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SOCIOECONOMIC INFLUENCES ON LATE-LIFE HEALTH AND MORTALITY: EXPLORING GENETIC AND ENVIRONMENTAL INTERPLAY

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Socioeconomic influences on late-life health and mortality: Exploring genetic and environmental interplay

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Till Maja

”Varje steg jag tar går jag i förfädernas liv”

-Varje löv är ett öga, Sara Lidman

ABSTRACT

The objective of this thesis was to increase the understanding of socioeconomic differences in health and mortality in old age - in a genetically informative setting. Data from the Swedish Twin Registry (STR), different statistical methods, and family-based designs were applied to investigate socioeconomic circumstances over the life-course and how these affect cognitive function, frailty, and mortality in late life.

In **Study I**, we studied the effect of rearing social class on late-life cognitive ability. An association between rearing social class and cognitive ability at age 65 was observed, but there was no effect on cognitive change. After controlling for familial influences, the association between rearing social class and late-life cognitive ability no longer remained and could instead be attributed to genetic influences.

In **Study II**, we used a classical twin design to investigate if childhood and attained socioeconomic indicators moderates the effects of genes and environment on late-life cognitive abilities. Cognitive ability was measured via four cognitive tests and a general ability score. Estimates of intercepts from growth models centered at age 75 and two linear slopes (before and after age 75) were utilized in the moderation models. The results from the moderator models for the four socioeconomic indicators showed similar patterns for the intercept. For cognitive change, moderation differed depending on cognitive test and socioeconomic indicator.

In **Study III**, we investigated mortality inequalities by comparing preventable and non-preventable mortality using a survival model. Familial confounding was analyzed using a co-twin control method. We observed a social gradient for mortality for the adult socioeconomic measures, which was stronger for preventable mortality than for non-preventable mortality. Adjustments for familial confounding did not change the observed associations between the attained socioeconomic indicators and mortality. However, the associations between rearing social class and mortality did not remain in the co-twin control analyses of the reared apart twins.

In **Study IV**, we explored the influence of attained socioeconomic indicators on frailty and mortality in men and women. Additional co-twin control analyses indicated familial confounding. Frailty was operationalized as the Frailty Index. There were robust sex differences in frailty. Socioeconomic influences on frailty were stronger for women than for men. In the co-twin control analyses, the effect remained the same for men, but for women the within-pair effect was strongly attenuated. No differences could be observed dependent on zygosity. The socioeconomic gradient in the relationship between frailty and mortality was stronger in men, but was not influenced by familial factors.

SAMMANFATTNING

Syftet med denna avhandling var att öka förståelsen för socioekonomiska skillnader i hälsa och dödlighet sent i livet - med hjälp av genetiskt informativ data. Det svenska tvillingregistret (STR), olika statistiska metoder och familjebaserade analyser användes för att undersöka socioekonomiska influenser under livsloppet och hur dessa relaterar till kognitiv funktion, skörhet och dödlighet sent i livet.

I **studie I** studerade vi effekten av socioekonomisk uppväxtmiljö på kognition sent i livet, med hjälp av säruppfostrade tvillingpar. Vi hittade en koppling mellan social klass i barndomen och kognitiv förmåga vid 65 års ålder, men inte på kognitiv förändring över tid. Efter att ha kontrollerat för delade faktorer hos tvillingparen, fanns inget återstående samband mellan social klass under uppväxten och kognitiva förmågor. Det tidigare observerade sambandet kunde istället härledas till genetiska influenser.

I **studie II** använde vi tvillinganalyser för att undersöka om socioekonomiska förhållanden under uppväxten samt senare i livet, modererar effekten av gener och miljö på kognitiva förmågor sent i livet. Kognitiv förmåga mättes utifrån fyra kognitiva test och ett mått på generell kognitiv förmåga. I modellerna undersöktes både kognition vid 75 års ålder samt kognitiv förändring. Vid 75 års ålder visade resultaten från moderatormodellerna likande mönster för de fyra socioekonomiska indikatorerna. För kognitiv förändring skilde sig moderationen åt, mellan de olika kognitiva testen och även de socioekonomiska indikatorerna.

I **studie III** undersökte vi socioekonomiska skillnader i dödlighet genom att jämföra förebyggbar och icke-förebyggbar dödlighet med hjälp av en överlevnadsmodell, betydelsen av familjära influenser analyserades med hjälp av en s.k. co-twin control. Vi observerade en social gradient för dödlighet som var mest framträdande för socioekonomiska förhållanden i vuxen ålder och starkare för förebyggbar dödlighet än för icke-förebyggbar dödlighet. Justeringar för familjära influenser förändrade inte de observerade sambanden mellan utbildning, social klass eller social mobilitet och dödlighet. Dock kvarstod inte sambandet mellan social klass i barndomen och dödlighet.

I **studie IV** undersökte vi effekten av egen socioekonomisk position på skörhet (s.k. frailty) och dödlighet hos män och kvinnor. Tvillinganalyser användes för att undersöka influenser av genetik och delad miljö. Resultaten visade på robusta könsskillnader i skörhet. Socioekonomisk påverkan på skörhet var starkare bland kvinnor än bland män. I tvillinganalyserna förblev effekten oförändrad bland männen, men bland kvinnorna dämpades effekten betydligt. Inga skillnader kunde observeras beroende på zygositet. Den socioekonomiska gradienten i förhållandet mellan skörhet och dödlighet var starkare hos män, men påverkades inte av familjära faktorer.

LIST OF SCIENTIFIC PAPERS

I. **Ericsson**, **M**., Lundholm, C., Fors, S., Dahl Aslan, A. K., Zavala, C., Reynolds, C. A., & Pedersen, N. L. (2017). Childhood social class and cognitive aging in the Swedish Adoption/Twin Study of Aging. *Proceedings of the National Academy of Sciences*, 114(27), 7001-7006. doi:10.1073/pnas.1620603114

II. **Ericsson**, **M**., Kuja-Halkola, R., Dahl Aslan, A. K., Fors, S., Zavala, C., Reynolds, C. A., & Pedersen, N. L. Socioeconomic status as a moderator of late-life cognitive abilities: Exploring childhood and attained socioeconomic circumstances.
Manuscript

III. **Ericsson**, **M**., Pedersen, N. L., Johansson, A. L. V., Fors, S., & Dahl Aslan, A. K. (2019). Life-course socioeconomic differences and social mobility in preventable and non-preventable mortality: a study of Swedish twins. *Int J Epidemiol.* doi:10.1093/ije/dyz042

IV. **Ericsson**, **M**., Pedersen, N. L., Fors, S., Kuja-Halkola, R., Mosing, M., Li, X., Jylhävä, J., and Dahl Aslan, A. K. Frailty and mortality: Investigating sex differences and socioeconomic influences using same-sex and opposite-sex Swedish twins
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CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of daily living
AIC	Akaike information criterion
BIC	Bayesian information criterion
CDR	The Swedish Cause of Death Register
CI	Confidence interval
DF	Degrees of freedom
FI	Frailty Index
GENDER	Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behavior and Health among the Elderly
GOS	GENDER, OCTO-Twin, and SATSA
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
ISCED	International Standard Classification of Education
MZ	Monozygotic
OCTO-Twin	The Origin of Variances in the Oldest-Old: Octogenarian Twins
OSDZ	Opposite-sex dizygotic
SALT	The Screening Across the Lifespan Twin Study
SATSA	The Swedish Adoption/Twin Study of Aging
SE	Standard error
SEI	Swedish Socioeconomic Index
SES	Socioeconomic status
SSDZ	Same-sex dizygotic
STR	Swedish Twin Registry

1 INTRODUCTION

Aging is a life-long process, which includes both gains and declines in abilities over the life span. The early part of life is normally characterized by growing, development and learning, while the later part of life is a period of decline in abilities. Late life may also be influenced by a higher disease incidence and eventually also increased vulnerability and death. However, late life is a heterogeneous period with great variability in health, function, and disability – between individuals as well as between social groups.

Aging research is of great importance and interest to society today, where population aging has rapidly increased over the last decades and a greater proportion survives up to the highest ages, a trend that is expected to continue. These achievements can be attributed to the medical advances that have occurred over the past century but also to increased prosperity [3]. Extended survival also entails that more people will be of advanced age for longer periods of time. This leads to higher prevalence of age-related diseases and in turn to increased need for care and support, although these consequences are suggested to be mitigated to some extent by great advances in treatment strategies and care.

Still, health advances leading to a longer life span and healthy old age are not attainable for all [4-6]. Why people fare so differently, seems to be more structural than random. There are clear between-country differences, and the great improvements in health and life-expectancy are (as expected) more prominent in higher income countries and in societies with greater equality and more developed welfare systems [7-9]. However, differences can also be observed within countries. Differences in health emerge across the social strata, where lower socioeconomic groups have more adverse health and shorter life spans compared to higher socioeconomic groups, (be it education, social class or income). These health inequities have been observed also in countries with a rather generous well-fare state and comparably equal distribution of health care, such as Sweden [10-12].

The notion that people age differently in terms of health, function, and longevity has repeatedly been the target for epidemiological and medical aging research. Aging research is not only important, but also interesting and rewarding, as old age may provide answers to how factors over the life span influences health. Understanding late-life aging from a life-course perspective also entails a challenging perspective, as there are many contributing factors that may interact.

1.1 HEALTH IN LATE LIFE

Studying health in old age is complex and entails numerous aspects of health from the biological perspective on the cell-level to psychological and social factors and the organization of health care. In this thesis, the focus is on the individual level and specifically on cognitive aging (*Study I* and *II*), frailty (*Study IV*), and mortality (*Study III* and *IV*). These aspects may together reflect a comprehensive illustration of late-life health. There is also previous research indicating clear health inequalities in all these outcomes.

1.1.1 Cognitive aging

Cognitive ability is a concept that describes the mental capacity to understand, process, and store information and knowledge [13]. It can be defined from a variety of specific functions, which are subsequently subordinated to different overall domains that jointly can be described as human intelligence. Based on tests intended to measure specific cognitive abilities, it is possible to study the cognitive function of individuals, both for medical and research purposes [14]. The four cognitive domains studied in this thesis are verbal ability, perceptual speed, memory, spatial/fluid ability, as well as general cognitive ability. The cognitive domains vary in their sensitivity to genetic and environmental influences, and the development of these domains and the pattern of change differs across the life course. All cognitive abilities increase from childhood into young adulthood or into middle age, but the peak as well as the breakpoints when the abilities starts to decline varies between the cognitive domains [15].

Verbal or crystallized ability, which is the capacity to use verbal skills, knowledge, and experience, is measured through the vocabulary and general knowledge tasks in this thesis. It continues to develop throughout adulthood and is stable up to around age 70 [16-18]. Perceptual speed or processing speed is the rate at which a cognitive task can be performed. The decline in this domain is rather steep in old age. It is also suggested that processing speed influences ability and decline in other cognitive domains [19, 14]. Memory refers to the ability to recall and hold information in mind, as well as to use it. Memory can roughly be divided into short and long-term memory [14]. While short-term memory is considered to be rather stable into very late life, long-term memory such as episodic memory decline more rapidly. Spatial or fluid ability is the capacity to think logically and solve problems in novel situations and to estimate and interpret spatial relationships. Decline in this domain starts in early mid-life [20, 14]. Age is, by comparison to other factors, the strongest predictor for cognitive decline [19].

Genes have also been shown to account for the largest part of the variation in cognition [21]. Genetic influences thus affects cognitive development over the life course, but not exclusively - both shared and person-specific environmental factors have been shown to influence cognition both directly and in interplay with genetic propensities. To fully understand within and between-person differences and the progression of decline in cognition there is a need for longitudinal data. With cognitive assessments from childhood up to late life, researchers using data from The Scottish Mental Surveys have showed that individual differences in cognitive abilities are partly stable over the life span, but also that environmental impacts are of great importance [22, 23]. Early cognitive performance has been found to vary as a function of parental socioeconomic factors where lower socioeconomic status was associated with lower cognitive performance [24, 25]. Adoption studies have indicated the importance for rearing environment by showing that adoption to a higher SES family positively affects the IQ of the adoptees, when compared to non-adopted biological siblings [26, 27].

There is evidence to suggest that genetic influences on cognition differ depending on socioeconomic level. Genetic influences are assumed to explain more of the variance at higher SES levels, while the environment appears to have a greater influence under more adverse circumstances [28, 29]. However, these interactions between cognitive abilities and socioeconomic status have mainly been observed in very deprived environments where for example access to education is low [2]. In fact, many other studies have failed to replicate these findings [30-32]. Others studies have observed an opposite relationship, especially regarding cognition in adulthood [33, 34]. These studies have mainly been focused on the moderating effects of childhood SES on cognitive ability using cross-sectional data.

How and what environmental factors that influence cognitive change can help us to understand differences in cognitive aging. During the 20th century there have been considerable IQ gains, where later born birth cohorts have had higher IQ than the previous ones, commonly referred to as the "Flynn effect" [35], indicating that environmental factors have a considerable impact on cognition. These observed birth cohort effects have also been replicated in the older population, where differences were found both on the mean level and on change over time. However, differences were also observed across educational levels, where lower educated groups had a smaller increase than more highly educated groups [36].

Education is also the environmental factor most frequently studied in order to understand differences in cognitive abilities [37-40]. It may be of importance both for onset and rate of cognitive decline [41]. But the results are not consistent, where others have found that there is no support for education to affect cognitive change [42]. Educational factors have also been suggested to be an important mediator between adverse rearing circumstances and cognitive performance in later life [43, 44]. However, childhood cognitive ability may also predict educational performance [45]. Also other socioeconomic circumstances have been studied in order to understand differences in late-life cognitive abilities. Higher social class over the life-course has in several studies been found to be positively associated with cognitive performance in late life [46-48]. However, few studies have examined longitudinal cognitive change and SES while taking into account the genetic and environmental components

1.1.2 Frailty

The concept of frailty reflects a state of vulnerability owing to multiple health failures and poor homeostasis. Frailty is largely a geriatric condition, but not exclusively and it commonly precedes death [49]. In fact, it has been found to be a more precise predictor of mortality than chronological age [50]. There are numerous frailty measures, used both clinically and for research purposes. This complicates the comparability between studies, and thus ultimately also the understanding of the condition. As there is no gold standard or consensus definition of frailty it is also difficult to evaluate the different instruments [51]. The choice of measure subsequently depends on the available data and what opportunities for testing there are [52]. The frailty Index [53] is one of the more commonly used instruments. It is constructed by a number of clinical deficits based on, for example, diseases and abilities in the activities of daily living (ADL).

A social gradient has been observed in frailty incidence and severity [54]. This gradient has been observed repeatedly, whether in terms of social class, education, or income, where lower SES levels have been linked to higher risk of developing frailty [55-57]. In a study of Australian women, the authors observed that late-life SES was more strongly associated to frailty compared to SES earlier in life [58]. A Finnish study found no evidence of early-life SES on risk of frailty. However, they did observe that early life programming, measured as low birth weight, was associated to an increased risk of developing frailty [56].

Women have a higher risk of developing frailty than men and also with differences in severity and manifestation [57]. However, although women are more likely to be frail than men, they still have a better life-expectancy [59, 60]. These contradictory sex differences in the relationship between frailty and mortality may be understood from the male-female health-survival paradox, which states that women have worse health but yet live longer [61]. Other than environmental influences on frailty there also seems to be a genetic component [62, 63].

1.1.3 Mortality

Mortality is an indicator of health, which independently from at what age it occurs will reflect a severe health aggravation. Although it may be imprecise as a specific health measure, it robustly reflects health. Mortality is also an indicator that has been documented since very far back, and in Sweden there is a full coverage since 1960 at the individual level [64], which makes it a valuable estimate of health in the present context. Both age at death and cause of death may be informative in understanding mortality inequalities and how different environmental factors impacts health.

