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INTELLIGENCE AND CARDIOVASCULAR HEALTH

EPIDEMIOLOGICAL STUDIES OF SWEDISH MEN

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Life is what is going on while you are busy making other plans

John Lennon

To my mother and grandmother
– two strong and independent women

ABSTRACT

Aim: A first aim of this thesis was to examine the relationship between intelligence in early adulthood and health outcomes, mainly cardiovascular morbidity and mortality, CVD, later in life using register-based data on Swedish men. A second aim was to increase understanding of the pathways between intelligence and CVD morbidity/mortality by studying the association between intelligence and smoking habits and nicotine dependence, who might act as mediators of the association between intelligence and mortality.

Material and methods: The study populations in this thesis were created through record linkage of several national registers where IQ was collected from the Military Conscription Register. The analyses were based on all Swedish men born 1951 to 1984, depending on the paper, that went through conscription examinations. Also, for paper II parents of the men were analysed. Paper IV and V were based on Swedish male twins. The association between IQ and mortality was analyzed with Cox proportional hazards regression and conditional logistic regression models. The association between IQ and smoking status was analysed with linear, logistic and polytomous regression models and the association between IQ and nicotine dependence with quantitative genetic analyses.

Results: In general, paper I-III support previous research about inverse associations between IQ and CVD morbidity/mortality. In addition to previous research our results revealed that IQ was associated with coronary heart disease, CHD, independently of socioeconomic position, SEP, (paper I) and that IQ was inversely and significantly associated with major subtypes of stroke (paper III). The strongest association found for hemorrhagic stroke. Further, the effect of IQ on mortality was found to be present also when offspring IQ was used as a proxy for parental IQ (paper II). In paper IV and V when the association of IQ and smoking and nicotine dependence was studied no evidence of a causal association was found. In paper IV smoking was associated with IQ but appeared to be the result of early environmental factors rather than resulting from a causal effect of intelligence. In paper V both IQ and nicotine dependence showed moderate heritability (0.58 and 0.39 respectively); however the phenotypic correlation was marginal (-0.08) and the overlap between genetic factors influencing IQ and nicotine dependence was small (-0.19).

Conclusion: In this thesis, inverse associations between IQ score at the age of 18 and mortality later in life, mainly CVD, is presented. These associations were found within all socioeconomic strata, were robust to adjustment for indicators of SEP in childhood and adulthood and were present also when using offspring IQ as a proxy for parental IQ. Further, our results gave no support for IQ to be causally associated with smoking or that smoking or nicotine dependence act as important mediators of the IQ-CVD association. Finally, no evidence was provided for a common genetic factor behind IQ and nicotine dependence. This thesis provides information about the pathways of intelligence and mortality. However, more research is needed before any conclusions can be drawn with regard to public health policy.

SAMMANFATTNING (SWEDISH SUMMARY)

Syfte: Det övergripande syftet med avhandlingen har varit att undersöka sambandet mellan intelligens uppmätt vid 18 års ålder och hälsoutfall senare i livet, i huvudsak kardiovaskulär sjuklighet och dödlighet. Vidare var syftet även att bidra med ökad förståelse till möjliga mekanismer bakom sambandet intelligens och dödlighet. genom att studera sambandet mellan intelligens och rökning och nikotinberoende, föreslagna som medierande faktorer.

Material och metod: Den studiepopulation som avhandlingen baseras på är skapad genom registersamkörning av ett flertal nationella register, där IQ hämtades in från Mönstringsregistret. Analyserna baserades på alla svenska män som var födda mellan åren 1951 och 1984, beroende på studie, och som genomgick mönstring. I studie II studerades även föräldrarna till männen. Studie IV och V baserades på svenska manliga tvillingar. Sambandet mellan intelligens och dödlighet analyserades med Cox proportional hazard regression samt betingad logistisk regression. Sambandet mellan intelligens och rökning analyserades med linjär, logistisk och polytom regression och sambandet mellan intelligens och nikotinberoende analyserades med kvantitativa genetiska modeller.

Resultat: Sammanfattningsvis så visar studie I-III, i linje med tidigare forskning, på ett omvänt samband mellan intelligens och dödlighet. Dessutom visade våra resultat att sambandet mellan IQ och CHD var oberoende av social position (studie I). Vidare återfanns omvända samband för IQ och olika subtyper av stroke där det starkaste sambandet återfanns för hemorrhagisk stroke (studie III). Vidare påvisades samband mellan intelligens och dödlighet även då sonens IQ användes som en indikator för föräldrarnas IQ (studie II). I studie IV och V studerades sambandet mellan IQ och rökning och nikotinberoende. Inga bevis återfanns för ett kausalt samband mellan IQ och rökning eller nikotinberoende. Även om vi fann ett starkt omvänt samband mellan IQ och rökstatus så gavs inget stöd för att sambandet skulle vara kausalt utan kunde snarare kopplas till gemensamma miljöfaktorer. I studie V återfanns relativt hög heritabilitet för både IQ och nikotinberoende (0.58 respektive 0.39), dock var den phenotypiska korrelationen svag (-0.08) och överlappande genetik för intelligens och nikotinberoende bedömdes som marginell.

Slutsats: Avhandlingen visar på ett omvänt samband mellan uppmätt intelligens vid 18 års ålder och kardiovaskulär dödlighet senare i livet. Sambandet återfanns i samtliga socioekonomiska strata och kvarstod även efter justering för indikatorer för social position i barndomen och i vuxen ålder. Vidare återfanns sambandet mellan IQ och dödlighet även då sonens IQ användes som en indikator på föräldrarnas IQ. Vidare ger avhandlingens resultat inget stöd för att intelligens skulle ha en kausal effekt på rökning eller nikotinberoende, två föreslagna medierande faktorer till sambandet mellan intelligens och dödlighet. Inga bevis återfanns heller för en gemensam genetik för intelligens och nikotinberoende. Avhandlingen bidrar med information om underliggande mekanismer bakom sambandet mellan intelligens och dödlighet. För att kunna föreslå preventiva åtgärder krävs dock fler studier.

LIST OF PUBLICATIONS

This thesis is based on the following five publications.

I. Silventoinen, K, **Modig Wennerstad, K**, Tynelius, P, Rasmussen, F.
Association between intelligence and coronary heart disease mortality: a population-based cohort study of 682,361 Swedish men
European Journal of Cardiovasc Prevention and Rehabilitation. 2007 Aug;14(4):555-60.

II. **Modig Wennerstad, K**, Silventoinen, K, Batty, G.D, Tynelius, P, Bergman, L, Rasmussen, F.
Association between offspring intelligence and parental mortality: a population-based cohort study of one million Swedish men and their parents.
Journal of Epidemiol Community Health. 2008 Aug;62(8):722-7.

III. **Modig Wennerstad, K**, Silventoinen, K, Tynelius, P, Bergman, L, Rasmussen, F.
Association between intelligence and type specific stroke: a population-based cohort study of early fatal and non-fatal stroke in one million Swedish men
Journal of Epidemiol Community Health. 2009 Oct 14. [Epub ahead of print]

IV. **Modig Wennerstad, K**, Silventoinen, K, Tynelius, P, Bergman, L, Kaprio, J, Rasmussen, F.
Associations between IQ and cigarette smoking among Swedish male twins
Social Science & Medicine, Volume 70, Issue 4, February 2010, Pages 575-581.

V. **Modig Wennerstad, K**, Silventoinen, K, Tynelius, P, Kaprio, J, Rasmussen, F.
Genetics of the association between intelligence and nicotine dependence: a study of Swedish male twins
Re-submitted to Addiction

CONTENTS

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CPD	Cigarettes Per Day
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	Dizygotic (twins)
FTND	Fagerström Test of Nicotine Dependence
G	General intelligence
Gc	Crystallised intelligence
Gf	Fluid intelligence
HDL	High-density lipoprotein
HR	Hazard Ratios
ICD	International Statistical Classification of Diseases and Related Health Problems
IQ	Intelligence quotient. In this thesis IQ is used as an abbreviation for intelligence test scores in general, derived from psychometric tests
LDL	Low-density lipoprotein
LOUISE	Longitudinal Database of Education, Income and Occupation
MZ	Monozygotic (twins)
OR	Odds Ratios
SALT	Screening Across the Lifespan Twin study
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEM	Structural Equation Modeling
SEP	Socioeconomic Position
STAGE	Study of Twin Adults: Genes and Environment

1 INTRODUCTION

How smart or intelligent you are – can it really have an impact on your risk of dying or being hospitalised? This question is often raised when presenting the research field of cognitive epidemiology. The second question that is raised is "What is the point of studying this topic – not much can be done with the information, especially if intelligence is genetically determined". In this thesis I will present some answers to these questions together with a background of the research field.

What is it that makes some people live longer than others or make some people's cardiovascular system age much earlier than others'? There are several well documented adverse risk factors such as high cholesterol, hypertension and diabetes. Also, we know that several health behaviours, such as smoking, physical inactivity and unhealthy nutrition have negative health effects. However, even if health behaviours are predictive they do not explain all the differences in health outcomes in a population. We all consist of an individual genome, and there seems to be a separate effect of socioeconomic differences, perhaps through psychosocial stress.

Studying socio-economic differences in health has, for a long time, been a broad area of research. The differences are evident but the underlying mechanisms are not as clear. We know that more highly educated people live longer and have better health. But why is that? Is it because they behave differently and are more aware of the secret keys to a better health, or is it because they stay away from unhealthy working environments for longer times and perhaps never enter them at all? Or are highly educated people genetically different from those who do not achieve the same high educational levels? Studying intelligence in this context can give us another dimension of the underlying mechanisms of education and socioeconomic differences in health.

Even if cognitive epidemiology is a relatively new area of research, the associations of intelligence and health outcomes are well documented. However, there are still many unanswered questions. It is important to shed light on the pathways by which intelligence affects health, and on the underlying mechanisms of the association.
If it is due to behavioural risk factors, the public health implications are strong. Are our public health recommendations tailored to suit a population of normal intelligence and if so, do they get register with the lowest quarter of the IQ-distribution?

If, however, the primary underlying mechanism is genetic, the public health aspect is not as clear, although it is still an important finding in terms of ruling out the behavioural explanation. It may also serve as a predictive tool for identifying certain risk groups.

The overall aim of this thesis has been to investigate the relationship between intelligence and health outcomes, mainly cardiovascular mortality and to study the potential pathway of mediation by smoking. In addition, there will be a discussion about different pathways based on the results of this thesis, together with the results by others.

2 BACKGROUND

2.1 COGNITIVE EPIDEMIOLOGY

Epidemiology is “The study of the distribution and determinants of disease frequency”. The studies on which this thesis is based belong to a new field of epidemiology known as cognitive epidemiology. The research field of cognitive epidemiology has been defined by Ian Deary (1-4) but originally came into existence in response to calls in the psychological literature that information on individual differences, such as intelligence, in population-based samples could be informative and important in studying health outcomes and that they should be studied to a greater extent (5-7). The suggested definition of the research field is: “*Cognitive epidemiology examines the associations between intelligence—usually from early in life—and later morbidity and mortality. In addition to exploring and establishing associations, studies within cognitive epidemiology attempt to explain them, by testing possible confounders and mediators, and complex pathways, of intelligence–health associations*”(8).

Researchers in this field use different terms such as cognition, cognitive ability and mental ability but most often they all refer to intelligence as measured by cognitive ability test scores derived from psychometric tests. Whilst this research field has existed for a long time, it has experienced rapid expansion over the past decade.

2.2 INTELLIGENCE

The word intelligence derives from the Latin verb *intelligere* “to understand”, “to choose between”. The abbreviation IQ stands for ”Intelligence Quotient”, a measure of intelligence, and was originally a ratio of mental age to chronological age. Even though the term IQ is still commonly used (also as an abbreviation for intelligence), the scoring of modern IQ tests is now based on a projection of the subject's measured rank on the Gaussian bell curve with a mean of 100 and a standard deviation (SD) of 15. However, not all tests are constructed according to that scale, and the IQ test used in this thesis is based on a stanine scale with a mean of 5 and a SD of 2.

The branch of psychology which is concerned with the study of the nature, origins and applications of individual differences is called differential psychology (9). Its principal topics are cognitive abilities and personality but it also addresses attitudes, moods and other psychological traits. Broadly speaking, there are two different approaches to the study of cognition in psychology; the experimental approach and the differential approach. The former concerns itself with the modal structure of the mind and those functions that are common to all of us. The latter deals with individual differences and studies of the nature, causes and consequences of variances in people’s cognitive performance (3). The field of cognitive epidemiology is more closely connected to the differential approach.

2.2.1 What is intelligence?

The concept of intelligence has a long history; as early as 380 BC, Plato argued that the human soul had three elements which could be identified as intellect, emotion and will (10). This rational soul or intellect was according to Plato the thinking portion within each of us, which discerns what is real and not merely apparent, judges what is true and what is false, and wisely makes the rational decisions (11). Since then the concept has been developed and studied, over the past century mainly by psychologists.

2.2.1.1 Intelligence and brain size

The brain is very complex. It tells us what to do and when, all through small connections of nerve signals. The working of the brain is based on its composition, which in turn is based on a range of genetic and environmental factors. For a long time, the size of the brain, or even the head size as a proxy, was thought to be the main explanatory factor of intelligence. A research group led by Tony Vernon reviewed all studies up to 1999 that had examined the size of the living brain using a modern brain-scanning machine and had correlated the size of the brain to the performance on mental ability tests. The average correlation was 0.4 (12). A more recent review study supports this and shows a mean correlation between brain size and general mental ability among humans of the same size, 0.4 (13). However, which factors decide the size of the brain? It could be more nerve cells, or the same number of nerve cells but with more connections. An increased brain size could also be caused by an increased thickness of the fatty layers surrounding the nerve cells. These myelin sheets are the electrical insulation which surround the nerve cells' "cables" and help them to send messages more quickly. More recent studies of brain size and intelligence focus on certain areas of the brain which correlate most highly with ability test scores. For example, IQ has been shown to be positively associated to cortical thickness (14). Ullén and his colleagues found that stability of tapping (an automatic timing task) and intelligence were correlated to regional volume in overlapping right prefrontal white matter regions (15). They suggested that a more extensive prefrontal connectivity underlies individual differences in intelligence. Posthuma and associates have shown that for example processing speed was related to white matter volume (16;17). Further, they concluded that brain volumes are genetically related to intelligence. In a recent review of the modern neuroimaging studies Jung and Haier found that different parts of the brain are activated depending on the task at hand. Variations in a specific area predicted individual differences in intelligence and reasoning tasks. To simplify, the tasks connected to reasoning and planning activate areas in the prefrontal cortex which in their turn activate the parietal, occipital, and temporal lobes to collect more knowledge-based information (18).

2.2.1.2 Definitions of intelligence

Even though the definitions of intelligence are similar to one another there is no single standard definition. In December 1994, as a response to the highly debated book "The Bell Curve" (19), the concept of intelligence was defined on a full page declaration in the Wall street journal. It was signed by 52 well known researchers and in its first statement the concept of intelligence is defined:

Intelligence is a very general mental capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill, or test taking smarts. Rather, it reflects a broader and deeper capability for comprehending our surroundings – "catching on", making sense of things or "figuring out" what to do (3).

Another, similar definition is that by the American Psychological Association:

Individuals differ from one another in their ability to understand complex ideas, to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, to overcome obstacles by taking thought. Although these individual differences can be substantial, they are never entirely consistent: a given person's intellectual performance will vary on different occasions, in different domains, as judged by different criteria. Concepts of "intelligence" are attempts to clarify and organize this complex set of phenomena (20).

Within psychology, intelligence is a central concept that has been intensively studied during the last century. There is a fair degree of consensus among most researchers in the field regarding the measurement and validity of differences in human intelligence (3;20). Within the fields of medicine and epidemiology, intelligence has been less studied and the fact that it has no exact definition worries some critics. How can one measure something that has no exact definition? There is no clear answer to that question but intelligence can be perceived as a broad concept of an underlying ability, delineating general mental ability. It is measured by different types of tests. The tests are not equivalent to one another but give highly correlated measurements. Obesity might be a useful example of a similar concept in the medical field. It is not entirely clear what obesity really stands for, neither as a risk factor nor in terms of its definition and measurement. It is often measured with, and defined by, BMI, but there are other measures such as fat percent or waist circumference. They will give different results from the BMI, but they will be highly correlated with it. As intelligence is a complex trait, as defined in the cited text above, there is no exact way of measuring it. I will return to this in section 2.2.4 "How to measure intelligence".

In the same way as body size, sports or art aptitude and health outcomes vary between individuals, so does cognitive ability or intelligence vary. And in the same way as these traits or abilities are dependent both on environmental and genetic factors, so is intelligence (more about this in 2.2.3).

Intelligence is stable over time in the sense that individuals tend to hold approximately the same position relative to their age cohort from childhood into old age (21-23).

2.2.2 Intelligence or intelligences

2.2.2.1 Is there a general intelligence factor?

Intelligence tests usually consist of several subtests and the tendency to do well, or badly, in all of these caused the discussion on the presence of a general intelligence, a g-factor. The first person to describe the g-factor was Charles Spearman in a famous paper in 1904. He examined school children's scores on different academic subjects and found them to be correlated. Spearman concluded that the correlation among the variables could best be explained by assuming that there was a single factor that underlay them (23). This early work formed the basis of factor analysis. Over the following decades this was investigated and questioned by many researchers and it is now known that many more factors are needed to describe a person's intelligence. In 1993 John Carroll published his book, Human Cognitive Abilities: A Survey of factor Analytic Studies (24). He collected as many studies as possible on human intelligence that he considered to be of good quality and then re-analysed the studies, over 400 sets of data. One of his findings was what he named the "three stratum model", where the g-factor is on top and eight types of broad mental abilities are found underneath it. He considered the g-factor to be general in the sense that it was likely to be present to some degree in nearly all measures of cognitive ability (24).

