Aspects of Health-Related Quality of Life

Associations with psychosocial and biological factors, and use as patient-reported outcome in routine health care

Evalill Nilsson

Department of Social and Welfare Studies & Division of Community Medicine, Department of Medical and Health Sciences Linköping University, Sweden

Linköping 2012
To Ulf, Marcus & Oscar

Allting är svårt innan det är enkelt
## CONTENTS

ABSTRACT ................................................................................................................................. 1

LIST OF PAPERS ....................................................................................................................... 3

ABBREVIATIONS ..................................................................................................................... 5

INTRODUCTION ......................................................................................................................... 7
  The concept of Health-Related Quality of Life ................................................................. 7
  Determinants of Health-Related Quality of Life ............................................................ 12
    Models of Health-Related Quality of Life ................................................................. 13
    Health-Related Quality of Life as a determinant of mortality ..................................... 15
  Measures of Health-Related Quality of Life ................................................................. 19
    EQ-5D ................................................................................................................................. 20
    SF-36 ............................................................................................................................... 22
  Health-Related Quality of Life as patient-reported outcome in routine health care .......... 24
    Usefulness of measures of Health-Related Quality of Life ........................................ 25
  Aims of the thesis ................................................................................................................. 28

METHODS .................................................................................................................................. 29
  Papers I and II ..................................................................................................................... 29
  Paper III ............................................................................................................................... 32
  Paper IV ............................................................................................................................... 34

RESULTS .................................................................................................................................... 36
  Associations of Health-Related Quality of Life with psychosocial and biological factors .......................................................................................................................... 36
  Use of Health-Related Quality of Life as a patient-reported outcome in routine health care ......................................................................................................................... 39
DISCUSSION .................................................................................................................. 43
  Associations of Health-Related Quality of Life with psychosocial and biological factors .................................................................................................................. 43
  Use of Health-Related Quality of Life as patient-reported outcome in routine health care .................................................................................................................. 46
    Measurement of Health-Related Quality of Life as an innovation ................. 49
  Methodological discussions ............................................................................... 51
  Summary .................................................................................................................... 55
  Conclusions ............................................................................................................. 56
  Future directions .................................................................................................... 57

ACKNOWLEDGEMENTS ............................................................................................ 58

REFERENCES ............................................................................................................ 59
Abstract

Background Health-related quality of life (HRQoL) is increasingly recognised as an important patient-reported outcome in health care research. However, the use is still restricted and several questions remain about the value and feasibility of using measures of HRQoL in routine health care. The general aims of the thesis were therefore to increase the understanding of these issues by studying 1) associations of HRQoL with psychological and biological factors, 2) comorbidity adjustments of HRQoL measurement results, and 3) the patient-perceived value and feasibility regarding the use of measures of HRQoL as patient-reported outcome in routine health care.

Methods Three different data sets were used; baseline data (questionnaire, anthropometric, and biological) from the ongoing Life conditions, Stress, and Health Study (n=1007, papers I and II), data from a population survey from the County Council of Östergötland in combination with data from two national Swedish registries, the National Inpatient Register and the Causes of Death Register (n=6086, paper III), and data (questionnaire) from the multicentre Swedish Health Promoting Hospitals Network Health outcome assessment project (n=463, paper IV). The HRQoL measures used were the SF-36 and the EQ-5D. Statistical methods include variance, correlation and regression analyses.

Results Psychological resources (Self-esteem, Sense of Coherence, and Perceived Control) as well as psychological risk factors (depressive mood) were found to relate independently to HRQoL (SF-36) in the expected directions (positive relations for resources and negative relations for risk factors), but with fewer sex differences than expected (Paper I). Low HRQoL (SF-36) was found to relate to higher levels of inflammatory biological factors (C-reactive protein, Interleukin-6, and MatrixMetalloProteinase-9), and, especially regarding Interleukin-6, many association remained significant, though attenuated, after adjustment for factors of known importance to HRQoL (age, sex, disease, lifestyle and psychological factors) (Paper II). A new comorbidity index, the Health-related Quality of Life Comorbidity Index (HRQL-CI), explicitly developed for use in HRQoL outcomes studies, showed higher explanatory power (higher R² values) than the commonly used Charlson Comorbidity Index (CCI) regarding impact of comorbidity on
HRQoL (SF-36 and EQ-5D). However, regarding mortality the CCI discriminated better between those who died within a year from answering the HRQoL questionnaires, died within ten years, or who were still alive after ten years. This result is in line with the CCI’s original purpose as a mortality predictor. Using morbidity data from mandatory, highly valid national health data bases was found to be useful in a large study of this kind, where using data from medical records might be impractical. (Paper III). Using measures of HRQoL as patient-reported outcome measures in routine health care was regarded as valuable by the majority of the patients in the Health outcome assessment project. A new concept was introduced, respondent satisfaction, and the respondent satisfaction summary score was in most cases equal, i.e. SF-36 and EQ-5D were found to be quite similar regarding the cognitive response process (understanding and responding to the items in the EQ-5D and the SF-36) and patient-perceived content validity (if EQ-5D and SF-36 gave patients the ability to describe their health in a comprehensive way) (Paper IV).

Conclusions The four papers investigated different aspects of HRQoL that are important for the implementation of the use of measures of HRQoL within the health care system. In conclusion, 1) the use of measures of HRQoL to identify patients with low HRQoL for further health promoting interventions might be supported on a psychological (psychological resources are related to better HRQoL) and biological basis (low HRQoL being an important sign of increased biological vulnerability), 2) a comorbidity index specifically aimed to adjust for comorbidity in patient HRQoL outcomes studies was found to be valid in a normal population (that might serve as a reference population in future studies), and 3) patients perceived the use of measures of HRQoL to be valuable and feasible in routine health care, and questionnaire length and ease of response were not found to be crucial arguments in the choice between SF-36 and EQ-5D. Hence, in their own way, they all and together, contribute to removing obstacles in the implementation process of using patient-reported outcome measures in the health care system for quality improvement.
LIST OF PAPERS

Paper I

Paper II
Nilsson, Garvin, Ernerudh & Kristenson. Associations between SF-36 and inflammatory biomarkers CRP, CXCL8, IL-1β, IL-6, IL-10, and MMP-9 in a normal middle-aged Swedish population.

Paper III
Nilsson, Borgstedt Risberg, Orwelius, Unosson, Sjöberg & Kristenson. Impact of comorbidity on health-related quality of life; a population-based study using the Charlson Comorbidity Index and the new Health-Related Quality of Life Comorbidity Index, with data from the Swedish National Inpatient Register.

Paper IV
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BP</td>
<td>Bodily Pain</td>
</tr>
<tr>
<td>CCI</td>
<td>Charlson Comorbidity Index</td>
</tr>
<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies Depression scale</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQol - 5 Dimensions</td>
</tr>
<tr>
<td>FIT</td>
<td>Feedback Intervention Theory</td>
</tr>
<tr>
<td>GH</td>
<td>General Health</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamus-Pituitary-Adrenal</td>
</tr>
<tr>
<td>HPH</td>
<td>Health Promoting Hospitals</td>
</tr>
<tr>
<td>HRQL-CI</td>
<td>Health-Related Quality of Life - Comorbidity Index</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases and causes of death</td>
</tr>
<tr>
<td>LSH</td>
<td>Life conditions, Stress and Health</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental Component Scale</td>
</tr>
<tr>
<td>MH</td>
<td>Mental Health</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Matrixmetalloproteinase – 9</td>
</tr>
<tr>
<td>NHP</td>
<td>Nottingham Health Profile</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical Component Scale</td>
</tr>
<tr>
<td>PF</td>
<td>Physical Functioning</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RE</td>
<td>Role functioning – Emotional</td>
</tr>
<tr>
<td>RP</td>
<td>Role functioning – Physical</td>
</tr>
<tr>
<td>SF</td>
<td>Social Functioning</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form - 36</td>
</tr>
<tr>
<td>SIP</td>
<td>Sickness Impact Profile</td>
</tr>
<tr>
<td>SOC</td>
<td>Sense of Coherence</td>
</tr>
<tr>
<td>SRH</td>
<td>Self Rated Health</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VT</td>
<td>Vitality</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
INTRODUCTION

The concept of Health-Related Quality of Life

Health-related quality of life (HRQoL) is a term that is being increasingly used in the medical scientific literature. A literature search using the search term “health-related quality of life” yielded 18812 hits on the 1st January 2012 (Table 1). There is an increase both in the number of articles about studies using HRQoL as patient-reported outcome (the patients’ view of their health and the results of the care given) and in articles discussing the concept in different ways, including guides about how to choose the proper HRQoL measure.

Although numerous studies claim to have measured HRQoL, their authors do not always explain what it is the term connotes (stands for). Mostly the authors let HRQoL denote (refer to) the measures used, or they just use the term without offering much of an explanation, as if it were common knowledge and not in need of further clarification.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Number of hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979 and before</td>
<td>0</td>
</tr>
<tr>
<td>1980-1989</td>
<td>15 (the first in 1982)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>1695</td>
</tr>
<tr>
<td>2000 and after</td>
<td>17102</td>
</tr>
<tr>
<td>whereof in 2010</td>
<td>2110</td>
</tr>
<tr>
<td>whereof in 2011</td>
<td>2511</td>
</tr>
<tr>
<td>In total on the 1st January 2012</td>
<td><strong>18812</strong></td>
</tr>
</tbody>
</table>

The term HRQoL is a combination of two other terms, namely Health and Quality of Life (QoL). Numerous definitions of both these terms have been presented over the years. Therefore, health is a vague term, and/or a term with various meanings, i.e. it has several connotations. It is also a general term since
it lacks a reference, i.e. has no denotation [1]. However, two main views on health can be clearly distinguished, the biomedical and the humanistic. The biomedical view can today be said to be dominated by Christopher Boorse’s biostatistical definition [1]. In short, according to this definition health connotes body and mind functioning according to, for human beings, typical, statistically normal patterns, i.e. having no biomedical dysfunction. The most prominent of the humanistic views is the holistic view, where health often connotes well-being or ability (under reasonable circumstances) to function and achieve vital goals [1], irrespectively of having a biomedical dysfunction or not.

The internationally most well-known and influential definition of health is the WHO (World Health Organization) definition\textsuperscript{1} from 1948 which states that health is “a state of complete physical, mental and social well-being, and not merely absence of disease or infirmity”. To include not only physical but also mental and social aspects provides a holistic view of health that was considered quite radical at the time, not at least because these aspects were regarded as going beyond the responsibility of the health care system.

One demand that can be made on a definition is that it should be able to operationalise, i.e. be able to measure [2]. To measure health according to the WHO definition, traditional medical survival and disease specific data were not sufficient. The emphasis of the definition of health on well-being led researchers to the QoL research area, where measures were already available. In ordinary (Swedish) dictionaries the concept of HRQoL is not acknowledged; nor, in many cases, is the concept of health. However, QoL is defined as non-material, positive contents of life [3]. While health is considered an ancient concept, the term QoL was coined in the early twentieth century, as a political term [4]. Soon a need for accurate measures of QoL emerged, which led to the development of several QoL questionnaires. In the 1990s, WHO decided to develop an international measure of QoL, the WHOQOL-100, and some years later also the shortened WHOQOL-BREF [5]. During this work, the preceding process of concept clarification resulted in the WHO definition of QoL as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a

\textsuperscript{1}Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19 June - 22 July 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948. The definition has not been amended since 1948.
complex way by the person’s physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment”.

Brülde and Tengland have discussed the connection between health and QoL, and argue for differentiating between the concepts. Even if both concepts are related to well-being, and both are often improved when well-being is improved, there may still be improvements that are not health-related, e.g. in the areas of love and work. Furthermore, even if the most important associations between health and QoL are causal and a better health will often lead to better QoL, the opposite might not hold true [1]. In his book “Teorier om livskvalitet” (Theories on quality of life) Brülde further discusses how QoL, just like health, has several connotations [6]. Patients themselves, in their role as respondents to different measures of health status, QoL, and HRQoL, have been reported to consider health status and QoL to be distinct constructs, including more mental health aspects in the latter than in the former [7].

How did we move from the two terms Health and Quality of life to the compound term Health-related quality of life? Many researchers, in the 1980s as well as today, have reported about the confusion about the use of the terms [4, 8]. According to Guyatt et al, the term HRQoL was introduced to solve the problem that QoL denotes a variety of medical as well as non-medical things. The term HRQoL was intended to narrow the focus to the effects of health, illness and treatment on QoL [9]. As a renowned researcher in the field, John E Ware, puts it [8, 10]: “To distinguish the new multidimensional conceptualisation of health from the old (i.e. health in terms of death and disease), the term quality of life was adopted. It became fashionable to lump all measures that defines health beyond traditional indicators of biological functioning into a single category of quality of life measures. However, quality of life as traditionally defined is a much broader concept than health. Quality of life encompasses standard of living, quality of housing and neighbourhood, job satisfaction, health, and other factors. The goal of the health care system is to maximize the health component of quality of life, i.e. health status, also referred to as health-related quality of life.”

