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EARLY LIFE DETERMINANTS OF SOCIOECONOMIC AND HEALTH INEQUALITIES

LIFE COURSE STUDIES WITHIN AND ACROSS GENERATIONS

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Early Life Determinants of Socioeconomic and Health Inequalities: Life Course Studies Within and Across Generations

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my parents Samiza Khatun & Mohammad Giasuddin

To my wife Morsheda Sumi

“A person’s past social experiences become written into the physiology and pathology of their body.” – David Blane

POPULAR SCIENCE SUMMARY OF THE THESIS

A social gradient in health is known to exist in every society where people at the bottom of the social hierarchy show higher burden of diseases and deaths. The social inequalities in health are not necessarily smaller in Sweden which has one of the strongest egalitarian social structures in the world. People do not, however, randomly end up in lower social class and worse health. On the contrary, these may have their systematic origins in early life. Therefore, a better understanding of health inequalities requires investigations of the early life determinants of health.

In this PhD thesis, I looked at health inequalities through the lens of life course epidemiology, with a focus on how early life social and health disadvantages later impact on socioeconomic success and adult health. I used novel methodological approaches to overcome some of the major limitations that most previous studies commonly suffered from. Moreover, while past studies typically examined the early life origins of health or health inequalities within the immediate first generation, this thesis generated new knowledge by exploring whether the socioeconomic and health inequalities originating in early life pass on to future generations. The unique multigenerational linkage data available in Sweden made it possible.

The thesis illustrates an increased risk of adult cardiovascular mortality associated with lower social class at birth, which partially operated through adult socioeconomic and behavioral mechanisms. In a similar vein, upward social mobility was found to be protective of mortality from a range of causes. The lower social class at birth and reduced fetal growth were associated with lower social class and higher risk of ischemic heart disease in adulthood. The associations of lower social class at birth and reduced fetal growth with ischemic heart disease were similar in magnitude in both the parental generation and their offspring.

Further, linking grandparents' and parents' characteristics with the next generation's socioeconomic and health outcomes in adulthood, we found that grandparents' social class and fathers' premature birth negatively affected the socioeconomic achievement and ischemic heart disease of the grandchildren. Grandmothers with younger or older ages at the time of parents' birth were more likely to have grandchildren with elevated risk of ischemic heart disease compared to grandmothers aged 25-29 years at parental birth.

The findings of the thesis warrant increased attention of researchers and policy makers to some early life disadvantages which may have long-lasting effects not only within one's own lifetime but also across multiple generations. The effect of early life socioeconomic disadvantage on adult health and mortality can be compensated, at least partially, by attained socioeconomic conditions over a generation. However, to protect the health of both current and future generations, long-term investment is needed to improve parents' preconception health and well-being in a way that all children can have a healthy start of their lives and eventually optimize their capacities as adults to plan for and parent the future offspring.

ABSTRACT

The role of the early life social and maternal environments in the production of health inequalities was widely documented in the past few decades but the underlying mechanisms were often subject to suboptimal analytic practices. The developmental origins of health and disease (DOHaD) paradigm came with a promise to better document the early life programming of adult diseases, with an emphasis on the postnatal modifiers of prenatal influences. However, DOHaD as a transgenerational phenomenon (i.e., across more than 2 generations) is rarely acknowledged in human observational studies, despite growing evidence from animal experiments. Moreover, evidence is currently lacking as to whether health inequalities attributable to early life disadvantages have become narrower or wider over historical time in response to major shifts in social structures.

This PhD thesis builds on life course epidemiology to provide improved insights and generate new knowledge on the early life origins of health inequalities, their persistence over time, and transmissions across generations. To this end, the project focuses on a range of social and biological disadvantages as predictors of attained socioeconomic position (SEP) and adult health outcomes within the life course and across generations, using register-based and survey data from Sweden.

In Study I, I used the inverse odds weighted approach to causal mediation analysis and demonstrated that two adult socioeconomic indicators – education and occupation – jointly mediated about one third of the association between parental SEP and cardiovascular mortality in adulthood. The health behavioral risk factors – smoking, alcohol drinking, poor diet, physical inactivity – and body mass index additionally mediated around one tenth of the association.

In Study II, SEP was measured across four time points over the life course: at birth, around age 10, in mid adulthood, and late adulthood. The longitudinal trajectories of SEP were constructed using latent class analysis, with the aim to investigate the associations between the latent SEP trajectories and mortality. Compared to lifetime low SEP, upward mobility trajectories showed reduced hazard ratios of all-cause mortality and mortality from a variety of causes including cardiovascular diseases.

Study III aimed to investigate the early life determinants of adult SEP, assessed as an index of education and occupation combined, within and across generations. The association between parental SEP and participants' SEP became weaker in the offspring generation when compared to their parents, but the association between small-for-gestational age and adult SEP did not exhibit any significant change. Further, lower SEP of grandparents, unmarried status of grandmothers, and paternal preterm birth were associated with lower SEP attained by the offspring.

In Study IV, I mainly extended the analysis of Study III to the incidence of ischemic heart disease (IHD) and found that the associations of parental SEP and birthweight-for-gestational age with adult IHD did not change between generations. Additionally, low SEP of grandparents, younger and older childbearing ages of grandmothers, and paternal preterm birth increased the risks of IHD in the adult offspring.

To conclude, the thesis highlights the importance of some early life social and biological disadvantages in shaping future socioeconomic and health outcomes not only over the life course but also over historical time and across generations, whilst adding to the scant literature on transgenerational developmental programming of health in humans. Future life course research can benefit from shedding lights into the mechanisms through which health inequalities originating in early life persist over time and are transmitted across multiple generations.

Keywords: causal mediation; health inequality; fetal growth; social mobility; social change; transgenerational.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following four scientific articles, which are referred to in the text by Roman numerals I-IV:

I. **Hossin MZ**, Koupil I, Falkstedt D. Early life socioeconomic position and mortality from cardiovascular diseases: an application of causal mediation analysis in the Stockholm Public Health Cohort. BMJ Open. 2019; 9(6): 1–10.
II. **Hossin MZ**, Heshmati A, Koupil I, Goodman A, Mishra G. Latent class trajectories of socioeconomic position over four time points and mortality: The Uppsala Birth Cohort Study. Submitted.
III. **Hossin MZ**, Björk J, Koupil I. Early-life social and health determinants of adult socioeconomic position: associations and trends across generations. Journal of Epidemiology and Community Health. 2020; 74(5): 412-420.
IV. **Hossin MZ**, Falkstedt D, Allebeck P, Mishra G, Koupil I. Early life programming of adult ischemic heart disease within and across generations: the role of the socioeconomic context. Social Science & Medicine 2021; 275: 113811.

CONTENTS

LIST OF ABBREVIATIONS

ß	Beta Coefficient
CI	Confidence Interval
CVD	Cardiovascular Disease
DOHaD	Developmental Origins of Health and Disease
G	Generation
HR	Hazard Ratio
IHD	Ischemic Heart Disease
IOW	Inverse Odds Weighting
IRR	Incidence Rate Ratio
LCA	Latent Class Analysis
LGA	Large for Gestational Age
LISA	Longitudinal Integration Database for Health Insurance and Labor Market Studies
PH	Proportionality of Hazards
SEP	Socioeconomic Position
SGA	Small for Gestational Age
UBCoS Multigen	Uppsala Birth Cohort Multigenerational Study

1 INTRODUCTION

Every human being will eventually die. Death in this sense is a "great equalizer" since everyone is equal in the face of death. However, the length and quality of life that people live are not the same for all; it varies from one individual to another and from one social class to another both within and between countries in a single point in time, and from one historical time to the next. Thus, when we see that infants born in Central African Republic expect to live on average about 29 years shorter than their counterparts born in Sweden (54 vs 83 yrs) (1), it becomes extremely relevant to look at the uneven social structure within which individuals are born, grow, live, work, and age. While the traditional biomedical model underscores the role of pathogen in the process of diseases and deaths, it fails to explain why an infectious agent generates illness in one individual but not in another. Is it due to misfortune? The answer is 'no'; some groups of people are systematically more vulnerable to diseases and die earlier than others.

Despite remarkable advancements in medical care and improvements in population health in the past few decades, a persistent challenge in public health policy and research has been the socioeconomic disparities in health (2). In every society where data are available, health is socially patterned in a fashion that people at the lower end of the socioeconomic spectrum carry a greater burden of morbidity and live shorter than their counterparts at the upper spectrum (3). Known as the social gradient in health, this ubiquitous phenomenon persists over time and across societies for a broad spectrum of health conditions and across a number of socioeconomic position (SEP) measures – education, occupation and income. Paradoxically, the Nordic countries with their most generous welfare provisions and egalitarian social structures do not demonstrate smaller health inequalities compared to countries with less egalitarian and restricted welfare arrangements (4,5). This Nordic health paradox has sparked fresh scientific debates about the causal mechanisms through which social disadvantages are "biologically embedded" or "get under the skin" (4–8).

Throughout the twentieth century, the vast majority of the literature exploring the SEP-health association and the underlying mechanisms was dominated by a focus on the risk factors in adulthood (9). The adult etiological model of disease has its limitations from a prevention perspective since many diseases in adulthood, especially the metabolic and cardiovascular conditions, have their causal roots in the early life social and intrauterine environments (10–12). In parallel with the SEP-health gradient in adulthood, a socioeconomic gradient in child health and development has been observed in early life (8,13,14). This suggests that the socioeconomic origins of health inequalities cannot be adequately understood without reference to the early life social environment that may program the human biological system during critical periods of development and condition both socioeconomic trajectories and disease risks in later life (8,10).

Conventionally, the socioeconomic inequalities in health were explained by two competing theoretical paradigms: social causation and health selection (15). The fundamental difference lies in the directions of the association between SEP and health. From a social causation perspective, SEP precedes and influences health while the

selection perspective argues that health is the causal predecessor of SEP since people are selected into SEP either directly on the basis of their health or indirectly through the determinants of health (16). In recent times, scholars have suggested bridging the gap between social causation and health selection perspectives within the broader life course framework (9,17,18). Originated in social sciences (19), the life course approach to health is an increasingly popular and widely acknowledged perspective that views health as a developmental process and sheds light simultaneously on both social and biological risk processes to understand the origins of diseases and health inequalities (20).

2 BACKGROUND

2.1 Theoretical background

2.1.1 The concept of health inequalities

The concept of health inequalities has been given a variety of meanings. Hilary Graham (21) identified three distinct analytic approaches to defining health inequalities, i.e., health differences between i) individuals, ii) population groups, and iii) groups occupying unequal positions in society.

The first approach defines health inequalities as "uneven distribution of health across all units in a population, independent of population subgroup" (22). The explicit focus of this view is on the individual which provides a univariate picture of health with no reference to how health differences are produced. It, therefore, drew criticisms from various quarters for diverting the attention away from the unequal distribution of health and resources among different groups in the social hierarchy.

The second approach emphasizes the social patterning of health by focusing on the population subgroups based on, for examples, their age, gender, and income. While this perspective acknowledges the existence of health variations across different population segments, it does not explicitly recognize the connection between social inequalities and variations in people's health. The researchers and policy makers favoring this approach tend to refrain from openly talking about "health inequalities" and instead strategically choose the phrases "health disparities" and "health variations" (21).

The third and most common approach, which the current thesis draws on, sees health inequalities as social in origin and looks at the social processes that systematically work to produce differential health outcomes. For example, it tries to explain why a particular social group is at higher risk of morbidity or mortality than others and in doing so, links it to how the society is organized (21).

A distinction is often drawn between health inequalities and health inequities. The latter can be defined as the systematic, avoidable, and unjust differences in morbidity, mortality, and healthcare among different social groups in terms of their gender, ethnicity, class position, and similar other axes of social stratification. While any health differences between individuals and social groups, regardless of avoidable and unavoidable, may constitute the broad domain of health inequalities, health inequities refer to a specific type of health inequalities that are unfair and preventable. Thus, the term health inequality is descriptive and measurable whereas health inequity is a normative term that invokes a moral judgment and hence is not directly measurable (21,23).

There are two approaches to measuring health inequalities: i) absolute difference - the difference in the rates of the health outcome (e.g., mortality) between two groups; ii) relative difference - the ratio of the rates of health outcome between two groups. In the current thesis, health inequalities were mostly assessed on the relative scale.

2.1.2 The life course perspective to health inequalities

The life course perspective is considered fundamental to an understanding of the etiology of health inequalities (24). The adverse conditions in the early stages of life are of key focus in life course research as these are likely to interfere with the child's physical growth and brain development, leading to poorer educational, occupational and health outcomes in adult life. It has the potential to advance health inequality research by contributing toward an in-depth and realistic understanding of how social experiences are "biologically embedded" (8) to produce the patterns of health inequalities over the life course and across generations (9). In life course epidemiology, health outcomes at adult ages are linked to the physical and social exposures acting during preconception, gestation, infancy, childhood, adolescence, adult life, and across generations (20).

2.1.3 The theory of fetal/developmental origins of disease

While the life course perspective emerged in the social sciences in the 1960s (19), the interest in life course approach to health got impetus in the late 1980s (25) with the emergence of the fetal origins of adult disease hypothesis proposed by David Barker (26–28). The biological basis of Barker's fetal origins hypothesis lies in the concept of developmental plasticity. Similar to other animal organisms, the human fetus is plastic. Plasticity is defined as the ability of the genotype to adapt its phenotype in response to different environmental conditions (29,30). Through the placenta, the fetus gets a "weather forecast" of the external environment. If the environment is nutrition poor, the developing organism starts to match its phenotypic trajectory with the environment within which it is expected to grow up. For instance, in response to restricted placental supply of nutrients, the fetus may engage in trade-offs by protecting its most vital organs such as the brain and the heart at the expense of other organs (29,31). Drawing on the already existing "thrifty genotype" hypothesis (32), Hales and Barker (31) termed such adaptation as a thrifty strategy of coping with the nutrition-deficient environment. According to the thrifty phenotype hypothesis, an undernourished fetus may slow its growth rate by developing insulin resistance, which might be beneficial for immediate survival but detrimental in the long run if the postnatal environment is nutrition abundant.

Barker's fetal origins hypothesis builds on the theory of developmental plasticity (29,33) and posits that adaptation to undernutrition, especially during middle and late gestation, can cause permanent damage to the developing tissues and organs and negatively affect the body's morphology, physiology and metabolism, leading to the emergence of cardiac and metabolic disorders in adult life (11,34). The process is sometimes described as the "fetal programming" of adult disease (35). The central tenet of Barker's hypothesis was that the nutritional state in the mother's uterus determines the fetal growth and maturation which in turn determines chronic diseases

in later life. From this point of view, the associations found between low birthweight and adult chronic diseases (27,28) reflect maternal nutritional deficiencies during critical periods of intrauterine growth.

Later on, evidence from studies on the Dutch Hunger Winter of 1944-45 was emerging to suggest that undernutrition during early gestation can predispose the fetus to later disease risks without affecting birthweight or fetal growth, while exposure to undernutrition at different critical phases in the utero was associated with different adult diseases and disorders (36–38). Similarly, exposure to starvation at the onset of puberty, which is considered to be a critical or sensitive period during postnatal, was shown to be associated with increased susceptibility to later CVD risk (39). It also became evident that impaired growth in the utero, when accompanied with an accelerated or "compensatory" weight gain in early childhood, amplifies the disease risks in later life (40).

To recognize the importance of a wide spectrum of prenatal and postnatal influences on different long-term physiological and morphological consequences, the original fetal origins hypothesis was subsequently expanded into a broader paradigm known as the Developmental Origins of Health and Disease or DOHaD in brief (30,41,42). Although the metabolic and cardiovascular diseases were of primary interest in Barker's hypothesis, the DOHaD model of disease pathogenesis encompasses a variety of other disorders and emphasizes the role of environmental, genetic, and epigenetic processes in the susceptibility to later diseases (12,42).

2.1.4 Pathways linking early life disadvantages to adult health

From a life course perspective, there is usually a long stretch of time between the commencement of risk factors and the clinical presentation of the disease outcomes. Therefore, an important agenda of life course research is to identify relevant mechanisms and pathways, so that timely interventions can be undertaken to halt the progression of diseases (43). Early life social and biological disadvantages, e.g., poor socioeconomic conditions and slow fetal growth, can affect later life health either independently or in combination with later exposures operating at various stages across the life course. Moreover, early life biological disadvantages, such as preterm birth and low birthweight, can themselves act as mediating mechanisms in the pathway between parental social circumstances and the health status of children as adults (10).

At least four broad and overlapping pathways can be identified in the process, as simplified in **Figure 1**. Path A represents a "social pathway" whereby the social environment at birth, parental social class for example, may affect adult health by influencing health behaviors (e.g., smoking, drinking, diet) during adolescence and adulthood and/or by acting through socioeconomic trajectories e.g., education and employment. Path B represents a "socio-biological pathway" whereby early life circumstances may affect fetal or childhood health related to growth and development

i.e., the physical, cognitive, and emotional well-being which in turn impact upon adult health (10). Path C involves a "biosocial pathway" whereby health in early life operates through later socioeconomic circumstances and behavioral factors to affect health in adulthood. Path D represents a predominantly "biological pathway" whereby childhood health can have a direct effect on adult health without mediating through adulthood circumstances, for instance, suboptimal lung function in infancy may lead to respiratory illnesses in adulthood (9,10).

