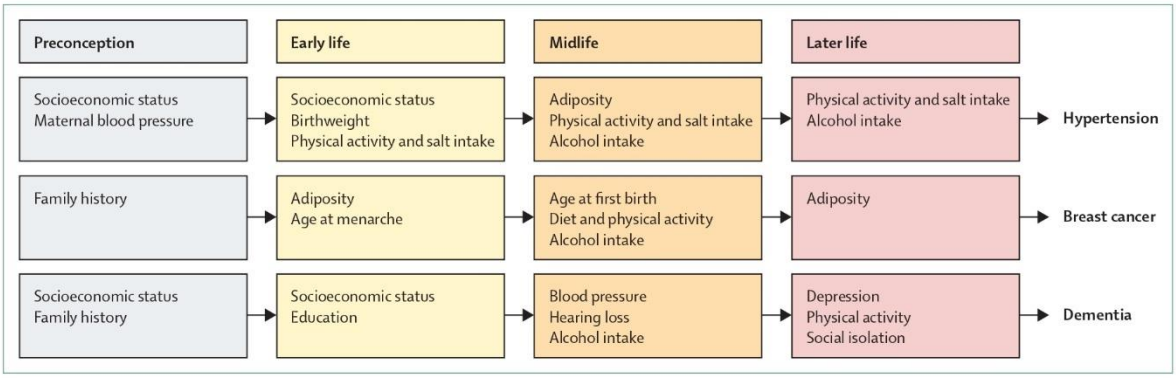

Figure 2: **Selected determinants of hypertension, breast cancer, and dementia risks across the life course**
Some determinants have an effect during a specific period of the life course and others during multiple periods.

Health and Development Study).[28] Birth cohorts typically consist of population-based samples of individuals born in a given period of time and followed up from birth or later in life over many years, if not across generations. The advancement of life course epidemiology has also been facilitated by biobanks linked to cohorts, aiming to assess the exposome of large samples of the population.[29] The strength of such large-scale cohorts lies in the collection of individual, biological, social, and environmental data over long periods of time, spanning decades of life. Together with the accumulation of these data came the development of advanced statistical methods for multicohort and big data research that make their analysis possible.[30]

Life course perspective on chronic diseases

A life course epidemiological approach can be applied to the study of any type of disease, but it has been especially useful in the understanding and prevention of chronic diseases. Life course epidemiology offers a framework for examining the cause of chronic disease across life stages with appropriate concepts and vocabulary (appendix pp 1–2) and, as a result, shapes disease definitions, health-related beliefs and fears, and preventive strategies.[31] In this section, we review how life course epidemiology has changed the way hypertension, breast cancer, and dementia are understood and its impact on their prevention (figure 2). These examples were chosen due to their high public health burden and suitability for a life course perspective.

Hypertension

Hypertension is a state of sustained elevated blood pressure and is a major modifiable risk factor for cardiovascular diseases—the leading cause of death worldwide.[20,32–34] The study of cardiovascular diseases lends itself particularly well to a life course approach since most cardiovascular diseases happen in later life and are typically understood as the outcomes of a lifetime exposure to causal risk factors, including smoking, dyslipidaemia, obesity, diabetes, and hypertension.[33,35] Although these risk factors were initially focused on during midlife, a growing number of studies have pointed at early life as a sensitive period for the development of these factors, establishing their effect on cardiovascular diseases in later life.[9]

Causes of hypertension can be identified across the entire life course, starting at conception and the first 1000 days of life.[36–38] Hypertension has been associated with fetal exposure to maternal smoking,[39] undernutrition while in utero,[3] low birthweight,[40] and increased salt intake in the first months of life.[19,41] In midlife and later life, elevated blood pressure is a major cause of cardiovascular diseases[42] and a large number of drug trials have shown that lowering blood pressure reduces the occurrence of these diseases (and related mortality)[33,43] and dementia.[44] Additionally, exposure to hypertensive risk factors is at its peak during midlife and later life, including high alcohol intake,[45] high salt intake,[46] and high BMI.[47]

With the identification of risk factors across the life course comes the opportunity for targeted life stage-specific interventions, with the aim of directing the health–disease trajectory towards an optimal path (figure 3). An extensive and in-depth guide to possible interventions is listed in the *Lancet* Commission on hypertension's call to action[20] for a life course strategy to address the global burden of hypertension. To summarise, intervention strategies should be multifaceted and target prevention, diagnosis, and treatment at the population and individual levels depending on the absolute risk of cardiovascular diseases. Clinical approaches at the individual level, including drug treatments, should target subpopulations at high risk (ie, people with a high absolute risk of cardiovascular disease) typically in midlife and later life. At the population level, interventions can be tailored to the life course. At all life stages, primordial prevention can be achieved via reduced salt intake, increased physical activity, and improved dietary habits. Early in life and during adolescence, the focus should be on effective health education; screening for hypertension is not

See Online for appendix

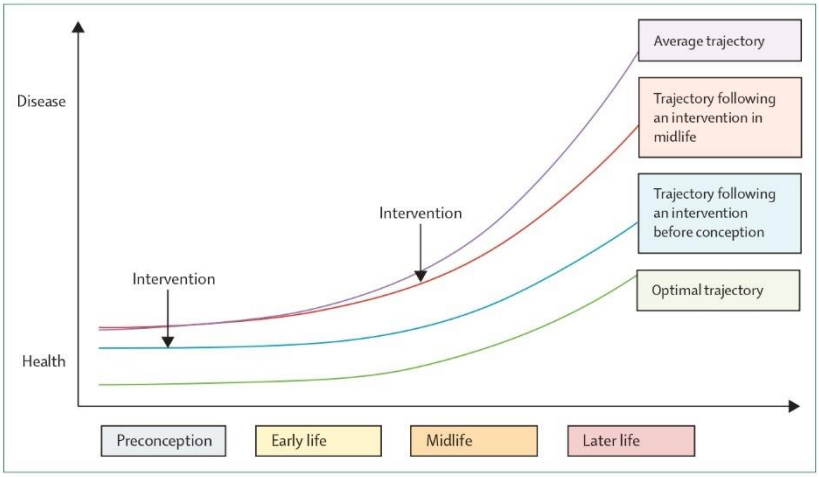

Figure 3: **Life course trajectories across the continuum of health and disease and how they are modified by interventions applied during different periods of life**
Depending on the timing and type of intervention, and the causal process at stake, the effect on the trajectory will be different. The arrows signify which trajectory the interventions apply to.