This model has been supported by other researchers and for other intelligence tests. One of the most well-known tests, the Wechsler Adult Intelligence Scale, version III, WAIS-III, consists of 13 sub-tests. The subtests are ordered in four groups of abilities, processing speed, working memory, perceptual organisation, and verbal comprehension (12). The WAIS-III was developed and marketed by the Psychological Corporation in the USA and the UK. It has been broadly used and it was found that all tests correlated positively with each other. There was no subtest unrelated to any other subtest and no near-to-zero correlations. The highest correlation was found between vocabulary and information, (r=0.8) and the average correlation was r=0.5. Tests of vocabulary, information, similarities and comprehension had especially high associations with each other. The same is true for digit span, arithmetics and letter-number sequencing. These are called group factors. Just as for the subgroups, the four group factors correlate with each other between 0.6 and 0.8. This supports the notion of a strong g-factor (25).

2.2.2.2 Fluid and crystallized intelligence

In addition to the discussion about the g-factor and factor analyses of intelligence, there has been a distinction between intelligence as an inherited capacity and intelligence as a result of knowledge and schooling. Psychologists distinguish between what they call fluid intelligence, Gf, and crystallized intelligence, Gc. It was Horn and Cattell who first put forward the notion in the 1960s that fluid intelligence depends primarily on genetic processes and that crystallized intelligence is more dependent on environmental factors such as the cultural environment (26;27). Gf would then reflect the basic abilities in reasoning and higher mental processes and Gc the extent to which the individual has been able to learn and profit from education, culture and experience. The distinction can also be seen in terms of testing as culture-bond and culture-fair intelligences (11). Even if these two types of intelligences correlate, a

person can have a high fluid intelligence but a lower crystallized intelligence, depending on the environment, while a low fluid intelligence would make it difficult to score high on crystallized intelligence despite a favourable environment. Some researchers believe that fluid intelligence is identical to g and Gustafsson presented data which indicate that Gf as formulated in the Horn-Cattell model is equal to g as described in the British models of Spearman and Vernon (28).

2.2.3 Genetic or environmental

Intelligence runs in families. The average correlation for IQ of biological parents and offspring and for siblings raised together is about 0.45 (29). The question is to which extent this is due to genetic and environmental factors, respectively.

Family studies, such as twin-, adoption- and parental-offspring studies, are useful when trying to separate genetic effects from environmental effects. In studies of monozygotic twins reared apart and together the IQ correlation has shown to be very similar, around 0.70-0.78 (12;29). In a paper from 1997, Plomin and Petrill summarise data from twin and adoption studies and conclude that about half of the variation in IQ is attributable to genetic factors (29). Twins reared apart do, however, share the pre-natal environment (even though it can differ as well) which could be important in explaining intelligence. This effect is treated as a genetic factor in such studies. Also, the twins in some of the adoption studies were somewhat older than the twins in other heritability studies and heritability estimates tend to increase with age (about 40% in childhood, 60% in early adulthood and 80% in later life) (29-31). A possible explanation to this is that genetic factors nudge us towards environments that accentuate our genetic propensities, thus leading to increased heritability throughout the life span.

In later research of the heritability of intelligence several twin studies have found heritability estimates in the range of 0.5 to 0.7 (32-34). The heritability estimates increase with age suggesting that environmental factors play a larger role in early childhood (35). The heritability estimates presented are from samples representing normal ranges of intelligence. Little is known about the etiology at the low or high ends of the intelligence distribution (29). However, a recent study found that the developmental etiology of high IQ did not significantly differ from that found for the continuous measure (36).

So if genetic factors explain about half of the variation in intelligence, environmental factors must explain the other half. The question is which type of environmental factors that is most important, environmental factors shared by co-twins or family members or environmental factors unique to each individual? Shared environments are, for example, pre-natal conditions and early life environmental factors such as the socioeconomic conditions in the home. Examples of non-shared factors are birth order, peers and sometimes schooling. Fetal life environment can be considered a shared environment (if twins) but also non-shared (if siblings or if twins share their placenta which may lead to unequal distribution of blood between the twins). However, even if a mother's nutrition might differ between her two children, it is

likely that it is still much more similar than for another two siblings born by a different mother. Since environmental effects have been shown to have a large impact early in life and then decrease with age, it is likely that such early environmental factors play a role. Adoption studies show almost no correlation of IQ between offspring and adoptive mother or offspring and their adoptive siblings (12). This would indicate very little effect of shared environmental factors. However, the environmental effect from life in utero is not taken into account as an shared environmental factor in such study designs. Another possible effect could be the effect of breastfeeding, which has been shown to have a positive impact on IQ (37;38). Der and associates, however, showed that breastfeeding is more common among mothers with higher IQ. Consequently, controlling for this and other confounders resulted in no effect from breastfeeding on the IQ in children in their study (39).

When it comes to the effects of pre-natal conditions, there are studies showing no association between birth weight and IQ (40). Others have looked at birth weight within the normal range and found a small positive association with IQ (41). There is, however, a difference between low birth weight reflecting premature delivery and low birth weight due to the infant's size being small for its gestational age. Bergvall and colleagues found that men who were born preterm with a very short birth length or a very small head circumference for gestational age faced a near doubled risk (after adjustment for maternal and socioeconomic factors) for low intellectual performance compared with their appropriate peers. Among men who were born at term, risk for low intellectual performance was increased among those with very or moderately low birth weight, birth length, or head circumference for gestational age (42;43). These results are in line with previous research on the association between being small for gestational age and the risk of low IQ (44;45), but it is difficult to know to which extent intrauterine growth is due to genetic or environmental factors.

For Swedish data there have been a few longitudinal studies on cohorts born in the 1940s on the effect of schooling on intelligence. They found enhancements in IQ as a function of schooling, with about 2-2.5 IQ points for each additional year of academic schooling (46;47). Furthermore, more recent studies have reached the same conclusion - schooling affects intelligence (47;48).

When trying to separate the variance to either genetic or environmental factors, the possibility of gene-environment interaction tends to be neglected, even though it is highly likely that such an interaction exists. Dickens and Flynn argue in their paper "Heritability Estimates versus large environmental effects"(49) that
it may appear contradictory that whilst intelligence is largely heritable, at the same time one can see large environmentally-induced IQ gains between generations, which would suggest an important role for environment in the shaping of intelligence.
They present a model in which both environment and genes are important in explaining people's intelligence. Simplified, it suggests that people who have a genetic propensity for a particular trait will become matched with superior environments for that trait; and that genes can derive a great advantage from this because genetic differences are persistent. They give an example of a tall and quick person, who is likely to be somewhat better at basketball than the average person. The genetic advantage is upgrading the environment, the amount of time he plays and practices,

and this enhanced environment will in turn upgrade his skill. In this way, small genetic differences match people with different environments. Thus, identical genes tend to produce very similar environments—even when children are raised in separate homes.

As I have described in chapter 2.2.2, intelligence consists of several abilities and the effect of genes and environment can of course vary between these. When discussing genetic and environmental influences, it has been done considering intelligence as general intelligence and not gone into details of specific abilities.

2.2.4 How to measure intelligence

When thinking about measuring intelligence one should keep in mind that intelligence is a concept and not a thing. Psychologists try to define and measure this concept using different methods. They try to capture the brain's ability to reason, solve problems and plan ahead with various tests found to work well in this respect. Eysenck describes in his book "The Structure and Measurement of Intelligence" (11) that all concepts are elusive and difficult to pin down. He gives examples of mass, gravitation, and temperature. Intelligence tests were developed and used for practical reasons, for example to select officers in the army, or talented children for schools or occupational selection in industry and they have worked well for these purposes. There are several culture-bound tests where the tests measure the candidate's background knowledge and his/her ability to use his/her intelligence for the purpose of taking in information and benefit from instructions, for example the Swedish Scholastic Aptitude Test ("högskoleprovet"). These tests will by definition vary by culture and over time. In science we may wish to have time- and culture-independent tests. Such tests should in a perfect situation be independent of environmental influences such as schooling and socioeconomic position. The distinction between culture-bound and culture-fair intelligence is often known as fluid versus crystallised intelligence, described previously in 2.2.2.2.

Alfred Binet, a French psychologist, was the first to publish a modern intelligence test, the Binet-Simon intelligence scale, in 1905, with the purpose of distinguishing mentally retarded children from those with behavioural problems (20). Together with Théodore Simon, Binet published revisions of his intelligence scale in 1908 and 1911.
In 1916 Terman published a refined version of the Binet scale, which he named the Stanford-Binet Intelligence Scale. It is still used today, in its modified form.
The Binet test battery was the first widely used mental test of cognitive ability. Today there are many such tests, but two of the most well-known and validated tests are the Wechsler Adult Intelligence test and Raven´s Progressive Matrices.

2.2.4.1 The Swedish conscripts testing

In the papers that constitute this thesis intelligence was measured by the intelligence test from the Swedish military conscription testing. This test has been used since 1944 on all Swedish men conducting conscription examinations, which was compulsory by law until 2007.

The purpose of measuring individual differences in intellectual capacity was to select conscripts to different positions in the military organisation with greater efficiency (50). The enlistment battery of 1944 was developed by Torsten Husén with the American "The general classification test" (Bingham 1942) serving as the model (28;46). It was strongly influenced by Spearman and his concept of general ability. It consisted of eight subtests which were together assumed to measure general intelligence, g. In 1948 the test was improved to increase its reliability. Items of the same type were administered together, the test instructions were separated from the problems of the test, time limits were not as tight, multiple choice responses were given, etc. (46). Thurstone's primary factor model had a very powerful influence on the view of individual differences and on test development. This influence was also obvious in the enlistment test batteries used up to 1994 (46).

Validation of the g-loading was made by analysing the results with factor analysis according to Thurstone's method of repeated analysis (51), in which some tests showed higher g loadings than others. The test was developed and changed from 1947 to 1967 when it reached a version that lasted until 1980. The 1967 version is also the version that most of the papers in this thesis are based upon. The enlistment battery of 1967 consisted of four subtests; instructions, concept discrimination, paper form board, and technical comprehension. The instructions and concept discrimination were judged as measuring the general verbal ability of the conscript. The paper form board and technical comprehension were considered to show aptitude for technical and mechanical training. Each test was evaluated as a normalised nine-point scale per test, added into a sum and then transformed into a standard nine scale, named "provgrupp" and meant to be a measure of general intelligence. The inter-correlations of the subtests ranged from 0.49 to 0.72 and the general IQ correlated between 0.75 and 0.85 with the subtests (50). The highest correlation was with instructions and the lowest with paper form board. In 1971 test-retest reliability was studied for each of the subtests. The time span was 1 to 3 years and the overall reliability was 0.81 (50). There was a clear linear trend in general IQ according to the conscripts' educational level, ranging from 4.07 for those with the lowest education to 7.22 for those with the highest education on the 1 to 9 scale (50).

In 1980 a new enlistment battery was introduced. Concept discrimination was replaced by a test of synonyms and paper form board was replaced by a metal folding test (28). It still consisted of four tests and the aim was to measure g. The correlation with the test of 1967 was high (50). Models for the tests were Swedish test batteries used outside the military such as The Delta Battery, DBA, and Wit III (28). When developing the test of 1980 there was an increased interest in the prognostic validity of the test, since the aim of the intelligence test was to predict to which extent the individuals would benefit from the training. A comparison of IQ test scores with school grades showed significant correlations for three out of four educational categories with correlation coefficients ranging from 0.29 to 0.55 (50). Carlstedt and Mardberg have evaluated whether the test battery of 1980 really measure g (52). Their results showed that the g loading was high for all tests (0.84-0.90). They conclude that the sum of the normalised scores (used in this thesis) can be seen as a good estimate of general ability (52).

In the 1967 version, the four subtests consisted of 25 to 52 items, but in the 1980 version all subtest were made equally long with 40 items each. For this thesis this is not a major issue since we have based our analyses on the standardised scores, ranging from 1 to 9. In 1994 the Enlistment Battery broke off its previous strong influence from the hierarchical model. Instead it was influenced by item response theory and computer administrative testing was used.

The tests were adjusted to the approximated normal distribution. For instance, the levels of the tasks were determined by letting a group of individuals get unlimited time to solve as many tasks as they could on all four subtests. Thereafter the tasks were ordered and time limits were set to get the results approximately normally distributed with the purpose of differentiating between both the least and the most talented.

Before 1954 the intelligence quotient was used to standardise the test scores. However, it was considered too differentiated for its purpose, which is why a stanine scale was used after 1954. The standard scale was revised every year so that the 1956 scale was based on the results of 1955 (50), but it is unclear for how long this procedure lasted. The stanine scale corresponds to the traditional IQ scale (with mean 100 and SD of 15) so that 1 equals IQ -74, 2 equals IQ 74-81, 3 equals IQ 82-89, 4 equals IQ 90-95, 5 equals IQ 96-104, 6 equals 105-110, 7 equals 111-118, 8 equals 119-126 and 9 equals IQ 126 and over. It corresponds to 4%, 7%, 12%, 17%, 20%, 17%, 12%, 7%, and 4% of the distribution (50;53).

2.2.5 Ageing and intelligence

As pointed out earlier there is substantial stability in the rank-ordering of human intelligence across the life span, but still the correlation coefficient is far from 1. For instance, Deary and associates studied retests of the Moray House test and found that those who did well in 1932 tended to do well in 1998, too, with a correlation of 0.6 to 0.7 (12). Even so, there has been research showing a relatively large reduction in intelligence with ageing. Early studies on this topic showed a considerable drop in performance with age. However, they were cross-sectional studies of different cohorts, facing methodological problems such as the comparison of different cohorts (54). Later on, studies of longitudinal design have been conducted and have been able to present a more balanced picture. K. Werner Shaie wanted to find out whether the average level of ability improved or declined with age. In the Seattle study he showed that there was a fairly straight decline from 25 to 80 years in inductive reasoning, spatial orientation, perceptual speed, and verbal memory. For verbal and numerical ability on the other hand, there was a peak in middle age and much less age-related decline. Tests that involve knowledge or educational experience (crystallised intelligence) are not associated with impaired performance in older age (55). Schaie also found that the following factors contributed to keeping up mental abilities; being free from cardiovascular diseases and other chronic diseases, living in a favourable environment which is stimulating and complex, living with a spouse with high mental ability, etc. Salthouse is another researcher who has been exploring this field for a

long time. His theory is that cognitive performance is degraded because of a decrease in the speed with which many processing operations can be executed (56).

Even if cognition in general seems to decline with age, there are several factors affecting the speed with which this operates, for example presence of the metabolic syndrome and high levels of inflammation (57) as well as hypertension and diabetes (58).

2.2.6 The Flynn effect

Over the past century there has been an increase in intelligence test scores from one generation to another. This phenomenon has been called the Flynn effect after Professor James R Flynn. Flynn himself, however, is not convinced that there actually has been an effect of people becoming more intelligent. In his book "What is Intelligence? Beyond the Flynn Effect" (59) he states four paradoxes why it is unlikely to be true. For example he raises the point that if the raise in IQ scores reflects a true increase in intelligence, we should be struck by the extraordinary subtlety of our children's conversation, and would have to make allowances for the limitations of our parents. Rather than a true increase in intelligence, Flynn believes that we have become better at solving the intelligence tests. Others have suggested cultural effects, education and better nutrition as explanatory factors behind the rising IQ scores. Whatever the reason behind the effect, the evidence of its existence is quite substantial and the effect size has been about 3 IQ points (over the traditional IQ scale with a mean of 100 and a SD of 15) per decade during the 20th century on tests such as the WAIS and Ravens progressive matrices.

Sundet and colleagues studied the Flynn effect in Norwegian conscripts from the 1950s to 2002. They found a clear increase in general ability until the mid 1990. They conclude that the Flynn effect may have come to an end in the mid to late 1990s in Norway (60).

In Sweden, Rönnlund and Nilsson studied the Flynn effect in a cohort born 1909 to 1969 and found IQ gains of about 1SD unit (61). Further, Emanuelson and associates studied changes in verbal, spatial and reasoning intelligence for a later cohort, Swedish 13-year-olds between 1960 and 1990, and saw rising scores up to 1990. However the largest increase took place during the 60s and 70s (62).

2.3 INTELLIGENCE AND MORBIDITY/ MORTALITY

The research field to date is quite substantial and more than 60 papers have been published on the association of early life intelligence and later health outcomes including a review study (63). Most have studied all cause mortality (64-75), but also cardiovascular diseases (76-80), injuries (81;82), suicide (83;84), schizophrenia (53;85;86), anxiety and depression (87), and cancer (65;88). Many have looked at mortality or survival but there are also studies on illness or morbidity (65;89). Different intelligence tests have been used, but despite this almost all studies have shown inverse associations, meaning that the lower the intelligence, the greater the

risk of mortality. This has been shown for all outcomes except for cancer (90), or cancer other than lung cancer and skin cancer (65;88). Many studies have found a graded effect on mortality over the IQ distribution (68;77;78;91-93) where others suggest that the effect is more evident in lower socioeconomic groups (65;70;80). One study of gifted individuals showed a linear trend up to IQ of 163, beyond that the risk of death plateaued (71).