Adverse socioeconomic circumstances have repeatedly been shown to be associated to premature mortality and shorter life expectancy [65]. Unfavorable socioeconomic conditions in childhood have been shown to be associated with increased mortality in middle age [66]. In a study on Danish twin pairs, Madsen et al. [67] found that early life shared familial factors partly explained the observed association between level of education and mortality. Specifically, large differences in mortality have been observed between educational levels [68-70]. Occupational class differences in mortality follow the same pattern as for educational differences and have been found to be related to differences in mortality risk in both all cause and cause-specific mortality [71]. However, the socio-economic differences in mortality also differ with regards to cause of death [72].

Causes of death may be divided into preventable and non-preventable causes of death as an instrument to detect health inequalities. This idea was introduced by Phelan et al. [73]. Their hypothesis was that if there is a stronger social gradient in causes of death that are preventable compared to causes of death that are less preventable, this would be a strong indicator of socioeconomic influences on health and mortality. They also found support for this hypothesis in several studies based on US data [74, 73, 75]. The hypothesis has also been tested in other contexts, for example using European data, and has been further developed by

separating preventable causes of death into different types of preventability, such as due to health care interventions, injury prevention, and life-style factors [76]. Plug et al. [77] found that preventable mortality related to health care was associated to a higher degree of socioeconomic inequalities than other preventable causes of death. In a more recent study Mackenbach et al. [78] found that the mortality decline over time for highly educated groups was more rapid in preventable causes of death compared to non-preventable causes.

Genetic influence may also be part of explanation for longevity and mortality differences. There are different explanatory models for this, for example, that specific genes would be linked directly to life expectancy or that genes may be indirectly linked to certain diseases or mortality risk in other ways. Interestingly, the genetic influence on life expectancy has been shown to increase after the age of 60 [79].

1.2 HEALTH INEQUALITIES AND SOCIOECONOMIC INDICATORS

Studies of health inequalities are based on the fact that people with lower socioeconomic status on average have worse health than people who are in a better social position. This has been observed regardless of whether it concerns education or working life and could also mean that socioeconomic adversities in childhood may have long lasting effects.

1.2.1 Rearing socioeconomic circumstances

Childhood may be viewed as a sensitive period with regards to later life health and also to adult social trajectories [80]. A sensitive period refers to that specific periods of life, such as childhood, can be particularly sensitive to stressors. The fact that childhood is assumed to be such a period relates to children's development, which involves complicated developmental processes. If these are disturbed it could have long-lasting effects later in life, regarding health or perhaps socioeconomic opportunities. Factors in childhood that have been emphasized as stressors are for example rearing occupational class and education, and also circumstances closely related to these, such as family financial assets, living conditions, and neighborhood characteristics [81]. In studies of aging, rearing socioeconomic circumstances are commonly retrospectively self-reported which may entail recall bias, which depending on whether it is over- or under stated, can affect the observed effect to be inflated or attenuated.

Childhood SES is suggested to be associated to mortality mainly indirectly through adult SES and adverse health trajectories [82, 83] as well as life-style factors [84]. However, direct effects of childhood social class on cause-specific adult mortality have been observed [85].

1.2.2 Social class

Measures based on occupation are widely used and are expected to represent the social position in society which is perhaps most closely related to skills, income, and physical strain [81]. Occupation has even been suggested to be a better predictor of mortality inequalities than education as it may vary over the life-course. It may therefore more accurately reflect socioeconomic circumstances compared to education which is attained in early adulthood and then remains fixed over the life-course [85], especially in older cohorts where access to

higher education was limited. Social class is also strongly linked to several aspects of people's economic situation: income and financial security, both in the short and long term [86].

Occupational based measures can be classified in many different ways, which differs over time and also across nations [87]. However, although different classification systems are generally highly correlated with each other, attention must be put into the choice of classification, so that the measurement accurately corresponds to the hypothesis and not to lose precision in the analyzes [88]. How well a classification system reflects the occupational class may depend on nationality, birth cohort, and also on the purpose and research question. This implies challenges in applying and analyzing occupational indicators with a life-course approach, i.e. using measures from both childhood and adulthood. Social class can also reflect different aspects of the position in the labor market, it can partly reflect the degree of physical and mental strain but also represent the hierarchical position in the labor market. This can be particularly complicated in studies in older cohorts where there was both little variation in social class in a larger part of the population and at the same time substantial class differences, where also men and women had different access to the labor market. Social class can therefore be measured both at an individual level and at a household level (a household measure allows for both breadwinners to have the highest level of social class) where the former reflects an actual position within the labor market, but the household measure more closely reflects a measure of the social position [89].

1.2.3 Education

Education is one of the most commonly used socioeconomic indicators for studying health gradients [90, 91]. It is also a strong predictor for a large variety of health behaviors [92]. As education generally is attained and completed in childhood and early adulthood it can be assumed to be a robust indicator that additionally is related to parental assets [81]. Education can, for example, be assumed to reflect own resources, access to society, and social position. It is therefore also partly linked to other attained socioeconomic circumstances, such as social class. However, similar to social class, attained level of education is sensitive to context as the meaning and influence on health differs over time [93].

The educational system in Sweden has undergone major changes over the last century. In the 50’s and 60’s large educational reforms were implemented in Sweden, which granted access to higher education to larger part of the population [94]. These national educational changes in Sweden entailed increased educational levels in the population but also had other consequences, such as a generally higher incomes [95]

1.2.4 Social mobility

Social mobility reflects socioeconomic trajectories from social origin to adulthood and can be described as either intergenerational or intra-individual. The class of origin is the rearing socioeconomic circumstances which then can take different paths to the adult socioeconomic position: either upward, downward or remain stable [96]. The relationship between social mobility and health is closely interconnected. Health problems may affect social mobility

which can complicate the understanding and interpretation of the association between health and socioeconomic trajectories [97, 98]. It has also been shown that the intergenerational transmission of socioeconomic status, i.e. between parent and children, has both social and heritable origins [99].

1.2.5 Sex differences in health

There are many well-known sex differences in the incidence and prevalence of diseases and longevity, and these may be attributed to various biological and social mechanisms, such as tendency to seek medical care, lifestyle, and other underlying factors [3]. In late life, a puzzling pattern has been observed in which women have higher morbidity than men but at the same time they live longer. This is described as the male-female health-survival paradox [61]. This observation has also been made regarding the relationship between frailty and death where women are more frail than men but live longer [100]. How sex differences in health and mortality relate to socioeconomic conditions is less clear.

1.3 FAMILIAL INFLUENCES ON HEALTH INEQUALITIES

The influence of familial factors on health inequalities depicts a complex relationship. Familial influences refer to factors shared within families, both genetic and common factors such as intrauterine and rearing environment. There is substantial evidence that familial influences play a part both in health over the life span and for our socioeconomic opportunities [101, 102].

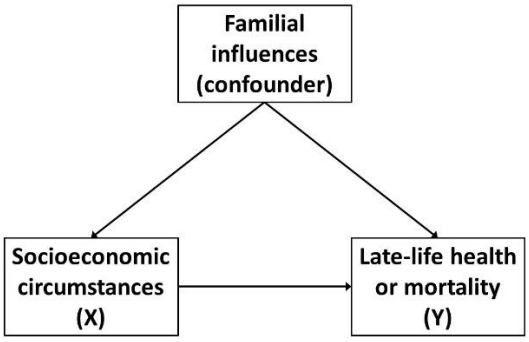


Figure 1. Diagram of genetic confounding

If we want to investigate if SES has a causal effect on health in late life, we have to make sure that the observed relationship is not confounded, for example by familial influences. A confounder is a variable that influence both the exposure (X) and the outcome (Y) and thereby causes a spurious association between X and Y. Familial factors would be a confounder if they affect both the attained level of SES and the specific health outcome under study. If we take familial factors into account and the effect of X on Y no longer remain, we can conclude that the relationship was in fact confounded by familial influences. However, if

the association remains we can assume a causal relationship between X and Y (under the assumption that there are no other confounding factors). This is a simplified explanation and there are several other factors that may violate these conclusions. The conceptual model behind this hypothesis can simplified be depicted as in Figure 1.

1.3.1 Genetic influences on socioeconomic circumstances

As aforementioned, socioeconomic circumstances have a genetic component. Education is both influenced by social position and opportunities as well as genetic predisposition [103]. Recent GWAS studies have also found evidence for gene involvement in the variance of educational attainment [104, 105]. Genetic influences are also important for socioeconomic trajectories. Social mobility has been shown to be directly influenced by genetic factors but also that the early environment is influenced by the parents' genetic influences for social opportunities [106]. This finding indicates an intricate interplay between environment and genes over the course of life –between genes, rearing circumstances, and other environmental influences.

The life-course perspective proposes that adverse life events and stressors affects health not only directly but that they may contribute to socioeconomic and health trajectories. Genetic propensities should also be considered in the understanding of how this may operate. Genetic influences can be assumed to contribute to early vulnerability and may influence and emphasize sensitivity to adverse events and stressors. However, genetic propensities may also interact with beneficial environmental influences and enhance favorable traits.

1.3.2 Gene x Environment correlation

Genetic factors, both independently and in correlation with the environment are important properties in understanding the variance in phenotypes (a phenotype refers to the combination and interaction of genetic and environmental factors that constitutes a trait). Using twin or adoption data may provide further understanding of the impact of genetic and environmental factors. The correlation between genes and environment can be explained through three major pathways: passive, reactive, and active. These reflect how the gene-environment correlation can be independent of the individual, i.e. genetic predisposition and rearing environment (passive), how the environment responds differently to different people (reactive), or how a person also contributes to their environment and actively seek environments that correlate with their genotype (active) [107].

1.3.3 Gene x Environment interaction

Gene-environment interaction is a construct to explain how genetic and environmental factors influence each other shaping behaviors and abilities [108]. Sometimes, it may be that it is not the disease itself that is heritable, but instead it is the sensitivity for disease risk factors, which is inherited. This means that people are affected differently by the same environmental exposure because of different genotypes. This interaction thus generates a phenotype based

on genetic susceptibility that can be enhanced or attenuated due to environmental influences [109]

1.4 THEORETICAL PERSPECTIVES

This thesis includes several theoretical perspectives. How to incorporate them in a meaningful way and to benefit from the wider perspective is one of the challenges in this project. The adopted aging perspective presumes aging as a life-long process, which therefore could include both gains and declines in abilities. Specifically, in this thesis the focus is to study how various socioeconomic and genetic factors influences the later part of life. The different life-stages are not separate but rather a process where subsequent stages are dependent on the preceding ones. This development is dependent on the unique influences of every individual's life-span but may also have similarities in social strata or other population groups, such as by sex or birth cohort.

1.4.1 Life-course epidemiology

The life course theory was developed in order to incorporate societal, social, psychological, and biological understanding into the research of human development [110]. In life-course epidemiology, the focus is shifted towards health and disease, and on the long-term effects of different exposures and pathways throughout the life span [111]. In this project the focus is to investigate if the influence of socioeconomic stratifications is independent of genetic predispositions regarding differences in health and mortality in late life. Applying a life-course perspective in examining the association between socioeconomic circumstances and late-life health outcomes will enable a better understanding of these exposures and pathways throughout the life-span. Adopting a comprehensive approach to explore these associations includes a focus on longitudinal pathways, specific exposure periods and also different types of mechanisms [111]

1.4.2 Direct and indirect health selection

To assume a life-course perspective in the understanding of socioeconomic influences on late-life health and survival, requires an interpretation based on the interplay between SES and health. If the socioeconomic influence on health is to be assumed causal this would be through indirect determinants of health, where SES influences health through behaviors and context directly caused by SES. Contrary to this assumption is the health selection hypothesis, which states that the pathway from SES to health is instead reversed. Health determines the socioeconomic position and direction of social mobility. Poor health will lead to lower SES as it may interfere with attaining a higher education or the ability to work [112]. However, it is also possible that there are factors that influence both SES and health, for example personal characteristics and cognitive ability. These factors would be determinants for attained SES and social mobility but also affect health through, for example, health behaviors. This indirect health selection has been proposed to explain the consistent health inequalities across different welfare systems. Higher prevalence of risky health behaviors have been observed among low SES groups but risky health behaviors can only in part

explain the elevated mortality risk among low SES groups [113]. However, if there was a direct effect of SES and health, health inequalities should be substantially attenuated in countries with generous welfare systems, where access to both education and health care are granted to all. However, this has not proved true, a contradiction described as the Nordic paradox [114, 10]. Using European population based data, Hoffmann et al. [115] found evidence that different selection paths explained health inequalities at different times in life and where the social causation became increasingly important with aging. However, the authors were not able to test indirect selection specifically. Factors underlying the indirect selection hypothesis, such as cognitive ability and personality traits are known to have a genetic component. Twin and family based designs may therefore provide further clarification on the SES and health interplay over the life course, as well as provide further insights into the possible causal effects of SES on health [116].

1.4.3 Social enhancement and Diathesis-stress models

How genes and the environment interact and how this interplay may explain the variance in different phenotypes is complex, and in order to understand these processes it has been suggested that several different explanatory models are needed [117]. Several influential studies have argued that genetic influences on for example IQ, varies as a function of social class. The variance on IQ differs across the social strata, where in advantaged environments the genetic influences are of greater importance while under disadvantaged circumstances the environment is more influential [118, 119, 29]. This may be understood from the social-enhancement model, which states that genetic resilience or predisposition for a positive trait, for example high IQ, is enhanced in advantaged environments. Genetic influences will therefore explain most of the variance at high SES levels while it will have little influence at lower SES levels where the variance instead may be explained by environmental factors [120, 117]. However, genetic factors may also be of importance under adverse influences. The diathesis-stress model is instead focused on genetic vulnerability, and states that this vulnerability is amplified under difficult conditions, which results in a greater part of the variance of a trait being explained by genetic influences precisely as they are triggered by negative influences, such as socioeconomic adversity [120, 117]. These two models may seem contradictory, but both are useful from different perspectives. The interplay between genes and environment are complex and include both genetic vulnerability and resilience which means that depending on the phenotype, environmental factors and contexts, we may need different theories for understanding these interactions.

2 AIMS

The objective of this project was to increase the understanding of socioeconomic differences in health and mortality in old age - in a genetically informative setting. Data from the Swedish Twin Registry (STR), different statistical methods, and family-based designs were applied to investigate life-course socioeconomic circumstances and how these relate to cognitive function, frailty, and mortality in late life. Within the framework of this objective, the following specific aims were addressed:

I. To investigate the role of childhood social class on cognitive abilities and change in late adulthood

II. To investigate the moderation effect of rearing and attained socioeconomic circumstances on genetic and environmental influences on the variance in late-life cognitive abilities

III. To investigate preventable and non-preventable mortality as functions of life-course socioeconomic circumstances (childhood, midlife, and social mobility)

IV. To investigate whether socioeconomic influences on frailty differ between men and women, and if sex differences in the relationship between frailty and mortality are influenced by socioeconomic factors?

3 DATA SOURCES AND MEASUREMENTS

All studies in this thesis are based on data from the Swedish Twin Registry (STR) [121-123]. Study I and II, utilize data from three sub-studies of aging with longitudinal data. Study III uses data from all twins born before 1935, and Study IV was based on cross-sectional data from the Screening Across the Lifespan Twins (SALT) data collection in 1998-2002 (Figure 2).

3.1 THE SWEDISH TWIN REGISTRY (STR)

The STR is one of the largest twin data resources today. The STR was initiated in the late 1950s, where all same-sex twins born 1886-1925 were identified through parish records and contacted through a first questionnaire in 1960-61, this cohort is referred to as the Old cohort. Follow-up questionnaires were sent out to those pairs where both responded again in 1963, 1967, and 1970. The collected data included demographic information such as occupation and education, as well as health-related issues. In 1970, twins born 1926-1958 were identified; this sample is referred to as the Middle cohort. These same-sex pairs were contacted through a questionnaire in 1973 [121]. The STR has subsequently continued to collect data on later born twin cohorts and performed follow-up data collections. Identification of twins is currently obtained through the National Board of Health and Welfare. Through linkage using the personal identification number unique to all citizens of Sweden, the STR may also be linked to other national and quality registers in Sweden. This makes the STR a valuable and unique twin data resource.

