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Cardiovascular Disease and Hypertension

Population-Based Studies on Self-Rated Health and Health-Related Quality of Life in Sweden

BY

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ABSTRACT

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The aim with this thesis was to study cardiovascular disease and hypertension, use of drugs and health from an epidemiological perspective. Various methods – self-rated health (SRH), health related quality of life (HRQL) - the 36-item short form questionnaire (SF-36) - and health utility measurements - the rating scale (RS) and the time-trade off (TTO) methods – were employed.

Data from the Swedish Adoption/Twin Study of Aging (SATSA) in 1984, 1987, 1990, and 1993 as well as a general population survey conducted in Uppsala County in 1995 were used.

Persons who have cardiovascular disease, both with and without drug treatment, were found to have a lower SRH as compared to others in the population. Longitudinal analyses showed that SRH was relatively stable over time among persons with cardiovascular disease. Both having a low SRH and having cardiovascular disease were associated with a higher mortality rate.

Hypertensives were found to have a lower HRQL than do others in the general population as measured by the SF-36. The lowest scoring was found in the general health perception scale (GH), whereas role emotional (RE) and mental health (MH) were the scales least affected by hypertension.

Nearly 20 percent of the antihypertensive drug users reported side effects. The pattern of side effects was similar to that reported in clinical trials. Both hypertension itself and the drug treatment were found to have an impact on the patient's health-state utility as measured by the RS. Comparative analyses showed that health utilities and psychometric quality-of-life instruments were only moderately correlated among hypertensives.

The results also showed that inequalities in HRQL were present with respect to several sociodemographic factors.

In summary, this thesis revealed that persons with cardiovascular disease and/or with hypertension experience poorer health than others in the population. The poor health may be caused both by the disease and/or the drug treatment. The results in this thesis also suggested that special attention and care should be directed to persons with cardiovascular disease and/or hypertension reporting ill health. This especially is important given that low HRQL can be a riskfactor for subsequent cardiovascular events or complications which in turn might result in higher mortality rate.

Key words: Cardiovascular disease, hypertension, antihypertensive treatment, side effects, self-rated health, health-related quality of life, health-state utilities, SF-36 Health Survey, rating scale, time trade-off, general population, twins.

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Papers discussed

The thesis is based on the following papers, which will be referred to by their Roman numerals:

I. **Svärdh C, Isacson D, Pedersen N L.** Self-rated health among cardiovascular drug users in a study of Swedish twins. Scandinavian Journal of Social Medicine 1998;26:223-31.

II. **Bardage C, Isacson D, Pedersen N L.** Self-rated health as a predictor of mortality among persons with cardiovascular disease in Sweden. Scandinavian Journal of Public Health 2000: (In press).

III. **Bardage C, Isacson D.** Hypertension and health-related quality of life: an epidemiological study in Sweden. Journal of Clinical Epidemiology 2000: (In press).

IV. **Bardage C, Isacson D.** Self-reported side effects of antihypertensive drugs: an epidemiological study on prevalence and impact on health-state utility. Blood Pressure 2000: (In press).

V. **Bardage C, Isacson D, Lundberg L, Bingefors K.** An epidemiological study on the relationship between the SF-36 and health-state utilities to measure health in hypertension. (Submitted for publication).

VI. **Lundberg L, Bardage C, Johannesson M, Bingefors K, Isacson D.** Health-related quality of life in a general Swedish population from a gender perspective. (Submitted for publication).

Contents

Background

Cardiovascular diseases and hypertension as public health problems

Cardiovascular diseases are among the most common causes of morbidity and mortality in the Western industrialised world (Kaplan, 1994) and hence are a public health problem (Lenfant, 1996). In Sweden, cardiovascular diseases are responsible for 30 percent of all institutional care days, 10 percent of the diagnoses in non-institutional care, and 11% of all new disability pensions (Socialstyrelsen, 1997). As one of the most prevalent vascular disease, hypertension also poses a major public health problem (Joint National Committee, 1997). In most countries as much as 20 percent of the adults suffer from hypertension (WHO, 1996), which is also about the proportion of hypertensives in Sweden (Samuelsson, 1995).

Cardiovascular diseases are multifactorial in origin. More than 250 risk factors have been described in the literature (Strasser, 1990). Apart from previous cardiovascular disease, age, gender, and hereditary factors, the most important risk factors for cardiovascular disease are high blood pressure and high blood fats in combination with tobacco smoking, high consumption of saturated fats, and physical inactivity (Joint National Committee, 1997; Jackson, 1994; Kannel, 1989). Hypertension is a well-known major risk factor for all forms of cardiovascular and renal disease (Collins and MacMahon, 1994; Kannel, 1996; MacMahon *et al*., 1990). High blood pressure often coexists with other risk factors such as obesity and diabetes as a part of a larger framework of cardiovascular risk factors known as the metabolic syndrome (Hjermann, 1992).

Cardiovascular diseases cause half of all deaths in Sweden. Of total mortality, about 60 percent among men and 45 percent among women was due to ischaemic heart disease with stroke accounting for another 20 and 25 percent, respectively (Socialstyrelsen, 1997). Although the trend for cardiovascular disease and mortality has been declining over the past 25 years throughout the western world, cardiovascular mortality still

accounts for 20-50 percent of all death (WHO, 1996). The decline in total mortality follows a decline in incidence of cardiovascular disease, myocardial infarction. The decrease in mortality rate is, among other things, a consequence of the decline in important risk factors such as smoking (Rosengren *et al*., 2000). In addition, better methods of treatment have meant that those who are ill live longer than formerly.

The use of cardiovascular drugs to prevent (e.g., blood pressure lowering agents and lipid lowering drugs) and palliate (e.g., nitrates) cardiovascular disorders are common (Samuelsson, 1995; WHO, 1999). In 1999, the sales of cardiovascular drugs in Sweden were 271.5 defined daily doses (DDD) per 1 000 inhabitants per day. The majority of these were diuretics, representing 80.6; ATC inhibitors, representing 48.9; beta blocking agents, 42.6; and calcium channel blockers, 33.2, DDD per 1 000 inhabitants per day (Apoteksbolaget AB, 1999). Moreover, antihypertensive treatment is costly due to the extensive and often lifelong use of medication (Mancia *et al*., 1994). In Sweden, the annual cost of drug treatment of hypertension reached approximately SEK 1.6 billion (SEK, Swedish crowns, exchange rate 2000 1US$=SEK 9.41USD) (The Swedish Council, 1995).

Today, people live longer with hypertension and cardiovascular diseases. Clinical trials and epidemiological studies during the last decades have shown that high blood pressure could be successfully lowered by pharmacological treatments and the cardiovascular morbidity and mortality reduced (Collins *et al*., 1990; He and Whelton, 1997; Mosterd *et al*., 1999; Sytowski *et al*., 1996). Patients with these diseases face many years with their chronic disease and treatment is usually lifelong. The aim of treatment is prevention and improvement in function rather than cure. While efficacy and safety of the treatment have been documented extensively, much less emphasis has been placed on assessment of the patient's perception of drug treatment.

During the recent years, however, the interest in patient-based assessments of health i.e., health-related quality of life (HRQL) has increased. HRQL measurements are useful for assessing the health of a population or an individual, as a complement to the established measurements of medically defined health based upon biomedical values, morbidity, and mortality. In an era of increasing demands for health services and scarce resources,

HRQL has come to be regarded as an important outcome of health care, and hence a measure of effectiveness.

Self-rated health and health-related quality of life

Definitions and concepts

Most HRQL-instruments are based on the WHO's definition of health as a 'state of complete physical, mental and social well-being and not merely the absence of disease and infirmity´ (WHO, 1948). Although there is no consensus on the definition of HRQL, there are fairly good agreements that HRQL is a multidimensional concept, incorporating impairments, functional states, health perceptions, social opportunities, and duration of life (Patrick and Deyo, 1989). There are also several agreements that HRQL measurements are based on patient functioning, i.e., ability to perform activities of daily living, perception of medical diagnoses, disease symptoms, medications, psychosocial problem/symptoms, and well-being (Bowling, 1995, Bullinger *et al.*, 1993; Kaplan, 1987; Patrick and Erickson, 1993; Ware, 1995).

Self-rated health (SRH) is the individual's perception and evaluation of his or her health. SRH, health status, and HRQL have often been used interchangeably. There are, however, some suggestions that SRH is included in the concept of general health status which again is included in the concept of HRQL (FRN report, 1996). This is the approach taken here. As mentioned previously, HRQL is considered to be multidimensional and thus is a broader concept than SRH.

Measurements of self-rated health

The most common way of measuring SRH is with a single question in which the individual is asked to make a general statement of his/her health (Appels *et al.*, 1996; Idler *et al.*, 1990; Kaplan and Camacho, 1983; Wannamethee and Shaper, 1991). There are three main categories of questions used: global non-comparative, global age-comparative, and global-time comparative. In the first case, a person rates his/her health generally; in the second, in relation to others of the same age; and in the third, in comparison with a specific time in the past (FRN report, 1996).

The non-comparative method is the most common way of measuring SRH. Quite a few studies have measured global age-comparative SRH. Time-comparative measures are used less often as a single question. On the other hand this kind of question is included in the Short Form (SF) 36 questionnaire (Ware *et al*., 1993), a commonly used HRQL instrument. It is also one of the items in the SRH measurement, from the Older American's Resources and Services Mental Health Survey, used in this thesis. An age comparative question is also included in the SRH measure used here (Duke University Medical Centre, 1978; Harris *et al*., 1992).

Measurements of health related quality of life

HRQL instruments can broadly be divided into two groups, generic and disease-specific. Whereas generic instruments have been designed to cover all aspects of life, the disease-specific instruments are deliberately narrow in scope and oriented towards particular diseases (Guyatt *et al*., 1993; Patrick and Deyo, 1989). Generic instruments may, compared with disease-specific instruments, be unresponsive to changes in specific conditions. These instruments, however, have the advantage that they can be used to compare patients who had different conditions, and the same measures can be applied to both general and patient populations.

Generic instruments can further be dived into health profiles and utility measures. Health profiles are mainly descriptive, i.e., they describe HRQL in a number of different areas. Health profiles and disease-specific instruments are often referred to as psychometric due to their development from methods within psychology. One of the most widely used health profiles is the SF-36 (Ware, 1993). The Sickness Impact Profile (SIP) (Bergner *et al*., 1981), the Nottingham Health Profile (NHP) (Hunt *et al*., 1986), and the McMaster Health Index Questionnaire (MHIQ) (Chambers, 1993) are other commonly used health profiles. The other type of generic instrument, utility measures, is derived from economic and decision theory. The main approach in health economics has been to value HRQL in a single weighted measure, quality adjusted life years (QALYs), which reflect a patient's preferences for different health states in relation to death (Drummond *et al*., 1997; Torrance, 1986). The QALY weights of different health states are often referred to as health-state utility. Health utility measures health-related quality of life along a cardinal scale from death (0) to full health (1). The QALY weights of different health states are commonly used as effectiveness measures

in cost-utility analyses (Drummond *et al*., 1997). There are three main methods to measure health-state utilities; the rating scale (RS), the time trade off (TTO), and the standard gamble (SG) (Torrance, 1986). The utility measures are of importance in the allocation of scarce health resources.

Cardiovascular disease and self-rated health

Self-rated health presumably presents a summary statement of how the individual perceives various health conditions (Idler and Kasl, 1991, Undén and Elofsson, 2000). Therefore, self-rated health may be associated with severity of the disease, therapeutic outcome of the drug treatment, and mortality. Although poor self-rated health is not proven as a cause of mortality, it is well established that self-rated health is a strong and independent predictor of mortality (McCallum *et al*., 1994; Mossey and Shapiro, 1982; Wolinsky and Johnson, 1992). Thus, self-rated health measurements might be useful tools for identifying high-risk groups, sub-optimal drug therapy, and future events such as mortality among persons with cardiovascular disease.

Cardiovascular disease and drug use

Several studies have shown that cardiovascular diseases adversely affect SRH (Johnson and Wolinsky, 1993; Maeland and Havik, 1988; Tibblin *et al*., 1990). In the study by Tibblin et al. SRH was associated with myocardial infarction, heart failure, and stroke. Maeland and Havik found an reduction in SRH after myocardial infarction. In another study, Idler found that angina pectoris, heart attack, and stroke impact on patient's perceived health (Idler, 1993). The study by Johnson and Wolinsky showed an association between coronary heart disease and poor SRH. There are also studies indicating that self-rated health may be reduced among those on cardiovascular drug treatment (Fylkesnes and Fɒrde, 1991; Harlan, *et al*., 1986). It is therefore of interest to study how these diseases, both with and without drug treatment, can influence the perception of health.

It is obvious that drug therapy for cardiovascular disease is lifesaving and necessary to limit the complications of the disease. Therefore it is important that treatment is well tolerated and makes the patient feel better. Some studies have shown low concordance between the patient's and the physician's evaluations of treatment and health (Jashuck,

et al., 1982; LaRue, *et al*., 1979). In a multicenter clinical trial evaluating antihypertensive therapy, physicians were less sensitive to the overall impact of side effects, reporting only 14.9 percent of symptoms reported by the patient (Testa *et al*., 1993). Distressing side effects from drug treatment often lead to or contribute to withdrawing from medication or low compliance (Hussler and Messerli, 1981). It is estimated that 20-80 percent of patients prescribed cardiovascular drugs fail to adhere to the treatment regimen sufficiently to realise therapeutic benefits (Burke, *et al*., 1997). This highlights the importance of taking patient health perceptions into account when evaluating drug therapy.

The effects of drugs on the health perception of patients with cardiovascular diseases have primarily been assessed in clinical trials, and in the context of quality of life, in order to compare how well different drugs are tolerated (Croog *et al*., 1986; Fletcher and Bullpitt, 1992). Most of the studies have been fairly small, among very selected subsets in clinical trials, and without a multivariate approach to identify associations that are independent of lifestyle and mental health.