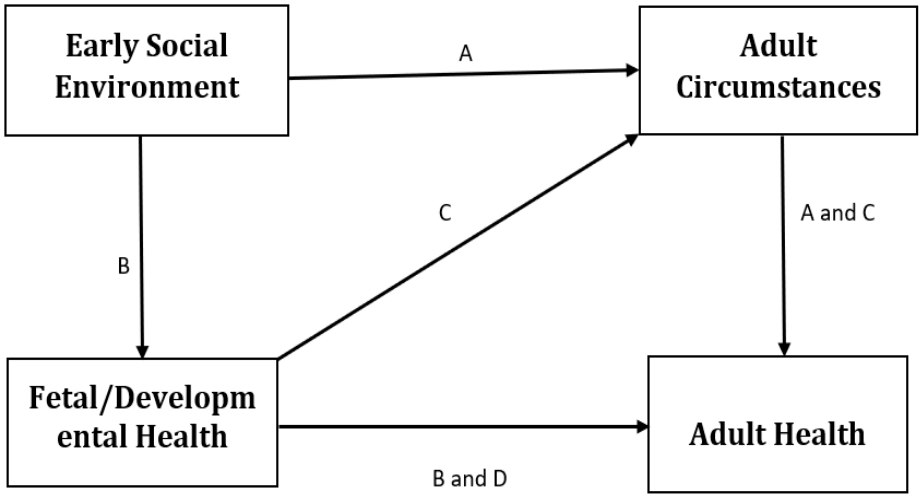


Figure 1. A simplified framework illustrating causal pathways through which early life circumstances affect adult health, adapted from Graham and Power 2004 (10)

The different pathways linking early life disadvantages to adult health are not mutually exclusive; they can often occur simultaneously and combine in real life and may also extend across generations through social, epigenetic, and genetic mechanisms. **Figure 1,** however, is intended to be a crude illustration and does not specifically delineate the multigenerational pathways for which more comprehensive models have been suggested elsewhere (25,44). It has been suggested, for instance, that exposure to suboptimal intrauterine environment increases the chance of diseases in later life by altering the soma and the germline of the fetus, with the possibility of passing such programming effects to future generations along the paternal or maternal line or both (44,45). There is currently a lack of universal consensus about the mechanisms underlying the transmission of developmental programming of diseases across multiple generations, but there is no disagreement that the mechanisms are likely to differ by paternal and maternal lineages. The paternal line transmission is commonly explained by the epigenetic alteration of the germline while the maternal line transmission can involve multiple complex routes including germline modification, somatic epigenetic reprogramming, modulation of the reproductive tract, and the mitochondria (44).

2.1.5 Conceptual models in life course epidemiology

The life course perspective offers a temporal frame to identify the key stages of life when exposures to health-damaging agents are particularly detrimental, thereby suggesting timing for appropriate interventions. Several theoretical models have been proposed to conceptualize and test the timing and ordering of exposure variables with regard to the health outcomes: critical/sensitive period model, accumulation model, and chain of risks model (46).

The **critical period** refers to a particular point in time during which an exposure to a risk factor can have an exclusive effect on the subsequent health outcome. Under the hypothesis of critical period, the timing of exposure is crucial to develop a disease and hence there is no excess risk associated with the similar exposure at some other time-point across the life-course. The critical period model forms the basis of Barker's fetal origins of adult disease hypothesis (11). Contrary to the critical period model, the **sensitive period** model assumes that the effect of an exposure on a disease risk is greater or lesser in one time point than another. For example, childhood SEP, middle-age SEP, and late adult SEP are all individually linked to deaths from cardiovascular diseases (CVD), but the late adult SEP was found to be the strongest predictor (47).

The **accumulation** model postulates that multiple exposures to risk factors (e.g., social, behavioral, or biological) cumulatively increase the risk of diseases in later adulthood irrespective of the time-point at which the subject is exposed. The exposures may affect the health outcome independently or in a dose-response fashion, i.e., the greater the number, duration, or severity of the exposure, the higher the disease risk. Different risk factors may also form a cluster to affect the outcome. For instance, the health-risk behaviors, e.g., smoking and drinking, are likely to be more prevalent in people from low family SEP compared to those with a high family SEP (48,49).

The **chain of risks** model, also known as pathway model, depicts a scenario of a sequence of multiple linked exposures, with one exposure leading to the next exposure/s until the outcome occurs. In this model, the final exposure in the causal chain is said to have a 'trigger effect' on the outcome since the preceding exposures are not allowed to affect the outcome except through the final link. Thus, the exposure-outcome association disappears when the final link between the outcome and the exposure nearest to the outcome is deactivated. The real world, however, is more complex, and the exposures might operate through direct and indirect pathways. This latter scenario can be thought of as a hybrid model combining both the accumulation and pathway models (46).

Each of the life-course models carries substantial importance from a population health standpoint since they have distinct implications for the choice of when and how to intervene to prevent diseases and reduce health inequalities. The different life course

models, however, are not mutually exclusive, and it has been a big challenge to empirically tease them out from each other (50–52). More recently, methodological strategies to simultaneously test different life course models have been developed (53) and their application to life course data has also been demonstrated (47,54).

2.2 Literature review

2.2.1 The early life social environment and adult health

The influence of the childhood social environment on future mortality was first suggested by Kermack and colleagues in a study conducted in Great Britain and Sweden as early as in the 1930s (55). However, it was only in 1970s that the childhood conditions as developmental precursors of adult diseases (e.g., obesity, arteriosclerosis, and diabetes) and mortality gained impetus through a series of pioneering epidemiological investigations led by Anders Forsdahl in Norway (56) and the endocrinologist Gunter Dörner in East Germany, as reviewed in Gluckman et al (41). Today, there is a large body of epidemiological studies linking social disadvantages at birth to a broad range of diseases and mortality later in life (52,57–59).

A systematic review conducted by Galobardes et al. (57) reveals that 18 out of 22 studies found associations between childhood socioeconomic circumstances and overall mortality. Further, associations were found with overall CVD mortality as well as mortality from ischemic heart disease (IHD) and stroke. Although childhood social circumstances were not generally found to be associated with overall cancer mortality, strong associations were found with mortality from lung cancer and stomach cancer (60). Updating these findings four years later, Galobardes et al. (58) confirmed in another systematic review that the observed associations generally hold true for both men and women and across older and younger generations. Parental occupation has been more frequently used in the literature than parental education or home ownership as a proxy measure for childhood SEP (57,59). Among the other indicators of social disadvantages in childhood, number of siblings (61) and mother's marital status (62) were shown to have increased risks of mortality.

Existing studies exploring the causal mechanisms of the associations between childhood socioeconomic conditions and adult health have yielded mixed evidence. A large number of studies find both direct and indirect effects of childhood SEP on mortality whereas some studies report only an indirect effect (58,59). An indirect effect indicates that childhood SEP affects mortality only through its association with adult circumstances while a direct effect indicates an effect that persists regardless of the conditions in adult life. However, the magnitude of associations and the pathways involved may differ across diseases, with each specific disease likely having its own unique etiology (52,60).

The majority of studies reported that the associations of childhood social conditions with adult health are unexplained by adult socioeconomic circumstances and/or adult risk factors, lending support to the critical period hypothesis (52,57,63–66). A large Swedish cohort comprising over 1.8 million individuals showed that those from manual social class background compared with non-manual social class were at greater risk of mortality from a range of diseases including IHD, stroke, and diabetes after own education and adult social class were adjusted for (66). The support for critical period effect is particularly evident for stomach cancer and hemorrhagic stroke (60,61,67). As found in the Collaborative study in Scotland (60,61), men with manual social class background and greater number of siblings had higher risks of adult mortality from various causes. The control for adult social and health risk factors diminished the risks of mortality from coronary heart disease and respiratory diseases while the risks of mortality from stroke and stomach cancer remained unaltered. A similar pattern of the influence of childhood socioeconomic conditions on deaths from stomach cancer was reported in women (67) .

A series of studies are in agreement with the accumulation hypothesis, with childhood SEP affecting adult health indirectly through its association with adult circumstances (47,59,68–71). For instance, the GLOBE study in the Netherlands investigated the contributions of the childhood socioeconomic circumstances and risk factors in adulthood with respect to CVD mortality. The authors concluded that the association between childhood SEP and CVD mortality was largely explained by adulthood material, behavioral and psychosocial risk factors mainly due to the association of childhood SEP with adult SEP and CVD risk factors (70,71).

Furthermore, studies measuring SEP at two or more time points indicate that SEP at different stages of the life course may have differential effects on health in adult life (47,51,54,59,72–77). Those with disadvantaged SEP across the life course or who have been downwardly mobile are at particularly elevated risks of diseases and mortality (51,59,72–79). The evidence regarding the effect of being upwardly mobile on later life health is mixed, with both protective and detrimental health effects reported in previous studies (51,79–82). Part of the debate surrounding the increased or decreased risks associated with upward mobility stems from which reference group the results were compared with. For instance, a study conducted among 1.9 million Swedish adults demonstrated that upwardly mobile individuals had a decreased risk of premature CVD mortality compared to those who did not experience any occupational class mobility. However, when the results were compared with the stable high nonmanual class, the risk was slightly raised in those moving from low manual to high nonmanual (81).

2.2.2 Early life health and later socioeconomic outcomes

There has been a plethora of research on the influence of health disadvantages at birth on the future socioeconomic trajectories such as educational attainment, occupation, and income in adult life. Education is thought to be one of the important routes linking childhood health to the adult socioeconomic environment (10). Birthweight has been the most widely used indicator of health status in early life (83). A Swedish cohort study comprising over 2 million children born during 1973-94 demonstrates that being born small for gestational age (SGA) was later associated with poorer educational performance in schools. The association persisted even when the possible residual confounding due to unobserved family factors was accounted for among the matched siblings (84). The twin studies exploring the implications of birthweight are also suggestive of strong causal effects on educational outcomes (85).

Preterm birth, defined as birth occurring before 37 weeks of completed gestation (86,87), is another commonly studied in-utero exposure that has been shown to compromise educational outcomes and other measures of human capital accumulation. A meta-analysis and systematic review including 74 studies concluded that compared to their term-born peers, the children born prematurely had worse neurodevelopmental outcomes such as lower cognitive scores and poorer motor skills and worse academic performance in both primary and secondary schools (88).

Using data from the 1958 British Birth Cohort, Case et al. (89) demonstrated that adverse fetal conditions and poorer childhood medical conditions lead to lower educational attainment and lower chance of employment in adulthood regardless of parental income, education, and occupational class. Similar findings were reported in an American study using 35000 children with sibling clusters (90). A child's general health status appeared to have strong effects on several key measures of adult SEP including income. Moreover, early life health disadvantages may affect the socioeconomic achievements of future generations, although the empirical evidence is limited. Goodman and colleagues (91), for instance, found that grandparent's low birthweight is associated with grandchildren's educational attainment.

2.2.3 Size at birth and the fetal origins of disease

Barker's fetal origins hypothesis drew stimulus from the landmark epidemiological observations on the geographic distributions of mortality rates illustrated by Forsdahl in Norway (56) and by Barker and Osmond in England and Wales (26). These studies revealed that the geographic differences in mortality rates from adult IHD were correlated with the geographic differences in infant mortality rates in the past. Such ecological correlations led Barker to hypothesize that the variations of nutritional deprivation during fetal development might be driving the variations in both past infant mortality and current heart disease mortality across different geographic locations. Low birthweight as a proxy of fetal undernutrition was suspected to be a responsible factor

because of its known association with infant mortality. Using available individual level data on the English cohorts, Barker and colleagues later demonstrated that small body size at birth or during infancy was associated with elevated risks of type 2 diabetes and CVDs including IHD in adulthood (27,28)

Several biomarkers of CVDs such as blood pressure (92) and plasma concentrations of glucose (93), insulin (93), and fibrinogen (94) were reported to be associated with birthweight. Barker's original findings were replicated and confirmed in numerous epidemiological studies conducted in different populations in Europe and elsewhere (95–98). For instance, a meta-analysis on 40 000 deaths in 0.4 million adults reveals an inverse association between low birth weight and mortality in both men and women, with per one kg higher birth weight associated with 12% and 6% lower rates of mortality from CVDs and all causes, respectively (98).

Low birthweight can be a direct consequence of shorter gestation or retarded intrauterine growth which can be regulated by socioeconomic and genetic factors (99). However, the reported associations between birthweight and adult health are explained neither by duration of gestation (100,101) nor by socioeconomic factors (97), and are not mediated by adult lifestyle risk factors which tend to have additive effects (28). According to the fetal programming hypothesis, the increased health risks found in low birthweight babies can be attributed to the slow rate of growth resulting from the restricted supply of nutrients and oxygen in the intrauterine environment (28).

2.2.4 Preterm birth and adult health

Although most preterm births are low birthweights, not all low birthweights are preterm births (99). In addition to smaller birthweight, preterm birth has been demonstrated to be associated with hypertension (102) diabetes (103), stroke (104,105), heart failure (106), and mortality from CVDs (107). The long-term impact of preterm birth on adult chronic diseases is plausible given the link of preterm birth with abnormal organogenesis of vital organs including the kidney, pancreas, lung, and the vascular tree (108).

Existing literature shows that the children born preterm have elevated risk of insulin resistance (109) as well as developing high blood pressure throughout the life course, e.g., in early childhood (110), young adulthood (102,111) and later in life (87,112). The increased risk of insulin resistance and high blood pressure may condition the later development of chronic diseases among the individuals born preterm. The observed risks were found to be independent of birthweight for gestational age (102,109,112), suggesting that preterm birth is a key role player in the developmental programming of diseases (108), although it was not addressed adequately in Barker's early studies.

Compared to low birthweight, however, preterm birth as a risk factor for IHD is less evident. While the majority of studies found no association between preterm birth and

IHD (104,105,113,114), a recent Swedish study reported an increased risk of developing IHD in both preterm and early term (gestational age 37-38 weeks) children, with the shared genetic or family environmental factors only partly explaining the association (115).

2.2.5 Epigenetic inheritance of health across generations

Epigenetics is a burgeoning area of interest in the DOHaD field where the role of epigenetics in understanding the molecular basis of the developmental programming of chronic diseases is increasingly being recognized (116,117). Although there is no consensus on the definition of epigenetics, it usually refers to the heritable changes in gene expression without changes in the DNA sequence. While the epigenetic regulation of gene expression is a normal biological event in the process of conception, growth, and aging, exposures to environmental shocks such as stress, nutrition, and toxicants during crucial times of development may permanently alter the epigenome and enhance disease susceptibility at a later stage (116,118).

Further, experiments in mammals suggest that the epigenetic marks can be carried over to the next generations, especially when the environmental factors induce permanent epigenetic alterations in the germline (119–121). The transfer of epigenetic characteristics across multiple generations is described as "transgenerational epigenetic inheritance" defined as the transmission of environmentally determined epigenetic information from one generation to the next, without direct exposure of the progeny to the environmental (i.e., nongenetic) risk factor (122).

Our knowledge on the transgenerational inheritance of environmentally triggered epigenetic changes mostly comes from animal experiments (121,123,124). In human populations, the transgenerational effects of developmental programming on adult diseases have been rarely investigated since reliable data over three or four generations usually needed for transgenerational investigations are difficult to obtain. The exceptions are a series of studies based on three small generations born in the remote Överkalix town in the north of Sweden (125–128).

The Överkalix studies showed that the ancestral food supply during the slow growth period in mid-childhood, defined as age 9-12 years for boys and age 8-10 years for girls, triggered a transgenerational response in their adult grandchildren in a sex-specific manner. For instance, paternal grandfathers' plentiful supply of food during their slow growth period was associated with higher risk of adult mortality in grandsons, whereas the paternal grandmothers' plentiful food supply was associated with higher risk of adult mortality in granddaughters (127). Besides, a sharp change in food supply from good to poor between age 0 and 13 years of paternal grandmothers was associated with a high risk of CVD mortality among their adult granddaughters (128). The authors summarized the findings of the historical Överkalix studies in a review and concluded

that the transgenerational response to grandparental food surfeit during the sensitive pre-puberty period is not likely to be due to cultural or genetic inheritance but the germ-line mediated epigenetic inheritance is a candidate pathway (45).

Although the Överkalix studies received a lot of attention worldwide, the credibility of the findings has been questioned due to inadequate statistical power as well as failure to account for multiple testing and correlations between siblings or first cousins with common grandparents (129). However, the findings were later strengthened by evidence derived from the Dutch famine cohort of 1944-45 (130,131) and the German famine cohort of 1916-18 (132). More recently, a replication study conducted by another group of Swedish researchers on a larger multigenerational cohort in northern Sweden partially confirmed the findings of the original Överkalix studies (133).

2.3 Knowledge gaps

Although the early life social and biological conditions, e.g., parental SEP, birthweight, and preterm birth, have been well-established in the epidemiologic literature as predictors of adult disease and mortality, the causal mechanisms that underlie the associations have often been poorly assessed. Many studies aiming to examine the mediating mechanisms relied on conventional regression models that often violate the fundamental assumptions of causal mediation and tend to produce invalid estimates in the presence of exposure-mediator interactions (134,135).

