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FACTORS OF IMPORTANCE FOR SELF-RATED HEALTH

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ABSTRACT

Even though self-rated health is increasingly accepted as an important measure of health status, there are several uncertainties as to why people differ in their health perception. The extent of age differences across the life span and whether there are different determinants in men than in women is unclear. The overall objective of this thesis was to increase understanding as to why individuals differ in their health perception through quantitative genetic and epidemiological approaches using sub-samples from the Swedish Twin Registry. By studying twins, it is possible to estimate the relative importance of genetic and environmental factors for self-rated health.

In Paper I we included both like- and opposite sexed twins in adult ages in order to evaluate cross-sectional age group and sex differences in the relative importance of genetic and environmental factors for self-rated health. Individual specific environmental variance is the most important component in adults under 45 years whereas the increase in total variance in the older age groups (45-74) is primarily due to genetic influences. The individual specific environment becomes more important again in the oldest age group (>74). No significant sex differences were found in variance components. Similarly, the same genetic effects were of importance in men and women. Paper II investigated decreases in means and increases in individual differences with age longitudinally. Results indicate that previously reported changes in self-rated health over the life span primarily reflect cohort differences rather than age changes. Stability between time points reflects both environmental and genetic factors.

Intact cognitive functioning is an important aspect of health with increasing age, therefore, Paper III focused on the associations between self-rated health and cognitive abilities in normal aging. There was only slight evidence that associations between self-rated health and cognitive test scores were mediated by chronic disease conditions. In the age group younger than 67 years, associations between self-rated health and spatial reasoning and perceptual speed were found, mediated by both genetic and environmental factors. In the older age group (≥ 67 years), associations between self-rated health and verbal ability, spatial reasoning, perceptual speed and visual memory were entirely due to genetic factors. Paper IV investigated the importance of health behavior and risk factors for future self-ratings of health. We found that recurrent headache, back- and neck pain, lack of exercise, smoking, obesity, perceived stress, unemployment and personality were associated with poor self-rated health, some 25+ years later. Genetic and familial factors only slightly influenced the relationships between recurrent headache, exercise, obesity, and poor self-rated health.

In conclusion, both genetic and environmental factors are of importance for individual differences in self-rated health and the effect is equal for men and women. Genetic effects for self-rated health can probably be explained by genetic influences on disease status. Childhood socioeconomic status did not explain the finding of cohort differences in self-rated health. Societal changes not tapped by our measure more likely explain these differences. We found weak associations between self-rated health and cognitive abilities, indicating that cognition is not substantially influencing self-rated health in a normally aging population. Finally, health behavior and risk factors are of importance for self-rated health. Life-style changes such as reduced weight and more exercise might help prevent people from experiencing their health as poor in the future. This in turn might result in a decrease in morbidity and increase in survival.

Keywords: self-rated health, twins, genetic factors, environmental factors, sex, age, aging, cognitive abilities, epidemiology, health behavior

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LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their roman numerals (I-IV).

I. **Svedberg P**., Lichtenstein P., Pedersen N.L.
Age and sex differences in genetic and environmental factors for self-rated health: a twin study.
Journal of Gerontology: Social Sciences. 2001, 56B, 171-178.

II. **Svedberg P**., Gatz M., Lichtenstein P., Sandin S., Pedersen N.L.
Self-rated health in a longitudinal perspective: a 9-year follow-up twin study.
Journal of Gerontology: Social Sciences. 2005, 60B, 331-340.

III. **Svedberg P**., Gatz M., Pedersen N.L.
Genetic and environmental mediation of the association between self-rated health and cognitive abilities. *Submitted.*

IV. **Svedberg P**., Bardage C., Sandin S., Pedersen N.L.
A prospective study of health, life-style and psychosocial predictors of self-rated health. *Submitted.*

CONTENTS

LIST OF ABBREVIATIONS

AIC	Akaike's information criteria
A	Additive genetic factor
C	Shared environmental factor
CI	Confidence interval
D	Dominance
DZ	Dizygotic
E	Nonshared environmental factor
HRQoL	Health Related Quality of Life
h^2	Heritability
IPT	In-person testing
MZ	Monozygotic
OR	Odds ratio
OS	Opposite-sexed
r_g	Genetic correlation
r_c	Shared environmental correlation
SATSA	Swedish Adoption/Twin Study of Aging
SALT	Screening Across the Life Span Twin Study
SEI	The Swedish socioeconomic status classification scheme codes
SES	Socioeconomic status
SRH	Self-rated health
TRA	Twins reared apart
TRT	Twins reared together
WHO	The World Health Organisation
QoL	Quality of Life

1 INTRODUCTION

Life expectancy is continuously increasing in many countries and expectations of good health in advanced age increases as well. However, living longer today than we did perhaps 50 years ago does not necessarily mean experiencing good health status at all times and at advanced age. It is widely known that health is multi-dimensional and to measure health status might not be trivial. Health means absence of pain and illness for some people while for others health is a more general feeling of well-being. In order to construct a definition that would function as a foundation for work within preventive medicine The World Health Organization (WHO) declared more than 50 years ago that health is "the state of complete physical, mental and social well-being and not merely the absence of illness" (WHO, 1948) since then "dynamic" has been added to state in the definition (WHO, 2003). The WHO definition points to the complexity of health, not only reflecting absence of illness; the definition underlines the notion that health encompasses much more. Health and illness refers to presence or absence of illness while health perception refers to self-rated health. From the individuals' perspective health perception and the physical disease-oriented dimensions most likely interact, which may result in a movement between the pools of ill health and health at different times and ages (see figure 1a and b). However, it may also be that there are different determinants for poor and good health perception (Bjorner et al., 1996).

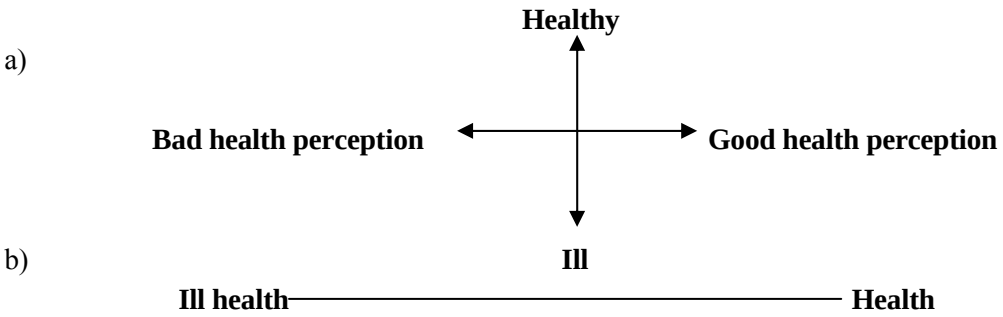

Figure 1a. The health concept can have different dimensions. Health and illness reflects physical aspects of health while bad or good health perception refers to self-rated health. ***1b.*** In reality an interaction most likely occur between physical and perceived health that leads to thoughts of a continuum between the pools of ill health and health.

The concept of health as defined by WHO, might represent an unreachable ideal state that can be hard to use as a realistic goal in medical care. However, the WHO definition should rather be interpreted as a normative goal for health policy and practice. The WHO definition contributed initially to a broader discussion of health than the traditional biological disease-oriented definition offered. Health is also a personal experience and may exist in the presence or absence of disease, dysfunction or disability. The only person that can rate an individual's health or ill-health from this perspective is that person him or herself.

2 SELF-RATED HEALTH

2.1 THE CONCEPT

Self-rated health, an overall assessment of health status, has long been a focus of interdisciplinary research on social and psychological factors in health. The first generation of researchers who worked with self-rated health were not interested in perceived health ratings themselves, but instead sought a simple measure as a substitute and tool in place for clinical examinations. During the past 25 years there has been a change in attitude and interest in self-rated health and researchers began to show an interest in establishing correlates and predictors of self-rated health. The most provocative finding in studies of self-rated health is that subjective health assessments are often superior to clinical assessments for predicting mortality.

The first study on self-rated health and mortality appeared in 1982 (Mossey & Shapiro, 1982), but there were decades of study before that, showing that individuals' ratings did not always agree with other, more objective sources of information about their health. Since early 1980s, more than 50 studies from around the world have been published that tested the association between self-rated health and mortality (Bath, 2003; Idler, 2003; Idler & Benyamini, 1997). In the great majority of these studies a significant association emerged, even in multivariate analyses.

There are several ways in which health surveys ask people to rate their own health with a single question. Single item global ratings are used in health surveys all over the world, in many languages, to serve as health indicators for the population and to track trends over time. Note that the question concerns the individual's state of *health*, not disease or illness. The responses to any of these questions can be called *self-ratings of health*.

Global, non-comparative is the most common way of asking respondents about their self-rated health; “how would you rate your own health?” Another way of asking is by a general age-comparative question such as “how would you rate your general health status compared to others in your age group?” A third way of asking respondents about their self-rated health is to let them compare their present general health status to how it was some years ago (time-comparative). Usually, answers to these questions are given on a 3 to 7 unit scale ranging from poor to excellent self-rated health (Bjorner et al., 1996). A general assessment of health can also be achieved by questionnaires where several items are combined into a scale.

Population based studies make it possible to assess the general health level in a population and enable comparisons between different groups within a population, for example socioeconomic groups and age groups, and to analyze change in health status over time.

Among the first systematic studies of self-rated health were made in the US at Duke University beginning in the 1950s. Healthy elderly volunteers were administered

repeated medical examinations, and also rated their own health. Data from the 1960s and 1970s showed some association between self-rated health and physicians' ratings, but not a perfect correspondence. When there were differences between the ratings, self-rated health was more often in the direction of better health than the physician's rating. The older the study subject was, the more likely they were to give an optimistic rating of their health, considering their higher levels of chronic illness and disability. Some of the studies also showed that, over time, the self-ratings were very good predictors of future physicians' ratings. In fact, they were better at predicting future physicians' ratings than physicians' ratings were at predicting future self-ratings of health (Bjorner et al., 1996; Maddox & Douglass, 1973).

Self-rated health versus Quality of Life and Health Related Quality of Life

Quality of Life (QoL) and Health Related Quality of Life (HRQoL) are multidimensional concepts. The study of QoL is an examination of influences upon the goodness and meaning in life, as well as people's happiness and well-being. While QoL is a much broader concept, HRQoL instruments capture different dimensions related to limitations in health such as physical function, mental health and pain (Patrick & Bergner, 1990). Self-rated health offers a summary score of the self-evaluation of health in a single item measure or scale that does not divide people's health perception into different dimensions. Self-rated health and HRQoL have often been used interchangeably and are both included in the concept of general health status (Bjorner et al., 1996), although, HRQoL generally is considered being a broader concept than self-rated health that also includes self-rated health. Two basic approaches to HRQoL measurement are available: generic instruments that provide a summary of HRQoL, and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function (Guyatt, Feeny, & Patrick, 1993). As has been described by others (Bjorner et al., 1996), self-rated health along with functional ability is included in the concept of general health status and even though self-rated health includes perception of symptoms, well-being and general health it should not be mixed up with the broader concepts of QoL and HRQoL, a perspective adopted in this thesis.

2.2 COVARIATES AND PREDICTORS OF SELF-RATED HEALTH

What do global self-rated health items measure? – Cross-sectional studies have demonstrated that not just one factor but rather a large number of factors are of importance for self-rated health. Even though physical, functional and mental health usually shows the greatest association, age, life-style and behavioral factors, work and leisure time activities, and socio-demographic factors are also associated with self-rated health directly or indirectly (Bjorner et al., 1996; Undén & Elofsson, 1998) along with longstanding illness and increasing number of new illnesses (Murray, Dunn, & Tarnopolsky, 1982). Women generally live longer but complain more than men do about their health, however reports of sex differences in self-rated health have been mixed. Social and psychological determinants are of greater importance for women than men for which behavioral determinants seem to be of greater importance (Denton,

Prus, & Walters, 2004). Approximately two thirds of the studies considering sex differences in self-rated health report lack of association when other factors are taken into consideration (Bjorner et al., 1996). In studies reporting sex differences women generally report poorer health status than men although this sex difference in self-rated health tends to decrease or disappear as people grow older (McCullough & Laurenceau, 2004; Undén & Elofsson, 1998).

Self-rated health has been shown to be associated with risk factors such as pain, obesity and underweight along with health behaviors such as exercise, smoking and alcohol consumption (Bjorner et al., 1996; Ferraro & Yu, 1995; Fylkesnes & Forde, 1991; Lamb, Roberts, & Brodie, 1990; Manderbacka, Lundberg, & Martikainen, 1999; Mantyselka, Turunen, Ahonen, & Kumpusalo, 2003; Månsson & Merlo, 2001; Schulz et al., 1994). Over the years there has also been an interest in the influence of marital status and widowhood on health. In general the findings support marriage as protective of people's health (Markides & Lee, 1990). The association between socioeconomic status (SES) and self-rated health has been investigated and confirmed in both cross-sectional and longitudinal studies (Borg & Kristensen, 2000; Power, 1991; Power, Matthews, & Manor, 1998; Undén & Elofsson, 1998). Repetitive work, job insecurity and high ergonomic exposures predicted worsening of self-rated health over 5 years (Borg, Kristensen, & Burr, 2000). Even though self-rated health has been shown to be associated with measures of psychological well-being, including depression and personality variables such as optimism, pessimism, and neuroticism (Mossey, 1995), there is surprisingly little research on personality and self-rated health. Distress was found to be related to more negative health perceptions among adults both cross-sectional and longitudinally (Farmer & Ferraro, 1997).

Qualitative research approaches using interviews or open-ended answers to self-rated health items have revealed that some study participants refer to specific health problems or absence of ill-health when asked to rate their health, while others think of general physical functioning, life situation or their health behavior. In addition, these specific references or factors may also vary by age (Idler, Hudson, & Leventhal, 1999; Krause & Jay, 1994; Manderbacka, 1998).

Most studies have used self-rated health as a predictor of future events, such as premature mortality. Few studies have been focused on self-rated health as an outcome variable longitudinally, hence, less is known about the factors influencing our future health status.

2.3 SELF-RATED HEALTH, AGE AND AGING

A recurring observation from studies of many health related endpoints in the elderly is individual variability. Older adults often experience and report poorer self-rated health than younger adults. Despite this shift towards poorer health ratings there are many healthy elderly with ratings corresponding to younger adults; hence, there is often an increase in variance. Although not specifically designed to address questions of age differences, many studies report worse self-rated health in older age groups, and a

concomitant increase in individual differences (Bjorner et al., 1996; Earles, Connor, Smith, & Park, 1997; Roberts, 1999; Undén & Elofsson, 1998). An increase in total variance with age has been demonstrated for many health-related variables in cross-sectional studies (Nelson & Dannefer, 1992) and is consistent with life-span developmental theories (Baltes, Reese, & Lipsett, 1980). Relatively little is known about the causes of these individual differences across the life span.

Of the few longitudinal studies focusing on self-rated health as an outcome, some have reported change while others report stability in level of self-rated health with age. The Los Angeles Health Survey (Goldstein, Siegel, & Boyer, 1984) found that self-rated health remained relatively stable over one year. Changes, i.e. better or worse rating of self-rated health status than before, were not associated with any indicators of objective health or health beliefs. In their fifteen-year longitudinal study, Maddox and Douglass (Maddox & Douglass, 1973) reported a substantial stability of self-rated health and persistent high positive congruence between medical evaluations and self-rated health. A Swedish longitudinal study showed no overall change in self-rated health from 60 to 67 years of age (Tibblin, Cato, & Svardsudd, 1990; Tibblin, Tibblin, Peciva, Kullman, & Svardsudd, 1990), other studies found similar results in elderly samples (Leinonen, Heikkinen, & Jylha, 1998, 2002), although yet another study reported a slight decline of self-rated health over an eight-year period (Markides & Lee, 1990). Nonetheless, results from the National Health and Nutrition Examination Survey-I Follow-up Study suggest that not only is self-rated health sensitive to deterioration in physical health over a 20 year period, but declines over time in self-rated health are associated with mortality (Ferraro & Kelley-Moore, 2001). Idler tested in her six year follow up study (Idler, 1993), whether the observed optimism in self-rated health was attributable to changes in age, cohort or to survivorship with a sample of elderly (65 years or older). She concluded that none of the explanations could be ruled out; selective survivorship, processes of aging and cohort differences all seem to play important roles.

Age group differences in variance reported in previous cross-sectional gerontological genetic studies (Harris, Pedersen, McClearn, Plomin, & Nesselroade, 1992) could also reflect cohort differences in which earlier born cohorts have a greater range of socioeconomic and cultural influences than later born cohorts. Alternatively, terminal decline, a rapid change in social, physiological and psychological functioning prior to death, has been suggested as a possible source of individual differences in late life (Berg, 1996). When studying elderly people, the population can be presumed to include both elite survivors and an unknown number of individuals that are experiencing a terminal decline phase in their physical functioning.

Taken together, cross-sectional and longitudinal studies suggest that age related change in self-rated health may not be great, while cohort differences may be present but generally overlooked.