Cardiovascular disease and mortality

In most of the earlier studies on the association between self-rated health and mortality, time related change in self-rated health was not examined (Idler and Angel, 1990; Kaplan and Camacho, 1983; Wolinsky and Johnson, 1992). A few longitudinal studies have shown that the same variables are associated with self-rated health as in cross-sectional studies (Johnson *et al*., 1991), and that self-rated health is quite stable over time (Maddox and Douglas, 1973; Rodin and McAvay, 1992). However, little is known concerning what effect impairment due to disease may have on changes in self-rated health and, in turn, subsequent influences of change in self-rated health on mortality among persons with cardiovascular disease.

Behavioural genetic research has revealed the importance of both genetic and environmental influences for self-rated health (Harris *et al*., 1992a; Lichtenstein, 1993). Other studies suggest that self-assessments of health reflect a personal estimate of longevity, based not only on the respondent's own health, but also on knowledge of familial risk factors (Idler and Kasl, 1991; Idler and Benyamin, 1997). Because genetic effects are known to be of importance for cardiovascular disease (Berg, 1989), self-rated

health, and to some extent for death from cardiovascular disease (Marenberg *et al*., 1994), possible environmental effects such as drug use on health and mortality may be masked by these genetic effects. Studies from the Swedish Twin Registry found that genetic factors influence death due to coronary heart disease in both women and men (Marenberg *et al*., 1994). However, the importance of drug use on cardiovascular disease and mortality has not been considered in these studies.

Hypertension and health-related quality of life

Hypertension

Hypertension, especially in mild to moderate stages, is usually considered as an asymptomatic condition. However, whether hypertension is a condition associated with alterations in well-being and health-related quality of life (HRQL) (Hasford, 1992; Mancia *et al*., 1994) is still a controversial issue. A hypertension diagnosis may increase an individual's awareness of bodily symptoms and make an otherwise "healthy" person ill (Haynes *et al*., 1978; Wagner and Strogatz, 1984). The Medical Outcome Study in America found lower general health perception in hypertensive patients compared with those patients without chronic conditions (Stewart *et al*., 1989). In a recent population-based study, hypertensive individuals were found to have lower health status as compared with individuals free from hypertension (Lawrence *et al*., 1996). In some studies, hypertension has been associated with headache, dizziness, and tiredness (Bulpitt *et al*., 1976; Kjellgren *et al*., 1998). Hypertensives also have been described as more depressed and more anxious than "normotensives" (Lysketos *et al*., 1982; Rabkin *et al*., 1983). In other studies, however, no relationship between hypertension and symptoms have been found (Chatellier *et al*., 1982; Kottke *et al*., 1979). Inconsistency between studies might result from use of different study populations, different scales, and selection of methods. Some of the instruments that have been used are also unsatisfactorily documented in terms of reliability and validity. Further epidemiological studies on HRQL in hypertension using well-validated instruments are required.

Comorbidity with other diseases associated with hypertension may influence how persons with hypertension rate their HRQL. In some studies, it has even been argued that the low health-related quality of life among those with hypertension is due to

subsequent complications of the disease, not to hypertension in itself (Lahad and Yodfar, 1993; Stewart *et al*., 1989).

Antihypertensive drug use

Antihypertensive treatment is associated with several types of symptoms and side effects, such as tiredness, changes in mood, sleep disturbances, dry mouth, blurry vision, and impotence (Hansson, 1994; Shoenberger *et al*., 1990). In the treatment of hypertensives, side effects and the patient's perceptions of them play an important role in the success of the therapeutic regimen. In some studies, patients even perceive the use of hypertensive medication to be more troubling than their seemingly symptomless disease (Battersby *et al*., 1995; Croog *et al*., 1986; Dimenäs *et al*., 1989), whereas other studies have indicated that antihypertensive medication improves health-related quality of life (Neaton *et al*., 1993; Wiklund *et al*., 1997). Distressing drug side effects can lead to non-compliance and adversely affect health-related quality of life (Curb *et al*., 1985).

The effects of hypertension and antihypertensive medication on health-related quality of life have been assessed in randomised clinical trials in order to compare how well different drugs are tolerated (Applegate *et al*., 1991; Croog *et al*., 1986; Testa *et al*., 1991). Most of the studies, however, have been fairly small, and may not well reflect clinical practice due to the necessities of the study design (Hunt, 1997). Patients selected and studied in clinical trials often have not been representative of the general hypertensive population as a whole (The Swedish Council, 1995). Few studies are available concerning reports of side effects among hypertensives in a general population.

Relationship between psychometric measures and health-state utilities

Different instruments, both psychometric quality of life instruments and health utility measures, have been used to assess various aspects of health-related quality of life, among hypertensives. Although considerable progress has been made in reaching consensus about HRQL (Patrick and Erickson, 1993; Reivicki, 1993) there are differences in the way the concepts are operationalised and measured. There are some studies on the relationship between health state utility and psychometric health status

outcomes (Fryback *et al*., 1997; Lundberg *et al*., 1999; Revicki and Kaplan, 1993; Tsevat *et al*., 1991). In the study by Lundberg et al., the relationship between a shorter version of the SF-36, the SF-12 and health-state utilities in this population was analysed. In that study about 50% of the variance in the RS responses and about 25% in the TTO responses was explained. However, a greater understanding of the relationship between health utilities and multidimensional HRQL-instruments in different patient groups is also required. Among hypertensives, only a few studies are available about the relationship between psychometric multidimensional instruments and health-state utilities (Read *et al*., 1987; Reivicki *et al*., 1992). Considering that results from various studies using different methods are compared it is important to analyse how these measurements correlate with each other.

Sociodemographic factors and health-related quality of life

The impact of sociodemographic factors on health and health care utilisation has been reported throughout the literature. Health surveys repeatedly show that females have higher rates of illnesses, disability days, drug- and health-services use (Verbugge and Wingard, 1987), but men more often complain of diseases of severe character and die earlier (Statistics Sweden, 1992). Other studies have shown that women generally report worse health and tend to report more symptoms than do men (Bengtsson *et al*., 1987; Tibblin *et al*., 1990; Verbrugge, 1985). Gender differences have been reported to be inconsistent across age and health measures (Matthews *et al*., 1999; Wingard *et al*., 1989). Because there still are doubts about why men and women rate their health differently, gender differences are especially important to consider in assessments of HRQL.

The Black report drew attention to the inequalities in health status among socio-economic groups (Black *et al*., 1982). Several studies have shown that higher social class is associated with better health and higher HRQL (Didrechsen, 1990; Hemingway *et al*., 1997; Hunt *et al*., 1985; Otterblad Olausson, 1991; Vågerö and Norell, 1989). Other studies also indicate that social relationships promote good health status both for men and women in various populations, including samples of the elderly and the seriously ill (Berkman *et al*., 1992; Orth-Gomer and Johnsson, 1987; Welin *et al*., 1985; Welin *et al*., 1992). Marital status has been demonstrated to affect health status, with single persons have lower health than married persons (Davies, 1995). These findings

emphasise the importance of considering the impact of socioeconomic variables and social relationships in assessments of HRQL.

Because prior population studies in non-patient samples have shown an impact of demographic and socio-economic status on health-related quality of life in the SF-36, (Hemingway *et al*., 1997, Stansfeld *et al*., 1998) an effect among hypertensives is also to be expected. However, in prior studies on hypertension using the SF-36, sociodemographic factors other than age and sex were not taken into account.

Aims

General aim

To analyse, the relationship between self-perceived health and cardiovascular disease, and to describe the association between health-related quality of life and hypertension from an epidemiological perspective.

Specific aims

- To assess self-rated health among persons with cardiovascular disease with and without drug treatment.

- To analyse the association between cardiovascular diseases, self-rated health, and mortality.

- To describe the relationship between hypertension and health-related quality of life in a general population using the 36-item short form questionnaire (SF-36).

- To estimate the relationship among antihypertensive drug use, side effects, and health utility using the Rating Scale (RS) method.

- To determine the relationship between a psychometric health-related quality of life instrument and health utilities among hypertensives.

- To examine the relationship between health-related quality of life and sociodemographic factors in a general population, with focus on differences between men and women.

Study populations and methods

This thesis is based on a sample of Swedish twins from the Swedish Adoption/Twin Study of Aging and a general population survey conducted in Uppsala County, Sweden.

The Swedish Adoption/Twin Study of Aging

The ongoing Swedish Adoption/Twin Study of Aging (SATSA) is based on a sub-sample from the Swedish Twin Registry (Cederlöf and Lorich, 1978). The SATSA study comprises twins reared apart and control twins reared together matched for age, sex, and county of birth. The details of the sampling and testing procedures for SATSA have been described elsewhere (Pedersen *et al*., 1991). SATSA is a longitudinal study with a three-year interval between measurement occasions. A first questionnaire (Q1) was mailed in 1984 to 2,854 twins. Responses to this questionnaire were received from 2 018 individuals (71 percent). New questionnaires (Q2, Q3, and Q4) were sent out in 1987, 1990, and 1993, respectively. The response rates among individuals who responded to a previous questionnaire were 91 percent (Q1-Q2), 92 percent (Q2-Q3), and 95 percent (Q3-Q4). The main reasons for non-response are debilitating illness or death of the co-twin such that the surviving twin assumes that his/her response is of no value. Paper I is based on data from the mail-out questionnaire in 1984. Paper II is based on data from mail-out questionnaires in 1984, 1987, 1990, and 1993 and mortality data from the National Cause of Death Register through 1996.

The average age of the twins was 58.6 years at the time of the first questionnaire (Q1), ranging from 26 to 87 years. However, the age distribution is skewed because separation became more and more rare as the 20th century progressed. Therefore, over 70 percent of the sample were older than 50 years.

Study populations

Analysing cardiovascular disease and self-rated health (Paper I)

The analyses in Paper I were conducted in two steps. Because the sample comprises twins, the assumptions of independence of observations may not be fulfilled. Thus, in

the part of the study not including co-twin analyses, one individual in each twin pair from the questionnaire in 1984 (Q1) was randomly selected and included in the analyses. In non-intact twin pairs, the surviving individual was included in the study, giving a total study population of 1,147 persons. The mean age was 60 years at the time of the questionnaire in 1984, ranging from 30 to 86 years, and 71.9 percent were older than 50 years. Women comprised 57.2 percent of the sample.

Co-twin control analyses

In the second part of Paper I, four types of discordant twin pairs were included in the analyses: 112 twin pairs discordant for cardiovascular disease, 88 twin pairs discordant both for cardiovascular disease and for drug use, 35 twin pairs with no cardiovascular disease but discordant for drug use, and 34 twin pairs with cardiovascular disease but discordant for drug use.

Analysing cardiovascular disease, self-rated health, and mortality 1984-1996 (Paper II)

These analyses were carried out with respect to mortality among the cohort identified in 1984 (Q1). The sample included in these analyses is the same as in the first part of Paper I described above. The study population was followed for 12 years through the National Cause of Death Register.

Co-twin control analyses

Four types of twin pairs discordant for data from the baseline in 1984 (Q1) were included: 101 twin pairs discordant both for cardiovascular disease and for drug use, 187 twin pairs discordant for self-rated health, 47 twins pairs in which both individuals perceived their health to be good but discordant for cardiovascular disease and drug use, and 16 twin pairs concordant for bad self-rated health but discordant for cardiovascular disease and drug use.

Analysing changes in cardiovascular disease and self-rated health between 1984-1990 and mortality 1991-1996 (Paper II)

Among the 1,147 persons who responded in 1984, 146 persons had died and 373 persons did not respond to the questions about self-rated health in the questionnaire in

1990, resulting in a study population of 628. They were followed for six years (until 1996) through the National Cause of Death Register. The average age was 65 years, ranging from 36 to 93 years, and 55.9 percent were women.

Based on information from questionnaires Q1, Q2, and Q3, this sample was classified into the following categories: *No CVD or drug use*, those who reported no cardiovascular disease or drug use in Q1, Q2, and Q3; *Developed CVD and started to use drugs*, those who reported no cardiovascular disease in Q1, but disease and drug use by Q3; *Had CVD and used drugs*, those who reported cardiovascular disease in Q1 and drug treatment in Q1, Q2, or Q3.

Self-rated health was divided into four levels based on information from questionnaires Q1 and Q3: Respondents without a change between the assessments were classified as having g*ood* or *bad self-rated health*. Respondents experiencing a positive or negative change in self-rated health were classified as having *improved* or *worsened self-rated health,* respectively.

Concepts and definitions

Cardiovascular disease (Papers I and II)

In order to be classified as having *cardiovascular disease* (CVD), a person reported one or several of the following diseases: Angina pectoris or myocardial infarction according to Rose questionnaire; claudication; high blood pressure or any other cardiovascular disorder (i.e., stroke, phlebitis or thrombosis) (Rose *et al*., 1977).

Cardiovascular drug use (Papers I and II)

Cardiovascular drug users were defined as persons who indicated that they have used antihypertensives, diuretics, cardiac therapy and/or myocardial therapy during the past month.

Self-rated health (Papers I and II)

Self-rated health - The measure consists of four items. Three were taken from The Older American's Resources and Services Mental Health Survey ("How would you rate your general health status?", "How would you rate your health compared to 5 years ago?", "Do you think your health prevents you from doing things you would like to do?") (Duke University Medical Center, 1978), and an additional item inquires about

the respondent's health in comparison with others in the same age group (Harris *et al*., 1992b). Each item was coded from one to three and reversed so that high scores indicate better health. In the present analyses, the self-rated scale was classified into two levels: "good/between" constituted the 75 percent of the sample with the highest health ratings and "bad" was the quarter with low health ratings.

Demographic and social factors (Papers I and II)

The demographic and social variables included were sex, age (Paper I and II), marital status, and perception of social support network (Paper II).

Marital status - Subjects were categorised as married or unmarried.

Perception of social support network - The scale consists of nine questions rating the respondent's perception of social support (Bergeman *et al*., 1990). Each item was coded 'one' if satisfied and 'zero' if not satisfied, and summed so that a high score means satisfied with the social support. In the present analyses, the perceived support scale was classified into two levels: "satisfied" constituted the 75 percent of the sample with the highest ratings and "less satisfied" was the quarter with low ratings.

Lifestyle factors (Papers I and II)

Life style factors included were alcohol consumption, smoking habit, and body mass index (BMI).

Alcohol consumption - Respondents were classified as non-drinkers or drinkers, based on their responses to a series of items concerning alcohol consumption.