The first study on the association between intelligence and mortality that used Swedish data that we are aware of was published in 1985 by Furu et al. (94). In this study IQ was found to be inversely correlated with mortality, especially early mortality, 10-29 years. The results were not explained by the families' economic standard. However, the power was quite low. Some other early studies on this topic (95;96) found IQ to be associated with longevity and with lower risk of Alzheimer's disease.

The association of intelligence with type 2 diabetes is inconsistent, with some studies unable to find any associations (97;98) and others showing inverse associations (99).

The inverse association between intelligence and mortality/morbidity has been consistent in populations followed until middle age or below the age of 65. One study did not find any association for participants older than 65 years (76). However, Batterham and associates investigated the association among older individuals, 70 years and above, and found an inverse association (100). Intelligence was then measured in older age. The association was more evident for measures of fluid intelligence than for measures of crystallised intelligence. Shipley et al. studied the effect of different types of tests on different age groups and found choice reaction time to be most strongly associated with mortality among the youngest age group, 20-39 years of age (101). Verbal declarative memory, however, was only significantly associated with mortality among the oldest age group, which the authors believed was due to the small number of deaths in the youngest age group, rather than a true difference between the age groups.

Even if it is difficult to compare the risk estimates for different factors with each other, it is of great interest to put intelligence in relation to other risk factors for CVD. Batty et al. made an attempt to compare different risk factors by transforming them to Relative Indices of Inequality, RII scores. Even if one may question the accuracy in doing this, it can give some perception of the size of the risk of intelligence in comparison with other risk factors. When CVD mortality was the outcome, cigarette smoking was the number one risk factor, second was intelligence and thereafter income, systolic blood pressure and physical activity (102).

2.3.1.1 Associations for women?

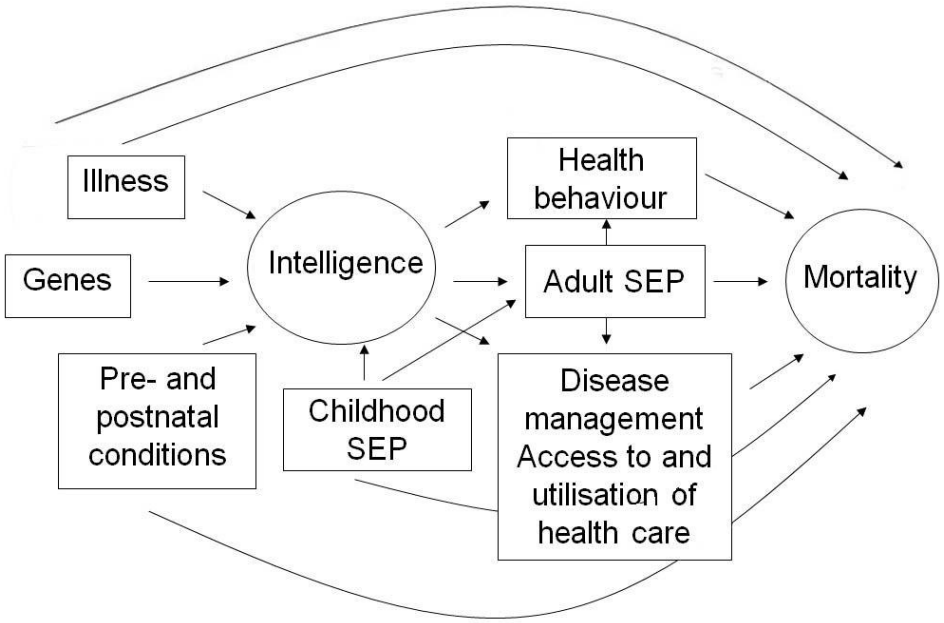
Most of the conducted studies have focused on men only, but there are some studies on the association between intelligence and mortality/morbidity for women, and these studies show contradictory results. A recent Swedish study found inverse associations for men but no associations for women (93). These results are supported by a few other studies (70;74), whereas they are contradicted by others, who found

associations for women similar to those of men (75;95;103). Two studies found stronger association between intelligence and mortality among women than men (79;91).

2.3.2 Potential mechanisms

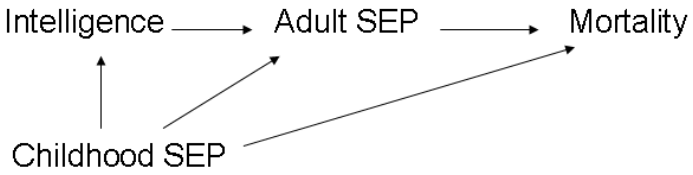
Even if the association between intelligence and mortality/morbidity is interesting in its own right, it is even more important to try and sort out the mechanisms behind the association and to study whether the association is causal or not. The research field has now turned to focus more on the underlying mechanisms of the association, such as possible genetic and behavioural mechanisms as well as unadjusted confounding from socioeconomic position, mainly in childhood. As early as 1972, Riegel and Riegel proposed two main theories through which cognitive decline and mortality could operate. The first was a biological theory in which physiological mechanisms related to cell ageing were responsible for cognitive decline and death. The other was a sociological theory in which disadvantages in life such as lower socioeconomic position, SEP, and lifestyle factors would affect cognitive performance and survival rates. These theories have been developed and discussed in later literature, for example by Whalley and Deary and by Batterham and associates (91;100). Below I will comment on possible mechanisms, including the two theories described above, and give some references to studies that have addressed the question. Firstly, a path diagram is presented, visualising potential pathways.

Figure 1a. Path diagram of potential pathways between intelligence and mortality



2.3.2.1 Confounding by or mediated through socioeconomic factors

Figure 1b. Path diagram for confounding/mediation through SEP



As mentioned previously a common perception is that the association between intelligence and health outcomes is mainly the result of confounding and/or mediation from socioeconomic factors, either in childhood or in older age. The first pathway refers to the idea that childhood SEP affect intelligence, adult SEP and mortality. The second pathway refers to the idea that intelligence affect adult SEP. Intelligence and measures of SEP, especially education, correlate positively and rather strongly. Several studies have tried to adjust for SEP by adjusting for different indicators of SEP in regression analysis. In most of the studies, childhood SEP, as measured by parental occupation or income, has no or only a weak effect on the association, whereas adult SEP, measured as educational level or occupation has a greater effect but cannot fully explain the association between intelligence and mortality/morbidity (65;70). One of the early studies on Swedish data by Lindgärde and colleagues (104) found a strong inverse association between early IQ and essential hypertension at the age of 48 years. They found no effect of having belonged to a lower social class during the first ten years of life. However, the sample size was small in this study (n=379).

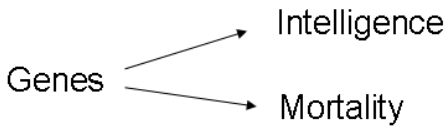
In addition to the question of whether or not the association between intelligence and mortality is confounded by SEP, some studies have raised the question whether intelligence can explain the socioeconomic differences in health (93;105;106). In the studies exploring this question, intelligence has been shown to have an independent effect on adult mortality, in addition to SEP. Michael Marmot has suggested that intelligence might have a causal effect on adult SEP and health behaviours and also being a marker of early life exposures (107). A fourth possible explanation could be the ability to cope with stress. Lager et al. investigated in a Swedish cohort whether mortality differences by own educational attainment were explained by early IQ and found that this was not the case (93). Batty and associates investigated whether IQ explained socioeconomic differences in total and CVD mortality in two different cohorts. These authors found that IQ attenuated the effect of adult SEP substantially but not completely (106;108). Osler and colleagues investigated the association of childhood SEP with adult mortality and adjusted for IQ at the age of 12 (92). The associations remained, however attenuated, suggesting a separate effect of childhood SEP from that of intelligence.

Only one twin study has been conducted on early intelligence and longevity (33). In that study the association between intelligence and mortality vanished within twin pairs, indicating that either genetic and/or early environmental factors explained the association between intelligence and mortality. Since the study was not based on

structural equation modelling it was not possible to quantify the genetic versus the environmental contributions to the association.

2.3.2.2 Confounding by genetic factors

Figure 1c. Path diagram for confounding by genetic factors

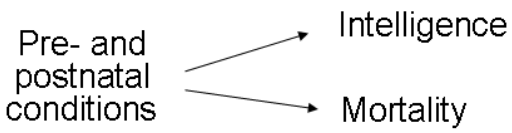


Another possible explanation is that common genetic factors could affect both intelligence and the risk of mortality. It has also been described as caused by some sort of bodily integrity system. For example, if the brain works optimally, with fast neural connections, it could well mean that the other organs of the body, such as the cardiovascular system, are working optimally as well. This would imply that the genetic factors which determine brain function also determine functions of other organs in the body. If this is the case, intelligence would be a proxy of those underlying genetic factors meaning that the association of intelligence with mortality/morbidity is confounded by genetic factors. This is difficult to study other than in twin studies. As mentioned in the previous section we are only aware of one twin study looking at intelligence and mortality and then genetic factors could not be separated from early environmental factors (33).

Reaction time can be seen as a crude measure of the brain's efficiency to process information and compared to psychometric intelligence tests it should be less sensitive to social factors and could be seen as a proxy of a genetic setting. Deary and Der found that reaction time explained the association between IQ and mortality (1). However, in that study reaction time was measured at the age of 56 where disease processes could have started to lower both IQ and reaction time.

2.3.2.3 Childhood intelligence as a record of bodily insults in early life

Figure 1d. Path diagram for confounding through pre- and postnatal conditions



Low intelligence might be one of the pathways, mediators, through which impaired growth in foetal life exerts its effect on mortality in adulthood. Insults in foetal life or early postnatal life with or without growth restriction could affect the developing brain (65). Low birth weight for gestational age is related to IQ (42;109). Also height has been shown to be a significant predictor of childhood IQ (40). Intelligence might represent a record of the body's insults in early life, primarily from environmental and

behavioural factors resulting from social circumstances (92). Several studies have adjusted for low birth weight but it did not have any, or only a weak effect in explaining the association between intelligence and mortality (78). However, low birth weight as used in these studies might not be a proper indicator of the record of bodily insults in childhood. A combination of other markers might have a more pronounced effect.

Another example of childhood disease affecting intelligence and mortality is type 1 diabetes. Children with early onset of type 1 diabetes are more likely to score relatively poorly on cognitive tests (110;111). Ferguson and associates (111) found that early type 1 diabetes was associated with coexistent structural brain differences. Their results support an organic contribution to the etiology but do not exclude influences of psychosocial factors.

2.3.2.4 Mediation through health behaviours

Figure 1e. Path diagram for mediation through health behaviours

Another possible mechanism behind the association between intelligence and mortality is mediation through health behaviours. It would assume that individuals with low intelligence have problems understanding health messages and/or acting in accordance with these. Such health behaviours can be smoking, alcohol use, unhealthy eating habits, physical activity etc. Several studies have explored this proposed mechanism (97;112;113). Some have studied the association of intelligence with health behaviour whilst others have focused on the association of intelligence with mortality/morbidity and controlled for health behaviour. There is strong support in the literature for associations between low intelligence and unfavourable health behaviours, but it is still unclear whether these associations are causal or not. It may be that they correlate but have independent effects on mortality.

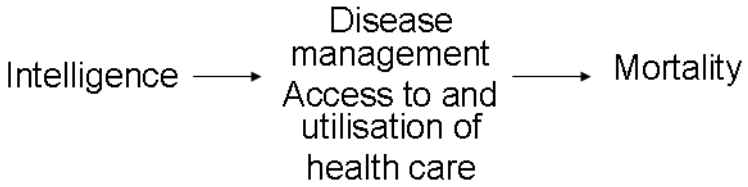
The association between intelligence and smoking has been explored in some studies and all of them have found inverse associations, meaning that a lower intelligence increases the risk of smoking (69;97;114-118). In some of the studies the associations were attenuated or disappeared after adjustment for indicators of social class (69;97;114). A few studies have explored the association of intelligence with mortality and controlled for smoking. Kuh and colleagues (2004) found no evidence of smoking being a mediator of the association between intelligence and mortality (70) whereas Batty and associates (2008) found that adjustment for smoking marginally attenuated the IQ–mortality association (69). The conclusion is that there seems to be an inverse association between intelligence and smoking, but whether this can be explained by socioeconomic or other factors, and if so, to which extent, remains unclear. The evidence for smoking being an important mediator of the association between intelligence and mortality is weak.

Some studies have examined the association between intelligence and alcohol abuse and found inverse associations (87). Further, intelligence has been found to be related to the metabolic syndrome. In a study by Batty and his colleagues, IQ was inversely associated to four of the five individual components comprising the metabolic syndrome: hypertension, high BMI, high triglycerides and high blood glucose (119). Structural equation modelling revealed that education was not a mediator of the relationship. The metabolic syndrome partially mediated the IQ-CVD association but not the association between IQ and total mortality. Further, Starr and associates found an inverse association between childhood IQ and adult hypertension (120) and in a cross-sectional study of men aged 66 to 75 years a higher crystallised IQ was associated with lower levels of carotid atherosclerosis (121). Whether the latter association is caused by intelligence, health behaviours, genetics or reverse causality is unclear, however, based on the study design.

Finally, Singh-Manoux and associates presented positive correlations of IQ and more physical activity, greater alcohol consumption, more fruit and vegetable consumption (80).

2.3.2.5 Disease management and/or availability to health care

Figure 1f. Path diagram for mediation through disease management



The idea behind this proposed mechanism is that both preventing and managing a disease is a complex task that requires information processing, or as stated in the paper by Gottfredson and Deary (122) ”Maintaining health, protecting oneself against chronic disease and accidents, and adhering to treatment regimens can be construed as one of life’s jobs, and success in this job might be associated with cognitive competence as measured by psychometric intelligence tests”. Few studies have been conducted based on this hypothesis. Beier and associates (123) studied the associations of cognitive ability and ten areas of health knowledge in two relatively small samples of college students and adults. The results showed that cognitive ability accounted for most of the variance in health knowledge. In another study higher verbal intelligence was associated with persisting with medication during a study period of two years (124). However, participants were recruited in a randomized controlled trial and the drug was aspirin. The result might therefore represent compliance rather than disease management, if people were truly ill the result might have been different.

In addition to a high intelligence facilitating the understanding of symptoms and being able to manage a chronic condition it could also be a question of availability of the health care system or a discrepancy in the received medical care between higher and

lower IQ-scoring individuals. To the best of my knowledge, there are no studies exploring this association.

Unequal access to medical care could be either due to belonging to a lower socioeconomic stratum and consequently a lack the sufficient recourses or to a lower ability to demand a good medical care. In Sweden, however, the health care is universal and almost free of charge, which is why this explanation is not likely to play an important role as an explanatory variable behind the inverse association of intelligence and mortality in Swedish data.

2.3.2.6 Reverse causality or confounding by illness

Figure 1g. Path diagram for reverse causality or confounding by illness

There are several cross-sectional studies where intelligence is measured at the same time or closely to the health outcome measures. Such studies give interesting information about associations and sometimes also prognostic validity but do not provide good information about causality. For instance, in a longitudinal study of ageing of individuals 50 years and older, free from history of stroke or dementia, high subclinical cerebrovascular disease burden was associated with worse cognitive function in multiple domains (125). From the study it was, however, not clear whether the IQ had decreased due to pre-morbid processes (not detectable at the time) and in that way predicted stroke, or if it reflected a low intelligence from origin. Other examples of studies where IQ is measured in middle age is McGuire and colleagues who found, in a cohort of 70 years and older, that low and normal levels of cognition were associated with a higher risk of dying or becoming disabled from diabetes (126). Pavlik et al. found that cognitive function in middle age appeared to have prognostic importance for life expectancy similar to that reported in elderly adults (73) and Gatto et al. found that the metabolic syndrome was associated with lower cognitive function in healthy middle aged and older adults (127). Gelder et al. studied only the cognitive decline as a risk factor, regardless of the absolute level and found that cognitive decline during a five year period was associated with a doubled risk of dying in the following five years (128).

In the research field of cognitive epidemiology reverse causality is, however, not a big problem. Most studies of today have a longitudinal design where IQ is measured early in life and health outcomes later.

2.4 CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) is the number one cause of death throughout the world, accounting for 29% of all global deaths in 2004 (129). It is a chronic disease and

the two main outcomes are coronary heart disease (CHD) and cerebrovascular disease (stroke). CVD is caused by atherosclerosis, a gradual build up of plaque in the arteries. Based on the composition of risk factors this can occur rather early in life and cause morbidity and mortality. During the past decades Sweden, together with most other developing countries, has experienced a quite dramatically decline in age-adjusted CVD rates. The reasons behind the decline are found both within clinical treatments but also within changes in health behaviours such as a declining smoking prevalence. In a study of changes in CVD rates in the US between 1980-2000, 47% of the decrease was attributable to changes in treatments, and 44% to changes in risk factors (130). In another study Capewell et al. showed that modest reductions in the prevalence of several major cardiovascular disease risk factors accounted for more than twice as many life-years gained as did treatments. However, the gains were partially offset by substantial increases in obesity and type-2 diabetes (131).