recommended during this period of life.[48] In midlife and later life, education should continue in the form of wide distributions of evidence-based knowledge and recommendations to promote cardiovascular health, and screening for hypertension and treatment programmes should be implemented.

Breast cancer

Breast cancer constitutes approximately 25% of all cancer diagnoses in women and roughly 16% of cancer deaths in women.[49] A classic life course perspective on breast cancer follows reproductive stages—ie, pre-menarche, menarche to first birth, pregnancy, and post-menopause.[50] The effect of breast cancer risk factors differs among these sensitive periods. For example, adiposity in early life, during premenarche, has been associated with lower risk of breast cancer,[51,52] whereas adiposity after menopause has been associated with higher risk.[53] Breast cancer can also be seen as the result of accumulated risk factors, particularly in relation to the timings of births and menarche. The Pike model postulates that the rate of breast tissue ageing, a risk factor for cancer development, slows down with each birth and after menopause, and is highest in the period between menarche and first birth.[50,54] Thus, depending on when a woman experiences menarche, and when and whether she gives birth once or multiple times could change her lifetime breast cancer risk. This relationship exemplifies how identifying risk factors for breast cancer is not enough—a life course perspective can add the context needed to design targeted prevention strategies.[55]

For the prevention of breast cancer, multiple windows for intervention exist along the life course. Much emphasis has been put on secondary prevention through screening for early disease detection in midlife. The US Preventive Services Task Force recommends mammography screenings for women aged 40–74 years.[56] The timings for screenings based on this traditional approach of early disease detection are informed by clinical trials.[56] Developments in the life course epidemiology of breast cancer offer new perspectives for primordial prevention strategies that are set earlier in life. Apart from genetic susceptibility and hormonal risk factors, large population-based studies have suggested that health behaviours (eg, alcohol intake, diet, and physical inactivity) could be modifiable risk factors for breast cancer and thus potential targets for preventive strategies.[50] Some studies suggest that environmental exposures (eg, dioxins, air pollution, and heavy metals) might also be involved.[57] Hence, rather than being limited to screening in midlife and later life, breast cancer prevention could start in early life within an eco-social preventive approach that targets both health behaviours and environmental risk factors at a population level.

Dementia

Worldwide, people live longer and are thus more exposed to age-related diseases such as dementia. Dementia is the loss of cognitive function typically attributable to vascular and neurodegenerative brain damage.[58] The occurrence of dementia in later life is affected by exposure to risk factors across the life course that diminish cognitive reserves—ie, an individual's ability to cope with brain damage.[59] Increasing and maintaining cognitive reserves throughout the life course could therefore prevent or delay the onset of dementia.[60]

In early life, education (as a form of mental activity) stands out as a target for intervention, since there is consistent evidence for education having a protective effect on later-life cognition,[61,62] for example through its association with healthier behaviours.[63,64] Nevertheless, mental activity might be beneficial across the entire life course and not only in the form of formal education. An individual participant data meta-analysis[65] found that people who perform cognitively challenging jobs have a lower risk of dementia, regardless of their education. Furthermore, there is evidence that the longer people are exposed to socioeconomic hardships, the lower their level of memory function and the higher their rate of later-life memory decline.[66] This evidence indicates that interventions are possible at every life stage, making dementia prevention a lifelong prospect that should combine widespread social and public health policies with individually tailored interventions at different life stages.[60,67]

A life course perspective for the prevention of dementia in early life, midlife, and later life has been adopted in policy and clinical guidelines. The 2020 report of the *Lancet* Commission on dementia prevention, intervention, and care, for example, identified 12 potentially modifiable risk

factors and incorporated these into a life course model of dementia prevention. These risk factors are, in early life: low educational attainment; in midlife: elevated blood pressure, hearing impairment, traumatic brain injury, high alcohol intake, and obesity; and in later life: depression, physical inactivity, diabetes, smoking, social isolation, and air pollution.[60] This model illustrates the value of intervening early and continuously throughout the life course.

Causality and the life course

Since the turn of the 21st century, developments in causal inference methods based on observational data have helped life course epidemiology move from a rich conceptual way of thinking towards a truly preventive strategy information tool. The three main data science tasks in epidemiology are description, prediction, and causality.[68] Description aims to describe the world as it is, prediction aims to predict how the world might be, and causality aims to estimate how an outcome would change if we were to intervene on an exposure. One major issue in epidemiology is the enduring confusion between association and causality when explicit causal inference is necessary to guide prevention.[7] This issue is especially true in life course, social, and environmental epidemiology in which evidence stems largely from observations and rarely from experiments such as randomised trials.[69–71]

Within observational studies, an increasingly adopted approach is based on the potential outcomes or counterfactual framework, with statistical models informed by expert knowledge encoded into graphical causal models and statistical estimation (notably via G methods).[72,73] This approach has advantages for life course epidemiology compared with traditional regression-based or adjustment-based methods, as these informed statistical models can better handle exposure-induced or time-varying measured confounding and reduce over-adjustment bias or mutual adjustment fallacies through appropriate covariate selection.[74,75] Other methods useful for life course research encompass causal evaluation of risk factors via instrumental variables (eg, genetic and non-genetic instruments) and policy evaluations via econometric methods (eg, difference-in-difference, regression discontinuity, and interrupted time series).[76–79]