Smoking habit - Subjects were classified as non-smokers, ex smokers, or current smokers.

Body Mass Index - Body mass index (BMI) was calculated from self-reports of height and weight and classified into three levels: underweight (lower or equal to 20.1 for men and 18.7 for women), normal weight (between 20.1 and 25.0 for men and between 18.7 and 23.8 for women), and overweight (more than 25.0 for men and 23.8 for women).

Mental health (Papers I and II)

Depression – One sub-scale from The Older American's Resources and Services Mental Health Survey was used to estimate depressive symptoms (Gatz *et al*., 1987). The scale consisted of not waking up rested, not finding life interesting, not being able to "get going", sleeping fitfully, and unhappiness (Papers I and II).

Alienation in interpersonal relations - One sub-scale from the Short Psychiatric Evaluation Schedule was use to estimate interpersonal relations (Gatz *et al*., 1987). The scale involved feeling misunderstood, useful, paranoid, lonely, and wanting to leave home (Paper I).

Neuroticism - Items included in the measure evaluate psychosocial status (neuroticism) from a short version of Eysenck Personality Inventory (Paper I) (Floderus-Myrhed *et al*., 1980).

Chronic diseases (Paper II)

Chronic diseases (other than cardiovascular diseases) included in the analyses were diabetes mellitus, respiratory problems, and cancer. Respondents with these diseases were defined as those who selected these diseases from a list following the question: "Do you have or have had any of the following diseases or symptoms?".

General population survey in Uppsala County

Papers III-VI were based on a sample from the population register in the county of Uppsala, Sweden. A postal questionnaire, after local piloting, was sent to 8,000 inhabitants, aged 20-84 years, independently and randomly selected from the population register in 1995. Uppsala County consists of a university city, smaller towns, and agricultural areas. The county had 288,475 inhabitants in 1995. The population in Uppsala County is younger than the total Swedish population. The proportion of persons younger than 30 years was 22 percent in Uppsala and 18 percent in the total Swedish population. The questionnaire was designed to elicit information about health, health care utilisation, medication use, and health-related quality of life. No incentives were provided. In all, 5,404 persons answered the questionnaire, after two reminding letters, giving a response rate of 68 percent. The majority of non-respondents gave no reason for not responding (n=2,274); a much smaller group of individuals (n=132) stated that they did not want to participate, and some questionnaires (n=94) were returned due to wrong address. To preserve the anonymity of the respondents, no sample information was kept after the questionnaires were posted. Therefore, a strict dropout analysis could not be conducted. However, no important differences were found in the distributions on gender, age, marital status, and educational level among respondents and the total population of Uppsala County.

Study populations

Papers III-VI were based on all respondents to the questionnaire. i.e., 5,404 persons. In Papers III-IV persons with hypertension were studied. Those reporting no hypertension were used as reference population.

Concepts and definitions

Hypertension (Papers III-V)

Respondents with hypertension were defined as those who selected hypertension from a list following the question: "Do you have any of the following diseases or symptoms".

Comorbidity (Paper III)

Other diseases associated with hypertension included in the analyses were diabetes, angina pectoris, stroke, and heart attack. Respondents with diabetes and angina pectoris were defined as those who selected these diseases from a list following the question: "Do you have any of the following diseases or symptoms?". Subjects with previous stroke or myocardial infarction were defined as those who reported that they have had a stroke or heart attack.

Antihypertensive drug use (Paper V)

According to the Anatomical Therapeutical Chemical Classification system, antihypertensive drug users were defined as those who indicated current use of antihypertensives (code C02) i.e., methyldopa, clonidine, moxonidine, ∀-blockers, and hydralazine; diuretics (C03) i.e., thiazides, and thiazide-like diuretics, loop diuretics, and potassium-retaining diuretics; beta-blockers (C07) i.e., $\exists_1$- and $\exists_2$-blockers, $\exists_1$-blockers, $\forall_1$- and ∃-blockers; calcium channel blockers (C08), and ACE inhibitors (C09) (Capellà, 1993).

Side effects from antihypertensive drug treatment (Paper V)

Antihypertensive drug users with side effects were defined as those who indicated that they had perceived side effects from the treatment. The side effects were divided into the following groups: miscellaneous symptoms, i.e., dry mouth, dizziness, visual

disorders, headache, and cough; emotional distress, i.e., insomnia, tiredness, and depression; peripheral circulatory symptoms, i.e., cold hands and feet and swollen ankles; gastrointestinal symptoms; i.e., nausea and constipation; and finally impotence.

Sociodemographic factors (Papers III and VI)

The sociodemographic factors included in Paper III and Paper VI were age, sex, marital status, education, monthly income, social group, and employment status. Marital status was measured as married/cohabiting, single, and divorced/widowed. Education was divided into three levels: compulsory school, high school, and university. Monthly income was divided into the following groups: <10,000 SEK, 10-20,000 SEK, and >20,000 SEK (Paper III). In Paper VI the income group 10-20,000 SEK was divided into 10,000-14,999 SEK and 15,000-20,000 SEK (SEK, Swedish crowns, exchange rate 1995 1US$=SEK 7.30). Social group was divided into three categories: blue-collar workers, white-collar workers, and self-employed.

Measures of generic psychometric health-related quality of life (Papers III, V, and VI)

The 36-item short form questionnaire (SF-36) was used as a measure of health-related quality of life in Papers III, V, and VI. The SF-36 is an outgrowth of initial work performed within the RAND Corporation's Health Insurance Experiment in the United States which was conducted within the Medical Outcome Study (MOS) and resulted in the release of the MOS SF-36 standard version in 1990 (Ware *et al*., 1993). The SF-36 was constructed to provide a brief alternative for use in health policy evaluations, general population surveys, clinical research and practice, and other applications involving diverse populations. The SF-36 covers eight domains of health: physical functioning (PF), role limitation because of physical health (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitation because of emotional health problems (RE), and mental health (MH) (Ware and Sherbourne, 1992). These scales are scored from 0 (poorest health) to 100 (optimal health). Here we used the Swedish version of the SF-36 instrument (Sullivan *et al*., 1994). Psychometric validation of the Swedish SF-36 showed that results for data completeness, scaling assumptions, reliability, and construct validity compare well with the results of the U.S. evaluation (Sullivan *et al*., 1995). Normative data have been

estimated for the general non-institutionalised adult Swedish population (Sullivan *et al.*, 1994).

Health-state utility measures (Papers IV-V)

In Paper V, measurements of health state utilities were carried out using the Rating Scale (RS) method and the time trade off (TTO) technique (Drummond, *et al.*, 1997; Torrance, 1986). In Paper IV only the RS method was used.

The RS is a vertical, calibrated visual-analogue scale with labelled anchors of 'death' (at 0) and 'full health' (at 100). The respondents are asked to mark with an arrow the point on this scale that they feel best illustrates their current health state. The 0-1 health-state utility is obtained by dividing the number on the scale by 100. In the linear regression analysis in Paper V the RS utilities were scaled 0 to100.

In the time trade off question, respondents are asked to choose between living for 20 years in their current health state or living a shorter period of time in full health. The respondents indicate with a cross on a line the number of years of full health that they think is of equal value to 20 years in their current health state. The 0-1 health-state utility is obtained by dividing this response by 20. In the linear regression analysis in Paper V the TTO utilities were scaled 0 to 100.

Statistical analyses

In Papers I-V, descriptive statistics were obtained by using the using the SAS system for Windows, release 6.12, statistical analysis package (SAS Institute Inc., 1990a). In Paper VI statistical analyses were carried out using SPSS and Microsoft Excel (Microsoft Corporation, 1994; SPSS Inc., 1999).

Descriptive analyses

In Paper I the factors related to poor self-rated health were analysed separately for men and women. In Paper II the factors related to mortality rate were calculated first for men and women separately and then together. The Chi-square analysis was used for testing statistical significance of difference between proportions. In cases where the expected

number did not exceed five in a cell, the Fisher exact test was used for testing significance (SAS Institute Inc. 1990b).

Mean scores and standard deviations for each of the eight domains in the SF-36 (Papers III and V), the RS, and the TTO (Paper V) were compared between persons with and without hypertension. Statistical significance was tested with the non-parametric Wilcoxon rank-sum test of two independent sample means. In the SAS statistical package, the Wilcoxon test is equal to the Mann-Whitney U-test (SAS Institute Inc., 1990b). The Spearman's correlation coefficients were used to analyse the relationship between the TTO and RS values (SAS Institute Inc, 1990a).

In Paper VI the mean scores and standard deviations for each of the eight domains in the SF-36 were calculated. The study mean scores were compared with the mean scores for the Swedish normdata (Sullivan *et al* 1994). Statistical significance was tested with Students T-test (Colton, 1974). Men and women were analysed separately.

Logistic and linear regression analyses

Different multivariate methods of analysis can be used in order to relate two or more independent variables to an outcome or dependent variable. In multivariate analyses the estimated β-coefficient shows the impact of each independent variable on the outcome variable while adjusting for all other variables. Logistic regression analysis is used when the independent variable of interest is dichotomous (Paper I). The estimated β-coefficients obtained from the logistic regression analysis can be converted to an odds ratio. Further, confidence intervals can be calculated from the β-estimate and its related standard error. Logistic regression is described in detail in epidemiological texts (Hosmer and Lemeshaw, 1989; Kleinbaum *et al*., 1988). Linear regression is used when the independent variable is continuos (Papers III-VI). The estimated β-coefficients obtained from the linear regression analysis give a direct measure of the magnitude of the increase or decrease in the dependent variable with one unit increase of the explanatory variable. The adjusted R values give the proportion of the variance in the dependent variable explained by the model (Greene, 1993).

In Paper I the logistic regression analyses were conducted in the following way: The importance of cardiovascular disease with and without drug use on self-rated health was

estimated adjusting simultaneously for a number of confounding factors. Besides age and sex, alcohol consumption, smoking habits, body mass index, neuroticism, depression and alienation were controlled for as confounders in the analyses. These analyses gave information on each variable, statistical significance, and importance for the model. This information was used in deciding which variables to keep in the final logistic regression model. The CATMOD procedure in the SAS statistics program was used for the logistic regression analyses (SAS Institute Inc., 1990a). Odds ratios and confidence intervals were calculated from the β-estimates obtained. Interactions between variables in the final model were tested but no interactions of importance were found.

Linear regression analysis was elected for the multivariate approach in Papers III-VI. In Paper III, regression analyses were used to estimate the impact of hypertension on the eight scales in the SF-36 instrument. Analyses were adjusted for age, sex, marital status, education, monthly income, social group, diabetes, angina pectoris, myocardial infarction, and stroke. In Paper IV, linear regression analyses were used to estimate the impact of hypertension, drug use, and side effects on the rating scale, while adjusting for age and sex. In Paper V, the analyses were used to estimate the relationship between the domains of the SF-36 and health-state utilities while adjusting for age and sex. In Paper VI, linear regression analysis was used to estimate the independent effect of age, education, income, social group, marital status, and employment status on the eight scales in the SF-36 instrument. All the explanatory variables were entered as dummy variables (Papers III-VI). The Linreg procedure in the SAS statistics program was used for the analyses in Papers III-V (SAS Institute Inc., 1990a). The analyses in Paper VI were carried out using SPSS and Microsoft Excel (Microsoft Corporation, 1994; SPSS Inc., 1999)

Survival data analyses

Annual mortality (Paper II) was analysed using Kaplan-Meier estimates from the Lifereg procedure (SAS Institute Inc, 1990b). Log-rank tests were used for significance testing. Cox proportional hazards regression from the Phreg procedure was elected for the multivariate approach (SAS Institute Inc., 1992). In these analyses, individuals who developed cardiovascular disease were censored from the analyses at the time of the event. Self-rated health was included as a time-dependent variable (Kleinbaum, 1996).

More detailed information on the Kaplan-Meier technique and Cox-regression is available elsewhere (Kalbfleisch and Prentice, 1980; Kleinbaum, 1996).

Cox regression analyses were conducted as follows: Grouped and dichotomous variables were used. The effect of cardiovascular disease with and without drug use on all-cause mortality during 12 years was estimated. Self-rated health was controlled for in the analyses. Besides age and sex, alcohol consumption, smoking, body mass index, diabetes mellitus, respiratory problems, cancer, depression, social network, and marital status were simultaneously controlled for as confounders in the analyses. These analyses gave information on each variable, about the statistical significance, theoretical relevance and importance for the model. This information was used in deciding which variables to consider as confounders in subsequent analyses. Interactions between variables included in the final model were tested but no important interactions were found.

Co-twin control analyses

In the analyses monozygotic twin pairs were evaluated separately and together with dizygotic twin pairs. The statistical analyses were performed using the T-test procedure in SAS (Papers I-II) (SAS Institute Inc., 1990b).

In the co-twin control analyses in Paper I, paired T-tests (two-tailed) (Colton, 1974) were used to compare mean intra-pair differences on self-rated health scores for twins discordant for having a cardiovascular disease where neither twin used drugs, and in the next analysis, mean intra-pair differences for twins discordant for both disease and drug use were evaluated. These analyses told us whether cardiovascular disease has an effect on health alone and with drug use. Mean intra-pair differences were also calculated for twins concordant for not having a cardiovascular disease, with one in the pair using drugs and for twins concordant for having a cardiovascular disease with one in the pair using drugs. These analyses indicated whether drug use has an effect beyond cardiovascular disease. Self-rated health was used as a continuous variable.

In Paper II paired T-tests (two-tailed) were used to compare mean intra-pair differences in survival (continuous from 0-12 years) for pairs discordant for having a cardiovascular disease and drug use. These analyses told us whether cardiovascular disease and drug

use has an effect on survival. In the next analysis, the mean intra-pair differences for twins discordant for self-rated health were evaluated. In the final analyses, mean intra-pair differences were calculated for twins concordant for self-rated health, and discordant for drug-treated cardiovascular disease. These analyses indicated whether cardiovascular disease and drug use have an effect beyond self-rated health.

Results

Paper I

Self-rated health among cardiovascular drug users in a study of Swedish twins

The aim of the study was to analyse the relationship between self-rated health and cardiovascular disease with and without drug treatment. Another aim was to analyse the influence of cardiovascular disease and drug use on self-rated health while controlling for genetic effects.