Neither the burdens of low birthweight and preterm birth nor the social circumstances affecting them are static but are contingent on historical contexts. In many high income countries, for example, there has been a shift in the distribution of birthweight over the past decades, with a secular increase in mean birthweights (136,137). The rising trend of heavy birthweights might be driven by an elevation of the standard of living, increased prevalence of maternal obesity as well as a reduction in maternal smoking (137) which is the single most powerful determinant of birthweight with different prevalence in different historical periods. Furthermore, thanks to the advances in obstetric and neonatal care, the chances of survival till adulthood have increased over time among the preterm and low birthweight neonates, with implications for their long term health (111).

In Sweden, the gradual establishment of the social welfare regime after the World War II is an important point of departure and a major milestone on the road to social justice and health equity. Thus, the generations who were born before and after the development of the social welfare system were different with respect to the intra-uterine nutritional environment they experienced before birth and the extra-uterine social environment within which they grew up. Consequently, it is not only the time within the individual's life course but also the historical time that is of importance to ascertain the impact of early life environment on adult health in a changing societal

context. However, the empirical evidence on the cross-cohort changes in the established associations is very limited.

One potential mechanism through which the effects of early life disadvantages on adult health may persist across generations is transgenerational epigenetic inheritance (120). While animal experiments have generated compelling evidence that environmental stressors during critical periods of growth and development may negatively affect health across multiple generations (44), the corresponding evidence in humans is scarce and demands increased research attention.

3 AIM AND RESEARCH QUESTIONS

Building on life course epidemiology, the current doctoral thesis has the ambition to contribute, with novel methodological strategies and high-quality data, to the expansion of our understanding of the developmental origins of health inequalities. The overarching aim is to provide improved insights and generate new knowledge on health inequalities originating in early life, by investigating the associations of a range of early life social and biological disadvantages with later socioeconomic achievement and health over the life course and across generations. Specifically, the thesis aimed to answer the following research questions through four individual studies, as outlined in **Figure 2**:

	Focus Area	Research Question	Data Source	Study
From early life SEP to adult SEP and health: 2-generation approach	Mediated effect of early-life SEP	To what extent is the association between early life SEP and CVD mortality mediated by adult SEP and health behaviors?	Stockholm Public Health Cohort (n=19 720)	I
	Life course SEP & mortality	-How are the latent class trajectories of SEP associated with late life mortality? -Is upward mobility protective of mortality?	Uppsala Birth Cohort (G1, n= 11 336)	II
	Selection into adult SEP	-Have the associations of early life social and health disadvantages with adult SEP changed across generations? -Are parents' early life social and health dis-advantages associated offspring's adult SEP?	Uppsala Birth Cohorts (G1, n=10 233; G2, n=6055)	III
From early life conditions to adult SEP and health: 3-generation approach	Early-life programming of IHD	-Have the associations of early life social and health disadvantages with adult IHD changed across generations? -Are parents' early life social and health disadvantages associated with adult offspring's IHD?	Uppsala Birth Cohorts (G1, n=10 538; G2, n=6546)	IV

SEP, Socio-economic Position; G, Generation; CVD, Cardiovascular Disease; IHD, Ischemic Heart Disease

Figure 2. A conceptual framework outlining the four studies.

4 DATA AND METHODS

4.1 Study design and data sources

The cohort study design was used in all studies to address the research questions. A cohort study design is of advantage when estimating causal effects, due to a temporal sequence between the exposure and the outcome (138). For Study I, data were mainly drawn from the Stockholm Public Health Cohort survey (139), while the Studies II-IV were a part of the Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen) (140). These cohorts were linked with different population and health registers available in Sweden. The linkages between different databases were done on the individual level through the Swedish personal identity numbers (141). An overview of the study populations, data, and methods used in this thesis is shown in **Table 1**.

4.1.1 Stockholm Public Health Cohort survey

The Stockholm Public Health Cohort survey was designed by the Region Stockholm (former Stockholm County Council) and the data collection was performed by Statistics Sweden. The survey serves as a hallmark for documenting, monitoring, and improving the general health status of the overall population living in Stockholm. In 2002, a postal questionnaire containing items on social circumstances, health conditions, and health risk factors was sent to 50 067 randomly selected adults living in the Stockholm County, aged 18-84 years (139). The response rate was 62% (n=31 182). Subsequently, the participants were followed up in repeated surveys carried out every fourth year and in routine registers. The survey data were linked to the National Population and Housing Censuses in Sweden during 1960-1990 and to the register-based information from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA by Swedish acronym) of 1990-2008 (142). Follow-up with regard to health conditions was done through existing linkages with the Swedish inpatient register (143) and the cause of death register (144), both held by the National Board of Health and Welfare.

4.1.2 Uppsala Birth Cohort Multigenerational Study

The UBCoS Multigen started with a historical cohort of 14 192 men and women who were born in the Uppsala University Hospital from 1915 to 1929 (140). The obstetric, sociodemographic, and health-related data of this cohort were derived from a variety of sources: church and parish records, school archives, obstetric records, Census 1930, and the routine registers. In Sweden, most of the administrative registers became available in the 1960s and therefore the data prior to this period had to be manually collected mostly from archives. At the time of birth, information on the socioeconomic profile of the parents was also collected. Given that greater than 97% of the original cohort members were successfully traced through archive and/or register data, the potential selection bias

Table 1. An overview of the study populations, data, and methods used in the PhD studies

	Study I	Study II	Study III	Study IV
Study Title	Early life socioeconomic position and mortality from cardiovascular diseases: an application of causal mediation analysis in the Stockholm Public Health Cohort	Latent class trajectories of socioeconomic position over four time points and mortality: the Uppsala Birth Cohort Study	Early-life social and health determinants of adult socioeconomic position: associations and trends across generations	Early life programming of adult ischemic heart disease within and across generations: the role of the socioeconomic context
Main data source	Stockholm Public Health Cohort survey	UBCoS Multigen (G1)	UBCoS Multigen (G1, G2)	UBCoS Multigen (G1, G2)
Study population	Adult citizens, aged 40-84 years, living in Stockholm County in 2002 (n=19 720)	Children born in the Uppsala university hospital in 1915-1929, alive and living in Sweden in 1980 (n=11 336)	Children born in the Uppsala university hospital in 1915-1929 and their offspring born in the Uppsala region in 1932-1960, alive and living in Sweden at age 30 or above in 1960/1980/1990 (G1, n=10 233; G2, n=6055)	Singletons born in the Uppsala university hospital in 1915-1929 and their offspring born in the Uppsala region in 1932-1972, alive and living in Sweden at age 32 or above any time during 1964-2008 (G1, n=10 538; G2, n=6546)
Outcome	-CVD mortality -Non-CVD mortality	-All-cause mortality -Cause-specific mortality	Adult SEP (education+ occupation combined)	Incident IHD
Exposure	Parental SEP	SEP trajectories (SEP assessed at 4 life stages)	-Parental SEP -Standardized birthweight -Gestational age -Multiplicity of birth -Mother's marital status -Mother's parity	-Parental SEP -Standardized birthweight -Ponderal index -Gestational age -Mother's marital status -Mother's parity
Mediator	Education, occupation, smoking, risky alcohol drinking, diet, physical activity, and BMI		Parents' education, occupation, and income	Education and income
Statistical analysis	-Poisson regression -IOW method of mediation	-Latent class analysis -Cox regression	Linear regression	-Cox regression -IOW method of mediation

UBCoS Multigen, Uppsala Birth Cohort Multigenerational Study; G, Generation; SEP, Socio-economic Position; CVD, Cardiovascular disease; IHD, Ischemic Heart Disease; BMI, Body mass index; IOW, Inverse Odds Weighting

in the sample was low. Moreover, the cohort appeared to be representative of the general Swedish population in terms of the infant mortality and fertility rates which were consistent with the national level data during that period (145).

In 2004, the cohort could be linked to all descendants born up to 2009, through the Swedish Multigenerational register (146). The resulting multigenerational study consists of more than 150 000 individuals, including cohort members, parents, descendants, and partners (147). In 2007-2012, the period of follow-up in routine registers was extended till end of 2009 and additional data was collected from the archives. The UBCoS Multigen allows one to follow the first generation from before birth until age 81-95 years and to study health and social mobility across 5 generations. However, the research in this thesis focused on the first generation (G1) and their adult offspring (G2) as well as their predecessors (G0). As the thesis has an explicit focus on adult socioeconomic and health outcomes, the younger generations were not eligible for inclusion.

4.1.3 Linkage with population and health registers

In this thesis, data from the UBCoS Multigen and Stockholm Public Health Cohort survey were linked to the following registers, depending on the research question of interest: the cause of death register (144) for data on CVD mortality and other cause-specific mortality outcomes; the inpatient register(143) for data on hospitalizations due to IHD; the population and housing censuses and LISA (142) for data on education, occupation and income; the total population register (148) for data on dates of deaths and emigration; and the multigenerational register (146) for linking data across generations.

4.2 Study populations

A summary of different study populations used in the thesis is provided in **Table 1.** The study population in Study I were the individuals who responded to the Stockholm Public Health Cohort survey and were at least 40 years old at baseline. Since CVD mortality before age 40 was uncommon in this cohort, the younger adults were excluded (n= 11 308). Thus, a total of 19 720 men and women, aged 40-84 years and born during 1918-1962, were included in the analytical sample and were followed up for CVD mortality during 2002-2011.

In Study II, the study population was the G1 members of the UBCoS Multigen, who were born in 1915-1929 but were alive in Sweden until the start of follow-up on September 15, 1980, with available SEP data in at least one timepoint from birth until the start of follow-up (n=11 336).

The study population in Studies III and IV included both G1 and G2 members of the UBCoS Multigen. The G2 individuals are the biological children of G1 and were born from the year 1932 onwards (n=20 727). However, the G2 study population was mostly restricted to those whose parents were resident in the Uppsala region and for whom obstetric data

could be obtained (n=9248). Since adult SEP was used as an outcome in Study III, the samples for this study were further restricted to those who were born until 1960 and alive in Sweden in 1960, so that the study subjects attain at least 30 years of age during the population and housing censuses conducted in the period 1960-1990 (**Figure 3**). In Study IV where the study subjects were followed up for incident cases of IHD, both G1 and G2 samples were restricted to those members who were alive and living in Sweden on January 1, 1964 (**Figure 4**) when the first hospital discharge registry became available in Sweden (143).

To study the associations between parental/grandparental characteristics and offspring SEP or IHD in adulthood, the transgenerational analyses in Studies III and IV were carried out on two subsamples created from the original analytic sample of G2 members, who could be linked to their grandparents either via the paternal or the maternal lineage (**Figure 3** and **Figure 4**).

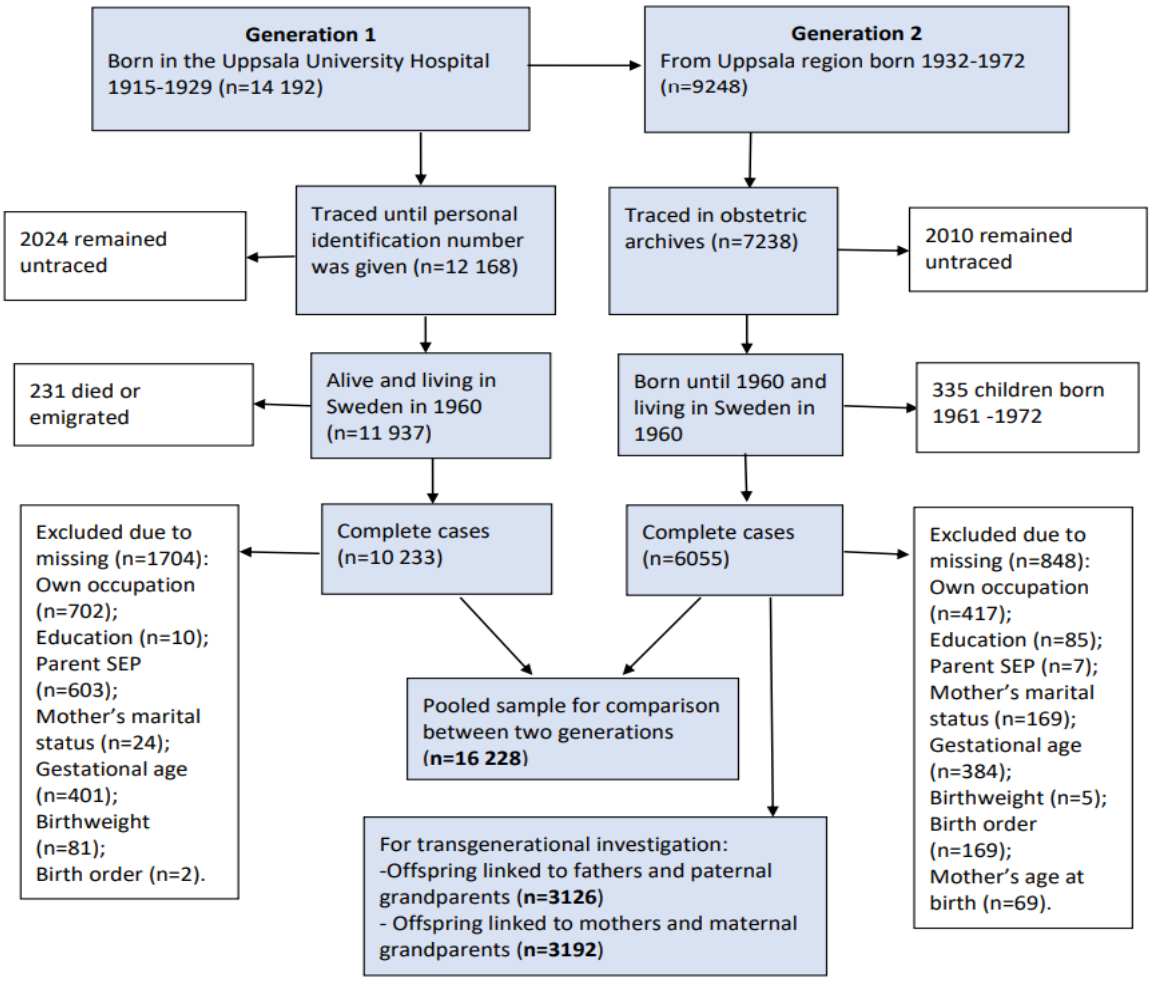


Figure 3. Flow diagram of sample selection in Study III.

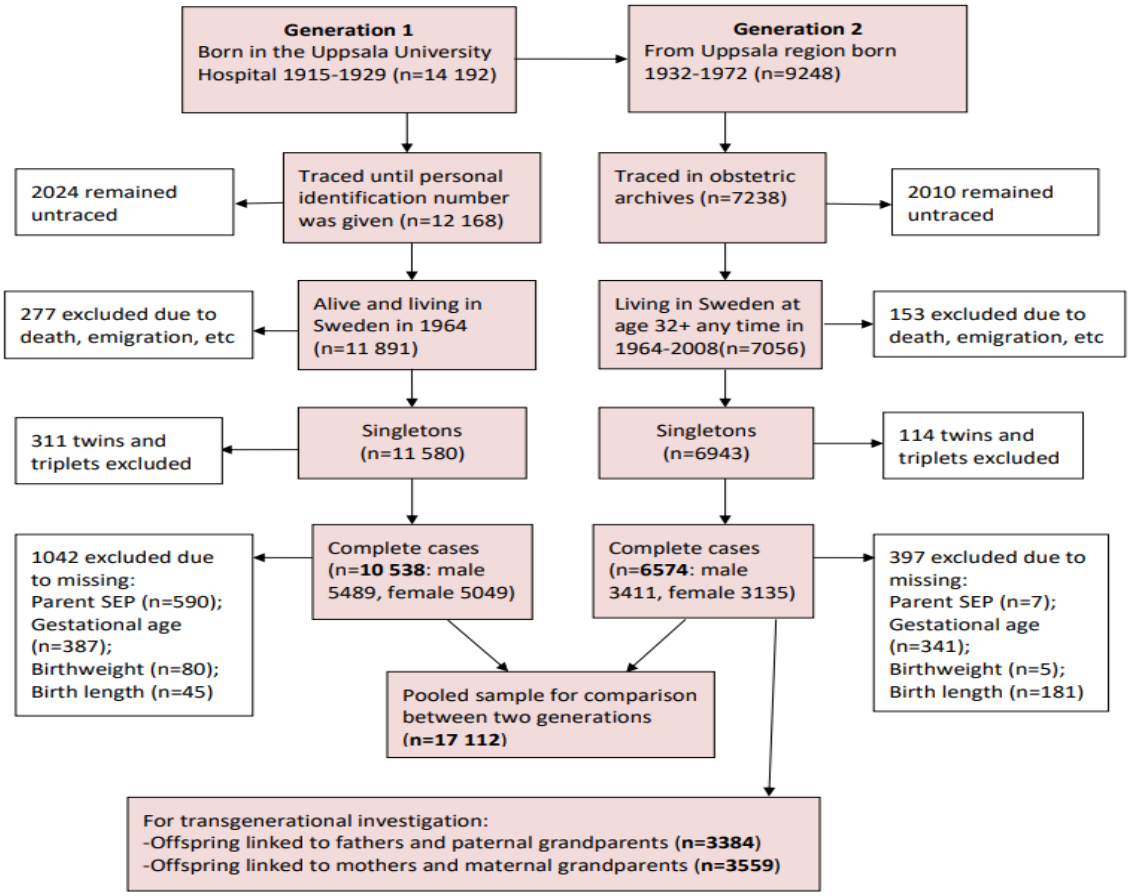


Figure 4. Flow diagram of sample selection in Study IV (Reproduced from Figure 2 of Study IV).