For instance, the effect of BMI on all-cause mortality is a classic and highly complex question in life course research, which is plagued by confounding and reverse causation issues that are intractable by typical epidemiological methods.[80] Instrumental variables help overcome these limitations. In a large, population-based, intergenerational prospective study, when offspring BMI was used as an instrumental variable for paternal BMI, the estimated association between BMI and paternal cardiovascular disease mortality (hazard ratio [HR] per standard deviation of BMI 1·82, 95% CI 1·17–2·83) was stronger than that indicated by the directly observed association between individuals' own BMIs and their cardiovascular disease mortality (HR 1·45, 1·31–1·61).[80] Another example is how the life course mendelian randomisation technique can enlighten complex time-varying effects of age-dependent lifestyle factors on risk of chronic disease.[81]

Furthermore, advances in biobanks and omics have provided capacity for the joint measurement of thousands of biomarkers, such as proteins and metabolites, from a single stored sample. This increased availability of biomarkers has allowed for a better understanding of biological mechanisms across the life course, linking an exposure and a disease through the analysis of the mediating role of these biomarkers.[65,81]

Policy implications

To translate life course research into policies for chronic disease prevention, what determines health on a population level and how to intervene to improve it must both be made clear.[82] A relevant framework is the eco-social perspective that frames how health stems from interactions with the social environment.[83,84] In this perspective, the individual is embedded within multiple social circles, starting from the immediate family, and moving on to include peers, neighbourhoods, cities, and countries of residence. Each level has an influence on health at a personal level and therefore determines the patterns of chronic diseases at a population level.

When considering eco-social and life course perspectives together, different strategies for chronic disease prevention emerge that target different eco-social levels across the life course, and these preventive interventions can either work together or independently of each other. We give an example of prevention strategies for hypertension from an eco-social and life course perspective (figure 4).[20] In early life and in immediate social surroundings, policies targeting socioeconomic inequalities can create healthy family environments that allow children to engage in education and leisure activities, and to learn health-promoting behaviours early in life. Moving up a level, community-based projects can raise awareness of hypertension and grant universal access to screening and anti-hypertensive drugs in midlife and later life. On a city level, health-promoting urban spaces (eg, cycle lanes and walkable cities) can facilitate an active lifestyle in the entire population from childhood to old age. On a country level, legislators can protect the health of the population at all life stages via regulations, such as mandated salt limits in food production. Finally, at all ages and on a country-wide level, effective surveillance of hypertension and its risk factors are needed to ensure that prevention works.

Challenges

Research in life course epidemiology faces several challenges. Longitudinal cohorts are expensive and

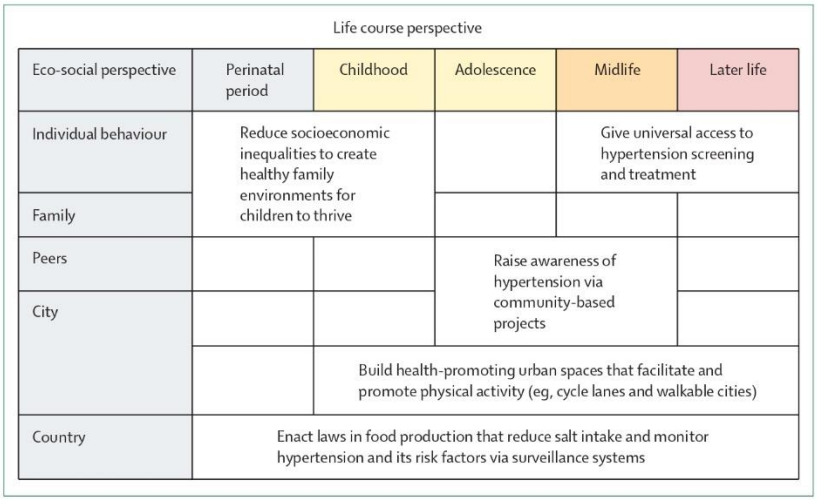

Figure 4: **Examples of hypertension prevention across eco-social and life course dimensions[83]**

Search strategy and selection criteria

The starting point of study selection for this Review was based on the expertise of all authors, who listed important life course epidemiological concepts that needed to be addressed. We identified key studies, reviews, or textbooks in our fields (appendix p 3), which were summarised and placed into context with the other papers included in this Review. We conducted a broad search on MEDLINE and Google Scholar to identify additional papers and reviews on the topic of life course epidemiology. We considered only full-text articles published in English; there were no limitations regarding article publication dates. We concentrated our Review on influential concepts within life course epidemiology from the past three decades, aware of the potential bias stemming from a subjective study selection. Furthermore, we particularly considered studies and reviews on the life course epidemiology of hypertension, breast cancer, and dementia. These diseases were selected due to their high public health burden and suitability for a life course perspective. References were chosen for their importance, ease of access, and usefulness to readers who might want further high-quality reading options in this field.

time-consuming to establish, and long periods of follow-up are needed before valuable data are available. These requirements, in turn, often result in life course research being questioned for its reproducibility and generalisability—can findings from a generation born 50 years ago be applied to the current generation?[85] Other study designs, such as case–control studies or trials, are limited when it comes to addressing life course epidemiological research questions.[86] Measurement of exposures across the life course is also a major source of bias. This results in life course research often having to rely on incomplete or poor-quality data.