Prevalence of cardiovascular disease and drug use

In the sample, 38 percent reported cardiovascular disease; 40 percent of the women and 35 percent of the men reported cardiovascular disease. Sixty percent of those with cardiovascular disease reported drug use. Men and women used drugs to the same extent.

Cardiovascular disease, drug use, and self-rated health

Table 1 shows the descriptive analyses for men and women separately. Significantly more women (29.4 percent) than men (22.8 percent) reported bad self-rated health ($p<0.01$). Both men and women with a cardiovascular disease reported bad health to a greater extent than did those who had no cardiovascular disease. The proportion with bad self-rated health was largest among those with drug-treated disease. In the multivariate analyses a strong relationship between self-rated health and cardiovascular disease remained regardless of drug use and despite control for mental health (Table 2). The multivariate analyses also showed a stronger relationship between low self-rated health and treated cardiovascular disease among men than among women. However, many factors related to self-rated health were the same among men and women.

Table 1. *Percent of respondents reporting poor self-rated health by cardiovascular disease (CVD) and/or cardiovascular drug use, age, smoking, alcohol consumption, body mass index, diabetes, neuroticism, depression and alienation.*

	Men		**Women**		**Total**	
	n	Percentage with bad self-rated health	n	Percentage with bad self-rated health	n	Percentage with bad self-rated health
Total	491	22.8	656	29.4	1147	26.6
CVD and/or drug use						
No CVD⊥	318	12.9	395	15.4	713	14.3
CVD, No drug	74	31.1***	98	43.9***	172	38.4***
CVD, Drug	99	48.5***	163	54.6***	262	52.3***
Missing value						
Age						
30-44⊥	83	18.1	95	10.5	178	14.0
45-64	227	21.6	247	22.7*	47	22.2*
65-74	130	24.6	198	37.4***	328	32.3***
75-	51	31.4*	116	45.7***	167	41.3***
Smoker						
Non-smoker⊥	182	15.9	419	29.1	601	25.1
Ex smoker	135	27.4*	88	30.7	223	28.7
Current smoker	173	26.6*	140	27.9	313	27.2
Missing value:	1		9		10	
Alcohol consumption						
Drinkers⊥	387	21.7	354	21.5	741	21.6
Non-drinkers	103	27.2	287	38.7***	390	35.6***
Missing value:	1		15		16	
Body mass index (BMI)						
Underweight	24	33.3	22	40.9	46	37.0
Normalweight⊥	240	24.6	267	25.1	507	24.9
Overweight	213	20.2	341	30.5	554	26.5
Missing value:	14		26		40	
Diabetes						
No⊥	458	22.3	596	27.0	1054	54.7
Yes	21	28.6	43	67.4***	64	25.0***
Missing value:	12		1		29	
Neurotisism (high score=neurotic) (no. of yes answers)						
0⊥	104	12.5	114	13.2	218	12.8
1-2	189	16.9	184	21.2	373	19.0*
3-5	139	30.9**	215	29.3**	354	29.9***
6-9	48	47.9***	116	56.0***	164	53.7***
Missing value:	11		27		38	

Continued

Table 1. *Continued*

	Men		Women		Total			
	n	Percentage with bad self-rated health	n	Percentage with bad self-rated health	n	Percentage with bad self-rated health		
Depression (High score means better mental health)								
5⊥		204	16.7	169	12.4	373	14.8	
4	126	15.1	162	20.4*	288	18.1		
3	52	23.1	117	30.8***	169	28.4***		
0-2	59	66.1***	104	55.8***	163	59.5***		
Missing value:	50		104		154			
Alienation (High score means better mental health)								
5⊥		323	18.3	351	21.9		674	20.2
3-4	106	29.2*	155	29.7	261	29.5**		
0-2	29	48.3***	76	52.6***	105	51.4***		
Missing value:	33		74		107			

⊥Reference group. Statistically significant differences between reference group and comparing group(s): *p<0.05; **p<0.01; ***p<0.001

Co-twin control analyses

Results from the co-twin control analyses are given in Table 3. In monozygotic (MZ) and dizygotic (DZ) pairs combined, twins with cardiovascular disease but no drug use had significantly lower health compared with their healthy co-twin ($p<0.05$). No significant differences were found exclusively within MZ twin pairs. Cardiovascular disease (CVD) and drug treatment have a negative effect on health when both MZ and DZ twin pairs were included in the analyses. No significant differences within MZ twin pairs were found. However, the findings were in the same direction as for the pooled sample. Further, cardiovascular drugs have a negative effect on health in pairs without self-reported cardiovascular disease. This was found when MZ and DZ pairs were included in the analyses ($p<0.05$). There were borderline significant differences for negative health effects in monozygotic twin pairs. In twin pairs concordant for cardiovascular disease, the cardiovascular drug treated twin did not report poorer health.

Table 2. *Logistic regression models for men and women relating cardiovascular disease (CVD) and/or cardiovascular drugs, age, smoking, depression and neuroticism to self-rated health.*

	Men				**Women**			
	Beta-estimate	OR	95% CI Low	95% CI High	Beta-estimate	OR	95% CI Low	95% CI High
Intercept	-3.8181				-4.2056			
CVD and/or drug use								
CVD,No drug	1.1122	3.04	1.46	6.32	1.2495	3.49	1.91	6.36
CVD,Drug	1.9864	7.29	3.82	13.90	1.6029	4.97	2.90	8.50
No CVD⊥								
Age								
45-64	0.2542	1.29	0.56	2.96	0.8971	2.45	1.03	5.85
65-74	0.1869	1.21	0.48	3.01	1.0959	2.99	1.22	7.36
75-	1.2430	3.47	1.19	10.07	1.7568	5.79	2.18	15.41
30-44⊥								
Smoking								
Current smoker	0.7487	2.11	1.05	4.26	NS	-	-	-
Ex smoker	0.8477	2.33	1.18	4.60	NS	-	-	-
Non-smoker⊥								
Depression (High score means better mental health)								
0-2	2.0560	7.81	3.26	18.71	1.7250	5.61	2.72	11.60
3	-0.1793	0.84	0.35	2.01	0.9593	2.61	1.32	5.17
4	-0.5845	0.56	0.27	1.13	0.4130	1.51	0.79	2.90
5⊥								
Neuroticism (High score=neurotic)								
1-2	0.5943	1.81	0.79	4.15	0.6527	1.92	0.86	4.28
3-5	1.5316	4.63	1.95	10.97	0.7628	2.14	0.99	4.64
6-9	1.1470	3.15	1.01	9.77	1.3432	3.83	1.61	9.13
0⊥								
Goodness of fit:	X2		df	p-value	X2		df	p-value
	193.59		196	0.535	145.98		122	0.068

⊥Reference group. OR= Odds ratio, CI= Confidence interval

Table 3. *Results from the paired t-tests (2-tailed) in cardiovascular disease (CVD) discordant twin pairs. Mean intra-pair differences in the self-rated health score given to twins in a pair.*

		MD+DZ self-rated health				MZ self-rated health			
Twin A	**Twin B**	No. of pairs	Mean diff.	t	p	No. of pairs	Mean diff.	t	p
CVD,no drug	Healthy	112	-0.88	2.54	0.012	40	-0.33	0.53	0.601
CVD,drug	Healthy	88	-2.18	4.95	0.000	34	-1.33	1.71	0.096
CVD, drug	CVD,no drug	34	-0.83	1.26	0.217	5	-0.73	0.63	0.563
Healthy,drug	Healthy	35	-1.56	2.95	0.006	10	-2.79	1.81	0.104

MZ= monozygotic twin pairs, DZ= dizygotic twin pairs

Paper II

Self-rated health as a predictor of mortality among persons with cardiovascular disease in Sweden

The study aimed to analyse the association between cardiovascular diseases, self-rated health, and all-cause mortality during a 12-year follow-up. A second objective was to analyse the importance of cardiovascular disease, drug use, and self-rated health on all-cause mortality while controlling for genetic effects.

Cardiovascular disease, self-rated health and mortality 1984-1996

Table 4 shows the descriptive analyses for men and women separately. Among the persons in the study population, 26.8 percent died during the 12-year follow-up. In the group free of cardiovascular disease at baseline, 245 persons (34.4 percent) developed cardiovascular disease during the follow-up. More deaths occurred among subjects with cardiovascular disease than among subjects free of cardiovascular disease ($p<0.01$). Both men and women with drug-treated cardiovascular disease had a higher mortality rate than did those without cardiovascular drug use ($p<0.05$ and $p<0.001$, respectively). Mortality was higher among both men and women with bad self-rated health as compared to those with good self-rated health.

In the multivariate analyses, both cardiovascular disease and low self-rated health were related to higher mortality (Table 5). Besides age and sex, diabetes was the only

Table 4. *Twelve-year mortality in the study population 1984. Results from Kaplan-Meier analyses with censoring of individuals who developed cardiovascular disease during the period 1984 to 1993. Self-rated health was included as a time-dependent variable.*

	Men		Women		Total	
	n	Mortality (%)	n	Mortality (%)	n	Mortality (%)
CVD and/or drug use						
No, CVD⊥	318	18.2	395	14.7	713	16.3
CVD, No drug	74	31.6*	98	24.0*	171	27.3**
CVD, Drug	99	50.5***	163	48.1***	262	49.0***
Age						
30-54⊥	177	6.2	195	3.7	372	4.9
55-64	133	20.2***	147	13.6**	280	16.8***
65-74	130	50.2***	198	30.7***	328	38.3***
75-	50	74.9***	116	68.8***	167	70.6***
Self-rated Health						
Good⊥	379	21.6	463	17.5	842	19.3
Bad	112	58.2***	193	54.3***	305	55.7**
Total	491	28.0	656	25.8	1147	26.8

⊥Reference group. Statistically significant differences between reference group and comparing group(s): *p<0.05; **p<0.01; ***p<0.001

variable associated with cardiovascular disease or self-rated health, or both, in the multivariate analyses. Diabetes was significantly associated with higher mortality after controlling for the other factors. Alcohol consumption, smoking habits, marital status, body mass index, respiratory diseases, cancer, depression, and perceived social support network are known to be related to higher mortality. However, neither of them turned out to be confounders in the multivariate analyses, and were therefore not included in the final model.

Changes in cardiovascular disease and in self-rated health between 1984-1990 and mortality 1991-1996

As shown in Table 6, among those with no cardiovascular disease in 1984, 316 persons (71 percent) remained free from cardiovascular disease and 129 persons (29 percent) developed cardiovascular disease during the period 1984 to 1990. All of the incident cases were on cardiovascular treatment in 1990.

Table 5. *Cox´s regression models relating cardiovascular disease and/or cardiovascular drugs, age in 1984, sex, self-rated health as a time-dependent variable, and diabetes at baseline to twelve-year mortality. Censoring of individuals who developed cardiovascular disease during the follow-up.*

	Parameter Estimate	Relative risk	95% Confidence interval Low	High
CVD and/or drug use				
No, CVD⊥				
CVD, No drug	0.5301	1.70	1.16	2.48
CVD, Drug	0.3986	1.49	1.10	2.02
Age				
30-54⊥				
55-64	1.3047	3.69	1.99	6.84
65-74	2.1199	8.33	4.70	14.75
75-	3.0496	21.11	11.75	37.90
Sex				
Women⊥				
Men	0.5738	1.77	1.37	2.30
Self-rated Health (Time-dependent)				
Good⊥				
Bad	0.8577	2.36	1.79	3.11
Diabetes				
No⊥				
Yes	0.6198	1.86	1.28	2.70

⊥Reference group

Among the individuals with good self-rated health in 1984, 407 persons (82.5 percent) still rated their health as good in 1990. Ninety-three persons (68.8 percent) with bad self-rated health in 1984 still perceived their health bad in 1990. In the different cardiovascular groups, significantly more individuals with disease than individuals free from disease during 1984 to 1990 reported worsened self-rated health in 1990 ($p<0.001$). This was also the case when comparing persons who developed cardiovascular disease and started to use drugs with persons that remained free from disease ($p<0.001$).

Among the persons in the study population, 12.7 percent died between 1991 and 1996. Mortality was higher among subjects who developed cardiovascular disease ($p<0.05$),

Table 6. *Mortality rate between 1991 and 1996 among respondents in 1990 by cardiovascular disease and drug use as well as self rated health during 1984-1990.*

	Respondents alive in 1990		
	n	Percentage	Mortality (%) during 1991-1996
CVD and drug use 1984-1990			
No CVD or drug use ⊥	316	50.3	6.6
Developed CVD and started to use drugs	129	20.5	13.9*
Had CVD and used drugs	183	29.1	22.4**
Self-rated health 1984-1990			
Good during the time period⊥	407	64.8	7.9
Improved	42	6.7	16.7
Worsened	86	13.7	16.3*
Bad during the time period	93	14.8	29.0**
Total	628	100.0	12.7

⊥Reference group Statistically significant differences between reference group and comparing group(s): *p<0.05; **p<0.01

and among subjects with disease during the whole follow-up period, compared to those free from disease (p<0.01). The results remained significant only among those with cardiovascular disease during the entire follow-up period, when adjusting for age as a confounder (data not shown).

Mortality was higher among those with worsened or bad self-rated health compared to those with good self-rated health (p<0.05 and p<0.01). Further analyses showed that the mortality rate remained significantly higher only in subjects with bad self-rated health, after adjusting for age (data not shown). Within each of the three different cardiovascular groups, mortality was significantly higher only in those with bad self-rated health during the entire follow-up period compared to those who perceived good health.