Known risk factors for CVD are hypertension, smoking, obesity, low levels of physical activity, diabetes, low levels of high-density lipoprotein, HDL, cholesterol and high levels of low-density lipoprotein, LDL, cholesterol and genetic factors. Also, low socioeconomic position is a well documented risk factor for CVD (79;132-134). The mechanisms through which it operates are not clear, however, clustering of risk factors such as unhealthy behaviours (135-139), psychosocial stress and job strain (140) are documented mechanisms. In this context socioeconomic disparities in health care resources have also been observed (141). More recently, intelligence has been suggested as one explanatory factor of socioeconomic differences in CVD (105;106;108), but the explanations are multifactoral (142).

2.5 SMOKING AND SNUS USE

2.5.1 Prevalence

Cigarette smoking is related to an increased risk of several diseases including CVD (143;144). Fortunately the proportion of smokers in Sweden has declined substantially over the past 25 years. The proportion of daily smokers has decreased from 35 percent to 14 percent among men and from 28 to 18 percent among women (145). It is a result of both giving up smoking and a reduction in smoking initiation. There is a strong socioeconomic gradient to smoking prevalence, especially among women, where the social differences appear to have grown stronger over the past 20-25 years (145). At the same time as the smoking prevalence decreases, the use of Swedish moisture snuff, snus, has increased. In 2006 daily use of snus was more common (23%) than cigarette smoking (14%) among males (145). Among young males aged 16-24 years, the difference was even larger (33% and 9%, respectively). Also, dual use is common. Furberg et al. showed that 44% of Swedish male twins reported a combination of tobacco use from cigarettes and snus (146). Another study showed that dual users are as numerous as 55% (147). When looking at the level of nicotine from different sources, Fagerström (148) reported that of the total amounts of nicotine consumed by males in Sweden, 62.5% came from snus.

2.5.2 Risk factors

Smoking behaviours aggregate in families and in peer networks. Both genetic and environmental influences affect the risk of becoming a smoker (149). Some studies have shown a considerable genetic contribution to smoking initiation (150;151) and several studies have shown that smoking cessation is associated with socioeconomic status (152). Parental and siblings' smoking status seem to be important predictors (153) and having a high education decreases the risk (150). Peer influence has also been shown to be associated with smoking initiation (153).

When it comes to intelligence as a risk factor for smoking initiation several studies have found inverse associations (69;97;98;114). However, none of these studies support a causal relationship of intelligence and smoking status. Johnson et al. suggest that shared environmental factors are important in explaining the association between intelligence and smoking (154).

2.6 NICOTINE DEPENDENCE

The addictive substance in tobacco, both in cigarettes and snus, is nicotine. Nicotine makes smokers and snus users become dependent. When smoking a cigarette nicotine is quickly absorbed into the blood circulation and reaches the brain. Very soon after the first puff on a cigarette, the nicotine causes pleasurable and rewarding effects on cognitive functions and mood. The reward associated with nicotine and the withdrawal symptoms caused by a lack of nicotine have a clear neurobiological background (155). The psychopharmacological properties are similar to those of drugs such as amphetamine and cocaine. All three drugs cause arousal and stimulate locomotor activity when administered to experimental animals and human subjects and they also have 'rewarding' properties (155).

Nicotine dependence is conditional on smoke or snus initiation with all its documented risk factors. The heritability estimates for nicotine dependence have been in the range of 0.50-0.75 in several studies (149;156-158). It has been suggested that smokers today might be more nicotine dependent than smokers in the past since the prevalence has decreased and the less dependent smokers have quit. In a comparison of the Fagerström Test for Nicotine Dependence , FTND, across countries it appeared that in Sweden and the USA, where the smoking prevalence is low, the dependence was the highest, supporting this suggestion (159).

2.6.1 Measures of nicotine dependence

Nicotine dependence can be measured in several ways. A simple and often used proxy is number of cigarettes per day, CPD. Previous studies have shown that those who report higher CPD are less likely to stop smoking (160). However, there are two more sophisticated commonly used models to measure nicotine dependence. The first is a model of physical dependence, FTND, and the other is based on psychiatric diagnostic tradition, DSM-IV. FTND consists of a questionnaire with six questions and it is the scale that has been used in paper VI in this thesis (161). Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition, DSM-IV, was developed by the American

Psychiatric Association with the purpose of measuring alcohol dependence and has since been adapted to all substances, with the exception of substance-specific withdrawal criteria. In clinical work the ICD-10 for tobacco dependence is commonly used whereas in research the DSM classification is more often used.

3 AIMS

The overall aim of this thesis was to examine the relationship between intelligence and health outcomes, mainly cardiovascular mortality, within a life-course perspective by analysing register-based data on Swedish men.

The specific objectives of the thesis were:

1. To investigate strength and shape of associations between intelligence and (i) all-cause and cause-specific mortality in CHD and stroke, and (ii) cause-specific morbidity in stroke among Swedish men (III).

2. To investigate whether associations between intelligence in young adulthood and all-cause and cause-specific mortality in CHD and stroke are mediated or confounded by socioeconomic position in childhood and/or adulthood among Swedish men (I,III).

3. To investigate the extent to which associations between intelligence and CVD mortality are explained or modified by genetic or environmental factors. This association is studied among:
    a. Swedish men and their biological parents (II).
    b. Pairs of biological full-brothers (I).

4. To investigate associations between intelligence in young adulthood and smoking and nicotine dependence later in life and to what extent these associations can be explained or modified by genetic and/or childhood environmental factors among male twin pairs (IV,V).

4 MATERIAL AND METHODS

4.1 STUDY POPULATIONS

The study populations in this thesis were created through record linkage of several national registers. A target population was identified in the Multi-Generation register, then a linkage was made with the Register of the Total Population, the Swedish Military Service Conscription Register, The Population and Housing censuses, The Longitudinal Database of Education, Income and Occupation (LOUISE), The Cause of Death Register (study I,II,III), The Hospital Discharge Register (study III) and the Swedish Twin Registry (study IV,V).

4.1.1 Swedish National Registers

Statistics Sweden holds a number of registers. These are primarily administrative registers rather than registers created for research purposes. This means, for example, that the variables included in the registers are sometimes not optimal for conducting research. Even so, the quality is high and many of the registers offer valuable information for epidemiological research. According to Swedish law, the main rule is that all persons residing in the country shall be registered at the property unit in the parish where they reside. A ten digit personal identity number is assigned to every individual registered in the Population Registration System. This number follows a person from birth to death and is entered in most personal registers in Sweden, making it possible to identify individuals in different administrative materials.

4.1.1.1 Register of the Total Population

In 1966, Statistics Sweden was granted permission to set up and maintain a register of the entire national population, referred to as the Total Population Register. The register holds information on births, deaths, changes in marital status, changes in citizenship, internal migration, immigration and emigration (162). The register has some over-coverage due to the fact that people registered in the population statistics leave the country to settle permanently abroad without this being registered (163). Nevertheless the overall quality of the register is regarded as high (164).

4.1.1.2 Multi-Generation Register

The Multi-Generation Register is a register consisting of individuals registered in Sweden since 1961 and who were born in 1932 or later. These are called index persons and also include adopted individuals. The register contains connections between index persons and their biological parents. The register is a part of the Total Population Register, which receives its information from the National Tax Board. The data quality is good for the individuals covered within this thesis, born in 1950 and later, where 99% of index individuals are complete together with at least their mothers (165).

4.1.1.3 Population and Housing Census 1960-1990

Since 1960 compulsory population and housing censuses have been conducted every fifth year up until 1990. The Population and Housing Census of 1990 had a non-participation rate of 2.5% and overall the quality is regarded as high (166). The data has been collected mainly through questionnaires to the public but also from other registers. The register contains information both on individuals, such as occupational and educational level, and on households, such as number of individuals in the household and income.

4.1.1.4 Cause of Death Register and Hospital Discharge Register

Both The Cause of Death Register and the Hospital Discharge Register are registered by The National Board of Health and Welfare. They contain information about all deaths and causes of deaths in Sweden and dates of admission with ICD-diagnoses. The quality of the Cause of Death Register is considered high even though there might be some information lacking in the case of emigrated individuals. The coverage of the Hospital Discharge Register can be considered complete from 1987 and onwards (167). Before 1987 the coverage was not complete and differed between counties.

4.1.1.5 Swedish Military Service Conscription Register

During the years covered by this thesis (and up until 2007) military conscription examinations were compulsory for all men holding a Swedish citizenship, except for individuals suffering from severe disabilities or disabling conditions. The conscription examinations involved medical and psychological examinations including the intelligence test used throughout in this thesis. The examination took place at an approximate age of 18 years. Overall the quality of this register is high, although parts of the data for the years of 1978, 1984 and 1985 have been lost due to changes in the data management within the Swedish Military Service Conscription Register. Also during the later years of conscription (used in study IV and V) data for the years 1995-1997 was lost during a transitional period going from written questionnaires to computerized ones.

4.1.1.6 The Swedish Twin Register

The Swedish Twin Registry is a population-based ongoing register containing information on all twins born from the year 1886 and onwards (168). The register has been divided into three cohorts, twins born between 1886 to 1925, 1926 to 1958, and twins born from 1959 to 1990. Several projects and data collections have been carried out using this register, and the two data collections that have been used for this thesis are described below.

Screening Across the Lifespan Twin study (SALT)
This screening covers twins born from 1886 to 1958. The study was initiated in 1998 with the purpose of screening for the most common complex diseases. It was conducted by a computer-assisted telephone interview between 1998 and 2002 where older twins were interviewed first. The response rate for twins born 1926 to 1958 (participants in this thesis) was 74%. There is an ongoing project to start a biobank containing samples from some of the twins in SALT (168).

Study of Twin Adults: Genes and Environment: STAGE
The STAGE cohort consists of all twins in the Swedish Twin Registry born 1959–1985 and where both siblings were alive and living in the country. The purpose was as in SALT to screen for common complex diseases but also to evaluate relevant exposure in young adulthood and in midlife. The study was conducted through a large web-based survey containing approximately 1300 questions. The response rate for STAGE was 60%, although it was lower for men, 53% (168).

Both in SALT and STAGE determination of zygosity was based on questions about childhood physical resemblance. The questions were; "During childhood, were you and your twin partner as alike as 'two peas in a pod' or not more alike than siblings in general?" and "How often did strangers have difficulty in distinguishing between you and your twin partner when you were children?" Twin pairs who responded that they had been like two peas in a pod on the first question and "almost always" or "often" on the second were classified as monozygotic (MZ). If both twins responded that they had not been more alike than siblings in general for the first question and "seldom", "almost never", or "never" for the second, they were classified as dizygotic (DZ). All other twins were classified as not determined. In SALT the procedure was validated for a sub-sample with 13 DNA markers and found to be 99% accurate(169). Also in STAGE a validation procedure was conducted with a panel of 47 single nucleotide polymorphisms in a random sample of 198 twin pairs, 95% were correctly classified (170).

4.2 STUDY VARIABLES

4.2.1 Exposures

The exposure in all papers in this thesis was intelligence measured by IQ test scores at the conscription examination tests when participants were 18 years old. They were collected through national registers from The National Service Administration and The Military Archives. All analyses have been performed using standardised values of IQ. In all papers the standardised global IQ was used. In paper I and paper V we also looked at subtests of intelligence. The IQ scores were classified on a stanine scale and were used both as a categorical and a continuous variable in the analyses. A more detailed description of the tests was given in 2.2.4.1.

4.2.2 Outcomes

The outcome variable for study I was CHD, based on the Swedish Cause of Death Register, which covers the entire Swedish population by matching their unique personal identification number to health care registers. CHD deaths were identified according to the Ninth and Tenth Revisions of the International Classification of Diseases (ICD) (codes 410-414 in ICD-9 and I20-I25 in ICD-10).

In study II the outcome was all cause mortality, CVD, CHD and diabetes. Mortality was defined from the underlying causes of death based on the ICD 8, 9, or 10 codes

contained in the Cause of Death Register. Cause specific mortality was categorised into all CVD (ICD-8 and ICD-9 codes 390–459, ICD-10 I00-I99), CHD (ICD-8 and ICD-9 410–414, ICD-10 I20-I25, I51.6), stroke (ICD-8 293.1, 430-438, 344, ICD-9 430–438, 290.4, 342, 344, ICD-10 I64, I67-I69) and diabetes (ICD-8 and ICD-9 250, ICD-10 E10-E14).

In study III the outcome was subtypes of stroke and they were categorised as ischemic stroke, 433 (ICD 8), 434 (ICD 9) and I63 (ICD 10), hemorrhagic stroke, 431 (ICD 8 & 9) and I61 (ICD 10), subarachnoid bleeding, 430 (ICD 8 & 9) and I60 (ICD 10), and other stroke 436.9 and 434 (ICD 8), 432, 437, 438, 435 (ICD 8 & 9), and 433 (ICD 9) and I62, I64-69, G45 (ICD 10).

In Study IV the outcome was smoking status, self-reported in the Swedish Twin Register. Smoking was reported in terms of having smoked regularly, currently or in the past, having smoked occasionally (now and then or at parties, currently or in the past), never smoked or only experimented. Participants also reported the number of cigarettes smoked and age when they started smoking. Smoking was treated both as a dichotomous variable and as a categorical variable with four categories, (never smokers, occasional, regular past and regular current). Number of cigarettes smoked per day was treated as a continuous variable.

In Study V the outcome was nicotine dependence, self-reported and based on the Fagerström Test for Nicotine Dependence, FTND. We analysed nicotine dependence both from cigarette smoking and from snus use, as well as total nicotine dependence (highest from either cigarettes or snus). The FTND was treated as a continuous variable in the analyses ranging from 0-9 for cigarette smoking and 0-7 for snus use.

Table 1. The Fagerström Test for Nicotine Dependence

1. How soon after you wake up do you smoke your first cigarette?		
	5 minutes	3 points
	6-30 minutes	2 points
	31-60 minutes	1 point
	After 60 minutes	0 points
2. Do you find it difficult to refrain from smoking in places where it is forbidden?		
	Yes	1 point
	No	0 points
3. Which cigarette would you hate most to give up?		
	First cigarette in the morning	1 point
	Some other cigarette	0 points
4. How many cigarettes per day do you smoke?		
	1-10 cigarettes	0 points
	11-20 cigarettes	1 point
	21-30 cigarettes	2 points
	31 or more	3 points
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?		
	Yes	1 point
	No	0 points

6. Do you smoke when you are so ill that you are in bed most of the day?	
Yes	1 point
No	0 points

Table 2. The Fagerström Test for Nicotine Dependence (snus) used in study V

1. How soon after you wake up do you put in your first snus?	
0-30 minutes	2 points
31-60 minutes	1 point
After 60 minutes	0 points
2. Which snus would you hate most to give up?	
First snus in the morning	1 point
Some other	0 points
3. How much snuff do you consume over one week?	
0-3 boxes	0 points
4-6 boxes	1 point
7-9 cigarettes	2 points
10 or more	3 points
4. Do you use snus more frequently during the first hours after waking than during the rest of the day?	
Yes	1 point
No	0 points

4.2.3 Confounding factors/potential mediators

In the analyses we have adjusted for a range of confounders and/or mediating factors. One might question the accuracy of adjusting associations for mediating factors. However, when studying the associations between intelligence and health outcomes, it is far from clear whether for example adult education is a confounder or a mediator, and probably it is both. Even if intelligence is measured before the individual has reached their highest attained education, it does not mean that there is necessarily causality in that time span. The IQ score attained at the age of 18 could just as well have been measured at the age of 4 or 25 and would then most probably have given a very similar relative score. In addition, attained education at 25 was probably to a large extent determined much earlier in life. The analyses have thus been adjusted for these potential confounders/mediating factors and results were presented both with and without adjustments.

4.2.3.1 Socioeconomic factors

Childhood SEP was measured as parental occupational code (all studies), parental education (study I, II) and parental income (study II), and was attained from national registers. Income was assessed as yearly income from work.

Parental occupation was assessed through the Statistics Sweden's socioeconomic index and was extracted from the Population and Housing Censuses when the

participants were 1 to 10 years of age. We used a six -stage classification as a categorical variable in the analyses: (6) higher level non-manuals, (5) middle level non-manuals, (4) lower level non-manuals, (3) skilled workers, (2) unskilled workers, and (1) others including farmers, students, home makers, and subjects with disability pension. In paper I farmers were put into a separate category.

Data on participants' own occupation was classified according to the same categories when the participants were aged 28 years or older.

Education was extracted from the Longitudinal Database of Education, Income and Occupation. Level of education was classified into seven categories: (7) PhD education, (6) other higher education >15 years, (5) higher education 13-15 years, (4) full secondary education (11 -12 years), (3) secondary education <11 years, (2) 9-10 years of primary school education and (1) less than 9 years of primary school. In paper IV and V level of education was classified into four categories: (4) PhD education, (3) higher education 13-15 years, (2) full secondary education 11-12 years, and (1) up to 10 years of compulsory school.

Conscription age, test centre and type of municipality (urban/rural) were also tested for as potential confounders in the analyses as they can be considered as markers of socioeconomic conditions. However, these variables did not have any impact on the estimates in any of the studies, which is why they were never used in the final models.

4.2.3.2 Biological factors

As risk factors for CVD both body mass index, BMI, and diastolic blood pressure, DBP, and systolic blood pressure, SBP, were considered as confounders in the analyses of IQ score and CHD (study I) and IQ and stroke (study III). They were treated as continuous variables in the analyses and were derived from conscription examinations when the participants were on average 18 years old.

4.2.3.3 Life style factors

Besides being an outcome in study III, smoking was seen as a confounder in the analyses of IQ and CHD (paper I). It was self reported at military conscription, classified into five categories based on number of cigarettes smoked per day.