2.4 HEALTH AND COGNITIVE FUNCTIONING

A very important aspect of health perception and quality of life in the elderly is intact cognitive functioning. It is well known that deficits in cognitive performance are associated with the normal aging process (Salthouse, Babcock, & Shaw, 1991). However, despite its normality, cognitive slowing with age does not necessarily pass unnoticed by the individual and it may therefore be reflected in self-ratings of health. Studies have shown that respondents who report poorer self-rated health have lower cognitive test scores (Hultsch, Hammer, & Small, 1993), but the mechanisms behind this relationship are largely unknown.

It is possible that self-rated health reflects feelings of slowing and memory loss. Conversely some studies have also suggested that health factors may be a part of age-related memory performance in old age, however, results on the relationship of self-rated health and recall tasks have been mixed (Jelicic, Jonker, & Deeg, 1999; Perlmutter & Nyquist, 1990; Salthouse, Kausler, & Saults, 1990). Earles et al. (1997) found that self-rated health predicts processing speed better than it predicts memory. Wahlin and co-authors (Wahlin, Maitland, Backman, & Dixon, 2003) investigated whether self-rated health and episodic memory are related in persons aged 75-84 years. They concluded that the cross-sectional relationship was non-significant, although longitudinal change in self-rated health over a 3-year time period was related to change in episodic memory performance. Rosnick and collaborators (Rosnick, Small, Graves, & Mortimer, 2004) suggest that health status is associated to a greater extent with lower order cognitive processes, like processing speed, rather than with higher order cognitive processes, such as memory.

It has also been suggested that decrements in cognition are not only due to primary biological aging processes but also to systemic medical diseases, such as cardiovascular disease, that are common in older adults (Waldstein, 2000). Several studies have shown that various forms of vascular disease, such as atherosclerosis and cerebrovascular disease are associated with lower levels of performance, in particular for psychomotor speed (Elias, Elias, & Elias, 1990). Cardiovascular symptoms were found to predict performance on tests of episodic memory and visuospatial skill in a Swedish sample aged 75 to 96 years (Fahlander et al., 2000). Presence of stroke and poorer health ratings predicted poorer cognitive performance in a nationally representative US sample aged 70 to 103 years (Zelinski, Crimmins, Reynolds, & Seeman, 1998). Long duration of Type 2 diabetes mellitus has also been shown to be related to lower test performance across several cognitive domains, but not for short-term memory (Hassing et al., 2004; Zelinski et al., 1998). In addition, hypertension and Type 2 diabetes mellitus combined were also associated with detectable cognitive decrements in persons less than 60 years of age (Knopman et al., 2001; Pavlik, Hyman, & Doody, 2005). Neurological problems such as Parkinson's disease and multiple sclerosis have shown to be related to decrements in cognition (Achiron & Barak, 2003; Albrecht et al., 1994). It has also been reported that cancer treatment is related to cognitive functioning and quality of life (Ahles & Saykin, 2001). Chronic pain is strongly associated with poor self-rated health (Mantyselka et al., 2003). It may also be that pain has some

impact on cognitive functions. Apkarian and co-authors found support for impairment on an emotional decision-making task (Iowa Gambling task), although not for general intelligence, short-term memory or attention (Apkarian et al., 2004). Poor self-rated health is highly correlated with number of medical diagnoses, physical symptoms and morbidity, such as diabetes, arthritis, cancer (Bjorner et al., 1996; Idler, 1993) and cardiovascular disease (Svardh, Isacson, & Pedersen, 1998). It is therefore possible and of interest to investigate if the self-rated health-cognition relationship is mediated through common complex diseases. Identifying potential modifiers may be beneficial for interventions to improve cognitive functioning as well as improvement in self-ratings of health status.

2.5 TWINS AS A TOOL FOR UNDERSTANDING INDIVIDUAL DIFFERENCES

Even though self-rated health has been shown to be associated with a variety of measures and is increasingly accepted as an important measure of health, there are several uncertainties as to why people differ in their health perception. Unclear is also the extent of age differences across the life span and whether there are different determinants in men than in women.

When this present thesis project started, few studies exploring individual differences in self-rated health using twin or family data were published. Even fewer studies included opposite-sexed (OS) twins. By studying twins it is possible to determine the extent to which genetic and environmental influences are important for variation in a trait or disease. This means that we can portion the total variation for self-rated health into genetic and environmental components of variance.

Differences in similarity between identical (monozygotic) and fraternal (dizygotic) twins provide information about genetic and environmental effects that may be present. For example, if the monozygotic (MZ) twin pairs are more similar than dizygotic (DZ) twin pairs, genetic effects are indicated. Genetic and familial (shared environment) factors represent illnesses, functional capacity, personality, socioeconomic status, family environment and contact throughout life and other influences that in turn affect self-rated health. Shared environmental effects refer to nongenetic influences that contribute to similarity within pairs of twins regardless of zygosity. Nonshared environmental effects are individual-specific influences not shared within a twin pair, such as accidents or occupations. To the extent that twin pairs are dissimilar, nonshared environmental effects are indicated. Genetic differences also contribute to dissimilarities within DZ twin pairs. Heritability estimates (h^2) i.e. the proportion of the total variance that is attributable to genetic variance is often reported in twin studies. The quantitative genetic analytical approach is described in more detail in the analytical procedures section.

Increase in variance for health outcomes with age has been a topic of interest and discussion in life span developmental as well as in gerontology research. Baltes and colleagues (Baltes et al., 1980) proposed that increases in variance should be due to

increase in environmental variance as people accumulate their experiences and exposures over time. From a quantitative genetic perspective alternatives have been discussed and several other mechanisms by which total variance may increase for genetic reasons have been suggested i.e. switching on of new genetic systems at different ages (Eaves, Long, & Heath, 1986). However, there are still relatively few studies that have explored the sources of variance in health related phenotypes in elderly people.

Previous cross-sectional studies have demonstrated that genetic factors are of moderate importance for individual differences in self-rated health (Christensen, Holm, McGue, Corder, & Vaupel, 1999; Harris, Pedersen, McClearn et al., 1992). This may not be surprising given that disease status is to some extent genetically influenced, and epidemiological studies confirm a substantial genetic susceptibility to death (Iachine et al., 1998; Marenberg, Risch, Berkman, Floderus, & deFaire, 1994; Yashin, Iachine, & Harris, 1999). Thus, we would expect genetic influences for self-rated health. Nevertheless, it is notable that the increase in variance in self-rated health from late adulthood onward is for the most part attributable to increases in environmental variance (Christensen et al., 1999; Harris, Pedersen, McClearn et al., 1992). Furthermore, genetic and environmental factors mediate the association between psychosocial factors and self-rated health, although the sources of the covariation are dependent on the age of the sample (Harris, Pedersen, Stacey, McClearn, & Nesselroade, 1992). Genetic factors mediate the association in one cohort, but less so in another. Although it seems apparent that the role of genetic and environmental influences on individual differences in self-rated health varies with age group, earlier studies focused predominantly on older subjects, *i.e.* those over 50 years of age, and have relatively few or no younger subjects.

Finding mean differences does not necessarily imply variance differences between the sexes, although one twin study has suggested sex differences in the relative importance of genetic effects for self-rated health and psychosocial factors. Genetic factors mediated the relationships for women, but not for men (Lichtenstein & Pedersen, 1995). The authors suggested earlier biological aging for men than women as a possible explanation to the findings. Inclusion of opposite-sexed twins is essential for evaluating whether different sets of genes and/or different environments are operating in the two sexes or whether their relative importance differs. Thus, Paper I included both like-sexed and opposite sexed twins in order to address this topic.

Longitudinal quantitative genetic data can contribute to an increased understanding about genetic and environmental explanations for increasing individual differences and was the focus in Paper II. Generally, longitudinal changes in both means and variance have been smaller than cross-sectional differences (Finkel, Reynolds, McArdle, Gatz, & Pedersen, 2003; Pedersen & Reynolds, 1998; Viken, Rose, Kaprio, & Koskenvuo, 1994). Longitudinal analyses of number of organ systems affected by disease were investigated in a Swedish twin study (Pedersen, Steffensson, Berg, Johansson, & McClearn, 1999). For those twin pairs that survived to the age of 80 or more there were

longitudinal increases in variance across a 30-year period, entirely attributable to increases in environmental influences. Finkel, Pedersen et al., (2003) found support for increases in environmental variance with age for grip strength and well-being while genetic variance remained stable.

To our knowledge there are few studies exploring the genetic and environmental mediation of the relationship between self-rated health and cognitive abilities. However, preliminary analyses from the Swedish Adoption/Twin Study of Aging (SATSA) sample showed a small association between number of chronic illness and cognition and a larger association between functional abilities such as general motor function, upper body strength and performance and cognition (Harris & Pedersen, 1994). Age differences in the etiology of the relationship between functional and cognitive abilities showed environmental effects to be more important than genetic effects with greater age. Other results from the SATSA data showed an association between self-rated health and the speed of processing measure (Pedersen & Harris, 1992). Cognitive abilities are moderately heritable (for speed $h^2 = .65$, and for memory $h^2 = .40$) (Pedersen, Plomin, Nesselroade, & McClearn, 1992), self-rated health less so ($h^2 = .40$), with less genetic variance for earlier born cohorts. Thus, both genetic and environmental influences in common to self-rated health and cognition may mediate the association.

3 AIMS

The overall objective of this thesis is to increase the understanding on why individuals differ in their self-ratings of health.

The aims of the studies included in this thesis are:

- To investigate if there are cross-sectional age group and sex differences in total variance and in the relative importance of genetic and environmental sources of variation for self-rated health using like- and opposite-sexed twins in adult ages (Paper I)

- To investigate individual differences in self-rated health over a 9-year time interval and between four age groups. The research questions of focus were first, whether the cross-sectional decreases in mean values, increases in total variance and differences in sources of variation reported in earlier studies were paralleled in longitudinal changes, or if those differences represent cohort effects, and second to investigate whether genetic and/or environmental factors contribute to stability in self-rated health over time (Paper II)

- To investigate if self-rated health and cognitive abilities are associated and if the associations are mediated by genetic and/or environmental factors (Paper III)

- To investigate the prospective association between pain, smoking, exercise, obesity, overweight, overtime, shift work, unemployment, strenuous physical work, perceived stress and personality measured in 1973 and self-rated health assessed 1998 – 2002 (Paper IV)

And while doing so, learning and applying quantitative genetic and epidemiological research methods.

4 PARTICIPANTS

4.1 THE SWEDISH TWIN REGISTRY

The Swedish Twin Registry was established in the late 1950s and has developed into a unique resource for research. The registry comprises in principle all twin births in Sweden since 1886 and consists of three cohorts; twins born 1886-1925, 1926-1958, and 1959-1990. To date most twins born 1958 or earlier have been invited one or several times to participate in questionnaires, physical examinations and telephone interviews for studies of health and aging, risk factors for common complex diseases and health behavior (Lichtenstein et al., 2002).

A mailed questionnaire from 1973 answered by the cohort born 1926-1958 and two sub-samples from the Swedish Twin Registry were used in this thesis to identify factors of importance for self-rated health.

4.1.1 Screening Across the Life-span Twin study – SALT
Paper I and IV

Screening Across the Life-span Twin study (SALT) was a computer assisted telephone interview screening for a variety of common complex diseases, symptoms, health behavior, familial relationships, and socioeconomic status. SALT started with a pilot data collection during fall 1996 and spring 1997 when a random sub-sample of 850 pairs of twins from the Swedish Twin Registry was contacted. Approximately equal numbers of pairs were contacted for each birth year and age ranged from age 17 to 85. Between the years 1998-2002 the SALT study was expanded to include all twins in the registry born before 1958 (N=61,767) resulting in a contact with 45,809 individuals (response rate 74%).

Paper I is based on the SALT pilot sample plus the like- and opposite sexed twins 65 years or older who had been contacted before October 1998 and participated in SALT. In total 1262 complete twin pairs were included. Mean age of the sample was 60.5 years and 56% of the sample was female.

The sample included for analyses in Paper IV consists of like-sexed twins born 1926-1950 (N=16,080, whereof 6026 complete pairs of twins) that participated in a mailed questionnaire in 1973 and in SALT. At first contact in 1973 age ranged from 23 to 47 years and mean age of the sample was 33.2 years. Age ranged from 49 to 74 years and mean age of the sample was 59.6 years at second contact. Fifty-four percent of the sample was female. The non-responders i.e. participating in 1973 but not in SALT (N=8316), were similar to the responders in terms of how they responded to the questionnaire in 1973. For these non-responders attrition between measurement occasions was due to death (8.2%), refusals (38.3%), being inaccessible for telephone interviews (19% e.g. emigrated, no telephone number available), and non-response for unknown reasons (34.5%).

4.1.2 The Swedish Adoption/Twin Study of Aging – SATSA
Paper II and III

The Swedish Adoption/Twin Study of Aging (SATSA) sample is a well-defined subset of the Swedish Twin Registry. The subset includes all twins who were reared apart (TRA) – separated before the age of 11 years – and a matched sample of twins reared together (TRT). The sample is studied with regard to normal aging by a series of questionnaires and in-person testing occasions that began in 1984. Questionnaire data include measures of physical and psychological health, personality, cognitive status, life-events, self-rated health etc. Twins were first mailed questionnaires in 1984 and 2,018 individuals responded. A sub-sample of those pairs in which both twins responded and were 50 years and older and alive in 1986 was invited to participate in an in-person test (IPT) entailing examination of health and cognitive abilities (Finkel & Pedersen, 2004; Pedersen et al., 1991). In-person testing took place in a location convenient to the twins, such as district nurses' offices, health-care schools, and long-term care clinics. Testing by trained nurses was completed during a single 4-hour visit. At the first occasion (IPT1), no self-rated health questions were asked. A second wave of in-person testing (IPT2) occurred three years later and a third wave of in-person testing (IPT3) was conducted after an additional three-year interval. The SATSA study is still ongoing (Finkel & Pedersen, 2004).

In paper II data from four waves of questionnaires with 3-year follow-up intervals were included (1984, 1987, 1990 and 1993). Data were divided into four age groups based on age at first contact; younger than 50 years, 50-59 years, 60-69 years, and older than 70 years. Age ranges from 26 to 86 years and mean age of the sample was 58.6 years, and 60% of the sample was female.

In paper III data from IPT2 and IPT3 were used. IPT2 was the first IPT when self-rated health and cognitive information was collected at the same time and hence chosen as baseline. For twins who were added to the IPT sample after IPT2 (as they became 50 years), IPT3 served as baseline. The sample comprised 640 individuals, including 292 complete twin pairs with known zygosity, and 59% was female. Data were divided into two age groups based on mean age of the sample (67 years).

5 MEASURES

5.1 SELF-RATED HEALTH

The self-rated health items developed for the older Americans resource survey at Duke University (OARS, 1978) and included in the SALT and SATSA studies were used:

(1) How would you rate your general health status?, with response alternatives: *Excellent, Good, Moderate, Fairly poor, Poor (in SALT)*
Good, Reasonable, Bad (in SATSA)
(2) How would you rate your health status compared to 5 years ago?, with response alternatives: *Better, Almost the same, Poorer*
(3) Do you think your health status prevents you from doing things you would like to do?, with response alternatives: *Not at all, Partially, To a great extent*
(4) How would you rate your health status compared to others in your age group?, with response alternatives: *Worse, About the same, Better*

In paper I items 1-3 (item number 4 was not available) were standardized separately ($M = 0$, $SD = 1$) and then summed. To achieve a positive scale, 10 points were added to the sum. A high score indicates a more positive health rating. Cronbach's coefficient alpha was 0.67. Thus, including three items in the definition of self-rated health resulted in modest but adequate reliability. In a principal components analysis of the three items, general health status has the highest loading (0.85) while health status compared to five years ago has the lowest loading (0.66) suggesting that these three items might tap different dimensions of self-rated health. Given these psychometric properties, we decided to analyze both the summed health scale and item number (1)"How would you rate your general health status?" separately in paper I. In paper II and III, all four items were used, standardized and summed as described above. In paper IV only the first general health question was included.

5.2 ZYGOSITY DETERMINATION

Zygosity for all twins in the registry born 1958 or earlier, hence contacted in the SALT study, was based on responses to questions regarding childhood similarity ("during childhood, were you and your twin partner as like as 'two peas in a pod'?"). This method has proven to diagnose more than 95% of the twins correctly. Zygosity diagnosis was evaluated in the SALT-pilot study using 13 DNA markers and was correct in 99% of the pairs (N=199 pairs). In SATSA, zygosity is based on serological markers (Lichtenstein et al., 2002).

5.3 COVARIATES – PAPER II

We included a measure of the number of organ systems affected by a *chronic illness* (sum of illness) as an "objective" indicator of health. This scale is based upon 51 health-related items that were reduced to 13 categories; cardiovascular, respiratory, neurological, metabolic, gastrointestinal, musculoskeletal, urologic, female

reproductive, visual, auditory, allergies, skin and cancer. A score for the scale was then computed as the sum of all categories that were reported to be affected by at least one health problem (Harris, Pedersen, McClearn et al., 1992). A high score indicates more health problems.