Co-twin control analyses

No significant differences in survival time were found in pairs concordant for good self-rated health but discordant for cardiovascular disease and drug use, regardless of zygosity (Table 7). Twin pairs discordant for health-ratings differed significantly from each other in survival time, when both MZ and DZ pairs were included. Twins with

Table 7. *Results from the paired t-tests (2-tailed) in twin pairs discordant for cardiovascular disease (CVD), drug use, and health ratings. Mean intra-pair differences in survival time are given.*

		MD+DZ survival time				MZ survival time			
Twin A	**Twin B**	No. of pairs	Mean diff.	t	p	No. of pairs	Mean diff.	t	p
CVD, drug	Healthy	101	-0.39	1.13	0.260	40	-0.26	0.42	0.677
Bad SRH	Good SRH	187	-0.57	2.44	0.016	69	-0.23	0.58	0.567
Good,CVD, drug	Good, healthy	47	-0.08	0.22	0.824	17	-0.79	1.10	0.288
Bad, CVD, drug	Bad, healthy	16	-2.57	2.53	0.023	4	-0.77	1.00	0.391

MZ= monozygotic twin pairs, DZ= dizygotic twin pairs, SRH= self-rated health

both bad self-rated health and drug-treated cardiovascular disease had a significantly lower survival time compared to their CVD healthy but bad health self-rating twin partners. However, no significant differences were found exclusively within MZ twin pairs.

Paper III

Hypertension and health-related quality of life: an epidemiological study in Sweden

The aim of the study was to describe the relationship between hypertension and health-related quality of life in a general population using the SF-36 instrument and to estimate this relationship while controlling for age, sex, sociodemographic factors, diabetes, angina pectoris, myocardial infarction, and stroke.

Prevalence of hypertension

Characteristics of the study population are shown in Table 8. The mean age was 46 years, and 54 percent were women. In the sample, 504 persons, 9 percent reported hypertension; 10 percent of the women and 8 percent of the men reported hypertension. The mean age among persons with hypertension was 61 years, ranging from 21 to 84 years. A greater proportion of hypertensives were divorced or widowed. There was more hypertension among persons with less than high school education and low income than among those with higher education and income. This was most apparent among women. In different social groups the proportions with hypertension were similar, about

Table 8. *Numbers and percentage proportions reporting hypertension by age, marital status, education level, social group, diabetes, angina, myocardial infarction, and stroke, Uppsala, Sweden 1995.*

	Men		Women		Total	
	n	Proportion with hypertension (%)	n	Proportion with hypertension (%)	n	Proportion with hypertension (%)
Total	2477	7.9	2927	10.5	5404	9.3
Age	2477		2927		5404	
20-44	1204	1.4	1500	2.9	2704	2.3
45-64	882	10.4	920	13.3	1802	11.9
65-74	256	23.1	303	23.4	559	23.3
75-84	135	21.5	204	34.3	339	29.2
Marital status	2455		2910		5365	
Married/cohabitors	1756	8.8	1996	10.1	3752	9.5
Single	500	4.6	453	4.9	953	4.7
Divorced/widowed	199	9.0	461	18.2	660	15.5
Education level	2414		2857		5271	
Compulsory school	795	12.6	944	18.7	1739	15.9
High school	1018	5.4	1124	5.2	2142	5.3
University	601	5.8	789	7.6	1390	6.8
Income SEK*	2426		2866		5292	
<10 000	560	8.2	1385	12.6	1945	11.4
10-20 000	1364	7.3	1354	8.3	2718	7.8
>20 000	502	9.6	127	8.7	629	9.4
Social group	2025		2316		4341	
Blue-collar worker	818	6.4	905	9.8	1723	8.2
White-collar worker	900	8.1	1284	8.6	2184	8.4
Self-employed	307	8.5	127	5.5	434	7.6
Diabetes	2477		2927		5404	
Yes	84	30.9	74	43.2	158	36.7
No	2393	7.1	2853	9.6	5246	8.5
Angina	2477		2927		5404	
Yes	80	23.7	74	50.0	154	36.4
No	2394	7.4	2853	9.5	5250	8.5
Myocardial infarction	2477		2927		5404	
Yes	72	18.1	39	48.7	111	28.8
No	2405	7.7	2888	10.0	5293	8.9
Stroke	2477		2927		5404	
Yes	23	60.9	18	44.4	41	53.7
No	2454	7.5	2909	10.3	5363	9.0

*SEK=Swedish crowns, exchange rate 1995 US$1=7.30

8 percent. A greater proportion of respondents with diabetes, angina, infarction, and stroke reported hypertension. More women with diabetes, angina, and infarction than men had hypertension, whereas a greater proportion of hypertensive men was found among respondents with stroke.

Hypertension and health-related quality of life

As shown in Tables 9 and 10, persons with hypertension generally scored lower in all domains of the SF-36 instrument than did those without hypertension. Lower scores in the domains intended to measure physical health, i.e., physical functioning, role physical, bodily pain, and general health, were most apparent, whereas lower scores in the domains intended to measure mental health, i.e., vitality, social functioning, role emotional, and mental health, were less pronounced. The lowest scoring was in the general health perception scale, whereas role emotional and mental health were the scales least affected by hypertension, after controlling for age, sex, sociodemographic factors, and comorbidity.

Those with diabetes showed lower scores in all the SF-36 domains, except in role emotional and mental health, than did those without diabetes. Individuals with angina pectoris scored significantly lower in most domains of the SF-36, except in social functioning and role emotional. Respondents who have had an infarction scored lower in general health and vitality. Those with a previous stroke had lower scores in physical functioning, general health, vitality, and social functioning. Respondents suffering from these diseases also scored lower than hypertensives in many scales. This was most obvious in general health and vitality.

Table 9. *Results of linear regression analysis of the SF- 36 scores; Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), and General Health (GH), Uppsala, Sweden 1995.*

	PF	RP	BP	GH
Explanatory variables	∃-estimate	∃-estimate	∃-estimate	∃-estimate
Constant	87.377***	80.244***	68.935***	73.183***
Hypertension				
Yes	-6.580***	-4.367*	-5.930***	-7.613***
Not†				
Age				
45-64	-5.617***	-2.821*	-2.180*	-4.399***
65-74	-10.660***	-6.971***	-1.379	-5.913***
75-84	-25.324***	- 29.083***	-3.950*	-11.306***
20-44†				
Sex				
Men	1.963***	2.187*	5.351***	0.608
Women†				
Marital status				
Single	0.045	0.506	1.859	-1.068
Divorced/widowed	-1.756*	-4.418**	-1.962	-3.238***
Married/cohabitor†				
Education level				
High school	3.647***	1.046	3.564***	2.688 ***
University	2.873***	-1.145	4.837***	1.234
Compulsory school†				
Income SEK[a]				
10-20 000	2.921***	7.454***	1.654	4.122***
>20 000	6.275***	11.788***	8.188***	7.671***
<10 000†				
Social group				
White-collar worker	2.187***	1.788	2.902**	1.483*
Self-employed	3.282***	3.387	4.402**	3.498**
Blue-collar worker†				
Diabetes				
Yes	-8.200***	-10.877***	-5.408*	-15.790***
Not†				
Angina				
Yes	-13.333***	-16.404***	-11.001***	-12.647***
Not†				
Myocardial infarction				
Yes	-3.576	-4.711	-3.187	-8.987**
Not†				
Stroke				
Yes	-10.617*	-14.093	-9.219	-10.708*
Not†				
Number of observations	4167	4143	4257	4174
R squared	0.253	0.099	0.082	0.133
Standard error	0.738	1.415	1.101	0.921
F	82.766***	26.801***	22.227***	37.576***

† Reference group, * =p<0.05, ** =p<0.01, *** =p<0.001. [a] SEK=Swedish crowns, exchange rate 1995 US$1=7.30

Table 10. *Results of linear regression analysis of the SF- 36 scores; Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH), Uppsala, Sweden 1995.*

	VT	SF	RE	MH
Explanatory variables	∃-estimate	∃-estimate	∃-estimate	∃-estimate
Constant	60.208***	84.928***	80.203***	75.203***
Hypertension				
Yes	-4.003**	-3.356**	-2.139	-1.691
Not†				
Age				
45-64	4.094***	0.558	2.236*	1.766**
65-74	10.820***	2.674*	1.878	5.757***
75-84	1.095	-4.643**	12.718***	2.284
20-44†				
Sex				
Men	5.597***	2.822***	2.520*	2.515***
Women†				
Marital status				
Single	-1.495	-2.716**	-5.210***	-4.269***
Divorced/widowed	-7.216***	-6.442***	-9.880***	-8.574***
Married/cohabitor†				
Education level				
High school	0.334	0.156	-0.868	1.116
University	-1.348	-1.112	-0.541	-0.621
Compulsory school†				
Income SEK[a]				
10-20 000	2.868***	3.628***	8.547***	3.958***
>20 000	5.465***	6.174***	9.917***	6.337***
<10 000†				
Social group				
White-collar worker	0.606	-0.453	0.019	0.466
Self-employed	1.490	-0.488	0.632	0.095
Blue-collar worker†				
Diabetes				
Yes	-6.891**	-6.021**	-3.657	-2.670
Not†				
Angina				
Yes	-10.860***	-3.388	-3.957	-5.045*
Not†				
Myocardial infarction				
Yes	-7.786**	-3.823	-6.129	-1.673
Not†				
Stroke				
Yes	-14.264**	-11.118*	-5.284	-3.183
Not†				
Number of observations	4198	4263	4144	4192
R squared	0.074	0.048	0.059	0.059
Standard error	1.018	0.933	1.392	1.070
F	19.664***	12.631***	15.214***	15.481***

† Reference group, * =p<0.05, ** =p<0.01, *** =p<0.001. [a] SEK=Swedish crowns, exchange rate 1995 US$1=7.30

Paper IV

Self-reported side effects of antihypertensive drugs: an epidemiological study on prevalence and impact on health-state utility

The aim of the study was to assess, firstly the frequency and type of self-reported side effects among hypertensives in a general population, and secondly to assess the relationship between drug use and side effects, measuring health utility using the Rating Scale (RS) method.

Diseases (other than hypertension) were more common among those with hypertension than among normotensives. The proportions of these diseases among hypertensives and non-hypertensives were respectively: 36% and 22% for back problems, 19% and 11% for frequent headache or migraine, 9% and 2% for diabetes, 5% and 2% for angina pectoris, 8% and 5% for asthma, and finally 6% and 4% for depression. Persons with hypertension also used more drugs. The most commonly used drugs, apart from antihypertensive drugs, among those with and without hypertension were respectively: analgesics 14% and 9%, tranquillisers and sedatives 7% and 4%, diabetes medication 6% and 2%, anti-asthmatics 8% and 4%, antidepressants 5% and 2%, and drugs for treatment of peptic ulcer 4% and 2 % (data not presented). All proportions were age standardised with the direct method using the whole study population as the standard.

Antihypertensive drug use

As shown in Table 11, of the 504 persons with hypertension, 394 were drug treated, i.e., 78 percent. Among those with drug-treated hypertension, 23% used beta-blockers, 12% were on ACE inhibitors, 11% used calcium-channel blockers, 7% used diuretics, and 1% used antihypertensives as monotherapy. One percent used a fixed-dose combination of two substances in one preparation. Thirty-four percent used a combination of two antihypertensive drugs and 10% a combination of three or more drugs.

Prevalence of side effects

Nearly 20 percent of the users of medication reported side effects. Men and women reported side effects to nearly the same extent, 18 percent of the men and 20 percent of the women reported symptoms related to the treatment. Among those undergoing

Table 11. *Numbers and percentage proportions reporting drug use and side effects by pharmacological classes and use of more than one antihypertensive drug. Uppsala, Sweden 1995.*

	Numbers	Proportion with side-effects (%)
Monotherapy		
Antihypertensives (C02)	4	0
Diuretics (C03)	28	21.4
Betablockers (C07)	92	17.4
Calcium-channel blockers (C08)	44	18.2
ACE inhibitors (C09)	48	12.5
Fixed-dose combination antihypertensives	4	0
Two antihypertensive drugs	134	23.1
Three or more antihypertensive drugs	40	27.5
Total	394	19.8

Table 12. *Percentage proportions of antihypertensive drug user by different types of side effects. Uppsala, Sweden 1995.*

	Proportion of drug users with the side effect (%) (n=394)
Miscellaneous symptoms	
Dry mouth, dizziness, visual disorders, headache, and cough	10.4
Emotional distress	
Insomnia, tiredness, and depression	5.6
Peripheral circulatory symptoms	
Cold hands and feet and swollen ankles	5.3
Gastrointestinal symptoms	
Nausea and constipation	1.8
Impotence*	6.0

*among men (n=167)

monotherapy, 16 percent reported side effects. Twenty-three percent of those with use of two drugs and 27 percent of those with use of more than two drugs reported side effects (Table 11).

The prevalence of side effects reported by hypertensives with drug use is presented in Table 12. Miscellaneous symptoms such as dry mouth, dizziness, visual disorders, headache, and cough were most frequently reported by those who perceived side effects from the treatment. Emotional distress such as insomnia, tiredness, and depression were found among nearly 6 percent. About 5 percent of the drug users related peripheral circulatory symptoms to the treatment. Gastrointestinal symptoms were also reported. Among men, 6 percent reported impotence due to drug use. Further analyses, among different pharmacological classes showed that dizziness and visual disorders were the side effects most often reported among users in all pharmacological classes except among users of ACE-inhibitors. They more often reported peripheral circulatory symptoms, such as cold hands and feet and swollen ankles (data not presented).

Impact on health-state utility

In Table 13 the results from the multivariate analyses are given. Model 1 includes hypertension with and without drug use and side effects. In Model 2, side effects were divided into different types. As shown, those in older ages had significantly lower values in the Rating Scale. Men showed higher health utilities than did women. Those with hypertension, whether they were on drug use or not, rated lower health utilities, -5.9 and -7.1 respectively, than did normotensives. The lowest value, -8.7, was found among drug users with side effects (Model 2).

Model 2 shows that, of the different types of side effects reported, miscellaneous symptoms and emotional distress were related to significantly lower RS values. These side effects were also most frequently reported. The lowest value -9.1 was found for emotional distress. Further stratified analyses by sex showed that among men, impotence was the side effect resulting in lowest health utility (-11.2). Among women it was miscellaneous symptoms (-8.7) (data not shown).