4.3 Main measures

4.3.1 Exposures

Parental SEP (Studies I, III, IV)

In Study I, parental SEP was based on father's occupation and was reported by the index individual interviewed through the baseline Stockholm Public Health Cohort survey in 2002. In line with the Swedish socioeconomic classification (149), the occupational data were classified into the following groups: i) unskilled workers, ii) skilled workers, iii) lower non-manuals, iv) mid-level non-manuals, v) upper non-manuals, vi) self-employed professionals, vii) farmers, and viii) unclassifiable. For the convenience of the causal mediation analysis, I dichotomized these socioeconomic groups as manual SEP (unskilled and skilled workers) and non-manual SEP (self-employed professionals; lower, middle, and upper non-manuals; and farmers). The unclassified individuals were treated as missing observations.

In Studies III-IV, parental occupational information of G1 was derived from obstetric records, school archives, and Census 1930 (150). Parental SEP in G1 was primarily based

on father's occupation but was, if unavailable, replaced by mother's occupation. In G2, the Census 1960 provided data on parents' occupation, and the occupation of the household head was used to define parental SEP. Parental SEP was classified as follows: high (upper and middle non-manuals; self-employed professionals), medium (lower non-manuals; self-employed excluding the professionals; farmers; military), and low (unskilled and skilled workers; parents with no occupation).

SEP trajectories (Study II)

In Study II, SEP was repeatedly assessed at four time points over the life course: at birth and age 10 based on parental occupation, and at the age of 30-45 years and 50-65 years based on own occupation. SEP was coded as high (high and intermediate non-manuals), medium (lower non-manuals, skilled manual workers, entrepreneurs, and farmers), and low (unskilled manual workers and those not working). The longitudinal socioeconomic trajectories were constructed from the repeated measures of SEP, using group-based latent class trajectory modeling (151).

Birthweight standardized for gestational age (Studies III and IV)

The data on birthweight and gestational age were derived from obstetric records. Both birthweight and gestational age of infants with implausibly high values of birthweight given their gestational age (152) were coded as missing (n=83). Birthweight was used as an indicator of fetal growth rate and was standardized for gestational age and sex of the infants. In G1, the mean birthweight and standard deviation of the UBCoS cohort (n=13 599) in a given gestational week was used as an internal reference for standardization among infants born at 30 or more completed weeks of gestation (153). For those born at 22-29 completed weeks of gestation (n=86), an external reference was used based on a large sample of Canadian births born 1994-1996 (154) since the numbers of G1 infants in these categories of gestational age were too few to serve as internal reference. On the other hand, the reference for G2 infants was the national birthweight data derived from the Swedish Medical Birth Register in 1973-1978.

In Study III, the percentile distribution of the standardized birthweight variable was split into three categories: Small for Gestational Age (SGA; <10th percentile), Appropriate for Gestational Age (AGA; between 10th and 90th percentile), and Large for Gestational Age (LGA; >90th percentile). In Study IV, the standardized birthweight variable was used as both continuous scores and quintiles.

Gestational age (Studies III and IV)

Gestational age was measured in completed weeks and was determined based on the date of the last menstrual period of the mother. The length of gestation was divided into three categories: preterm (≤36 weeks), term (37-41 weeks), and post-term (≥42 weeks) (155).

Ponderal index (Study IV)

Ponderal index was a measure of thinness and was used as another indicator of fetal growth, calculated by birthweight/birth length $(m)^3$. There are suggestions that the ponderal index is a better predictor of neonatal morbidity associated with intrauterine growth restriction than birthweight for gestational age (156).

Other birth characteristics (Studies III and IV)

The obstetric records also provided information on the following characteristics that were used as exposures in Studies III and IV: maternal age at birth (<20, 20-24, 25-29, 30-34, ≥35 yrs), mother's marital status (married vs unmarried including the single, divorced, and widowed), and mother's parity (1, 2, and ≥3). Additionally, multiplicity of birth (singleton vs twin/triplet) was studied as an exposure in Study III.

4.3.2 Outcomes

The primary outcome in Study I was mortality from CVD assessed during 2002-2011 and defined according to the 10th revision of the WHO International Classification of Diseases (ICD). All deaths with ICD codes I00-I99 were classified as CVD mortality. Non-CVD mortality, defined as deaths from causes other than CVD, was analyzed as a secondary outcome.

In Study II, the outcomes were all-cause mortality and cause specific mortality including mortality from CVD, cancer, injuries and poisoning, respiratory diseases, mental disorders including Alzheimer, and other causes. Mortality was assessed during the follow-up period 1980-2008 and the causes of mortality were determined by ICD-8, ICD-9, and ICD-10, whichever was in use in Sweden during the different time periods. All mortality data came from the causes of death register.

In Study III, the outcome of interest was adult SEP which was examined through a metric called the Hollingshead Index of Social Position (HISP). The HISP was proposed by the American sociologist August Hollingshead in 1957 (157,158). It is a two-factor index combining education and occupation, each graded on a 7-point hierarchical scale ranging from the lowest (coded as I) to the highest (coded as VII) categories. In the 1950s, the index was validated by Hollingshead and Redlich (158) in the New Haven community in the United States. It also appeared to be a good discriminator of health outcomes including obesity and mortality in the Swedish context (73,159). The data on adult occupation for Study III was obtained from the censuses of 1960, 1980 and 1990 whereas the data on education came from both censuses and the education registers until 2008. Individual's own occupation was assessed to generate the index, although household head occupation was also used in G1 if own occupation was missing. Applying Hollingshead's formula

(158), the values of education (I-VII) were multiplied by 4 and the values of occupation (I-VII) by 7, yielding a total score in the range between 11 and 77. The lower the score, the lower the position on the socioeconomic scale. The original HISP scores were transformed into percentages for the ease of interpretations of the study results.

In Study IV, the outcome was the first incidence of IHD morbidity or mortality. The data on incident IHD were derived from the Inpatient Register (also known as Hospital Discharge Register) and the Cause of Death Register. The ICD-7, ICD-8, ICD-9, and ICD-10 were used to define IHD which was assessed during a long follow up period from 1964 until 2008.

4.3.3 Mediators

Health behaviors

The following health behavioral factors, assessed through the baseline questionnaire of Stockholm Public Health Cohort survey, were used as mediators in Study I: smoking (never smoker, former smoker, and current smoker), risky alcohol drinking (no/yes), physical inactivity (inactive, slightly active, moderately active, and active), consumption of fruits/berries as an indicator of diet (≤ 1 time per week, almost daily/a few times per week, > 1 time per day). Body Mass Index (BMI) was also used as a mediator and was categorized as obese (≥30), overweight (25-<30), normal weight (18.5-<25), and underweight (<18.5).

Socioeconomic mediators

The three socioeconomic mediators used were the participants' education (Study I and IV), occupation (Study I), and income (Study IV). The information on educational attainment was obtained from the population censuses and the LISA database and was categorized as follows: high (postsecondary ≥3 years/university education), medium (upper secondary or post-secondary <3 years), and low (primary or lower secondary). The data on occupation in Study I came from the survey questionnaire and was classified into three groups: nonmanual (upper, middle, and lower nonmanual workers), manual (unskilled and skilled workers), and unclassifiable. On the other hand, the data on income was provided by the population census of 1970 and the yearly database of LISA during 1990-2008. In each calendar year, income was calculated in relation to family size and was standardized for age and gender. The standardized income was averaged over all calendar years during which the participants were aged 21-65 years and was used as tertiles in the analysis. Moreover, in Studies III and IV, the parental education, occupation (derived from Census 1960), and income were used as control variables, when relevant, in the analyses concerning the transgenerational associations between parental/grandparental exposures and offspring outcomes in adulthood.

4.4 Statistical Analyses

The Stata V.15 was used in all studies to perform data management and statistical analyses. As time-to-event data were the outcomes of interest in three out of the four PhD studies, survival analysis has become a predominant feature in this thesis. The survival analysis was carried out using either Poisson or Cox regression models under the Proportionality of Hazards (PH) assumption indicating that the hazards of the outcome in the exposed and the unexposed groups are parallel over the follow-up time. The PH assumption was checked by the Schoenfeld residuals test whereby an association between the residuals and time would indicate a poor model fit and violation of proportionality. Additionally, the time-dependent effects of the exposures of interest were also explored. In our data, the PH assumption was held in both the Schoenfeld residuals and the time-dependent covariate tests.

4.4.1 Study I

The Poisson regression analysis was used in Study I to estimate the incident rate ratios (IRR) for the associations between parental SEP and CVD mortality. Time since entry into the study was used as the underlying timescale while adjusting for age. A Poisson regression model assumes that the incidence rates of the event are constant throughout the follow up time. If this assumption is violated, the estimated exposure-outcome association would be confounded by time. I therefore split the follow-up time into years in the fitted models, thereby allowing the mortality rates to vary at each year during the 9.5-year follow-up period in 2002-2011.

The mediation analysis aiming to estimate the natural direct and indirect effects on CVD mortality was implemented by using a relatively new weighting approach to counterfactual mediation, known as Inverse Odds Weighting (IOW) (160). The mediation analysis was repeated using traditional regression models for the sake of comparison. The traditional regression models may produce invalid estimates when an exposure-mediator interaction is present (161–163). A major shortcoming of conventional mediation models lies in the assumption that there are no exposure-mediator, mediator-mediator, and mediator-confounder interactions. However, in the event of synergism or clustering of the mediating risk factors, their combined effect exceeds the sum of the individual risk factors, potentially leading to an underestimation of their overall mediation effect (164). A big methodological challenge arises particularly due to the exposure-mediator interaction that leads to a mathematical inconsistency when partitioning the exposure effect.

Since the traditional mediation framework fails to decompose the total exposure effect into direct and indirect effects in the presence of exposure-mediator interactions, the counterfactual based methods e.g., mediation formula and g-computation, have been proposed as alternatives (161,165,166). Despite gaining popularity in epidemiological

research, these methods are limited by the number and measurement scales of the mediators and are not generally suited to multiple- or multi-categorical mediator settings (134,160,167). The IOW is a powerful counterfactual tool that can validly estimate causal mediation parameters in the presence of exposure-mediator interactions, mediator-mediator interactions, and multiple mediators. Unlike the standard counterfactual methods, the IOW method can accommodate mediators of all types of measurement scales e.g., binary, continuous, categorical or a combination of all these mediators. The IOW-based mediation analysis was performed in 6 steps as follows:

Step 1: Fit a logistic model where the exposure (parental SEP) was entered as an outcome and all mediators of interest and relevant confounders were entered as exposures.

Step 2: Obtain predicted probabilities for each observation from the fitted logistic model and convert them into odds. Take the inverse of the odds and use the inverse odds as weights for the exposed group while letting the unexposed take the reference value 1.

Step 3: Estimate the Total Effect of the exposure by fitting a Poisson regression model with a log link function, adjusting for the confounders.

Step 4: Estimate the Natural Direct Effect by fitting a similar model as above but including the inverse odds weights created at Step 2.

Step 5: Calculate the Natural Indirect Effect by taking the difference between the total effect and the natural direct effect.

Step 6: Fit a bootstrap model with 1000 replications to obtain the Confidence Intervals (CI) for the indirect, direct, and total effects.

4.4.2 Study II

The analyses in Study II were conducted at two stages: First, I employed a latent class analysis (LCA) to define and identify distinct classes of SEP trajectories from the repeated measures of SEP. LCA is measurement model by which individuals can be grouped into mutually exclusive classes based on their response patterns on a set of observed indicator variables (151). The recently developed LCA Stata Plugin (168) was used to fit the latent class models and obtained two types of parameters: the probability of class memberships and the probability of item-response conditional on the class membership.

The latent class models were fitted under the assumption of local independence meaning that the indicators would be uncorrelated within a given latent class (169). I ran a series of latent class models specifying different number of classes in different models. The 5-class trajectory model provided the best fit to our data considering the statistical fit indices such as the Bayesian Information Criteria (BIC), sample size adjusted BIC, Akaike Information Criteria (AIC), the entropy index as well as the posterior probabilities of the

latent class memberships and the substantive meaning of the latent classes. Next, I estimated the hazard ratios (HR) of the associations linking the five latent class trajectories of SEP to all-cause and cause specific mortality outcomes using the Cox's proportional hazards model, with attained age used as the underlying timescale.

4.4.3 Study III

In Study III, linear regression models were used to estimate the magnitude of the associations between early life characteristics and the adult socioeconomic index. As a first step of analysis, the effect heterogeneity of the associations was assessed in the total sample combining G1 and G2 by incorporating an exposure*generation interaction term in the regression model. The generation-specific beta coefficients of the associations were obtained in postestimation through the "lincom" command of Stata. I also explored whether the magnitude of the estimated effect modification depends on the gender of the study subjects (moderated moderation). The associations showing a three-way interaction, i.e., exposure*generation*gender, were further stratified by gender.

At the next stage, the transgenerational associations between parental early life characteristics and offspring's adult SEP were estimated separately along the paternal and maternal lines. Parent's education, adult SEP, and income were adjusted for to assess whether the associations are explained by the parental socioeconomic conditions.

4.4.4 Study IV

The analyses in Study IV were carried out using the Cox proportional hazard models where attained age was used as the timescale. To investigate if the associations between early life characteristics and incident IHD in adulthood differ between the two generations, the analytic samples consisting of G1 and G2 were pooled into a single dataset and the statistical analyses were stratified by gender. The potential effect modification by generation was tested by introducing an exposure*generation interaction term in the model, whereby a significant interaction would indicate a change of the association. The HRs of the associations in each generation were obtained in postestimation from the fitted interaction model, using Stata's "lincom" command. For the associations that were statistically significant, we further examined if the associations were mediated by education and income in adulthood. The mediation analysis was performed separately for each generation and gender. The natural direct and indirect effects were calculated by the IOW method as described for Study I above.

The transgenerational associations between parental early life characteristics and offspring's adult IHD were explored by stratifying the analyses on the gender of the parents. The robustness of the estimated associations was checked by statistically controlling for the parent's education, income, and IHD diagnosis.

4.5 Missing data

The missing data in Studies I and II were dealt with multiple imputation and maximum likelihood, respectively. On the other hand, complete case analysis was done in Studies III and IV where the percentages of missing data were comparatively low.

In Study I, the total proportion of missing observations across all the analytic variables was 23%. Multiple imputation by chained equations (170) was used to deal with potential selection bias originating from the missing data. A total of 25 imputed datasets were generated from an imputation model under the assumption of missing at random. According to this assumption, the probability of the data being missing is independent of the unobserved data, conditional on the observed variables. The plausibility of the assumption was checked to the extent possible by identifying a set of predictors of missingness from the available dataset. In addition to the analytic variables, the imputation model included the Nelson-Aalen estimate of the cumulative hazard function as well as a few auxiliary variables that were found to be associated with missingness. Each of the 25 imputed datasets was analyzed separately and the estimates (coefficients and standard errors) across all imputed datasets were pooled using Rubin's rule (171).

In Study II where SEP was longitudinally measured over four time points, the study subjects with missing information on all measures of SEP were excluded (n=9). Any missing data of the subjects with available data on at least one measure of SEP were adjusted for by the maximum likelihood procedure. The maximum likelihood is a typical method of handling missing data in LCA and is available in most LCA software packages. Unlike the multiple imputation approach, it does not require the user to fit any separate imputation model apart from the latent class model itself (169). The maximum likelihood method can provide unbiased estimates under the assumption of missing at random only when the missing data are in the outcome variable (and not in the covariates) of the latent class model (168,172).

4.6 Ethical considerations

All four studies in this thesis involved personal data and necessary ethical permits were obtained prior to collecting and using the data for analysis. The studies were approved by the regional ethics board in Stockholm. A potential risk in register data research is the breach of individual's integrity which may result from the mismanagement of data related to personal identification (173). The Declaration of Helsinki stipulates that every precaution is undertaken "to protect the privacy of research subjects and the confidentiality of their personal information". The right to privacy of the study subjects was safeguarded by de-identification of sensitive personal data after the data linkage by replacing the personal identity numbers with study numbers, and by appropriate storage of the data in conformity with the routines established at the university, the requirements from data providers as well as the demands of the Declaration of Helsinki.

Further, access was restricted to a limited number of variables and subset of the populations.