3.1.1 SATSA

The Swedish Adoption/Twin Study of Aging (SATSA) was initiated after the discovery that a number of twins had not been reared together [124, 125]. This was further investigated, and a first questionnaire (Q1) was subsequently sent out in 1984 to both the reared apart twins and a sample of twins reared together, matched on birth year, birth county and sex, all of whom were same-sex twins. Out of the 2 845 who received Q1, 71% responded (n=2 018). SATSA participants are both from the Old and Middle cohort in STR. The reared apart twins had been separated before age 11, but the majority were separated at age 2 or earlier.

SATSA is a longitudinal study covering the later part of the life span. It consist of data from mailed questionnaires and in-person testing (IPTs). A total of 9 questionnaires have been sent out (1984, 1987, 1990, 1993, 2004, 2007, 2010, 2012, and 2014). The first questionnaire included questions related to the rearing and socioeconomic environment. The first IPT was carried out in 1986-1988 and twin pairs where both twins had responded to Q1 and were 50 years or older were invited to participate. Mean age at IPT1 was 63.6 (SD 8.8). The IPTs included extensive health assessments, including a cognitive battery, physical and functional health examinations. Follow-up IPTs were conducted in 1989-1991 (IPT2), 1992-1994 (IPT3), 1995-1997 (IPT4), 1999-2001 (IPT5), 2002-2004 (IPT6), 2005-2007 (IPT7), 2008-2010 (IPT8), 2010-212 (IPT9), and 2012-2014 (IPT10). *Study I* and *II* were based on data from up to IPT 9. However, IPT4 included only a sub set of the participants (n=40) and thus

data from IPT4 is not included in the analyses. A total of 859 twins have participated in at least one IPT and 76% have participated in three IPTs or more [20].

3.1.2 OCTO-Twin

The Origin of Variances in the Oldest-Old: Octogenarian Twins (OCTO-Twin) was initiated to study twin pairs whom had reached the highest ages. The sample was restricted to twins over 80 years of age, born 1893-1913 [126]. Complete twin pairs (n=549) were invited to patriciate, out of whom 351 pairs participated in wave 1. OCTO-twin consists of 5 assessment waves, conducted every two year from the first wave in 1991-1994. Following waves took place 1993-1996 (wave 2), 1995-1998 (wave 3), 1997-200 (wave 4), and 1999-2002 (wave 5). Wave assessments included cognitive tests, health measurements, tests of physical function and well-being.

3.1.3 GENDER

To study sex and gender differences in health and aging, the Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behavior and Health among the Elderly (GENDER) was initiated. Opposite-sex twin pairs that had not originally been invited to participate in the Old cohort, although data on the twin births had been collected from parish records, were invited. A total of 1843 opposite-sex twins (605 complete pairs) born 1906-1925 responded to the first questionnaire [127]. Out of these 498 twins (249 pairs) age 70-79 participated in the first IPT (1994-1997). Two follow up IPTs were conducted at 4 year intervals. A second questionnaire was sent out in 2007. Both the questionnaire and IPTs were modelled after assessments in SATSA and OCTO-Twin [127].

3.1.4 SALT

The Screening Across the Life Span Twin study (SALT) is an extensive computer-assisted telephone interview that was carried out 1998 to 2002. It was aimed at same and opposite-sex twin pairs born 1958 or earlier. Out of the 52 080 twins that were contacted, at total of 44 919 twins participated. The response rate was 65% for the Old cohort participants (born 1886-1925) and 74% for the Middle cohort (born 1925-1958) [121, 122]. The screening was conducted by trained interviewers with medical knowledge and consisted of a comprehensive health screening and demographic information including educational attainment and occupational status. Participants 65 years and older were also administered a cognitive screening [122]. Additionally, birth data including occupational status of the parents were retrieved from archived birth journals on twins born after 1926 [123].

3.1.5 Zygosity assignment

In the Old and Middle cohort, zygosity was determined through questions regarding twin pair similarity. The twins were asked if, when they were children they were as like as “two peas in a pod” [“lika som bär” in Swedish] or if they had been as similar as other siblings. If both twins in a pair agreed to the “peas in a pod” similarity, they were classified as MZ and otherwise as DZ [121]. In SALT, twins that were still undetermined were asked an additional

question regarding whether strangers commonly confused the twins with each other when they were children. If they answered “always” or “often” they were classified as MZ. Determining zygosity based on these questions had been shown to have good reliability [128-130]. The zygosity ascertainment was also validated in a SALT sub-sample using DNA markers, which showed excellent accuracy [121].

3.2 THE SWEDISH CAUSE OF DEATH REGISTER (CDR)

The CDR contains data and provides statistics on all registered deaths in Sweden. The data are updated yearly and provide causes of deaths in accordance with the International Classification of Diseases (ICD) since 1961 [64]. Both primary cause of death and underlying causes of death are available from the register. Causes of death are reported to the registry from the physician responsible for issuing the death certificate. The quality of the register is thus also dependent on the accuracy of these certificates [131]. The CDR may be linked to the STR through the Swedish personal identification number.

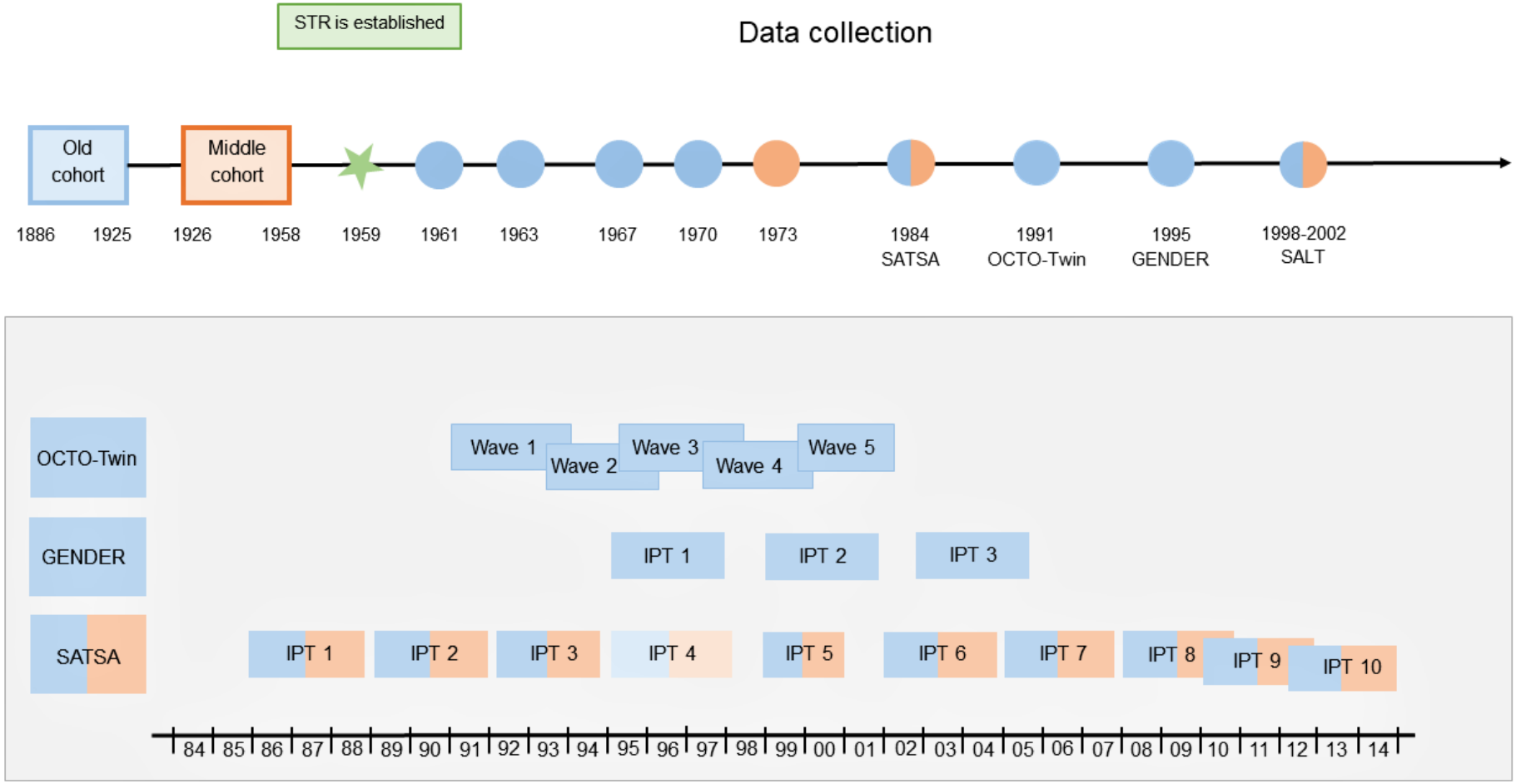


Figure 2. Overview of the STR and the sub-studies of aging included in this thesis. IPT = in person testing. Modified from Eriksson [1]

3.3 COGNITIVE MEASURES

Study I and *II* in this thesis investigated socioeconomic influences on cognitive change in late life using longitudinal cognitive data. Analyses in Study I was based on SATSA, and Study II utilized data from three aging studies in STR: SATSA, OCTO-twin, and GENDER (GOS). In these three studies, cognitive data were collected during the IPTs (see section 3.1 and Figure 2) where the participants underwent extensive cognitive testing. Although the cognitive assessments were similar across studies, they were not identical.

3.3.1 Cognitive domains in SATSA

Study I utilized cognitive data from eight IPTs in SATSA. By using eight tests from the cognitive battery, four specific cognitive domains and a general ability score were generated using principal component analysis. The four specific domains were verbal (crystallized) ability (Information and Synonyms test), perceptual speed (Symbol Digit and Figure Identification Form A), memory (Digit Span and Thurnstone's picture memory test), and spatial (fluid) ability (Koh's Block Design and Card Rotations Form A). The general ability score was generated from all eight tests [132]. To facilitate interpretation of results, the final factors scores were rescaled to classic IQ units (mean 100, SD 15).

3.3.2 Cognitive tests in GOS

In *study II*, cognitive data from all three studies in GOS were utilized. Because there were differences in which tests constituted the cognitive domains in the different studies, four tests in common were chosen instead. The test were: Synonyms, Block Design, Thurstone's Picture Memory Task, and Symbol Digit [133, 134]. All tests were rescaled as percent correct in the combined data set. A general ability score was derived through principal component analysis of the four tests.

3.4 THE FRAILTY INDEX

In Study *IV*, sex differences in the relationship between socioeconomic status (SES), frailty and mortality were investigated. To operationalize frailty, the Frailty Index (FI) was created. The FI is constructed from various deficits, related to health, function, and well-being. The FI represents an accumulation of deficits and the number of health-related items may vary when the index is compiled. In the SALT data (see section 3.1.4), there were 44 items available that had a prevalence of ≥1% and a missingness of ≤10% and were included in the final FI (Table 1). Missing values were imputed. Predicting values of imputation were based on remaining FI items, age, sex, BMI, education level, and smoking status. The imputed FI values in SALT has been validated [135]. Following the standard for constructing the FI score [136, 135], each individual FI score is calculated as the rate of deficits in relation to the full scale, resulting in a score between 0-1.

Table 1. List of items included to create the FI in SALT, modified from Li et al. [135].

General health	stroke	neck pain	migraine
Health status prevents you from doing things you want to do.	TIA attacks	Diabetes	Asthma
Number of serious infections/year (not respiratory)	Irregular cardiac rhythm/atrial fibrillation	Goiter	Allergy
Buzzing in the ears	Chronic lung disease	Glandular diseases (excluding goiter)	Recurrent periods of coughing
Angina pectoris	Dizziness	Gall bladder problem	Felt depressed
Heart attack	Rheumatoid arthritis	Liver disease	Felt happy
Heart failure	Knee joint problem	Gout	Felt lonely
High blood pressure	Sciatica	Kidney disease	Physical handicap
Lipid disorder	Osteoporosis	Stomach or intestine problems	Crohn's disease or Ulcerative colitis
Vascular spasm in the legs	Hip joint problem	Recurring urinary tract problems	Vision
Venous thrombosis	Back pain	Cancer, tumor disease or leukemia	Hearing

3.5 PREVENTABLE AND NON-PREVENTABLE MORTALITY

In *study III*, mortality inequalities were investigated by separating causes of death into preventable and non-preventable mortality. Preventable mortality was defined in accordance with the extended list presented by Avoidable Mortality in the European Union (AMIEHS) [137]. Causes of death due to injuries and suicide were not included in this list, but have been included as preventable causes in other studies [76]; we therefore added these causes of death to our definition. Causes of death were provided by the CDR (see section 3.2). Mortality was measured from the first study entry in 1960 up to 2014; classification of causes of death therefore needed to be harmonized across versions of the ICD (7-10). A full list causes of death classified as preventable is presented in Table 2. Non-preventable mortality was classified as all causes of death not coded as preventable.

Table 2. Preventable causes of death

Respiratory Tuberculosis	Cancer of the female breast	Rheumatic heart disease	Intestinal obstruction with no mention of hernia
Meningococcal infection	Malignant neoplasm of cervix uteri and cancer of the body of the uterus	Chronic bronchitis, emphysema and chronic airways obstruction, not elsewhere classified. Asthma	Renal failure
Hepatitis	Malignant neoplasm of testes	Ischemic heart disease	Complications of pregnancy, childbirth and puerperium
HIV	Neoplasm of the kidney and bladder	Heart failure	Conditions originating in the perinatal period
Cancer of the stomach	Hodgkin's disease and lymphocytic leukemia	Cerebrovascular disease	Congenital anomalies (incl. congenital heart disease)
Malignant colorectal neoplasm	Aplastic anemia	Influenza, bronchitis and pneumonia	Sudden infant death
Neoplasm of the liver	Diabetes	Hypertension	Falls
Cancer of the larynx. lung, bronchus and trachea	Bacterial meningitis	Peptic ulcer	Suicide
Primary cancer of bone	Parkinson's Disease	Acute appendicitis	Alcohol related deaths
Neoplasm of the skin and lip	Multiple sclerosis	Abdominal hernias	

3.6 SOCIOECONOMIC INDICATORS

The aspects of socioeconomic status investigated in this thesis reflect both rearing (childhood) and attained (adulthood) circumstances. The indicators were based on both social class and education. There are obviously many different aspects of SES that are relevant in their relation to health, such as income, assets and subjective measures. The selected indicators in this thesis are chosen on the basis of availability in the various data sets and over time (rearing and attained), because they are broad measures of SES, reflecting work, income and educational conditions and therefore may be more comparable over time and also to other studies.

3.6.1 Rearing and attained social class

Rearing social class was included in *Study I-III* as an independent variable, and in *Study IV* as a matching variable. In SATSA, OCTO-twin, GENDER and SALT, rearing social class was based on both parents' occupation and recoded into a household measure in order of

dominance, meaning that the measure was based on the parent with the highest level. The social class classification was coded in accordance with the Swedish Socioeconomic Index (SEI) [138]. In *Study I, II*, and *IV*, SEI was recoded into a five level scale following [139]. In *Study III*, rearing social class was retrieved from several data sources, The Old cohort, SATSA, and SALT. In the Old cohort, the variable was based on the father's social class and had been pre coded into the three level social group classification (Social grupp I, II,II), previously used in Sweden, mainly for election statistics [87]. Rearing social class data from the two other samples were harmonized to this three-level classification. Rearing social class was self-reported, except in SALT where parental occupation was retrieved from birth journals [123].

Attained social class was used in *Study II-IV*. The measure was assessed based on self-reported occupation and coded in the same way as rearing social class, using a five-level scale (Table 3). Attained social class was based on the individual participant's social class and was not coded as a household measure.

Table 3. Social class classification in Study I-IV.