Therefore, according to Ware, the terms HRQoL and health (when defined as physical, mental and social well-being and functioning) can be regarded as synonyms.

How do researchers using measures of HRQoL in their research define the term HRQoL? When the term was quite new researchers would presumably have been very accurate in describing what they meant by it, so looking at the
earliest articles from the 1980s might provide the answer. Five of the articles contained brief mentions in the abstract about definitions and/or use of the term HRQoL. Two examples:

- “Quality of life is a broad concept that incorporates all aspects of an individual’s existence. Health-related quality of life is a subset relating only to the health domain of that existence.”[11]
- “HQOL is a multi-dimensional concept that includes the physical, psychological, and social functioning associated with an illness or its treatment.”[12]

This observation, together with the content of the other abstracts implies that the concept was not regarded as altogether new. Moreover, in the full-text articles an explanation was not always present. One example:

- “Over the last 15 years, medical and health services researchers have developed new ways to assess health status quantitatively. These measures are often called quality of life measures. Because they are used exclusively to evaluate health status, the more descriptive health-related quality of life is preferred.”[13]

As a contrast the latest articles found using the term “health-related quality of life” were also collected. On the 1st January 2012, 29 articles had already been registered for the year 2012. In only one of these abstracts was the meaning of HRQoL mentioned. Moreover, in the full-text articles it often seems to be taken for granted that the definition of HRQoL is common knowledge. A striking feature is that measures of HRQoL are often mentioned by name directly in abstracts, without stating that they measure HRQoL. Could the definition of HRQoL in many cases perhaps have become an operational definition (describing how to decide if the phenomenon exists instead of stating the characteristics of the phenomenon), i.e. your HRQoL is low because you score low on the measure of HRQoL, and vice versa? Perhaps HRQoL has in many people’s eyes become synonymous with that which we measure with the common measures of HRQoL used today?

The impact of disease (and treatments) on QoL seems to be imperative in many definitions and descriptions of HRQoL, probably due to its origin in patient-related studies. Does that imply that, in many cases, HRQoL is in fact DRQoL, i.e. disease-related quality of life? Is seeing HRQoL as impact of
disease really compatible with seeing health and HRQoL as synonyms (provided that you see health as more than the absence of disease)? However, HRQoL is also used outside the context of disease, e.g. as a subjective measure in population studies. Does this custom in fact imply two different connotations of HRQoL? That is, as an impact of disease vs. as well-being and functioning in general, independent of any disease?

The lack of consensus about a definition of the term HRQoL is sometimes regarded as a problem. Though some call for a universal definition of HRQoL, most researchers seem to use the term in their articles without reflecting upon its meaning, and also sometimes use the terms health (or health status), QoL and HRQoL interchangeably. It is probably as difficult to find a consensus definition for HRQoL as it is for health (and quality of life), and maybe it would not be necessary if everyone always clearly stated what they were referring to, when using the term(s). In “Teorier om livskvalitet” Brülde calls attention to the fact that within the health care system the term QoL is not used in the traditional philosophical way, distinguishing between final (a goal, e.g. happiness) and instrumental (a means to achieve your goal, e.g. money) values. Instead the outcome perspective of the health care system has resulted in “all” psychosocial factors indiscriminately being called QoL or HRQoL. Consequently the concepts of QoL and health (defined holistically) tend to become blurred. Furthermore, without being based on formal definitions and well thought-out theories, final and instrumental values may without deeper reflection become mixed into the same measure, which, Brülde claims, is often the case today [6].

In the present thesis HRQoL is defined as physical, mental and social wellbeing and functioning, in line with the comprehensive WHO definition of health. HRQoL might then be seen as the patient-reported part of the WHO definition, if absence of disease or infirmity is the profession-reported part, based on medical diagnoses.
Determinants of Health-Related Quality of Life

Determinants of HRQoL have been much studied, especially in patient-based research. HRQoL is influenced by a number of sociodemographic, psychosocial as well as lifestyle and biomedical factors. A related area of interest is the observation that HRQoL itself may in turn be a determinant of mortality.

Sociodemographic determinants
The impact of sociodemographic factors such as socioeconomic status, ethnicity, marital status, sex, and age on HRQoL is now well established and consequent [14]; low socioeconomic status, immigrant status, and single/nonmarital status are all related to poorer HRQoL. However, one problem is that many of these determinants are interrelated and may act as proxies for each other; for example, ethnicity might be a proxy for socioeconomic status. However, ethnicity has been shown to have an (independent) association with HRQoL among persons of dissimilar ethnicity, but sharing the same sociocultural context [15]. Furthermore, determinants may have varied importance in different age periods [16], and it has been shown that younger people have fewer problems in the physical than in the mental dimensions of HRQoL, but for the elderly it is the other way around [17].

Regarding sex, it is today recognised that women often receive lower scores on measures of HRQoL than men [18]. One possible explanation is that men and women think about different things when they assess their own health. Women have been suggested to be more inclusive than men, or at least to put different emphasis on things though including the same things. While men tend to rate disease, lifestyle and function ability as most important, women tend to give more weight to emotional factors that are not always disease-related [19]. Another possibility is of course that women in fact have a lower HRQoL, perhaps due to worse life conditions and/or a more vulnerable social role (gender research) [20, 21]. Nevertheless, many studies of HRQoL only adjust for the effect of sex, and differences between men and women are seldom further explored.
Psychosocial determinants
Several types of psychosocial factors have been suggested to influence HRQoL [14]. Psychosocial factors may be divided into extrinsic (social environment, social support) and intrinsic (individual, psychological characteristics). The latter, in turn, can be subdivided into 1) those resources that enhance health and HRQoL, and 2) factors associated with increased risk of disease. Such risk factors include negative emotions (e.g., anxiety and depression) and cognitions (e.g., hopelessness and hostility), while coping ability, sense of coherence, and perceived control over life are examples of resources [14]. Many studies have shown that psychological resources are positively related to patients’ HRQoL, while psychological risk factors are negatively related [22-31], but there are few population-based studies [32-34].

Lifestyle and biomedical factors
Studies regarding the influence of lifestyle factors (i.e., smoking, physical activity, etc) on HRQoL are still in dispute and no firm conclusions can be made at present [35-40].

The presence of disease has, maybe self-evident for many people, repeatedly been shown to have an inverse relation to HRQoL [17, 41-46], and medical symptoms such as pain (which is probably the most common symptom in a general population) are also known to relate to a poorer HRQoL [47, 48]. However, if the main objective of health care is to optimise the HRQoL for each patient, it may not be that self-evident for presence of disease and medical symptoms to invariably have a negative impact on HRQoL?

Models of Health-Related Quality of Life
In 1995, Wilson & Cleary developed a causal model of HRQoL [49]. This was prompted by the need for a model that could be used in planning health care interventions to improve patients’ HRQoL, indicating the relations between the determinants as well as identifying them. The Wilson & Cleary model was further revised by Ferrans et al in 2005 [50]. This revised model presents five ordered domains of patient outcomes, from biological function (e.g. presence of disease) via symptoms, functional status, and general health perceptions to overall quality of life, implicating a one-way main causal relation. The characteristics of the individual (demographic, biological, e.g. genetics, and
psychological factors) as well as characteristics of the environment (social and physical factors), are furthermore described to affect, in a one-way direction, all of the five outcomes, thereby completing the model (Figure 1).

![Causal model of HRQoL]

**Figure 1.** Causal model of HRQoL, revised by Ferrans et al (2005) from the original model by Wilson & Cleary (1995). Reprinted with the permission of publisher John Wiley and Sons.

However, though claiming to be a model of HRQoL, the term is actually not visible in the model. Instead the term used is QoL, which may be an example of the confusion in the usage of the terms described earlier (chapter - The concept of Health-Related Quality of Life). Furthermore, lifestyle factors are not explicitly included in Characteristics of the individual, which may be the most reasonable box to place them in.

The Wilson & Cleary model has furthermore been criticised for over-emphasising the influence of what the authors refer to as health-related factors (the factors in the central boxes) on QoL [51]. According to Anderson & Burckhardt [51], such factors only have indirect effects on QoL, while psychosocial factors exert direct effects, and therefore should be in the centre of the model. Moreover, Anderson & Burckhardt raises the issue of QoL as a suitable outcome for health care. If so interventions ought to address psychosocial factors to a greater extent, in order to better achieve the goal of improved QoL of patients. According to the authors, the medical interventions of today, which are mainly directed towards disease symptoms and functional ability, will only affect QoL if they first result in changes in self-perception, perceived social support etc.
Though the best known, the Wilson & Cleary model is not the only model of HRQoL. For example, Ashing-Giwa [52] argues that models of HRQoL should have a stronger focus on ethnical and cultural differences than is the case today. Valderas & Alonso [53] has presented a model based on the Wilson & Cleary model together with the WHO classification systems ICD (International Classification of Diseases and causes of death) and ICF (International Classification of Functioning, disability and health). In their model the final right box is actually changed from QoL to HRQoL, but also expanded to contain other related outcomes, such as satisfaction with care and resilience (coping ability, handling stress and illness). The intention behind the development of this model was that it should constitute a conceptional basis to support the choice of patient-reported outcome (as represented by the four boxes Symptoms, Functional status, General health perceptions, and Health-Related Quality of Life).

Health-Related Quality of Life as a determinant of mortality

The final outcome of the Wilson & Cleary/Ferrans model is QoL (HRQoL). However, low HRQoL has been shown to predict mortality [54-56], similarly to what earlier was shown for low self-rated health (SRH) [57, 58], a term used to denote a single-item measure of global health, in contrast to the use of multi-dimensional, multi-item measures of HRQoL [59].

Regarding SRH, four main hypotheses exist to explain its ability to predict mortality, even after adjustment for present disease [58].

- SRH catches symptoms from yet undiagnosed diseases and unmeasured illness or specific co/multimorbidity concerns
- SRH measures the anticipated future health (health trajectories)
- low SRH is related to poorer health behaviour (including lifestyle factors)
- SRH reflects pathological psychosocial stress

Are the same hypotheses applicable to the wider concept of HRQoL? If so, to all dimensions or just some? While SRH allows the respondent to be as inclusive as he or she wishes, most measures of HRQoL contain the dimensions assumed by researchers and health professionals to be relevant for
the patients (as further discussed in the chapter Measures of Health-related Quality of Life).

**Psychoneuroimmunology**

Regarding the above hypothesis that low SRH (and low HRQoL?) predicts mortality because it reflects psychosocial stress, knowledge from the field of psychoneuroimmunology about behavioural-neural-endocrine-immune system interactions [60], might shed some light on the matter. Psychosocial stress and negative emotions are known to predict illness and mortality [61], but they are also related to increased levels of inflammatory cytokines, *e.g.* interleukin (IL)-1β and IL-6 [62, 63].

**Interleukins**

The name interleukin was originally given to cytokines secreted by, and acting on, leukocytes. Cytokines are low molecular weight proteins secreted by cells to regulate other cells, in either an autocrine (acting on the cell that secreted it), paracrine (acting on nearby cells) or endocrine (acting on distant cells through spreading via the blood circulation) fashion. Cytokines can be categorised in families according to function or structure. They may affect both the innate and the adaptive immune systems [64].

Interleukin (IL)-6 is a monomer made up of 184 amino acids and belongs structurally to the hematopoetin family [64], and is secreted by T-cells, macrophages and endothelial cells. Activators of the IL-6 gene expression include IL-1β and Tumor Necrosis Factor (TNF) α [65]. Together these three (IL-1β IL-6 and TNFα) are known as the pro-inflammatory cytokines [64]. However, they also seem to have anti-inflammatory qualities, and furthermore seem to both up- and down-regulate each other [66, 67]. The facts that the regulation of IL-6 seems very complicated and that elevated levels of IL-6 is implicated in several diseases, such as cardiovascular disease, cancer, diabetes mellitus/insulin resistance, and rheumatoid arthritis [68], imply a strong need for the body to keep this potent interleukin under strict control. IL-6 induces, among other things, the production of acute-phase proteins from the liver, such as the C-reactive protein (CRP). CRP opsonises bacteria by binding to the phosphorylcholine portion of lipopolysaccharides in the bacterial cell-walls. It also activates the classical complement (C) cascade, by binding to cascade
factor C1q [64]. Though the effects of CRP in some instances can be regarded as echoing those of IL-6, CRP and IL-6 also have their own properties.