As for the Stockholm Public Health Cohort survey data, caution was taken to respect the autonomy of the study participants and uphold their ethical rights at all stages: before, during, and after the implementation of the survey. A written informed consent, which is central ethical principle, was obtained. A postal questionnaire together with an introductory letter describing the general purpose of the study was sent out to the participant's address. The participation in the study was voluntary. To make the survey less cumbersome for the participants, information about education, work, income, and family relationships was retrieved from the register for which the participants had given their consent when filling out the survey questionnaire.

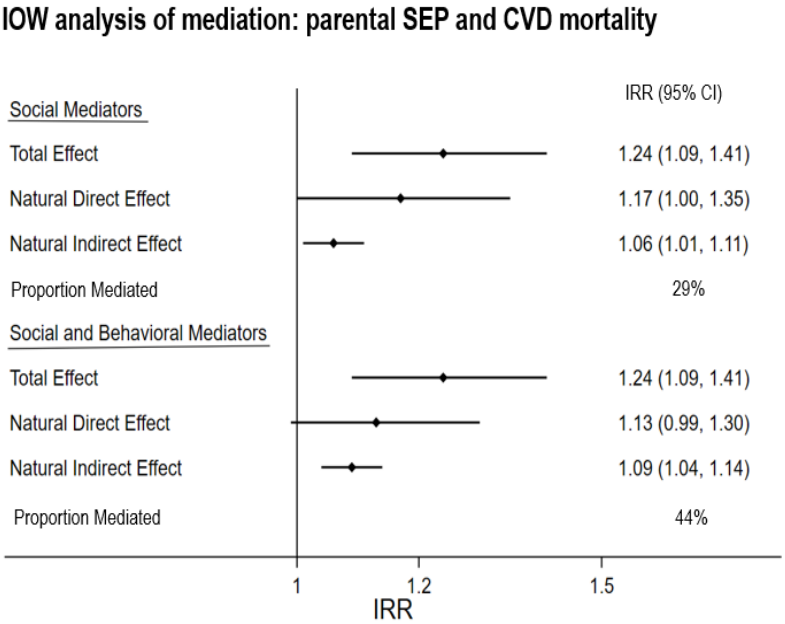
Therefore, potential risks associated with participation in the studies were minimal and most likely to be outweighed by the anticipated benefits. Although direct medical benefits for the study subjects cannot be discerned, those who are still alive may benefit from increased knowledge of the natural history and risk factors of their diseases (173). Moreover, the study findings can be of particular interest to the researchers and policymakers on both national and international levels and benefit population health in general.

5 OVERVIEW OF RESULTS

5.1 Early life SEP and adult cardiovascular mortality

The aim of Study I was to document the association between parental SEP and participants' adult CVD mortality and assess the contribution of adult social and behavioral factors to the association. The results showed that parent's manual occupation compared with non-manual occupation was associated with 24% higher rate of CVD mortality (IRR $^{\text{Total Effect}}$ 1.24; 95% CI: 1.09, 1.41) among men and women of the Stockholm Public Health Cohort.

The results from the mediation analysis based on the IOW method are demonstrated in **Figure 5.** About 44% of the total effect of parental SEP on CVD mortality was mediated by participants' adult socio-economic and health behavioral factors including BMI (IRR $^{\text{Natural Indirect Effect}}$ 1.09; 95% CI: 1.04, 1.14). The two social mediators – education and occupation – accounted for 29% of the total effect of parental SEP. The health behaviors additionally mediated 15% (i.e., 44%-29%) of the total effect. There was also a borderline significant direct effect of parental SEP on CVD mortality, which was not mediated by socioeconomic factors (IRR $^{\text{Natural Direct Effect}}$ 1.17; 95% CI: 1.00, 1.35). However, the observed direct effect became weaker when behavioral mediators were accounted for.



IOW, Inverse Odds Weighting; IRR, Incidence Rate Ratio; CI, Confidence Interval; SEP, Socioeconomic Position; CVD, Cardiovascular Disease.
The IRRs were adjusted for the following confounders: participants' age, gender, country of birth, and marital status.
Social mediators refer to education and occupation; behavioral mediators include smoking, alcohol drinking, physical inactivity, poor diet and body mass index.

Figure 5. Graphical presentation of the contribution of social and behavioral mediators to the association between parental socioeconomic position and participants' adult cardiovascular mortality assessed in Poisson regression models: the Stockholm Public Health Cohort, Sweden (n=19 720. Reproduced from Table 4 of Study I).

Additional analysis found a relatively weak association of parental SEP with non-CVD mortality ($IRR^{Total\ Effect}$ 1.15; 95% CI: 1.04, 1.27), but the patterns of mediation were more or less similar to CVD mortality. Moreover, the magnitude of mediation estimated from the traditional mediation model tended to be overestimated when compared to the IOW model, although the 95% CIs of the Natural Indirect Effects in the two models overlapped with each other (see Table 4 in Study I).

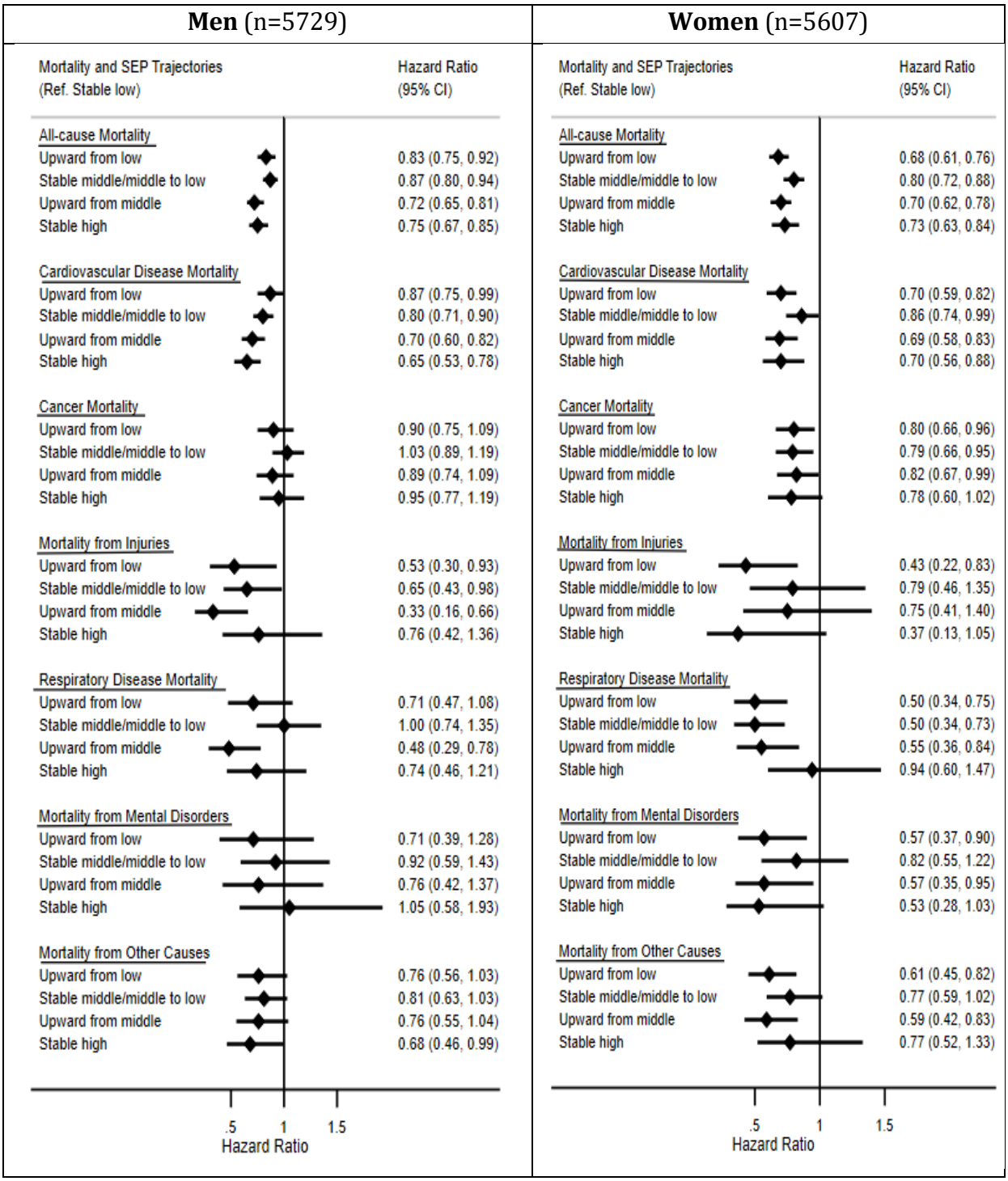
5.2 Life course socioeconomic trajectories and mortality

The aim of Study II was to examine the associations between longitudinal trajectories of SEP across the life course and mortality in later life in G1 of the UBCoS Multigen. The LCA analysis identified five latent class trajectories of SEP in both men and women: i) stable high SEP, ii) upwardly mobile from middle SEP, iii) stable middle or middle to low SEP, iv) upwardly mobile from low SEP, and iv) stable low SEP (see Supplementary Figures S1 and S2 in Study II).

The associations between SEP trajectories and mortality outcomes were estimated in Cox regression models and the gender-stratified results are presented in **Figure 6**. It was found that compared to those with stable low SEP trajectory, the hazards of all-cause mortality were smaller for those who were stable high across the life course (Men: HR 0.75; Women: HR 0.73), upwardly mobile from middle SEP (Men: HR 0.72; Women: HR 0.70), upwardly mobile from low SEP (Men: HR 0.83; Women: HR 0.68), and stable middle/middle to low SEP (Men: HR 0.87; Women: HR 0.80). Mortality from CVD accounted for 47% and 41% of all deaths in men and women, respectively (see Figure 1 in Study II). The magnitudes of the HRs of CVD mortality in different SEP trajectories were very similar to those of all-cause mortality.

Among men, the HRs of mortality from CVDs and injuries were significantly lower in the upward from middle and upward from low trajectories compared to the stable low trajectory. The upward from middle SEP was also associated with decreased HR of respiratory disease mortality in men. Among women, compared to the stable low trajectory, both upward from middle and upward from low trajectories showed consistently reduced HRs for all of the studied cause-specific mortality outcomes, with the exception of mortality from injuries.

Sensitivity analyses further suggest that the effect sizes of the estimated associations did not change considerably by the statistical control for gestational ages, birthweight relative to gestational age, and marital status of the study subjects (not shown).



Note: The hazard ratios were adjusted for age and birth cohorts.
CI, Confidence Interval; SEP, Socioeconomic Position

Figure 6. Graphical presentation of the hazard ratios (with 95% CI) from Cox regression models estimating the associations between latent class socioeconomic trajectories and mortality: Generation 1 of the Uppsala Birth Cohort Multigenerational Study (n=11 336. Figure reproduced from Table 3 and Table 4 of Study II).

5.3 Early life determinants of SEP across generations

Study III was based on G1 and G2 of the UBCoS Multigen and aimed to explore whether the associations of a range of early life social and health-related factors with adult SEP persist over time and are transmitted across generations. The results indicate that the average socioeconomic score was 7 percentage point higher in G2 compared to G1 on the 100-point scale. **Table 2** shows that compared to the group with high parental SEP, the group with low parental SEP scored around 29 percentage points lower in G1 (B: -29.4, 95% CI: -31.3, -27.6) and 14 percentage points lower in G2 (B: -13.6, 95% CI: -15.3, -12.1) after adjusting for birth year and mother's marital status, indicating an attenuated association in the younger generation.

Being born to mothers with high parity, unmarried marital status or young aged mothers were associated with offspring's lower SEP in adulthood. The association of mother's parity with offspring SEP did not show any change across generations whereas mother's unmarried status and younger childbearing ages showed stronger associations in G2. SGA was associated with lower socioeconomic score among both men and women in G1 while the association in G2 was observed in women. The SGA-SEP association, however, did not differ between generations.

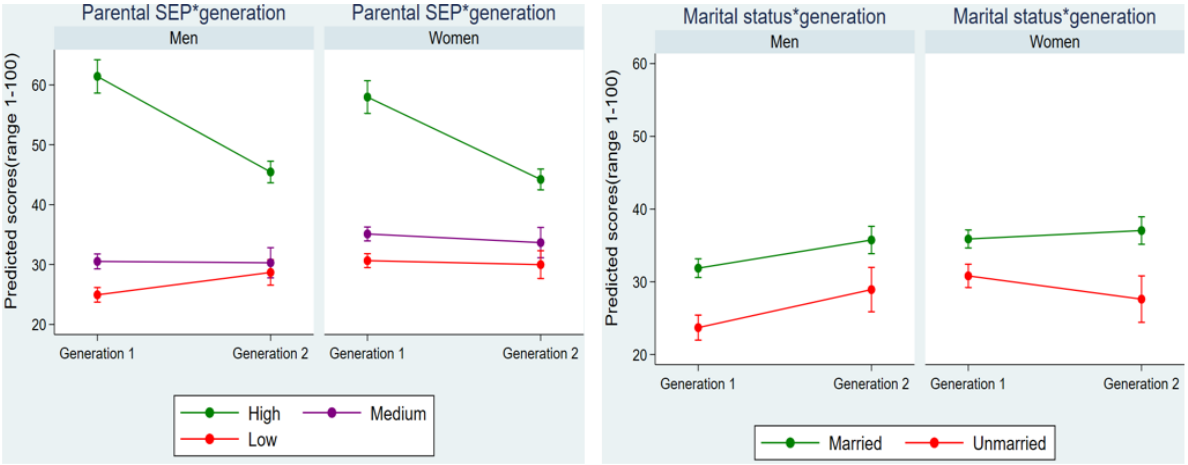
Table 2. Results from linear regression models assessing the generational differences in the associations between early life characteristics and adult socioeconomic position measured by Hollingshead Index: the Uppsala Birth Cohort Multigenerational Study, Sweden (n=10 233 in G1 and 6055 in G2. Reproduced from Table 2 of Study III).

Early life Characteristics	Model 1 [1]			Model 2 [2]		
	Generation 1	Generation 2	Difference in association	Generation 1	Generation 2	Difference in association
	ß (95% CI) [4]	ß (95% CI) [4]	ß change (95% CI) [3]	ß (95% CI) [4]	ß (95% CI) [4]	ß change (95% CI) [3]
Parental SEP						
High	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	**-24.9**	**-10.8**	**14.1**	**-24.9**	**-10.8**	**14.1**
	(-26.8, -23.1)	(-12.7, -8.9)	(11.4, 16.8) †	(-26.8, -23.0)	(-12.8, -8.9)	(11.4, 16.7) †
Low	**-30.3**	**-13.7**	**16.5**	**-29.4**	**-13.6**	**15.8**
	(-32.1, -28.4)	(-15.4, -12.1)	(14.0, 19.0) †	(-20.7, -18.2)	(-15.3, -12.01)	(13.3, 18.3) †
Mother's marital status						
Married	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Unmarried	**-5.9**	**-7.4**	-1.5	-1.0	**-6.9**	**-5.9**
	(-7.2, -4.7)	(-9.4, -5.3)	(-3.8, 1.0) †	(-2.4, 0.3)	(-8.9, -4.9)	(-8.2, -3.4) †
Mother's parity						
1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2	**-2.1**	**-3.4**	-1.3	**-4.3**	**-4.6**	-0.3
	(-3.3, -0.9)	(-4.7, -2.1)	(-3.0, 0.5)	(-5.5, -3.1)	(-5.9, -3.3)	(-2.0, 1.4)
⩾ 3	**-7.7**	**-8.2**	-0.5	**-11.4**	**-9.6**	1.8
	(-8.8, -6.6)	(-9.9, -6.5)	(-2.6, 1.5)	(-12.7, -10.2)	(-11.3, -7.9)	(-0.2, 3.8)
Birthweight (standardized)						
SGA	**-2.9**	-1.6 †	1.3	**-3.00**	-1.5 †	1.5
	(-4.7, -1.2)	(-3.8, 0.5)	(-1.4, 4.1)	(-4.6, -1.4)	(-3.6, 0.5)	(-1.1, 4.1)
Normal	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
LGA	-0.1	1.4	2.4	-0.1	**2.5**	2.6
	(-2.6, 0.7)	(-0.8, 3.6)	(-0.3, 5.2)	(-1.6, 1.5)	(0.4, 4.6)	(-0.0, 5.2)

Gestational age						
Pre-term (≤36 weeks)	-1.2	-1.6	-0.4	-0.1	-1.3	-1.2
	(-3.1, 0.8)	(-4.5, 1.3)	(-3.91, 3.07)	(-2.0, 1.7)	(-4.1, 1.4)	(-4.4, 2.1)
Term (37-41 weeks)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Post-term (≥42 weeks)	**-3.1**	**-2.6**	0.5	**-2.3**	-1.7	0.6
	(-4.6, -1.6)	(-4.6, -0.4)	(-2.03, 2.96)	(-3.7, -0.9)	(-3.5, 0.2)	(-1.7, 2.9)
Multiplicity of birth						
Singleton	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Twin/triplet	-2.8	**-6.0**	-3.2	-2.7	-4.5	-1.8
	(-6.6, 0.9)	(-11.6, -0.4)	(-9.9, 3.5)	(-6.1, 0.7)	(-10.1, 1.1)	(-8.3, 4.7)
Mother's age at birth						
<20	**-4.6**	**-7.1**	-2.5	0.3	**-5.7**	**-6.0**
	(-6.9, -2.2)	(-9.5, -4.7)	(-5.9, 0.8)	(-2.1, 2.7)	(-8.1, -3.3)	(-9.3, -2.7)
20-24	**-2.9**	**-3.7**	-0.8	-0.5	**-2.9**	**-2.4**
	(-4.3, -1.6)	(-5.3, -2.2)	(-2.8, 1.2)	(-1.8, -0.8)	(-4.4, -1.5)	(-4.2, -0.5)
25-29	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
30-34	1.0	0.7	-0.3	0.2	0.8	0.6
	(-0.4, 2.5)	(-1.2, 2.5)	(-2.7, 2.0)	(-1.1, 1.5)	(-1.0, 2.6)	(-1.7, 2.8)
⩾35 years	**-1.7**	-1.0	0.7	**-2.6**	-0.9	1.7
	(-3.2, -0.2)	(-4.3, 2.4)	(-2.9, 4.4)	(-4.0, -1.1)	(-4.1, 2.4)	(-1.8, 5.2)

ß, Beta coefficient; CI, Confidence Interval; SGA, Small for Gestational Age; LGA, Large for Gestational Age; SEP, Socioeconomic Position.
Bold typeface indicates statistical significance<0.05.
[1]Model 1 adjusted for birth year (gender was also adjusted for when estimating the association for gestational age).
[2] Model 2 additionally adjusted for different sets of confounders for different exposures. The estimates for parental SEP and mother's marital status were adjusted for each other. The estimates for mother's parity were adjusted for parental SEP, multiplicity of birth, mother's marital status and mother's age at childbirth. The estimates for standardized birthweight, gestational age and multiplicity of births were estimated by adjusting for all exposures. The estimates for mother's age at birth was adjusted for parental SEP and mother's marital status. An exposure*generation interaction term was fitted in all models to assess if the associations vary by generation. Since a significant interaction between parental SEP and generation was detected in Model 1, this interaction was adjusted for in Model 2 when appropriate.
[3] Obtained from linear regression models by fitting an exposure*generation interaction term.
[4] Obtained in post-estimation from the fitted linear regression models.
[†]Estimates modified by gender: p-value for parental SEP*generation*gender = 0.009; p-value for marital status*generation*gender =0.016. See also Figure 7.