4.3 STATISTICAL ANALYSES

4.3.1 Survival analysis

Survival analysis encompasses a wide variety of methods for analysing time to event; in this context, time to death or hospitalisation (171). Subjects are followed over time and it is observed at which point in time they experience the event of interest, if at all. Usually, studies do not span enough time to observe the events for all the subjects in the study, which is why a time of censoring is included. Subjects can be censored earlier by several reasons, e.g. by leaving the study population. In all the studies constituting this thesis censoring could be regarded as non-informative, i.e. the

reasons were unrelated to study outcomes and thus, bias should not have been introduced due to censoring.

The Cox proportional hazards model is a useful statistical model to analyse survival data. It allows determination of the impact of one or more risk factors over a time when the outcome occurs. The model is semi-parametric in the sense that the probability distribution of the baseline hazard is neither specified nor estimated. One of the main assumptions of the Cox proportional hazard model is proportionality. It means that the ratio of the estimated hazards over time is constant. It should also be pointed out that the hazard ratios attained by the model represent the estimated risk for a whole population. It cannot be attributed on an individual basis.

In paper I, II and III un- and multiadjusted Cox proportional hazards models were performed to examine the association between intelligence and CHD (paper I), all cause and cause specific mortality (paper II), and stroke mortality and morbidity (paper III). There was no evidence of violence of the proportional hazards assumption when investigated graphically by log-log curves or when tested with Schoenfeld residuals for each variable. Hazard ratios (HRs) were estimated together with their 95% confidence intervals (CI) with the phreg procedure in the SAS version 9.1 except for paper I where the STATA statistical package was used. The analyses were first performed using IQ score as a categorical variable with nine levels. When the effect of IQ appeared to be linear over the whole IQ distribution, IQ was used as a continuous variable. We also tested inclusion of a quadratic term in the models with IQ as continuous linear variable and the p-values were not significant.

In paper I, the follow-up ended at the date of death, date of emigration or on 31st December 2001, whichever came first. The results were adjusted for age, DBP, SBP and BMI, own education, own social position, and finally for mother's and father's education and social position. The associations between IQ and CHD mortality were also analysed separately within each socioeconomic category (strata) to study whether socioeconomic position modified the IQ-CHD associations. Interaction between IQ and socioeconomic indicators was computed using the socioeconomic factors as categorical variables. Furthermore, IQ and CHD risk was examined by computing odds ratios (OR) for the association between IQ and risk for CHD death within discordant brother pairs using conditional logistic regression analysis.

In paper II the follow-up ended at the date of death, date of emigration or on 31st December 2003, whichever came first. Because the material included families with multiple sons who were correlated and, thus, violates the usual independence assumption, standard errors were adjusted with a robust sandwich estimator.

In paper III the follow-up ended at the date of death or hospitalisation, date of emigration or on 31st December 2004 for mortality or 31st December 2006 for morbidity, whichever came first. For non-fatal stroke, first event was used for all stroke and first specific event for type specific stroke. Analyses were adjusted for BMI and SBP, childhood SEP (considered confounding factors) and own education and occupation (seen as mediating factors). We also tested for cohort effects by using birth year in five year strata.

4.3.2 Logistic regression

Logistic regression models were used to predict the OR, of being a smoker using the Genmod procedure in SAS (paper V). Also, polytomous logistic regression with a categorised outcome variable with four classes was used. This analysis was performed with the mlogit command in STATA, version 9.0, in order to get robust standard errors due to within-pair correlations. This regression model allowed us to compare different smoking categories over the IQ distribution. In this model, the between-pair effect was parameterised as the mean IQ of the brother-pairs and the within-pair effect as the twins' differences from the pair mean. The within-pair effect is then by design matched for all common environmental and genetic factors (for MZ pairs, 100 % and for DZ pairs on average 50% of the segregating genes) i.e. any within-pair effect represents an association that is free from confounding due to factors which are shared by the two twins in a pair.

Conditional logistic regression was used in paper I and IV in which twin brothers pairs discordant for CHD (paper I) and smoking (paper IV) were compared with respect to IQ. The ORs for being the twin who had CHD/smoked compared to his non-smoking co-twin were estimated for MZ and DZ pairs.

4.3.3 Family studies

Studies of families and relatives offer possibilities to study the contribution of genes and environmental factors on different outcomes. Depending on the structure of such analyses different conclusions can be drawn. I will present and discuss two types of family studies which have been used in this thesis.

4.3.3.1 Parents and their offspring

Studies of parents and their offspring can give information about genetic and common environmental influences. Parents might not contribute equally to the shared environment of their offspring, and therefore it is possible to detect maternal and paternal effects. Also, non-biological parents might influence their step children even if they are not genetically related. In paper II we estimated the effects of IQ on parental mortality using IQ of sons. We looked at paternal and maternal effects in both biological as well as non-biological parent-offspring pairs. A stronger IQ - mortality association between parents and their biological sons and a weaker association for stepsons would indicate a genetic effect, e.g. the same sets of genes might influence both mortality and intelligence. If an association was found among parents and step sons, it might instead indicate that environmental factors are influencing the IQ-mortality association. If the effect is greater for paternal than maternal mortality, or vice versa, it would indicate a difference of the contribution of environmental factors to the offspring. Other possible explanations could be genomic imprinting or biological effects related to foetal life.

4.3.3.2 Studies of twins

Twins offer a unique possibility to study genetic and environmental influences on different outcomes. Using pairs of twins when studying a relationship enables control for common environmental factors such as social class in childhood, parental effects, family culture etc. Also, for MZ twins it enables full control for genetic factors since they in principle have all their genes in common. DZ twins share on average half of their segregating genes, just like common siblings. The basic principle of twin design is to compare correlations within pairs of MZ twins with correlations within pairs of DZ twins. If there is greater similarity in MZ than in DZ twins it is regarded as evidence of an effect of genetic factors. Twin design covers different types of analytic strategies and below I describe two strategies which I have used in this thesis.

Differences within and between pairs

This design is built on the principle that differences between pairs of twins are compared with differences within twin pairs in order to detect any influence of either common environmental factors and/or genetic factors. Since twin pairs are by design matched for age, shared environment and genes any difference within MZ twin pairs must be because of non-shared environmental factors. Greater differences within DZ pairs than within MZ pairs can be considered to be due to genetic factors influencing the trait. This can be studied with correlations (paper V) or regression coefficients (paper IV). Analyses were made using generalised estimating equations (GEE) with the Genmod procedure available in the SAS statistical package. In this model, the between-pair effect was parameterised as the mean IQ of the brother-pairs and the within-pair effect as the twins' differences from the pair mean. This design may indicate environmental or genetic effects but not cannot quantify the size of these effects (172;173).

Quantitative genetic analysis of twins

In quantitative genetic analyses of twins it is possible to decompose observed variation for a trait into latent components, i.e. we can estimate the proportion of the variance that is explained by genetic or environmental factors. This is done by studying the variance of a trait and comparing the co-variances for MZ and DZ twins. In a bivariate approach, we can also estimate the genetic correlation, i.e. the amount of overlapping genes for two traits. The components of phenotypic variation can be divided into:

Additative genetic variation, A
Additative effect of alleles over all relevant loci inherited from parents of offspring
Dominant genetic variation, D
Dominance of one allele over its pair
Genetic effect because of reshuffling of genes in offspring
Shared environmental variation, C
All environmental factors common to the twins in a pair
Non-shared environmental factors, E
All environmental factors specific to a twin within a pair
Epigenetic heritability
Measurement error

Figure 2. Univariate model

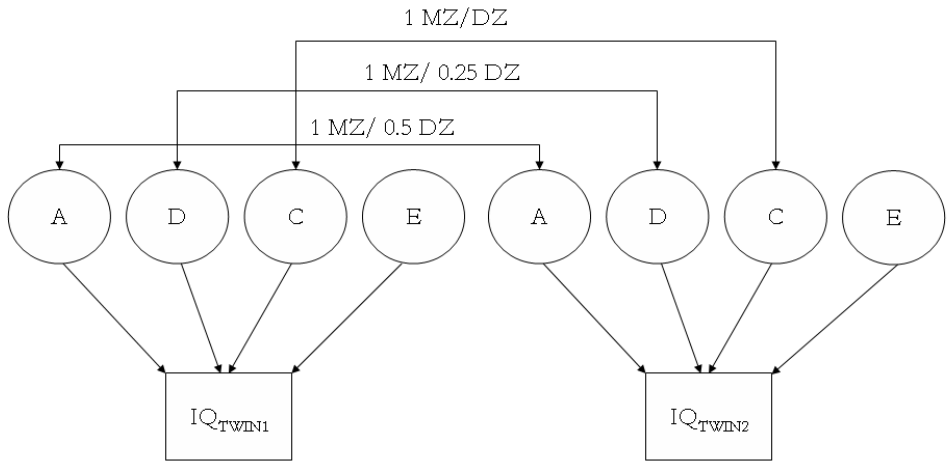
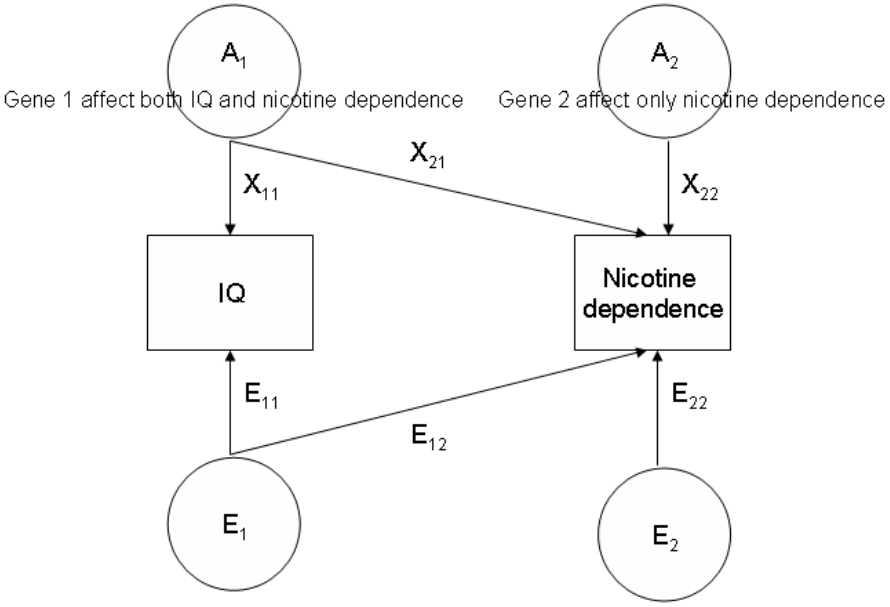


Figure 3. Cholesky decomposition



4.3.3.3 Heritability

We modelled heritability in a broad sense, which is defined as the proportion of the total phenotypic variance that can be accounted for by all genetic components (i.e. additative and dominance). Heritability is a characteristic of populations which is affected by both genetic and environmental effects and mirrors the relative contribution. i.e. in populations where genetic variance is small, environmental factors will play a larger role (174).

4.3.3.4 Assumptions and limitations of twin modelling

There are some important assumptions in twin modelling in general and in also in our models in particular. These are equal environment for both MZ and DZ twins, random mating and no gene-environment interaction.

The assumption about equal environment means that we assume equal non-shared as well as equal shared environments for MZ and DZ twins. It is however very likely that parents treat MZ twins more similarly than DZ twins. This is because MZ twins behave more similarly and thus evoke more similar responses from their parents than DZ twins. This effect is (correctly) modeled as part of genetic variation (parental behavior is the production of the child genes). For the shared environment we assume that it has similar effect on both MZ and DZ twins, it also means that we assume that there are no differences in families with DZ twins compared with families with MZ twins. Furthermore, in two thirds of the cases MZ twins share their placenta and therefore the prenatal environment is more dissimilar than for twins who have their own placenta (since blood may be unequally distributed)(175). If there is different amount of environmental variation in DZ twins compared to MZ twins the assumption is violated. This assumption can be tested in the analysis by comparing the suggested model to the saturated model.

There are two possible types of assortative mating (as opposed to random mating). Firstly there is mating based on relatedness, inbreeding, which is not so common in western societies. The other type of assortative mating is the tendency for like to marry like, a positive correlation of phenotypes for the mates. However, mating can appear to be more assortative than it really is due to social interaction, meaning that couples tend to become more similar when living together or because they have similar social background. Inbreeding and phenotypic assortment increase genetic similarities between DZ twins more than the assumed 0.5 and consequently they will become more similar relative to MZ twins. Since the estimate of the genetic component is based on the difference between MZ correlations and DZ correlations it will be biased downwards (underestimation of the proportion of variance attributable to heritability) and the shared environmental effect will be overestimated (174).

Gene-environment interaction (G*E) refers to the fact that the same environment gives a different effect depending on genotype, or the other way around, that the same genotype will give a different effect depending on the environment. It relates to the actual way that genes and environments affect the phenotype. One example is that genetically susceptible individuals will be free of a disease only for as long as the environment stays free of the pathogen, while resistant individuals will remain free of the disease even in a pathogenic environment (174). The chances of detecting G*E are greater when we can measure the relevant environments, such as diet, stress or smoking.

In addition to gene-environment interactions there are also gene-environment correlations meaning that the environment will differ depending on genotype (176;177). It reflects a non-random distribution of environments among different genotypes. For example if parents are smokers, the offspring will be exposed to an

environment which is increasing the probability of smoking and will most likely have genotypes more susceptible to smoking as well. If the genotypes of individuals create environments, cross-sectional twin studies will not be able to distinguish gene-environment correlation from any other effects of genes. Positive gene-environment correlations will increase estimates of genetic components and negative gene-environment correlations will decrease them.

4.3.3.5 Analyses in paper V

In paper V analyses were made using structural equation models (SEM) in the statistical software MX and Mplus. SEM differs from other regression models in the sense that it allows for latent (unobserved) variables. In our case we do not directly measure the genotypes and environments but their influence is inferred through the covariances between the twins. In figures 2 and 3 the latent variables are shown as circles and the observed (measured) phenotypes as squares.

We used univariate models to estimate the relative contribution of genetic and environmental factors for intelligence and nicotine dependence. A bivariate Cholesky decomposition was fitted to the data in order to estimate the genetic correlation between IQ and nicotine dependence. The best model, identified by comparing the χ^2-goodness-of-fit statistics, was then retained in the subsequent analyses. The model assumes that specific factors affect each phenotype as well as the other phenotype. The genetic correlation between the phenotypes is obtained by standardising the covariates by the variance components. The genetic covariance is divided by the genetic variation of the two phenotypes.

4.4 ETHICAL CONSIDERATIONS

The studies in this thesis were approved by the Regional Ethics committee, Stockholm, Sweden. This is primarily based on the requirement that all data are anonymous to the researchers using them. Even so, there are ethical issues worth discussing.

As soon as differences among individuals are used as exposures for mortality or morbidity there is always someone who reacts to it. In this specific case, when intelligence is the exposure, the ethical reactions might be even stronger. Perhaps this relates back to the history of intelligence research where hierarchical ordering between races and individuals were made. The purpose of our studies, however, is not to heighten the superiority of very intelligent people but to try to understand how and if low intelligence affects health. And as public health researchers, the overall aim of our research is of course to increase people's health. This is discussed in somewhat more detail under 6.4.

5 RESULTS

In this chapter a summary of the five papers will be presented. Methods have been described in chapter 4, which is why the focus here is on the results. An overview is given in Table 3.

5.1 INTELLIGENCE AND CHD MORTALITY (PAPER I)

In paper I the association between IQ and CHD mortality was explored among 682 361 Swedish men born 1951-1965. In addition to the analyses of individuals, the effect was also studied within 215 brother pairs discordant for CHD mortality and IQ. The effect of IQ on CHD mortality was studied in different socioeconomic strata and the effect from global IQ as well as from the different subtests were analyzed.

Data were analyzed by Cox regression and conditional logistic regression models. In total 737 CHD deaths were observed during the follow-up period. An inverse association was found between IQ and CHD mortality after adjustment for parental and own education and social position, BMI and blood pressure (HR 0.92 95% CI 0.88, 0.96). The associations were similar for all four subtests of intelligence, see Table 4. The associations were also of similar strengths within all socioeconomic strata and an association was also found within 215 brother pairs discordant for CHD mortality and IQ (OR 0.76 95% CI 0.58, 1.00). Table 5 presents associations between IQ and CHD within strata of fathers' occupational class. The results show an effect of IQ in all strata (except for lower level non-manuals), p-value for interaction was 0.12. Table 6 shows associations between IQ and CHD within strata for own socioeconomic position. Results shows that also within own SEP an effect of IQ on CHD was present for all strata, p-value for was interaction 0.35.

We also repeated the analyses in a subset of participants for whom we had information on smoking (data not shown). In this subset, the age adjusted HR for global IQ was 0.82 (95% CI 0.74–0.91) and adjustment for smoking as a classified variable decreased it slightly (HR 0.85; 95% CI 0.76–0.94). Since the number of CHD cases was small in this subset (96 deaths), there was not enough power to carry out the fully adjusted model.