Another major challenge is that life course epidemiology often deals with weak effect sizes at an individual level.[87] As for all fields of epidemiology, weak effects can be difficult to distinguish from bias introduced by study design, measurement errors, analyses, and residual confounding.[88] The best ways to mitigate these issues are the same as for other epidemiological fields: use multiple approaches to verify results; strengthen statistical knowledge to prevent misuse of analyses; place importance on transparent and reproducible study protocols; and give researchers the right incentives to favour quality over quantity when publishing research.[88,89] However, even with adequate study designs and analyses, weak effect sizes across the life course complexify policy making in terms of deciding where, when, and how to intervene, especially within a consequentialist perspective.[90]

One important question is to what extent life course epidemiology informs population-level or individual-level preventive interventions. Epidemiology in general, and life course epidemiology in particular, is primarily focused on population-level or group-level effects, providing evidence for population-wide and high-risk preventive interventions. Even a small effect size at an individual level might have major impacts at a population level if a large share of the population is exposed to the determinant in question. This fact is a major argument for the population-based preventive strategy advocated by Rose,[82] which is built on the insight that both risk and health are a continuum distributed in the population, implying that targeting the whole population rather than only the people at high risk of a disease is better for reducing disease burden. Many exposures examined in life course studies are highly prevalent, and this prevalence is part of the reason why a life course perspective is increasingly adopted for optimising the timing of population-level preventive programmes.[91,92]

The life course approach is also increasingly mentioned in clinical guidelines[93] and family medicine,[94] but the potential benefit at this level should not be overestimated because it can lead to inefficient pseudo-high-risk preventive strategies.[95] Evidence from life course and social epidemiology also informs vulnerable population preventive strategies, promoting the mitigation of health inequities by tailoring preventive strategies towards vulnerable populations.[27]

Finally, the translation of life course epidemiological findings into preventive strategies is a balance between precision and simplicity. Policy makers could aim for precision, for example by acting early in life to reduce risk factor exposure during a sensitive period, but they might do so at the cost of simplicity (ie, by not acting at all ages to reduce overall risk exposure). For example, identifying smoking as a major risk for cardiovascular diseases in midlife does not mean that smoking prevention should not target other life periods. This translational challenge extends towards populations as well, for which the right balance between segmentation into subpopulations with targeted needs and wide population-based interventions needs to be found.[96] A further challenge with implementing a life course approach in policy is the difficulty of persuading both the public and policy makers to embrace preventive interventions whose benefits can take decades to appear.

Conclusions

Over the past three decades, research in life course epidemiology has flourished. The origins of many chronic diseases can now be traced back to early life, allowing for new intervention strategies that target specific times during the life course. With examples from research on hypertension, breast cancer, and dementia, we have described how the field has grown from the idea of fetal programming and findings from social epidemiology to a multidisciplinary research approach that informs public health policy making.

Life course epidemiology offers the evidence needed to design primordial prevention of chronic diseases. It has brought new understanding of the transitions between health and disease, which are now conceived more than ever as continuums, linking the life course exposome to biomarkers, diseases, disability, and death. This field refines Rose's population-based preventive strategy[82] by tailoring interventions to distinct life stages and, to a lesser extent, informs high-risk preventive strategies.

The future of the field is promising and will most likely be characterised by even stronger multidisciplinary collaborations, particularly by advances in causal inference and a broadening of research foci to capture disease trajectories and multimorbidity in addition to single diseases, facilitating a more comprehensive evaluation of morbidity associated with life course exposures.

Contributors

CW, CC, SC, and AC conceptualised this Review. CW wrote the first draft. All authors were involved in draft revisions and approving the final draft for submission. All authors approved the final manuscript and accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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THE LANCET
Public Health

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Wagner C, Carmeli C, Jackisch J, et al. Life course epidemiology and public health. *Lancet Public Health* 2024; **9:** e261–69.

Supplementary materials

Table of Contents

Table 1 Concepts often used in the field of life course epidemiology

Term	Definition
Clustering	In the context of life course epidemiology, clustering refers to the tendency or multiple risk factors or exposures to co-occur or cluster together within individuals or populations over their lifetimes.[1] Certain environmental, lifestyle, or socioeconomic factors may not act in isolation but rather tend to group or cluster, potentially amplifying their collective effect on health. Understanding the clustering of risk factors is an asset of life course epidemiology because it helps identify high-risk groups and design interventions or public health strategies that target multiple risk factors simultaneously, to prevent multiple diseases and promote health across the lifespan.
Embodiment	Embodiment describes how social influences become incorporated into the human body. For instance, unequal access to resources, such as healthy food, stress-free work environments, or pollution-free air, translates into physio-anatomic differences in the human body resulting in health disparities in the population.[2] Both social disadvantage and its biological consequences can accumulate and interact to increase the risk of diseases in later life.[3] The mechanisms behind embodiment are better understood thanks to access to large cohorts with measurements of multiple exposures and biomarkers across the life course, as well as causal (mediation) analyses techniques, among other developments in life course epidemiology.
Exposome	The exposome encompasses the totality of environmental exposures individuals encounter throughout their lifetime, with the idea of examining their health effects, on their own or in combination, starting from early life and continuing through various life stages.[4] Researchers in life course epidemiology study how these complex, lifelong, and interacting exposures influence population health trajectories, from childhood to old age, spanning traditional environmental factors such as pollutants and chemicals but also factors like diet, lifestyle, stress, and socioeconomic status. The concept of exposome is increasingly used in the study of relationships between environmental factors and health.
First 1,000 days of life	The first 1,000 days of life, i.e., from conception to two years of age, have been described as a critical period in a child's development that can have long-lasting health effects into later life. During this period of rapid physiological development, the exposure to specific risk factors can have an effect on body structure and function.[5]
Healthy ageing and frailty	Life course epidemiology has contributed to a better understanding of healthy ageing[6] and frailty.[7] Healthy ageing refers to molecular processes underlying biological aging as well as to interventions to delay disease occurrence and promote healthy longevity.[8] Frailty is