A measure of *socioeconomic status* in childhood (rearing home) measured at the first questionnaire occasion in 1984 was also included. The socioeconomic status scale (SES) includes three components: material resources within the household, highest education and highest occupational status of the parents. This scale is based on factor analyses. Variables were standardized to a mean of 0 and a standard deviation of 1 before summing. A higher score on the scale reflects higher SES level (Lichtenstein, Harris, Pedersen, & McClearn, 1992).

5.4 COVARIATES – PAPER III

5.4.1 Chronic illnesses and cognitive abilities

We included measures of organ systems affected by a chronic illness as described above (Paper II) (Harris, Pedersen, McClearn et al., 1992). Seven categories described in Table 1 were included in our analysis. Each category served as a single item indicator of whether that category of chronic illness was reported by the respondent as present or not.

The SATSA cognitive test battery includes cognitive measures drawn from various sources and chosen to assess different areas of cognitive abilities (Nesselroade, Pedersen, McClearn, Plomin, & Bergeman, 1988; Pedersen et al., 1992). The cognitive tests were selected to provide representation of the domains of verbal ability, spatial reasoning, perceptual speed, working memory and visual memory.

A Swedish version of the *WAIS Information* subtest (verbal ability) (Jonsson & Molander, 1964) includes 22 items assessing general knowledge (e.g., "What is the population of Sweden?"). Respondents are allowed 20 seconds to answer each question. *Koh's Block Design* is a spatial reasoning test, similar to the WAIS Block Design subtest, in which respondents create designs using colored blocks (Dureman, Kebbon, & Osterberg, 1971). Each of its seven items is scored from 0 to 6 based on the amount of time the respondent takes to correctly complete the design. In *Symbol Digit*, respondents verbally report digits that correspond to symbols. They have 45 seconds to complete each of 10 groups of 10 items. Symbol digit measures perceptual speed. *Digit Span Backward* (working memory), was scored as the sum of the highest number of digits the respondent was able to repeat correctly backwards (Jonsson & Molander, 1964). Respondents were given two trials of different strings of digits; correct performance on either string was counted toward their final score. *Thurstone's Picture Memory* tests visual (recognition) memory of 28 drawings of common items such as a truck and a table (Dureman et al., 1971). Respondents are shown each picture for five seconds; their response is not timed.

Table 1. Chronic disorders and cognitive abilities included in paper III

Chronic disorders	**Item contents**
Cardiovascular	Angina pectoris, heart infarct, heart insufficiency, heart attack, high blood pressure, thrombosis, stroke, circulations problems in limbs, and claudication
Respiratory	Prolonged cough, asthma, emphysema, chronic bronchitis, tuberculosis, and lung problems
Musculoskeletal	Back pain, shoulder pain, neck pain, rheumatoid arthritis, arthritis, sciatic problems, osteoporosis, hip, joint and muscle problems
Allergy	Problems associated with allergic responses, conditions such as hay fever
Central nervous system (CNS) related disorders	Migraine, dizziness, seizures, epilepsy, Parkinson's disease, multiple sclerosis, speech problems and polio
Metabolic disorders	Diabetes, goiter, anemia and gout
Cancer	Includes leukemia or tumors
Cognitive measure	**Ability**
WAIS Information	Verbal ability – assess general knowledge
Koh's Block Design	Spatial reasoning test
Symbol Digit	Perceptual speed
Digit Span Backward	Working memory
Thurstone's Picture Memory	Visual memory (recognition)

The reliabilities for these tests range from .82 to .96 (Pedersen et al., 1992). For every test except Block Design, answers were reported orally to the examiner to minimize the effect of motor speed on performance. The cognitive battery was designed to allow analyses for split-halves of some tests to maximize the sample-size by allowing for inclusion of the participants who failed to complete the second portion of the test. First-halves performance was used for the Information test and Symbol Digit. In IPT 2 and 3 the tests were standardized with the weights (means and SD) from the first measurement occasion in order to maintain the comparability of the tests across measurement occasion.

5.5 EXPOSURES AND COVARIATES – PAPER IV

All exposures and covariates selected for inclusion in Paper IV are listed in Table 2. The Swedish socioeconomic status (SES) classification scheme (SEI) codes based on occupation were used (Statistics-Sweden, 1983). Age (based on birth year), sex, illness, education and SES were entered into the models as covariates. Information about presence of common illnesses and symptoms was collected in the SALT interview and presence of malignant cancers was obtained from the Swedish Cancer Registry. Instead of counting number of illnesses, a measure that reflects seriousness of health problems

was created based on Gold and colleagues' ratings of severity of health problems (Gold, Malmberg, McClearn, Pedersen, & Berg, 2002).

Table 2. Covariates from SALT and exposures from the 1973 questionnaire and included in Paper IV

Name	Code	Source
Age	1 – 5 (age groups based on birth year; 1926-1930, 1931-1935, 1936-1940, 1941-1945, 1946-1950)	SALT
Sex	1, 2 (male, female)	SALT
Illness	0 – 3 (healthy, no life-threatening condition, somewhat life-threatening condition, very life-threatening condition, see table 1)	SALT
Education	0, 1 (0 = <13 years in school, 1 = 13 years or more in school i.e. college and university)	SALT
SES	Socioeconomic status based on occupation 1 – 7	SALT
Zygostity	1, 2 (mz, dz)	SALT
Marital status	1, 2 (unmarried/divorced/widow, married)	1973
Smoking	0 – 2 (no, current, past)	1973
BMI	0 – 3 (normal 18.5-24.9, underweight <18.5, overweight 25-29.9, obesity >30)	1973
Exercise	1 – 4 (no, little, moderate, much)	1973
Perceived Stress	0, 1 (no, yes)	1973
Working overtime	0, 1 (no, yes)	1973
Shift work	0, 1 (no, yes)	1973
Unemployment	0, 1 (no, yes)	1973
Physical activity at work	1 – 4 (sedentary, standing/walking, carrying, strenuous/heavy lifting)	1973
Back pain	0, 1 (no, yes)	1973
Shoulder pain	0, 1 (no, yes)	1973
Neck pain	0, 1 (no, yes)	1973
Recurrent headache	0, 1 (no, yes)	1973
Migraine	0, 1 (no, yes)	1973
Extraversion	0 – 2 (low, moderate, high)	1973
Neuroticism	0 – 2 (low, moderate, high)	1973

6 ANALYTICAL PROCEDURES

6.1 QUANTITATIVE GENETIC METHOD

The aim of quantitative genetic analysis is to examine the nature of individual differences and to determine the extent to which genetic and environmental influences are important for variation in a trait, in this thesis self-rated health.

Intraclass correlations

A measure of similarity between twins is the intraclass correlations. Intraclass correlations are calculated to provide a preliminary view of genetic and environmental effects for the measure of interest. Comparisons between the intraclass correlations for MZ and DZ twins provide information about the presence of genetic and environmental influences. Intraclass correlations were calculated in Paper I to III.

Cross-twin-cross-trait correlations

In Paper III, cross-twin-cross-trait correlations were calculated between twin A's score on self-rated health and twin B's score on the different measures of cognitive abilities. Cross-twin-cross-trait correlations provide a preliminary view about covariation between traits. For example, greater MZ than DZ cross-twin-cross-trait correlations suggest that genetic effects contribute to covariation for the traits studied.

The next step of analysis is biometrical model fitting in which expected patterns of intrapair similarity are fitted to raw data (Paper I and II) or to observed variance-covariance matrices (Paper III). Fitting to raw data allows for inclusion of single responders and therefore increases power in the analyses and provides population based estimates of total variance.

Univariate analyses

If additive genetic influences (A) are important for self-rated health, then MZ twins should be significantly more similar than DZ twins as MZ twins share an identical genetic makeup while DZ twins share on average 50% of their segregating genes. Quantitative genetic theory assumes that alleles at a locus and across loci add up to have an effect on the trait studied. Shared environmental influences (C) refer to non-genetic influences that contribute to similarity within pairs of twins regardless of zygosity, such as shared family environment, uterine environment and contact throughout life. Nonshared environmental influences (E) are those individual specific influences (*e.g.* accidents, illnesses, different experiences or occupations) that make family members different from one another, including measurement error. Thus, the total phenotypic variance (Vp) can be described in terms of the following components of variance:

$$Vp = A + C + E$$

where A denotes the variance associated with genetic influences, C the variance associated with shared environmental influences, and E the variance associated with nonshared environmental influences. Heritability is a commonly used measure and represents the proportion of phenotypic variance due to genetic influences.

Intrapair similarity across the twin types is based on the following expectations:

$$cov\ (MZ) = A + C$$
$$cov\ (DZ) = 1/2A + C$$

The univariate path diagram for one twin pair is illustrated in Figure 2. The relationship between the measured phenotype (depicted in rectangles) in two members of a pair and the latent factors (depicted in circles; A, C, E). The genetic correlation (r_g) between MZ twin pairs is set to 1, while it is set to 0.5 for DZ twin pairs, based on their genetic resemblance. The shared environmental correlation is set to 1 for both zygosity groups, based on the equal environment assumption. By definition there is no within pair correlation for nonshared environment.

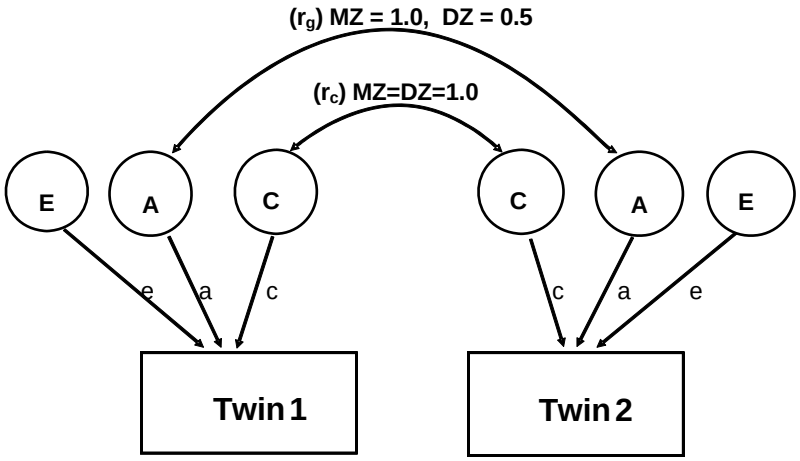

Figure 2. Univariate twin model depicting genetic and environmental effects

Note: A=additive genetic factor, a=additive genetic loading, C=shared environmental factor, c=shared environmental loading, E=non shared environmental factor, e=non shared environmental loading, r_g = genetic correlation, r_c= shared environmental correlation

Nonadditive genetic effects (dominance [D]) may be present. If this is the case DZ twin pairs share only 25% of the genetic variance due to interactions between alleles at a locus (dominance) and little genetic variance due to epistasis i.e. interactions across loci. However, MZ twins share the same genetic makeup by definition. Therefore, if dominance is of importance for self-rated health then the correlations for DZ twins will be less than 50% of the correlation for MZ twins (Plomin, DeFries, McClearn, & McGuffin, 2001). Effects of this kind are relatively uncommon in complex traits but it is possible to model for these effects and was done in paper III. If dominance is present and ignored in the model, most of the variance will be estimated as additive genetic variance and a small portion of the non-additive genetic variance would be captured as nonshared environmental variance. A and D can be estimated at the same time but there

is not enough information in the model to distinguish between dominance and shared environmental effects (C and D), therefore the basic univariate twin model only includes additive genetic factors (Evans, Gillespie, & Martin, 2002).

Because the SATSA sample consists of both TRT and TRA, a second series of analyses were undertaken where rearing status was taken into account in paper II and III. Inclusion of TRT and TRA enables us to estimate the importance of similarities in the rearing environment, as distinct from other shared environmental influences that might occur in adult life. In these analyses, a fourth parameter was included by a unity correlation between these latent factors for TRT and a zero correlation for TRA, representing influences that result in greater similarity of TRT than TRA (Lichtenstein et al., 1992; Plomin et al., 2001).

Structural Equation Modeling

Structural Equation Modeling is commonly employed in twin studies to provide maximum-likelihood estimates of the relative importance of genetic and environmental variance components of total variance (Neale & Cardon, 1992). By using data from all twins and comparing the covariances between zygosity groups, genetic and environmental components of variance are obtained. The significance of parameters is evaluated through nested model comparisons using the Mx program (Neale, Boker, Xie, & Maes, 2002). Akaike's Information Criterion (AIC), reflecting both the goodness of fit of the model and its parsimony, is computed (χ^2 -2df) and the model with the lowest (*i.e.*, largest negative) AIC value is said to fit best or to be the most parsimonious model (Neale et al., 2002).

6.2 PAPER I

6.2.1 Sex and age group differences

Studies of like-sexed twins enable one to evaluate whether there are (a) sex differences in the total variance and (b) whether there are sex differences in the relative importance of genetic and environmental influences. Including opposite-sexed pairs provides the opportunity to test whether *different* genes and *different* environments are operating in the two sexes (Neale & Cardon, 1992). Lower intraclass correlations for the opposite sexed twins than for the like-sexed DZ twins suggest a sex-specific effect, *i.e.* that different genes or environments are operating in men and women. In order to obtain parameter estimates for a, c and e and a parameter, R_g, which indicates whether genetic effects are the same or different in males and females, we used all five twin groups (MZ female, MZ male, DZ female, DZ male, OS) simultaneously and a series of models were tested (Neale & Cardon, 1992). 1) A model allowing different values of a, c, and e for males and females and that allowed the genetic or shared environmental correlation between OS twin pairs to vary. 2) A model that constrains estimates (a, c, e) to be equal across sexes and the genetic correlation (R_g) fixed i.e. same sets of genes for men and women. 3) A model assuming that the same sets of genes and environments are of importance from males and females, but the variance may differ. 4) Constraining the standardized variance components (*e.g.*, heritability estimates) to be equal to a

scalar multiple across sex, but total variance may differ. In a similar manner one can allow the shared environmental correlation (r_c) to vary. It should be noted though that it is not possible in the twin design to estimate both the genetic and environmental correlation at the same time.

Analyses were performed separately for each age group and compared across age groups. In paper I we tested for differences in genetic and environmental effects between the age groups in a manner similar to that for sex differences. First, a model where parameters (a, c and e) are constrained to be equal across all groups was compared to a model in which the parameters are estimated for each group separately. In the next model, variance components for the age groups are all constrained to be equal to a scalar multiple across groups. As a result, the standardized variance components (*e.g.*, heritability estimates) are equal across age groups, but total variance may differ across age groups.

6.3 PAPER II – LONGITUDINAL ANALYSES

6.3.1 Analysis of means and variances

Linear mixed effect models with repeated measures and unstructured covariance structures, different for different age groups, were fitted to the SATSA data from four measurement occasions by running the Proc Mixed procedure in SAS (SAS/STAT, 1999-2001). First, a model was fitted to data to test for differences in means in self-rated health over time, within and between age groups. Second, a model was fitted to the data in the same manner, including sum of illness and childhood SES as covariates. Two-sample Student *t* tests were calculated using the SAS Proc ttest procedure to test for differences in mean childhood SES between age groups. Then, similar models were fitted to test for differences in variances.

6.3.2 Multivariate Cholesky decomposition

To investigate what factors contribute to the variance in self-rated health over a 9-year time span in the four different age groups, a series of models was fitted to the raw data. The series of models began with the fully parameterized Cholesky model in a temporal context illustrated in Figure 3 (Loehlin, 1996; Neale & Maes, 2002). The figure depicts a simplified version of the model including only one twin in a pair. T_1–T_4 represents measurement of self-rated health at four successive time points (1984–1993). Three sources of variation were considered at each time: genetic ($A_{1–4}$), shared environmental ($C_{1–4}$), and nonshared environmental ($E_{1–4}$) variance (including measurement error). A, C, and E give information about anonymous influences that are not actually measured. Thus, A tells us that there are genetic influences but not which gene. Using this multivariate model, we can separate genetic and environmental effects specific to each time point from effects that are in common to the previous time points. Within this framework with four measurements (time points), the first genetic factor (A) loads on all of the measures, a second genetic factor loads on all but the first measure, a third genetic factor loads on all but the first two of the measures, etc. Shared environmental (C) and nonshared environmental (E) factors load on the four measurements in patterns

similar to that of the genetic factors. The relative importance of genetic and environmental effects on each of the measurement occasions is calculated by squaring and summing the parameter estimates for each measure and dividing the squared parameter estimates by the sum of squares. Total variance estimates from the model and the decomposition into genetic and environmental variance at each measurement occasion are presented. Heritability estimates for each time occasion may be obtained by taking the overall genetic variance over total variance. First, we fitted a full model (ACE) for each age group. A series of sub models were then fitted when we dropped a, c, and e parameters that contribute to transmission from the full model (i.e., only time-specific a_{11}, a_{22}, a_{33}, a_{44}, c_{11}, c_{22}, c_{33}, c_{44}, e_{11}, e_{22}, e_{33}, and e_{44} were kept in the model; see Figure 2) to evaluate the hypothesis concerning transmission of stability. The a_{21}, a_{31}, a_{41}, c_{21}, c_{31}, c_{41}, e_{21}, e_{31} etc paths are the contribution of latent etiological factors to the covariance between the different time points.