Upon activation of the hypothalamus by the pro-inflammatory cytokines the so called “sickness behaviour” is provoked, affecting, among other things, sleep, eating behaviour and mood states, making a person experience feelings of “sickness”, discomfort and low energy [69]. The hypothesis is that elevated levels of the pro-inflammatory interleukins are meant to lead to behaviour changes in order to keep the body out of danger until it has recovered, i.e. you should crawl back to your cave and rest, not engage in new fights or exhausting food searches. Interestingly, the same kinds of symptoms are associated with low SRH [70, 71], which in turn is known to correlate with IL-1β and/or IL-6 [70, 72, 73].

Furthermore, IL-1β and IL-6 activate the HPA (hypothalamus-pituitary-adrenal)-axis, a system that is also known to be activated during stress, leading to an increase in the cortisol production in the adrenal cortex. Cortisol, in turn, has an anti-inflammatory effect, through inhibiting the production of the pro-inflammatory interleukins. However, prolonged stress could presumably lead to down-regulation of cortisol receptors, or otherwise interfere with normal HPA axis/cortisol responses, with a subsequent chronic, low-grade inflammation as a result [71, 74]. This inflammation is called low-grade because the production of cytokines during prolonged stress does not reach the same high level as during the response to microorganisms, rather it stays at a maximum level of 3-5 times the normal. Though the stress reaction is necessary for survival in acute stress situations, the pro-inflammatory effects of a dysfunctional HPA-axis during prolonged stress are potentially harmful, as elevated levels of cytokines are implicated in the pathogenesis of several diseases (see above) and have been found to predict mortality in older people, independently of the presence of disease [75, 76].

**Inflammation and health-related quality of life**

Studies so far about the relation between inflammatory biomarkers and HRQoL have mainly been patient-based, and often relatively small. Besides IL-1β and IL-6, other cytokines investigated in these studies are for example IL-10, a general inhibitor of inflammatory reactions, and the pro-inflammatory chemokine CXCL8 (chemokine (C-X-C motif) ligand 8, formerly known as IL-8). Although some significant associations have been found for cytokines and measures of HRQoL in some of the studies, the results are still inconclusive.
and no trend is discernible [77-87]. Similarly, inconclusive results have also been found regarding the relation between HRQoL and CRP [83, 88-91].

Another inflammatory biomarker of theoretical interest since it has recently been shown to have an association to all-cause mortality [92], is the matrix metalloproteinase 9 (MMP-9), an extra-cellular matrix degrading enzyme. MMP-9 has shown high activity in inflamed atherosclerotic plaques, implying a role in plaque instability and ischemic cardiac disease [93-96]. The enzyme is up-regulated by inflammation, and higher MMP-9 levels have been related to poorer lifestyle and psychosocial status [97, 98], but it has not been studied in the HRQoL context.

The first box in the causal Wilson & Cleary/Ferrans model of HRQoL is *Biological function*. The content of this box is only generally described, but more biologically detailed models are available. McCain et al have presented a PsychoNeuroImmunoology (PNI) framework to explain how psychological stress and coping relate to health outcome (in this case quality of life, psychosocial functioning, and physical health), via the neuroendocrine and immune systems, in that order [99]. The N (both the HPA and the Sympathetic-Adrenomedullary systems) and the I (interleukins etc.) components are regarded as mediators, while the P component is seen as a moderator. Just as in the Valderas & Alonso model, the framework is intended to provide a guide for both interventions and measurement regarding chronic and severe diseases, facilitating a holistic view of health and disease management, as exemplified by McCain et al in the cases of cancer and HIV (human immunodeficiency viral) disease.
Introduction

Measures of Health-Related Quality of Life

Today, there is an abundance of so-called HRQoL-instruments (validated questionnaires), either generic, i.e. measuring general health problems, or disease-specific, i.e. measuring health issues of vital importance for a certain disease or condition. The former allows the possibility of comparing different patient groups, and may give answers to questions about the patient’s situation that nobody has thought to ask, while the latter may be necessary to cover all disease symptoms and functional limitations of already known importance for a certain disease. However, it has been argued that this distinction is actually less clear-cut, since many of the disease-specific instruments contain generic domains as well [53].

Internationally well-known and widely used generic HRQoL-instruments include the Quality of Well-Being Index (QWB) and the Sickness Impact Profile (SIP) from the 1970s, the Nottingham Health Profile (NHP) and the Quality of Life Index (QLI) from the 1980s, and the Medical Outcome Study Short Form-36 (SF-36) and the EuroQol Index (now EQ-5D) from the 1990s. Numerous disease-specific HRQoL-instruments exist, and will not be expanded on here. ProQolid is an international free access database, which is intended to provide an overview of existing patient-reported outcome measures such as the HRQoL-instruments, and to facilitate the choice of appropriate instruments (http://www.proqolid.org/). Articles guiding the choice are also available [100-102].

The majority of HRQoL-instruments consist of predetermined health dimensions, chosen by the researcher to cover the concept of HRQoL and to get the patients’ view of their health situation, i.e. yield patient-reported outcome. However, these instruments have been criticised for not being as patient-centred as one would think, since a true patient-centred instrument would let the patients themselves decide which dimensions were of importance for them [103]. One example of such an instrument is the Schedule for Evaluation of Individual Quality of Life (SEIQoL) [104].

The most used generic HRQoL-instruments in Sweden today are two of the newer instruments, the EQ-5D and the SF-36. Older instruments, such as the NHP and the SIP, are often considered to have comparatively more
disadvantages, such as being lengthy, having binary response alternatives (leading to low responsiveness), etc. However, the choice of instrument should always depend on the context in which it is to be used.

**EQ-5D**

The EQ-5D (EuroQol 5 Dimensions) [105], formerly known just as EuroQoL (the name of the European research group from five different countries, including Sweden, that created the instrument), was initially developed to create a summary index to use for health economics, comprising the five dimensions considered most important to patients, four physically oriented and one psychologically oriented. Originally, the EQ-5D was intended to be a self-administered complement to other, more comprehensive HRQOL instruments, but is nowadays increasingly used as a stand-alone instrument. (http://www.euroqol.org)

The EQ-5D has two parts, one in which the respondent states his or her present functional ability within each one of the five health dimensions, and one in which the respondent rates his or her present general health on a vertical scale from 1-100 (sometimes referred to as the EQ-5D thermometer). The five health dimensions are mobility, self-care, daily activities, pain/discomfort, and anxiety/depression.

Each dimension includes three statements, indicating no, some or severe problems in that dimension. One of these statements is chosen for each of the five dimensions, resulting in a total of $3^5=243$ different combinations of answers. Every combination has then received a “quality of life weight”, which means that the combination has been valued in relation to full health (using e.g. the Time Trade-Off method). The weighting procedure has sometimes been criticised for using people from the general population for the valuation procedure instead of persons in the actual health states [106]. The reason for this criticism is that it is well known that healthy persons tend to rate their quality of life for fictitious diseases lower than patients do, a phenomena called response shift (adaption to the situation, coping; change of internal standards) [107-110]. The population weights were meant to reflect the opinion of the general tax payers (and future patients), since the EQ-5D was created to allow for health economic analyses, but it could be argued that patient-based valuations are more veridical, and they might be superior in health outcome studies in routine health care [106].
Finally, a summary index value is calculated, for use in health economic analyses.

Besides the index value, EQ-5D may be presented by using the five dimensions directly, which gives the opportunity to see in which dimensions the problems lie, as opposed to just using means values of the EQ-5D index. Devlin et al have proposed the Pareto method to yield more useful information in outcome studies, where using only the mean values of the index value may hide important variation in the material [111]. The Pareto method divides the change in each of the five dimensions into only improvement, only worsening, no change, and undecided change (some dimensions have improved, but others have deteriorated).

Concurrent criterion validity tests of the EQ-5D have shown an acceptable correlation to the SF-36, while construct validity tests have shown that EQ-5D discriminates in the expected way between different groups, e.g. with and without disease. However, it might work less well in a population with a lesser amount of disease severity [112]. The reliability has been tested using the test-retest method, showing good stability [113, 114].

Besides its validity and reliability, the responsiveness of the instrument is vital when it is used in outcome studies. EQ-5D is known to have ceiling and floor effects (=too few and/or skewed response alternatives, leading to too many respondents choosing the best or worst response alternative, respectively). Since you only can choose between no, moderate or severe problems, you may well have improved, but not enough to change from moderate to no problem. To improve responsiveness and overcome the ceiling and floor effects the EuroQol group has developed a new, improved version, the EQ-5D-5L, with five response alternatives instead (no, slight, moderate, severe, or extreme problems). The EQ-5D-5L has been shown to be valid and reliable, but studies confirming the improved responsiveness have still not been published (January 2012) [115]. Correspondingly, the original version is now called EQ-5D-3L. Additionally, a version for children has been developed, the EQ-5D-Y, for children 7 to 12 years old [116, 117].

A novelty is the use of so called dimension extensions (or bolt-ons), where extra items of relevance to a specific patient group are added to the five original ones. In general, the use of combinations of generic and disease specific
HRQOL-instruments is increasing, allowing a more complete picture of the patient’s situation to be obtained.

**SF-36**

The SF-36[10], which was developed in the United States of America, is probably the internationally most used generic measure. It originates from a more comprehensive instrument used in the RAND Corporation (an American non-profit research organisation) Medical Outcomes Study, MOS (http://www.rand.org/health/surveys_tools/mos.html), and which has 40 subscales and more than 100 items, and is intended to cover the WHO definition of health. However, to allow the instrument to be used in routine health care, a shorter and more user-friendly instrument was created, with 36 items in eight subscales, chosen among other things for their strong correlation to disease. The still relatively large number of items was considered necessary to cover all important aspects in each subscale. The eight subscales are

- **PF** Physical Functioning
- **RP** Role functioning - Physical
- **BP** Bodily Pain
- **GH** General Health
- **VT** Vitality
- **SF** Social Functioning
- **RE** Role functioning – Emotional
- **MH** Mental Health

The eight subscales are divided into physically (PF, RP, BP & GH) or psychosocially oriented scales (VT, SF, RE & MH), sometimes brought together into two summary scores (initially created using factor analysis), the PCS (Physical Component Scale) and the MCS (Mental Component Scale), respectively [118]. However, the principle behind these algorithms has been criticised [119]. PCS will receive high scores not only if levels on the physically oriented scales are high, but also if levels are very low on the psychosocially oriented scales. Thus, if the psychosocially oriented scales have very low levels, a high PCS might reflect this fact instead of genuine high levels for the physically oriented scales. The reverse is true for MCS. Therefore it is important to always interpret PCS and MCS together with all eight subscales. Furthermore, it has recently been shown that three summary scores are
superior to two [120]. It is the three role function subscales, RP, SF, and RE, that form a third summary score, the RCS (Role Component Summary), and to form a third summary score also improves the performance of the remaining PCS and MCS summary scores. The above study setting was the general population in Japan and it is still to be investigated whether three summary scores also outperform the traditional two summary scores in other populations.

Construct validity tests of the SF-36 have shown good or acceptable ability to distinguish the healthy from the sick, and to discriminate between physical and psychiatric disease groups, major common disease groups and disease stages and severity. The structure of the SF-36 allows for further reliability testing besides test-retest (which has shown acceptable stability). Testing the internal consistency of the SF-36 has yielded Cronbach $\alpha > 0.70$ for all subscales, and some of them even reached 0.90 or more, a level usually required for analyses on the individual level [113, 114, 121, 122]. For the new improved SF-36 version 2, even more subscales have acquired $\alpha > 0.90$, and the responsiveness is also enhanced (fewer ceiling and floor effects), since some of the items have changed from two to five response levels (in role functioning subscales RP and RE) [123].

The SF-36 belongs to a family of instruments that besides the SF-36 currently include the SF-12 (and SF-12 version 2), SF-8, and SF-6D. These instruments are appropriate in different research situations (according to the research question, sample size, population characteristics etc.). The SF-6D, like the EQ-5D, yields an index value that may be used for health economics [124]. Furthermore, there is an algorithm for SF-6D that may be applied to SF-36 datasets as well, i.e. you do not have to use the actual SF-6D to obtain an index. It should be kept in mind that comparative studies have shown that the EQ-5D and the SF-6D do not produce identical results [125, 126].