	a multidimensional geriatric syndrome characterized by an increased vulnerability, a loss of adaptability to stress, and an increased risk of chronic conditions and mortality.[9] Life course epidemiology informs the promotion of healthy ageing and the prevention of frailty across the life course.[6, 10]
Primordial prevention	Primary prevention aims to prevent the development of diseases, whereas secondary prevention aims to prevent the progression or re-occurrence of diseases, for example through screening and early diagnosis. Primordial prevention is a type of primary prevention that aims to prevent the development of risk factors themselves.[11] It typically encompasses upstream interventions that target structural factors such as socioeconomic determinants of health or hazardous environmental exposures, lowering the share of the population "at risk of risks".[12]
Reserves	Reserves describe the accumulation of resources over the life course, be they physiological, cognitive, social or economic, that are protective against adverse events.[13] Reserves are built over time and are meant to protect against the negative effects of ageing. For example, close social networks take time and effort to build and must be maintained over the life course – in later life, however, they can be relied on to avoid social isolation and its associated health-damaging effects.
Social epidemiology	A sub-field of epidemiology that is primarily concerned with the role of social factors on the patterning of health.[14] At the core of the field is the observation that social factors, such as class, power, or capital, are unequally distributed in society and can thus shape health inequalities across the life course. Life course epidemiology concepts are now central to social epidemiology.[15]
Trajectory	Trajectories describe the evolution of a repeated measure over time and are of central interest in life course epidemiology.[16] Trajectories can be both exposures (e.g., work trajectories) as well as health outcomes (e.g., obesity trajectories) and can be restricted to the lifepath of the individual or be described across generations. They can also be applied to macro-level factors, such as trajectories in social expenditures.
Vulnerability and plasticity	Vulnerability refers to the differential susceptibility of individuals to a health challenge, for example due to pre-existing health conditions, socioeconomic deprivation, or lacking health literacy.[13] Plasticity refers to the ability to change in response to a health challenge, such as lifestyle modifications (e.g. smoking cessation, increased physical exercise) when diagnosed with diabetes or cardiovascular disease. Vulnerability and plasticity are observed across the life course and aid in the conceptualization of population health interventions.

Table S2 List of references selected by the authors to serve as a starting point for the writing of this review.

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Chapter 8 | Discussion

Summary of main findings

In Chapter 4, we investigated empirical studies examining the association between life course socioeconomic conditions (SEC) and later-life multimorbidity, and assessed to which extent they supported different life course causal models: critical period, sensitive period, accumulation, pathway, or social mobility. We identified four studies (25,209 participants) with the first measure of SEC in childhood (before age 18) and five studies (91,236 participants) with the first measure of SEC in young adulthood (after age 18). In the former, childhood SEC was associated with multimorbidity in old age in all studies, and the associations were partially or fully attenuated upon adjustment for later-life SEC; in the latter, associations with multimorbidity in old age as well as the effects of adjustment for later-life SEC were inconclusive as they differed from one study to the other, depending on location, study population, and/or tested SEC. Among the nine included studies, none tested the social mobility nor the accumulation model, so no conclusion could be drawn about them. Of the tested models, the results were consistent with the sensitive period and the pathway models. This indicates that SEC in early life could have an effect on multimorbidity not entirely explained by SEC in adulthood.

In Chapter 5, we assessed the effect of intergenerational educational trajectories (High-High, Low-High, High-Low, Low-Low) on inequalities in multimorbidity, measured in multimorbidity-free years lost (MFYL). We found that regardless of parental education, individuals with low individual education (High-Low, Low-Low) experienced a loss of around 2.8 multimorbidity-free years, indicating that these inequalities primarily stemmed from individual education. Additionally, we assessed whether these inequalities were modified by sex and found that, when exposed to low individual education, women experienced a twice greater magnitude of inequalities compared to men. However, this sex difference could partially be explained via health-seeking behaviors in additional sensitivity analyses. Thus, potential sex differences in the size of inequalities require additional studies with multimorbidity ascertainment of higher validity.

In Chapter 6, we assessed the effect of intergenerational educational trajectories (High-High, Low-High, High-Low, Low-Low) on inequalities in longevity, measured in years of life lost (YLL). There were approximately 2.5 years of life lost when having a low individual education regardless of parental education, indicating that inequalities were driven by individual education. Next, we assessed the potential mitigation of inequalities by increased social expenditure of the country of

residence, and observed that the higher the social expenditure, the larger the life expectancy, but not smaller the inequalities. These findings suggest that in European countries, individual education could be the main driver of inequalities in longevity for adults older than 50 years of age and born before 1965. Further, higher social expenditure improved longevity for both high and low educated participants, and could therefore not reduce educational inequalities in longevity.

In Chapter 7, we described how life course epidemiology changed the way the etiology of chronic diseases is understood, taking the examples of hypertension, breast cancer, and dementia, and how life course epidemiology can guide preventive strategies. For hypertension, risk factors have been identified across the life course, starting from fetal exposure to undernutrition, to increased salt intake in the first months of life, and health-detrimental behaviors like smoking or high alcohol intake in mid and later life. For breast cancer, focus has shifted slightly away from hormonal risk factors and secondary prevention through mammography screenings in mid-life, towards a wider perspective that includes early-life and environmental risk factors like health behaviors and exposure to air pollution or heavy metals. For dementia, life course epidemiology suggests that increasing and maintaining cognitive reserves throughout the life course is key in preventing or delaying the onset of dementia. The origins of many chronic diseases can now be traced back to early life, opening the door to new intervention strategies that target specific times during the life course in order to reduce the burden of chronic diseases in the population.