Nested models were compared by likelihood-ratio chi-square. Degrees of freedom are equal to the number of parameters deleted from the full model. The reduced models where common a, c, and e were dropped from the model were compared with the fit of the full model.

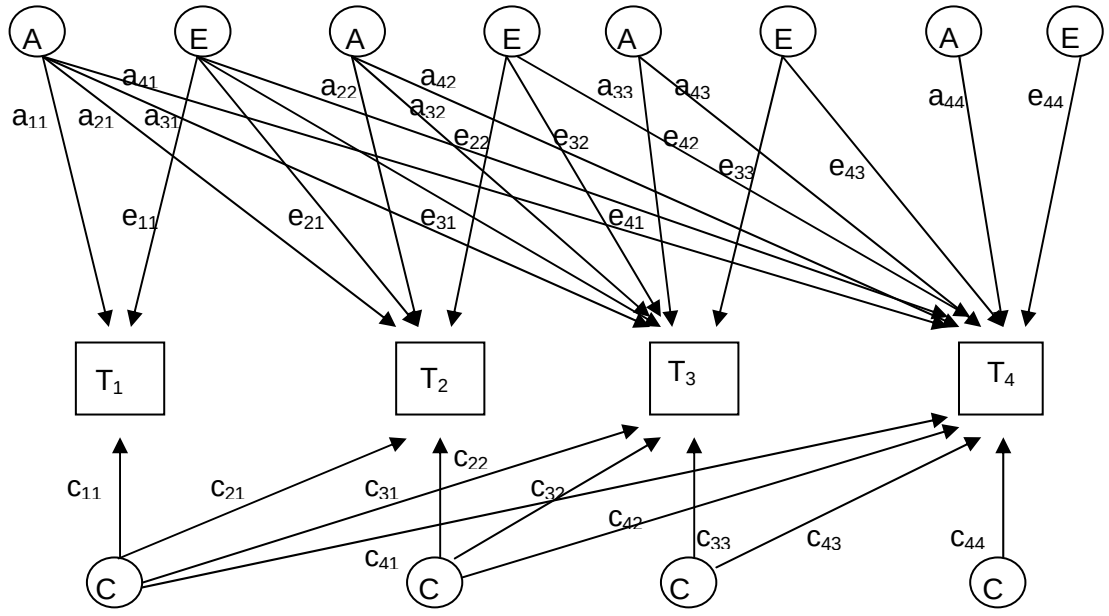

Figure 3. Cholesky path model depicting common and unique factors of genetic (A) and environmental (E = nonshared, C = shared) sources of variance at four consecutive time points (T_1-T_4).

Note: The genetic proportion of the estimated phenotypic correlation for self-rated health time 1 and 2 is: (a11*a21)/ (a11*a21+e11*e21+c11*c21), where a represents the genetic parameters, c represents the shared environmental parameters, e represent the nonshared environmental parameters.

The standardized path coefficients from the Cholesky model can be used to estimate how the correlations between self-rated health at different time points are mediated and thereby describe what factors contribute to stability over time. To evaluate longitudinal

stability, the proportions of the phenotypic correlation attributable to a, c, and e between time points for each age group were calculated (Plomin & DeFries, 1981). The genetic component of the estimated phenotypic correlation (r_P) for self-rated health between times 1 and 2 is $a_{11}*a_{21}$, the shared environmental portion is $c_{11}*c_{21}$, and the nonshared environmental portion is $e_{11}*e_{21}$. Following the same procedure among the other follow-up occasions, the estimated genetic portion of the phenotypic correlation for self-rated health between times 2 and 3 is $(a_{21}*a_{31}) + (a_{22}*a_{32})$, the shared environmental portion is $(c_{21}*c_{31}) + (c_{22}*c_{32})$, and the nonshared environmental portion is $(e_{21}*e_{31}) + (e_{22}*e_{32})$, and so on.

6.4 PAPER III – BIVARIATE ANALYSES OF ASSOCIATION

Pearson correlations were used to test the association between self-rated health and the different cognitive measures in two age groups (<67 and ≥67). Partial correlations were evaluated to test the strength of the association between self-rated health and cognitive abilities after controlling for the seven chronic illness indicators. In addition, to test the statistical significance of chronic illnesses as potential mediators, the Sobel test of regression coefficients was used (Baron & Kenny, 1986; Preacher, 2001).

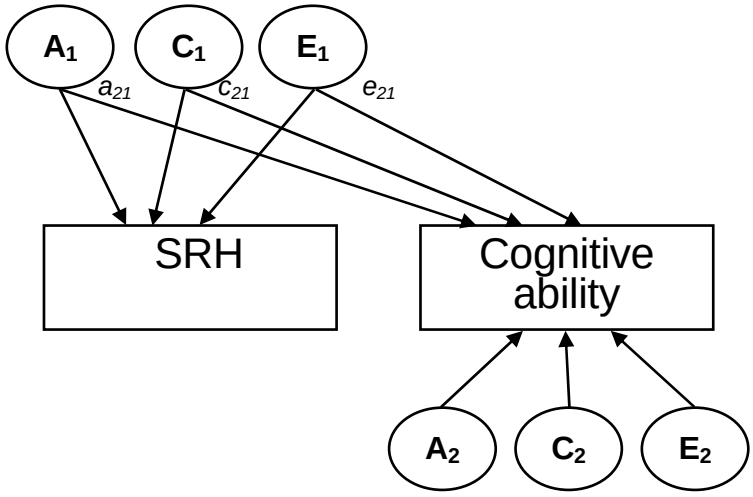

Figure 4. Bivariate Cholesky ACE decomposition

In Paper III we extended the univariate model to explore how environmental and genetic factors contribute to the covariation between self-rated health and cognitive abilities. The bivariate modeling was carried out only for those associations that showed phenotypic correlations (r_p) > 0.10. We expected that the influences on variation in self-rated health may also contribute to some extent to variation in cognitive abilities. This model is not causal; it only explores associations within cross-sectional data. Figure 4 is a simplified version of a bivariate Cholesky (ACE) model, including only one twin in a pair. Each single-headed arrow represents the loadings of a latent factor on an observed variable. The first set of latent factors, (A_1, C_1, E_1) is allowed to load on both observed traits (self-rated health and cognitive ability). The second set of latent factors (A_2, C_2, E_2) is allowed to load on only one observed trait

and thus represent the portion of the variation in cognitive ability that is not associated with score variance in self-rated health. The a_{21}, c_{21}, and e_{21} paths are the contribution of latent etiological factors to the covariance of the two observed factors.

We began with fitting a full ACE or ADE model, different for different age groups based on univariate model fitting results, and thereafter we performed tests of sub-models to test significance of genetic and shared environmental influences. Rearing status was not taken into account as little or no rearing effect was found in univariate analyses of the different cognitive measures and self-rated health (Pedersen et al., 1992). We tested whether a model with genetic and nonshared environmental influences only (AE) gave a significantly worse fit than the full model (ACE or ADE). We then tested whether a model without A (CE or DE) gave a significantly worse fit than the full model (ACE or ADE) and finally, we tested whether individual differences are based solely on nonshared environmental factors (E). The standardized path coefficients from the Cholesky model can be used to estimate how the correlations between self-rated health and the cognitive abilities are mediated, calculated as described for the multivariate model between time one and two. Thereby, we can describe what factors contribute to the phenotypic correlation.

All models (Paper I – III) were fitted to the standardized observations of self-rated health by full information maximum likelihood estimation implemented in the program Mx (Neale et al., 2002). The models assume that there is random mating operating in the parental generation, no interaction between genes and environment, and equivalent influence of shared environments for MZ and DZ twins, the equal environment assumption (Martin, Boomsma, & Machin, 1997). A more detailed discussion of these assumptions is found in the discussion section.

6.5 PAPER IV

6.5.1 Logistic regression

To find a model that explains data best we evaluated different logistic regression models including first all covariates (age, sex, illness, education and SES) then also including all exposures listed in Table 2 (page 16). We compared these models with reduced models including fewer than all of the exposures. For model selection we calculated the Akaike's Information Criteria (AIC) (Akaike, 1987) for which a lower AIC value indicate a better fit. For this purpose, we used the sample with all data available for unrelated individuals (N=10,053). In an initial analysis we modeled the entire self-rated health distribution on an ordinal scale using a cumulative logit model (McCullagh & Nelder, 1989). For goodness of fit the model with the lowest AIC value was compared with a generalized logit model (Pawitan, 2001). A likelihood ratio test rejected the cumulative logit model. As a consequence, we modeled self-rated health using logistic regression on a binary scale where excellent and good self-rated health were grouped together, and poor, fairly poor and moderate self-rated health were grouped together. Repeating the AIC model selection resulted in a model including the same variables as selected for the cumulative logit model. The simpler model showed no lack of fit. When the evaluation of models was completed, we used the entire sample

of both twin pairs and single responders (total N=16,080) for further analyses with self-rated health as a binary scale. 3,139 respondents had missing data on one or more of the variables. Because the sample was comprised of twins, we used generalized estimation equations (GEE) to adjust for the non-independence of members of a twin pair. The correlation within twin pairs was accounted for by means of alternating logistic regression allowing for different odds ratio (OR) association for MZ and DZ twins. This statistical technique model the association between twins by OR's instead of correlations. The generalized estimation equations model is equivalent to a case-control analysis.

6.5.2 Conditional logistic regression – Co-twin control

Co-twin control analyses were performed using conditional logistic regression with complete twin pairs of known zygosity. The purpose of any matched design is to control for confounding. The co-twin control design automatically controls for age, sex (using like-sexed twin pairs) and familial environmental influences. In addition, MZ co-twin analyses control for genetic influences on self-rated health and the risk factor of study. The results from this analysis show the odds that the exposed twin is at an elevated risk of having poor self-rated health compared with the co-twin being unexposed to the risk factors under study. It there is a reduction in risk compared to the results from the GEE model, genetic and familial factors are indicated to contribute to the associations found, i.e. there are indications of familial confounding.

For all methods in Paper IV 95% confidence intervals (CI) were computed.

7 MAIN RESULTS

7.1 AGE AND SEX DIFFERENCES – PAPER I AND II

Cross-sectional findings

Variance increased across age group for both self-rated health and the general health item. Compared to the younger participants, the older twins tended to rate their health less positively (F = 34.03, 3 df, p = .0001 for self-rated health and F = 68.75, 3 df, p = .0001 for the general health item). No significant sex differences were found in means or variances.

In these cross-sectional analyses of SALT data (Paper I) the pattern of intraclass correlations for self-rated health and the general health item are similar. The correlations of opposite sexed twins do not suggest that there are sex differences in the youngest groups, but possibly in the older groups. Lower intraclass correlations for the opposite sexed twins than for the DZ twins suggests a sex-specific effect.

For all age groups, models constraining estimates (a^2, c^2, e^2) to be equal across sexes and the genetic correlation (R_g) fixed to 0.5 do not fit worse than those models allowing parameter estimates to differ in men and women.

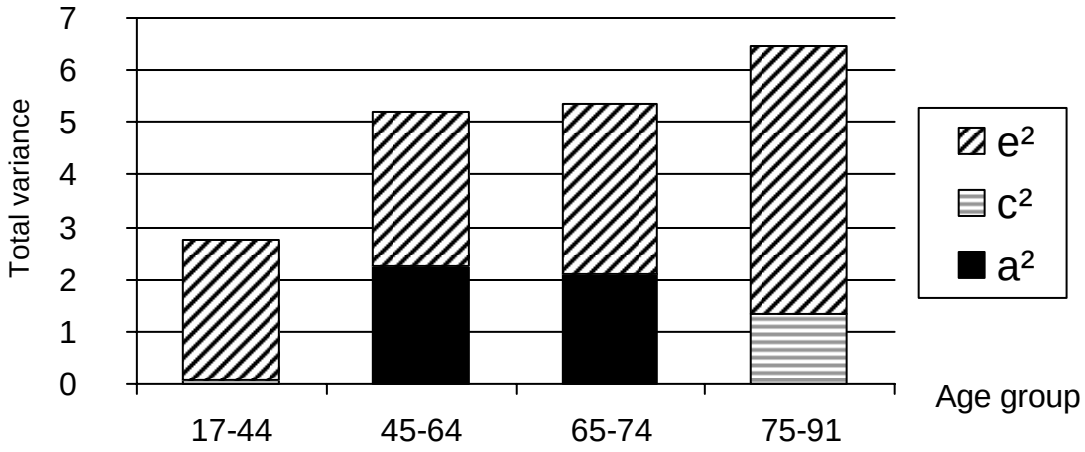

Figure 5. Proportions of variance explained by genetic and environmental variance by age group for self-rated health, based on 1243 pairs of Swedish twins

Note: For all age groups in the most parsimonious models, estimates for men and women are equal. a^2 = additive genetic variance, c^2 = shared environmental variance, e^2 = nonshared environmental variance

These results indicate a lack of sex differences in genetic and shared environmental influences on self-rated health. Nonshared environmental influences are of greatest importance for all age groups. Genetic variation is significant for middle-aged twins (45-64 years = 44%) and the group aged 65-74 (40%). Shared environmental effects,

but not genetic variance, account for 21% of the variation in the oldest age group (see Figure 5). Results for the general health item correspond to that of the composite scale i.e. no evidence of sex differences in the etiology of the general health item; parameter estimates are similar to that for self-rated health and nonshared environmental influences were the most important source of individual differences in all groups. Genetic variance was significant in the two middle age groups, and shared environmental variance was significant in the oldest group.

In the second series of analyses we tested for differences based on age group membership for self-rated health. The chi-square difference test of the model that constrained parameters (a^2, c^2, e^2) to be equal across all age groups compared to the model in which parameters are estimated freely for each group showed a significant effect of age group (χ^2 difference = 105.51, 9 df, p = .001). Even when a scalar effect was added, the variance components were significantly different across the age groups indicating that the relative importance of genetic and environmental effects differs by age group (χ^2 difference = 27.67, 3 df, p = .001).

Longitudinal findings

The aims in Paper II were to investigate further how mean levels change with time and whether the increases in total variance and variance components with age seen in Paper I are replicated in a longitudinal study. Four age groups were constructed based on birth year. Younger adults were more positive about their health status than older adults at baseline. A linear mixed effect model was fitted to the SATSA data controlling for sex, rearing, and zygosity. Figure 6 illustrates mean values and 95% confidence intervals for self-rated health at the four measurement occasions within the four age groups regardless of participation pattern. There were statistically significant mean effects for age group and time, and a significant age group by time interaction ($p < .05$). Within each age group, change between successive pair-wise time points (1984 and 1987, 1987 and 1990, and 1990 and 1993) was not significant ($p > .05$), although statistically significant changes between time points more distant apart were found for the youngest and the two oldest age groups. For the age group younger than 50 years, mean self-rated health was significantly lower in 1993 than in 1984 and 1987 ($p < .05$). For the age group 60–69 years, the mean value in 1993 was significantly lower than the three earlier years ($p < .003$). For the oldest age group (70 years and older), the mean value in 1993 was statistically lower than in the years 1987 and 1984, and the mean value in 1990 was statistically lower than in the year 1984 ($p < .05$).

Before testing the model with childhood SES and sum of illness variables as covariates, we tested for mean differences in childhood SES across age groups. The pattern of means was linear for SES and illness and confirmed greater advantage for later-born cohorts compared to earlier born cohorts.

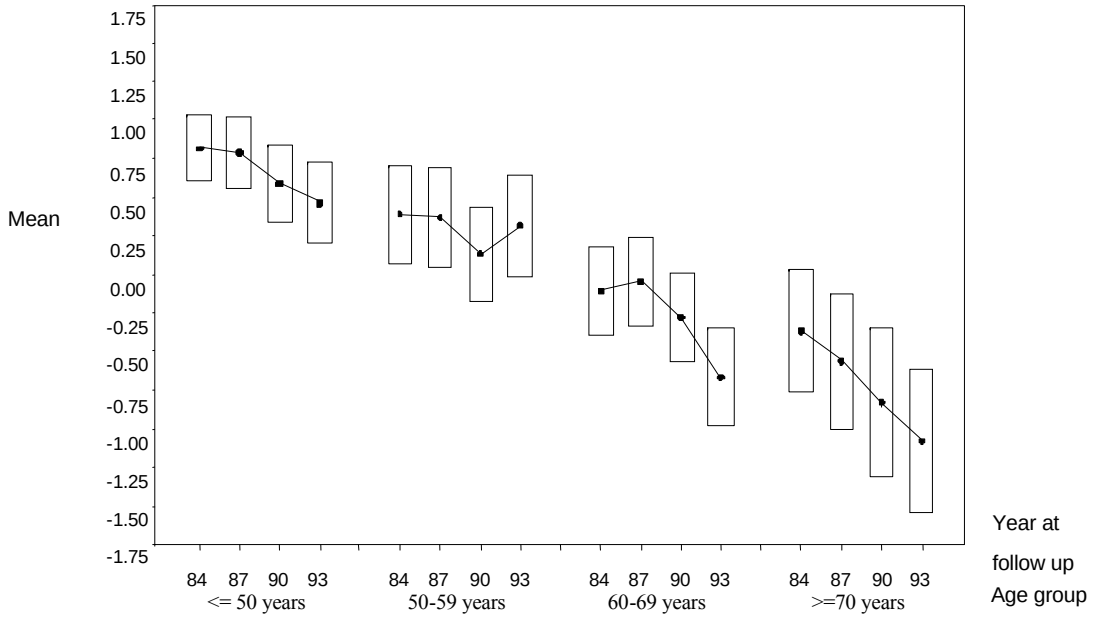

Figure 6. Estimated mean values of self-rated health and associated two-sided 95% confidence intervals by age group and four time points (1984 to 1993).