Both the SF-36 and the EQ-5D are, in research situations, known to be useful as health outcome measures, but the question remains whether they are as good in routine health care, especially if used for the purpose of improvements in health care, and not only for follow-up or health economics. Will these, and other, instruments be able to help in identifying patients whose HRQoL has not improved, or even has deteriorated, despite the health care given, and who is in need of further (e.g. after a seemingly successful surgical procedure) or altered (e.g. during the lifelong management of diabetes) interventions?
Health-Related Quality of Life as patient-reported outcome in routine health care

Health care outcomes research came into fashion in the United States in the early 1980s, as the more academic counterpart to health policy research [127]. Outcomes research studies “the impact of health care on the health outcomes of patients and populations” [127]. Hence, this research spans from developing new health-related outcome measures (beyond traditional outcome measures such as hospital readmission rates, laboratory test results, treatment complications and death) to implementation of the results of outcomes research in the health care system. The latter means that the research setting is the real-life world as opposed to controlled clinical trials, i.e. effectiveness rather than efficacy research, to find out which medical treatments actually worked, and in which situations. Furthermore, variations in medical practice have been discovered that cannot be explained by known patient characteristics or by the medical resources in a community, and traditional measures have been rendered insufficient when the treatment goal was the improvement of HRQoL rather than the (unattainable) cure of a disease, as in patients with multiple chronic conditions and functional limitations. The final goal is the creating of highly functional Outcomes Management Systems within health care [128, 129].

Casemix problems, especially co/multimorbidity
Measurement of HRQoL was considered a key factor and a catalytic element in the implementation of Outcomes Management [128], making the interpretation of the results of these measurements a crucial step in the implementation process. An important issue when interpreting the results of HRQoL measurements, and especially when using generic instruments, is the casemix-problem. Other factors, such as sex, age, disease severity, disease history, comorbidity, socioeconomic status, and social support, are likely to influence the result, and therefore adjustments are necessary [100, 130-132].

Regarding co/multimorbidity there are a number of adjustment methods [133, 134]. Rather uncomplicated ways are to simply recognize the presence of multi-morbidity or to add up the number of diseases, but these methods do not take into consideration that diseases may differ in severity and health impact. To address these aspects comorbidity indices, giving different weights to different diseases and conditions, were developed. In mortality risk
Introduction

studies a common way to adjust for comorbidity is to use the Charlson Comorbidity Index (CCI) \([135, 136]\), but in HRQoL outcome studies the CCI performs less well \([137]\), and it has been criticised for not including all potentially important conditions \([138]\). Therefore, other solutions have been presented, such as having a single comorbidity measure but with different algorithms depending on the nature of the outcome \([138]\), or developing comorbidity indices for explicit use in HRQoL studies, like the Health-Related Quality of Life Comorbidity Index (HRQL-CI), which is still in need of further validation \([139]\). Although the terms co- and multimorbidity are sometimes used interchangeably, a difference is that the latter takes into consideration all of the patient’s diseases, while the former is used for all of the patient’s diseases besides the disease of interest, the index disease \([140]\). Furthermore, it has been suggested that diseases related to the index disease, \textit{i.e.} complications, should not be regarded as comorbid diseases \([138]\).

A related issue in interpreting the results of HRQoL measurements is how to decide what is the minimum change in the score of the HRQoL instrument that will be perceived by patients as important, the so-called Minimal Important Difference (MID), also known as Minimal Clinically Important Difference (MCID), Minimal Important Change (MIC), etc. \([141-143]\). Probably, different study populations and contexts will require different MID’s for one and the same HRQoL-instrument, but more research is needed in the area.

Usefulness of measures of Health-Related Quality of Life

Higginson & Carr \([144]\) have presented the following motives for using HRQoL measures in routine health care:
- identifying and prioritising problems
- facilitating communication
- screening for hidden problems
- facilitating shared clinical decision-making
- monitoring changes or responses to treatment

There are a small but increasing number of scientific articles being published regarding evidence for the usefulness of measures of HRQoL for health care improvements \([130, 144-153]\), and especially in the field of cancer. This is not very surprising, since the number of people surviving cancer is greater than
ever, and they will have to live with the sequelae of both the disease and the treatment, perhaps for the rest of their lives, and this will often affect their health-related quality of life and functional ability. The use of measures of HRQoL has proved to be beneficial for the patient - health professional encounter and communication, e.g. if doctors have the results of the HRQoL measurement available during the patient encounter it allows the most important current health issues for the patient to be directly addressed [130, 144-153]. Patients are also reported to feel more empowered maybe because the use of this kind of measurements encourages them to reflect upon their situation, thereby increasing self-awareness, and it also indicates that the health care professionals will be interested in listening to their problems [154].

Evidence for its ability to enhance HRQoL is still poor, and more and better designed studies are needed. Some impact on health that have been reported in organisations using patient-reported outcome measurement are lower incidence of pain at four-week follow-up (higher prescription of analgesics) and lower incidence of depression at six-month follow-up when using early screening for mental illness [145]. Others have reported discovering unknown problems in their patient groups, such as pain being a common symptom among patients with chronic obstructive pulmonary disease [155-157]. Suggested explanations to this lack of evidence are that the medical treatments may already be optimal or only small improvements possible, and therefore the responsiveness of the chosen HRQoL-instruments is crucial; that the results of the measurements are difficult to interpret; or that the results are not presented to the “right” persons, i.e. those responsible for the treatment plans, often the physicians [158]. It is important that the results are presented in a way that is easy to understand and draw conclusions from. For example, to present the result from before-and-after measurements in the form of Pareto changes (as described above for the EQ-5D) instead of just mean values would facilitate identifying the nature of the patient’s problem.

In an overview of RCT:s (Randomised Clinical Trials) including the SF-36 as one (and the only patient-reported) of the outcome measures, the results of the HRQoL measurements in several cases differed from the results of the traditional medical outcome measures, but this fact seldom affected the conclusions [159]. This lack of impact of patient-reported outcome measures on medical and managerial decision makers in the health care was discussed already in the 1990s in terms of Outcome management and Outcomes research [160-163]. Greenhalgh et al [164] have suggested that it is caused, at least in
part, by lack of theory, since, over the years, researchers have focused more on the development of new instruments than on reflecting upon the theoretical background of them and why they should be useful for health care improvements. Thus, we need to learn more about what we actually measure.

McClimans [165] has suggested that although researchers are aware of that questions used in measures of HRQoL may be context-dependent and their theoretical construct imperfectly understood, the consequence of this insight, i.e. that today’s quantitative instruments may not be optimal outcome measures, is ignored. She suggests a parallel use of qualitative data, both as a means for constant revision of existing instruments, and as a tool for interpreting quantitative data.

Using patient-reported outcomes can be regarded as a sort of feedback to the clinicians from the patients [166]. Carlier et al [167] found in a literature search that using the feedback system Routine Outcome Monitoring (systematic evaluation of treatment responses during the course of the treatment) had a significantly positive impact on health care professionals with respect to earlier adjustments of treatment plans etc., especially in the short term, in the majority of studies. Communication between professionals and patients was also improved, and more than half of the studies furthermore showed a positive impact on mental and/or physical health of the patients. The authors proposed that feedback theories, such as the Feedback Intervention Theory (FIT) might explain the positive results. According to the FIT, health care professionals, when given formerly unknown information about the patient, will become more focused on the task, and thus health care will improve. However, the effects of FIT have also been questioned [168].

**The patient perspective**

There are few studies concerning the patients’ perspective on the perceived value of HRQoL outcome assessments, or preferred HRQoL-instruments [169, 170]. In the choice of appropriate instruments the patients’ perspective is of vital importance [171, 172], and questionnaires should preferably be designed to make every part of the cognitive response process (comprehension of the question, retrieval of information, judgement based on retrieved information, and response selection) as easy as possible for the respondent [173]. Related aspects that are often discussed in the literature are respondent burden (questionnaire length and effort in answering) and patient perceived validity of the instrument [113, 174].
Aims of the thesis

The general aims of the thesis were to study the associations of HRQoL with psychological and biological factors, and the use of HRQoL as patient-reported outcome in routine health care.

Specifically, the four papers in the thesis aimed to investigate

- the association between HRQoL (SF-36) and psychological factors in a normal middle-aged population, especially differences and similarities between women and men (Paper I)

- the association between HRQoL (SF-36) and inflammatory biological factors with a known relation to disease and mortality (CRP, CXCL8, IL-1β, 6, and 10, and MMP-9), in a normal middle-aged population (Paper II)

- the impact of comorbidity on HRQoL (SF-36 and EQ-5D) in a normal Swedish population, and to test two different comorbidity indices (one older and often used, but designed for mortality studies, and one new, specifically designed for HRQoL studies), using national register data (Paper III)

- the patients’ point of view on using measures of HRQoL (SF-36 compared with EQ-5D) for health outcome assessments (i.e. as patient-reported outcome) in routine health care (Paper IV)
METHODS

Papers I and II

The data used in papers I and II were collected between October 2003 and May 2004, using random sampling (stratified according to the catchment areas of ten different primary health care centres, sex, and age at 5-year intervals) of the population in the county of Östergötland, Sweden. An invitation letter was sent by post, and by signing and returning a reply form the participants gave informed consent. The participants were enrolled until the predetermined sample size of 500 women and 500 men between the ages 45 and 69 was obtained (five 5-year age-groups with 50 women and 50 men in each), and finally resulted in 505 women and 502 men, with a response rate of 62.5%. This constituted the basis of the ongoing, prospective Life conditions, Stress, and Health (LSH) study (http://www.imh.liu.se/samhallsmedicin/socialmedicin/lsh-studien?l=en&sc=true). The LSH study was designed to investigate whether the relationship between socioeconomic status and coronary heart disease is mediated through biopsychosocial pathways. Since the primary outcome in this study is coronary heart disease, the age group 45-69 was chosen to optimize the number of outcomes. Exclusion criteria were ongoing serious physical or mental disease, or difficulty in understanding the Swedish language, but no exclusion for any of these factors became necessary. The study sample was representative of the population in terms of educational attainment, immigrant status, and employment rates.

As part of the protocol of the LSH study, participants visited their primary healthcare centres, where anthropometric and blood pressure measurements, in addition to blood, urine, and saliva samples, were obtained. All samples were collected in a fasting state. Out of the 1007 participants, blood samples were eligible for analysis from 961 participants (paper II). Patients were instructed to reschedule their appointment if they were currently experiencing any acute infections, e.g. a common cold. At the visit, information about the voluntary nature of participating in the study was given verbally. In order to ensure standardization of the data collection, the nurses collecting data at the ten primary healthcare centres were trained together. All other measures in
papers I and II, except for sex and age, were self-reported (from questionnaires).

**Disease, lifestyle, and psychosocial factors**
Self-reported disease data in the LSH-study were obtained using a checklist. The participants were asked if they had ever been diagnosed by a physician with any of the medical conditions in the list: myocardial infarction, angina pectoris, stroke, chronic obstructive pulmonary disease, cancer, asthma/allergy, dyspepsia/peptic ulcer, kidney disease, celiac disease, hypertension, hyperlipidemia, or diabetes mellitus. An open question asking about the presence of other medical conditions than the above concluded the checklist. The questionnaire also contained a question about the presence of musculoskeletal pain in the back of the neck and/or in the back (henceforth referred to as back pain). Lifestyle factors included smoking habits, alcohol consumption (from a validated food and beverage questionnaire) [175], physical activity [176], and Body Mass Index (BMI; used as a measure of weight control).

**Psychosocial factors**
The questionnaires in the LSH study included a broad range of instruments measuring psychosocial variables, including the following five validated instruments representing psychological resources (higher scores favourable) and risk factors (with lower scores being favourable). (1) *Self-esteem* [177] referred to a positive attitude towards oneself, while (2) *Sense of Coherence, SOC* [178], reflected the extent to which one felt one’s own life to be comprehensible, manageable, and meaningful. (3) *Perceived Control* included 11 statements adapted from the Whitehall II Study [179] and the New Barometer studies [180, 181] regarding perceived control over health and perceived control over life. (4) *The Center for Epidemiologic Studies Depression scale (CES-D)* [182] was developed in the 1970s to capture depressed moods in epidemiological studies. (5) *Cynicism* was one of six subscales from the Hostility Scale [183], reflecting a generally negative view of humanity, which depicts others as unworthy, deceitful, and selfish. Social support in terms of the availability of social contacts in the wider social context (social integration) and of close social relationships (emotional support) was measured using validated abbreviated forms of two subscales: the availability of social integration and the availability of attachment, both from the Interview Schedule for Social Interaction [184].
**Health-Related Quality of Life**
The Swedish version 1 of the internationally widespread instrument SF-36 was used to measure health-related quality of life, defined as physical and psychosocial well-being and functioning. [185].

**Biomarkers (paper II only)**
Plasma levels (EDTA plasma) of IL-1β, IL-6, IL-10, and CXCL8 were measured with ultrasensitive bead kit technology (Invitrogen Co, Carlsbad, CA, USA) according to the manufacturer’s instructions and analysed on a Luminex® 100TM system (Austin, TX, USA). The lower limit of detection was 0.38, 1.68, 1.36, and 0.64 pg/mL for IL-1β, IL-6, IL-10, and CXCL8, respectively. The corresponding proportions of samples with detectable levels were 50%, 40%, 14% and 97%, respectively. Samples below the detection levels were given a value that was half the limit of detection.