Discussion and comparison to the literature

The first paper of this thesis (Chapter 4) has found consistent evidence that the associations between childhood SEC and later-life multimorbidity are partially or fully attenuated by later-life SEC, and we could support this finding with our study using SHARE data (Chapter 5). Pavela and Latham (2016) found that lower childhood SEC (including parental education) was associated with increased number of chronic conditions; however, childhood SEC was no longer associated with chronic conditions after adjustment for adulthood SEC (including individual education). This mirrors the findings of our research presented in Chapters 5, describing an effect of individual education on multimorbidity, regardless of parental education. We did not examine the contribution of intermediate factors, like occupation or health behaviors, as this is outside this scope of this thesis work.

The studies presented in Chapter 5 and Chapter 6 are highly comparable, not only in their research design but also in their findings. Both studies indicated that educational inequalities in longevity and multimorbidity are determined by individual education and not parental education. Thus, these findings partially contradict the theory of cumulative dis/advantage, discussed in the Introduction, as we observed, one, that around one quarter of the study participants were upward socially mobile (Low-High), and two, that these upward socially mobile

participants had health outcomes basically indistinguishable from those with the most advantageous trajectory (High-High). However, this does not imply that parental education plays no role; rather it points to an indirect effect of parental education whereby parental education affects individual education but not the health outcome directly. The effect sizes of these inequalities, too, were similar with 2.9 (95% CI: 2.2 to 3.6) years of life lost and 2.6 (95% CI: 2.3 to 2.9) multimorbidity-free years lost for the lowest intergenerational trajectory (Low-Low) compared to the highest (High-High) between the ages of 50 and 90. Thus, our empirical studies point to the importance of achieving high education for these two health outcomes. This is in line with previous research showing an association between low education and an increased risk of multimorbidity (Pathirana & Jackson, 2018) and lower life expectancy (Mackenbach et al., 2019).

Where the two studies differ is in the role of sex. For longevity (Chapter 6), years of life lost due to low education were larger in men compared to women. For multimorbidity (Chapter 5), women experienced larger educational inequalities than men, though sensitivity analyses suggested that this could partially be due to differences in health-seeking behaviors. Nevertheless, it has consistently been observed that women generally live longer than men, but do so in poorer health – known as the gender paradox in health and mortality (Luy & Minagawa, 2014). Regarding the reasons underlying the differential effect of education on health between men and women, some evidence exists that low education may be more detrimental to women than to men. Ross and Mirowsky (2010) propose the theory of resource substitution that states that resources can substitute for each other, meaning the less there is of one resource, the more important other resources become for compensation. The authors suggest that women may have fewer socioeconomic resources than men, including power, authority, and high earnings, making a high education more important for them. It is possible that this is the reason for our observed sex inequalities in multimorbidity, but it does not explain why the opposite effect modification was observed for educational inequalities in longevity (YLL for Low-Low versus High-High were 4.0 years (2.6 to 4.6) in men and 2.0 years (1.3 to 2.7) in women). Ross et al. (2012) report similar patterns, with an effect of education that is larger in women for self-rated health and larger in men for mortality. A potential explanation can be found in the causes of death: sex differences in the effect of education were strongest for lung cancer, respiratory disease, stroke, homicide, suicide, and accidents. These causes of death are linked to behavioral risk factors like smoking, excessive alcohol consumption, and aggressive behaviors, which tend to be more socially patterned in men compared to women (Mackenbach et al., 1999). This might partially explain the contrasting sex differences found in Chapters 5 and 6 of this thesis.

Educational inequalities in longevity (Chapter 6) were not improved by higher social net expenditure of the country of residence since all trajectories benefitted equally. This mirrors the interpretation by Mackenbach et al. (2016), described in the Introduction, reporting that European improvements in absolute inequalities in longevity were not dependent on whether countries had employed national

strategies targeting health inequalities or not. This suggests that this progress could have been a side effect of population-wide behavioral changes and improvements in prevention and treatment, especially since the narrowing of absolute inequalities was most pronounced in mortality from ischemic heart disease, smoking-related causes, and causes amenable to medical intervention. What does this mean for public health? As suggested in Chapter 7, key for reducing the burden of many chronic diseases in the population is primordial prevention, i.e., the prevention of risk factors. By starting upstream, in early life, and targeting the entire population, more diseases can be prevented than by narrowing the focus on high-risk populations, as is done in many strategies targeting health inequalities (Rose, 1981).

Strengths and limitations

The work presented in this thesis has multiple limitations. For the original research studies presented in Chapters 5 and 6, methodological limitations exist. Our findings may be subject to misclassification bias, especially in the exposure since education is self-reported and recalled much later in life. To partially account for this, we have performed a sensitivity analysis in Chapter 6, classifying individual education into three instead of two levels, and have found no strong differences, indicating that the bias due to misclassification of education is likely to be small. There might also be a selection bias as our study population comprised individuals that survived until at least age 50. This limitation, however, is inherent to our research questions as we are interested in health in later life and thus are reliant on study participants surviving until that point. We are also aware that residual and unmeasured confounding might be present in both original research papers.

Another limitation is the measurement of multimorbidity in Chapters 4 and 5. As discussed in the Introduction, the definition of multimorbidity is not clear-cut and may differ from study to study. This was observed in the scoping review paper (Chapter 4), where multimorbidity was defined in almost all included studies as the co-occurrence of minimum two chronic conditions, but the number of conditions considered ranged from 5 to 46. Similarly, in the original research based on SHARE data (Chapter 5), 13 different conditions were considered for multimorbidity status, but some represented singular conditions (e.g., "high blood cholesterol"), while others combined multiple conditions (e.g., "other affective or emotional disorders, including anxiety, nervous or psychiatric problems"). This could lead to an underestimation of multimorbidity in the participants and thus a misclassification in the outcome.