Table 3. Summery of results

	Aim	Data	Method	Conclusion
Study I	Study the effect of intelligence on CHD	682 361 men born 1951-1965	Cox proportional hazards regression and conditional logistic regression	IQ was associated with CHD mortality independently of socioeconomic position.
Study II	Study association of sons' intelligence and parental mortality	931 825 men born 1951-1976 and their parents	Cox proportional hazards regression	An association between sons' IQ and parental mortality was found. The effect was somewhat stronger for maternal mortality. Also, a weak association was found for sons' IQ with the mortality of their stepmothers.
Study III	Study the effect of intelligence on subtypes of stroke	1 135 383 men born 1951-1976	Cox proportional hazards regression	Inverse associations were found between IQ and all stroke subtypes, fatal and non-fatal. The association for hemorrhagic stroke was somewhat stronger than for ischemic stroke.
Study V	Study the association between intelligence and smoking	11589 male twins born 1951-1984	Linear, logistic and polytomous regression	A strong inverse association was found between IQ and smoking but when analysed within twins pairs, i.e. adjusted for genetic and shared environmental factors, the effect disappeared.
Study VI	Study the genetics of intelligence and nicotine dependence	5040 male twins born 1951-1984	Quantitative genetic analyses	Both IQ and nicotine dependence showed moderate heritability; however the phenotypic correlation was weak and the overlap between genetic factors influencing IQ and nicotine dependence was marginal.

Table 4. Hazard ratios of CHD with 95% confidence intervals for subtests of intelligence and global intelligence

	Model 1	**Model 2**
Logical intelligence	0.84 (0.81-0.87)	0.95 (0.91-0.99)
Verbal intelligence	0.83 (0.80-0.87)	0.93 (0.89-0.97)
Spatial intelligence	0.85 (0.82-0.89)	0.93 (0.89-0.97)
Technical intelligence	0.84 (0.81-0.88)	0.93 (0.89-0.97)
Global intelligence	0.82 (0.79-0.85)	0.92 (0.88-0.96)

Model 1 adjusted for age

Model 2 additionally adjusted for maternal education, mother's social position, paternal education and father's social position

Table 5. Associations of IQ with CHD mortality within strata of paternal occupational class

	CHD deaths	**N**	**Deaths per 100 000 person years**	**HR**	**95% CI**
Higher level non-manuals	19	42 953	0.18	0.72	0.57, 0.90
Middle level non-manuals	99	133 619	0.30	0.81	0.73, 0.89
Lower level non-manuals	69	78 338	0.35	0.99	0.87, 1.12
Farmers	40	43 794	0.35	0.79	0.68, 0.93
Skilled workers	193	169 868	0.45	0.85	0.79, 0.92
Unskilled workers	295	201 677	0.58	0.84	0.79, 0.89

Table 6. Associations of IQ with CHD mortality within strata of own occupational class.

	CHD deaths	**N**	**Deaths per 100 000 person years**	**HR**	**95% CI**
Higher level non-manuals	44	79 214	0.21	0.78	0.66, 0.92
Middle level non-manuals	84	113 138	0.29	0.90	0.79, 1.02
Lower level non-manuals	68	72 490	0.37	0.87	0.76, 0.99
Skilled workers	189	174 468	0.43	0.89	0.82, 0.97
Unskilled workers	264	173 726	0.61	0.89	0.83, 0.95
Unclassified	79	56 221	0.67	0.79	0.71, 0.87

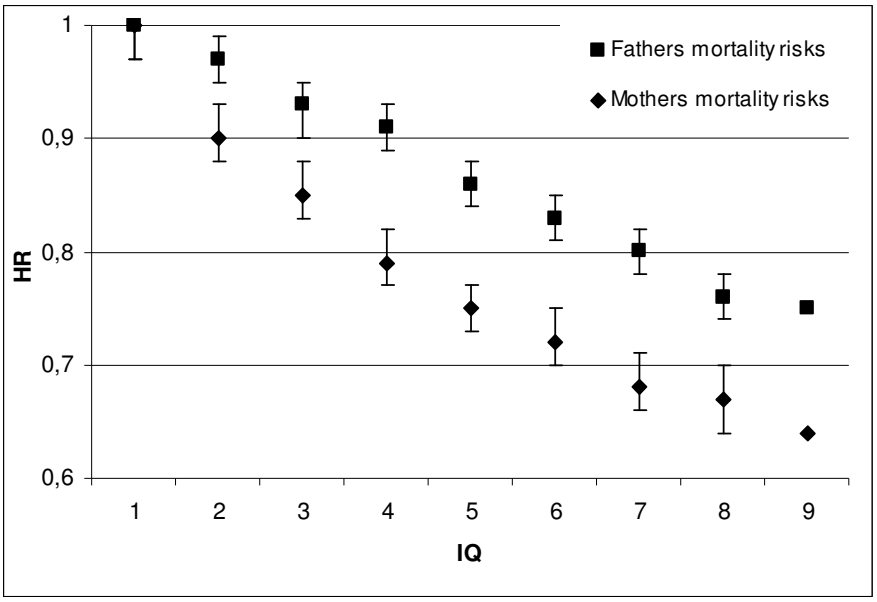
5.2 OFFSPRING INTELLIGENCE AND PARENTAL MORTALITY (PAPER II)

In paper II the association between offspring intelligence and the mortality of their parents was studied among biological and non-biological parent-offspring pairs. The study was based on all Swedish men born between 1951 and 1976 who went through conscription examinations. Data were analysed using Cox regression models with parents' age as the time axis.

The average follow-up time for all cause mortality was 21.2 years for mothers (SD 7.2) and 19.7 years for fathers (SD 7.3). Fathers and mothers were followed up, on average, to 68 years (SD 9 years) and 67 years (SD 9 years) of age, respectively.

We found inverse associations between IQ of offspring and parental mortality for all outcomes. The associations were stronger for maternal mortality than for paternal mortality and the strongest association was observed for diabetes mortality. Another consistent finding was that the associations were attenuated, but not entirely so, after adjustment for parental occupation, education and income. Figure 4 shows adjusted HR for paternal and maternal all cause mortality over the IQ distribution. The effect appeared to be linear.

Figure 4. Adjusted HR with 95% CI for paternal and maternal all cause mortality risk.



HR adjusted for own occupation, education and income.

A weak association was found between sons' IQ and all mortality outcomes of their stepmothers. After adjustment for occupation and education of the mother, the associations were attenuated and only statistically significant for all cause mortality (HR 0.97 95% CI 0.95,0.99). For sons's IQ and mortality of their step father there were weak associations for all cause, CVD and CHD mortality. After adjustment for occupation and education, none of the associations remained.

The weak association found in the non-biological family relationship, indicates an impact of shared family environmental factors. Assortative mating, i.e. that a person

selects a partner with similar characteristics, e.g. intelligence or height, may also explain the IQ–mortality association found in non-biological parent–offspring pairs.

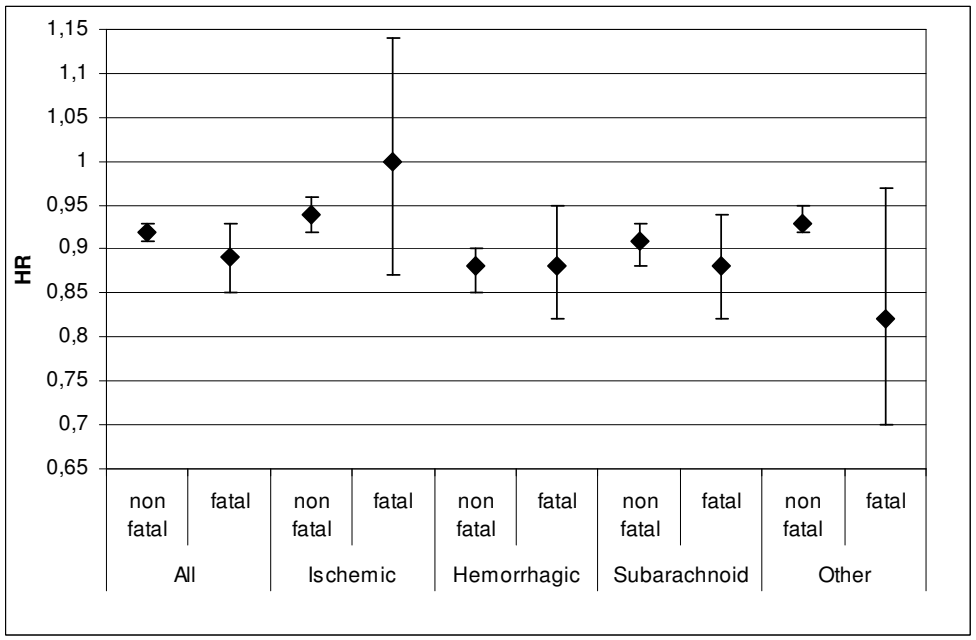
5.3 INTELLIGENCE AND TYPE SPECIFIC STROKE (PAPER III)

In study III we analysed the associations between IQ and subtypes of stroke. The study was based on all Swedish men born between 1951 and 1976 who went through conscription examinations and had complete data on the variables studied and who had not been hospitalized for stroke before the date of conscription (1 135 383 men together).

Data were analysed using Cox regression models with age as the time axis. The mean follow-up time from conscription to first admission to hospital inpatient care for a non-fatal stroke was 24 years (SD 7.9) and 22 years (SD 7.7) for a fatal stroke. During the follow-up period, 7661 non-fatal stroke events and 554 fatal stroke events occurred. The most common stroke subtype among fatal cases in our study population was hemorrhagic stroke (40% of the cases as compared to 11% for ischemic stroke). For non-fatal stroke, the order was the opposite (40% of the cases was ischemic compared to 17% for hemorrhagic stroke).

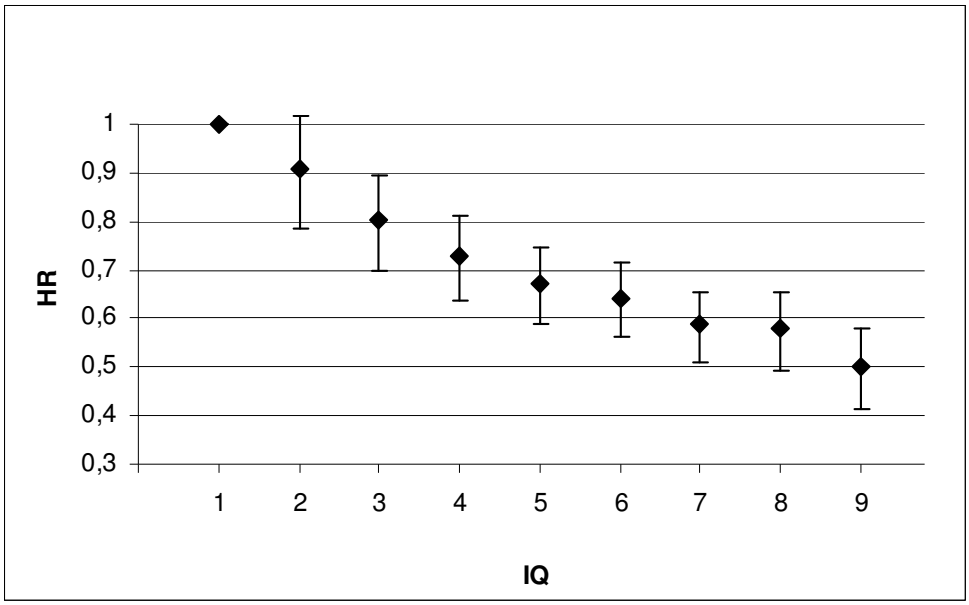
There were inverse associations between IQ and all stroke subtypes, with the strongest relative risk seen for fatal stroke of a type “other” than ischemic, hemorrhagic or subarachnoid bleeding, results presented in Figure 5. There was little evidence of an association of IQ with fatal ischemic stroke ($HR_{age\text{-}adjusted}$ =0.97 95% CI 0.86, 1.10). When adjusting for childhood SEP, BMI and SBP, there was only a slight attenuation of the estimates. Controlling for own education in the model further attenuated the estimates slightly, but inverse associations remained for all stroke subtypes. Significance was, however, lost for all fatal stroke outcomes except for all stroke and hemorrhagic stroke. For non-fatal stroke there were inverse associations between IQ and all stroke outcomes, even after full adjustments, and the strongest relative risk was found for hemorrhagic stroke. The results for fatal and non-fatal stroke were similar although the larger number of events made the estimates for non-fatal stroke more precise. The effect seemed to be linear over the nine graded IQ distribution, see Figure 6.

Figure 5. Adjusted HR with 95% CI for fatal and non-fatal subtypes of stroke.



HR adjusted for age parental occupation, SBP and BMI.

Figure 6. HR with 95% CI for all non-fatal stroke, over the IQ distribution.



HR adjusted for parental occupation, SBP and BMI.

5.4 INTELLIGENCE AND SMOKING AMONG SWEDISH MALE TWINS (PAPER IV)

In paper IV we investigated the association between IQ and smoking status in two large cohorts of Swedish male twins born 1951 – 1984.

We analysed the association between IQ and smoking status among all twins, treated as individuals but with adjustment for correlations within pairs, using logistic regression models estimated with generalised estimating equations (GEE). We also performed polytomous logistic regression, where we used a categorised outcome

variable with four classes. Finally we analysed only complete twin pairs and used logistic regression models to estimate effects between and within pairs.

Even though the proportion of smokers was much higher in SALT than in STAGE, the association between IQ and smoking was similar in both cohorts, with the smoking prevalence decreasing as IQ increased. There was also a trend towards a higher mean age of onset of smoking with higher IQ. The adjusted OR for current regular smoking were 0.86 (95% CI 0.82, 0.91) in SALT and 0.86 (95% CI 0.81, 0.92) in STAGE, indicating a 14% decrease in the odds of being a current regular smoker per unit increase (approximately 0.5 SD) in IQ over the 9-graded scale.

The tetrachoric correlation within twin brother pairs for regular smoking (past or currently) was high, 0.71 for DZ pairs and 0.85 for MZ pairs. For IQ the correlation was 0.54 for DZ pairs and 0.82 for MZ pairs. Therefore, the number of twin pairs discordant for IQ and smoking was small. Among the 2 241 complete twin pairs with information on both IQ and smoking in the two cohorts, the numbers of discordant pairs were 221 DZ and 138 MZ pairs.

Table 7 presents the between- and within-pair effects of IQ on smoking among DZ and MZ twins separately. The between-pair effect shows the association between pair means of IQ and smoking (ever having smoked regularly). The within-pair effect is based on the differences from the mean within twin pairs. Both the between- and the within-pair effects were similar in DZ and MZ twins. The between-pair effect was strong and significant (DZ OR=0.84 95%CI 0.78, 0.91 and MZ OR=0.83 95%CI 0.77, 0.90). The within-pair effect, taking common environmental factors and genetics into account, however, was weak and not statistically significant (DZ OR=0.95 95%CI 0.84, 1.07 and MZ OR=0.97 95%CI 0.80, 1.17). This suggests that genetic factors or factors in the shared environment underlie the association. Since the association disappeared both among MZ and DZ pairs, it suggests that there is no clear evidence of a contribution from genetic or non-shared factors.

Table 7. Adjusted odds ratios with 95% CI for ever regular smoking between and witin twin pairs.

	Between pair means of IQ	Within pair difference in IQ
All twins	0.78 (0.75,0.82)	0.93 (0.84,1.02)
DZ	0.79 (0.74,0.84)	0.92 (0.82,1.03)
MZ	0.78 (0.73,0.83)	0.95 (0.78,1.14)

OR adjusted for birth year

5.5 GENETIC AND ENVIRONMENTAL CONTRIBUTION TO INTELLIGENCE AND NICOTINE DEPENDENCE (PAPER V)

In study V we analysed the associations between IQ and nicotine dependence as well as the heritability and genetic correlation for the two traits. The study was based on 5040 Swedish male twin pairs and for the genetic analyses there were 880 complete pairs. Data were analysed using linear regression and by classical twin modeling based

on linear structural equation modelling. Nicotine dependence was measured by Fagerström Test for Nicotine Dependece, FTND, and we studied dependence based on both cigarette smoking and snus.

Results from the linear regression, treating the twins as individuals, showed weak associations between IQ and nicotine dependence. The association was strongest for nicotine dependence in the form of cigarette smoking. In the model adjusted for birth year one unit increase in IQ over the stanine scale resulted in a reduction of 0.13 (95% CI -0.16, -0.09) in nicotine dependence on the 0-9 scale. The corresponding value for nicotine dependence in the form of snus use, was -0.09 (95% CI -0.11, -0.07).

The heritability was found to be moderate for both IQ and nicotine dependence, values from univariate models was 0.58 and 0.39 respectively. The heritability for nicotine dependence was similar regardless of whether it was measured by cigarette smoking or snus use. The phenotypic correlation between IQ and nicotine dependence was weak and bivariate analysis revealed very little genetic overlap between IQ and nicotine dependence. Conclusions were therefore that nicotine dependence appeared to mainly be explained by non shared environmental factors and that it is unlikely to be an important mediating factor of the established inverse association between IQ and mortality.

6 DISCUSSION

The aim of this thesis was to contribute to a better understanding of the association between intelligence measured early in life and later cardiovascular health. Papers I-III support previous research about inverse associations between intelligence and CVD mortality and morbidity. In paper IV and V we studied the association between intelligence and smoking and nicotine dependence, suggested as mediators of the IQ-mortality association. The results of these studies do not support the mediation hypothesis; smoking was associated with intelligence but appeared to be the result of early environmental factors rather than the result of a causal effect of intelligence.