Table 13. *Results of linear regression analysis of QALY weights measured with the Rating Scale (RS). Uppsala, Sweden, 1995.*

Explanatory variables	Model 1 ∃-estimate	Model 2 ∃-estimate
Constant	84.8***	84.8***
Age		
20-44†		
45-64	-1.6***	-1.7***
65-74	-6.8***	-6.8***
75-84	-15.0***	-15.1***
Sex		
Women†		
Men	1.8***	1.8***
Hypertension		
No hypertension†		
Hypertension, no drug use	-6.0***	-5.9***
Hypertension, drug use, no side effects	-7.1***	-7.1***
Hypertension, drug use, side effects	-8.7***	
Type of side-effect		
Miscellaneous symptoms		-7.5**
Emotional distress		-8.5*
Peripheral circulatory symptoms		-6.5
Gastrointestinal symptoms		-6.5
Impotence		-14.0**
Number of observations	5178	5178
R squared	0.089	0.089
Adjusted R squared	0.088	0.087
Standard error	0.348	0.348
F	72.396	50.476
Signif F	<0.001	<0.001

† Reference group, * =p<0.05, ** =p<0.01, *** =p<0.001

Paper V

An epidemiological study on the relationship between the SF-36 and health-state utilities to measure health-related quality of life in hypertension in Sweden

The study aimed to determine the relationship between a psychometric health-related quality of life instrument--SF-36--and health utilities among hypertensives in a general population.

Means and standard deviations for the SF-36, rating scale, and time trade-off are presented in Table 14. Persons with hypertension generally scored lower in all domains of the SF-36 instrument than did those without hypertension. The corresponding results when using rating scale and time trade-off also showed lower ratings among hypertensives. The TTO method yielded higher values, i.e., better health, than did the RS method among both hypertensives and non-hypertensives.

Relationship between the RS and the TTO

The mean health-state utility in the whole sample was 0.83 (SD 0.16; range 0.0-1.0) with the RS method and 0.90 (SD 0.19; range 0.03-1.0) with the TTO method. The correlation between the two utility measures was moderate. The Spearman's correlation coefficients between the TTO and RS values were 0.44 among hypertensives and 0.41 among non-hypertensives (data not shown).

Relationship between the SF-36 and the RS and TTO

The results of the linear regression analyses of the relationship between the different dimensions in the SF-36 and each of the utility measures, the RS and TTO, are shown in Tables 15 and 16. The intercepts showed that the lowest values on the SF-36 dimensions represent values in the middle or somewhat higher on the RS. The regression coefficients for all scales of the SF-36 were significantly associated with the RS among persons with and without hypertension. Among hypertensives, the dimension most correlated with RS was the general health perception score followed by vitality, physical functioning, bodily pain, social functioning, role physical, role emotional, and mental health. Nearly the same pattern was found among those without hypertension.

Table 14. *Mean values and standard deviations for SF-36 dimensions, Rating scale, and Time trade-off among persons with and without hypertension.*

	Hypertension Mean (SD)	No hypertension Mean (SD)
SF-36 dimensions (0-100)		
Physical functioning	71.0 (27.4)	89.2 (18.6)
Role physical	66.5 (41.5)	83.9 (31.6)
Bodily pain	65.1 (27.7)	76.4 (24.6)
General Health	59.1 (22.7)	74.9 (21.1)
Vitality	59.2 (24.3)	65.6 (22.3)
Social functioning	82.0 (23.7)	85.5 (20.8)
Role emotional	77.2 (37.4)	84.2 (31.1)
Mental health	75.2 (21.0)	78.3 (19.0)
Health utilities (0-1)		
Rating scale	0.73 (0.3)	0.84 (0.1)
Time trade-off	0.81 (0.2)	0.91 (0.2)

Statistically significant differences between persons with and without hypertension were tested with the Wilcoxon 2-sample test and were highly significant $p<0.001$ (mental health $p<0.01$).

Table 15. *Results of linear regression analysis of the relationship between Rating scale and SF-36 scores among persons with and without hypertension. In the analysis were adjusted for age and sex. Rating scale was scaled 0-100.*

	Rating scale					
	Hypertension			No hypertension		
	Intercept	β-estimate	R^2	Intercept	β-estimate	R^2
SF-36						
Physical functioning	41.5	0.42	0.38	45.7	0.43	0.27
Role physical	61.0	0.21	0.27	66.6	0.22	0.24
Bodily pain	54.8	0.33	0.31	63.2	0.29	0.26
General health	44.0	0.54	0.54	47.2	0.49	0.48
Vitality	52.4	0.45	0.40	60.7	0.40	0.39
Social functioning	47.1	0.37	0.29	54.6	0.36	0.28
Role emotional	61.6	0.19	0.20	72.3	0.16	0.15
Mental health	52.0	0.34	0.21	55.2	0.39	0.29

All intercepts and β-estimates were highly significant $p<0.001$

But, the correlation between the domains in the SF-36 and health-utilities were higher, except in the mental health scale, among hypertensives than among non-hypertensives. The R^2 values ranging from 0.20 for role emotional to 0.54 for general health among hypertensives means that 20 percent and 54 percent of the variance in RS was explained

Table 16. *Results of linear regression analysis of the relationship between Time trade-off and SF-36 scores among persons with and without hypertension. In the analysis were adjusted for age and sex. Time trade-off was scaled 0-100.*

	Time trade-off					
	Hypertension			No hypertension		
	Intercept	β-estimate	R^2	Intercept	β-estimate	R^2
SF-36						
Physical functioning	58.3	0.30	0.22	68.6	0.26	0.17
Role physical	73.3	0.14	0.19	82.2	0.13	0.15
Bodily pain	67.5	0.24	0.22	81.4	0.15	0.15
General health	60.2	0.38	0.26	71.3	0.28	0.21
Vitality	66.9	0.30	0.22	80.3	0.21	0.17
Social functioning	62.7	0.26	0.21	72.3	0.24	0.18
Role emotional	68.9	0.19	0.21	84.8	0.10	0.13
Mental health	63.3	0.28	0.19	75.7	0.23	0.16

All intercepts and β-estimates were highly significant $p<0.001$

by role emotional and general health. Among those without hypertension, the R^2 values ranged between 0.16 for role emotional and 0.49 for general health.

The relationship between dimensions of health-related quality of life and the TTO method was weaker than for the RS scale among both hypertensives and non-hypertensives. The intercepts showed that the lowest values on the SF-36 dimensions represented values above the middle on the TTO. The regression coefficients for the scales in the SF-36 were significantly related to the TTO values among both hypertensives and non-hypertensives, but the regression models explained less of the variance than in the RS. The dimension most correlated with the TTO method was the general health perception score. The other SF-36 domains were overall less correlated with the TTO responses and differed little from each other. The R^2 values ranged between 0.19 for role physical and mental health and 0.26 for general health among hypertensives. The corresponding values among those without hypertension were between 0.13 for role emotional and 0.21 for general health.

Paper VI

Health-related quality of life in a general Swedish population from a gender perspective

The aim of the study was to examine the relationship between SF-36 and sociodemographic factors in a general population sample with focus on differences between men and women.

The age distribution was similar for both genders, as was the distribution of educational level. A third of the respondents had completed compulsory school and a fourth had some university education. Men had a higher mean income than did women, and a greater proportion of men were self-employed. About 70 percent of both genders were married, but a greater proportion of women were widows. The proportion of unemployed was 4 percent.

Physical dimensions

As shown in Table 17, women generally reported lower scores in the domains intended to measure physical health, i.e., physical functioning, role physical, bodily pain, and general health than did men. Among both men and women, those in the older ages rated lower scores in all physical dimensions.

Income was the sociodemographic factor of greatest importance. The scores were higher for those with higher income. Education level was significantly related to higher scores in physical functioning and bodily pain (only among men). Physical functioning and bodily pain were significantly higher among those in higher social groups. General health scale was significantly higher only among men in higher social groups. Divorced women rated lower in general health scale than did married women or cohabitors. Unemployment was not significantly associated with lower or higher health ratings among men or women.

Mental dimensions

Women also rated lower scores in the domains intended to measure mental health, i.e., vitality, social functioning, role emotional, and mental health than did men (Table 18). Men in the oldest ages rated significantly lower social functioning and vitality

Table 17. *Results of linear regression analysis of the PHYSICAL SF-36 dimensions for men and women*

	Physical Function		**Role-physical Function**		**Bodily pain**		**General Health**	
Explanatory	∃-estimate		∃-estimate		∃-estimate		∃-estimate	
Variables	men	women	men	women	men	women	men	women
Constant	92.1*	89.7	84.3*	83.0*	78.4*	71.9*	76.9*	76.7*
Age								
Age 20-29†								
Age 30-39	-3.2*	-3.7*	-4.9*	-3.7	-4.0*	-3.8*	-4.0*	-3.7*
Age 40-49	-5.5*	-6.1*	-6.5*	-3.6	-7.5*	-3.9*	-8.8*	-6.2*
Age 50-59	-8.8*	-12.2*	-9.4*	-7.1*	-9.2*	-6.2*	-10.9*	-11.2*
Age 60-69	-12.7*	-16.9*	-13.0*	-11.8*	-12.3*	-7.6*	-13.6*	-13.5*
Age 70-79	-22.5*	-25.5*	-27.7*	-21.6*	-13.1*	-10.2*	-18.7*	-17.5*
Age 80-	-33.6*	-35.7*	-49.8*	-30.8*	-18.0*	-7.0	-31.2*	-21.2*
Education								
Compulsory†								
High school	2.7*	3.5*	-0.2	0.7	1.7	2.4	1.7	1.9
University	1.7	2.3*	-0.8	-2.6	4.3*	3.5	0.1	0.4
Income SEK[a]								
<10 000†								
10-14999	1.4	2.4*	7.4*	6.9*	1.1	0.0	3.7*	2.8*
15-20 000	4.5*	5.3*	12.6*	9.5*	6.3*	4.1*	8.0*	8.3*
>20 000	6.7*	8.6*	14.9*	11.7*	10.8*	9.7*	9.8*	10.4*
Social group								
Worker†								
White collar	1.4	3.1*	2.4	1.2	2.8*	3.9*	1.7	1.4
Self-employed	3.1*	3.5*	4.0	2.2	3.7*	5.9*	3.4*	3.0
Marital status								
Married/cohabitor†								
Single	-1.3	0.2	-0.6	0.5	0.6	2.0	-2.0	-1.7
Divorced	-0.8	0.5	-2.6	-4.8	-2.1	-0.9	-1.9	-3.6*
Widow	-2.8	-3.0	-2.0	-5.1	3.2	-1.0	-0.3	-1.0
Unemployed§	-1.7	2.3	-1.5	5.9	1.5	-1.9	-3.8	-1.4
no obs	1889	2178	1888	2156	1941	2211	1909	2164
R squared	0.20	0.25	0.12	0.06	0.09	0.05	0.12	0.10
Adjusted R squared	0.19	0.24	0.11	0.06	0.08	0.04	0.12	0.09
Standard error	15.01	16.51	26.83	32.35	21.91	24.80	18.43	20.74
F	27.32	42.26	14.26	8.45	11.22	6.08	15.58	13.81
Signif F	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

†Reference group, § = Coded as 0 = employed, 1 = unemployed, * = p < 0.05. [a] SEK= Swedish crowns, exchange rate 1995 US$=7.30

(except in the age group 60-69 years) as compared with the youngest age group (20-29 years). Those in the age groups 40-49 years, 70-79 years, and 80 years and older had lower role emotional function. Men in the age group 30-49 years and the oldest (80 years and older) scored lower mental health. Women in the age group 60-69 years rated

Table 18. *Results of linear regression analysis of the MENTAL SF-36 dimensions for men and women*

	Vitality		**Social Function**		**Role-emotional**		**Mental Health**	
Explanatory variables	ß-estimate men	women	ß-estimate men	women	ß-estimate men	women	ß-estimate men	women
Constant	68.5*	60.5*	90.1*	87.1*	82.4*	81.2*	79.6*	77.3*
Age								
Age 20-29†								
Age 30-39	-5.4*	-1.2	-4.8*	-1.4	-3.6	1.0	-4.9*	0.1
Age 40-49	-3.7*	0.9	-5.6*	-1.4	-5.2*	1.0	-4.2*	1.2*
Age 50-59	-3.6*	- 2.8	-6.3*	-0.1	-4.4	3.8	-3.5*	- 0.9
Age 60-69	-0.9	- 7.7*	-6.4*	-1.9	-4.0	3.5	-1.2	1.6
Age 70-79	-5.0*	- 4.6	-8.8*	-4.7*	-10.0*	-8.4*	-2.9	0.5
Age 80-	-16.6*	-3.1	-20.7*	-6.3	-30.2*	-9.2	-9.6*	4.5
Education								
Compulsory†								
High school	-1.2	0.6	-0.4	-0.4	-0.9	-1.0	1.3	-0.1
University	-1.5	-1.9	-0.6	-1.6	-1.0	0.6	-1.1	-1.0
Income SEK[a]								
<10 000†								
10-14999	4.4*	1.2	5.4*	2.4*	11.9*	6.8*	5.8*	1.8
15-20 000	7.8*	5.1*	7.8*	3.1*	15.8*	4.5*	8.4*	4.0*
>20 000	8.7*	6.3*	9.6*	3.7	17.5*	2.9	9.8*	5.3*
Social group								
Worker†								
White collar	1.0	0.5	-0.3	-0.6	-1.1	0.3	-0.2	0.7
Self-employed	1.4	2.6	-0.9	0.2	-0.5	3.7	-0.6	1.1
Marital status								
Married/cohabitor†								
Single	-2.5	-0.6	-2.8*	-3.7*	-0.9	-9.4*	-4.0*	-4.9*
Divorced	-5.1*	-9.1*	-5.1*	-9.0*	-6.8*	-11.2*	-6.7*	-10.5*
Widow	-7.1*	-4.7	-1.6	-1.0	-11.2*	-7.2*	-7.2*	-5.3*
Unemployed§	-2.9	0.7	-8.1*	-1.3	-16.8*	-5.9	-9.7*	-5.6*
no obs	1915	2180	1942	2216	1891	2154	1913	2177
R squared	0.05	0.03	0.07	0.02	0.09	0.05	0.08	0.04
Adjusted R squared	0.04	0.02	0.06	0.02	0.08	0.04	0.07	0.04
Standard error	20.31	22.98	17.81	21.52	25.62	31.65	16.74	18.74
F	5.40	4.09	7.94	3.13	11.02	6.00	9.45	5.62
Signif F	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

†Reference group, § = Coded as 0 = employed, 1 = unemployed, * = p < 0.05.
[a] SEK= Swedish crowns, exchange rate 1995 US$=7.30

higher vitality. Social functioning and role emotional were significantly lower for women in the age group 70-79 years.