One key strength of this work is the use of a large longitudinal data set that is population-based and offers multi-generational and multi-country data. Further, we are explicit in our causal aims, with transparent identifying assumptions to interpret inequalities as effects of education. We also report absolute measures of inequalities, which are more relevant in the evaluation of potential policy and public

health actions. Finally, with our scoping reviews (Chapters 4 and 7) we gave informative overviews over two broad yet important research questions ("What is the available evidence on the association between socioeconomic trajectories throughout the life course and multimorbidity in later life?" and "How can life course epidemiology inform public health preventive strategies?") which would not have been possible with systematic reviews.

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Chapter 9 | Conclusion

This thesis examined the interplay between socioeconomic trajectories and health in later life, ascertained through multimorbidity and mortality. Throughout this research, we have applied a life course framework to understand how health and health inequalities in later life are shaped throughout the life course, and even being influenced by the previous generation. Our findings only partially underscore the influence of early-life circumstances on health outcomes in later life. Educational inequalities were observed in both multimorbidity and mortality, but with individual education as the main driver. The influence of parental education was more indirect than direct, by making offspring more likely to obtain the same level of educational attainment, but not affecting multimorbidity or longevity directly. Thus, our work supports the importance of achieving a high education, and of interventions facilitating it.

Taken together, the findings of this thesis suggest that early life sets the foundations for life-long health trajectories, but that these trajectories can be changed with the right interventions. It is a reassuring finding that the longevity and multimorbidity risk of those with upward social mobility were indistinguishable from those with consistently high educational trajectories. It indicates that a detrimental start into life can be overcome if the right resources are invested at the right time, for example by supporting high educational attainments. It is also important to note that while increased social net expenditure of the country of residence did not reduce inequalities in longevity, it did improve life expectancy for everyone equally, thus overall improving the health of the population. Thus, continuous and supportive social policies are vital to improve population health in later life.

Future research in this field could aim to further specify the type and timing of interventions needed to reduce social inequalities in health. While there is some evidence in this thesis for the positive effects of wide-spread population-based interventions, like the above-mentioned effect of social net expenditure on longevity (Chapter 6) or of reduced salt intake on hypertension (Chapter 7), more targeted high-risk interventions might be needed to mitigate social inequalities and these need to be explored more across the life course. Further, since multimorbidity is likely to remain a major public health challenge, future research should address the key challenge of how best to define and measure it. As it stands, capturing the burden of multimorbidity is still challenging and without strong descriptive data effective interventions cannot be designed. Comparable and reproducible research findings are key to address this health issue and a consistent definition is the first step in the right direction.

Ultimately, this thesis underscores the importance of considering the entire life course when examining health outcomes in later life. In our research we could

observe an effect of education on multimorbidity and longevity decades after the highest educational attainment was reached. This effect unfortunately results in social inequalities in health and more research is needed to effectively address this persistent social issue. By adopting a comprehensive approach that considers the lifelong impact of socioeconomic trajectories, we can work towards a more equal and healthier future for all individuals, regardless of their socioeconomic background.

List of publications, presentations, and courses

Publications in peer-reviewed scientific journals

Wagner, C., Cullati, S., Sieber, S., Huijts, T., Chiolero, A., & Carmeli, C. (2023). Intergenerational educational trajectories and inequalities in longevity: A population-based study of adults born before 1965 in 14 European countries. *SSM-Population Health*, 101367.

Daniore, P., Moser, A., Höglinger, M., Probst Hensch, N., Imboden, M., ..., **Wagner, C.**, ... & von Wyl, V. (2023). Interplay of Digital Proximity App Use and SARS-CoV-2 Vaccine Uptake in Switzerland: Analysis of Two Population-Based Cohort Studies. *International journal of public health*, 68, 1605812.

Tancredi, S., Ulytė, A., **Wagner, C.**, Keidel, D., Witzig, M., Imboden, M., ... & Cullati, S. (2023). Changes in socioeconomic resources and mental health after the second COVID-19 wave (2020–2021): a longitudinal study in Switzerland. *International journal for equity in health*, *22*(1), 51.

Tancredi, S., Chiolero, A., **Wagner, C.**, Haller, M. L., Chocano-Bedoya, P., Ortega, N., ... & Cullati, S. (2023). Seroprevalence trends of anti-SARS-CoV-2 antibodies and associated risk factors: a population-based study. *Infection*, 1-13.

Wagner, C., Carmeli, C., Chiolero, A., & Cullati, S. (2022). Life course socioeconomic conditions and multimorbidity in old age–A scoping review. *Ageing research reviews*, 101630.

Publications in non-peer-reviewed journals and reports

El May E, Cullati S, Anker D, **Wagner C**, Epure A, Schmid A, Rodondi PY, Tancredi S, Chiolero A, au nom du groupe de recherche Corona Immunitas. Covid-19 : inquiétudes quant à sa santé et celle de ses proches. News n°3, Avril 2022. Laboratoire de santé des populations (#PopHealthLab), Université de Fribourg.

El May E, Cullati S, Anker D, **Wagner C**, Schmid A, Rodondi PY, Chiolero A, au nom du groupe de recherche Corona Immunitas. COVID-19 : le port du masque à Fribourg, News n°2, Juillet 2021. Laboratoire de santé des populations (#PopHealthLab), Université de Fribourg.