Figure 7 presents the gender-stratified associations that showed effect modifications by both generation and gender. The attenuation of the association between parental and offspring SEPs appeared to be steeper in men compared to women. The association between mother's marital status and offspring SEP became stronger in G2 women compared to G1 women.



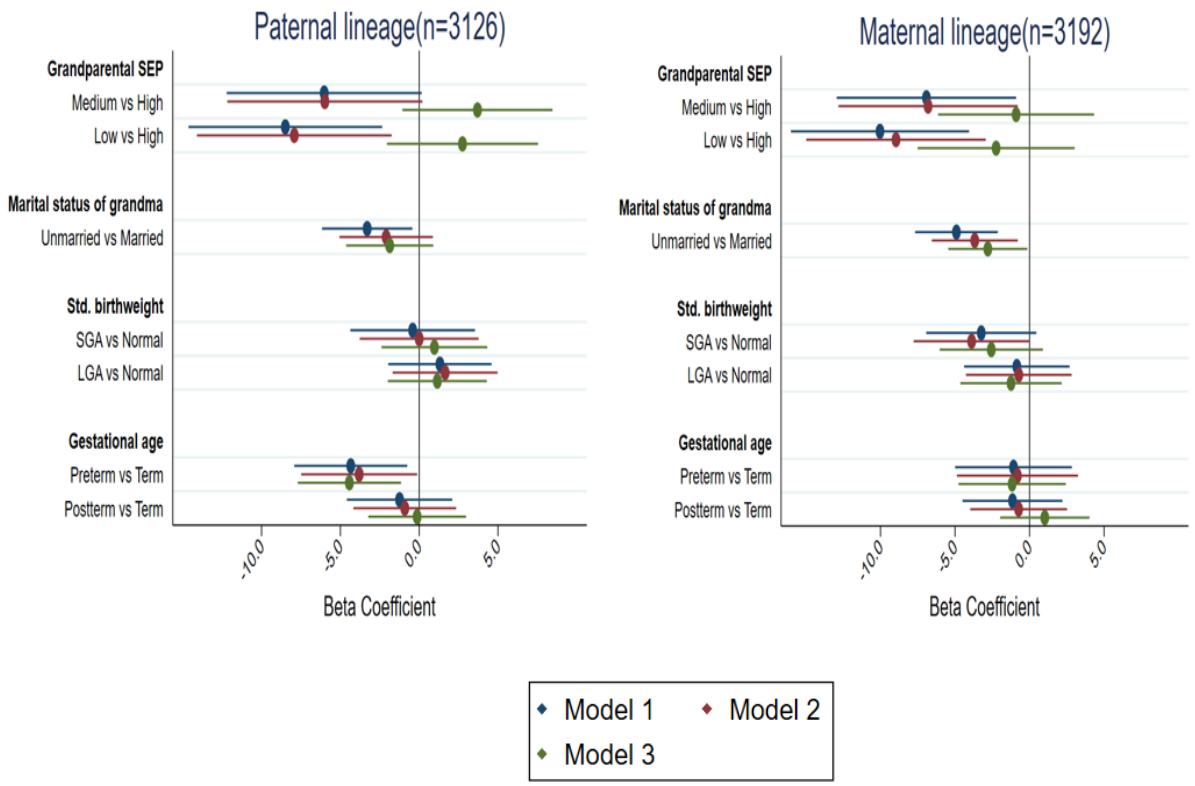
(SEP, Socioeconomic Position. The association with parental SEP was adjusted for year of birth and mother's marital status. The association with mother's marital status was adjusted for year of birth, parental SEP, and parental SEP*generation.)

Figure 7. Plots showing the generational and gender differences in the associations of parental socioeconomic position and mother's marital status with offspring's adult socioeconomic position, estimated through linear regression models: the Uppsala Birth Cohort Multigenerational Study, Sweden (n=8513 in men and 7775 in women. Figure reproduced from Table 3 of Study III).

The results from transgenerational analysis linking selected early life characteristics of G1 (including adult characteristics of G0) to adult SEP of G2 are illustrated in **Figure 8**. It was found that low grandparental SEP at parent's birth was associated with lower SEP of the adult offspring (i.e., grandchildren). The association was evident along both maternal and paternal lineages but became weaker with the adjustment for mothers' or fathers' respective education, occupation, and income (Model 3).

Grandmother's marital status at parent's birth was associated with adult offspring's SEP along both maternal and paternal lineages. While this association was mediated by father's adult socioeconomic conditions along paternal lineage, the association along the maternal lineage attenuated when mother's socioeconomic conditions were adjusted for. There was also an association between paternal preterm birth and offspring SEP, with the preterm fathers showing greater likelihood of having children with lower adult SEP. This

association was not explained by fathers' early life characteristics and adult socioeconomic conditions (**Figure 8**).



(**Note:** SGA, Small for Gestational Age; LGA, Large for Gestational Age. **Model 1** adjusted for mother's/father's respective birth year and offspring's birth year. In **Model 2**, the estimates of grandparental SEP and grandmother's marital status were adjusted for each other. The estimates for parent's standardized birthweight and gestational age were adjusted for each other as well as for grandparental SEP and grandmother's marital status, parity, age at parental birth and birth multiplicity. **Model 3** further adjusted for mother's/father's respective education, occupation, and income).

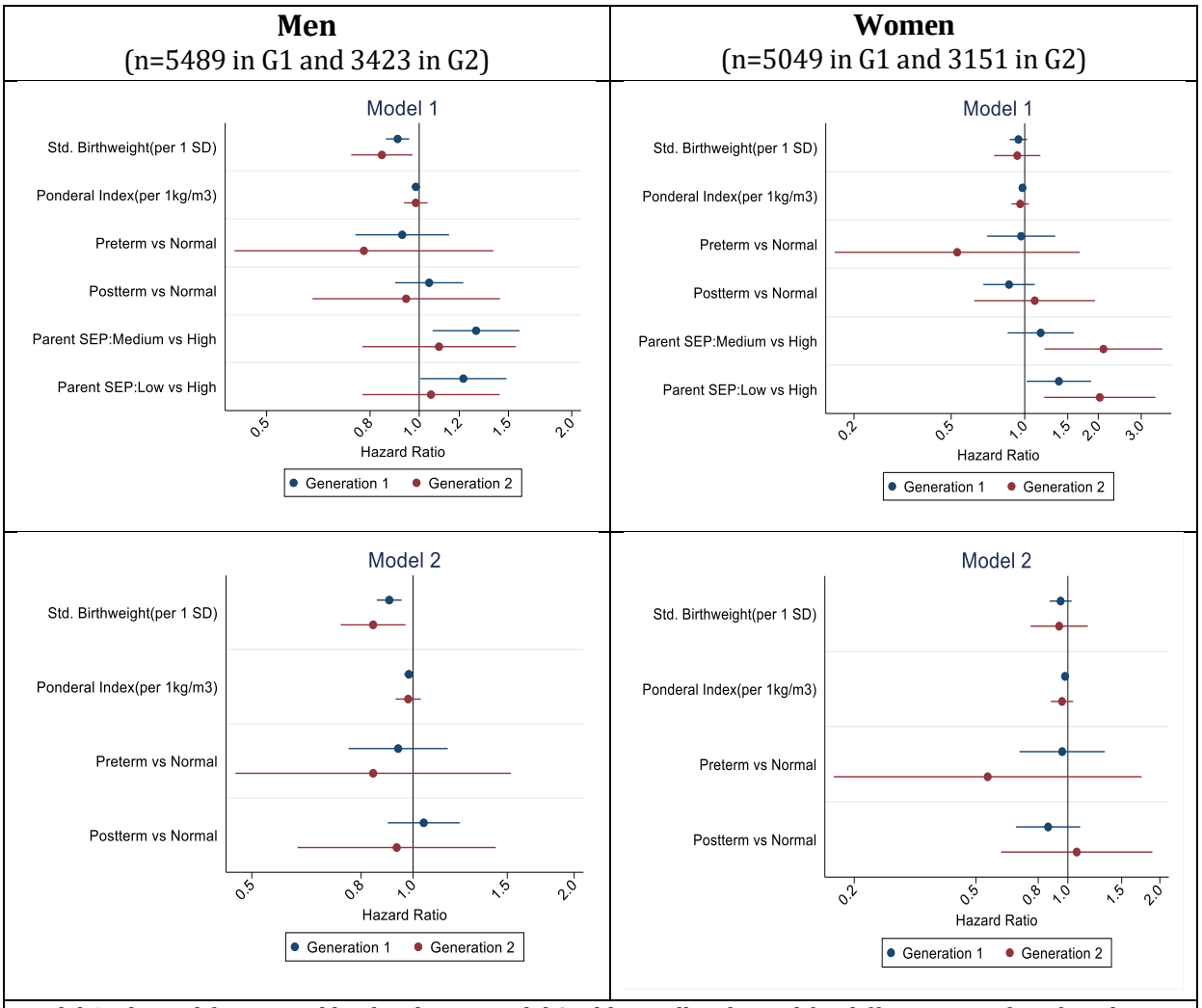
Figure 8. Plots of the beta coefficients (with 95% CI) from linear regression models estimating the transgenerational associations between parents' selected early life characteristics and adult offspring's socioeconomic position: the Uppsala Birth Cohort Multigenerational Study, Sweden (n=6318. Figure reproduced from Table 4 of Study III).

5.4 Early life programming of ischemic heart disease across generations

Study IV aimed to examine whether the associations of specific early life social and health disadvantages with incident IHD in adulthood persist over time and are transmitted across generations, using data from the UBCoS Multigen. Results suggest that the mean birthweight of both men and women was nearly 0.1kg higher in G2 than in G1, and the proportion of men and women born preterm was slightly smaller in G2.

Figure 9 shows that one standard deviation unit increase in standardized birthweight among men was associated with 10% lower rate of IHD in G1 (HR 0.90; 95% CI: 0.86, 0.95) and 16% lower rate in G2 (HR 0.84; 95% CI: 0.73, 0.96). Among women, no association between standardized birthweight and IHD was observed in any generation. Compared to high parental SEP, low parental SEP was associated with higher rates of IHD among both men (HR 1.22; 95% CI: 1.01, 1.48) and women (HR 1.38; 95% CI: 1.02, 1.87) in G1 while the association in G2 was found among women only (HR 2.04; 95% CI: 1.21, 3.45). The interaction tests, however, did not yield any evidence of effect heterogeneity across generations in men or women (see Table 2 and Table 3 in Study IV), suggesting that the magnitudes of the associations were similar in both generations.

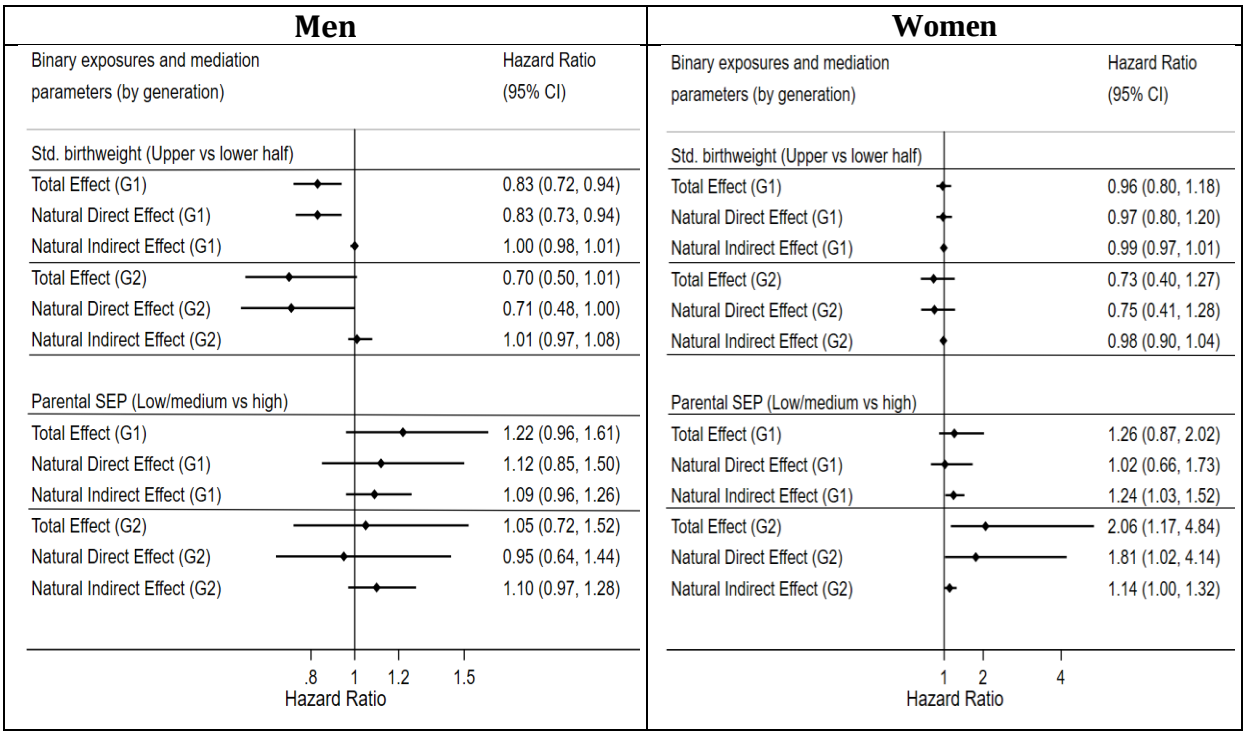
In additional analyses, mother's unmarried status showed elevated IHD rates, albeit marginally significant, among both men and women in G1. Mother's high parity was associated with increased IHD rates among men in both generations, with no evidence of effect heterogeneity across generations. Maternal age was not found to be associated with offspring IHD (not shown).



Model 1 adjusted for age and birth cohorts. Model 2 additionally adjusted for different sets of confounders for different exposures: the hazard ratio for standardized birthweight was adjusted for parental socioeconomic position (SEP); the hazard ratio for ponderal index was adjusted for gestational weeks and parental SEP; the hazard ratios for preterm and post term births were adjusted for standardized birthweight and parental SEP.

Figure 9. Plots of the hazard ratios (with 95% CI) from Cox regression models comparing the associations between early life exposures and incident ischemic heart disease across two generations, aged 32-75 years: the Uppsala Birth Cohort Multigenerational Study, Sweden (Figure reproduced from Table 2 and Table 3 of Study IV).