Social class			**Social group (Social grupp I-III)**	
Level		SEI code	Level	SEI code
1	Unskilled manual workers	11-12	**III**	11-12
2	Skilled manual workers, lower non-manual employees, farmers	21-22, 33-36, & 86-89	**II**	21-22, 33-36, 44-46, & 86-89 (+ upper secondary level students)
3	Self-employed (not including professionals)	76-79	**I**	55-57, 60, & 76-79 (+ university students)
4	Intermediate non-manual worker	44-46		
5	Higher non-manual worker (including professionals)	55-57 & 60		

3.6.2 Rearing and attained level of education

In *Study II*, a measure of rearing parents' education was available in SATSA and GENDER, but not in OCTO-twin. The measure was self-reported with information on level of education from both the mother and father. A household measure was created based on the parent with the highest education. The variable was applied in the models as a four level scale, roughly following International Classification of Education (ISCED) levels [140].

Attained level of education was retrieved from several different sources of data and was used in *Study I-IV*. In the GOS data, attained education was self-reported with various number of

levels: four in SATSA, eight in OCTO-twin and six in GENDER, based on highest level of attained education. In *Study III*, attained education was retrieved from Q63 (Old cohort), Q73 (Middle cohort), and the SALT data collection. Due to overlap between these three data collections, individuals were coded in accordance with their latest reported achieved level of education. In *Study I-III*, highest attained education was classified at four levels and in *Study IV* at five levels (Table 4) following ISCED classification.

Table 4. Education levels and classification

ISCED 2011*		Study I-III	Study IV
Score	Level		
0	Less than primary	**1**	**1**
1	Primary (grades 1-6)		
2	Lower secondary education (grades 7-9)	**2**	**2**
3	Upper secondary education (grades 10-12)	**3**	**3**
4	Post-secondary non-tertiary education		**4**
5	Short-cycle tertiary education		
6	Bachelor's or equivalent	**4**	**5**
7	Master's or equivalent		
8	Doctoral or equivalent		

* The education levels are grouped based on their match to the ISCED 2011.

3.6.3 Social mobility

Social mobility was investigated in *Study III*. The measure was created based on rearing social class as the class of origin and attained education as the destination class. Both socioeconomic indicators were coded as binary with the lowest level as low and all other levels as high. Social mobility was defined with four categories: Low to Low, Low to High, High to Low, and High to High.

3.7 COVARIATES

3.7.1 Parental attitudes toward education

In *Study I*, we used a measure related to parental attitudes towards education. This variable was a composite score created from five different items from Q1 in SATSA (see section 3.1.2) [128]. The questions were (translated from Swedish): 1) My parents urged me to obtain an education beyond primary school, 2) My parents were interested in my school work, 3) My parents came to school and met the teacher when I started school, 4) My parents thought it was important to read, and 5) My parents often read aloud to me. These were all Likert type items with values from 1-5, that ranged from completely disagree to completely agree.

3.7.2 Degree of relatedness to rearing parents

In *Study I*, models were adjusted for degree of relatedness to rearing parents as some separated twins grew up in homes with other relatives or in some cases only one twin was adopted away. A three-level scale was created: 1. Biological parents or siblings, 2. Other relatives, and 3. Not related.

3.7.3 Birth cohort

Birth cohort was classified based on birth years defining the Old and Middle cohort in STR, born ≤ 1925 or after.

4 STATISTICAL ANALYSES

The objective of this thesis was to study late-life health and mortality as a function of rearing and attained SES, using longitudinal cohort data. In addition to this, the purpose was to investigate whether there were genetic factors that could influence these possible relationships. Due to the complexity of the different outcomes and how they interplay with both genetic and socioeconomic influences, different statistical methods have been utilized both at the population level and considering the twin characteristics of the data. Analyses aiming to understand the relationship between SES and health in the total population are in this thesis described as population level models. The models where familial confounding is accounted for, or investigated in a biometric model takes advantage of the twin structure of the data.

The statistical software STATA IC version 14.2 and 15 [141, 142] was used in all studies. In Study II, SAS 9.4 was used to model the Empirical Bayes (EB) estimates and the biometric main analyses using structural equation modeling was performed using the R software [143] and the package OpenMx [144].

4.1 REGRESSION ANALYSIS

In this thesis, linear regression, multilevel mixed-effects linear regression, and Cox regression were used. All regression analyses were estimated with 95% confidence intervals (CI). Point estimates are presented with CI's or standard error (SE), both of which are informative about the variability of the data and the precision of the estimate. The confidence interval is calculated using the point estimate and the estimated standard error under the assumption of normality. The range of the interval will depend on the sample size, the SE and the confidence level. A narrower confidence interval or lower SE indicates better precision. If the confidence interval includes zero (given the confidence level set and the data), it is generally assumed that the point estimate is insignificant, not distinguishable from zero.

4.1.1 Linear regression

Linear regression models (ordinary least squares, OLS) estimates the relationship between an independent (x) variable and a dependent (y) variable based on a linearity assumption. The regression coefficient consists of the intercept (β_0) and the slope (β_1) of the relationship, the slope represents the unit increase in y for every unit increase of x.

$$y = \beta_0 + \beta_1 x + e$$

A linear regression model where several independent variables are included is a multiple linear regression. This is commonly applied to allow for adjustments for possible confounders, for example sex or age.

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 \ldots$$

Linear regression was used in *Study IV*, to investigate FI in men and women and as a function of SES. The analyses were performed in two steps. First, to investigate the magnitude of sex differences in FI by accounting for potential familial influences, we created clusters of artificial (unrelated) opposite-sex twin pairs derived from the same-sex twin pairs. Each cluster contained unrelated males and females with the same birth year and same level of parental social class. Sex differences in frailty were estimated in a linear regression by comparing the sample of unrelated clusters to a sample restricted to opposite-sex twin pairs.

Secondly, we analyzed FI as a function of attained social class and education in men and women using linear regression models, both on the total sample and stratified by age group (age at interview). Stratification allows the baseline effect to differ between the groups.

4.1.2 Multilevel mixed-effects linear regression

Multilevel mixed-effects linear regression was used to model latent growth curves of late-life cognitive abilities in *Study I* and *Study II*. This analysis is suitable to estimate change over time in longitudinal data. It captures the general characteristics of change for both the group as a whole and for the individuals within the group. The models contains both fixed effects and random effects. The fixed effects estimates coefficients of the linear relationship, while the random effects estimates variance and covariance around the mean [145].

In *Study I*, the latent growth curve models were fit to the data to investigate mean level cognitive ability and cognitive change as a function of rearing social class. Models were adjusted for attained education, parental attitudes toward education, sex, age, and degree of separation. Analyses were performed in two major steps, first to study the effects of childhood socioeconomic environment on cognition in later life on a population level and secondly, in a twin model using a between-within study design (see section 4.2.1). The growth curve analysis was performed separately on the different cognitive domains and the general ability score. The intercept age was set at age 65. Analyses were performed step wise. First, an unconditional model was fit to the data. Childhood social class was then added to the model, first as a linear term and subsequently as a quadratic term. The same step-wise procedure was applied when parental attitudes toward education, and attained education were included in the model. Two information criteria, AIC and BIC, were used to determine best model fit when comparing the models.

In *Study II*, mixed effects models were used to produce the EB-estimates. In these analyses the best model fit was provided by a two slope model, with one linear slope (Slope A) before the centering age at age 75, and one slope after (Slope B). The EB estimates are separate values for Slope A, Intercept_{75}, and Slope B that were produced and saved. The EB-estimates were subsequently applied in the moderator model in *Study II* (see section 4.2.2.1).

4.1.3 Cox proportional hazard regression

Cox regression is a method to estimate mortality using time-to-event data. In *Study III*, Cox regression was performed to estimate the association between mortality rates and different

levels of SES and in *Study IV*, to investigate mortality as a function of the FI. Cox regression estimates hazard ratios across an underlying time scale, under the assumption that hazards are proportional for all levels of the predictor over time. However, there are no other assumptions regarding the shape of the underlying hazards of the model. The Hazard Ratios (HRs) are ratios of event rates between different exposure groups. In *Study III* and *IV*, the underlying time-scale was chronological age. By applying age as the time scale, the Hazard Ratios are automatically adjusted for age. Predictors may be continuous (*Study IV*) or added as dichotomous or categorical (dummy) variables (*Study III*). The model produces relative rates for each level of the predictor compared to a reference group.

In *Study III*, all-cause and cause-specific (categorized as preventable and non-preventable causes) were investigated as a function of rearing and attained SES. As the data were retrieved from three different study cohorts in the STR (see section 3), person-years of follow-up were calculated starting from the study entry year of the three cohorts up to date of death, emigration or end of study which was set at 31 December 2014, which ever came first. Age-standardized mortality rates were calculated and corresponded to the age distribution of the study sample, based on the total number of deaths over total person years for the three mortality outcomes, by all covariates. Preventable, and non-preventable mortality were investigated separately by censoring all causes of death that were not under study. The socioeconomic indicators were added as categorical (dummy variables) in the models and studied separately. To differentiate between premature and late-life mortality, time bands were created by splitting the follow-up time, as mortality before age 70 and after. Dummy variables based on time band and SES level were then simultaneously analyzed in the model. Additional adjustments were made for study entry date (STR cohort) and sex.

In *Study IV*, Cox regression was applied to investigate all-cause mortality as a function of FI by level of SES in men and women. Mortality data were available up to the end of April, 2019 and person-years of follow-up were estimated from the SALT entry date in 1998 up to the end of study, or censoring due to death or emigration. All models were stratified by sex to obtain difference in mortality risk as a function of FI in men and women. Additional stratification based on level of attained social class and education was performed in the main models. All models were adjusted for birth cohort and age at interview. Additionally, the models were stratified by age group (age at interview) at 10 year intervals.

4.1.4 Twin-relatedness in population level models

When using a sample of twins but where the objective is to analyze effects at a general population level, i.e. not focused on investigating how twin similarity and relatedness may influence an association, intra-pair similarities must be accounted for. All models in this thesis performed at the population level were adjusted for relatedness within twin pairs by including cluster-robust standard errors.

4.2 TWIN AND FAMILY BASED STUDIES

In *Study I, III,* and *IV* familial influences were investigated under the assumption that these influences could be a confounder (see section 1.3). Thus, the twin status was used to examine whether within-pairs estimates differed from the population estimates and between MZ and DZ twins (co-twin control). In *Study II,* a different approach was applied and instead of adjusting for familial confounding genetic and environmental influences were quantified in a biometric model.

4.2.1 Co-twin control models

Co-twin control is a method to evaluate potential familial confounding. There are two co-twin control models commonly used - the fixed effects model and the between-within model. Both analytic approaches produces within-pair estimates, adjusted for twin similarity in the sample i.e. the effect independent of familial effects. The within-pair effect will indicate if the effect of the exposure remains if familial factors are taken into account and thereby theoretically provides an estimate of the effect adjusted for any confounders shared between the twins in the pair (e.g. genetic effect and shared rearing environment in MZ twins). The within-pair estimate is interesting when compared to the population level estimate, which provides the effect in the population (potentially) confounded by familial influences. Further stratifying these analyses on zygosity, provides a separate within-pair estimate for the MZ and DZ twins, it allows the model to distinguish between genetic and shared environmental effects. The interpretation of these estimates is based on the fact that MZ are genetically identical, while DZ twins share 50 percent of their co-segregating alleles on average, but both types of twins share their rearing environment such as intrauterine environment, upbringing, and parental SES. Consequently, if the MZ within-pair estimate is attenuated to null and the DZ estimate is partly attenuated, the observed effects is likely entirely attributed to genetic influences. A similar attenuation in both MZ and DZ within-pair effect indicates confounding by shared environmental factors [146].

In the between-within model, two estimates are modelled. A between-pair estimate of the pair mean, providing the group estimate and a within-pair estimate based on how the individual deviates from the pair mean, providing the individual estimate [147]. These two indicators are analyzed simultaneously in a regression model whereby they also control for each other. The between-within model was applied in *Study I* using a mixed effects model, to investigate possible familial influences on the association between rearing SES and cognitive ability observed at the population level. The between-within estimates were only modelled using the reared apart twins as these twins were discordant for rearing social class.

In the fixed effects model, the analysis is performed by conditioning the model on the twin-pair i.e. the twin-pair identifier. In this way only pairs discordant on both the exposure and the outcome will contribute to the analysis, thereby providing an estimate adjusted for twin similarity. In *Study III*, this co-twin control method was applied using Cox-regression to investigate familial influences on the observed association between SES (rearing social class,

attained social class and education, and social mobility) and mortality observed at the population level. All models were additionally stratified on zygosity. In *study IV*, it was used to adjust for familial confounding using linear regression, investigating the relationship between attained SES (social class and education) and FI. It was also applied in the Cox regression to investigate familial influences on the association between FI, SES and mortality. In *Study IV*, all models were stratified on sex to investigate if familial influences differed between men and women.

4.2.2 Quantitative genetic analysis

Twin- and family-based research has traditionally focused on estimating the proportion of variance in a phenotype (in a population) that may be attributed to environmental and genetic components. The latter, is also often referred to as heritability. The proportion of variance in a phenotype due to genetic factors can include both additive effect (A) and dominant effects (D), while the proportion due to the environment can be further decomposed into common environmental effects (C) which is the shared environmental effect within the twin pair, such as intrauterine environment and upbringing, and person-specific environment (E) which is the environmental effect unique to the individual and which contribute to differences between twins. The E component will also include any misclassification or measurement error in the model. The underlying assumption behind the model is that MZ twins share 100% of their genes while DZ twins share approximately 50% of their segregating genes. By definition the C effects are all influences, which are shared between the two twins of a pair and make them more similar to each other and, therefore, C would impact MZ and DZ twin-pairs to a similar degree, if they have been reared together. Finally, the E component comprises all influences, which make the twins of a pair different from each other and, therefore, is assumed to be unique to the individual twin. Thus, the total phenotypic variance equals A+C+D+E, however, the classical twin model typically estimates three of these components, either ACE or ADE. C and D are commonly not estimated in the same model as dominant effects (D) increase the correlation of MZ relative to DZ, while shared effects (C) effects make DZ more similar to MZ twins. Based on estimated twin correlations, it is therefore possible to assume whether C or D components are important for the models. If the MZ correlations are twice or more than in DZ twins, there are reasons to expect dominance effects [148, 109].

4.2.2.1 Moderator model

An extension of the classical twin model is the Moderator model [149]. This model allows for testing whether the variance due to A, C, and E for phenotype changes as a function of a moderator variable. In the moderation model, the magnitude of the variance components are typically modeled as a squared-linear function of the moderator, which in *Study II* was the socioeconomic indicators. The model thereby estimates the ACE variance at the centering point of the socioeconomic indicator, which then is allowed to vary squared-linearly as the socioeconomic indicator deviates from the centering point.

In *Study II*, the moderator model was applied using the GOS data to test the moderating effect of both rearing and attained SES on the variance in late-life cognitive abilities. Cognition was operationalized by four specific tests and a general ability score. Initially, intra-pair correlation were estimated for the cognitive abilities. A comparison between intra-pair correlations in MZ and DZ pairs provides an assessment of whether there is a genetic component in the phenotype. A larger correlation in the MZ pairs than in the DZ pairs indicates genetic influences. Additionally, cross-twin cross-trait correlations for the socioeconomic indicators and cognitive abilities were estimated to assess the genetic component in the relationship between SES and cognition by comparing the correlation coefficients in MZ and DZ twin pairs. The intra-pair correlations indicated an ACE model as the difference between rMZ and rDZ was less than half. The moderator model that was fit to the data was fashioned after Turkheimer et al. [2] (Figure 3). The cognitive tests were applied in the models using the EB-estimates derived from longitudinal cognitive data. All cognitive tests including the general ability score were tested separately with two slopes (A and B) and the intercept at age 75, by all the socioeconomic indicators. As the data included both reared together and reared apart twins the C component had to be adjusted accordingly with these premises. For the reared together twins, C was assumed to be shared at 100% but for the reared apart twins it was assumed to be zero. All models were adjusted for sex.