El May E, Anker D, Epure A, **Wagner C**, Magnin JL, Schmid A, Carmeli C, Rodondi PY, Chiolero A, Cullati S, au nom du groupe de recherche Corona Immunitas. Corona Immunitas Fribourg : Immunité de la population, épisode 3/2021, Laboratoire de santé des populations (#PopHealthLab), Université de Fribourg. doi : 10.5281/zenodo.5665477

List of presentations

Date	Event and Location	Format
October 2023	**SLLS Annual International Conference, Munich, Germany.** Wagner C, Jackisch J, Ortega N, Cullati S, Chiolero A, Carmeli C. *Intergenerational educational trajectories and inequalities in multimorbidity in older European adults.*	Oral
May 2023	**World Congress on Public Health, Rome, Italy.** Wagner C, Cullati S, Sieber S, Huijts T, Chiolero A, Carmeli C. *Educational trajectories and inequalities in longevity: a comparison across 14 European countries.*	Poster
March 2023	**Research Day in Medicine, Fribourg, Switzerland.** Wagner C, van der Linden B. *Sequence analysis in life course epidemiology: conceptualization and application.*	Oral, Poster
November 2022	**European Public Health Conference 2022, Berlin, Germany.** Wagner C, Carmeli C, Chiolero A, Cullati S. *How life course socioeconomic conditions shape multimorbidity in old age – a scoping review.* Part of workshop, "Health equity and Chronic diseases: Public health and Primary care roles".	Oral
October 2022	**SLLS Annual International Conference, Cleveland, USA.** Wagner C, Carmeli C, Chiolero A, Cullati S. *Life course socioeconomic conditions and multimorbidity in old age – a scoping review.*	Poster
August 2021	**Swiss Public Health Conference, Bern, Switzerland.** Wagner C, Carmeli C, Chiolero A, Cullati S. *Life course socioeconomic determinants of multimorbidity in old age – a mapping review.*	Poster

List of courses

Date	Name	Location	ECTS
February 2021	Winter School in Data Analytics and Machine Learning - Introduction to R	Online (Fribourg)	0.5 ECTS
May 2021	Big Data in Public Health	Online (Zurich)	2 ECTS
June 2021	Life Course Epidemiology and Public Health	Fribourg	1 ECTS
March - November 2021	Book Club Medical Statistics	Bern	3 ECTS
March - November 2021	Book Club Epidemiology	Bern	3 ECTS
September 2021	Writing a Journal Article … and Getting it Published	Bern	2 ECTS
November 2021	Fundamental Concepts in Epidemiology	Bern	2 ECTS
May – September 2021	ScienceFlashTalk Training	Online (Zurich)	1 ECTS
September 2022	Missing data in observational epidemiologic studies including non-detects	Basel	1 ECTS
September, October 2022	Foundations of Public Health Sciences	Lugano, Fribourg	2 ECTS
February 2023	Basics of scientific writing in English: A structured method for organizing and writing better, faster papers	Online (Bern)	2 ECTS
April 2023	Understanding social inequalities and social problems in health!	Basel	1 ECTS
Total ECTS			**20.5 ECTS**

Educational trajectories and inequalities in longevity: a comparison across 14 European countries

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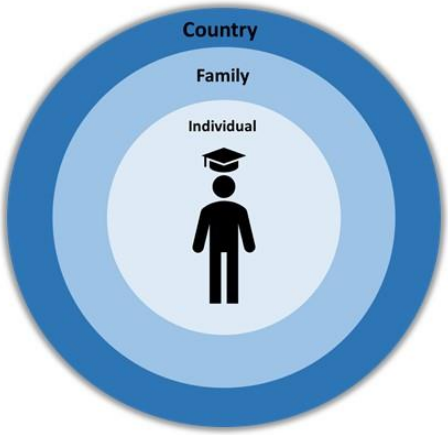


1 BACKGROUND

- Higher education is associated with longer **life expectancy**
- **Parental education**: strong predictor of offspring education, proxy for socioeconomic status, socialization into "typical" health behaviors
- **Country:** moderator of individual-level health determinants

2 OBJECTIVES

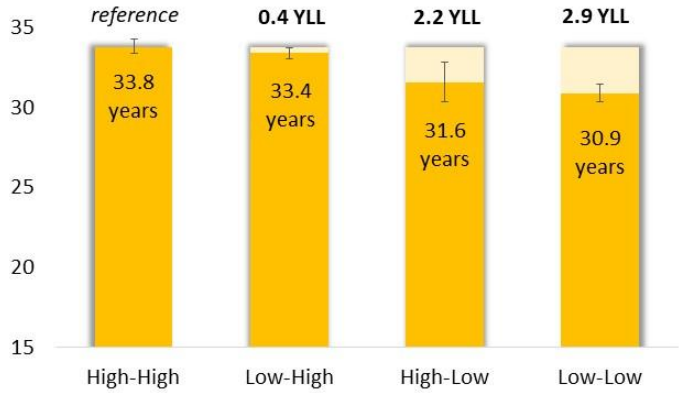
1. What is the role of **parental-individual educational trajectories** in shaping inequalities in longevity?
2. Can **country-level social net expenditure** mitigate these inequalities?

3 METHODS

- **SHARE cohort:** 52,271 adults (mean age 67.2 years), 14 European countries
- Outcome: **all-cause mortality** (2013-2020)
- Parental – Individual **educational trajectories**: High-High (reference), Low-High, High-Low, Low-Low
- **Years of life lost (YLL):** differences in the area under standardized survival curves, between ages 50 – 90 years
- **Meta-regression:** association between country-level social net expenditure and YLL

4 RESULTS

- **High-High life expectancy**: 33.8 years (i.e. **83.8 years of age**)
- **Low-High:** 0.4 YLL (95% CIs: – 0.2 to 0.9); **High-Low**: 2.2 YLL (1.0 to 3.5); **Low-Low**: 2.9 YLL (2.2 to 3.6)
- **Higher social net expenditure** was associated with a longer life expectancy but not smaller YLL (i.e. inequalities)
- **1% increase in social net expenditure:** 0.2 years for High-Low (0 to 0.5), and Low-Low (0 to 0.5) gained



5 KEY MESSAGE

Low individual education drives differences in life expectancies, regardless of parental education.
A **higher social net expenditure** of the country of residence is associated with a longer life expectancy for all educational trajectories – it therefore **does not reduce inequalities** in longevity.

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