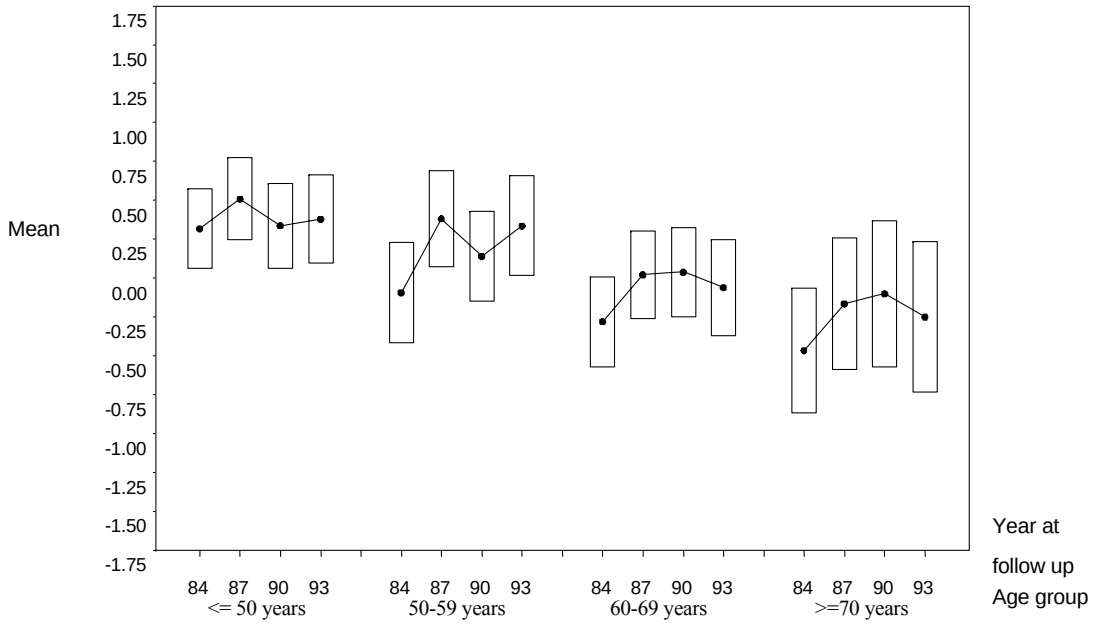

Figure 7. Estimated mean values of self-rated health and associated two-sided 95% confidence intervals by age and four time points controlling for sum of illness and SES.

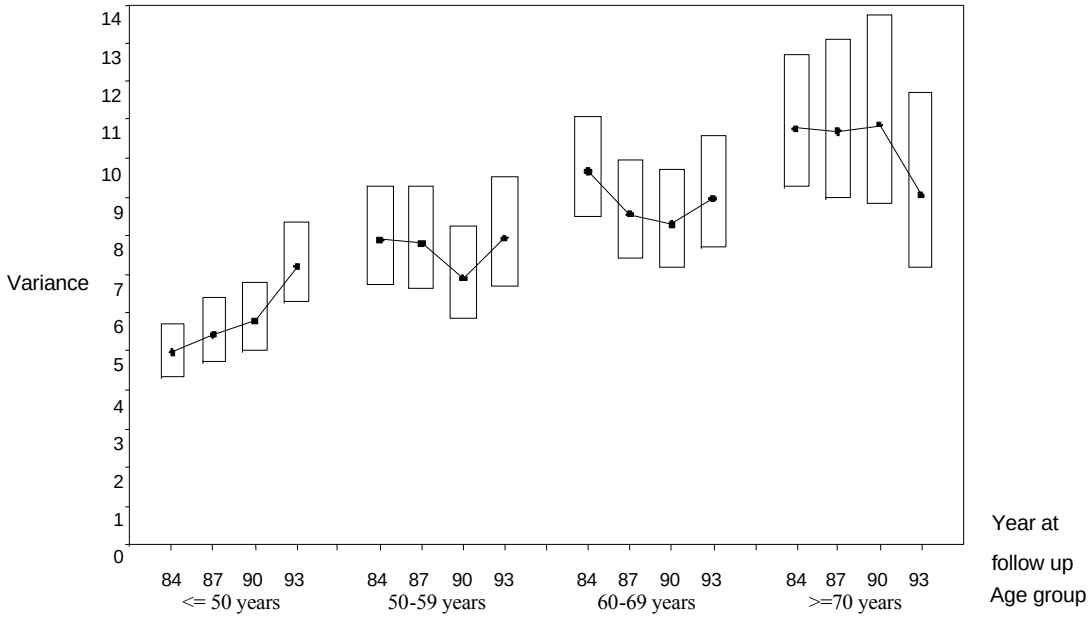

Figure 8. Estimated variances of self-rated health and associated two-sided 95% confidence intervals by age group and four time points (1984 to 1993).

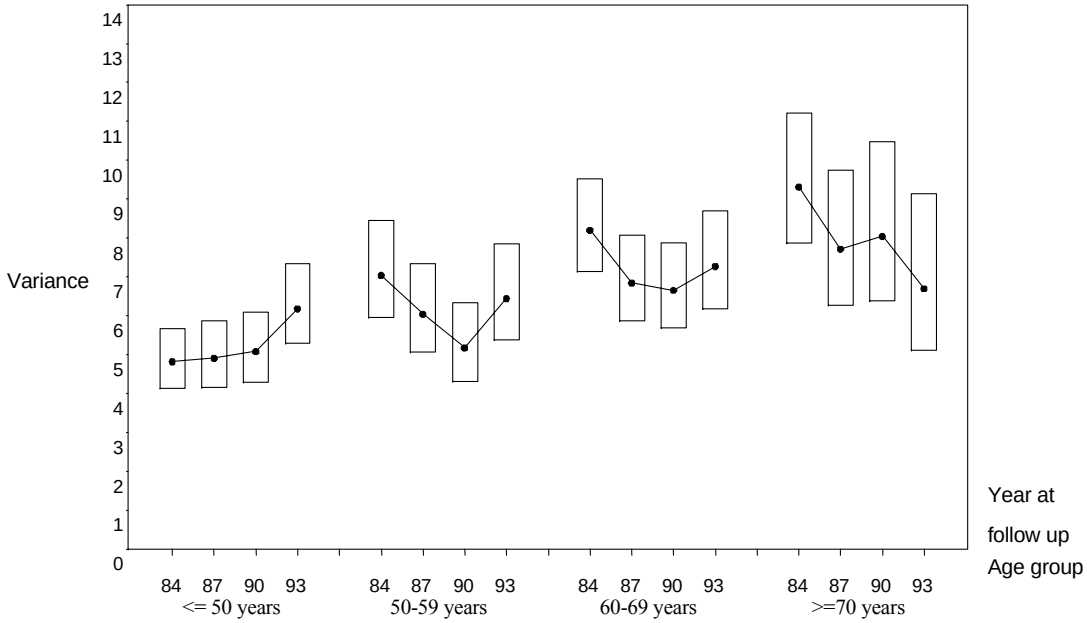

Figure 9. Estimated variances of self-rated health and associated two-sided 95% confidence intervals by age and four time points controlling for sum of illness and SES.

When we included childhood SES and sum of illness variables as linear covariates in the model, the main effects of age group, time, and sum of illness were significant. The age group by time interaction was no longer significant. Results are illustrated in Figure 7. There were no changes in mean values of self-rated health within age groups

between 1987, 1990, and 1993. The time effect was due to each age group having significantly lower self-rated health at baseline in 1984 compared with all of the following measurement occasions (1987, 1990, and 1993; $p < .01$, .01, and .02 respectively). These results indicate that sum of illness accounted for a significant amount of change over time in self-rated health but did not explain cohort differences. Age group differences remained. The oldest age group showed statistically significant lower mean self-rated health than age groups 50–59 years and younger than 50 years, and the age group 60–69 years showed significantly lower mean self-rated health than age group younger than 50 years.

Figure 8 illustrates variances for self-rated health using the same approach as for the mean values. In our first model, the data did not show any substantial change in total variance within age group across the 9-year interval apart from the youngest age group, although significant between-group differences were found. To evaluate this further, we compared a model with no restrictions on the variances and covariances with a model with equal variances at all four time points and equal correlations between data measured with an equal distance apart (a model with different age group-specific Toeplitz covariance structures). A likelihood-ratio test was calculated, and the data supported the simpler model with the same variance at all four time-points but increasing variance across age groups (log likelihood difference = 20.36, $p = .3127$). Including sum of illness and SES as covariates did not affect the main result, although, differences between age groups were smaller (log likelihood difference = 27.08, $p = 0.0774$) (see Figure 9).

Longitudinal genetic analyses

There were no significant differences in intrapair similarity between the two rearing groups, and shared rearing environmental effects did not explain significant proportions of the variance. Thus, in the multivariate cholesky decomposition, we focus on the results where rearing is not specifically taken into account.

Figure 10 illustrates the total raw variances and the genetic and environmental variances based on the most parsimonious model evaluated from the four occasions 1984–1993 for each of the four age groups as well as average total variance over time for each age group. The most parsimonious model based on Akaike information criteria (AIC) for all of the age groups suggests that shared environmental factors (C) in common with the four measurement occasions could be dropped from the model; that is, only shared environmental factors unique to each time point were kept in the model. Nonshared environmental variance was the greatest source of variance for all age groups at most of the measurement occasions, except for the last measurement occasion for the oldest age group. Most of the remaining variance was explained by genetic factors.

Stability coefficients (i.e., phenotypic correlations [r_P]) from the most parsimonious model and their decomposition into genetic and nonshared environmental components,

respectively, were calculated. The youngest age group has the lowest correlation coefficients (r_P) around .45. Nonshared environmental factors are the primary source of stability over a 9-year time span for the youngest age group (under 50 years), whereas in the older age groups, both nonshared environmental and genetic factors account for almost equal portions of the total correlation.

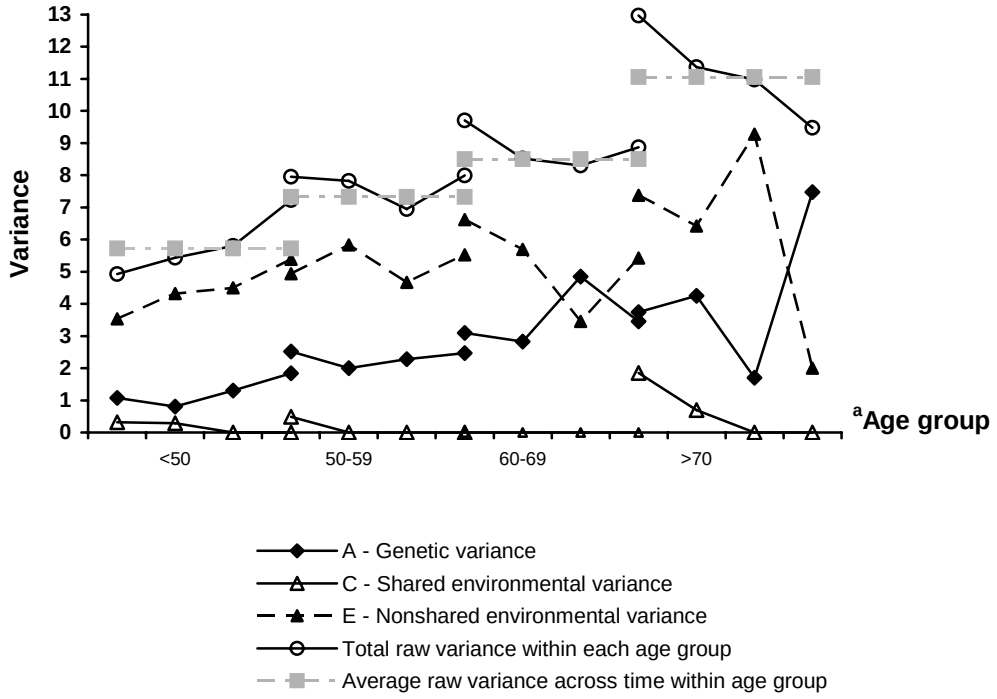

Figure 10. Total raw variances divided into genetic and environmental variance of self-rated health at 4 occasions (1984 to 1993), within 4 age groups. The best model is presented were we dropped shared environmental effects (C). Time specific A, C and E is still in the model as well as common A and common E.

Note: A = Genetic variance, C = shared environmental variance, E = nonshared environmental variance.

[a]Twins less than 50 years of age were all born after 1934, age group 50-59 years was born between 1925 and 1934, age group 60 to 69 years was born between 1915 and 1924 and age group ≥70 years old was born before 1915.

7.2 COGNITIVE ABILITIES AND HEALTH – PAPER III

Phenotypic correlations between self-rated health and the different cognitive measures range from -0.03 to 0.26 with the lowest correlation for the total sample between Digits backward (i.e. short-term/working memory) and self-rated health and the highest correlation between Block design (i.e. reasoning/spatial ability) and self-rated health. The correlations were stronger in the younger age group (<67 year) than in the older age group (≥67 years) for spatial reasoning (0.26 vs. 0.13) and perceptual speed (0.18 vs. 0.15), although the difference was not statistically significant. For memory though,

we found a significant correlation between self-rated health and visual memory only in the older age group (0.20).

Inspection of Pearson correlations between specific disease categories and self-rated health and the specific cognitive abilities revealed very few associations in common to health and cognition. Central nervous system related (CNS) disorders and musculoskeletal disorders were associated with both self-rated health and Block design and Symbol digit in the younger age group and with self-rated health and Information in the older age group. Further testing of mediation using the Sobel test (Baron & Kenny, 1986) indicated only one significant mediation, that between self-rated health, Central nervous system related disorder, and the Information test (Sobel test statistics = 2.03, $p = 0.04$) in the older age group. No other test of mediation achieved statistical significance for either age group.

Intraclass correlations and cross-twin-cross-trait correlations for self-rated health and all cognitive measures showed greater MZ than DZ correlations for all measures in both age groups and suggest that genetic effects contribute to variability. Greater MZ than DZ cross-twin-cross-trait correlations suggest that genetic effects contribute to covariation for verbal ability, spatial reasoning and visual memory in both age groups.

All scales were first analyzed separately to determine which influences were important sources of variation for each scale. Our estimates match those previously reported in SATSA (Harris, Pedersen, Stacey et al., 1992; Pedersen et al., 1992). Both genetic and nonshared environmental factors are important to self-rated health and all cognitive scales. Genetic effects are more important than environmental effects for Information, Koh's Block Design and Symbol Digit. For Self-rated health, Thurstone's picture memory and Digits backwards, the environmental variance is higher than the genetic.

Bivariate model-fitting procedures showed that ADE models fit best, i.e., provide the most parsimonious explanations to data, for the younger age group (<67 years) while ACE models with an AE sub-model fit best for the older age group (67 years or older). Based on the phenotypic correlations we did not perform bivariate analyses for the measures without an association, only for correlations > 0.10. Univariate models are the most parsimonious explanation of the data for these tests (i.e. in the youngest age group; verbal ability, working memory and visual memory and in the oldest age group; working memory as there is no statistically significant association.