To evaluate moderation effects and which parameters explain the data best, maximum likelihood estimation is used. This is done by comparing goodness of fit using the Likelihood ratio test (chi-square ($\chi 2$) between sub-models within the nested full ACE model. The best model fit but with the least number of parameters (degrees of freedom (df)) indicates the best fitting model. A significant ($p > 0.05$) difference between a sub-model and the full model (within the nested model) indicates a worse fit and thus implies that the sub-model fits worse than the full model [148]. In *Study II*, model fit estimations comparing the full ACE model and the reduced AE model indicated that C generally could be removed without significant loss of fit.

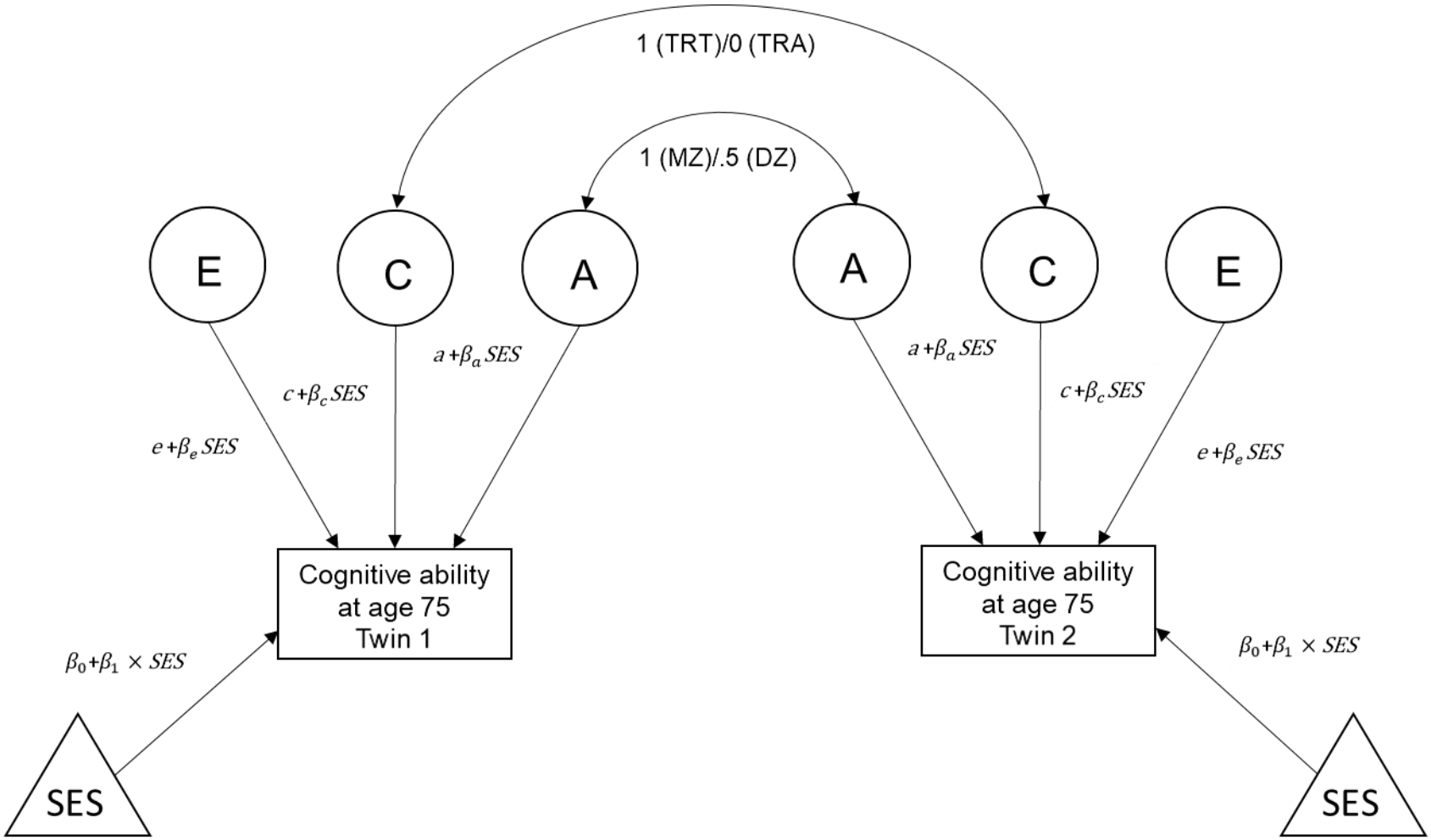


Figure 3. Path diagram of full moderation model. As parametrized by Turkheimer et al. [2]

5 STUDY SUMMARIES AND RESULTS

Below are brief summaries of the four individual studies included in this thesis, including objective, methods and results.

5.1 STUDY I - CHILDHOOD SOCIAL CLASS AND COGNITIVE AGING

5.1.1 Objective

In *Study I*, we addressed the effect of rearing social class on late-life cognitive abilities. Additionally, the mediating effect of educational factors were investigated, and lastly if familial influences confounded the proposed relationship.

5.1.2 Method

Study participants were retrieved from the SATSA study, with twins reared apart and a matched sample of twins reared together (n=859). Study participants that had taken part in the cognitive in-person testings' and with information on rearing social class were included in the final sample (n= 803)

Latent growth curve models (see section 4.1.2) were fit to the data to investigate mean level cognitive ability at age 65 and cognitive change as a function of rearing social class. Between–within twin pair analyses (see section 4.2.1) were used to adjust for familial confounding. Models were adjusted for attained education, a measure of parental attitudes toward education, sex, age, and degree of separation. Analyses were performed in two major steps, first on the total sample, to study the effects of childhood socioeconomic environment on cognition in later life on a population level. In the second step, analyses were performed on the reared apart twins using the between-within pair study design. These analyses were further stratified by zygosity, enabling a comparison between MZ and DZ twins.

5.1.3 Results

Based on the latent growth-curve models at the population level, we observed an association between rearing social class and cognitive performance at age 65 (Figure 4). There was no effect of rearing social class on trajectories of cognitive change. In the between-within analyses, adjusted for familial confounding, the effect was largely attenuated. Effect sizes were further attenuated in the MZ twins, indicating that the effect was mainly due to genetic influences (Table 5).

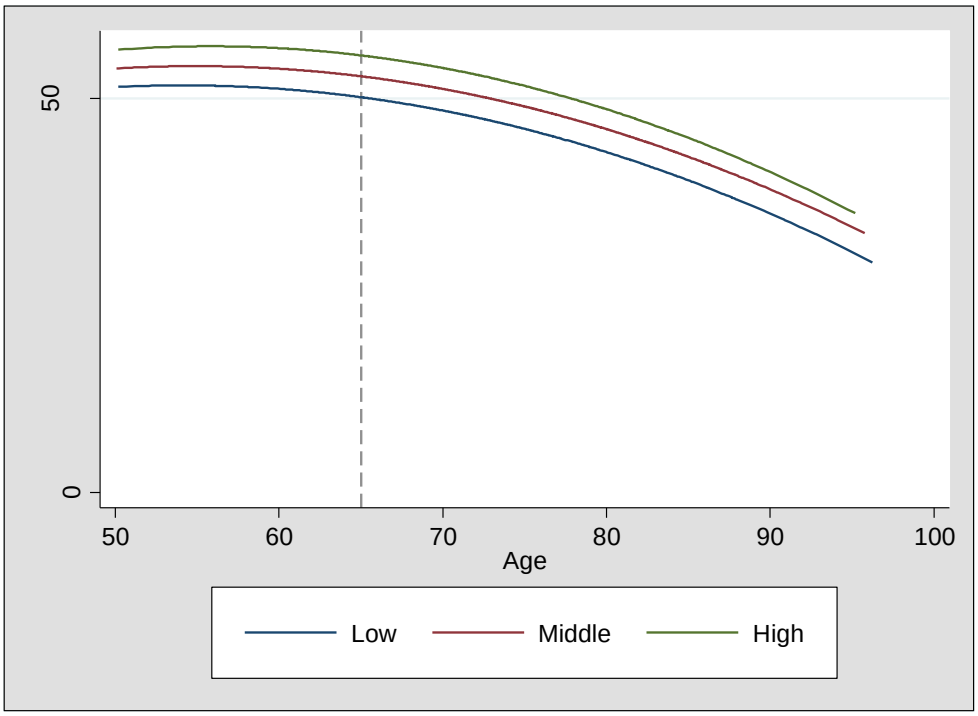


Figure 4. Example of the effect of rearing social class (low, middle and high) on levels of general cognitive ability at age 65 (significant) and cognitive change (not significant).

Table 5. Association between rearing social class at cognitive ability at intercept65. Analyses performed at the population level and in a between-within model. Results from fully adjusted model, controlled for parental attitudes towards education, attained education, age, and sex. Between-within models were additionally adjusted for age at separation and degree of relationship with biological parents. Statistically significant estimates (95% CI) are presented in bold.

	General ability	**Verbal ability**	**Spatial ability**	**Memory**	**Perceptual speed**
	β (CI)	β (CI)	β (CI)	β (CI)	β (CI)
Population level Total sample					
Rearing social class	**1.51** (0.52, 2.50)	**1.32** (0.35, 2.29)	0.45 (-0.59, 1.49)	**1.51** (0.47, 2.56)	**1.21** (0.24, 2.19)
Between-within model Twins reared apart					
Between estimate	**2.57** (0.53, 4.62)	2.08 (−0.09, 4.25)	0.79 (−1.35, 2.93)	**3.25** (1.18, 5.31)	**2.18** (0.18, 4.17)
Within estimate	0.48 (−1.26, 2.21)	−0.56 (−2.35, 1.22)	0.30 (−1.51, 2.11)	1.22 (−0.62, 3.07)	0.15 (−1.54, 1.84)

5.2 STUDY II - SOCIOECONMIC STATUS AS A MODERATOR OF LATE-LIFE COGNTIVE ABILITIES

5.2.1 Objective

In *Study II*, the aim was to investigate the moderation effect of rearing and attained socioeconomic indicators on variance in late-life cognitive abilities using an extension of the classical twin design.

5.2.2 Method

The study population (n = 2059) was derived from three studies from the STR: SATSA (n = 859), OCTO-Twin (n = 702), and GENDER (n = 498). All studies had longitudinal cognitive data from the later part of life, retrieved from in-person testing's. Twins were between 40 and 104 years of age (mean age 76, SD 10.4). Cognitive data were retrieved from four cognitive tests representing different cognitive domains: Synonyms (verbal abilities), Block Design (spatial abilities), Thurstone's Picture Memory task (memory), and Symbol Digit (perceptual speed). Additionally, a general cognitive ability score was derived. EB-estimates of intercept$_{75}$ and two linear slopes, before (A) and after (B) age 75 were derived from mixed models. Four socioeconomic indicators were applied, rearing and attained social class and rearing and attained education. To investigate if SES moderates the effects of genes and environments the intercept75 and two slopes for each of the cognitive abilities in a moderator model (see section 4.2.2.1) was fitted to the data.

5.2.3 Results

The model without the C parameter (AE) did not fit significantly worse than the full model (ACE), therefore this parameter was removed and results presented henceforth are based on the AE model. Additionally, the A and E parameters and all SES moderation were removed in separate steps to investigate if removing these changed the model fit. A summary of moderation is presented in Table 6.

For the intercept level at age 75, the results from the moderator models for the four socioeconomic indicators showed similar patterns (Figure 4 & 5). There was statistically significant moderation only for the Synonyms test, for which total and genetic variance decreased with higher levels of all socioeconomic indicators except rearing social class. In the models using the linear slopes significant moderation was observed for all socioeconomic indicators. However, moderation was not consistent but dependent on tests and on slope. The direction of moderation i.e. whether it increased or decreased with higher SES differed between slope A and B and also between cognitive domain.

Table 6. Overview of significant moderation in all models

Measure	Rearing Education	Attained Education	Rearing Social class	Attained Social class
General Cognitive Abilities				
Slope A	-	-	M^{1}	-
Intercept at 75	(A)	-	-	-
Slope B	-	-	$M^{1,2}$	-
Synonyms				
Slope A	$M^{1,2}$	AE	-	M^{2}
Intercept 75	$M^{1,2}$	A	-	A
Slope B	-	E	-	E
Block Design				
Slope A	E	E	-	E
Intercept 75	-	$M^{1(A)}$	-	-
Slope B	-	M^{1}	-	(E)
Symbol Digit				
Slope A	-	(E)	-	-
Intercept 75	A	-	-	-
Slope B	-	AE	-	-
Thurstone's memory				
Slope A	AE	-	A	-
Intercept 75	-	-	M^{2}	-
Slope B	(A)	$M^{1,2}$	$M^{1,2}$	E

M_1 = Significant moderation in the ACE model, M_2 = Significant moderation in the AE model.
No significant moderation on a specific parameter (A or E).
Note. Parenthesis=no total significant moderation in either ACE or AE model but significant moderation on A or E in the AE model

Figure 4. Moderation by rearing and attained social class on variance of the Synonyms test, at slope A, intercept$_{75}$ and slope B.

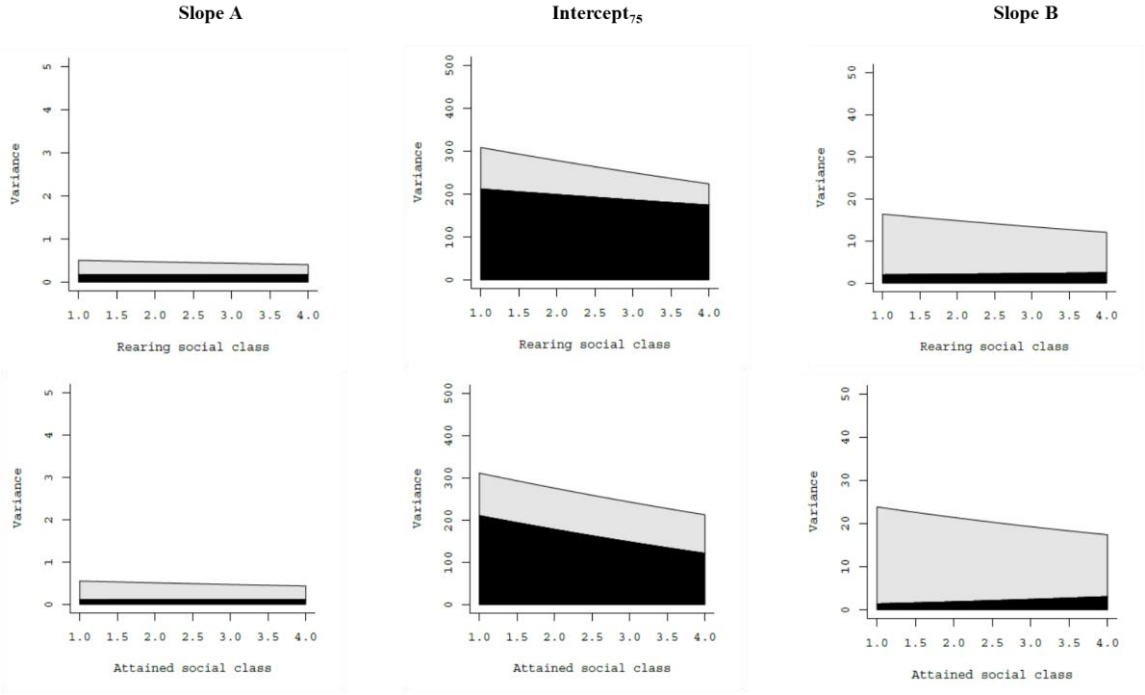
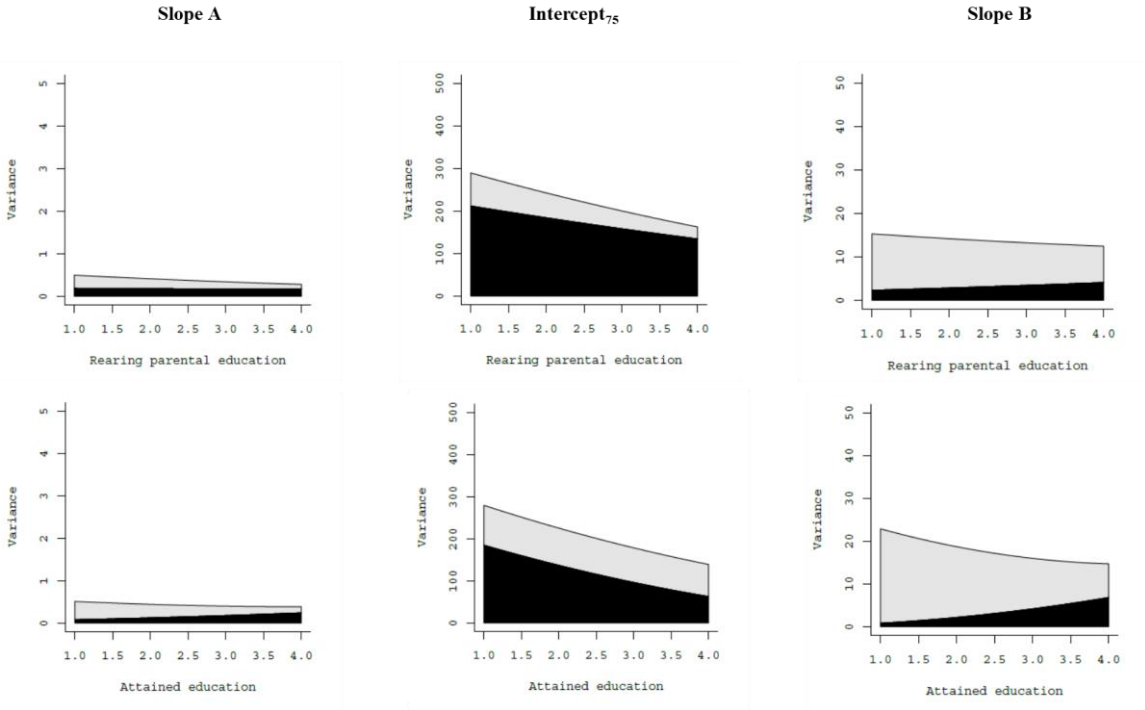


Figure 5. Moderation by rearing and attained education on variance of the Synonyms test, at slope A, intercept$_{75}$ and slope B.