Income level was related to higher scores in all mental dimensions among both men and women. Neither education nor social group had any significant association, when controlling for all other variables. Being single, divorced, or widowed was associated with lower scores for most domains when compared with married persons or cohabitors. Unemployed men rated significantly lower in social functioning, role-emotional, and mental health, whereas unemployed women only rated lower mental health.

Discussion

Methodological considerations

Surveys

This thesis is based two surveys: the SATSA survey and a general population survey conducted in Uppsala County. Prescription record databases are another source of information used in pharmacoepidemiological research. Prescription records are considered to be more objective than surveys and the data validity is higher. Surveys, however, make it possible to collect important information related to disease and drug use e.g., health-related quality of life data, that is not available in prescription records. Another advantage of survey technique is that persons are likely to report on drugs they actually used. Among disadvantages of self-reports are problems with recall and reporting bias. And, in surveys, detailed information on the drug use, such as types of substances used and doses prescribed, can be difficult to obtain. In surveys relying on self-reports on disease and drug use, it is often not feasible to include extensive diagnostic criteria or drug dosage.

Surveys are often used methods of gathering HRQL data. Questionnaires could either be administered by trained interviewer or self-administered (Guyatt, 1993). Here we use self-administered questionnaires. This approach is less expensive than using interviewers. The disadvantages of self-administered questionnaires are that there is a greater likelihood of low-response rate, missing items, and misunderstanding. The time-trade off method might be especially difficult to understand, and some respondents may be offended by questions about trading life years. The TTO method is usually administered in face-to-face interviews, which decreases errors of misunderstanding. In Paper V, we used a self-administered questionnaire, which may have increased the measurement error in the TTO method used in the study. The disadvantage by using interviews, however, are that they are more resource intensive and they may be biased by the interviewer.

An important problem with surveys is achieving a high response rate and that the non-respondents may differ in some way from the responders so that the results cannot be

generalised to the total population from which the sample is drawn (Sibbald, *et al*., 1994). In the SATSA survey, the response rate of the first questionnaire (Q1) sent out in 1984 was 71 percent. As part of a study of genetic and environmental risk factors for dementia, the non-respondents to the SATSA questionnaires have been thoroughly examined (Pedersen, *et al*.,1989). SATSA consists of an elderly sample, and cognitive impairment was one of several possible mental and physical health reasons for not responding to the questionnaires (Gatz *et al*., 1993; Pedersen, *et al*.,1989). Therefore, those who simply did not want to participate probably represented a small percentage of the non-respondents. The main reasons for non-response to a follow-up questionnaire were debilitating illness or death of the co-twin such that the surviving twin assumes that his/her response is of no value (Paper II).

The response rate in the survey conducted in Uppsala County was lower, 68 percent. In this survey it was not possible to study non-respondents in detail. However, a comparison between those who participated in the survey and the total population in Uppsala County showed that there were no important differences in the distributions on sex, age, marital status, and education level (Antonov, 1997). Other factors, besides those mentioned, may also influence response rate of the questionnaire, which here focused on health-related matters. Non-respondents may include those who were unable to participate due to disability, dementia, illiteracy, or language barriers. Further, persons that perceived themselves as healthy might be less motivated to participate. Thus, measures of disease and drug use might be both over- and underestimated. And, persons with other ethnicity than Swedish are likely to be underrepresented. In 1995, approximately 11 percent of the population in Uppsala County was of foreign birth.

Definitions of cardiovascular disease and hypertension

Respondents with cardiovascular disease and/or hypertension were defined by self-report. Cardiovascular drug users were also identified through self-report. Response bias may be a problem with data relying on self-reports. Self-reports could be validated by comparison of responses with data from the same variables from other sources. The prevalence of cardiovascular disease and hypertension found here are similar to that found in the same age groups in Sweden as a whole, i.e., 40-50 percent and 7 percent, respectively (Socialstyrelsen, 1997).

In Papers I and II, we used several items combined into an index in order to classify individuals as having cardiovascular disease. This index has the advantage of a higher reliability in longitudinal analyses than the single questions on different cardiovascular disorders. By using this index, a broad group of individuals with different cardiovascular disorders and a comparison group free from these diseases were identified.

Cross-sectional data

Causality is a central issue in epidemiology and various criteria for establishing causality have been presented. The criteria presented by Hill are most often cited and include strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy (Hill, 1965). These criteria have been discussed and some have suggested that falsification based on Popper's philosophy should be used instead (Rothman, 1988). However, the temporality criterion, that the cause must precede the outcome, has not been questioned.

In interpreting the results it is important to bear in mind that most studies in this thesis are cross-sectional, and therefore do not provide any information about the direction of causation. Treatment is related to severity of disease; the design and methods used here limit the opportunity to determine the causal relationship between the disease and drug treatment. It may be that disease severity and drug treatment are closely linked, and the bad health found here results from both. It is also often difficult to determine whether side effects perceived by the patient are caused by the disease; complications, side effects from other medication; the knowledge of having a disease, i.e., the "labelling" phenomenon; or some other reason.

Relationship among socioeconomic factors and different aspects of health are also difficult to study in cross-sectional materials due to the healthy worker effect (Östlin, 1989). Less healthy persons may select occupations that are less physically demanding. It may therefore be that low HRQL affects socioeconomic factors rather than the other way round.

In conclusion, the studies in this thesis share the same methodological reservation with most other studies based on information from surveys relying on self-reports. However,

it is also important to emphasise the main advantage, namely that the studies are population based and not based on information from patients visiting physicians that may be subject to selection bias**.** The SATSA survey is one of the most comprehensive, population-based studies with a longitudinal approach in Sweden and as such it provides a good opportunity to study the associations among cardiovascular disease, drug use, self-rated health, and mortality in a natural setting. Further, there is an added benefit of being able to evaluate the result in a co-twin fashion. The survey in Uppsala County provides information on HRQL across a range of domains among individuals suffering from hypertension in a general population.

General discussion

Cardiovascular disease, drug use, and self-rated health

In this study, many factors related to self-rated health were the same among men and women. However, significantly more women than men reported bad health (Paper I). Other studies have also found that women generally tend to report more symptoms than men, in particular depression, headache, insomnia, and dizziness (Chatellier *et al*., 1982; Tibblin *et al*., 1990). This study showed that men with drug-treated cardiovascular disease have lower self-rated health than do women with drug-treated disease. Health surveys have shown that females have higher rates of illnesses, disability days, drug- and health-services use (Verbrugge and Wingard, 1987), but men more often complain of diseases of severe character (Statistics Sweden, 1992). This is one explanation, among others, why men to a greater extent are prescribed newer and more potent cardiovascular drugs (Apotektsbolaget AB, 1999). Further, it may also explain the bad health shown in this study among men with drug-treated cardiovascular disease.

The association between cardiovascular disorders and self-rated health found in this thesis may be explained in different ways: First, a chronic disease may negatively affect self-rated health. Therefore, the poor self-rated health among those with drug-treated cardiovascular disease may be due to worsening of the disease that in turn requires drug treatment. Second, the drug therapy may affect self-rated health. This has been confirmed in other studies that have indicated that self-rated health appears to be reduced in association with cardiovascular drug treatment (Fylkesnes and Førde, 1991; Harlan *et al*., 1986). Further, the co-twin control analyses indicated that cardiovascular

drugs have at most a marginal negative effect on health beyond the effect of the disease and genetic liability to low perceived health. Third, impaired self-rated health may relate to utilisation of health services and use of medication. Self-rated health status is considered as one of the most important determinants for medication use (Furu *et al*., 1997). Persons with poor health are more likely to seek treatment for their symptoms and to have frequent contacts with the health care system (Verbrugge and Ascione, 1987), which increases the likelihood of having drugs prescribed. Fourth and finally, the knowledge of having a chronic disease and being on a lifelong treatment may also affect self-rated health. The literature has suggested that self-rated health represents a summary statement of how various health conditions are perceived by the individual, and that people include various kinds of information on their present and future health when rating their health (Idler and Kasl, 1991). Therefore, besides symptoms and health problems directly experienced by the respondent, information given and action taken by doctors and other medical professions may influence the patient's health rating.

Cardiovascular disease, self-rated health, and mortality

Paper II shows that both cardiovascular disease and low self-rated health were related to higher mortality. The results presented here also indicated that the combination of having both cardiovascular disease and bad self-rated health leads to a higher mortality rate. These findings add credibility to the hypothesis that self-related health is an important predictor of mortality (Appels *et al*., 1996; Kryzyzanowski and Wysocki, 1986; Pijls *et al*., 1993; Wannathee and Shaper, 1991), and that this may also be the case among persons with cardiovascular disease. The results in this study suggest that special attention and care should be directed to persons with cardiovascular disease reporting ill health.

The few existing studies with a longitudinal approach found that self-rated health is quite stable over time (Idler, 1993; Kaplan and Camacho, 1983; Maddox and Douglas, 1973). In Paper II, the analyses of changes in self-rated health showed that the majority of the respondents in 1990 perceived their health to be unchanged between 1984-1990. However, in the study, development of cardiovascular disease and drug use was related to a decline in self-perceived health. The latter findings correspond with reported associations between worsening health conditions, increased medication use, and negative changes in self-rated health (Hershman *et al*., 1995; Rodin and McAvay, 1992;

Svärdsudd and Tibblin, 1990). Thus, self-rated health measurements might be useful tools for identifying high-risk groups among persons with cardiovascular diseases. Moreover, the results showed the highest mortality rate among those with unchanged bad self-rated health.

Surprisingly, mortality was nearly the same among subjects who perceived a change in their health in either direction, improved or worsened. A reason for this might be that there are similarities within the groups. Persons in both groups may perceived changes in their health for some reasons more often, than those with unchanged self-rated health. An explanation for the relatively low mortality, among those with worsened health, might be that they "recently" perceived a decline in their health without any subsequent affection in survival time yet.

A number of explanations may account for the association found between cardiovascular disorders, self-rated health and mortality: A poor self-rated health among those with cardiovascular disease may be due to worsening of the disease or coincident diseases. The results in this thesis showed a significant association between diabetes mellitus and mortality, which also has been shown in epidemiological studies on the elderly (Idler and Kasl, 1991; Gustafsson *et al*., 1998) and in earlier studies of self-rated health and mortality in diabetics (Daschman *et al*., 1994; Hiltunen *et al*., 1996). As mentioned previously, the poor self-rated health among those on medication most likely reflects the increased severity of the disease. A poor self-rated health may also be an indicator of inefficiency of drug therapy resulting in an impaired prognosis of the disease. People's perception of health could also influence their illness behaviour, resulting in low compliance to drug treatment that in turn leads to an impaired prognosis of the disease and earlier death. This has been shown in previous studies indicating that poor perception of health leads to less engagement in preventive practises or self-care (Haug *et al*., 1989; Lamb *et al*., 1990; Rakowski and Mor, 1992).

Self-rated health could also be associated with known risk behaviours for cardiovascular disease and mortality, such as smoking, drinking alcohol, eating a fatty diet, and lack of exercise (Idler and Kasl, 1991; Møller *et al*., 1996; Seeman *et al*., 1993). In this work, neither smoking, alcohol consumption, nor body mass index was related to mortality when included in the multivariate analyses as possible confounders. A reason for this

lack of association could be that detailed information about life style factors can be difficult to obtain in surveys. Another reason could be that persons with cardiovascular disease change their earlier risky behaviour when they get ill. An explanation might also be the rather high age of our study population. Elderly people engage less in risk-taking behaviour or those behaviours are of less importance in older ages. Despite the wide range of ages in this population, the average age can be considered as at least "young-old".

Similarities within twin pairs for illness, perceived health, and mortality, be they genetic or environmental, were controlled for in the co-twin control analyses. The number of MZ pairs was small for many of the comparisons, limiting our power to find significant differences in this group. Because a significant difference remained after controlling for these effects only when MZ and DZ pairs were pooled, the results imply that the influence of cardiovascular disease, drug treatment, and self-rated health remain despite control for genetic and familial influences on these characteristics. Had the results been significant for MZ only, we would have conclusive evidence that these influences (disease, drug treatment, and self-rated health) are important despite complete control for genetic and familial influences.

Hypertension and health-related quality-of-life

The studies in this thesis show that persons with hypertension scored lower on the SF-36, RS, and TTO than did those without hypertension. Although different measurements were used, similar results were found in the studies. This is in agreement with studies that have reported that persons with hypertension have lower health status than do normotensives (Battersby *et al*., 1995; Fernández-Lopépez *et al*., Krousel-Wood and Re, 1994). In some studies, however, it has been argued that the low health-related quality of life among those with hypertension is due to subsequent complications of the disease, not to hypertension itself (Lahad, 1993, Stewart, *et al*., 1989). The Medical Outcome Study in America found that hypertensive patients did not rate lower HRQL than did those without chronic conditions except for general health perception (Stewart, *et al*., 1989). That study also showed that compared with patients with other chronic conditions (e.g. arthritis, diabetes, and back problems), patients with hypertension reported better mental health and better physical, role, and social functioning. In Paper

III, hypertensives reported lower scores than did those without hypertension in most domains in the SF-36 except in role emotional and mental health, even after adjusting for comorbidity.

The results from the studies in this thesis also showed that hypertension mostly influences the general health perception scale, which is assumed to reflect both physical and mental health. Further, this scale is considered to be the SF-36 scale most closely associated with physical illness (McHorney *et al*., 1993; Persson *et al*., 1998; Ware *et al*., 1993). The results found here are consistent with earlier studies analysing health measured by the SF-36 scales among hypertensives (Fryback *et al*., 1993; Lawrence, *et al*., 1996). Similar results also have been shown in clinical-based studies (Lyons *et al*., 1994; Stewart *et al*., 1989).