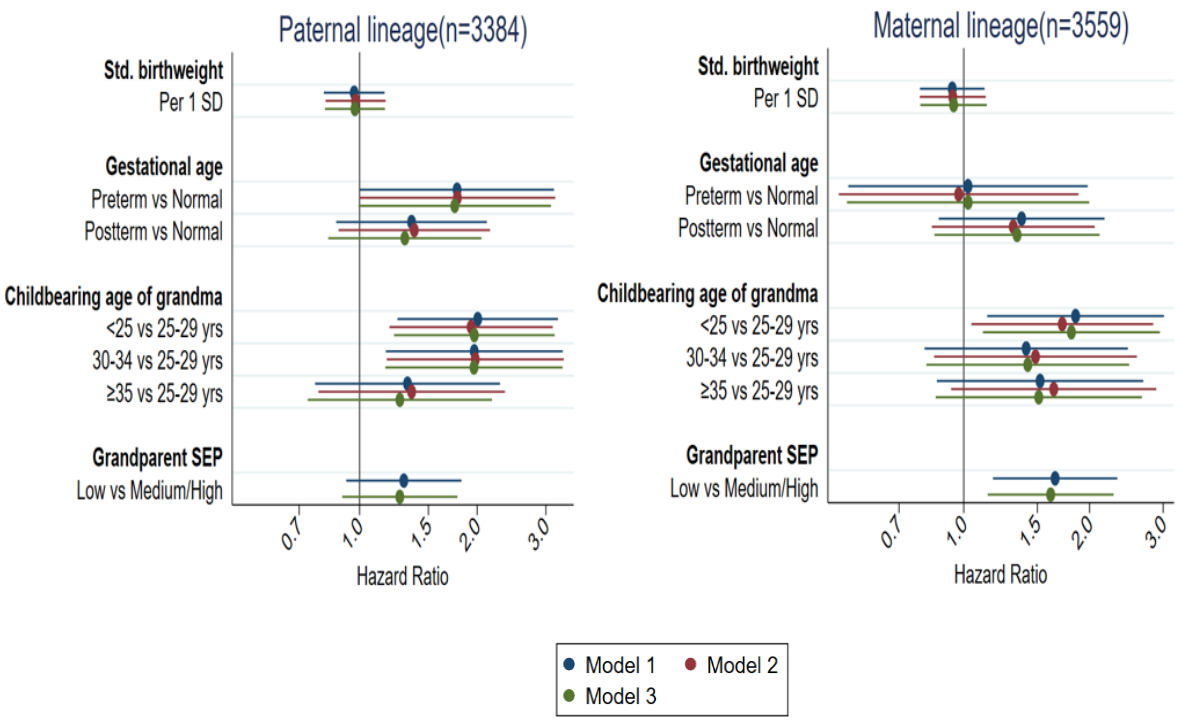
Figure 10 further demonstrates that the adult socioeconomic circumstances, i.e., education and income, partially mediated the association between parental SEP and adult IHD. Among women in G2, about 24% of the total effect of parental was mediated by the two socioeconomic factors (HR $^{\text{Natural Indirect Effect}}$ 1.14; 95% CI: 1.00, 1.32) while a strong natural direct effect (HR $^{\text{Natural Direct Effect}}$ 1.81; 95% CI: 1.02, 4.14) was also detected. On the other hand, the association between standardized birthweight and IHD was not at all mediated by education and income in any generation.



Note: G, Generation; CI, Confidence Interval; SEP, Socioeconomic Position. The hazard ratios for standardized birthweight were adjusted for age and parental SEP; the hazard ratios for parental SEP were age-adjusted. The 95% CIs were obtained from bootstrap models with 1000 replications.

Figure 10. Graphical presentation of the contribution of education and income to the associations of standardized birthweight and parental socioeconomic position with incident ischemic heart disease, estimated in Cox regression models through the Inverse Odds Weighting method of mediation: the Uppsala Birth Cohort Multigenerational Study, Sweden (Figure reproduced from Table 4 of Study IV).

The transgenerational associations between selected early life characteristics of parents and/or adult characteristics of grandparents and the incident IHD of adult offspring are illustrated in **Figure 11**. An increased rate of IHD was found among offspring of fathers who were born preterm (HR 1.78; 95% CI: 1.01, 3.15). Grandmothers' childbearing ages were associated with IHD of the adult offspring along both maternal and paternal lineages. The association showed a U-shaped pattern, which was strongly pronounced along the paternal line. Thus, increased hazards of IHD were observed among offspring whose grandmothers had lower (<25 years) or advanced maternal age (30-34 years) at the time of the parent's birth. On the other hand, grandfathers' age at parents' birth did not exhibit any association with offspring IHD (not shown). Further, lower SEP of grandparents was negatively associated with offspring's adult IHD along the maternal line. The transgenerational associations were robust to the statistical controls for parents' education and income. The associations remained unattenuated when parent's IHD and the offspring's early life exposure to the same risk factors were controlled for (not shown).



Note: Model 1 adjusted for offspring's and parent's age. Model 2 adjusted for grandparental SEP. Model 3 adjusted for parent's education and income.

Figure 11. Plots of the hazard ratios (with 95% CI) from Cox regression models estimating the transgenerational associations between selected early life characteristics of parents and adult offspring's risk of incident ischemic heart disease: the Uppsala Birth Cohort Multigenerational Study, Sweden (Figure reproduced from Table 5 and Table 6 of Study IV).

6 DISCUSSION

6.1 Main Findings

The overarching aim of this PhD thesis was to enhance our understanding of the effects of early life social and health disadvantages on adult socioeconomic and health outcomes across the life course and across generations, using data from the Swedish men and women. The main findings of the thesis are as follows:

- The adult socioeconomic and health-related behavioral factors considerably mediated the association between parental SEP and adult CVD mortality. However, more than half of the total effect of parental SEP appears to be unexplained by the studied mediators.

- Compared to individuals with a life-time low SEP, those with a consistently high SEP across the life course as well as those with upward socioeconomic trajectories exhibited lower risk of mortality in late life.

- The association of parental SEP with adult SEP showed an attenuation over historical time while its association with incident cases of IHD appears unchanged. On the other hand, the associations of impaired fetal growth, measured by birthweight for gestational age, with adult SEP and incident IHD tended to stay stable between generations.

- The low SEP of grandparents and fathers' preterm birth were associated with lower SEP and higher risk of incident IHD among adult offspring. Further, the offspring with older and younger paternal grandmothers and the offspring with younger maternal grandmothers showed higher IHD risks compared to offspring with grandmothers who were 25-29 years old at the time of parent's birth.

6.2 Interpretations and comparisons with existing literature

6.2.1 Is there a critical period effect of early life socioeconomic position?

In line with the existing literature (58), I found clear associations linking disadvantaged parental SEP to CVD mortality in the Stockholm cohort (Study I) and to incident cases of IHD in two generations of the UBCoS Multigen (Study IV). Grounded in a causal mediation framework, Study I shows substantial attenuation of the total effect of parental SEP on CVD mortality when the mediating variables such as education, occupation, smoking, alcohol drinking, physical inactivity, poor diet, and BMI were jointly accounted for. This finding is supported by the pathway/chain of risks model, implying that a disadvantaged socioeconomic background in the family of origin may lead to adverse socioeconomic circumstances and unhealthy lifestyles and thereby increases the risk of mortality in adult life.

However, a direct effect of parental SEP on CVD mortality, which was not mediated by the socioeconomic pathway, was detected in the Stockholm cohort. A strong direct effect of parental SEP on the incidence of IHD, unmediated by education and income in adulthood, was also observed in G2 women of the UBCoS Multigen (Study IV). Although the existence of a direct effect of early life SEP is apparently consistent with the critical period model and was reported in numerous studies (52,58), the finding requires a cautious interpretation. While the possibility of a true critical period effect cannot be ruled out, it is more likely that the observed direct effect represents unmeasured/uncontrolled mediators or causal pathways. This was supported by the sequential mediation analysis in Study I where the estimated direct effect, which was unexplained by the socioeconomic mediators, became weaker once behavioral mediators were taken into account.

Previous studies that aimed to investigate the causal pathways from SEP in early life to morbidity and mortality in later life have generated inconclusive evidence. Most studies reported that adverse socioeconomic conditions in childhood may exert effects on later health directly without mediating through adulthood risk factors (63–66,174) while some studies found only an indirect effect that goes through risk factors in adulthood (47,68–71). Variations in the type and number of analyzed mediators across studies may account for part of the divergent findings. In addition, most of the earlier studies examining the mediating pathways used the conventional difference or product of coefficients methods and hence were subject to model misspecifications due to, for example, ignoring exposure-mediator interactions and unmeasured mediator-outcome confounding (134). Consequently, the underestimation or overestimation of the direct/indirect effects were plausible, as demonstrated in Study I of this thesis.

6.2.2 Can upward mobility offset mortality related to early life SEP?

In Study II which measured SEP over four time points and employed a latent class modelling strategy to identify the longitudinal trajectories of SEP, both men and women who were consistently in the high SEP over their life course, as opposed to those who were in stable low SEP, displayed lower risks of mortality from all-causes and CVDs. Moreover, an upward trajectory from middle or low SEP appeared to be protective, to similar extent as stable high SEP, against all-cause mortality and a range of other cause-specific mortality outcomes, especially among women. This finding stands in contrast to previous studies that showed elevated risks of mortality associated with upward mobility compared to stable high SEP (80,175). The disagreement in findings can be partly attributed to the differences in the measures of SEP and methodological approaches used in different studies.

Social mobility is an indication of social justice, allowing people to freely move along the social hierarchy. Nonetheless, whether social mobility is beneficial or harmful for health has been debated in the theoretical literature (176–178). The dissociative hypothesis,

proposed by Sorokin (176), posits that the movement from one social strata to another, regardless of direction, demands disconnection from the native class and assimilation in the new class position. Thus, the journey of social class mobility is potentially a source of chronic stress, social isolation, and psychological strain that can trigger detrimental effects on health. The acculturation hypothesis, in contrast, postulates that the health of socially mobile individuals is principally a function of the class they join, not that of the class they leave behind. Accordingly, the health and well-being of the socially mobile is hypothesized to be closely resembling that of the current social class (177). The protective effect of upward mobility trajectories, as shown in this thesis, is more compatible with the acculturation hypothesis and appears more plausible than Sorokin's dissociative hypothesis. Mechanistically, upward mobility may translate into greater access to material resources and healthy lifestyles (48,179,180) which can protect against illness and premature mortality, although the current thesis has limited ability to test these mechanisms.

As previous studies on social mobility rarely employed a similar methodological approach, a direct comparison of the findings related to the latent class trajectories of SEP is difficult to make. However, the finding that the risk of dying among the upwardly mobile was nearly as low as the always advantaged socioeconomic group is consistent with another study of an Italian cohort (181). The authors of that study illustrated that among the socioeconomically poor children, an upward trajectory in both education and material circumstances reduced all-cause mortality to a similar level as in the stable high group.

Therefore, it can be reasonably concluded that improved socioeconomic circumstances in adulthood may counterbalance the negative effects of childhood socioeconomic disadvantages on mortality in later life. This conclusion is indirectly supported by a recent study (54) which was based on the same data as used in Study II but adopted a different methodological strategy to empirically disentangle the critical, sensitive, and accumulation models. The study found the sensitive period model best describing the effect of SEP across the life course on total mortality and suggested that the latest SEP at ages 50-65 have the strongest effect on mortality.

6.2.3 Persistent health inequalities by early life disadvantages

A key question in health inequality research is whether the inequalities are widening or narrowing over time in response to changes in the macro level social structures and policies. Although health inequalities by adult SEP were shown to have widened or remained stable in most European countries in the past few decades (182,183), very few investigations were carried out to explore whether the magnitude of health inequalities associated with early life SEP has changed across different birth cohorts (184,185).

In the current thesis, there was no evidence that the risk of IHD by early life SEP has changed between the first (born 1915-1929) and second generations (born 1932-1972) of the UBCoS Multigen in Sweden. Using the same cohorts, we previously demonstrated that the association between parental SEP and hospitalization due to any major noncommunicable diseases remained unchanged over time (186). These findings are in accord with the recently published Finnish study (185) that compared two birth cohorts, born in 1950 and 1975, respectively and concluded that the associations between early life socioeconomic circumstances and mid-life mortality did not decline in the more recent cohort. Similarly, a stability in the association between parental SEP and all-cause mortality was demonstrated earlier in a Danish study conducted in a cohort of men born in 1953 and their parents.

The persistence of health inequalities linked to early life socioeconomic conditions is unexpected given that the younger birth cohorts were brought up in a more modern and egalitarian environments compared to their predecessors. According to the fundamental cause theory, socioeconomic inequalities in health or mortality are nearly universal, i.e., persistent across geographic places and historical time, although the underlying mechanisms may vary in different contexts (187,188). While the association between parental SEP and offspring's adult SEP considerably declined (Study III), the stability of the association between parental SEP and IHD (Study IV) indicates possible changes in the major mechanisms over historical time.

Lower birthweight relative to gestational age also showed consistent associations with adult SEP and IHD in both generations in this thesis, with a slight increase in average birthweight in G2 but no sign of decline in the magnitude of the estimated association. In addition, the association between low birthweight for gestational age and increased risk of IHD was robust to the statistical control for childhood and adulthood socioeconomic conditions. This association is consistent with Barker's hypothesis and likely reflects the long-term influence of impaired fetal growth that can affect health in later life through latent biological pathways (189).

No study has been found to compare the finding concerning the persistence of the birthweight-IHD association between generations. Given the substantial improvements in maternal nutrition and standard of living over time (190), the stability of the association implies a change in the main determinants of the distribution of birthweight across generations (137,191). It can be speculated that the benefit of improved maternal nutrition on the fetal development of G2 subjects was neutralized by a detrimental effect of rising prevalence of maternal smoking. Another related issue is the possibly higher chance of surviving into adulthood among the growth restricted neonates in G2, which could underestimate the exposure effect in G1 relative to G2.

It is important to bear in mind that an increase or decrease of health inequalities over time may depend on the underlying scale used to measure inequalities: the absolute or

relative scale (192). Which of the two scales is more appropriate for tracking inequalities over different time periods can be debated. Although the relative measure might be of more analytic interest, the absolute measure is considered more crucial when it comes to assessing public health impact or achievements of welfare policies. An influential editorial recently published by Mackenbach (193) attributed the apparent policy failure to reduce health inequalities in advanced welfare societies to the "obsessive" research focus on relative inequalities and called for switching the focus to the absolute scale. A major argument was that as the overall rate of mortality or disease outcomes declines, the absolute differences between social groups tend to become narrower while relative differences still appear stable or even larger. However, an exclusive focus on absolute health inequalities may invoke the danger of diverting the attention away from the most vulnerable groups. Moreover, regardless of the scale on which health inequalities are measured, these should be preventable as they are mainly a function of social inequalities and thus are unfair and avoidable. Failure to reduce relative health inequalities, therefore, should be acknowledged as a failure of policy action and research (194), even when the absolute health inequalities are low.

6.2.4 Transgenerational epigenetic inheritance or effect?

The current thesis generated novel evidence on the transgenerational influences on socioeconomic and disease phenotypes by linking grandparental and parental exposures to adult offspring's SEP and risk of IHD. The findings that fathers' preterm birth, disadvantaged SEP of grandparents as well as the young and advanced maternal ages of grandmothers increased the risk of IHD in adult grandchildren (Study IV) are unique discoveries of the current thesis. While the observed association between grandparental and grandchildren SEPs is consistent with the existing literature (91,195,196), no study was found to compare the association between father's preterm birth and offspring's lower SEP in adulthood (Study III).

The thesis further examined whether the estimated transgenerational associations were robust to the control for paternal or maternal socioeconomic circumstances (Studies III and IV) as well as history of IHD (Study IV). It was found that the associations with IHD were unaffected by the adjustments for parents' socioeconomic conditions and IHD. This was opposite to the association between grandparental and grandchildren SEPs that tended to disappear with the statistical adjustment for parents' socioeconomic conditions. The transgenerational associations with IHD were not altered even when the same exposure (i.e., parental SEP/maternal age/own preterm birth) in the index generation was further taken into account.

Little is known about the transgenerational processes through which perturbations during critical periods of development in ancestors transmit disease risks to future generations without the presence of the exposure in the latter. A major challenge in identifying the precise mechanisms is to tease out genetic, epigenetic, and

environmental influences which may operate simultaneously and interact with each other. Although disease phenotypes can be inherited genetically, genetics seems less likely to be responsible for the transgenerational determination of phenotypes resulting from environmental exposures since a genetic mechanism would generally necessitate continued presence of the exposure in subsequent generations (197). What we know from animal experiments is that exposures to adverse environmental conditions may establish a transmissible epigenetic memory that can travel through several generations down the line (121,123,124,198). However, the relevance of this evidence for humans is yet to be clearly established. Epigenetic processes, such as DNA methylations, histone modifications, and changes in noncoding small RNAs, are presumably responsible for the fetal or developmental programming of disease phenotypes across multiple generations (45,119,199).

Alterations in the germline in response to nutritional and hormonal manipulations, as shown in mammalian models (121,123), have generated a widespread interest in the hypothesis of transgenerational epigenetic inheritance. According to this hypothesis, the process of transmitting epigenetic information across multiple generations is regulated by the germline (122,197,200). Using mice models, Franklin et al. (123), for instance, demonstrated that exposure to chronic stress due to maternal separation from postnatal day 1 to 14 subsequently altered the behavioral responses and the DNA methylation profile of the germ cells in adult mice and these alterations were maintained in the next generation offspring. In another example, Cropley et al. (121), demonstrated that an experimental exposure of the Agouti mice to dietary stimulus induced an epigenetic phenotype that affected five successive generations via the germline independently of the underlying genotype.