6.1 RESULTS IN RELATION TO PREVIOUS RESEARCH

At the time when study I was conducted, the number of studies thoroughly investigating the association between intelligence and CHD was small. A few previous studies had shown that IQ predicted the risk of CHD, even after adjustment for socioeconomic position in childhood and in adulthood (65;76;78). Since then, a few more studies on intelligence and CHD have been conducted (77;79). The results of study I are in line with these studies, presenting an inverse association between IQ and later risk of CHD. In agreement with most previous studies, we found a linear effect. Hart et al., however, only found an increased risk of CHD death for the lowest-scoring quarter of the IQ distribution (65). A tentative explanation to this could be the comparatively small sample size in that study, which would have led to a large sampling variation making it difficult to detect a linear effect.

We were also able to show that the effect of IQ on CHD was evident within all socioeconomic strata (even if some of them were not statistically significant). In addition, we analysed brother pairs discordant for IQ and CHD and showed that the effect was present within the pairs. This approach had not previously been employed to investigate the association between intelligence and mortality. In this analysis, however, our results revealed that the association between IQ and CHD was only found when variation in IQ was used as a dichotomised variable. This may indicate non-linearity between intelligence and mortality, although it is more likely that it is the result of low power.

Furthermore, in our analyses in study I, all subtests of intelligence were similarly associated with CHD mortality. This suggests that the association between intelligence and CHD mortality is not related to particular skills or to a specific dimension of intelligence. On the other hand, the tests conducted at the conscription examination, mostly measured fluid, rather than crystallised intelligence, which is why a difference between subtests might not be detectible. A previous study separating fluid from crystallized intelligence found that fluid intelligence had a stronger association with mortality than crystallised intelligence (100). This suggests that the underlying capacity of the brain might be more important than attained information and learned skills. However, more studies separating fluid from crystallized intelligence in relation to CVD mortality is needed in order to draw any conclusions.

The research field of intelligence and stroke was even sparser than that of intelligence and CHD. This might possibly have been due to low numbers of events, since stroke, compared with CHD, is a disease which often occurs rather late in life. Of the previous studies that had been conducted, none had found any statistically significant association between IQ and stroke in adjusted analyses (65;76-78). Since the time of publication of our study III, Lawlor and her colleagues studied the association of IQ and stroke and found the association to be stronger among women than among men(79). The associations were significant until adjustment for educational level in adulthood. The study by Hart and associates (65) was the only study separating hemorrhagic stroke from all stroke. The effect was stronger for hemorrhagic stroke, although it was not statistically significant. Given previous findings of a link between intelligence and CVD, an association with stroke, at least ischemic stroke, would be plausible given the, at least partly, shared pathophysiology. Therefore, we aimed at exploring this further in Study III.

In line with previous studies we found inverse associations between intelligence and all stroke but in contrast, our associations were statistically significant even after adjustment for measures of SEP (except for fatal ischemic stroke). In addition, our study was the first to perform separate analyses for all major subtypes of stroke and also to separate fatal stroke from non-fatal. Possible explanations for the absence of statistically significant associations in the previous studies are of course low statistical power but also that the effect might be more apparent when intelligence is measured in adolescence than in childhood. In the study by Lawlor et al. (79)the effect for men was only present when intelligence was measured at the age of 11 and not at the age of 7 or 9. In our study and in the study by Hemmingsson et al. (77), which were the only studies with statistically significant results, intelligence was measured at a mean age of 18. In all the other studies intelligence was measured at the age of 12 or earlier. Another possible reason is that in previous studies, subtypes of stroke were analysed together. Since stroke is a complex disease and hemorrhagic stroke is different from ischemic stroke, the results could be different when separating the subtypes. Our results revealed a stronger association for hemorrhagic stroke than for ischemic stroke.

In light of the earlier mentioned partly shared pathophysiology for CHD and ischemic stroke, it may appear somewhat surprising that the association between IQ and stroke is stronger for hemorrhagic stroke, rather than for ischemic stroke. Since the cases in our study represented early stroke events, we speculated that genetic factors may have a relatively larger effect on these cases compared to stroke events later in life, as found for CHD (178), where lifestyle factors have run their course for a longer period of time, producing pathophysiological effects. It may be that the genetic factors which are related to hemorrhagic processes in the brain are more closely connected to intelligence than the risk factors of atherosclerosis in the aorta or the large arteries to the brain which are the main risk factors of ischemic stroke. Another possible explanation could be that both low intelligence and hemorrhagic stroke are consequences of adverse circumstances in childhood. Others have found hemorrhagic stroke to be associated with large number of siblings (179) (however not statistically significant), lower adult height (180) and both ischemic and hemorrhagic stroke has been shown to be inversely associated with lower socioeconomic conditions in

childhood (181;182). Adult height can be seen as a marker of fetal growth, growth and nutrition in childhood and childhood infections (183). Mc Carrron et al. (180), who found hemorrhagic stroke to be more strongly related to adult height than ischemic stroke, discussed that persons of tall stature are likely to have had optimal foetal and childhood growth reducing the overall risk of stroke, in particular haemorrhagic stroke. However, the correlation between adult height and intelligence has in a twin study been shown to be largely explained by common genetic factors (184;185).

In paper II we used a study design that had not previously been applied in studies of intelligence and mortality. We studied the association between IQ of offspring (sons) and parental mortality. Due to the relatively high heritability of intelligence it is well established that parent intelligence is quite strongly associated with offspring intelligence. Therefore we used offspring IQ as a proxy for parental IQ. It is a similar design as using offspring IQ as an instrumental variable. An instrumental variable should be associated with the risk factor of interest (in this case parental intelligence) and only associated with the outcome because of its association with that risk factor. This approach has recently been used studying the association between offspring BMI and parental mortality (186). Even if we did not use offspring IQ as an instrumental variable in the analyses the principles of the studies are the same. An advantage is that measured and unmeasured confounding factors influencing the parental IQ-mortality association will presumably have less (or no) influence on the relations between offspring intelligence and parental mortality. Also, by studying the association of offspring IQ with parental mortality we could study both paternal and maternal mortality and benefit from a longer follow-up time, i.e. to an older age than for index persons. However, the main advantage was that based on the study design, we were able to compare biological parent-offspring pairs with non-biological pairs, i.e. step sons and their step parents. If any relation was to be found between step sons and their step parents it should mainly be attributed to environmental factors.

An interesting finding was that the association of sons' IQ was more strongly associated with maternal than paternal mortality and that there was a weak association between sons' IQ with step mothers' mortality. The association of sons' IQ with maternal mortality can be interpreted as an effect of intelligence on mortality among women, which is in line with some (70;74;93) but not all studies (75;91;95). It is also possible that offspring intelligence to some extent is a proxy of mothers socioeconomic position, health behaviours etc. to a greater extent than the fathers' lifestyle, or that there is a maternal effect on sons' intelligence based on foetal life conditions. Devlin et al. studied the heritability of intelligence and found that maternal effects, often assumed to be negligible, accounted for 20% of the covariance between twins and 5% of that between siblings (187). They concluded that the shared maternal environment may partly explain the striking correlation between the intelligence of twins, especially that of adult twins who were reared apart. The association found between sons' IQ and step mothers' mortality suggests an effect of shared environmental factors. However, it could also be the result of assortative mating. The strongest association was found for diabetes mortality. It may be a consequence of better self care or better access to and use of medical care among those with a higher intelligence. However, one may also speculate about weather the influence of diabetes during foetal life could influence offspring intelligence, which has been

shown for birth weight (188). If so, reverse causality could be part of the explanation for the association of IQ with diabetes mortality.

In papers IV and V we investigated the association between intelligence and smoking and nicotine dependence. The background for the studies was that smoking, together with other adverse health behaviours, had been suggested as potential mediators behind the IQ-mortality association. Since cigarette smoking is an important risk factor for CVD mortality and more prevalent among lower socioeconomic strata in the population, we hypothesised that smoking is a mediator of the IQ-CVD association. A few studies had looked at the association between IQ measured at an early age and later smoking status and found inverse associations (97;116;117;119). However, studies which controlled the IQ-mortality association for smoking (including paper I) did not find smoking to be an important confounder or mediator (69;70;73).

In line with all previous studies of intelligence and smoking, we found a strong inverse IQ-smoking association when analyzing the twins as individuals and between pairs of twins. However, when the effect was studied within twin pairs, it vanished. Since the association between IQ and smoking was attenuated to the same extent within both MZ and DZ pairs, shared environmental factors seem to be the most likely explanation to the association between IQ and smoking. Further, the results from the conditional logistic regression analyses gave no support for an effect of non-shared environmental factors. We are not aware of any other study that has used twins to attempt to separate the genetic and environmental effects of the IQ-smoking association. However, several studies have looked at genetic and environmental factors influencing smoking and found that environmental factors play an important role, for example exposure to parental and peer smoking (137;189;190). Also, Ferguson et al. (137) found, through SEM, that the associations between the latent factors of childhood disadvantage and later smoking were largely explained by a series of pathways involving cognitive/educational factors, adolescent behavioural adjustment and exposure to parental and peer smoking.

Our results from paper IV can be interpreted in several ways. The association between intelligence and smoking status may be confounded by childhood socioeconomic position, which previously used variables did not capture, or other factors in the shared environment may explain the association. Those factors might for example be parental smoking status, attitudes within families and psychosocial factors shared within families. Our results did not support a causal relationship between intelligence and smoking. Instead, the results from the discordant twin pairs suggested that smoking might be a confounder rather than a mediating factor of the IQ-mortality association. In summary, intelligence appear to correlate with early environmental factors shared by twin brothers which affect smoking status and thus smoking can be a confounder in the IQ-mortality association.

Paper IV focused on smoking status only. The effect of intelligence on persistence of and giving up smoking was not studied. However, the comparison between current and past smokers did suggest that intelligence was related to giving up smoking. Nicotine dependence is what keeps most smokers from giving up smoking and studying the association between intelligence and nicotine dependence, as well as the

shared genetic or environmental factors behind the two traits, could contribute to an increased knowledge about a possible association between intelligence and smoking persistence. Thus, in study V, we proceeded analysing the twin cohort and looked at the association between IQ and nicotine dependence as well as the heritability of IQ and nicotine dependence and the genetic correlation of the two traits. Among individuals we found an association between IQ and nicotine dependence, in line with others (191), although the association was weak. In addition, we were able to separate and quantify the environmental factors into shared and non-shared environmental factors. It turned out that for nicotine dependence, non-shared environmental factors were the most important in explaining the variance. This may seem somewhat contradictory to paper IV, where we suggested that shared environmental factors were the most important in explaining the IQ-smoking association. However, in paper IV we studied the association of IQ and smoking status which is a different outcome compared to nicotine dependence. Even if they are correlated, factors influencing initiation of smoking might be different from factors making it difficult for smokers to quit, e.g. nicotine dependence. Further, we found that the genetic correlation between IQ and nicotine dependence was weak. Therefore it seems unlikely that nicotine dependence is a main explanatory factor behind the established inverse association between intelligence and smoking and even less likely that nicotine dependence is an important mediator of the association of intelligence with CVD mortality.

6.2 RESULTS IN RELATION TO SUGGESTED MECHANISMS

Several suggested mechanisms were presented in chapter two together with studies supporting them. In this chapter, I will continue the discussion on potential mechanisms based on my own results and adding some personal reflections based on these results and the results of others.

6.2.1 Confounding and/or mediation by socioeconomic factors

Early-life social conditions can most easily be thought of as a confounder between intelligence and mortality, whereas social conditions in later life can be thought of both as a confounder and as a mediator. I will start with discussing early-life social conditions. In our studies, as well as in most of the others, adjustment for socioeconomic factors in childhood did not have any substantial effect on the IQ-mortality association. Also, in paper I an effect of intelligence on CHD was evident within brother pairs who were brought up under the same social conditions. Thus, if early environmental factors explained the inverse intelligence-CVD mortality association, they should not be related to shared family environment but rather be unique for each child in a family. On the other hand, in study IV, we speculate that the variables used to adjust for early-life SEP may not capture the shared environmental factors in childhood affecting smoking status. This could also be the case for intelligence and mortality, i.e. that we do not capture the factors in early life which affect both intelligence and disease status with the variables we use in our models. For example Hemmingsson and his colleagues showed that psychiatric diagnoses, social misbehaviour and low emotional control attenuated the association of intelligence and mortality to a large extent (72). They speculated that those factors

may be indicators of childhood experiences not captured by traditional measures of childhood social conditions. However, it may also be that they are characteristics which are more strongly related to intelligence than to social conditions.

In adult life, many health outcomes are dependent on SEP (109). There are several potential modifiable characteristics of the early environment that may have a lifelong impact on health as well as on intelligence. It is possible that low childhood intelligence results in social deprivation in adulthood, which in turn leads to an earlier death, i.e. adult SEP acts as a mediator between intelligence and later health. Adjusting for indicators of adult SEP attenuated the results more than did adjustments for indicators of childhood SEP, which is not surprising since adult SEP to some extent is a result of intelligence. The challenge in exploring this pathway lies in the separation of the part of adult SEP which is a consequence (or even the same measure as intelligence) of intelligence, mediation, from the part which is a result of early-life SEP, confounding. One may hypothesise about the pathways, but the underlying truth is difficult to uncover. Hart et al. investigated the pathway of intelligence, adult SEP and mortality through SEM and found that IQ had a direct effect on risk of death and also an indirect effect via deprivation (65).

The measure of adult SEP which had the greatest impact on the IQ-mortality association in our studies was education. As mentioned previously it is difficult to interpret this result. Some of the attenuating effect is likely due to a mediating or confounding effect of educational level, but some of the effect is probably due to over-adjustment since intelligence and education to some extent are measures of the same underlying ability.

The opinions about the role of adult SEP as an explanatory factor of the intelligence - mortality association are divided. Kuh and associates (70) concluded that greater cumulative exposure to poor lifetime socioeconomic conditions is the most likely explanation for the observed relationship between low cognitive ability in childhood and mortality in later life. Hemmingsson and his colleagues found that the association between IQ and mortality was mediated through adult social circumstances (72). In contrast, Pavlink et al. argued that residual confounding by SEP is an unlikely explanatory factor behind the IQ-mortality association (73). Kuh et al. also discussed the fact that serious illness in childhood was associated with low cognitive ability at 8 years of age and mortality between the ages of 9 and 54 years and that poor childhood socioeconomic conditions at the age of 4 years were associated with low cognitive ability and mortality. This would partly be an effect of reverse causality and partly an effect of confounding by early SEP. It is possible for childhood and adult SEP to be part of the explanation behind the association of intelligence and mortality but, as I see it, not the main one. Based on the weak attenuation of the effect when adjusting for early-life SEP, the effect found for CHD within brother pairs and the linear effect over the whole intelligence distribution, it is likely that other factors have a more important role in explaining the association behind intelligence and mortality. An argument against the importance of adult SEP as an explanatory factor is also the fact that IQ is related to early mortality where adult SEP should not have had so much influence. Hart and colleagues have reported that IQ was only related to

early mortality and not to mortality after 65 years of age, possibly indicating greater influence of social factors on mortality in later life (64).

If intelligence influences the susceptibility to ill-health in later life, for instance through adult SEP, then intelligence can be considered to have a causal effect on mortality. If, on the other hand, intelligence and the susceptibility to later ill-health in later life are affected by childhood SEP, then intelligence can be considered to have a non-causal effect on mortality.

6.2.2 Confounding by genetic or early environmental factors

This effect has sometimes been referred to as an effect resulting from a higher factor representing a system integrity effect, meaning that intelligence may be a proxy of optimal body functions in general, or an optimal cardiovascular system in particular. This could be either due to genetic factors or due to early environmental factors such as foetal life conditions. Study II suggests some genetic influences on the intelligence - mortality association based on the results of weak associations between non-biological parent-offspring pairs. Given a relatively high heritability of intelligence and assuming that socioeconomic factors were to a large extent accounted for in the analyses, the differences between biological and non-biological associations may to some extent be explained by pleiotropic genetic factors influencing intelligence and mortality. However, the design did not allow us to estimate genetic influences. It is also difficult to separate genetic factors from possible effects of insults in foetal or early postnatal life. The literature offers different ways of interpreting the support for genetic or foetal life mechanisms. For example, one of the earliest studies on Swedish data by Lindgärde et al. (104) could be interpreted as supporting genetic factors as well as mediation by SEP. In this study intelligence measured in early life was strongly associated with essential hypertension at the age of 48. There were no differences between the group with hypertension and the healthy group with regard to socioeconomic conditions during childhood. Thus, socioeconomic factors, at least in childhood, did not seem to be a confounder. Since the men were young, health behaviours adopted in adulthood probably did not affect their blood pressure much, which is why genetic influence is a plausible explanation. On the other hand, the hypertensive men reported lower levels of physical activity and were psychosocially more disadvantaged, both of which are related to hypertension. Also, in the group with hypertension there was a strong difference between fathers' education and sons' cognitive ability. This difference could be thought of as a stress factor, which also would indicate lifestyle as a potential explanation or mediator. Depending on the speed with which these health behaviours operate and affect the system, health behaviours or stress might be the mechanism, rather than genetics.

Arden et al. aimed to study the presence of a common genetic factor for intelligence and health through a "fitness factor", which consisted of eight abnormality counts (192). They found a small but weak support for the notion of a fitness factor influencing intelligence and physical health. However, the study had methodological limitations. In the only twin study that we are aware of which examines intelligence and mortality, the association disappeared in the pair-wise analyses (33). This indicates a genetic effect and/or an effect by shared environmental factors. The

association between intelligence and longevity vanished both within MZ and DZ twins, even if the estimates were not presented in the study (it could have been due to loss of power). This suggests environmental influences or that the specific genes behind intelligence and longevity are shared to the same extent for MZ and DZ twins. The environmental factors may be the effect of foetal life conditions. This mechanism can be seen as some biological or early-life insult which affects both intelligence and later health status. Intelligence would then be a proxy of early-life bodily insults. For example, the association between height and IQ and CVD risk, or low birth weight and IQ and CVD risk, can be seen as support for the hypothesis of a biological pathway. Such a pathway suggests that malnutrition or other non-optimal conditions in foetal life or early postnatal life affects the development of the brain and later cognitive function and also the risk of CVD.