5.3 STUDY III - LIFE-COURSE SOCIOECONOMIC DIFFERENCES IN PREVENTABLE AND NON-PREVENTABLE MORTALITY

5.3.1 Objective

In *Study III*, we investigated socioeconomic differences in mortality by comparing preventable and non-preventable mortality in a genetically informative setting

5.3.2 Method

Data were retrieved from the STR and included all twins born before 1935 (n=39 506). The participants were included in the STR at different time points: 1961 (Old cohort), 1973 (Middle cohort), and 1998 (SALT). The sample consisted of MZ, SSDZ, and OSDZ twins, a part of the sample had also been reared apart (n=1037). Only individuals with data on vital status and migration were included in the models (n= 35 248). The sample size also differed depending the response rate for the socioeconomic measures: Rearing social class (n=19 116), Attained social class (n=22 725), attained education (n=27 466), and social mobility (n=14 676).

Cox regression models (see section 4.1.3) were fit to the data to investigate all-cause, preventable, and non-preventable mortality as a function of SES. To investigate familial confounding co-twin control method were used (see section 4.2.1). Co-twin control of rearing social class was performed on the twins reared apart.

5.3.3 Results

We observed a social gradient in mortality, mainly for attained education and social class, which was slightly stronger for preventable mortality than for non-preventable mortality. The association was stronger but less precise in premature mortality (Table 6) Adjustments for familial confounding in the co-twin control did not alter the results. In social mobility, downward mobility and life-time low had the highest mortality (Table 7). There was a weak associations between rearing social class and mortality that did not remain in the co-twin control analyses of reared apart twins. However, these analyses were hampered by small sample sizes.

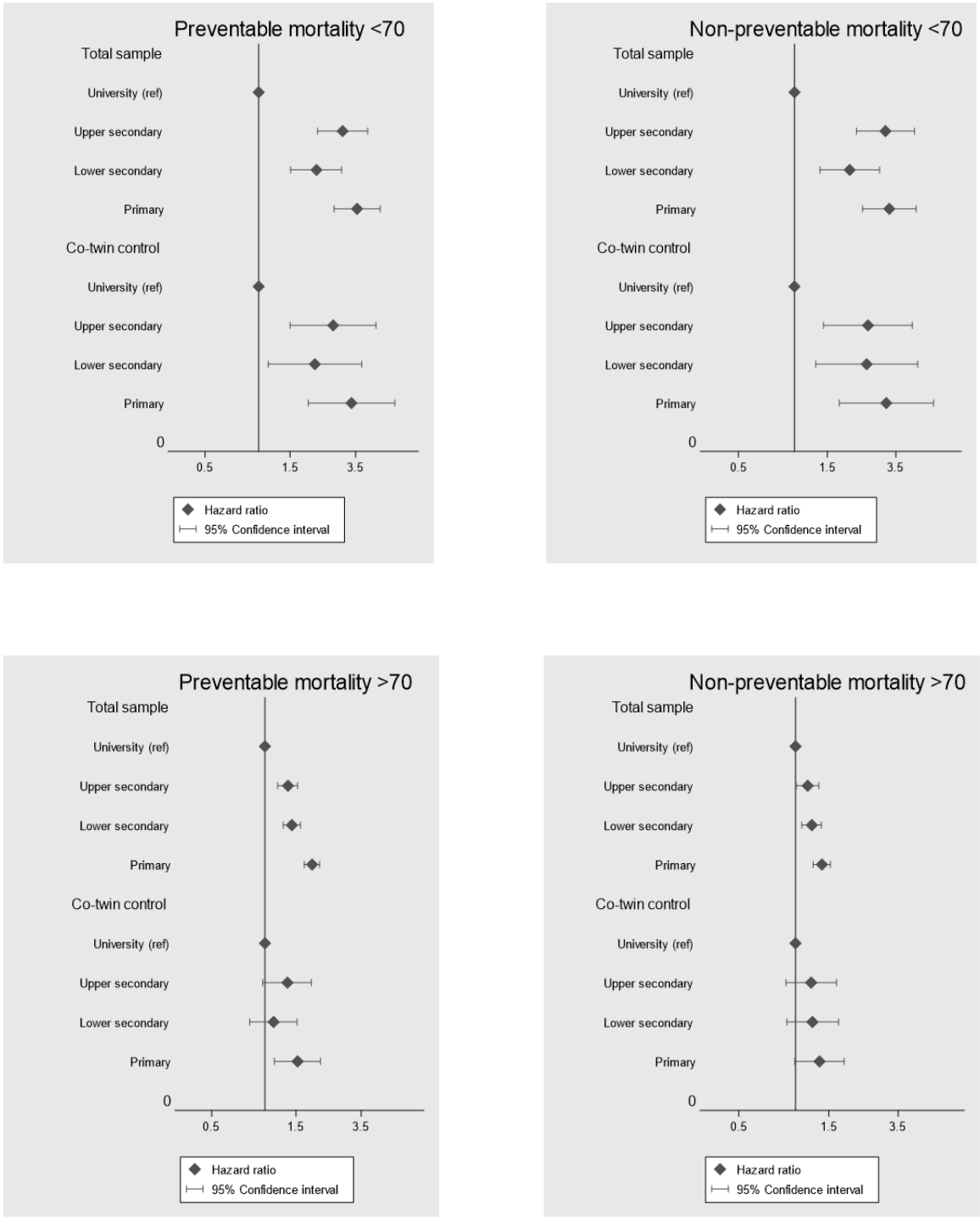


Figure 6. Forrest plots showing HR´s in total sample and co- twin control on educational attainment and early (<70) and late (>70) mortality, adjusted for STR sample and sex.

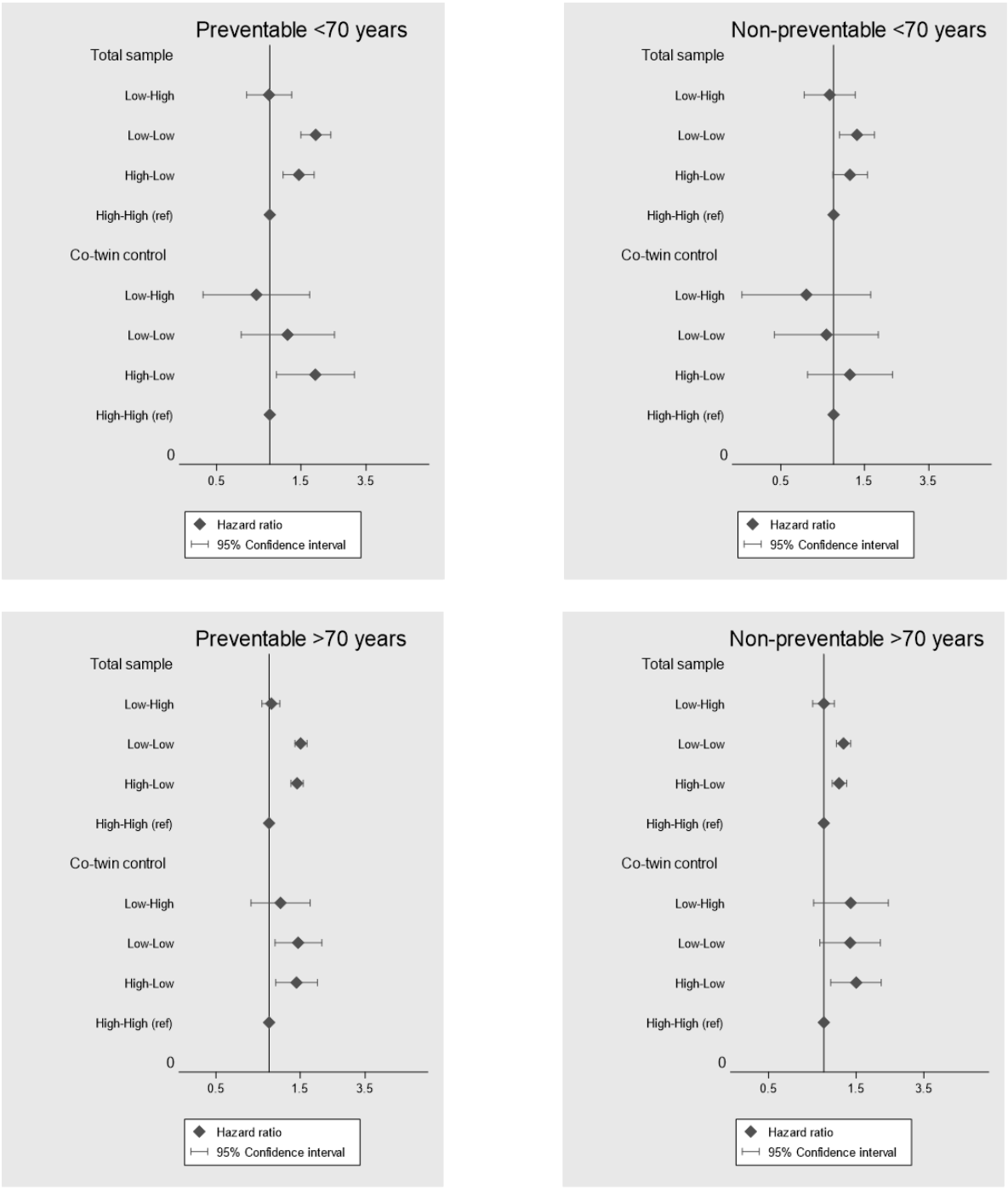


Figure 7. Forrest plots showing HR´s in total sample and co- twin control on social mobility and early (<70) and late (>70) mortality, adjusted for STR sample and sex.

5.4 STUDY IV - FRAILTY AND MORTALITY: INVESTIGATING SEX DIFFERENCES AND SOCIOECONOMIC INFLUENCES

5.4.1 Objective

In *Study IV,* we explored differences between men and women in the relationship between attained SES, frailty and mortality.

5.4.2 Method

Data were retrieved from the SALT cohort in the STR (n=43 636) and consisted of MZ, SSDZ, and OSDZ twins. Frailty was operationalized as the FI (see section 3.2.3). In *Study IV,* the score was multiplied by a 100 to produce a percentage score (Brinkman et al., 2018). Attained social class and education was self-reported and retrieved from the SALT questionnaire.

The analyses were performed in three steps. First, to investigate the magnitude of sex differences in FI a matched cohort of unrelated opposite-sex twins was created from same-sex twins, where male and female SS twins were matched on parental social class and birth year. This sample was then compared to the sample of related opposite-sex twins. Linear regression models (see section 4.1.1) were used to investigate FI in men and women, both on the total sample and stratified by age group. Additional co-twin control analyses indicated genetic or familial confounding

Lastly, we used Cox proportional hazard models to investigate mortality as a function of FI by level of SES and stratified by sex (see section 4.1.3). Additional co-twin control analyses indicated genetic or familial confounding (see section 4.2.1).

5.4.3 Results

Results revealed robust sex differences in FI, where women were more frail than men (Table 6). There was also a clear association between SES and frailty. The effect was stronger for women than for men. In the co-twin control analyses, the effect remained the same for men, but for women the within-pair effect was strongly attenuated. No differences could be observed dependent on zygosity. FI was more strongly related to mortality in men compared to women, where higher levels FI increased the mortality risk. The relationship was also stronger at lower SES levels but remained independent of socioeconomic status, age and familial influences.

Table 6. Frailty index as a function of sex, comparing opposite-sex twins with a matched sample of unrelated opposite-sex twin clusters.

	Model 1[1]		**Model 2**[2]		**Model 3**[3]	
	β (CI)	Diff. *p*	β (CI)	Diff. *p*	β (CI)	Diff. *p*
Sex	**2.05** (1.70, 2.39)	0.077	**1.84** (1.50, 2.21)	0.112	**2.09** (1.75, 2.43)	0.081
By age groups						
Age ≤50	**2.10** (1.51, 2.68)	0.644	**2.02** (1.42, 2.61)	0.626	**2.25** (1.66, 2.84)	0.667
Age 51-60	**2.18** (1.65, 2.71)	0.160	**1.95** (1.40, 2.49)	0.225	**2.25** (1.72, 2.79)	0.224
Age 61-70	**1.51** (0.73, 2.29)	0.567	**1.33** (0.52, 2.14)	0.882	**1.47** (0.68, 2.25)	0.602
Age 71-80	**2.31** (1.12, 3.51)	0.597	**2.04** (0.70, 3.37)	0.622	**2.10** (0.90, 3.30)	0.664
Age ≥81	3.41 (-0.09, 6.91)	0.293	2.39 (-2.07, 6.85)	0.279	3.43 (-0.27, 7.13)	0.326

Note. Model 1: Adjusted for age at interview, Model 2: Adjusted for age at interview and attained social class, Model 3: Adjusted for age at interview and attained education

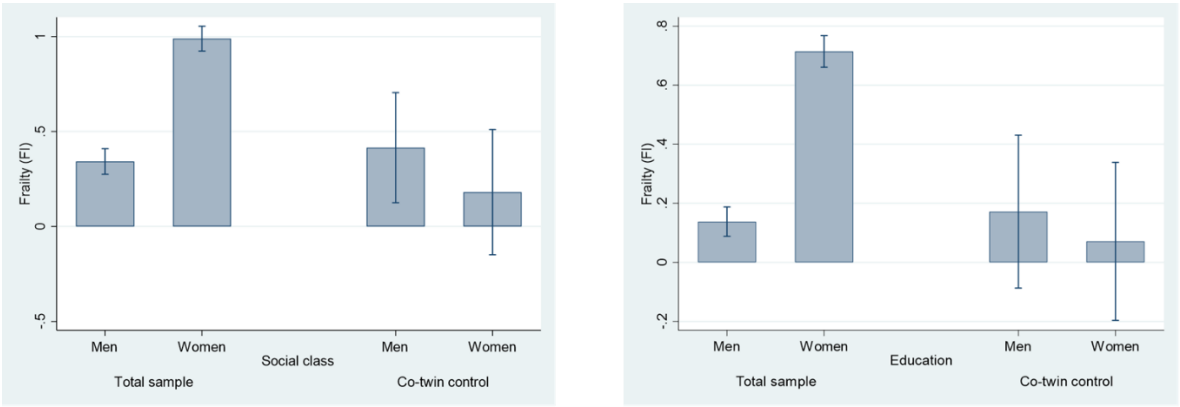


Figure 8. Frailty as a function of attained social class and education in men and women, adjusted age and birth cohort (born before or after 1925).
Note. The estimates indicate units of increase in FI at one unit increase of the socioeconomic indicators.