Whether the associations between G0/G1 exposures and G2's IHD in adult life, as found in the current thesis, represent true transgenerational epigenetic inheritance remains unresolved. If an adverse environmental exposure of grandparents (G0) affects the developing germline of the parents (G1) when in-utero, the germline of the grandchildren (G2) is also simultaneously exposed (122). This implies that the disease phenotypes must be studied in the great grandchildren (G3) to find mechanistic evidence for transgenerational inheritance along the maternal line, so that the direct effect of the exposure on the somatic and germ cells of G1 embryo and on the G2 germline can be confidently excluded. Along the paternal line, however, the observation of phenotypic outcomes in G2 is enough to ascertain transgenerational inheritance if the exposure alters the germline of G1 postnatally, e.g., during the prepuberty period (122,197).

A key advantage of assessing transgenerational inheritance along the paternal line is the elimination of confounding originating from the maternal environment, leaving the germline as the most plausible route of disease transmission (201). Although I was able to evaluate the associations along the paternal line, true transgenerational inheritance

cannot be confirmed since the examined grandparental and parental characteristics primarily reflect in-utero exposures and are more likely to dysregulate the germline prenatally than in postnatal life. Therefore, instead of interpreting the observed transgenerational associations as transgenerational epigenetic inheritance, it might be more appropriate to interpret them as intergenerational epigenetic inheritance (200) or "transgenerational epigenetic effects" (202). The latter does not make any assumption about the involvement of gametes or any underlying mechanisms and has been suggested to refer to any nongenetic determination of phenotype in successive generations (202).

Parents can be the asymptomatic carriers of altered epigenetic states, meaning that the transgenerational transmission of phenotypes can skip generations. As experimental studies suggest, parents can silently pass on the epigenetic changes or phenotypical traits to the offspring without themselves showing any abnormal physiology or disease phenotype (123,124). The transgenerational associations in the current thesis appear to support the idea of asymptomatic transmission since neither preterm birth nor maternal age at birth showed any association with adult IHD in the parental and offspring generations, whereas paternal preterm birth and grandmothers' advanced and younger ages at birth increased the risk of IHD in the offspring generation.

6.3 Methodological considerations

6.3.1 Selection bias and generalizability

By selection bias, epidemiologists usually refer to the bias arising from the procedure of selecting the study sample or the factors affecting the participation of the study subjects. In a new scholarly publication, Björk and colleagues (203) criticized the traditional definitions of selection bias for being too restrictive and ignoring the selection processes occurring on a population level. Selection bias may operate in the general population or the source population irrespective of the study-specific decisions as a result of, for instance, mortality, disease occurrence, and migration. Population level selection can exist even when the study sample is perfectly representative of the source population and hamper the validity of the results through selection into the exposure or altering the composition of the underlying population (203,204). The depletion of the susceptibles over time (205) serves an example of population-level selection in the context of the current thesis. Because children born to socioeconomically poor families and/or having impaired fetal growth might have experienced relatively high infant mortality, they were less likely to be included in the study cohorts as adults, which have possibly attenuated the observed estimates of parental SEP and fetal growth on the outcomes towards the null.

Non-response in surveys is a common source of selection bias. Although the response rate in the Stockholm Public Health Cohort survey was relatively high (62%) compared

to similar other surveys, the demographic and socioeconomic characteristics such as age, gender, country of origin, and social class were found to be associated with non-participation in the survey. It was shown that the men, young, immigrants, and lower socioeconomic groups were under-represented in the cohort when compared to the total population of the Stockholm County (139). I observed that the same factors also predicted internal missing in our data. While the systematic internal missing was carefully dealt with using multiple imputation, potential selection bias due to systematic non-response remains a concern. Given a somewhat lower participation of disadvantaged socioeconomic groups who are more likely to come from disadvantaged families, the potential selection bias is expected to underestimate the association between disadvantaged parental SEP and CVD mortality in Study I. Moreover, as the study cohort is composed of an urban population, generalizing the magnitude of the association to the national Swedish population is uncertain, although the direction of the association is more likely to generalize to other settings.

The G1 members of the UBCoS Multigen, who were born in the Uppsala Hospital, are considered to be broadly representative of all Swedish births born in the same period with respect to infant mortality and fertility rates (145). In some of the presented analyses, G2 study subjects were further restricted to the Uppsala region due to a lack of obstetric data of the children moving out of Uppsala. If staying in vs moving out of Uppsala were associated with both the early life exposures and adult outcomes studied, the concerned results would suffer from selection bias. However, sensitivity analysis, as shown in Study IV, suggests that although the analytic subjects had a slightly lower socioeconomic profile compared to the excluded subjects, the incidence rate of the IHD outcome did not differ between the two groups. Such unifactorial selection involving the exposure but not the outcome can compromise external validity when the exposure effects differ across population groups (203).

However, thanks to the generally high coverage and long history of the Swedish registers, the study subjects were followed up over long periods of time with little or no losses to follow, increasing the generalizability of the findings. Given that some of the estimated associations are fairly in line with other studies as well as consistent across G1 and G2, at least some findings can be potentially extrapolated to other contexts.

6.3.2 Confounding

Confounders, i.e., the common causes shared by both the exposure and the outcome in an association, are a major source of threat to internal validity and causal inference of the results obtained from any observational study. Compared to studies examining adult risk factors of diseases, an advantage of life course studies is the long induction period separating the exposures and the manifestation of disease, rendering such studies relatively less susceptible to confounding due to adult risk factors that are more likely to act as mediators than confounders. However, confounding due to parental

social, lifestyle, health, and genetic factors, if not appropriately accounted for, may overestimate or underestimate the effect sizes of early life exposures.

In the current thesis, I controlled for a range of social and obstetric parameters thought to be confounding the associations between early life exposures and outcomes in adult life. Yet, biases due to unknown or unmeasured confounders and residual confounding cannot be ruled out. As a case in point, the association between birthweight for gestational age and incident IHD was controlled for a broad set of birth characteristics but was still likely to be confounded by maternal lifestyle and genetic risk factors potentially affecting both birthweight and IHD. Interestingly, the sensitivity analysis linking offspring birthweight to the IHD of mothers and fathers separately did not suggest the presence of strong genetic confounding (Study IV).

Apart from the assumption that there is no unmeasured confounder affecting the exposure-outcome association, any causal mediation analysis relies on a set of additional assumptions about confounding that are to be met for a causal interpretation of the direct and indirect effects: no unmeasured confounder of the mediator-outcome association; no unmeasured confounder of the exposure-mediator association; and no intermediate confounder i.e., the mediator-outcome confounder which is a descendent of the exposure (134).

The IOW-based mediation analysis used in Studies I and IV rests on the no-confounding assumptions stated above and was carried out with careful attention paid to them. Past mediation studies based on the classical Baron and Kenny approach (206) have mainly focused on the exposure-outcome and exposure-mediator confounders, whereas the mediator-outcome confounders and the intermediate confounders have not been sufficiently emphasized. When assessing the mediating role of adult SEP in the association between parental SEP and adult CVD mortality (Study I), for instance, adjusting for common causes shared by parental SEP and CVD mortality would provide an unbiased estimate of the total effect while ignoring the confounders affecting both adult SEP and CVD mortality (e.g., gender and marital status) would bias the direct and indirect effects.

While the confounders of mediator-outcome association, if accurately measured, can be easily dealt with by statistical adjustments in standard regression models, the complication arises when the mediator-outcome association is confounded by a factor which itself is influenced by the exposure (i.e., the confounder is a mediator). In such a scenario which is very common in life course research (43), neither the Baron and Kenny framework nor Pearl's counterfactual mediation formula is able to yield valid mediation parameters (134,207). When isolating the indirect pathway via a single mediator, other mediators can act as intermediate confounders. An advantage of the weight-based IOW mediation analysis utilized in this thesis is the use of multiple mediators altogether, which renders the analysis less subject to, albeit not completely

free from, intermediate confounding. For the same reason, the estimated mediation parameters are also robust to the common causes of two or more mediators (208). Moreover, the IOW analysis is not bothered by the presence of exposure-mediator and mediator-mediator interactions which would bias the direct and indirect effects in the context of conventional mediation framework, as shown in Study I.

6.3.3 Measurement error

Erroneous measurement of variables may compromise the internal validity of study findings by generating information bias which arises mainly from misclassification of the exposures, mediators, and outcomes, e.g., the classification of the exposed as unexposed and vice versa (209). Misclassification can be either differential or nondifferential and is of particular concern when it is differential, i.e. related to both the exposure and the outcome. Since parental SEP in Study I was reported by the adult children, the measure was susceptible to misclassification due to recall bias which may result from systematic differences in the way participants remembered their parents' occupation. Thus, if individuals with disadvantaged parental SEP were less accurate in their report than those with advantaged parental SEP, this would lead to differential misclassification biasing the true total effect of parental SEP on CVD mortality towards the null. However, in Studies II-IV which are based on the UBCoS Multigen, all SEP indicators including parental SEP were mainly derived from censuses and registers, and were measured before the development of the studied health outcomes, thereby circumventing the issue of recall bias.

The subjective assessment of the mediators in Study I might yield measurement errors, especially in the behavioral risk factors such as smoking and risky alcohol drinking which are generally prone to be underreported due to the so-called "social desirability" bias. While the misclassification of binary mediators, even if nondifferential, can lead to a dilution of the natural indirect effect (bias toward the null) (210,211), the direction of bias due to misclassification of multi-categorical mediators is difficult to discern (212). The cross-sectional assessment of the mediators may further underestimate the magnitude of the mediated effect whereas the magnitude of mediation by repeated measures of mediators was previously demonstrated to be larger compared to cross-sectional mediators (213). However, the social mediators in this thesis, such as education and occupation, are relatively stable over time and their contribution to explaining the early life socioeconomic inequalities in mortality is less likely to be underestimated than behavioral mediators.

An innovation of Study II, in relation to past studies of social mobility, is the model-based measure of longitudinal socioeconomic trajectories. This has enabled visualization of mutually exclusive latent classes that clearly reflect the movement or stability of individuals sharing a common socioeconomic track over the life course. A downside of this modeling approach is that it does not allow individual-level random

variation within a latent class (214). Violation of this assumption of homogeneity may result in misclassification of the socioeconomic trajectories and bias the class-specific regression estimates.

The outcome IHD in Study IV was a combination of both hospitalized cases and deaths derived from the Swedish inpatient register and cause of death register, respectively. The Uppsala region was the first to initiate the inpatient register in Sweden, allowing the study subjects to be followed up from as early as 1964. However, the coverage of the inpatient register increased over time and was not complete until 1987 (143). The low coverage in the early years of follow up might have led to some false negative cases of IHD, especially in G1.

For a valid assessment of potential generational changes in the associations linking early life exposures to adult socioeconomic and health outcomes (Studies III and IV), the study variables in both G1 and G2 were defined as consistently as possible. Thanks to the UBCoS Multigen, we have had comparable obstetric, socioeconomic, and health measures across two adult generations at our disposal, which has offered this thesis a unique advantage to make historical comparisons of the associations of interest.

A major challenge in studying the trends in health inequalities over time is that the definitions and relevance of the measures themselves might change over time. This is particularly problematic when it comes to defining social class positions based on individual occupation. The occupational structure in Sweden has transitioned from the goods-producing industrial sector to the service-producing sector in the 1960s, accompanied by a shrink of manual occupations and the expansion of non-manual and semi-manual occupations (215). The relative social standing of a father employed as an agricultural laborer in the early 20th century, for instance, may not be the same as that of a father with the same occupation in the 1960s. I applied the official Swedish socio-economic classification system (149) to both generations to define the occupational categories which were further collapsed into three broad socioeconomic groups: high, medium, and low. I believe that despite changes in the occupational structure, these broad categories of SEP were able to meaningfully evaluate the cross-cohort differences in the effects of SEP.

7 CONCLUSIONS

The findings of the thesis suggest that health inequalities emanating from early life socioeconomic disadvantages were mediated to a large extent by adult socioeconomic circumstances including education, occupation, or income, which are amenable to policy interventions. In a similar vein, the thesis underscores the importance of upward mobility as a powerful social process to compensate the excess risk of adult mortality associated with a poorer socioeconomic start in early life. Accordingly, interventions to improve living conditions of the children from socioeconomically disadvantaged families are expected to improve health outcomes over the life course.

The findings of the thesis further suggest that low SEP of grandparents and fathers' preterm birth were associated with poorer socioeconomic achievement and higher risk of incident IHD among the adult grandchildren. Grandmothers with younger or older ages at the time of parents' birth were more likely to have grandchildren with elevated risk of IHD compared to grandmothers aged 25-29 years at parental birth. The precise mechanisms that brought about these transgenerational associations are not yet known but may involve germline-mediated epigenetic inheritance as a candidate mechanism, which is something that should be explored in future studies.

Overall, the thesis highlights the importance of some social and biological disadvantages in early life in shaping future socioeconomic and health outcomes not only over the life course but also over historical time and across generations. Given that inequalities in socioeconomic and disease phenotypes can be non-genetically influenced by ancestral experience of social disadvantages, studying health inequalities within the life course of a single generation would be insufficient to understand their origins and development and to inform appropriate policies for prevention on a population level.

7.1 Implications for policy

The findings of the thesis indicate that interventions targeted to improving adult socioeconomic conditions has the potential to reduce health inequalities generated by parental socioeconomic background over a generation. Accordingly, promoting upward social mobility can be an effective strategy for narrowing the health gaps among people with different socioeconomic backgrounds. However, the stubborn presence of the inequalities originating in early life in both older and younger generations, although the latter grew up in a more equitable social structure, calls for investigating temporal trends of the causal processes and corresponding adjustments of existing policies.

On the other hand, the association between fetal growth and incident IHD was not mediated by adult socioeconomic conditions. Optimal interventions to prevent IHD attributable to impaired fetal growth should start well before the moment of conception. Such interventions should be designed to promote healthy lifestyles, nutrition, and health of all future mothers to facilitate optimal fetal growth of their

future babies. However, prevention of intrauterine growth retardation as a means of preventing diseases in adulthood might be a challenging pursuit. Research identifying the compositional changes of the determinants of fetal growth over time would be worthwhile for informing appropriate policy interventions.

The transgenerational association linking grandparental SEP and the SEP of grandchildren was explained by paternal/maternal socioeconomic characteristics, suggesting opportunities for interventions in the middle generation to interrupt the transfer of socioeconomic disadvantages across generations. Contrarily, the transgenerational associations found with IHD were explained neither by parental SEP nor by the index generation's early life characteristics. Interventions aiming to break the transgenerational cycle of disease transmissions need to go beyond the current 2-generation approach that has a joint focus on the vulnerable children and their parents (216). A promising new direction can be the recently proposed 3-generation intervention approach which adopts a forward looking and universalistic strategy and aims to promote health of both current and future generations (217). Acknowledging the importance of life course trajectories, the 3-generation approach suggests extending policies beyond childhood through adolescence and young adulthood when the middle generation themselves are expected to parent the next generation.

7.2 Implications for future research

Results in this thesis show that influence of family socioeconomic background on future educational and occupational achievement has become weaker in the younger generation in Sweden (Study III). Yet, such reduction of social inequalities has not necessarily translated into a reduction of health inequalities originating in early life (Study IV). The persistence of IHD inequalities by early life socioeconomic disadvantages across different historical contexts warrants increased research efforts for continued monitoring of the underlying causal processes, and adjustments of policies aiming to tackle health inequalities. At the same time, it will be worthwhile to systematically use both the relative and absolute scales in future research, thereby illustrating a complete picture of the changes in health inequalities over time.

For a comprehensive understanding of the underlying mechanisms, future research ought to consider a wider range of mediators operating across the life course. From a policy point of view, it would be of interest to estimate the relative strengths of individual mediating factors, although this task is methodologically daunting. Because the mediators typically affect each other, decomposing mediator-specific effects into their total indirect effect is currently beyond the capacity of available mediation techniques, and thus requires further methodological innovations (208).

To better understand the reasons for the stability of the association between reduced fetal growth and the incidence of IHD across generations, further research is needed to track the driving forces of the distribution of birthweight over time. It can be

hypothesized that the associations of birthweight with adult disease outcomes in more recent times are driven by an increased prevalence of maternal overnutrition, high pre-pregnancy BMI, excessive gestational weight gain, and gestational diabetes.

Regarding the transgenerational associations, an important extension would be to replicate the findings in larger multigenerational cohorts in other settings and to test the transgenerational epigenetic inheritance hypothesis in the fourth generation (G3) and beyond. Experiments on mammals have demonstrated that transgenerational inheritance of disease phenotypes can occur in a sex specific manner, possibly due to differences in X and Y chromosomes between the sexes (45). The transgenerational analysis in this thesis lacked adequate statistical power to explore the sex stratified results, warranting further investigations to provide insights into the sex specific pathways. Given that it is plausible for environmental exposures to alter the germ cells both during fetal life and at the slow growth period (which is a critical period of sperm development around mid-childhood), it would be interesting to explore the sensitive period when an exposure triggers stronger transgenerational effect on descendants' health.

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