C-reactive protein (CRP) was measured in EDTA-plasma by a highly sensitive latex-enhanced turbidimetric immunoassay (Roche Diagnostics GmbH, Vienna, Austria) with a lower detection limit of 0.03 mg/L and interassay coefficient of variance (CV) of 1.7%. Detectable levels were found for all samples but one, which received a value of zero.

Concentrations of MMP-9 were measured in EDTA-plasma by human Biotrak ELISA systems (Amersham Biosciences, Uppsala, Sweden). The lower detection limit was 0.6 ng/ml, CV was 7.2 to 7.9 %. Detectable levels were found in all samples.

Aliquots of plasma (0.5 mL) were stored at -70°C Celsius for approximately 18 months before laboratory analysis of MMP-9, and approximately 40 months before analyses of CRP, interleukins and chemokines.

**Statistical analyses**
Correlation and partial correlation analyses were used to explore the relations between the SF-36 and psychological factors (paper I) and inflammatory biomarkers (paper II), adjusting for sex, age, disease, lifestyle and/or (psycho)social factors in different ways. Prior to the analyses, biomarker outliers were excluded from the study base. Cut-off levels were set on the basis of the biomarker distribution. Fischer r-z transformation was used to investigate differences in correlation coefficients between women and men when separate analyses were performed.
Linear regression analyses were used to further explore the relation between the SF-36 and the explanatory variables used in the regression analyses i.e. sex, age, disease, lifestyle, and/or (psycho)social factors, and, in paper II, biomarkers.

**Paper III**

The data used in paper III were collected from a random sample of 10 000 persons from the general population, aged 20-74, in the county of Östergötland (275 000 persons; total population 410 000 in 1999), which in spring 1999 was sent a public health survey from the county’s Public Health Centre for the purpose of monitoring the general health in the county (including HRQoL-instruments SF-36 version 1 and EQ-5D), with a final response rate of 60.93% (6093 participants). Of these responses, 6086 contained useful data for the study. Corresponding data on diseases (diagnoses) and causes of death were obtained from the Swedish National Inpatient Register (discharge data from hospitals; 1987 through 2009) and the Causes of Death register (1999 through 2009). The data was in the form of ICD codes; ICD-9 codes 1987 through 1996, and ICD-10 codes from 1997.

**Charlson Comorbidity Index (CCI)**

The CCI [135] includes 19 medical conditions, each given a weight of 1, 2, 3, or 6, according to severity. The sum of the weights constitutes the index value (range 0-37), with higher levels indicating an increased risk of death from comorbid diseases. Conditions can be collected manually from charts, but also with computer aid, by using ICD codes from administrative systems. In Sweden, administrative data are also recorded in mandatory national registries, the source of data in paper III. Since the date of transition from ICD-9 to ICD-10 codes in Sweden was the 1st January 1997, the study base in paper III contains both types of codes, and we attempted to achieve maximum agreement between them to ensure high validity of the study. Many different adaptation algorithms of both ICD-9 and ICD-10 codes to the CCI weights exist, all with their own features. Starting by identifying a common core in the existing adaptations, ICD-9 and ICD-10 adaptations were compiled, using the Swedish ICD-9/10 Translation Modules.
Health-related quality of Life Comorbidity Index (HRQL-CI)
As opposed to the uni-dimensional CCI, the HRQL-CI [139] is divided into two sub-indices, one covering the physically-oriented dimensions of health-related quality of life (including 20 medical conditions), and one covering the psychosocially-oriented dimensions (including 15 conditions). The conditions were originally selected from a larger set, and some conditions became included in both sub-indices, though they may have been given different weights (1-3) in the different sub-indices (e.g. diabetes has the weight 1 in the psychosocial sub-index, but the weight 2 in the physical), while others were included in only one of the sub-indices. Sex-specific medical conditions, such as diseases of the genital organs, were excluded to make the index generalisable. The sum of the weights form two index values (range 0-35 and 0-25, for the physical and psychosocial sub-indices respectively), with higher scores predicting lower health-related quality of life because of comorbidity. The HRQL-CI was originally created based on so-called Clinical Classification Codes (grouping similar diseases), not ICD codes directly, and no ICD adaptation algorithm is currently available. Therefore, instead of having a record of all possible codes matching all conditions in the HRQL-CI (which is the case for the CCI), only the ICD codes present in our own study database were matched with suitable medical conditions in the HRQL-CI.

Statistical analyses
A two-tailed t-test and an ANOVA analysis, with one-tailed Bonferroni post hoc corrections between selected CCI and HRQL-CI index levels (where a gradient was expected), or with two-tailed Tukey post hoc corrections (where a gradient was not expected) were used to study the relation between the comorbidity indices and HRQoL as well as mortality.

Linear regression analyses were used to further explore the impact of comorbidity on health-related quality of life. Physically-oriented (PF, RP, BP, GH) and psychosocially-oriented dimensions (VT, SF, RE, MH) of the SF-36 were investigated separately and only in relation to either the physical or the psychosocial sub-indices of the HRQL-CI. To test the construct validity of the CCI and the HRQL-CI, the known groups technique was used, analysing differences between groups, for example different comorbidity index values for those who had died and those who were still alive ten years after answering the questionnaire [186].
Methods

Paper IV

The data used in paper IV were collected from the Swedish WHO-network Health Promoting Hospitals (HPH) Health Outcome Assessment Project. In 2004, all Swedish member hospitals (23 at the time) were invited to find interested clinics to participate in this multicentre project. Preferably, these clinics cared for patients suffering with the following five common diagnoses: ischemic heart disease, chronic obstructive pulmonary disease, rheumatic disease, chronic pain, and knee/hip disorder. The staff then chose suitable patient intervention groups from within the clinic’s ordinary practice. Thus, the study design is a form of convenience sampling.

All patients in the chosen intervention groups were then asked to enter the project (after giving informed consent), thus creating a number of local sub-projects within the Health Outcome Assessment Project. Exclusion criteria were: <16 years old, patient was confused or demented, or had difficulties understanding the Swedish language. Each sub-project planned to include about 20 patients. This recruitment resulted in participation by 18 hospitals, comprising 573 patients divided into 31 sub-projects (1–4 sub-projects/hospital; 7-50 patients in each subproject). The majority of the intervention groups were so called patient education groups. Such multi-professional groups are designed to enhance patients’ capability to deal and cope with their own disease while improving their HRQoL. In addition to the five suggested diagnostic groups, three further groups were included (one sub-project of each); cardiac insufficiency, cardiac arrhythmia, and diabetes.

Patients were asked to respond to the HRQoL-instruments EQ-5D and SF-36 version 1 (in that order) before and after the interventions at the hospital in connection with the intervention. Of the 573 patients, 463 (80%) completed both measurements, and at the time of the second measurement they were asked to complete an evaluation form. The five evaluation questions concerned the cognitive response process (1. Understanding and 2. Responding to the items in the EQ-5D and the SF-36; five response alternatives each), patient-perceived content validity (3. Whether the instruments gave patients the ability to describe their health in a comprehensive way; five response alternatives), and patients’ perspectives on health outcome assessment (4. Was this kind of health outcome assessment within health care perceived as valuable in the future, and 5. If so, which instrument would they prefer?; three
response alternatives each). An open-ended question giving patients the opportunity to expand their answers concluded the evaluation form.

**Statistical analyses**
The answers to each of the first three evaluation questions (cognitive response process and patient-perceived content validity) regarding EQ-5D were compared with answers regarding SF-36, and the differences in the chosen response alternatives were used to compute a respondent satisfaction difference score, ranging from +4 (EQ-5D very easy/good and SF-36 very hard/bad) to –4 (SF-36 very easy/good and EQ-5D very hard/bad). Then these three scores were added together, forming a respondent satisfaction summary score (range +12 to –12). This summary score was further transformed into a category variable; in favour of EQ-5D (positive score) or SF-36 (negative score), or equal (zero score, *i.e.* no differences or differences that cancelled each other out). Only patients with complete data for all three respondent satisfaction questions for both SF-36 and EQ-5D (n = 392) were included in the analyses.

The two-sided McNemars’ test with Yate’s continuity correction or, when the number of discordant pairs was <10, the two-sided sign-test were used to test statistical significance for differences in respondent satisfaction and preferences between SF-36 and EQ-5D, in the total sample population as well as in the sample population categorised by sex and age (younger than 65 years old vs 65 or older)

The responses to the open-ended question were first sorted according to whether they discussed the value of health outcome assessment in routine health care (n = 27) or discussed their preference of instrument (n = 62), and then further sorted into groups, referred to as categories. Each category was illustrated by citations.
RESULTS

Associations of Health-Related Quality of Life with psychosocial and biological factors

Papers I and II addressed the issue of associations of HRQoL instruments with psychosocial and biological (inflammatory biomarkers) factors, to better understand what it is we actually measure by these HRQoL-measures.

Significant sex differences were seen for many of the variables. Back pain occurred significantly more often among women than men (46% vs 37%). More men than women had BMI>25 (72% vs 55%), and more men than women had high alcohol consumption (26% vs 8%). Regarding the SF-36 and the psychosocial instruments, men generally scored significantly more favourably than women, except with regard to Cynicism and Emotional Support, where women scored more favourably. Because of these sex differences, analyses were first carried out separately for men and women. However, in paper II Fischer r-z transformation did not show any significant differences in the HRQoL-biomarker correlation coefficients for women and men, and separating the analyses by sex did not change the main findings, but affected power. Hence, further analyses were adjusted for sex, but not performed separately for men and women in paper II.

In paper I the main results were that partial correlation coefficients for the relations between HRQoL and psychological resources (Self-esteem, SOC, and Perceived Control), as well as psychological risk factors (CES-D), were almost all significant and in the expected directions, i.e. higher score on resources and lower scores on risk factors in relation to higher HRQoL. They were generally lower for the physically-oriented SF-36 subscales (PF, RP, BP, GH; significant r=|0.11 - 0.38|) than the psychosocially-oriented subscales (VT, SF, RE, MH; significant r=|0.13 - 0.60|). CES-D generally displayed the highest correlation coefficients. In general, the results were similar for men and women, but women had significantly greater r values than men (p = 0.05) in the following correlations: Self-esteem–VT, Self-esteem–SF, Perceived Control–RE, SOC–RE,
Results

and CES-D–SF. The SF-36 subscales showing sex differences are therefore all psychosocially-oriented and predominantly role-functioning ones. Furthermore, multiple linear regression analyses were performed in order to verify the impact of psychological factors on HRQoL. For all subscales of SF-36, the addition of the five psychological instruments en bloc into the regression model resulted in significant $R^2$ changes for both men and women. The lowest explained variance was seen for RP and the highest for MH (for men and women alike), though among the physically-oriented scales RP showed the highest relative $R^2$ change (Table 2) regarding psychological factors, especially for men.

Table 2. Total explained variances ($R^2$) and $R^2$ change; multiple regression analyses exploring relations between health-related quality of life (SF-36) and psychological factors for middle-aged men and women.