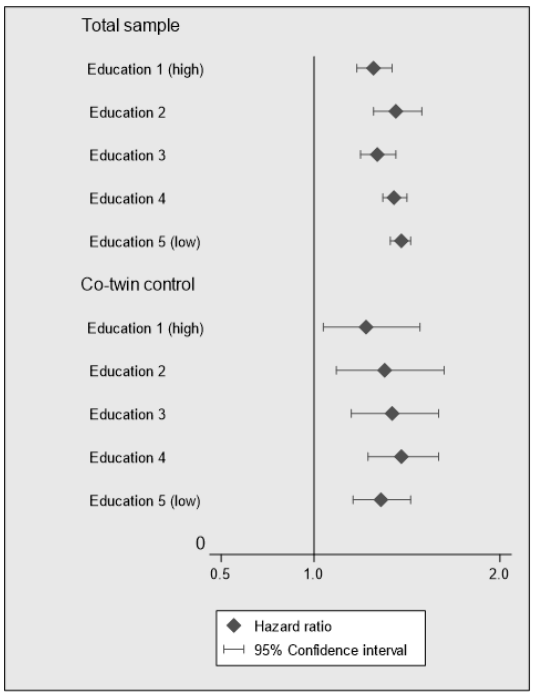


Figure 9. Men: Hazard ratios in all-cause mortality by 10 percent increase in FI by education. Total sample and co-twin-control.

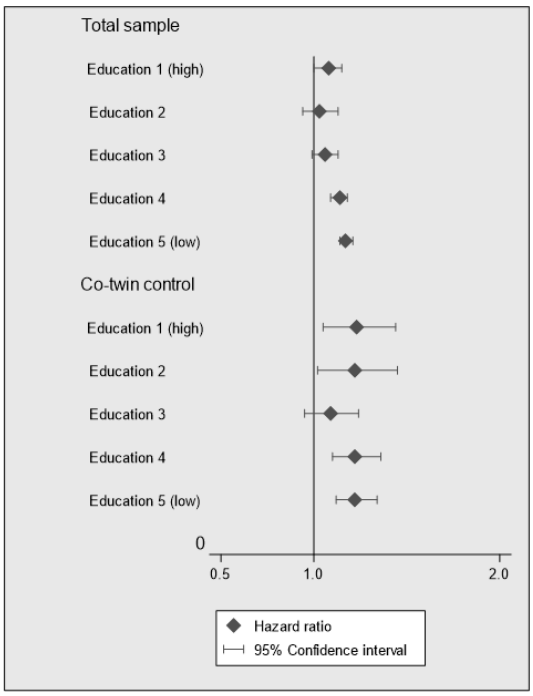


Figure 10. Women: Hazard ratios in all-cause mortality by 10 percent increase in FI by education. Total sample and co-twin-control.

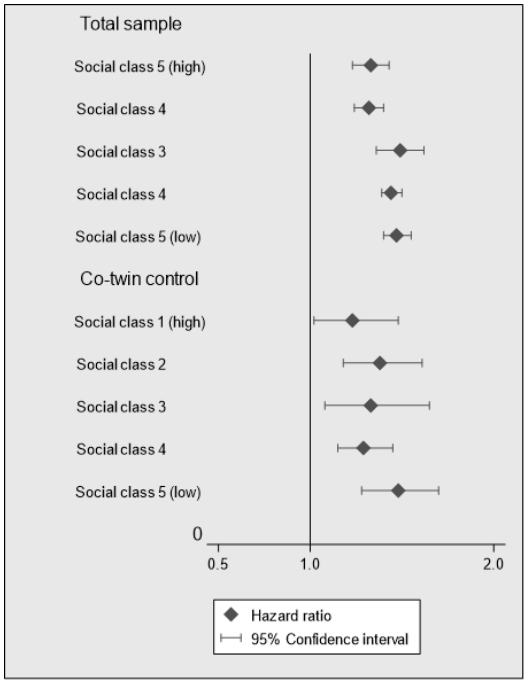


Figure 11. Men: Hazard ratios in all-cause mortality by 10 percent increase in FI by social class. Total sample and co-twin-control.

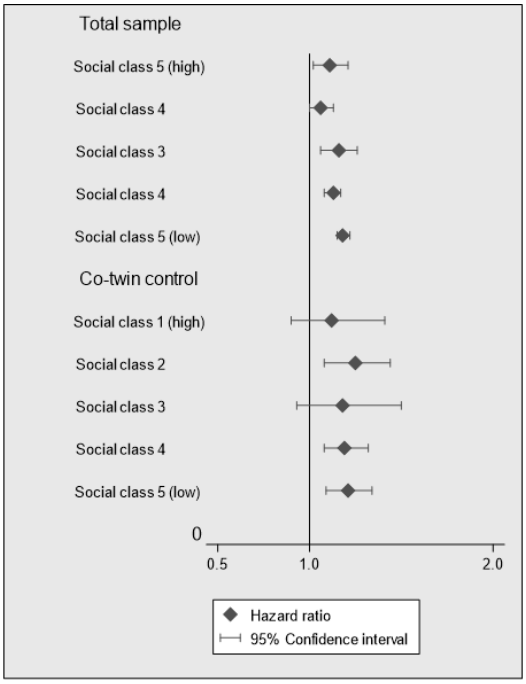


Figure 12. Women: Hazard ratios in all-cause mortality by 10 percent increase in FI by social class. Total sample and co-twin-control.

6 METHODOLOGICAL CONSIDERATIONS

Investigating aging and late-life health entails fundamental methodological issues related to the aging and the aging population. Data collections targeted at older populations, both cross-sectional and longitudinal, often suffer from low response rates due to poor health and physical and cognitive decline. However, the biggest challenge is that this selection is rarely random, but may reflect how different populations age differently due to socioeconomic circumstances, sex, or other influences during the life course. It will not only affect response-rate but may also contribute to selective mortality which will result in biased associations. Missing data on the older population needs to be discussed and taken into account when interpreting the results and is perhaps particularly problematic in studies of health inequities.

6.1 SELECTION BIASES IN THE CURRENT STUDY POPULATION

One major concern regarding our study design is the population. All participants were invited into the different data samples as adults and then followed up to old age, either by mortality data or in cross-sectional and longitudinal tests. There is a possibility of health selection that must be taken into account in the interpretation of the results. Research has shown that socioeconomic differences in health are declining with increasing age in the oldest age groups [150-152] This may partly be explained by selective mortality, which means that if people with lower SES have poorer health and thus higher mortality in earlier ages, the surviving cohort will to a higher extent include persons with higher SES and healthier individuals. It has also been shown that not only mortality selection but also selection through non-participation is larger among lower SES individuals in older cohorts [153]. In *Study I,* and *II* those with missing cognitive data also had lower childhood social class. As the results showed that lower rearing SES was associated to lower cognitive ability at the population level, it is possible that if these participants had been included, the association would have been even stronger as our sample was of higher SES and with possibly higher cognitive ability from the start.

Missing data can also be a problem in the statistical models. However, missing data points are managed in the mixed models but there is an issue related to that participants with only one observation only contributed to the intercept estimates and not to the slopes. It is possible that those that only participated in one IPT and those that participated in many are different regarding other aspects such as health status and SES. Thus, in *Study I* this may have influenced the slope estimates, but not our major finding – the discrepancy between the population level effects and the within-pair estimate on the intercept level. However, in *Study 2,* this may have been an issue as the EB-estimates rely heavily on the amount of data each person has. It is possible that this contributed to the small variance observed in the slope estimates. In *Study III*, participants had different entry dates into the study. The old cohort had the first observation in 1960 and the middle cohort in 1973, while the SALT cohort were included in 1998, and mortality obtained from the CDR provided registered deaths from these respective entry dates. This renders an obvious survival bias, not only in that there was no information on early-life mortality but also that the cohorts had compositional differences

related to health selection. However, the results from S*tudy III* were robust against stratifying on STR cohort and were also consistent in both premature and late mortality.

The issue regarding the SALT data entry date is also relevant for *Study IV* although in this study we included a wider age span, including birth years up to 1958. Mortality selection in *Study IV* may have caused the smaller socioeconomic differences in the oldest age groups. Both socioeconomic influences on FI and on mortality had an age gradient where there was a stronger effect in the younger age groups. It is possible that our results, especially regarding the oldest age groups, are biased due to both mortality and attrition selection. Despite these selection effects, we observed a social gradient in all age groups, also among the highest age groups although weaker compared to younger ages. Another important question to address is whether these selection effects also affects the twin models. For this to impact our twin model results there would need to be non-random differences between MZ and DZ twins related to selection and to SES, but for this we did not find any evidence. A genetic influence on longevity would have led to strongly attenuated results in the co-twin control models and especially after stratifying on zygosity. However, there was no evidence for that, neither in *Study III* nor *IV*. These problems are inherent to almost all aging research. Studies are therefore also comparable in that they share the limitations and generalizability.

6.2 MISCLASSIFICATION

Other challenges are related to the socioeconomic measures and what is included in the SES construct. This varies widely between studies and may sometimes depend on available measures but also because of common practice and convenience. There are differences between research fields, which somewhat complicates multidisciplinary investigations regarding attempts to harmonize measures across studies. The challenge is how to use socioeconomic measures in the best way to target the association and to avoid residual confounding. It is a balance between using optimal measures and to make studies comparable to other studies in the same field. Using socioeconomic variables from different cohorts and over time entails big challenges. The birth cohorts included in this thesis were not able to enjoy the major educational reforms in the 60's and 70's [94]. Meaning that educational opportunities were similar across cohorts, although the variation was low due to limited access to higher education for the majority of the population.

An obvious source of bias could be the retrospectively self-reported childhood measures which entails the possibility of misclassification due to recall bias. Unfortunately it was not possible to validate these self-reports with another data set, but intra-pair correlations of the self-reported measures in the reared together twins provided an estimation of how accurate these reports were. Intra-pair correlations of rearing social class was .8, which would indicate that the reports were sufficiently reliable. If this misclassification would increase or decrease the association is not possible to say. Previous research on accuracy of retrospective self-reported data on father's social class found that the accuracy was moderate and a discrepancy towards exaggerated levels of social class [154]. If this is applicable also in our data it would have led to an underestimated effect of rearing social class. However, the value of being able

to use retrospective data will hopefully outweigh the disadvantages. Using retrospectively reported data on for example rearing circumstances, enables longitudinal analyses otherwise not possible [115].

6.3 TWIN METHOD CONSIDERATIONS

Using twin data offers an advantageous approach to scrutinize the relationship between SES and health, both as it allows for adjusting for genetic confounding and also to quantify the interplay and influence of genetic and environmental factors. Nevertheless, there are challenges related to twin methods, and criticism has mainly been directed at the generalizability of twins compared to the other population and whether the assumptions in the twin methods hold.

It has been argued that twins are different from the general population, for example related to that getting twins is in itself a heritable trait, twins are commonly born prematurely, or that they are treated differently because of being twins. There has been little evidence that twins are significantly different from singletons [155]. In fact, large Swedish study used data from the Swedish Medical Birth Register to compare twins and singletons, they found that there was only small very differences in attained education and cognition between the two groups and no difference regarding vocational career [156]. Whether twins are comparable even at very high ages, has been studied using the OCTO-twin sample and there were no significant differences based on a number of health indicators between twins and singletons [157].

In addition to this, criticism has also been expressed regarding the possible influence of assortative mating. There is a certain degree of non-random mating in human populations [158]. As one of the underlying assumptions in twin methods is that parents are not genetically correlated with each other, it means that mating must be random. If it is not, the random genes from each parent may exceed 50%. This will not affect the MZ twins but for DZ twins it means that the assumption that they share approximately 50 percent of their co-segregating alleles may be understated. In the twin model this would lead to a lower expression of the A parameter and a higher influence of shared environment (C) [159].

Another issue regarding twin methods is the equal-environment assumption, which refers to that the shared environment in MZ and DZ twin pairs may not the same. This could in turn falsely generate an increased importance for the A component in a twin model. Although it may be expected that the shared environment of MZ and DZ twins is not the same, in terms of for example parenting, closeness between the twins, and peers. However, previous research has not found evidence that it would influence twin similarity [160, 161]. It is unclear how this may refer to twin similarity in old age, so it is not definite to say that this is not a problem in the studies in this thesis.

The co-twin design is also subjected to risk of bias, in terms of misclassification and shared confounding. It has been observed [162] that misclassification will lead to an attenuation of the effect, and even more so in the within-pair estimate. Misclassification will thereby "hide" the effect in the within-pair estimate. Similarly, if a confounder correlates (within the twin-

pairs) to a lower degree compared to the exposure, the within-pair estimate will also be attenuated. This bias could be expected to lead to an even larger attenuation in MZ twins as they correlate to a higher degree compared to DZ twins, in both exposure and outcome due to heritability. This generates even more biased estimates in the stratified analyses, falsely indicating genetic influences. Thus, if the association is caused by confounders that are instead less shared than the exposure, this would lead to a larger within-pair estimate.

In our analyses using rearing social class (*Study I* and *III*), confounders being less shared than the exposure would have been an obvious source of bias as the twins share their home environment and rearing SES. However, all co-twin analyses were performed on the twins reared apart and whom did not share their upbringing, thereby decreasing the risk of this specific bias in these analyses. In *Study III* and *IV*, attained SES measures were investigated as the main exposure. Attained social class and education were moderately correlated within twin pairs. It is possible that there are confounders that could be influencing the relationship between SES and mortality, mainly childhood SES or other socioeconomic circumstances such as neighborhood characteristics. However, in *Study III*, our social mobility estimates including both rearing and attained SES showed corresponding results to the models where attained SES was investigated separately. In *Study IV*, analyses focused on the differences between men and women, bias related to shared confounding should not be an issue in this case, if we assume that it is similar in female and male pairs.

6.4 VALIDITY AND GENERALIZABILITY

The validity and generalizability of studies is dependent on the possibility to reproduce the findings and replicate studies [163]. In *Study I, III*, and *IV* in thesis, we were able to reproduce findings from other studies on the population level. This strengthens the validity of these studies and facilitates the interpretation of the results from the subsequent twin models. In *Study II*, the results were consistent with findings from other studies but were not uniform and thus revealed the complexity of this issue. Most similar studies suffer from small study samples and so does our study. This makes it difficult to draw any definite conclusions apart from the complexity of the relationship. However, *Study II* provides new insights into the importance of longitudinal data when examining GxE interactions in late-life cognition. Similar results across studies may provide an indication of lower risk of bias, or possibly that studies are similarly biased.

Large sample-sizes also increase the validity of studies, in that it reduces uncertainty and increases precision of estimates. *Study III* and *IV* were based on large study samples while *Study I* and *II* were considerably smaller but with more extensive data that was also repeatedly collected, which provides other advantages. It is noticeable that our results were generally consistent across SES indicator, age groups and cohort. This strengthens the interpretations from the aggregated findings of this thesis which can may be based on, not only statistically significant estimates, but also from the pattern and direction of the results.

One major issue is that it will not be possible to replicate the rearing social class analyses in *Study 1* in other data sets, as there are no other studies with data on twins reared apart with the additional cognitive data. It is possible that our sample differs from the general population, which therefore compromises the generalizability of our results. However, the uniqueness of the data is also what makes these analyses and studies novel.