Hypertension was also related to lower scores both in physical functioning (i.e., limitations in performing physical activities) and role physical functioning (i.e., problems with work or other daily activities as a result of physical health). This finding is not in accordance with the results obtained from clinical-based studies using the SF-36 health survey (Krousel-Wood and Re, 1994; Stewart *et al*., 1989). However, other studies have shown a lower physical capacity among hypertensive individuals than that found in a general population (Fernández-Lopépez *et* al., 1994).

While hypertension is not a disease traditionally associated with bodily pain, this thesis showed such a relationship, which was not shown by other studies using the SF-36 questionnaire (Fryback *et al*., 1993; Stewart *et al*., 1989). There are, however, some clinical studies in which patients with a diastolic blood pressure higher than 100 mm Hg reported symptoms related to pain more frequently than did those with lower blood pressure (Bullpitt *et al*., 1976; Kjellgren *et al*., 1998; Kullman and Svärdsudd, 1990). These observations may reflect an association between disease severity and pain, and disease severity could not be measured in this thesis. Interestingly, in the study by Kjellgren et al., the intensity of symptoms related to hypertension was lower among patients on antihypertensive treatment. Inconsistency between studies might result from differences in study populations and the fact that different scales have been used. It is also possible that hypertension is associated with comorbidity that might contribute to the relationship found between hypertension and bodily pain.

In previous studies in which the SF-36 questionnaire has been used (Fryback *et al*., 1993; Lyons, *et al*., 1994), hypertension was related to lower vitality and mental health. In other studies, hypertensive individuals reported lower social functioning, mood, and psychological functioning than normotensive individuals (Battersby *et al*., 1995; Fernández-Lopépez *et al*., 1994). Hypertension also has been associated with symptoms such as headache, dizziness, depression, anxiety, and tiredness (Kjellgren *et al*., 1998; Mρller *et al*., 1996). In Paper III, hypertension was significantly related to lower scores in two of the scales intended to measure mental health: vitality and social functioning. One explanation for these results, besides perceived symptoms related to hypertension, might be that side effects from antihypertensive medication (such as tiredness, changes in mood, fatigue, and sleep disturbances) contribute to the lower measures (Avorn *et al*., 1986; Currie *et al*., 1988; Dimenäs *et al*., 1989; Isacson *et al*., 1995).

Side effects of antihypertensive drugs and impact on health-state utility

Paper IV shows that side effects from drug treatment are common among persons with hypertension in a general population. Although the frequency of side effects found here was somewhat higher, the types of side effects reported are the same as those found in clinical trials (Curb *et al*., 1988; Dahlöf *et al*., 1991; Hansson, 1994; Hansson and Zancetti, 1995).

Miscellaneous symptoms (such as dry mouth, dizziness, visual disorders, and headache) was the side effect most often reported. Interestingly, emotional distress and impotence had the strongest negative effect on health utility. There is some evidence that women tend to report more varied symptoms--such as general fatigue, headache, and dizziness--than do men (Bengtsson *et al*., 1987). In this work, men and women reported side effects to nearly the same extent. Naturally, only men reported impotence. Among men, impotence was also the side effect resulting in lowest health utility. Earlier studies have reported that impotence is a common and distressing side effect among hypertensive men (Bullpitt *et al*., 1976; Jensen *et al*., 1999). Among women, miscellaneous symptoms had the strongest impact on health utility.

Lower scores in health utilities were found among those with drug use and those with side effects. However, drug treatment was of less importance than that found in previous studies. In reports from some studies it has even been argued that the low values among those with hypertension is due to side effects from drug use and not to hypertension in itself (Battersby et *al*., 1995; Croog *et al*., 1986; Dimenäs, *et al*.1989). It was found here that hypertension has an impact on well being that could not be explained by side effects from drug treatment alone.

Studies using patient health utility assessments to evaluate the effect and side effects of antihypertensives in an unselected population are scarce. Most previous studies used physician-derived utility values. Physician ratings of patient health status and utility may differ from those of the patient (Froberg and Kane, 1989). The studies in this thesis showed somewhat lower scores among hypertensives, both untreated and treated, than those found in previous studies, based on physician judgement (Edelson *et al*., 1990; Kawachi and Malcolm, 1989; Kawachi and Malcolm, 1991). These differences might stem from differences in study populations and from the use of different utility methods. Physicians may also underestimate the burden of hypertension, medication use, and side effects. Some earlier studies have shown little accord between the patient's and the physician's evaluation of treatment and health (Hosie and Wiklund, 1995; Jachuck *et al*., 1982).

Relationship between psychometric measures and health-state utilities

The findings here showed low to moderate correlation between the health utility measures and the SF-36 domains. A similar pattern was found both among hypertensives and non-hypertensives, but overall the corrrelations were lower among the latter. Among hypertensives, 19 percent to 54 percent of the variance in the RS values and 19 percent to 26 percent in the TTO values was explained by the dimensions of the SF-36. In a study on hypertensives by Revicki et al., the RS scores and the SF-36 shared 34 percent of the variance when all scales in the SF-36 were included in the regression equation (Revicki, 1992). In this work, not surprisingly, the different domains in SF-36 were related to the utility measures by different degrees. The dimension most correlated with both health utility scores was the general health perception score. Some earlier studies have also found the general health perception

scale to be the SF-36 scale best correlated with health utilities (Fryback *et al*., 1993; Tsevat *et al*., 1992). As mentioned previously, the general perception scale is assumed to reflect both physical and mental health and is considered to be the SF-36 scale most closely associated with physical illness (McHorney *et al*., 1993; Persson *et al*., 1998; Ware *et al*., 1993). It therefore seems reasonable that the general health perception score is the scale of the SF-36 most highly correlated with a person's preference about "full health" and "death", i.e., health utilities. The role emotional and mental health scales were the domains least correlated with the RS and TTO scales.

Health utility measures and psychometric measures are constructed for different purposes, which could explain the low to moderate association between the SF-36 instrument and the RS and the TTO responses found here. The psychometric measure is designed to provide information along several domains of health-related quality of life. The general purpose of these instruments is to discriminate among levels of functioning between groups and to detect changes in function over time. The utility scales give information on an individual's judgement of health outcomes relative to death and complete health. They are designed for applications in cost-effectiveness analyses and could be useful to policy makers allocating health care resources. But, utility measures may fail to reveal the dimensions of HRQL in which patients improved versus those in which they worsened.

A moderate correlation was also found between the two utility measures, the TTO and RS methods. In the literature, the correlation between utility measures are also reported to be low to moderate (Froberg and Kane, 1989; Hornberger *et al*., 1992; Lalonde *et al*., 1999), which suggests that the different methods are not measuring the same construct. There is still a debate about which method is the most appropriate for use in cost-effectiveness analyses (Nord, 1999; Weinstein *et al*., 1996). For the present time, the use of simpler utility methods, more representative of the participant's health status, (such as the RS) seems justified. The RS method, however, is considered to have a weaker theoretical foundation than the TTO method (Bleichrodt and Johannesson, 1997).

It may be questioned if it is adequate to predict utilities based on a combination of different dimensions of HRQL. An approach in that direction has been to combine the

dimension scores into a single index using an assumed set of weights. A problem with this is that the dimension scores are not measures of utility and have not been based on people's preferences (Brazier, 1995). Another problem is that for use in cost-utility analyses the index would have to be combined with survival to form QALYs (Kaplan and Bush, 1982; Torrance, 1982). Some preliminary work to overcome these problems has recently been carried out by Brazier et al. In that study, the SF-36 was used to derive a utility matrix to predict health-state utilities, which showed promising results (Brazier *et al*., 1998). Psychometric instruments and health utility measures may also be perceived differently by patients. In a prior study on this sample there were reasons to believe that the SF-12, a shorter version of the SF-36, can be converted to health-state utilities, but that further work is required to reliably estimate the conversion function (Lundberg *et al*., 1999). There is not a simple way to convert one measure into another.

Socio-demographic factors and health-related quality of life

This thesis showed that most sociodemographic factors related to self-rated health and HRQL were of similar importance among men and women. However, the results presented here correspond with the findings in other studies that women generally report worse health and HRQL than do men (Fryback *et al*., Hemingway *et al*., Sullivan and Karlsson, 1998). Explanations of sex differences in health status have been viewed from different perspectives. Both biological and sociological explanations concerning physical health have been postulated. Verbrugge divided causes into 1) Biological risk, 2) Acquired risks, 3) Psychosocial aspects of symptoms and care, 4) Health reporting behaviour and 5) Prior health care and caretakers as causes (Verbrugge, 1985). Men have been suggested to have higher biological and acquired risk, while various psychosocial aspects (e.g., higher sensitivity and better recall of symptoms, higher acceptance of help seeking, and adoption of sick-role), higher health reporting behaviour and prior health care use contribute to a higher morbidity for women. But, even after controlling for likely causes gender has been shown to remain an important predictor of health care use, indicating that unidentified gender-related factors exist (Cleary *et al*., 1982; Green and Pope, 1999). However, it has been argued that different aspects of quality of life are important to men and women (Dibble *et al*., 1998). It might be that existing instruments do not capture these differences, and that gender specific instruments would give a different picture of gender differences in HRQL.

Further in this thesis, older age resulted in worse health-related quality of life in the SF-36 scales reflecting physical health, i.e., physical functioning, role physical, bodily pain, and general health, while this was not apparent in scales reflecting mental health, i.e., vitality, social functioning, role emotional, and mental health. There were greater differences between younger and older ages in physical health than in mental health. Similar results have been shown in the Swedish normative population (Sullivan and Karlsson, 1998), and in some previous studies analysing changes in SF-36 scales with increasing age (Hemingway *et al*., 1997; Jenkinson *et al*., 1993). An explanation for these results might be that older adults have a greater sense of mental control than do younger and middle-aged adults (Lachman and Weaver, 1998).

The studies here also showed an impact of socio-economic factors on health-related quality of life. The results are in accordance with the findings in other studies, using the SF-36 as well as other measures (Bengtsson *et al*.,1987; Fryback *et al*., 1993; Lawrence *et al*., 1996; Tibblin *et al*., 1990a). Lifestyle differs among social groups, with healthier life styles associated with higher status employment, and this might explain the higher HRQL among those in a high social group and with high income (Marmot *et al*., 1991).

Concluding remarks

The self-rating of health is an important psycho-social parameter in the evaluation of health status, in determining the prognosis of cardiovascular disease, in choosing drug treatment, and in analysing survival. There are, however, several other possible factors and intermediate variables not included in the studies in this thesis, that might explain the association among cardiovascular disease, self-rated health, and mortality (Idler and Benyamin, 1997). Therefore, future research on what lies in the concept of self-rated health and its prediction of mortality is of great interest. The accumulated results of studies on self-rated health and mortality have implications not only for future research but also in clinical practice.

This thesis suggested that special attention and care should be directed to persons with cardiovascular disease and/or hypertension reporting ill health. This especially is important given that low HRQL can be a riskfactor for subsequent cardiovascular

events or complications (Mρller *et al*., 1996; Svärdsudd and Tibblin, 1991; Weiler , 1989), which in turn might result in higher mortality rate.

It is obvious that antihypertensive treatment is lifesaving and also necessary in order to limit the complications of the disease. Therefore it is important that the treatment is well tolerated. Side effects from drug treatment and resulting lower quality of life may have a negative effect on compliance. The findings here stress the importance of considering side effects when evaluating drug treatment for adjustment or change.

Considering that side effects are the most common reason for changing drug therapy in clinical practice (Richardson *et al*., 1993; Wallenius, *et al*., 1995), the frequency of side effects in this thesis was higher than was expected. Future research should also examine to what extent side effects are known by physicians and how they deal with them. The extent, consequences, and costs of drug-related morbidity have been much discussed lately (Bootman *et al*., 1997; Lazarou *et al*., 1998). It is therefore important to further analyse the progress of the disease, and the initiation, continuation, and change in drug therapies.

Health utilities and psychometric measures represent different attributes of health. It is important to be aware of the differences between psychometric and utility measures when interpreting results from studies using different methods. Both measures are valuable for the evaluation of medical treatment and could be useful to patients, individual practitioners, and to health policy decision-makers selecting among alternative medical treatment.

Summary

In summary the studies in this thesis showed that:

- Persons who have cardiovascular disease, both with and without drug use, perceived and reported poor health to a different extent than did others without these features.

- Both cardiovascular disease and low self-rated health were related to higher mortality. The results added credibility to the hypothesis that self-related health is an important predictor of mortality.

- Cardiovascular drugs had a marginal negative effect on health beyond the effects of the disease and genetic liability to poor self-perceived health. This implies that there are other factors, besides genetic influences and cardiovascular drugs, important for health. The co-twin control analyses also suggest that drug-treated cardiovascular disease has a marginal effect on survival beyond the effects of bad self-rated health and genetic liability to a certain survival time.

- Persons with hypertension had lower health-related quality of life than did those without hypertension. Further, like individuals with other chronic conditions, those with hypertension were not uniformly limited in all health status domains.

- Side effects from drug treatment were common among persons with hypertension in a general population, and hypertensives reported variety of side effects. Both the disease and the drug treatment had an impact on the patient's health-state utility. However, drug treatment was of less importance than that found in previous studies.

- Health utilities and psychometric quality-of-life instruments were moderately correlated among hypertensives and non-hypertensives. The relationship between the dimensions in the Short Form (SF) 36 questionnaire and the rating scale (RS),

were stronger than for the time trade off (TTO) method. The results also showed a moderate correlation between the TTO and RS methods.

- Inequalities in health-related quality of life (HRQL) were present with respect to several sociodemographic factors. Women generally reported worse health and HRQL than did men. Older age resulted in worse HRQL in the SF-36 scales reflecting physical health, while this was not apparent in scales reflecting mental health. There were greater differences between younger and older ages in physical health than in mental health.

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ERRATA

Summary, p. 21, fourth paragraph, lines 5 and 10: "…the independent variable…" should be "…the dependent variable...".

Summary, p. 40, fourth paragraph, line 2: "…symptoms and emotional distress…" should be "…symptoms, emotional distress, and impotence…". Line 3: "…lowest value -9.1 was found for emotional distress…" should be "…lowest value -14.0 was found for impotence…". Lines 5 and 6: "…(-11.2)…" "…(-8.2)…" should be "…(-17.0)…" "…(-9.2)…"

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