<table>
<thead>
<tr>
<th></th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n=502)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta R^2$ other</td>
<td>0.22</td>
<td>0.10</td>
<td>0.29</td>
<td>0.21</td>
<td>0.20</td>
<td>0.05</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td>$\Delta R^2$ psych</td>
<td>0.05</td>
<td>0.07</td>
<td>0.05</td>
<td>0.15</td>
<td>0.23</td>
<td>0.18</td>
<td>0.23</td>
<td>0.36</td>
</tr>
<tr>
<td>Total $R^2$</td>
<td>0.27</td>
<td>0.17</td>
<td>0.34</td>
<td>0.36</td>
<td>0.43</td>
<td>0.23</td>
<td>0.29</td>
<td>0.47</td>
</tr>
<tr>
<td>Women (n=505)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta R^2$ other</td>
<td>0.31</td>
<td>0.18</td>
<td>0.36</td>
<td>0.36</td>
<td>0.34</td>
<td>0.15</td>
<td>0.11</td>
<td>0.20</td>
</tr>
<tr>
<td>$\Delta R^2$ psych</td>
<td>0.02</td>
<td>0.08</td>
<td>0.03</td>
<td>0.13</td>
<td>0.21</td>
<td>0.26</td>
<td>0.33</td>
<td>0.36</td>
</tr>
<tr>
<td>Total $R^2$</td>
<td>0.33</td>
<td>0.26</td>
<td>0.39</td>
<td>0.49</td>
<td>0.55</td>
<td>0.43</td>
<td>0.44</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Other=age, disease, pain, lifestyle (smoking, alcohol, BMI, and physical activity), and social support
Psych=psychological factors (sense of coherence, self-esteem, perceived control, depression, and cynicism)

In paper II the main results were that significant negative correlation coefficients for every subscale of the SF-36 (adjusting for sex and age) were found for IL-6 ($r=-0.103 - -0.170$; $p<0.001$), whereas CRP showed significant negative coefficients for all scales ($r=-0.073 - -0.155$; $p<0.05$) except the MH scale ($r=-0.025$; $p=0.458$). For MMP-9, significant negative correlations were seen for five out of the eight SF-36 scales (PF, BP, GH, SF, and MH; $r=-0.072 - -0.097$; $p<0.05$), although they were weaker than for IL-6 and CRP. In contrast, no or only scattered significant correlations were found for IL-1β, IL-10, and CXCL8. Based on these results, further regression analyses involving biomarkers were only conducted for IL-6, CRP and MMP-9.
The regression analyses were performed in five different ways; 1) adjusting for age and sex, 2) additionally adjusting for a) only lifestyle factors, b) only presence of disease/back pain, c) only psychological factors, and d) for all factors together (full model). Both IL-6 and CRP revealed significant beta coefficients for all subscales of the SF-36 when initially adjusting for age and sex (except the MH scale for CRP). Coefficients regarding IL-6 were somewhat attenuated (e.g. for PF the beta coefficients for the five analyses described above were -3.7, -2.8, -3.0, -3.3, and -2.2 respectively) after including the other explanatory factors, especially in the full model, although they only became non-significant for the VT and the RP scales (and only in the full model). Unlike IL-6, the beta coefficients for CRP became non-significant when adjusting for lifestyle factors for half of the subscales, and for VT when adjusting for the other explanatory factors as well. The full model yielded non-significant beta coefficients for CRP for all subscales except PF and RP. Regarding MMP-9, significant beta coefficients were found for the PF, BP, GH, and SF subscales after initial adjustment for age and sex. After further adjustments all coefficients became non-significant, except for the PF, BP, and GH scales when adjusting for the presence of disease/back pain. The results of the regression analyses regarding IL-6, CRP, and MMP-9 are seen in Table 3.

Table 3. Beta coefficients for the initial and full models, and total explained variances (R²) for the full model; multiple regression analyses exploring relations between health-related quality of life (SF-36) and inflammatory biomarkers IL-6, CRP, and MMP-9 for middle-aged men and women (n=729-791). Beta coefficients expressed as change in SF-36 scale per SD increment of the biomarker.

<table>
<thead>
<tr>
<th></th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>-3.7***</td>
<td>-4.2**</td>
<td>-3.2***</td>
<td>-3.6***</td>
<td>-2.7**</td>
<td>-3.2***</td>
<td>-5.0***</td>
<td>-2.2***</td>
</tr>
<tr>
<td>β full model</td>
<td>-2.2***</td>
<td>-1.9</td>
<td>-2.0**</td>
<td>-1.7**</td>
<td>-1.1</td>
<td>-1.9**</td>
<td>-3.2**</td>
<td>-1.1*</td>
</tr>
<tr>
<td>Total R²</td>
<td>0.36</td>
<td>0.18</td>
<td>0.32</td>
<td>0.38</td>
<td>0.43</td>
<td>0.32</td>
<td>0.29</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>-2.8***</td>
<td>-4.6***</td>
<td>-2.8**</td>
<td>-2.9***</td>
<td>-1.6*</td>
<td>-1.7*</td>
<td>-2.8**</td>
<td>-0.3</td>
</tr>
<tr>
<td>β full model</td>
<td>-1.0*</td>
<td>-2.9*</td>
<td>-1.5</td>
<td>-1.2</td>
<td>-0.4</td>
<td>-0.8</td>
<td>-1.8</td>
<td>-0.01</td>
</tr>
<tr>
<td>Total R²</td>
<td>0.32</td>
<td>0.16</td>
<td>0.31</td>
<td>0.36</td>
<td>0.43</td>
<td>0.29</td>
<td>0.29</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>MMP-9</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>-1.3*</td>
<td>-1.8</td>
<td>-1.8*</td>
<td>-2.0**</td>
<td>-0.7</td>
<td>-1.3*</td>
<td>-1.3</td>
<td>-1.0</td>
</tr>
<tr>
<td>β full model</td>
<td>-0.2</td>
<td>-0.2</td>
<td>-0.5</td>
<td>-0.2</td>
<td>-0.7</td>
<td>-0.2</td>
<td>-0.3</td>
<td>-0.1</td>
</tr>
<tr>
<td>Total R²</td>
<td>0.34</td>
<td>0.17</td>
<td>0.30</td>
<td>0.36</td>
<td>0.43</td>
<td>0.30</td>
<td>0.28</td>
<td>0.49</td>
</tr>
</tbody>
</table>

β = adjustments only for sex and age
β full model = adjustments for sex, age, disease, pain, lifestyle (smoking, alcohol, BMI, and physical activity), and psychological factors (sense of coherence and depression)

*p<0.05, **p<0.01, ***p<0.001
Use of Health-Related Quality of Life as a patient-reported outcome in routine health care

Papers III and IV addressed the issues of casemix problems when interpreting the results of HRQoL measurements, and the patient-perceived usefulness and feasibility of HRQoL instruments as patient-reported outcomes.

In the study population in paper III, investigating the impact of comorbidity on HRQoL, 3183 persons (52.3%) had been registered in the Inpatient register with ≥1 ICD codes before the public health survey was conducted, i.e. before 1st July 1999. The majority had not been registered with codes that were included in any of the comorbidity indices; 478 (15.0%) and 664 (20.8%)/418 (13.1%) persons out of the 3181 had been registered with ≥1 codes included in the CCI and the HRQL-CI physical/psychosocial, respectively.

Table 4. Linear regression analyses, with SF-36 and EQ-5D as outcome and the comorbidity indices CCI and HRQL-CI as explanatory variables for the participants registered with ≥1 ICD code between 1987 and the 30th June 1999 (n=3183). All β were significant (p<0.001).

<table>
<thead>
<tr>
<th></th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total R²</td>
<td>0.067</td>
<td>0.028</td>
<td>0.014</td>
<td>0.062</td>
<td>0.016</td>
<td>0.016</td>
<td>0.005</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>HRQL-CI ph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total R²</td>
<td>0.161</td>
<td>0.052</td>
<td>0.033</td>
<td>0.094</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HRQL-CI ps</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total R²</td>
<td>0.018</td>
<td>0.028</td>
<td>0.024</td>
<td>0.026</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>EQ-</th>
<th>EQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EQ index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CCI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total R²</td>
<td>0.031</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>HRQL-CI ph</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total R²</td>
<td>0.049</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>HRQL-CI ps</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total R²</td>
<td>0.040</td>
<td>0.035</td>
</tr>
</tbody>
</table>

CCI=Charlson Comorbidity Index  
HRQL-CI ph=Health Related Quality of Life-Comorbidity Index, physical subindex  
HRQL-CI ps=Health Related Quality of Life-Comorbidity Index, psychosocial subindex
The results of the linear regression analyses revealed HRQL-CI to have a stronger explanatory power (higher $R^2$) than the CCI regarding the impact on health-related quality of life. However, all $R^2$-values were generally very low, with the PF and GH subscales of the SF-36 showing the highest values for both indices (Table 4).

The ANOVA-analysis (post hoc contrasting one index level with the next) showed that both the CCI and the HRQL-CI consistently received lower scores for the EQ-5D and the SF-36 scales for all index levels compared with the index level 0 (i.e. ≥1 ICD code registered before 30th June 1999, but none that were included in the index), but the expected gradient was undecided. Significant differences between the other index levels were noted mostly for the physically-oriented dimensions of the two health-related quality of life instruments, especially the PF and GH scales, and the EQ-5D VAS.

Between 1999 and 2009, 371 (6.1%) persons in the study population died, and 25 died within one year of answering the questionnaires (i.e. before 1st July 2000). Almost all (22) of these 25 had been registered with ICD codes before answering the questionnaires. The CCI showed a clear, highly significant gradient between those who died within one year, up to ten years after the survey, or were still alive after ten years, while the trends for the HRQL-CI were less apparent, though the differences between those alive in 2009 and those who had died within one year were significant (Table 5).

Table 5. Mean values of the CCI and the HRQL-CI (for participants with ICD codes between 1987 and the 30th June 1999; n=3183), regarding those who died within one year or up to ten years after the survey, or who were still alive after ten years.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>mean (SD)</td>
</tr>
<tr>
<td>CCI</td>
<td>2.4 (2.3)*</td>
<td>1.0 (1.3)</td>
<td>0.1 (0.5)</td>
</tr>
<tr>
<td>HRQL-CI phys</td>
<td>0.9 (1.4)*</td>
<td>1.7 (2.1)</td>
<td>0.3 (0.9)</td>
</tr>
<tr>
<td>HRQL-CI psych</td>
<td>0.5 (0.9)</td>
<td>0.7 (1.3)</td>
<td>0.1 (0.6)</td>
</tr>
</tbody>
</table>

CCI=Charlson Comorbidity Index
HRQL-CI phys=Health Related Quality of Life-Comorbidity Index, physical sub-index
HRQL-CI psych=Health Related Quality of Life-Comorbidity Index, psychosocial sub-index
*significant differences (p<0.05) between deaths before and after 1st July 2000; all differences between those alive and those who died (before as well as after 1st July 2000) are significant (p<0.05)
The majority of the 392 patients in paper IV with complete data pertaining to the respondent satisfaction questions found both SF-36 and EQ-5D easy to understand (70/75%; p=0.005) and respond to (54/60%; p=0.001), even if EQ-5D was found to be significantly easier, particularly among women aged >65 years. While 7/4% found the instruments hard to understand, 12/8% found them hard to respond to. The ability to describe their health in a comprehensive way was also found to be mainly good for both instruments (68/68%), though 10/9% of patients regarded them as poor in this regard.

The three categories of the respondent satisfaction summary score were distributed in the following way; 20% in favour of EQ-5D, 13% SF-36, and 67% equal (mostly due to identical judgements for SF-36 and EQ-5D and not to different judgements cancelling each other out). Men aged >65 years were more often in favour of SF-36, while women aged >65 years were more often in favour of EQ-5D.

Of these 392 patients, 385 answered the question about the perceived value of health outcome assessment within routine health care, and 219 (57%) answers were found to be positive, while 15 (4%) were negative. Of the 219 patients giving positive answers, 210 answered the question about which instrument they would prefer for use in routine health care. Though the majority (68%, 142) stated no preference, three times as many preferred the SF-36 (25%, 52) as the EQ-5D (8%, 16), and usually these were men and women aged <65 years, while women aged ≥65 years showed no significant differences in preferences. In Table 6 this preference data was cross-tabulated with the respondent satisfaction summary score, showing that respondents with an equal summary score or a score in favour of SF-36 preferred the SF-36 for use in routine health care, while no significant difference was seen for those with a summary score in favour of EQ-5D.
Table 6. Patients’ preferences of HRQOL-instruments (SF-36 and EQ-5D) for use in routine care versus the respondent satisfaction summary score, among those responding positively towards health outcome assessments and who had answered the question about preference (n=210).

<table>
<thead>
<tr>
<th>Preference of instrument for use in routine care</th>
<th>Prefer SF-36</th>
<th>Prefer EQ-5D</th>
<th>No preference</th>
<th>P (SF-36 vs EQ-5D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondent satisfaction summary score</td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>In favour of SF-36 (n=34)</td>
<td>47 (16)</td>
<td>3 (1)</td>
<td>50 (17)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>In favour of EQ-5D (n=34)</td>
<td>26 (9)</td>
<td>32 (11)</td>
<td>41 (14)</td>
<td>0.82</td>
</tr>
<tr>
<td>Equal score (n=142)</td>
<td>19 (27)</td>
<td>3 (4)</td>
<td>78 (111)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Answers to the open-ended question contained both positive and negative reflections on health outcome assessment and the HRQoL-instruments. Some examples of citations are seen below.

Positive towards health outcome assessment:
“*It saves time at consultations*”
“*To find ill-health earlier*”
“*Someone cares!*”

Negative towards health outcome assessment:
“*I prefer health care to questionnaires!*”

The SF-36 was considered to have more and better response alternatives, but was also more likely to cause confusion. The EQ-5D was considered quicker and easier to answer, but also to have too few response alternatives, and one person felt “*too healthy for the questions*” in the EQ-5D.
DISCUSSION

Associations of Health-Related Quality of Life with psychosocial and biological factors

Both papers I and II confirmed that HRQoL is not an isolated measure of trivial importance, but instead that it has essential links to both psychological and biological factors of known value for health and disease.