Further, the theory of intelligence being a proxy of a system integrity effect of the cardiovascular system can perhaps be supported by the observed association between diabetes and lower cognitive performance. Diabetes is an important risk factor for CVD. The proposed mechanisms are the micro- and macro-vascular complications. For type 1 diabetes the micro-vascular complications, for example neuropathic, constitute the greatest part of the disease (193). In a meta-analysis of the effects of diabetes on cognitive performance, it was shown that compared to controls, the group with type 1 diabetes demonstrated a significant reduction of overall cognition, as well as a lowered intelligence (both fluid and crystallised) (194). However, the magnitude of most of these cognitive decrements was relatively modest (within one half standard deviation of the control group). Also, studies assessing cognition in children with diabetes observed that an early age of onset (before the age of five) appear to be associated with more severe impairments of cognitive performance (195). Northam et al. showed that six years after onset of disease, children with type 1 diabetes performed more poorly than control subjects on measures of intelligence, attention, processing speed, long-term memory, and executive skills (196). In an earlier study by the same authors, age of onset of type 1 diabetes predicted negative change on intelligence test, the earlier the worse (197). Perhaps the presence of retinal micro-vascular abnormalities could provide an explanation. A review study found the presence of retinal vascular signs to be associated with cognitive impairment in patients with diabetes (198). Biessels et al. proposed that clinically relevant diabetes-related cognitive decrements mainly occur at two crucial periods in life; when the brain is developing in childhood and when the brain undergoes neurodegenerative changes associated with ageing (199). We are aware of one study that looked at the association of IQ and mortality within older persons with diabetes (126). The results revealed within this group lower IQ was associated with higher mortality risk and higher risk of becoming disabled.

The association of very low intelligence and higher mortality risk has also been suggested as an effect of system integrity. Leon et al. found very high mortality among people with very low IQ in childhood, <70 (103). It was partly explained by the fact that these individuals were born with serious co-morbidities such as congenital anomalies and Down syndrome. The authors discussed that this finding was an obvious and extreme manifestation of intelligence being a measure of “system integrity”. On the other hand, adjusting for a range of other physical signs and health

indicators at birth and in childhood had little or no impact on the association of intelligence and mortality which led them to the conclusion that their analyses provided no support for the hypothesis of a general factor underlying intelligence and health. In our data individuals with very low intelligence are to a large extent missing since individuals with mental disabilities or severe diseases were excluded from conscription examinations.

Another finding which gives some support for intelligence being a proxy of a healthy cardiovascular system is that physical activity has been shown to improve cognitive functions in mice (200-202). Also, in a Swedish study, it was shown that in addition to a cross-sectional association of IQ with cardiovascular fitness, changes in fitness between the ages of 15 and 18 predicted cognitive performance at the age of 18 years in Swedish men (203). This allows speculation about the relationship between condition of the cardiovascular system and intelligence. However, a recent study did not find any support for intelligence being related to atherosclerosis in healthy middle aged and older American adults (204).

Finally, reaction time, a crude measure of the processing speed of the brain, has been suggested as a good proxy of intelligence, at least partly, and an indicator of some sort of system integrity. Both IQ and reaction times have shown inverse associations with mortality and in one study fully attenuate the association of IQ and mortality (1). This indicates that reaction time and IQ might be equally good indicators of the aspect of cognition which is of importance for mortality. In line with this, Shipley et al. found reaction time to be most strongly associated with mortality among the youngest age group in their study (101), suggesting that reaction time is not only an indicator of age-related physiological deteriorations but also, or rather, an indicator of the brain's more basic information processing ability. However, contrary to this finding, another study on elderly subjects (mean age of 75 years) was unable to show that reaction time could explain the effect of either fluid or crystallised intelligence on mortality risk (100).

To sum up, there are several factors supporting the theory of a system integrity effect such as the association between intelligence and a healthy cardiovascular system, the dose-response association between intelligence and mortality and the association between low birth weight for gestational age and low intelligence. What speaks against this explanation is the lack of an effect among women found in some studies and the fact that intelligence seems to be mainly associated with lifestyle-related diseases.

If the association between intelligence and later health is explained by common genetics (or foetal life conditions), then the effect of intelligence on mortality is non-causal.

6.2.3 Mediation via health behaviour

The idea that highly intelligent individuals adopt healthier behaviours is perhaps the most advocated theory among people in general when discussing intelligence and mortality. It is not unlikely to think that a person with high intelligence would have a

greater capacity to collect information about certain behaviours and to understand their effects on health outcomes, compared to lower scoring individuals. However, a problematic aspect of this explanation is the linear effect of intelligence on mortality. For the great majority clustered around the mean, one would expect no major differences compared to the higher scoring individuals in terms of understanding health messages. The ability to understand the health effects of smoking, or other adverse health behaviours, is unlikely to differ between individuals of, for example, stanine score 6 and stanine score 7 or 8. Therefore, if differences in health behaviour would explain the effect of intelligence on mortality, a threshold effect might be expected. A few studies have found a more evident effect (or an effect only) in the lowest scoring quartile. However, determining the shape of the effect requires a large sample size and it is the studies with the greatest sample sizes which have found a linear effect. However, it may not be the ability to understand the information about health behaviours that is linked to the intelligence distribution but rather the ability to act in accordance to this. It is well-established that there are only weak associations between knowledge and health behaviour. In terms of knowing what is good or bad for one's health a threshold effect in the lower scoring quartile may be expected, but perhaps is the ability to transfer this into action more strongly related to the whole intelligence distribution. Furthermore, personal characteristics may also be important in this context. The broad traits comprising the Big Five personality scale (introversion, low conscientiousness, low agreeableness, neuroticism and intellect-imagination) have all been shown to be associated with longevity, partly through health behaviours and could be confounders of the association between intelligence and mortality (205;206).

The most interesting aspect, however, is not whether intelligence is associated with smoking (or other health behaviours) but whether these health behaviours can explain the association of intelligence with mortality. The few studies that did control for smoking, including paper I, did not find much support for this. Further, in studies of social inequalities in health, health behavioural factors such as smoking have been shown to explain part of the association but not all of it (108;207). In studies of intelligence and mortality which have adjusted for the same type of risk factors, only a small effect has been found, which speaks in favour of other factors than lifestyle explaining the intelligence -mortality association. Also, in paper IV we found no support for IQ to be causally associated with smoking or in paper V for IQ to be associated with nicotine dependence, influencing smoking persistence.

Further, recent studies of lifestyle factors and health outcomes give support for the theory of accumulation of risk factors, both in terms of time under risk but also in the sense that several risk factors have a multiplicative effect on health outcomes. This would mean that adjusting for one of them, for example smoking or physical activity, is not enough. To capture the effect of lifestyle on an individual's health status, a package of risk factors might be needed. Thus, adjusting the IQ-mortality association for a combination of risk factors might attenuate the effect substantially. Also, the theory of a critical period model has been suggested in life course epidemiology (208). It postulates that during a specific period, mainly early in life, a certain exposure may have a critical role in how it affects the structure and functions of organs or body systems and in determining long-term health. This would, in this context, implicate

that adjusting for certain health behaviours (or SEP) would require the appropriate timing of such variables. In our studies we did not have access to a whole range of behavioural risk factors, nor did we have information on personality characteristics such as the Big Five. Access to these would have given us an opportunity to explore the possible mediating of the IQ-mortality association by mediation through behavioural factors more thoroughly.

A final argument in favour of health behaviors to be likely explanations for the IQ-mortality association is that the disease and mortality outcomes which are associated with intelligence appear to be outcomes related to lifestyle such as CVD, injuries, accidents, lung cancer and skin cancer, whereas for other forms of cancer there is no such relationship.

If the association between intelligence and later health is explained by health behaviour, through an inability to understand or to act in accordance to knowledge, then the effect of intelligence on mortality can be considered causal.

6.2.4 Concluding remarks on the suggested mechanisms

It is difficult to disentangle which factors are confounders, which are mediators and which are primary explanatory variables behind the association between intelligence and mortality. The studies constituting this thesis do not support the notion that early life SEP is an important confounder of the IQ-mortality association or that adult SEP is an important mediating factor. However, the strong inverse association of IQ and smoking, explained by shared environmental factors, may be interpreted as presence of residual confounding from early-life conditions. Further, our results give no evidence for smoking status or nicotine dependence to be important mediating factors of the IQ-mortality association.

6.3 METHODOLOGICAL CONSIDERATIONS

A number of epidemiological concepts could be mentioned and discussed in this section. However, I will restrict the text to a few key considerations which are the most important ones for this thesis.

6.3.1 Over-adjustment and effect modification

Epidemiological analyses should, of course, be adjusted for confounding, but adjustment for mediating factors might lead to over-adjustment, resulting in inappropriate attenuation of exposure-disease associations. When studying the association between early life intelligence and later mortality, the adjustment for variables measuring adult SEP is debatable since they can be considered as mediating factors. In particular, adjustment for own attained education is questionable when studying the effect of intelligence on mortality, since intelligence and education are highly correlated and can be considered as measures of the same underlying ability. However, in order to sort out the pathways of the intelligence-mortality association, information about mediating factors is important. Intelligence may be associated with morbidity/mortality outcomes through several pathways as suggested in Figure 1a.

Thus adjusting for these in the models will provide information about the role of such variables in attenuating the association. It is however difficult to disentangle the extent to which adult SEP (or attained educational level) is a mediator in one pathway and a confounding factor in another.

Some studies have found a more evident effect in lower socioeconomic strata or only an effect in the lower half of the IQ distribution. Singh-Manoux et al. 2009 suggest that low SEP is an effect modifier of the effect of intelligence on mortality. However, in paper I we did not find any support for an effect modification by SEP.

6.3.2 Strengths

The main strength of the studies which constitute this thesis is the large and fairly representative samples. It made it possible to explore the strength and shape of associations with adjustment for several confounding factors and to explore different disease outcomes separately with retained statistical power. Further, in general, register-based information is likely to be more reliable than self-reported data in terms of differential misclassification. For paper I-III our follow-up data covered the entire Swedish population and were thus not prone to selection bias. Baseline data on intelligence were obtained from national registers and reliable, although there is some selection bias since individuals suffering from severe chronic diseases are exempt from conscription examination.

6.3.3 Limitations

Our studies have some limitations, which should be kept in mind. Firstly, since all studies were based on men only, no conclusions regarding the association of intelligence and mortality and intelligence and smoking can be drawn for women (except for part of study II). It is a limitation in general in medical research but in this case in particular since information about associations for women could have increased the understanding about potential pathways.

Secondly, in study I and III participants were rather young at follow-up, and thus we were only able to study early CHD and stroke morbidity/mortality. We cannot draw any inference about intelligence and CHD/stroke in older age.

Regarding confounding and mediating factors we had information on BMI, DBP, SBP and SEP in childhood and adulthood and, for a subcohort, smoking in late adolescence. Information about behavioural risk factors such as dietary habits, physical activity, alcohol use, later smoking status and later hypertension would have been valuable. Since we were unable to adjust for later behavioural factors we were unable to investigate possible mediation of the IQ-mortality association related to for example nutrition or physical activity. Residual confounding is often an issue in large epidemiological studies. Adjusting for a broader range of behavioural risk factors, e.g. eating habits, physical activity and alcohol consumption, would have been useful. That would have enabled us to look for further attenuation of the IQ-morbidity/morality associations.

Furthermore, although we had extensive information about socioeconomic factors, this does not mean that we can exclude the possibility of residual confounding, as discussed previously. For example could measures of deprivation of residential area, lack of social support etc. have been important indicators of SEP. Further, using occupational code as a measure of SEP will lump together unemployed individuals with students, retired individuals etc. This may have lead to an underestimation of socioeconomic differentials within this group.

In study II we lacked information about the length of time for which the step sons lived with their non-biological mother/father. Thus, we could only speculate about environmental influence of step parents. More complete data on shared environmental influences would have been useful.

Regarding the twin studies (studies IV and V), the STAGE cohort was not representative of the general population. Due to overrepresentation of respondents with a high education, the prevalence of smokers was underestimated compared to the general population. In addition, the smoking variable was quite broad. In order to be able to study smoking in more detail, for instance to be able to relate it to the risk of CVD, one would need more detailed information on amount and duration of smoking.

A limitation of study IV was the low power in the analyses of twin pairs. This might have led us to overlook an association in the within-pair analyses (type II error), however, we believe that any such effect would have been relatively small considering the size of the ORs. Furthermore, information on covariates such as parental smoking status and other familial factors known to be predictors of smoking initiation would have been valuable, together with a good measure of cumulative smoking. Information on externalising behaviours, or personal characteristics such as the Big Five, among the twins, which could act as confounders of the IQ-smoking association, would also have been useful in determining which factors in the early family environment that accounts for the association between intelligence and smoking.

Furthermore, twin studies have some inherent limitations based on assumptions (described under 4.3.3.4). In paper V assortative mating with regard to smoking status might have influenced the results. If this was the case, the DZ twins and their co-twins would on average share more than 50% of their segregating genes related to a complex phenotype such as nicotine dependence, and when analyzing DZ and MZ twins together by SEM the A component (heritability) will be underestimated. However, if the A component was to be biased downward, the C component would be overestimated, which we did not observe. Another limitation when studying nicotine dependence is that we can only generalise our results to the exposed population, i.e. the individuals that have ever tried smoking or used snus.

Finally, the subtests measuring intelligence that was used throughout in this thesis did change somewhat during the years of our studies. However, since we used standardised IQ scores, mainly of global IQ, this should not be a big problem in our studies.

6.4 PUBLIC HEALTH IMPLICATIONS

The overall aim in public health research should be to conduct research that contributes with knowledge which can be used to improve health. Within social medicine we are also concerned with understanding differences in health and health care utilization among groups with different social status in society and narrowing the gap between them. Within cognitive epidemiology we are, however, not yet able to propose interventions or implementation of our results. This is because the causal pathways are not yet completely understood. However, at a later stage there will most likely be public health benefits from this research. Perhaps in terms of a better understanding of how people's health behaviours are linked to health and intelligence and through increased knowledge about how the cardiovascular system is related to cognitive abilities and vice versa. Perhaps could an intelligence test, used in a suitable context, serve as a valuable predictor of future health, both as a way of determining high versus low risk groups, but also to be used among older individuals as a marker of cardiovascular status. For example, it was found in a recent Swedish study that among 70-year-old men, free of dementia and stroke IQ was a good predictor of stroke in the years to come (209). It is, however, important to point out that all the associations presented in this thesis are found on a group level and the knowledge of how strong a predictor intelligence is for future health on an individual level is not known.

If the effect of intelligence on morbidity and mortality turns out to be highly genetic, it could possibly help individuals in risk groups to motivate themselves to better health behaviours. If on the other hand, evidence emerges that health behaviours comprise important mediating pathways (in spite of the results of this thesis), there would be new intervention studies to be conducted in order to implement the knowledge within the health care system and among the general public.

6.5 FUTURE RESEARCH

There is always a desire for further research and more studies, replicated for different cohorts and age groups. There are, however, a few types of studies which I find particularly important within the field of cognitive epidemiology. Firstly, more studies on women are needed in order to find out whether the association is similar to that of men or not. Studies on women could also be informative in order to find out more about potential confounding from early socioeconomic factors as well as from a common genetic factor. It is by design impossible to conduct randomised trials of intelligence and mortality and therefore studies on twins with high power and good quality variables of specific environmental factors as well as lifestyle factors would be very informative and contribute to the understanding of the pathways.

6.6 CONCLUSIONS

An inverse association between IQ and CHD mortality.
In line with previous research we found an inverse association between IQ in young adulthood and cardiovascular morbidity and mortality in later life.

Socioeconomic factors did not explain the inverse association of IQ and CHD.
The effect of IQ on CHD was evident and clear within all socioeconomic strata, parental and own, and the effect appeared to be similar within all strata.

IQ was inversely associated with all major subtypes of fatal and non-fatal stroke.
In contrast with previous studies we were able to show statistically significant inverse associations of IQ on all major subtypes of stroke (except for fatal ischemic stroke). The strongest association was seen for hemorrhagic stroke.

When investigating associations of offspring IQ with maternal and paternal all-cause and cause specific mortality, somewhat stronger inverse associations were found not only for mothers for whom intrauterine effects and residual confounding are possible, but also for fathers for whom residual confounding seems less likely.
The association was studied for all cause as well as for cause specific mortality. The associations were rather weak but statistically significant.

The association between IQ and smoking status was lost within twin pairs.
We found an inverse association between IQ and smoking when twins were analysed as individuals but no effect when genetics and shared environmental factors were taken into account in pair wise analyses. Therefore we found no support for IQ to be causally associated with smoking or that smoking would act as an important mediator of the IQ-mortality association.

There was only a weak association between IQ and nicotine dependence.
We found a weak phenotypic correlation between IQ and FTND and only a tiny proportion of this association could be explained by overlapping genetic factors. Therefore, no evidence was provided for a common genetic factor behind IQ and nicotine dependence.

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