Because of the age of the participants, it is possible that findings in this thesis are not generalizable to cohorts growing up today, at least not in countries similar to Sweden. However, our cohort enabled us to study socioeconomic inequalities in a past Swedish context. The participants included in this thesis grew up in a society with large class differences and widespread poverty. This thesis hopefully reflects the impact of socioeconomic adversities on late-life health and mortality in this specific setting. This is relevant both for the understanding and knowledge of this cohort, but can also be important for understanding contexts similar to Sweden in the first half of the 20th century.

7 ETHICAL CONCIDERATIONS

Ethical considerations have been taken regarding privacy infringement. Data in the STR are pseudonymized, and only data with serial numbers are analyzed and available to the researchers. The code keys are stored by the respective principal investigators for the projects. Those responsible at the Karolinska Institutet have extensive experience to administer large personal data materials. Therefore, no individuals could be identified during the work of this thesis. The greatest risk of treating sensitive personal data is the possibility of identification through back tracking. This risk was minimized by ensuring that only limited data were available when the data were analyzed. Informed consent was obtained at the time of data collection. Regarding register-based data, an informed consent is not required but instead an ethical approval is needed to use the data.

Another ethical consideration in this thesis is the risk of stigmatization. The objective of all studies was to investigate familial influences on the relationship between socioeconomic circumstances health inequities later in life. The ethical consideration can largely be attributed to the results and how these may be perceived and interpreted. Particularly the link between nature and nurture is a complex issue. Careful interpretation of the results and how these were communicated to both the research community and to the general public was taken, in order not to stigmatize groups or individuals.

7.1 ETHICAL APPROVALS

All studies included in this thesis have ethical approval. Diary number for each study are as follows, *Study I*: 84:61; 98:319, *Study II*: 84:61; 98:319; 03:124, 98:380 15:5/10, *Study III*: 2016/2:5, and *Study IV*: 00:132. Ethical approvals 15:5/10 and 2016/2:5 were issued by the Regional Ethical Review Board in Stockholm, all other were issued by the Ethical Review Board of Karolinska Institutet.

8 DISCUSSION

The studies in this thesis were all aimed at exploring the interplay between genes and socioeconomic environment in late life-health and mortality, using both rearing and attained socioeconomic indicators. Through analyzes at both the population level and by utilizing the twin structure of the data, this thesis contributes with additional insights regarding the relationship between SES and late-life health.

Overall, the results from this thesis provides little evidence for a causal relationship between rearing SES and late-life cognition and mortality. In *Study I* and *III*, where this association was tested for possible familial confounding, no remaining effect was observed. The unique SATSA data, combing adoption and twin study design enabled these analyses. However, these analyses were also hampered by modest sample size and as there are no other comparable studies it is not possible to replicate these findings today. It should also be noted that there was little variation in social class and education among the parents of these birth cohorts, which indicates that rearing socioeconomic circumstances were perhaps not so different. Still the results are conclusive on both cognition and mortality and additionally supported by the social mobility results where adult SES seems to be the most important indicator for mortality. In contrasts to rearing SES, the attained socioeconomic indicators seemed to be robustly associated with late-life health and mortality, with the exception for the socioeconomic influence on FI in women which was completely accounted for by familial influences.

Genetic and environmental influences on cognitive ability were quantified in a biometric model and the results from these models indicated a complex relationship where both rearing and attained SES moderated the variance in late life cognitive abilities in different directions depending cognitive domain but also differences regarding the mean level or slope.

8.1 REARING AND ATTAINED SOCIOECONMIC INFLUENCES ON LATE LIFE COGNTIVE ABILITY AND COGNTIVE CHANGE

The hypothesis that the rearing socioeconomic environment may influence cognitive ability, not only in childhood but also in later life, has been partly supported by observations from many previous studies [48, 46, 164]. This assumption builds on the life-course theory that proposes that environmental stressors at different point in life may have a specific impact depending on the timing (sensitive period) or be linked (chain of risk) or accumulate (accumulation of risk) over the life-span [111]. The understanding of how rearing socioeconomic circumstances may influence cognitive aging could for example be that if childhood is a sensitive period it is possible that adverse circumstances during this time could act as stressors and disturb formative processes which would lead to life-long consequences, in this case for cognitive abilities. In *Study I*, we found that rearing social class was indeed associated to mean level cognition at age 65 but not with cognitive change. This relationship was also partly mediated by attained education, indicating that social mobility may in part mitigate adverse childhood circumstance. That attained SES, such as education or occupation

may partly mitigate or mediate the effect of rearing SES on cognition has previously been shown [44, 165]. Stressors during childhood may comprise adversity during the rearing period such as poverty and harsh working conditions of the parents including long working hours, poor nutrition, parents with poor health, and also loss off parents. Factors such as these can all be assumed to affect the child negatively, both psychologically and in terms of resources. In the time when the participants of SATSA grew up, Sweden was a very different society from today. Interestingly, we did not find that factors related to if the rearing environment was supportive towards education, for example having books at home or if the parents took an interest in the children's education, influenced the association. At the time when these cohorts were born, the welfare state was not established, working conditions were harsh for the less privileged, and higher education was only available for a few, mainly individuals from high SES families [166, 94]. Adverse conditions may not only be influential during childhood but may also affect in utero, for example through the mother's malnourishment and health behaviors, stress, or other negative exposures during pregnancy [167]. Early life stressors occurring either in utero or during childhood are hard to disentangle as they are both related to the biological parents. However, the SATSA study offered a unique possibility to separate theses effects due to the adoption design and additionally provided the possibility to account for genetic influences. Therefore, we were able to investigate if these rearing socioeconomic circumstances were robustly associated with cognitive aging, due to shared environment of the twins, or due to genetic influences. In contrast to our initial findings and the majority of previous research [46, 164, 48], we could not observe the same relationship in the reared apart twins after adjusting for familial confounding. In the between-within pair models the within-pair estimates, that provide the effect of rearing social class that is not attributable to the shared pair-effect, were greatly attenuated compared to the population effect. After further separating the analyses between MZ and DZ twins, results indicated that the effect was entirely genetic. It is also important to remember that the exposure was rearing social class and that no other adverse circumstances during upbringing were investigated. Thus, we cannot draw any conclusions about other stressors during childhood. However, these findings illustrate that cognitive differences may not occur late in life but are established early in life, which indicates a cognitive stability over life [22, 168], but also that these early differences may be reinforced by the influence of the person-specific environment.

These results from *Study I* also implied a possible gene x environment interaction, and prompted further investigation of the mechanisms behind these findings. We therefore extended the investigation to a biometric model in *Study II*. By decomposing the variance in cognition explained by SES, into shared environment, person-specific environment, and genetic influences, we were able to get a more comprehensive picture of the complex relationship between socioeconomic circumstances and cognitive aging. By additionally having access to both rearing and attained socioeconomic indicators (education and social class) we could also investigate if the influence differed depending on type of socioeconomic indicator and thereby also temporal differences. Perhaps most importantly, we were also able

to utilize longitudinal cognitive data and through that, investigate the moderation of variance in mean level cognition at age 75 as well as cognitive change before and after age 75, from four different cognitive tests and a general ability score.

We found socioeconomic moderation in all cognitive domains, although it differed between the three measures (mean level and slopes). The direction of moderation also differed between cognitive measures and depending on the socioeconomic indicator. The shared-environment has previously been suggested to be an important factor for cognition at lower SES levels while genetics influences explain more of the variance at higher SES levels [29]. Understood from the social enhancement model, a favorable genetic predisposition is further emphasized by a socioeconomically advantaged environment while in the disadvantaged environment, positive genetic influences on cognition are suppressed, thus allowing greater leverage for the rearing environment. This relationship have mainly been observed on cognitive abilities measured in childhood or adolescence [21, 29] and could be assumed to increase over the life span if further emphasized by attained SES. Bates et al. [169] observed a similar relationship in adult cognition moderated by childhood SES. In our models, investigating variance in cognitive change we additionally observed a greater influence by genetics at higher SES levels but also that the person-specific environment explained the largest part of the variance in cognitive change. However, these findings were not consistent across domains and SES indicator and generally no clear pattern could be observed regarding cognitive change.

Furthermore, the direction of moderation at the mean level was more consistent across cognitive abilities, but only significant for verbal abilities (Synonyms). Typically, the genetic variance decreased with higher SES levels. Such pattern may instead be understood from the diathesis-stress model where it is hypothesized that genetic vulnerability for low cognitive ability is amplified by adverse social environments over the life-course.

Our results display a complex pattern, indicating that socioeconomic circumstances may interact differently with either increasing genetic vulnerability at lower SES levels, but also strengthening genetic predisposition at higher SES levels. This apparent contradiction is reflecting the complexity of the interaction between SES and late-life cognition and possibly that mean level cognition and cognitive change have different representations in terms of SES. Less variance at the mean level at higher SES levels could reflect that more individuals in this group had higher cognitive ability up to a later point. If lower SES individuals already have lower cognitive ability and cognitive decline has already begun, there should also be less variance in cognitive change at lower SES levels. However, this could only be observed in few cases and the slope estimates did not reveal any consistent pattern.

It should be stressed that the variance due to socioeconomic influences was small, especially on the slopes, again emphasizing the initial findings of *Study I*, where we did not find any socioeconomic influence on cognitive change and decline. All in all, these two studies shows that the influence of rearing and attained socioeconomic environment on late-life cognition is

not direct but that part of the variance may be explained by interaction with genetic influences but also with the person-specific environment.

8.2 LIFE-COURSE SOCIOECONOMIC INFLUENCES ON MORTALITY INEQUALITIES

In *Study III*, mortality inequalities were investigated in terms of socioeconomic influences on preventable and non-preventable mortality. Findings from *Study III* showed that mortality inequalities remained even after adjusting for familial confounding regarding attained SES. However, as aforementioned we did not find support for influence of childhood socioeconomic circumstances on mortality inequalities. This conclusion was based on two different results from our data. Direct test of childhood social class on mortality indicated modest effect sizes that did not remain significant after adjustments for familial confounding, although precision was low in these models. Results based on social mobility indicated similar patterns and social class of origin (childhood) was subordinate to the adult social location. This not only shows that social class in childhood seem to have a negligible impact on health in later life, but also gives an indication of the mechanisms that operate in the interplay between socioeconomic conditions and health over the life course. This interplay can either act through direct or indirect pathways. Direct pathways refer to that either SES affects health or health affects SES resulting in socioeconomic or health trajectories over the life course. Indirect selection instead refers to common underlying factors that may influence both health and SES, such as familial factors [116]. Not only health indicators but also socioeconomic indicators such as social mobility and education has been shown to also have a genetic component [106]. The intra-pair correlations of the different socioeconomic indicators also pointed to genetic influences, with higher SES correlations in MZ than DZ twins. However, the results from the co-twin control showed that the social gradient in mortality could not be explained by familial factors. This would suggest either an effect of attained SES on health but it also allows for the possibility of health selection, where health influences SES and subsequently later life health. The impact of such a selection mechanism is supported by the social mobility models but also by the social gradient in non-preventable causes of death. If low SES is associated to mortality independent of preventability, it could indicate an early health selection into both lower SES and poor health.

Findings from *Study IV* revealed a similar pattern as in Study *III*, but where mortality as function of FI and socioeconomic differences in FI where robust and not influenced by familial influences. This increased mortality risk with higher levels of FI was stronger in men than in women, a relationship that was consistent over levels of SES and age.

8.3 SEX DIFFERENCES IN THE RELATIONSSHIP BETWEEN ATTAINED SES AND FRAILTY - MALE-FEMALE HEALTH-SURVIVAL PARADOX

Results from *Study IV*, provided support for the male-female health-survival paradox. Women were more frail than men but the FI was more strongly related to mortality in men than in women. This also suggests that the underlying risk factors for frailty may be different for men and women. The socioeconomic gradient in frailty observed at the population level

did not remain for women after adjusting for familial confounding. Person-specific environmental factors, such as attained SES, have been found to explain approximately half of the variance in frailty [62]. Results from *Study IV*, indicate that these environmental factors may be gender specific. The effect observed at the population level for women, which did not remain in the co-twin control, possibly reflected the importance for shared environmental influences. The results also imply that the socioeconomic indicator of SES applied in this study may not have reflected actual SES in women. It is likely that men from this cohort had better opportunities over the social strata and also that the household SES is most often the same as the men's attained social class or education. While for women it may differ, and women with low SES could have a household SES across the social strata. This reflects that both educational and occupational opportunities were scarce for women at this time in Sweden. Unfortunately neither social class nor levels of education reflect household chores, rearing of children, or other unpaid work often carried out by women. If the household SES would be a better predictor for frailty in women, this could possibly indicates that frailty in women is more related to the factors related to the social position and not to for example the individual working position as it seems to be for men. These results raise questions about how best to measure social status in relation to health among women in these cohorts.

9 IMPLICATIONS FOR FUTURE RESEARCH

The novelty of this project was adding a comprising approach to studying the relationship between life-course SES and late-life health and mortality. The implication of this thesis is that some previous findings regarding the relationship between rearing and attained socioeconomic status and late-life abilities and mortality could be reconsidered. Efforts to equalize health outcomes cannot disregard genetic susceptibility and the different paths of gene-environment interplay. To approach inequalities we may also need to consider and compensate for genetic vulnerability.

The main implication of this thesis is related to including family based designs when investigating health inequities. Genetically informative populations may increase our understanding of the link between socioeconomic circumstances over the life course and health. Both related to getting a better understanding of direct and indirect selection effects on health and also to create a better understanding for how to target early genetic vulnerability. The studies in this thesis are not the first to investigate socioeconomic factors and health in genetically informative setting. However, perhaps surprisingly, such studies are still rare even though it is known that both SES and health have a genetic component. There are still several well established relationships between SES and health that have yet not been scrutinized for possible familial influences. This thesis does not provide any clear answers on whether the relationship between SES and late life health is causal but it surely shows that these relationships are complex and multifaceted and by including family-based data we can get a little better understanding of these pathways - which is an important implication for this research area. The use of family data, is in Sweden available not only through the STR but also through the different national registers, such as the Medical Birth Register and the Multi-Generation Register. Family based designs utilizes not only twins but can be applied using parents (biological and adoptive), full and half siblings, cousins and so on.

The findings in this thesis do not have any direct clinical or policy implications. However, it is of interest for society in general, and for other more applied research in particular - to understand the origins of health, mortality and cognitive ability in old age. More research is needed to understand these pathways and the interplay between the socioeconomic environment and genetic propensities. However, the aggregated results indicate the need for individual interventions and to target vulnerable populations. Not all people will be the same in terms of cognition, abilities, health, and other aging trajectories, but everyone deserves the same chance to reach their full potential. If these differences are not acknowledged it is possible that those already in disadvantage will increase their vulnerability over the life-course by a “negative” interaction with the environment, both passive, active and reactive. And, those already advantaged will be even more advantaged – thereby increasing health inequities over the life-course and also across generations.

10 CONCLUSIONS

This thesis provided an opportunity to achieve a greater understanding of the socioeconomic pathways from childhood to old age and how these relates to cognitive trajectories, frailty and mortality in late life, and by using twin design more could be understood of familial influences. On a population level, we found that both rearing and attained socioeconomic circumstances were associated to later-life health and mortality, where lower SES was associated with more adverse health outcomes; lower cognitive ability, higher degrees of frailty and earlier mortality. However, after taking familial influences into account a slightly different image appeared. The influence of rearing social class on both late-life cognitive abilities and mortality was confounded by familial influences. While the attained socioeconomic indicators were robustly associated with both mortality inequalities and frailty. SES influences on variance in cognition emphasized the complexity of the interplay between socioeconomic circumstances and genes where we found that the variance in late-life cognition could be influenced by an SES interaction both with genetic vulnerability and genetic propensities.

The results from this thesis emphasize the importance of acknowledging familial influences when studying the relationship between life-course socioeconomic circumstances and late-life health and mortality. From that conclusion it also raises the importance of applying family-based data and study designs. Findings also highlight the complexity of investigating social and socioeconomic influences in men and women – especially in older cohorts. This thesis therefore also shows that greater caution is needed to draw causal conclusions about the relationship between socioeconomic circumstances, health, and mortality in late life.

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