Regression analyses in paper I revealed positive associations between HRQoL (as measured by the SF-36) and psychological resources, and negative associations regarding psychological risk factors, also after adjusting for of disease, pain, lifestyle, and social support. In a similarly designed study as ours on haemodialysis patients (though we conducted separate analyses for women and men, while they adjusted for sex), the explained variance increased considerably after the addition of psychosocial variables, as with our results [27]. However, an even greater impact of psychosocial factors on the physically-oriented scales than ours was noted, but there was a smaller effect on the psychosocial scales. For patients afflicted with severe diseases, psychosocial factors may play a greater role in their perceptions of physical performance, as compared with a normal population. Discrepancies of this sort are important to identify in order to reduce the possible bias of generalising findings for populations with varying degrees of disability or disease. Further research is needed to investigate if and how systematic psychosocial interventions, together with medical treatments, will improve patients’ HRQoL. Examples of such interventions are patient education designed to enhance the coping abilities among patients with chronic illness and disease, or screening for comorbid depression among patients where the anticipated improvement in HRQoL did not occur.

We found fewer sex differences than expected, especially for two subscales, SF and RE. It was notable that both of these are role-oriented. SF measures “restrictions in social activities due to physical and mental health problems” and RE describes “restrictions in daily activities because of mental health problems”. Both of these scales had stronger correlations to measures of
“mood” (depression) and “confidence in oneself” (Self-esteem, SOC, and Perceived Control) among women, i.e., psychological factors seem to be more important for perceived social functioning for women compared with men. In a study investigating whether different factors explained global self-rated health in women and men in a normal population, Undén and Elofsson [187] found that women and men seemed to consider similar factors (including psychological ones, such as self-esteem and depression) when judging their self-rated health, although some sex differences were found for the strength of the relationships between psychological factors and self-rated health, in line with the results in paper I. Undén and Elofsson [187] concluded that an individual’s perspective is probably more important than a gender perspective when trying to improve self-rated health. A related subject is the importance of coping as a determinant of HRQoL, and women with myocardial infarction have been found to use a greater diversity of coping strategies than men, including more passive strategies [188].

The third role-oriented scale, RP, represents restrictions experienced in daily activities due to the respondent’s physical condition. This subscale showed a large relative increase in explained variance with the addition of psychological factors, especially for men. It is known that psychological factors may lead to avoidance of physical activity, as in kinesiophobia and “fear of movement” [189, 190]. As physical activity is increasingly recognized as a method for both rehabilitation and prevention, and “fear of falling” has in fact been shown to be a key predictor for functional recovery after hip fracture surgery, the above findings may be of importance when planning interventions regarding physical activity.

In a biomarker context, the LSH-study can be considered to have included a large number of participants. In paper II the relation between HRQoL and inflammatory biomarkers was investigated and the hypothesis was that if a relation could be found, it would be explained by factors of known importance to HRQoL (age, sex, disease/symptoms, lifestyle, and psychological factors). However, the SF-36 was found to be significantly and independently related to two well established measures of inflammation, IL-6 and CRP, especially the former (though beta coefficients for the biomarkers were attenuated after inclusion of the explanatory factors).

CRP is a “down-stream” molecule of IL-6, and therefore to a substantial extent reflects IL-6. However, IL-6 is a very pleiotropic cytokine, affecting several
biological processes besides the induction of CRP. Accordingly, IL-6 could be expected not to act identically to CRP. Another reason for including CRP as well as IL-6 is that CRP is an often used biomarker in clinical medicine, where CRP levels of <10mg/l traditionally have been regarded as normal, but the high-sensitivity CRP assays have made it possible to measure levels even below 1mg/l. Lower levels of CRP have been shown to have a graded association (<1 low risk, 1—3 average risk, >3 high risk) with myocardial infarction, though it is not established whether CRP is a mediator or just a risk marker [191]. Although no traditional clinical levels of low grade inflammation exist for the other biomarkers, the study blood sample levels indicated present inflammation to be low grade, and the few individuals who had high values (indicating highly active inflammation) were excluded from the analyses in paper II.

A novel finding in the study was that MMP-9, a new candidate in the research on inflammatory biomarkers and HRQoL, showed significant associations with several of the SF 36 scales (when adjusting for age and sex), all in the same direction as for IL-6 and CRP. This observation merits further investigation. The reason the other included biomarkers (IL-1β, IL-10, and CXCL8) did not show relations to HRQoL is not evident. Some of them might be too down-stream in the hierarchical process of inflammation for use in population studies, or they may be mainly induced in other routes, not related to factors included in paper II.

The hypothesis that a relation between HRQoL and inflammatory biomarkers would be explained by age, sex, disease/symptoms, lifestyle, and psychological factors was not fully supported by the results in paper II. For IL-6, the beta coefficients became non-significant in the full regression model only for the RP and VT scales but were still significant, though attenuated, for the other six scales of SF-36. This independent effect of IL-6 on HRQoL remains unexplained, but vital explanatory factors might still be missing. These could include yet undiagnosed diseases among the participants, other aspects of psychological stress besides those included in the present study, or other lifestyle factors, such as dietary factors with effects on the inflammation system. In the present study, the included lifestyle factors seem to be the explanatory factor of most importance in the case of CRP. Since all three biomarkers (IL-6, CRP, and MMP-9) are known to be associated with lifestyle factors [192-197] the reason for this finding is not obvious, but one explanation might be that IL-6, unlike its weaker reflector CRP, induces sickness
behaviour, which possibly exerts more influence on HRQoL than lifestyle factors do.

The inclusion of both IL-6 and CRP gives no conclusive answer to the question of whether CRP, which is easier and cheaper to analyse, could replace IL-6 as an inflammatory biomarker in this kind of study/analysis. The choice between CRP and IL-6 should be determined in each individual case by the context and the research question.

Although the Wilson & Cleary/Ferrans model of HRQoL [49, 50] unifies social science and biomedical perspectives of HRQoL, it does not include psychoneuroimmunology aspects. On the other hand, biological models such as the PNI Framework [99] are weak on the social and environmental aspects. Therefore, they seem to complement each other. Optimally, a new, combined model could be created. The results in papers I and II support the idea that biology may affect HRQoL in a direct manner, through sickness behaviour mechanisms, and not only through the chain depicted by the Wilson & Cleary/Ferrans model. The results also show that lifestyle factors may have a more apparent role than previously described in the models. Furthermore, the fact that low HRQoL has been shown to predict mortality (which is not included in the models), independently of present disease [54-56] is important to keep in mind, since it will affect the patients’ prognoses.

Use of Health-Related Quality of Life as patient-reported outcome in routine health care

The use of measures of HRQoL as patient-reported outcome is still poorly implemented in routine health care, and results of measurements seldom make a difference when making individual treatment plans, or when planning health care at large [164].

Paper III addressed an issue often pointed out by health care professionals as an obstacle to the implementation of the use of HRQoL-instruments, namely the casemix problem when interpreting general HRQoL data, and especially the case of the impact of comorbidity on HRQoL. Two different comorbidity indices were tested; the often used Charlson Comorbidity Index, CCI
(designed for mortality studies), and the new Health-Related Quality of Life Comorbidity Index, HRQL-CI (designed for HRQoL studies).

Linear regression analyses investigating the explanatory power of the two comorbidity indices on HRQoL showed results at the level of the original study on HRQL-CI, *i.e.* the explained variance (R² values) was rather low, but higher for the HRQL-CI than for the CCI. The fact that R² values were generally higher regarding physical dimensions is in line with the results of paper I, where presence of disease had a higher explanatory power for the physically oriented scales of the SF-36 than for the psychosocially oriented (in relative numbers).

The expected gradient in HRQoL for different levels of the comorbidity indices was not very visible, especially not for the CCI, although such indices were created to consider not only multimorbidity but also the severity and individual impact of different diseases, and therefore higher comorbidity index values could be anticipated to lead to lower scores on the HRQoL-instruments. A larger study might have resulted in more patients with higher index levels, facilitating more meticulous gradient studies. Another explanation for the lack of clear gradients is that there is too little disparity between the existing levels, and that the merging of the index levels was not optimal. Furthermore, a larger study would have allowed the identification of index diseases, to study true comorbidity; in the present study it is instead multimorbidity that is being considered. However, using comorbidity indices is an appealing way to study multimorbidity in the general population.

Unlike the CCI, the HRQL-CI does not include cancer. Since three quarters of those who died within a year of answering the survey died of cancer, this exclusion may explain why the index value gradient when dividing the participants into three groups (died within one year, died within ten years or still alive after ten years) was more obvious for the CCI (Table 5). Cancer was originally excluded from the HRQL-CI because in comparison with other diseases the HRQoL of cancer patients was rather high, which was also the case in our data material. Still, it was lower than for persons without disease, which might be due to the use of a 12-year look-back period leading to many of the persons with cancer-related ICD codes being cancer survivors, who often have been found not to reach the same high HRQoL as healthy controls, but more research is necessary [198, 199]. Perhaps cancer should be divided
into subgroups in this kind of study, e.g. cancer patients receiving curative treatment, patients with metastatic cancer, cancer survivors, etc.?

Self-reports are often used as a measure of disease and comorbidity, and are considered an acceptable method and the most realistic solution when trustworthy charts and/or administrative medical data are difficult to acquire, but may be impractical in larger studies [200, 201]. Sweden has a number of mandatory national health databases (based on personal identity numbers for all Swedish residents) which are attractive to use in health services research. One of these registries is the Swedish National Inpatient Register, which contains all hospital discharge data in Sweden from 1987 onwards. Validity aspects to keep in mind when interpreting data from the Inpatient Register include coding errors (the patient may have been given an incorrect ICD code, or even an incorrect diagnosis, by the health care professional, or the translation of codes from the medical chart to the register may have failed), the changing proportions of in- and outpatients over time, coding patterns in different hospitals, recent financial incitements to include more secondary codes, etc. [202-204]. The validity of the Inpatient Register has been found to vary among diagnoses, although considered to be high in many cases, and it has been suggested that the Inpatient Register may be better suited for large scale population studies, especially long-term, than for studies of specific diagnoses, where additional data sources and expert knowledge about the medical conditions are required [202-204]. This variance of validity among diagnoses is also true for another mandatory national register, the Causes of Death register. However, less than 1% missing deaths was found when comparing data from the Causes of Death register with data from the Swedish Tax agency, the public authority where all deaths are registered in Sweden, i.e. the coverage is very high [205], which is also the case for the Inpatient Register [202].

Paper IV introduces a new concept, respondent satisfaction. The idea is that respondents are not only concerned about things such as the burden of answering questionnaires, but also like to feel satisfied with their contribution. The results in Paper IV indicate, contrary to the belief of many health care professionals, that patients find the use of measures of HRQoL valuable enough to take the time and effort to answer them, and that the longer SF-36 was as easy to answer as the shorter EQ-5D. The finding that women aged >65 years found EQ-5D easier was in line with earlier findings that the elderly, and
especially women, have reported difficulties with the (self-administrated) SF-36 [206-208].

The fact that 39% of the patients chose not to take a stand about the usefulness of health outcome assessments may have been because they did not understand the objective of these assessments. However, answers to the open-ended question indicate that they did, e.g. “gives a better insight into the patient’s experience” or “it is in everyone’s interest if it leads to positive effects and changes”. A more possible explanation could be that patients are unaccustomed to their health being measured in routine health care, or do not think they have enough knowledge to have a say. Furthermore, the way we use the respondent’s own judgement as an indicator of the quality of an answer may be seen as somewhat questionable by those who argue that people are not very good at judging and reporting their ability to understand or correctly answer a survey question [209]. Nonetheless, the respondent’s feelings are never unimportant or insignificant. Again, answers to the open-ended questions show that the respondents brought up aspects such as the importance of being able to give truthful answers and of seeing the usefulness of their answers, in support of the concept of respondent satisfaction.

**Measurement of Health-Related Quality of Life as an innovation**

One explanation of why the implementation of the use of HRQoL-instruments has not been more successful might be that their use in routine health care is still regarded as an innovation by the supposed adopters, i.e. the health care professionals, if they are even aware of their existence. In Everett Rogers’ implementation theory, “Diffusion of innovations” [210], an innovation is defined as the object that is to be implemented, and that is perceived as new by the adopters, even though it may not be literally new. Adopters are all people (or organisations) that make a decision to accept and use the innovation. According to Rogers, the adoption of an innovation is influenced by its attributes; relative advantage, compatibility, complexity, trialability, and observability.

The relative advantage of using patient-reported outcome measures such as HRQoL instruments (compared with only using profession-reported
measures) is that they systematically provide the patients’ perspectives about their health and the results of the health care given.

The compatibility may be favourable regarding the values of the health care professionals and in the health care system in general, since the knowledge needed to evaluate both the overall goal of health care in Sweden, i.e. “assuring the entire population of good health” (Swedish Health and Medical Services Act), and the individual goal of health care professionals “good health for your patient” is exactly the kind of knowledge that the use of measures of HRQoL may add. It has been proposed that a health care system has moral implications to measure and show consideration for patients’ HRQoL [211]. The fact that the patients in Paper IV found health outcome assessments valuable broadens compatibility to also incorporate patients. Moreover, patients in favour of using measures of HRQoL in routine health may actively advocate the idea, for example through patient organisations, though these organisations have traditionally focused on waiting times and communication issues.