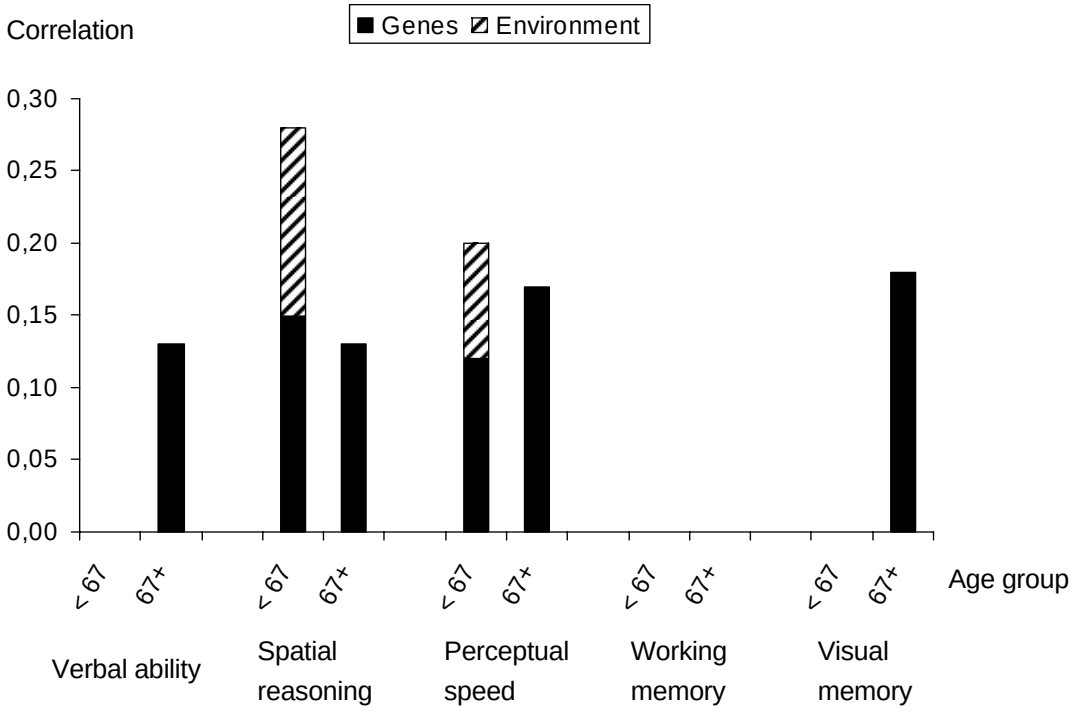

Figure 11. Genetic and environmental mediation of the association between self-rated health and cognitive abilities by age group.

In Figure 11 the genetic and environmental contribution to the phenotypic correlations in both age groups are illustrated. In the age group less than 67 years old, 54% of the correlation (r_p=0.27) between self-rated health and Block design is due to genetic factors in common to both traits while 46% is attributable to non-shared environmental factors. Sixty percent of the correlation (r_p=0.20) between self-rated health and Symbol digit is attributable to genetic factors in common to both traits and hence, 40% is due to non-shared environmental factors. In the oldest age group ($\geq$ 67 years) 100% of the correlations are due to genetic factors in common to self-rated health and Information test (r_p=0.13), self-rated health and Block design (r_p=0.13), self-rated health and Symbol digit (r_p=0.17) and finally self-rated health and Thurstone's picture memory (r_p=0.18). The environmental components found for the younger age group are no longer present.

7.3 HEALTH, LIFE-STYLE AND PSYCHOSOCIAL FACTORS – PAPER IV

In the SALT sample used in Paper IV approximately 2% of the respondents report poor health whereas over 30% rated their health as excellent (see figure 12). Women, earlier born cohorts, presence of severe illnesses, low education and manual work or self-employment indicated poorer self-rated health.

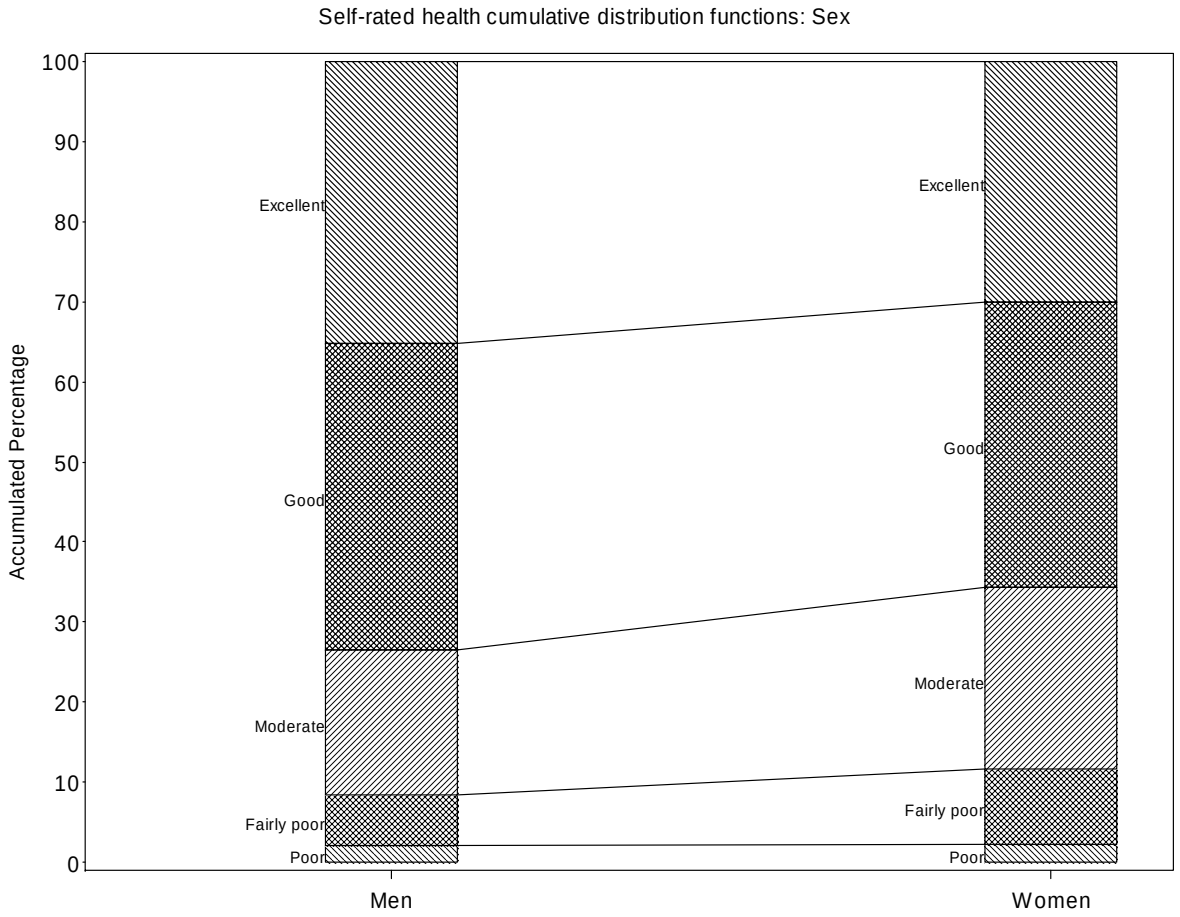

Figure 12. Cumulative distribution of self-rated health by sex.

Of the investigated exposures, shoulder pain, migraine, strenuous physical activity at work, shift work and working overtime were excluded for final analyses as they did not contribute significantly to the initial analyses. The remaining eleven exposures (headache, neck pain, back pain, exercise, smoking, BMI, marital status, perceived stress, unemployment, neuroticism and extraversion) and the five covariates (age, sex, education, SES and illness) were analyzed simultaneously in our most parsimonious logistic regression model and associations between the risk factors and self-rated health are presented in Table 4. The OR's for the different exposures were generally somewhat higher when analyzed separately with the covariates, than the OR's when full adjustment was made for the other exposures as well (see Table 4). A more than two-fold increased risk for poor self-rated health was found for obesity, whereas the magnitudes of the remaining adjusted OR's were fairly similar varying from 1.20 to 1.60, all statistically significant.

Table 4. Odds ratios (OR) and 95% confidence intervals (CI) for the exposures and future poor self-rated health. *Note*: [a] Age, sex, education, illness, SES were entered as covariates (confounders) in the model. [b]Reference. [c]Adjusted OR for all exposures listed in the first column, and for age, sex, education, illness, SES.

		GEE Analysis	
Model	**Comparison**	**[a]OR (CI) (N=13 652 to 14 355)**	**[c]Adjusted OR (CI) (N=12 941)**
Headache	Yes	1.94 (1.75 - 2.15)	1.30 (1.15 - 1.48)
	[b]No		
Neck pain	Yes	2.54 (2.18 - 2.97)	1.62 (1.35 - 1.95)
	[b]No		
Back pain	Yes	2.05 (1.87 - 2.25)	1.46 (1.31 - 1.63)
	[b]No		
Exercise	No exercise	1.17 (1.04 - 1.32)	1.09 (0.95 - 1.25)
	[b]Little exercise		
	No exercise	1.49 (1.33 - 1.67)	1.21 (1.06 - 1.39)
	[b]Moderate		
	No exercise	2.46 (2.07 - 2.93)	1.62 (1.32 - 2.00)
	[b]Much exercise		
Smoking	Current smoker	1.26 (1.16 - 1.36)	1.19 (1.09 - 1.31)
	[b]Non smoker		
	Current smoker	1.34 (1.21 - 1.50)	1.32 (1.17 - 1.51)
	[b]Past smoker		
BMI	Overweight	1.64 (1.49 - 1.81)	1.48 (1.32 - 1.66)
	Obese	3.25 (2.44 - 4.33)	2.18 (1.56 - 3.06)
	[b]Normal		
Marital status	Unmarried	1.01 (0.93 - 1.10)	1.13 (1.02 - 1.25)
	[b]Married		
Perceived Stress	Yes	1.38 (1.26 - 1.51)	1.17 (1.05 - 1.31)
	[b]No		
Unemployment	Yes	1.39 (1.22 - 1.58)	1.24 (1.07 - 1.44)
	[b]No		
Personality	High Neuroticism	2.03 (1.86 - 2.22)	1.48 (1.32 - 1.65)
	[b]Low Neuroticism		
	High Neuroticism	1.63 (1.49 - 1.78)	1.32 (1.19 - 1.47)
	[b]Moderate Neuroticism		
	Low extraversion	1.41 (1.29 - 1.53)	1.17 (1.05 - 1.29)
	[b]High extraversion		

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) for the exposures and future poor self-rated health. Conditional logistic regression model results for monozygotic (MZ) and dizygotic (DZ) twin pairs. *Note*: [b]Reference. [d]Adjusted for education, illness and SES.

		Co-twin Control Analysis	
Model	**Comparison**	**[d]MZ + DZ OR (CI) (N pairs = 4048)**	**[d]MZ OR (CI) (N pairs = 1740)**
Headache	Yes	1.59 (1.22 - 2.06)	1.15 (0.74 - 1.79)
	[b]No		
Neck pain	Yes	1.63 (1.08 - 2.46)	1.80 (0.86 - 3.76)
	[b]No		
Back pain	Yes	1.38 (1.09 - 1.74)	1.48 (0.97 - 2.25)
	[b]No		
Exercise	No exercise	0.95 (0.70 - 1.29)	0.89 (0.53 - 1.47)
	[b]Little exercise		
	No exercise	0.95 (0.70 - 1.28)	0.75 (0.44 - 1.27)
	[b]Moderate		
	No exercise	1.33 (0.84 - 2.10)	0.45 (0.20 - 1.01)
	[b]Much exercise		
Smoking	Current smoker	1.43 (1.13 - 1.81)	1.42 (0.90 - 2.26)
	[b]Non smoker		
	Current smoker	1.45 (1.12 - 1.90)	1.84 (1.14 - 2.97)
	[b]Past smoker		
BMI	Overweight	1.32 (0.99 - 1.74)	2.53 (1.36 - 4.71)
	Obese	3.28 (1.41 - 7.67)	1.42 (0.20 - 10.30)
	[b]Normal		
Marital status	Unmarried	1.39 (1.12 - 1.74)	1.30 (0.87 - 1.94)
	[b]Married		
Perceived Stress	Yes	1.14 (0.90 - 1.44)	1.13 (0.76 - 1.68)
	[b]No		
Unemployment	Yes	1.20 (0.90 - 1.61)	0.76 (0.45 - 1.28)
	[b]No		
Personality	High Neuroticism	1.49 (1.18 - 1.89)	1.39 (0.92 - 2.12)
	[b]Low Neuroticism		
	High Neuroticism	1.33 (1.07 - 1.65)	1.36 (0.95 - 1.96)
	[b]Moderate Neuroticism		
	Low extraversion	1.04 (0.83 - 1.30)	1.06 (0.71 - 1.58)
	[b]High extraversion		

Most of the associations for poor self-rated health remained in the intra-pair comparison among MZ and DZ twin pairs in which unmeasured genetic and shared environmental effects were accounted for (see Table 5). The odds ratios were almost of the same magnitude for the total sample (see GEE Table 4, column 3 and 4), MZ plus DZ (see Table 5, column 3) and MZ (Table 5, column 4) co-twin analysis separately for most of the risk factors studied. These comparisons indicate that genetic effects do not

contribute to the associations. However, genetic influences seem to be of importance for the relationships between headache, exercise, obesity and poor self-rated health, as evidenced by the changes (reduction) in OR from the MZ+DZ matched analysis to the matched MZ co-twin control analyses. For these items, the odds ratio for poor self-rated health is lower and no longer statistically significant in the matched MZ co-twin analysis. The OR for obesity vs. normal BMI for the total MZ plus DZ sample showed a more than three folded increase (OR=3.28, CI 1.41-7.67) but was considerably lower (OR=1.42, CI 0.20-10.30) in the MZ co-twin control analysis. The same pattern is shown for lack of leisure time exercise vs. much exercise and for recurrent headache vs. no headache.

8 DISCUSSION

8.1 INTERPRETATIONS AND IMPLICATIONS OF THE FINDINGS

Cross-sectional and longitudinal findings

Given the associations between functional abilities and self-rated health (Bjorner & Søndergaard Kristensen, 1999; Bjorner et al., 1996), and sex-differences in functional problems and performance measures (Merrill, Seeman, Kasl, & Berkman, 1997) one would expect sex-differences in self-rated health. Furthermore, previous analyses of the associations between self-rated health and psychosocial factors suggest that there is less genetic variance for self-rated health in men than in women (Lichtenstein & Pedersen, 1995). Unlike these previous reports and reports of sex differences in means (Bjorner et al., 1996; Undén & Elofsson, 1998), we found no significant sex differences in either means or variance components. As there is no significant genetic variation in the youngest and oldest age groups, it is meaningless to test for the significance of a significant difference in genetic effects for men and women. The cross-sectional findings in Paper I showed that the differences in amount of variance for self-rated health across age groups are attributable to increases in genetic variance and to nonshared environmental effects. Harris et al. (Harris, Pedersen, McClearn et al., 1992) reported a very similar pattern of results in the SATSA sample, even though her sample was poorly represented in younger age groups. There is a remarkable similarity in the components of variation in the oldest group in that and the present study. Strengths in our Paper I were the inclusion of opposite-sexed twins as well as all adult ages. These findings, based on cross-sectional data, suggest that it might be more fruitful to explore the origins of individual differences for self-rated health in the context of an individual's age and birth cohort rather than in the context of sex.

In our longitudinal study (Paper II) we found that previous cross-sectional results of a decrease in mean level and an increase in total variance with age are not fully replicated. We found mean levels to remain relatively stable over a period of 9-years within each age group after inclusion of morbidity data (sum of illness) in our model. The result of a relatively high stability in self-rated health might indicate that people adapt to their worsening of health as they age. However, we also found that younger age groups report a better self-rated health status than the older age groups. Age differences in mean level have been reported earlier, and in general, older people are more likely to rate their health as poor (e.g., (Murray et al., 1982; Roberts, 1999).

We evaluated the extent to which childhood SES and an index of illness account for cohort and longitudinal findings. Consistent with the role of health in accounting for self-rated health (Ferraro & Kelley-Moore, 2001; Undén & Elofsson, 1998), the effect of change over time was largely eliminated when disease status was taken into account. Similarly, Liang and colleagues (Liang et al., 2005) report only slight worsening of self-rated health longitudinally when using a composite self-rated health scale similar to ours between ages 60 and 85, after accounting for illnesses and other covariates. However, cohort differences remained in Paper II, suggesting that other factors play an

important role for self-rated health across different age groups. Different birth cohorts might be affected by societal changes in different ways (Fritzell & Lundberg, 2000). There has been a strong economic development in Sweden since 1940. Twins born 1914 or earlier grew up when Sweden was fairly poor and during a time of multiple epidemics such as influenza. Industrialization increased the standard of living, and the age groups born after World War I might have gained more from that development than the pre-war cohorts. In support of this hypothesis, our comparison of SES during childhood for the different age groups demonstrates that younger age groups had a higher childhood SES level. However, inclusion of childhood SES in our mixed effect model did not explain the cohort differences in self-rated health to any great extent. Societal changes not tapped by our SES measure are more likely to explain these differences.

Our results also show that the increase in total variance is greater between age groups than longitudinal contrasts within age groups. This finding is consistent with the literature that compares cross-sectional with longitudinal findings within the same study for other gerontological variables (Birren & Birren, 1990; Nelson & Dannefer, 1992; Schaie & Baltes, 1996). The age at the last measurement occasion of each age group is the same as the age of first occasion of the next age group. The total variance estimates at the last occasion for the youngest age group matches the estimates of the first occasion for the second age group. However, there are clearer differences in the start and ending points for the last two age groups (60–69 years and 70 years and older), suggesting clearer cohort differences and little longitudinal change in variance for these age groups. Neither childhood SES nor an index of morbidity explained these findings. The longitudinal study by Liang et al. (2005) found four sub trajectories underlying the observed age norm, namely; constant good health, early onset of decline in self-rated health, late onset of decline in health status and, finally, course of recovery from poor self-rated health. It seems possible that these underlying trajectories have an impact on the variability in an aging sample.

Behavioral genetic research has revealed the importance of both genetic and environmental influences on self-rated health (Christensen et al., 1999; Harris, Pedersen, McClearn et al., 1992; Harris, Pedersen, Stacey et al., 1992; Leinonen et al., 2005; Lichtenstein & Pedersen, 1995; Romeis et al., 2000) and Paper I and II replicate well what had been found in previous cross-sectional studies. With inclusion of a wider range of adult ages, opposite sexed twins and longitudinal follow-ups, Paper I and II also give additional insight into age and sex differences in variance components. Other non-twin studies suggest that self-assessment of health reflects a personal estimate of longevity, based not only on the respondent's own health, but also on knowledge of familial risk factors (Idler & Benyamini, 1997; Idler & Kasl, 1991).

What does genetic variance reflect?

Increasing genetic variability especially in the age group 45-74 might result from the fact that the twins are coming into the age when many chronic diseases that are

influenced by genetic effects have their debut, for example, coronary heart disease, hypertension, or diabetes, which have not yet been expressed in younger age groups (<45 years). Some people become affected and others remain disease-free, leading to increased individual differences. Many studies have shown that self-reports of health status correlate with more objective health measures (Liang, 1986; Schulz et al., 1994) and subjects also frequently mention absence or presence of illness as a component of their self-ratings (Idler et al., 1999). Analysis of age differences for a chronic illness scale (Pedersen et al., 1999) showed a cross-sectional increase in genetic effects until the age of 70 similar to that found for self-rated health (Harris, Pedersen, McClearn et al., 1992).

It is unclear whether the present patterns, with a lack of or reduction in genetic variance in the oldest age group in Paper I, represent longitudinal changes or age group effects due to loss of genetic variance for specific diseases. Genetic variance for an "objective" measure of chronic illnesses decreased longitudinally for men but was stable for women over a 30-year time span (from 50+ to 80+ years of age) (Pedersen et al., 1999). Thus, the results in Paper I may not simply reflect loss of genetic variance due to selective survival i.e. leaving only the healthy individuals in the sample. The lack of genetic influences on self-rated health in the oldest group may also reflect individual specific coping styles. Older individuals may learn to live with their illnesses over the years and by the age of 80 they may not continue to include chronic diseases in their own health evaluation. Other factors may become more important with age such as activities of daily living, social and familial relationships, and intact cognitive functioning.

What does environmental variance reflect?

Individual differences in self-rated health are primarily due to nonshared environmental effects regardless of the age of the sample. Other studies report similar results. A Danish study of twins 75 years of age and older (Christensen et al., 1999) found genetic variance but conclude that individual specific environmental influences are the most important source of individual differences in self-rated health in the elderly. A Norwegian study including younger adults (18 to 23 years old) also confirms this generalization (Røysamb, Harris, & Tambs, 1999). These environmental effects reflect (apart from random and measurement error) individual specific experiences like accidents, social relationships, socioeconomic status, work experiences, leisure activities, physical exercise, that may differ in their importance at different ages. For example, accidents and work experiences may be more important sources of variance at younger ages, whereas accumulated exposures to toxins at work, cigarette smoking, or alcohol may be a source of nonshared environmental variance at older ages.

Stability of self-rated health, i.e., the *interoccasion phenotypic correlations* estimated in Paper II, is lower for the youngest age group compared with the older age groups, which might reflect a restricted range in variation or the onset of health-related conditions. Again, primarily nonshared environmental factors contribute to stability for

the youngest age group, and both genetic and environmental factors contribute fairly equally to stability in the other age groups. A somewhat higher environmental component of stability indicates that the same environmental factors had an impact at more than one occasion. Such nonshared environmental factors could, for example, include social relationships, education, and accidents that have an enduring effect on self-rated health. Equal mediation by genetic and environmental effects has also been found for personality traits (Pedersen & Reynolds, 1998). The correlations between times are not explained by shared environmental effects in any of the age groups included in our study. This is consistent with our finding from the mixed effect model where childhood SES, a typical measure of shared environment, does not explain cohort differences in variance or time effects in self-rated health.

Health and cognitive abilities

As suggested in the literature (Rosnick et al., 2004) we found that self-rated health is associated with perceptual speed and spatial reasoning. Perlmutter (Perlmutter & Nyquist, 1990) and Rosnick (Rosnick et al., 2004) hypothesized that information processing and speed are more likely than memory to be affected by health. The prediction regarding speed is supported by our results for both age groups, but on the contrary, memory was also associated with self-rated health, however, only in the older age group. The association between self-rated health and memory in the older age group is not very surprising though given that elderly people are indeed worried about their memory (Anstey & Low, 2004). Thus, it is possible that bad memory is translated into poor self-rated health (see (Wahlin et al., 2003). Specific chronic illnesses only partially explained the associations found in Paper III.

Central nervous system (CNS) related disorders and musculoskeletal problems were important in both age groups. Migraine, dizziness, epilepsy, Parkinson's disease, multiple sclerosis, different kinds of pain, osteoporosis and muscle problems are all included in these sub-groups of illness. It may be that pain is the common factor underlying these relationships. In the working segment of the population, absence of pain is very important. Poor self-rated health is associated with chronic pain (Mantyselka et al., 2003) and there are indications that pain is also associated with cognition (Apkarian et al., 2004). It may also be that particular CNS problems have some direct impact on both health and cognition. Parkinson's patients may experience subtle cognitive changes that are related to verbal fluency and impaired retrieval of verbal material (Albrecht et al., 1994). Attention and verbal abilities have also shown to be affected among patients with multiple sclerosis (Achiron & Barak, 2003).

Although others have reported that cardiovascular disorders (Elias et al., 1990; Fahlander et al., 2000) and metabolic disorders (Zelinski et al., 1998) are related to poorer cognitive performance and poorer self-rated health, these disorders did not explain the association between self-rated health and cognitive abilities in our sample. It is possible that these relationships are due to something more finely graded like

variation in the atherosclerosis process not captured by our broad dichotomy of cardiovascular disorders.

Our findings indicate that other factors than illnesses seem to play a substantial role in the relationship between self-rated health and cognition. We conducted posthoc tests of whether either socioeconomic status in childhood or years of education played a significant mediating role and found no significant evidence of mediation. For a smaller sub-sample (N = 437) containing individuals participating in both IPT2 and IPT3 we performed a posthoc analysis to check the correlations between self-rated health measured at IPT2 against the cognitive measures at IPT3. Correlations were somewhat greater than when testing the opposite direction, except for visual memory that was relatively unaffected by the time order. These correlations suggest that poor self-rated health occur before limitations in cognitive functioning occur. However, longitudinal data are needed to provide additional insight into the issue of causality.

We found that in the younger age group (<67 years), the associations between self-rated health and perceptual speed, and between self-rated health and spatial ability are mediated by both genetic and environmental factors, whereas, in the oldest age group, 67 years and older, the associations between self-rated health and all the cognitive abilities were mediated by genetic influences alone. Environmental mediation could reflect a poorer DNA repair that shows up as environment in our models (Finch & Kirkwood, 2000) or reflect life style changes such as work related stressors, shift-work or retirement, which are particularly relevant to the younger, still working age group. Genetic mediation may reflect age-related physical changes and chronic illnesses not fully tapped by our indicators of specific chronic conditions, or general slowing processes (Birren & Fisher, 1995).

Health, life-style and psychosocial predictors

In general our findings in Paper IV show that previously reported factors of importance for poor self-rated health are also of importance in our study covering a much longer time period. More importantly, we also found that the associations exist beyond the influence of severity of illness, SES, education, age and sex for poor self-ratings of health.

We found recurrent headache, neck and back pain to be associated with future poor self-rated health. Chronic pain is common and was associated with self-rated health in a cross-sectional Finnish sample aged 15 to 74 years (Mantyselka et al., 2003). Back pain and neck pain are common, intermittent symptoms especially in old age, and were independently associated with poor self-rated health in a Danish study (Hartvigsen, Christensen, & Frederiksen, 2004). Associations between tension-type headache and poor self-rated health are also reported in cross-sectional studies and over a 12-year time period (Lyngberg, Rasmussen, Jorgensen, & Jensen, 2005).

Health behaviors such as smoking and exercise have been linked to many health outcomes like diabetes, cancer, functional abilities and cardiovascular disease. It is therefore not very surprising that we found both smoking and lack of leisure time exercise to be associated with poor self-rated health. The magnitude of the associations was somewhat reduced after controlling for illness and the other covariates, but still significant. Others have reported similar associations between exercise and poor self-rated health in cross-sectional studies, even after controlling for health problems and physical limitations (Fylkesnes & Forde, 1991; Manderbacka et al., 1999). Manderbacka and co-authors also showed the same magnitude of effect as we found for poor self-rated health among current smokers vs. nonsmokers (Manderbacka et al., 1999). We found a more than two-fold increased risk for poor self-rated health for obesity compared with normal weight, slightly less for overweight compared with normal weight, in line with previous findings (Manderbacka et al., 1999; Månsson & Merlo, 2001). Our results indicate that risky behavior such as smoking, lack of leisure time exercise and being overweight or obese have an effect on self-rated health over long periods of time, even in the absence of obvious health consequences such as disorders or illnesses. We believe that by encouraging people to change their health behavior, much could be gained. We might not only see a reduction in the effects of common chronic conditions that has been shown to be influenced by health behavior, but also peoples' health experience might change to the better. This in turn can result in a decrease in morbidity and increase in survival.

Research in occupational health has identified a variety of factors in the work environments that are linked to morbidity, mortality and subjective well-being. However, there are few studies that have investigated the association between work conditions and self-rated health. Repetitive work, job insecurity and high ergonomic exposures predicted worsening of self-rated health over 5 years (Borg et al., 2000). Positive consequences of employment for better self-ratings of health have been reported (Markides & Lee, 1990). Our results of an association between unemployment and poor self-rated health support that result. In the same study by Markides and Lee (Markides & Lee, 1990) marriage is also found to favor self-rated health. In accordance with those findings we found that being unmarried is a risk factor for future poor self-rated health.

The question of the impact of personality factors on self-rated health has been raised and sometimes it has been claimed that self-rated health is more influenced by neuroticism and hypochondria than by medical health. Individuals that experience emotional distress feel less healthy than those who are more psychologically stable (Barsky, Cleary, & Klerman, 1992). Although individuals who are high in neuroticism report more somatic complaints than their emotionally stable peers, they do not show different profiles on more objective, biological markers of disease. This has been shown in several studies of healthy individuals (Watson & Pennebaker, 1989) and in the context of coronary heart disease (Costa, 1987), cancer (Schapiro et al., 2001), and upper respiratory infection (Cohen et al., 1995). Emotional stability i.e. low on neuroticism has also shown to be associated with psychological quality of life and well-

being (Hagberg, Hagberg, & Saveman, 2002). Two recent studies using cross-sectional data from the Midlife Development in the United States Survey (MIDUS) support that personality is independently associated with self-rated health (Barger, 2006; Goodwin & Engstrom, 2002). Social support, extraversion and negative emotions independently predicted self-rated health in one of the reports (Barger, 2006). Openness to experience, extraversion, conscientiousness and low scores on neuroticism were associated with good self-rated health among persons aged 25-74 years, independent of presence of medical problems in the second study (Goodwin & Engstrom, 2002). Further, these results remained after controlling for age, sex, marital status and education. Goodwin and Engstrom (2002) conclude that the association between personality factors and self-ratings of health are not just an artifact of sampling bias, specific clinical samples or a tendency to seek medical treatment. Rather, results support the hypothesis of an association independent of selection or sample, consistent in population-based samples. It is possible that persons high on neuroticism tend to view themselves, others and the world negatively, and are thereby more inclined to rate their health as poor. Our results in Paper IV also yield statistically significant associations between neuroticism, extraversion and self-ratings of health after adjusting for illness, SES, education, age, and sex. Neuroticism and extraversion were measured in 1973 and self-rated health was measured 25 years later, thus giving us an indication of the order between personality and self-rated health.

Overtime, shift-work, strenuous physical work, shoulder pain and migraine did not contribute to our final model. Taken one by one these factors might be of importance for self-rated health but when controlling for all other factors the effect disappear. Shoulder pain and migraine probably become embedded within the other pain variables (i.e. neck pain and headache) in our model. Similarly, SES probably absorbed some of the work related measures. These factors might also be more sensitive to change and therefore do not contribute to the association with self-rated health to any great extent.

8.2 METHODOLOGICAL ISSUES

The studies included in this thesis share the same methodological considerations as many other studies that are based on surveys and self-reports. One of these is internal validity, another external. Internal validity refers to the validity of the conclusions drawn about the existence, non-existence of associations between variables and absence of systematic errors. External validity refers to the generalizability of the findings across alternate populations, settings and times. Several issues regarding internal validity related to this thesis work are commented on in the following sections. First, potential problems related to response rates and potential bias due to non-response, are discussed. Second, issues related to information bias are brought up. Third, confounding is elucidated. Fourth, problems associated with random errors are discussed and finally, reliability in terms of internal consistency for the self-rated health measure is discussed. Issues related to twin methodology and external validity will follow in separate paragraphs.

Achieving high *response rates* as well as evaluating whether *non-responders* might differ from responders in different aspects are issues of importance and deserve attention. In SATSA the response rate to the first questionnaire in 1984 was 71%. The SATSA study (Paper II and III) has been examined thoroughly with respect to non-response and the main reasons for non-response to follow-up occasions were health problems or death of the co-twin in this elderly sample (Pedersen et al., 1991). *Selection bias* is the systematic error that can arise from how subjects are selected for inclusion in a study or from factors that influence study participation. In population-based cohort studies this is usually not a big issue. In a longitudinal setting as in Paper II, non-participation may be a potential source of selection bias. There was a pattern of increasing missing frequency for higher age groups and over time in SATSA. If the missing data can be considered missing at random, the estimates obtained from the maximum likelihood estimation are unbiased. If this assumption is not true, the missing data are nonignorable and the missing mechanisms should be modeled (Little & Rubin, 1987). We performed a series of sensitivity analyses, testing the effects of assumptions regarding the "true" responses by those who missed a measurement occasion. We computed multiple imputations assuming correlated multivariate normal distribution for the data within twin pairs and then recalculated our original analysis. Data missing because of death were not imputed, but the data available before death were used. In four separate analyses, the imputed values were then decreased (or increased) by -0.5, +0.5, -2, and +2 units, respectively, to test the consequences of assuming that nonresponse represented worse (or better) true values. The results were consistent with the original analyses of means and variance development, with only minor differences from the original results. When imputed values were negatively adjusted, there were only slightly lower means and higher variances, whereas for a positive adjustment, the opposite was found.

Reasons for nonresponses were available for 44% of the missing subjects in Paper II (SATSA), with 28% having died during the follow-up period and 16% indicating that they were too sick to participate. On this basis, we believe the nonobserved self-rated health data represent poorer ratings rather than the contrary. This assumption is also supported by evaluating the means and variances for those who participated in the questionnaire follow-ups as a function of number of occasions of participation. There is a pattern resembling terminal decline with decreases in means at the last occasion of measurement. Those individuals participating in all four occasions have the greatest mean level stability, whereas the variance is higher for those who participated only the first time and lower for those who participated at several occasions. This finding suggests that these individuals are farther away from death and hence less variable because they are all healthier. With the additional analyses conducted in Paper II, we consider the results presented regarding variances and mean development in our longitudinal setting to be conservative in the sense that availability of the "true values" for missing data would probably only increase the variances at later time points and older ages and simultaneously decrease the mean values.

Misclassification or *information bias* deals with classification of exposure or outcome. If misclassification is non-differential, misclassification will be equally distributed in all groups involved in the analysis. Hence, results will be diluted and the associations between exposure and outcome will be underestimated. If instead differential misclassification occurs, results can be both under- and overestimated. Exposure misclassification may have been introduced since we lacked information on duration of exposures in Paper IV.

It would also have been good to be able to verify disorders and illnesses with medical records or physical examinations in our studies. However, by using number of illnesses as well as grading the reported illnesses and conditions into a measure that reflect severity of illness, we believe a reasonable estimate of medical conditions is provided for the current studies based on the SATSA and the SALT samples. Another issue with self-reported information is that people tend to underreport when they consider the information to be sensitive. For self-reports of smoking habits and weight, people tend to underreport. The consequences would be, if anything, underestimated true effects. On the other hand, smoking was common during the 70's and health consequences of smoking were not much discussed at the time. Therefore we do not believe this is a problem in our data. Rather the opposite; even if people change their health behavior we observe a persistent effect. However, for all exposures and covariates included any potential misclassification is likely to be non-differential and hence, does not explain our positive findings, but only dilutes the effects found (Rothman, 2002). Self-rated health information is by nature such that self-reports are the only possible and valid way to obtain information and surveys such as SATSA and SALT are most often used to collect this kind of information.

Confounding may also threaten the validity in a study. A confounder is defined by its association with both the disease/trait and the exposure, but not resulting from an exposure (Rothman, 2002). Age was adjusted for in all Papers, in addition adjustments were made for sex, SES, education, rearing and illness to different degrees and dependent on the research question addressed in the respective Papers. As self-rated health is an individual's own health perception it is also possible that the measure could be biased according to social desirability and expectations, known confounders in psychological and sociological measurement theory.

The purpose of any matched design is to control for confounding. Results from our matched co-twin control analyses in Paper IV, indicate that especially genetic and perhaps familial influences are of some importance for the relationships between recurrent headache, exercise, obesity, and poor self-rated health. In epidemiological terms, the associations to some degree reflect genetic and familial confounds. Another way of explaining this is that the same genes or familial factors are of importance for both self-rated health and e.g. recurrent headache.

Random errors are errors that may give a deviation from the true value in a study, but would not generate any deviation if the investigation is repeated an infinite number of

times. Random error should not be ruled out, however, chance alone is unlikely the explanation to the results presented in this thesis. SALT is a large cohort study and both Papers I and IV are based on this study. Precision is generally improved by large sample size and the confidence intervals (CI) provide information about the precision. Tighter confidence intervals indicate high precision. The SATSA sample is smaller and we cannot exclude the possibility of limited power to detect true effects concerning rearing effects if these explain less than 10-15% of the variability. In Paper I we performed power calculations to ensure that we had sufficient sample size to detect sex differences in self-rated health. Power calculations at a significance level of 0.05 and a heritability of 40%, as reported for the age groups 45-64 and 65-74, reveal that we have 80% and >95% power, respectively, to detect whether different genes are operating in men than in women in our cross-sectional analyses. In our longitudinal Paper II our results may be attenuated by attrition, especially in the oldest age group. Less healthy people tend to refuse or drop out of participation. In Paper III we could not put self-rated health, cognitive abilities and dichotomously coded illnesses in the same model due to power problems. In Paper IV less precision is indicated for the conditional logistic regression than for GEE analysis. Even though this sample is big enough for studying most of the exposures, it would have been desirable to be able to include even more twin pairs for the study of exposures such as obesity, for which twins in a pair rarely are dissimilar.

Reliability in terms of internal consistency for the self-rated health scale was computed in the SATSA and SALT, and Cronbach's coefficient alpha was 0.76 and 0.67, respectively. In a principal component analysis for the SALT sample loadings ranged between 0.66-0.85 with the highest loading for the global general health item. We considered the estimates to be reasonably good but we can not exclude the possibility that the items are tapping different dimensions of self-rated health. Given the psychometric properties we analyzed both the composite scale and the general health item separately in Paper I. However, we found no differences in variance components between a composite self-rated health measure including three items and the general health item, suggesting that the essence of self-rated health does not appear to differ when measured by one single general item or a summed scale. A study on construct validity and functioning of a five-item general health scale (Bjorner & Søndergaard Kristensen, 1999) suggested some degree of heterogeneity, but the items measuring current health had the highest loading. The authors conclude that the scale had good concurrent validity as judged from associations with physical, mental and functional problems. Another study comparing different measures of self-rated health (two global non comparative, and one age comparative) gave the overall impression that all measures represent parallel assessments of self-rated health even though a non-comparative measure seemed to be more appropriate in longitudinal settings (Eriksson, Undén, & Elofsson, 2001). We doubt that the age group differences in Paper I to III are a function of the use of a composite scale versus a single item. Nevertheless, the meaning of self-rated health may differ by age group and our findings may reflect shifts in the subjects' basis for health evaluation.

8.2.1 Assumptions in twin studies

Twin studies focus on individual differences (variability) and the underlying conceptual model in these studies is multifactorial. Disorders, illnesses, symptoms, and health behavior are influenced by multiple genes and environments. Hence, the classical twin approach deals with anonymous components of both genes *and* environments of importance for the traits studied. In twin studies there are some underlying assumptions that when violated may affect twin similarity and hence bias the results.

The equal environments assumption

The equal environments assumption assumes that environmental similarity for identical (MZ) twins equals that of fraternal (DZ) twins, i.e. that MZ and DZ twins are equally correlated for their exposure to environmental influences that are of importance for the trait under study (Kendler, Neale, Kessler, Heath, & Eaves, 1993). If MZ twins are treated more similarly than DZ twins, greater similarity in MZ twins for self-rated health could in part reflect this differential treatment. If this assumption is violated an excess resemblance of MZ over DZ twins could in fact be explained by environmental effects instead of the perceived result of genetic effects. For self-rated health the effect is unknown, however studies testing the equal environments assumption for behavioral similarity, personality, intelligence and attitudes using twins with mislabeled zygosity compared to twins with correct zygosity have found little or no effect (Kendler, Gardner, & Charles, 1998; Loehlin & Nichols, 1976; Scarr & Carter-Saltzman, 1979). Therefore, it is unlikely that the equal environments assumption is violated in our studies.

Assortative mating

Quantitative genetic analyses also assume a random mating. Failure to take assortative mating into account in twin studies may lead to underestimation of additive genetic effects and overestimation of shared environmental effects as a result of an increase in DZ correlations (Vanyukov, Neale, Moss, & Tarter, 1996). Assortative mating does not affect MZ correlations because MZ twins are genetically identical (Plomin et al., 2001). Non-random mating exists for traits in the domains of religion, general cognitive ability and education (Hur, 2003; Plomin et al., 2001; Price & Vandenberg, 1980; Vandenberg, 1972). Non-random mating for self-rated health is unknown as is the case for many diseases and other health measures. Thus, while no data exist for self-rated health we have no reason to believe that our estimates are upward or downward biased due to assortative mating.

Gene environment interaction and correlation

Model fitting to the classical twin design cannot reveal how the anonymous genetic and environmental variance components interact with each other. Gene environment interaction occurs when the effect of genes differs dependent on environment or vice

versa. Gene environmental correlation refers to non-random placement or association of genotypes with environments (Plomin et al., 2001). Our models cannot reveal how these anonymous variance components interact and associate with each other. We do not know, for example, if specific genes for chronic diseases could be expressed differentially depending on environmental factors. Evaluation of gene environment interaction and gene environment correlation is most efficiently evaluated if one has a candidate gene and measured environment of importance for the phenotype if interest. At this point neither genes nor environmental candidates are identified for self-rated health. However, it should be noted that interaction effects generally are small, suggesting that focus should be placed on main effects.

8.2.2 Generalizability

The external validity is the validity of the conclusions as they attribute to persons outside the source population (generalizability). Critics sometimes argue that results from twin studies do not apply to the general population because twins differ from singletons in several aspects. However, means, variances, prevalences and incidences for several diseases, symptoms and behaviors in twin studies are equal to results obtained in studies using singletons (Andrew et al., 2001; Kendler, Martin, Heath, & Eaves, 1995; Moilanen et al., 1999). For self-rated health we have no reason to believe that twin populations differ from singleton populations. Our results of frequencies, means and variances correspond well to what others have found in both Swedish (Manderbacka et al., 1999; Undén & Elofsson, 1998) and international samples (Bjorner et al., 1996). When comparing elderly (80+) twins with singletons, Simmons and co-authors (Simmons et al., 1997) indicate that twin pairs surviving into old age are similar to non-twins of the same age when it comes to health status and biobehavioral functioning. Their findings also support the generalizability of twin studies for understanding genetic and environmental influences of health and aging.

8.3 FUTURE DIRECTIONS

The studies presented in this thesis provide additional insight into individual differences and the factors involved in self-rated health in adult ages. There are a growing number of twins studies investigating topics related to ageing and health status, however there are still issues to be addressed.

There are too few analyses of twin studies with a multivariate approach. A recently published study from Finland using cross-sectional data of female twins revealed that self-rated health did not have its own specific genetic effect (Leinonen et al., 2005). Rather, there was a genetic component in common with the genetic components underlying liability to disease, functional ability and depressive symptoms. There are few longitudinal analyses and even fewer using a multivariate approach. Inclusion of several covariates in the biometrical models as in the study by Leinonen and colleagues (Leinonen et al., 2005) would provide additional insight into what is happening with self-rated health in an ageing population. Large sample sizes, and self-rated health measurements at several occasions are needed though to be able to resolve issues of causality.

Another relatively unexplored area is what biological processes might underlie a good or bad self-rated health. A small number of studies have investigated biological mechanisms and have found associations for poor self-rated health with higher levels of inflammatory cytokines in women (Lekander, Elofsson, Neve, Hansson, & Undén, 2004), and that good self-rated health is related to low concentrations of saliva baseline cortisol and to a strong cortisol response to stress (Kristenson, Olsson, & Kucinskiene, 2005). Given the established association between self-rated health and morbidity and mortality in epidemiological research the area of identifying biological correlates deserves further attention.

9 CONCLUSIONS

Paper I – We found age group differences in total variance and variance components for self-rated health, but no significant sex differences. We conclude that individual specific environmental factors are of greatest importance for individual differences in self-rated health at all ages. Genetic factors are also of importance in older ages (45-74) when chronic diseases start to be more common.

Paper II – Our findings suggest that previous reports of an increase in variance in self-rated health with increased age primarily reflect cohort differences and are not fully replicated longitudinally. Mean levels remain quite stable within age groups over time, and changes with age in level of self-rated health seem to be explained primarily by illness. For variance as well, we found more substantial cohort differences than longitudinal changes, suggesting that the influence of socially mediated and individual-specific environmental effects may be greater than individual differences due to onset of genetically influenced diseases. The phenotypic stability over a 9-year time period is explained almost equally by genetic and environmental factors for all adult ages.

Paper III – The results provide additional insight into the mediation mechanisms behind the associations between self-rated health and various cognitive abilities for middle aged and older adults. Both health and cognitive functioning are important among middle aged and elderly people, and it was shown in this study they are related to some extent. These associations are mediated by both environmental and genetic factors in the younger age group (<67 years), while for the older age group these associations are mediated by genetic factors alone. Central nervous system (CNS) related disorders and musculoskeletal problems were of some importance for the associations in both age groups.

Paper IV – We conclude that risky behavior such as lack of leisure time exercise and smoking contributes to future poor self-rated health. Other risk factors that also contribute to poor self-rated health some 25+ years later include; obesity or overweight, recurrent headache, back and neck pain, unemployment, perceived stress, being unmarried and personality. Genetic and familial factors are of importance only for some of these associations.

10 SVENSK SAMMANFATTNING

Faktorer av betydelse för självupplevd hälsa

Självupplevd eller självskattad hälsa (self-rated health) är ett subjektivt mått på den egna hälsan. Måttet används dels för att ge en bild av hälsotillståndet i olika befolkningar dels i epidemiologiska och medicinska studier där man mäter hälsostatus. Det vanligaste sättet att undersöka självupplevd hälsa är med en global fråga av typen ”Hur bedömer du ditt allmänna hälsotillstånd”? Följt av 3 – 7 svarsalternativ från mycket dåligt till utmärkt/mycket gott. Självupplevd hälsa har i ett stort antal epidemiologiska studier visat sig predicera sjuklighet och dödlighet många gånger bättre än medicinska diagnoser. Det har skett en ökning i användandet av självskattningsmåttet av hälsa på senare år och det är därför viktigt att ta reda på varför människor skiljer sig åt i sin hälsobedömning.

Syftet med föreliggande avhandling var att öka förståelsen för varför vi människor skiljer oss åt i vår hälsobedömning. Samtliga delarbeten baseras på data insamlade vid det svenska tvillingregistret. Genom att studera tvillingar kan man få reda på den relativa betydelsen av arv och miljö för självupplevd hälsa. De få tidigare tvärsnittsstudierna med tvillingmetodik som gjorts har visat att det är en större variation bland äldre än bland yngre individer i den självupplevda hälsan. Enligt dessa studier har framförallt miljömässiga faktorer speglat ökningen i variation med stigande ålder, men även ärftliga faktorer har visat sig vara viktiga för självupplevd hälsa.

Studie I visade att genetiska faktorer har betydelse för individuella skillnader i upplevd hälsa i åldrarna mellan 45 och 75 år. Detta kan förklaras med att sjukdom till viss del är genetiskt betingad och att många kroniska sjukdomar visar sig först i denna åldersgrupp. Den ökning i variation med stigande ålder som tidigare tvärsnittsstudier påvisat replikeras även i denna studie. Ökningen av variationen med stigande ålder berodde framförallt på miljömässiga faktorer. I denna studie undersöktes också om det fanns könsskillnader när det gäller betydelsen av arv och miljö. Genom att inkludera både lik- och olikkönade tvillingar i analyserna fanns möjlighet att studera om olika gener och olika miljöaspekter hade betydelse för mäns och kvinnors självupplevda hälsa. Resultatet visade att män och kvinnor var lika i detta avseende.

I *Studie II* undersöktes vad som sker med nivån och variationen i självupplevd hälsa över tid samt om yngre och äldre åldersgrupper skiljer sig åt i detta avseende. Resultatet visade en relativt stabil nivå i upplevd hälsa över en 9-års period, efter att hänsyn tagits till sjuklighet och socioekonomisk status. Resultatet visade också på större skillnader mellan åldersgrupperna avseende variationen, än på variationsförändringar över tid inom respektive åldersgrupp. Äldre åldersgrupper hade större variation och lägre nivå i upplevd hälsa än yngre personer. Dessa skillnader förklarades inte av socioekonomiska faktorer i barndomen. Ytterligare ett viktigt resultat var att både arv och miljö var av betydelse för stabiliteten i upplevd hälsa över tid. De ärftliga faktorerna kan spegla sjuklighet och fysisk funktion medan miljöfaktorer kan spegla arbetsplatsexponeringar,

rökning, alkoholkonsumtion, kost och motion, vilka ackumulerar över tid och har en bestående inverkan på hälsoupplevelsen. Det är möjligt att de samhälleliga förändringar som skett under 1900-talet har haft visst inflytande på hälsoupplevelsen, särskilt bland äldre människor. Olikheter i nivå och variation i upplevd hälsa mellan åldersgrupper kan t ex spegla att man har haft olika möjlighet till utbildning och ekonomisk utveckling.

I *Studie III* undersöktes om det finns ett samband mellan upplevd hälsa och kognitiv förmåga mätt med verbal förmåga (generell kunskap), spatial förmåga, perceptuell snabbhet, arbetsminne och visuellt minne. Intakt kognitiv förmåga är en viktig aspekt av åldrandet men i det normala åldrandet sker ofta en viss försämring av de kognitiva funktionerna. Även om denna försämring i sig inte är sjuklig, i frånvaro av demens, kan förändringarna avspeglas i människors självupplevda hälsa. Resultatet visade ett samband mellan låg spatial förmåga, låg perceptuell hastighet och sämre självupplevd hälsa i åldersgruppen 50-66 år. I åldersgruppen 67 år och äldre fanns samband mellan upplevd hälsa och samtliga kognitiva förmågor förutom arbetsminne. Vi undersökte om sjuklighet kan förklara de påvisade sambanden, men fann inget större stöd för detta. Ett intressant resultat var att mönstret mellan självupplevd hälsa och de kognitiva förmågorna såg olika ut mellan åldersgrupperna. I den yngre gruppen förklaras sambanden både av ärftliga och miljömässiga faktorer medan i den äldre åldersgruppen förklarade enbart genetiska faktorer sambanden. Tänkbara förklaringar till dessa miljöfaktorer kan vara pensionering och förändringar i livsstil som en följd av stigande ålder. Dessa kan vara betydelsefulla i den yngre åldersgruppen där många var arbetsverksamma men närmade sig pensionering. För den äldre åldersgruppen kan fysisk och funktionell nedsättning, något som inte fångats i våra sjuklighetsmått, ha betydelse.

I *Studie IV* undersöktes om det fanns ett samband mellan riskfaktorer och beteende mätt på 1970-talet och självupplevd hälsa mätt 25 år senare. Vi fann att smärta, såsom huvud- och ryggvärk, brist på motion, övervikt och fetma, upplevd stress, arbetslöshet och personlighet, hade ett samband med en framtida dålig hälsoupplevelse. Ärftliga faktorer påverkade dessa samband i liten utsträckning. Dessa resultat som var i linje med tidigare forskning inom området visade att det fanns ett samband mellan risk-, livsstilsfaktorer och upplevd hälsa. Dessutom fann vi samband över en så lång tidsperiod som 25-år, därtill med hänsyn tagen till ålder, kön, utbildning, sjuklighet och socioekonomiska faktorer. Dessa resultat indikerar att med en förändrad livsstil, som mer motion, viktreduktion och minskad stress skulle man kunna påverka sina möjligheter till en bättre hälsoupplevelse, vilket i sin tur kanske till och med kan leda till ökad livslängd.

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