However, compatibility also concerns how compatible the innovation is with existing routines in the organisation, which may need to change, even physically, to adopt an innovation. Luckily, starting to use PROM does not require very great investment. Some sort of computer aid is needed, scoring software, perhaps touch screens, web applications etc. Furthermore, personnel have to be designated to take care of all practical issues [212]. It is possible the innovation itself may have to change somewhat, in order to better meet the needs of the organisation in question. In fact, this is an important part of the implementation process, making the innovation more familiar to its potential users. However, the single most important action is for the organisation to be prepared to change the given care according to the results of the measurements if patients’ experiences are not the anticipated and/or desired ones.

One such practical issue is the identification of the optimal time points for measurements for particular patient groups, integrating the measurements in clinical guidelines and care plans. The use of continuous routine health assessments has been questioned on the grounds of being costly and time-consuming [213]. If health care professionals do not experience a direct usefulness of the assessments in the daily care of individual patients, implementation will be difficult (especially in practices where patients already
have established benefits from the treatments given). Instead, the use of periodic internal quality control measurements of patients’ HRQoL has been suggested, e.g. when new procedures are introduced [213, 214]. This is of course true for all outcomes measurements, not only for measurements of HRQoL. An advantage of continuous measurements is that they can be used in the individual encounters with all patients, as a basis for individual treatment plans.

Even if many patient-reported outcome measures at a glance may seem very straightforward, the complexity might be regarded as high; Which of all the hundreds or thousands of instruments should we choose, how should we collect and process data, how do we interpret the results of the measurements and handle the casemix problem, etc.? To use for example the HRQL-CI to adjust for comorbidity in casemix-analyses will help to moderate the complexity.

Trialability is less of a problem; it is very easy to start with small scale measurements, testing different patient-reported outcome measures.

Finally, observability refers to the visibility of the results of the innovation. First, the results of the measurements have to be presented to health care professionals in a way that is quick and easy to understand, and must be integrated with other medical data [212]. Then, most importantly, the usefulness of measures of HRQoL must become visible, and evident, i.e. using measures of HRQoL to gain a more holistic view of the patient and to point out possible areas for health gaining interventions must be shown to have improved health care and thereby the HRQoL of patients.

**Methodological discussions**

In all the papers, parametric methods suitable for variables with continuous and normal distributions were used, although the SF-36 (and the psychosocial instruments in papers I and II) are known to produce data that have discrete, bounded, and often skewed distributions (although assumed to reflect an underlying continuous conception). However, nonparametric methods showed similar results for all bivariate tests, and linear relationships were further supported by the bivariate scatter diagrams (not shown). Moreover, it
has been shown for the SF-36 that in larger studies (n > 100), multiple linear regression is fairly robust against violations of non-normality, probably as a result of the central limit theorem [215].

Another common problem is that the number of analyses performed may lead to a risk of mass significance, such as in the significance tests for differences between women and men in paper I. However, all sex differences found with respect to the correlation coefficients were in the same direction, i.e., psychological factors were of more importance to women than men, and were found in roughly the same scales of the SF-36, regardless of the psychological factor tested. This implies that the differences found were genuine. The general message seems to be that women and men are affected by the same range of psychological factors but may differ in the importance they tend to ascribe to them.

A limitation of both papers I and II was the cross-sectional study design, i.e. causality could not be investigated. Another limitation of paper II was that the proportions of samples with detectable plasma levels for IL-1β, IL-6, and IL-10 were low, which might have negatively influenced the correlation and regression analyses.

Unlike the other papers in this thesis, which have cross-sectional designs, paper III has a longitudinal design, where participants are observed both up to 12 years before and ten years after answering the questionnaire, enabling researchers to study change over time and cause-and-effect relationships. A 12-year look-back period was used in the study, which means that all data from the start of the Swedish National Inpatient Register in 1987 was included. A shorter look-back period might have been more appropriate to ensure that all codes pertained to diseases affecting the individuals at the time of answering the questionnaire, but this was not possible due to sample size. However, the diseases included in the indices are mostly chronic, severe diseases and are likely to impact a person’s life for a long time (though the impact may vary over time). The fact that the HRQL-CI does not include cancer may render it more useful than the CCI when used with longer look-back periods.

The long look-back period also had the consequence that we had to include both ICD-9 and ICD-10 codes in the material. Although, for the most part, the codes are similar they may also differ substantially (given the widespread
expansion in the ICD-10). However, the main results in paper III are not likely to be seriously influenced by any incongruities, because we did not have any problems in assigning the codes in the study material to either the ICD-9 or the ICD-10 systems.

The study design in paper IV can be seen as a kind of convenience sampling, and thus may suffer from two main problems; possible systematic bias and lack of external validity. However, this is also a multi-centre study, which is known to have a number of advantages; possibility to include a large number of participants in a short period of time, include people from different geographic locations (wider distribution of demographic factors) and a wider range of patient groups, and not at least, to give the possibility to compare results among centres. All these aspects will increase the generalisability of the study, i.e. the external validity. On the other hand, multi-centre studies require firm control regarding compliance to the protocol, and a highly developed coordinating centre.

Pre-selecting five different patient groups served two purposes, to allow for comparisons between patient groups in different hospitals but also to ensure that more than a few patient groups were represented, thereby increasing generalisation and reducing bias due to patient characteristics. Nevertheless, some important patient groups are missing, for example cancer patients, and thus the study cannot claim to represent patients in general. However, the chosen groups do cover five large and common, but quite dissimilar, patient groups. Furthermore, the health care professionals involved in the project were probably somewhat more favourably disposed towards health outcome assessments than in general, and it would have been very interesting to have had a more negative group to compare with, since the attitude of the health care professionals may influence the views of the patients. Also the patients in this sample were probably somewhat more positive towards questionnaires and health measurements than patients in general, since more hesitant patients presumably would be less likely to have agreed to participate in the project. On the other hand, not all our patients were positive and one would expect those who were more negative to prefer the shortest instrument (i.e. EQ-5D) when asked to choose. In our result, no definite answer can be gained by looking at those patients who were indifferent or negative towards health outcome assessment in routine health care. Compared to those who were positive, fewer patients (5% vs. 25%) preferred SF-36, but at the same time
about the same proportion of patients preferred EQ-5D (10% vs. 8%), *i.e.* more patients did not state a preference for either instrument.

Another point to be noted about *paper IV* is that conclusions about the preferences of HRQoL-instrument versus the respondent satisfaction summary score are based on a relatively small number of participants. Moreover, the validity of the respondent satisfaction summary score has not been tested on another material than that described in this paper.
Summary

The following is a brief summary of the results in relation to the aims of the thesis:

• Psychological resources (Self-esteem, SOC, and Perceived Control) as well as psychological risk factors (CES-D) were found to relate independently to HRQoL (SF-36) in the expected directions (positive relations for resources and negative relations for risk factors), but with fewer sex differences than expected. (Paper I)

• Low HRQoL (SF-36) was found to relate to higher levels of inflammatory biological factors (CRP, IL-6, and MMP-9), and, especially regarding IL-6, many association remained significant, though attenuated, after adjustment for age, sex, disease, lifestyle and psychological factors. (Paper II)

• The new comorbidity index HRQL-CI received higher R² values than the commonly used CCI regarding the impact of comorbidity on HRQoL (SF-36 and EQ-5D). However, regarding mortality the CCI showed a more obvious gradient between those who died within a year of answering the questionnaires, within ten years, or who were still alive after ten years. (Paper III)

• Using measures of HRQoL for health outcome assessments (i.e. as patient-reported outcome measures) in routine health care was regarded as valuable by the majority of the patients in the study. The respondent satisfaction summary score was in most cases equal, i.e. SF-36 and EQ-5D were found to be quite similar regarding the cognitive response process (understanding and responding to the items in the EQ-5D and the SF-36) and patient-perceived content validity (if the instruments gave patients the ability to describe their health in a comprehensive way). (Paper IV)
Conclusions

The four papers in the thesis investigated different aspects of HRQoL that are important for the implementation of the use of measures of HRQoL within the health care system. Hence, in their own way, they all and together, contribute to removing obstacles in the implementation process.

Specifically, the findings in paper I suggest that, for both sexes, measures of HRQoL do not merely provide an assessment of absolute function but are also conditioned by the way people perceive their own ability. The associations between HRQoL and the inflammatory biomarkers found in paper II present a possible explanation for the previously observed ability of HRQoL to predict mortality risk, implying that low HRQoL might be an important sign of increased biological vulnerability. The results of both papers I and II emphasize the importance of using patient-reported outcome measures within the health care system to identify patients with low HRQoL, for further health promoting interventions aiming at supporting patients psychological resources, such as coping ability and self esteem.

In paper III the new Health-related Quality of Life Comorbidity Index (HRQL-CI), explicitly developed for use in HRQoL outcomes studies, was further validated as a measure of comorbidity. It showed greater explanatory power than the frequently used Charlson Comorbidity Index (CCI) regarding impact on HRQoL. However, regarding mortality, the CCI discriminated better, in line with its original purpose as a mortality predictor. Utilising morbidity data in the form of ICD codes from mandatory, highly valid national health data bases (such as the Swedish National Inpatient register) instead of from medical records were found to be useful in a large study of this kind (where using data from medical records may be impractical).

Finally, paper IV reported that the majority of patients considered health outcome assessment within routine health care to be valuable. They found both HRQoL-instruments SF-36 and EQ-5D easy to understand and answer, but stated no preference regarding usage in routine health care. Among those who did state a preference, SF-36 was more often preferred than EQ-5D, even among those who found the shorter EQ-5D easier to use. Therefore, in the choice between SF-36 and EQ-5D, this study did not find questionnaire length and ease of response to be crucial arguments.
Future directions

The increased use of HRQoL instruments in health care is often part of an explicit goal of focusing on health outcomes so that the needs of people may be served in a more holistic and patient-centered manner. Since these measurements will be used as a basis for decision-making on health policy and medical interventions, it is essential that we continually update and re-evaluate what we are thereby measuring, as in *papers I and II*. The study population in *paper III* might be used as a reference population for patient-based HRQoL outcomes studies using the HRQL-CI to adjust for comorbidity, or be used for investigating HRQoL as a predictor of mortality in a general population, using the comorbidity index CCI for adjustments. The results of *paper IV* support the future involvement of patients in the continued development of patient-reported outcome measures and use of such measures to improve health care.

Additionally, besides the pressing need for studies specifically designed for examining the usefulness of HRQoL for quality improvement work, implementation studies are needed. These should investigate the implementation of the innovation “using HRQoL-instruments as patient-reported outcome in routine health care as a means of improving the care given”.

ACKNOWLEDGEMENTS

I would like to sincerely thank everyone who in any way has contributed to the completion of my thesis, and especially my supervisor professor Margareta Kristenson, my co-supervisor professor Mitra Unosson, my co-authors (in alphabetical order) Preben Bendtsen, Madeleine Borgstedt-Risberg, Jan Ernerudh, Peter Garvin, Lotti Orwelius, Folke Sjöberg, and Marika Wenemark, and also Sven Almér and Kristina Burström for valuable discussions and John Carstensen, Nadine Karlsson, Anders Nordlund, Lars Walter, and Elisabeth Wilhelm for excellent statistical advice through the years.

Furthermore, I would like to posthumously thank my former co-supervisors professor Lis-Karin Wahren and Ragnhild Raak, who both sadly passed away much too early.

Margareta, tack för ändlöst tålamod och ständigt stöd genom åren, och för att du frikostigt delat ditt stora kunnande inom detta forskningsområde med mig. Utan dig hade det aldrig blivit någon avhandling!
REFERENCES


14. Anonymous **Socioeconomic Status and Health in Industrial Nations: Social, Psychological and Biological Pathways.** 1999, .


44. Wee HL, Cheung YB, Li SC, Fong KY, Thumboo J: The impact of diabetes mellitus and other chronic medical conditions on health-related Quality of Life: is the whole greater than the sum of its parts? Health and quality of life outcomes 2005, 3:2.


91. Dagfinrud H, Vollestad NK, Loge JH, Kvien TK, Mengshoel AM: Fatigue in patients with ankylosing spondylitis: A comparison with the general


102. Palfreyman S: Patient-reported outcome measures and how they are used. Nurs Older People 2011, 23(1):31-36.


References


205. Socialstyrelsen: Dödsorsaksstatistik - historik, produktionsmetoder och tillförlitlighet. 2010, 2010-4-33:


