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HEALTH TRENDS OF THE AGEING POPULATION IN SWEDEN - ASSOCIATION OF MORTALITY REDUCTIONS WITH MORBIDITY AND QUALITY OF LIFE IMPROVEMENTS

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Health trends of the ageing population in Sweden - association of mortality reductions with morbidity and quality of life improvements

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Στην Αναστασία και το Νικόλα μου…

Σὰ βγεῖς στὸν πηγαιμὸ γιὰ τὴν Ἰθάκη,

νὰ εὔχεσαι νᾶναι μακρὺς ὁ δρόμος,

γεμάτος περιπέτειες, γεμάτος γνώσεις.

(…) Πάντα στὸ νοῦ σου νἄχῃς τὴν Ἰθάκη.

Τὸ φθάσιμον ἐκεῖ εἶν’ ὁ προορισμός σου.

Ἀλλὰ μὴ βιάζῃς τὸ ταξείδι διόλου.

Καλλίτερα χρόνια πολλὰ νὰ διαρκέσει.

Καὶ γέρος πιὰ ν᾿ ἀράξῃς στὸ νησί,

πλούσιος μὲ ὅσα κέρδισες στὸν δρόμο,

μὴ προσδοκώντας πλούτη νὰ σὲ δώσῃ ἡ Ἰθάκη.

Ἡ Ἰθάκη σ᾿ ἔδωσε τ᾿ ὡραῖο ταξίδι.

Χωρὶς αὐτὴν δὲν θἄβγαινες στὸν δρόμο.

Ἄλλα δὲν ἔχει νὰ σὲ δώσει πιά.

Κι ἂν πτωχικὴ τὴν βρῇς, ἡ Ἰθάκη δὲν σὲ γέλασε.

Ἔτσι σοφὸς ποὺ ἔγινες, μὲ τόση πείρα,

ἤδη θὰ τὸ κατάλαβες ἡ Ἰθάκες τί σημαίνουν.

~ Ἰθάκη (Ithaka), Κ. Π. Καβάφης

ABSTRACT

Since the beginning of the 19th century, and particularly after the 1950s, life expectancy of the elderly in all developed countries, including Sweden, has increased substantially, posing the question whether the health of the ageing population has also been improving over time. The aim of this PhD thesis was to investigate morbidity occurrence among the elderly in Sweden, attempting to answer the question of whether their overall health and quality of life has been improving over time in parallel with mortality reductions. Analysis was conducted using data from the national registers (studies I to III), combined in study IV with data from the Stockholm Public Health Cohort.

In Studies I and II, the time from age 60 until the first and subsequent morbidity, measured using hospital admissions of any cause as a proxy, was estimated for the years between 1995 and 2010; it was then associated with the change over time in the remaining life expectancy at the age of 60. Postponement to higher ages for both mortality and first and subsequent morbidity was observed, for both men and women, and for most ages.

In Study III, morbidity from hip fractures, which is a prominent disease among the elderly in Sweden, has been estimated. In addition, survival after the disease and the lifetime risk of the disease, have been measured. Incidence of hip fractures decreased over time for both men and women up to the age of 94, while no real improvements have been observed for survival after the first hip fracture or for the lifetime risk.

In addition to administrative information from registers about hospital admissions, which does not necessarily capture individuals' full disease panorama, the health-related quality of life (HRQoL) of individuals was used in study IV to determine whether a hospitalization could indicate the onset of a period of life for the elderly lived with compromised health. Results revealed that only one hospitalization had no long-term consequences on the quality of life; multiple ones, however, did lead to severe morbidity and quality of life reductions.

To conclude, morbidity among the elderly in Sweden seems to have been postponed to higher ages over the years, in parallel with survival improvements observed during the same period. However, individuals have not become more fragile, since the occurrence of subsequent morbidity events has also been prolonged. Lifestyle changes and the increasingly beneficial role preventive medicine plays for individuals' health, which could be leading to the reduction of the incidence of prominent diseases for the elderly such as cardiovascular conditions and hip fractures, could explain such health improvements over time.

LIST OF SCIENTIFIC PAPERS

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

I. **Karampampa K**, Drefahl S, Andersson T, Ahlbom A, Modig K. Trends in age at first hospital admission in relation to trends in life expectancy in Swedish men and women above the age of 60. *BMJ Open 2013;3:e003447.*

II. **Karampampa K**, Andersson T, Drefahl S, Ahlbom A, Modig K. Does improved survival lead to a more fragile population: time trends in second and third hospital admissions among men and women above the age of 60 in Sweden. *PLoS One 2014;9:e99034.*

III. **Karampampa K**, Ahlbom A, Michaelsson K, Andersson T, Drefahl S, Modig K. Declining incidence trends for hip fractures have not been accompanied by improvements in lifetime risk or post-fracture survival – a nationwide study of the Swedish population 60 years and older. *Bone 2015;78: 55-61*

IV. **Karampampa K**, Frumento P, Ahlbom A, Modig K. Change in quality of life after a hospital admission in individuals 65 years and above. *Submitted.*

CONTENTS

LIST OF ABBREVIATIONS

EQ5D	EuroQol 5 Dimensions
EUROSTAT	Statistical Office of the European Communities
HLE	Healthy Life Expectancy
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
LE	Life Expectancy
NPR	National Patient Register
OECD	Organization for Economic Co-operation and Development
QoL	Quality of Life

1 INTRODUCTION

During the second half of the twentieth century, life expectancy increased in all western countries including Sweden, with mortality reductions in the older ages significantly contributing to this increase [1]. It is estimated that by the year 2020, 33% of the population in developed countries will be older than 60 years [2]. In line with a continuously increasing life expectancy, it is of great interest to know if health has improved in parallel, given that all societies, including Sweden, are currently challenged with the distribution of healthcare and social care resources in the population [3-5].

Currently, there is no clear consensus in the literature regarding health trends of older populations. In order to estimate health trends, "health", along with relevant methods to measure morbidity, need to be defined, which is difficult to accomplish in one single way. Previous studies have often used self-reported information regarding individuals' disability as a proxy of the health status of the elderly and reported its changes over time or constructed disability weights to compute the healthy life expectancy of the population. Even though such morbidity measurements present important information regarding the health status of individuals, when they are not used in conjunction with recorded health data, they have limitations [6-11], rendering it difficult to compare them over time and therefore making them less suitable when examining trends of morbidity in the population. To overcome these limitations when looking into changes in the health of the elderly over the years, studies focusing on disease trends and capturing the onset of the disease based on hospital records (time and cause of admission to hospital) could be used instead [8].

This PhD thesis looks into the health of the ageing population in Sweden, utilizing national Swedish registers to obtain access to information regarding all deaths and hospitalizations all individuals in Sweden experience over time. In addition, survival trends and self-reported health-related quality of life after severe morbidity incidents have been studied, in order to investigate whether individuals have been living longer over time, but, at the same time, have been becoming more fragile. These components, hospitalizations as a proxy for overall morbidity, survival over time, and quality of life after severe morbidity incidents, render the contribution of this PhD thesis work important, given that it can describe the overall health trends of the older population living in Sweden in a novel and more complete way compared to previous studies.

2 BACKGROUND

2.1 THE PROCESS AND BURDEN OF AGEING

The process of ageing in humans can be defined as the "accumulation of diverse deleterious changes occurring in cells and tissues with advancing age that are responsible for the increased risk of disease and death" [12, 13]. There are two different groups of theories explaining why ageing appears: the error theory of ageing, according which an external environmental mechanism exists, attacking the cells and tissues of the body leading to damage and ageing [14]. Contrary to the idea of the external damage is the programmed theory of ageing, supporting that ageing is internal to the species, a natural purposeful process generated in our body and existing in our genetic code [15].

Regardless of the process of ageing, its consequences on individuals can be rapid and, in cases, severe, leading to mortality. As humans grow older, they demonstrate a deterioration of adaptability and certain physical signs, such as limitations in movement, slow walking etc., as well as psychosocial signs, for instance lack of concentration, depression, dementia, inability to socialize due to disorientation, etc. [4, 16]. Such problems burden individuals' everyday life, not only due to the objective limitations that they pose, but also due to causing emotional distress [17]. Number of published studies worldwide report that elderly people, with physical and mental limitations, have a lower quality of life compared to older individuals without these prevalent signs of ageing [18-21]. Therefore, the question is if and how the ageing process has an impact on individuals' health and quality of life.

2.2 LIFE EXPECTANCY IMPROVEMENTS

As previous studies indicate, the number of old and very old individuals in the population has been increasing over the years in most of the developed countries of the world [1]. The average number of years that a newborn girl is expected to live, measured in the longest lived country, has been increasing by 3 months every year since the year 1840 (Figure 1) [1]. This measure of the health status of individuals, i.e. the "average number of years that a newborn is expected to live if current mortality rates continue to apply", is defined as the life expectancy at birth for a population [22, 23].

Overall, for men, the increase in life expectancy has been lower compared to women, but in recent years they tend to experience comparable, if not equal, improvements [24, 1, 2]. In Nordic countries, life expectancy (at birth and at later ages) has been continuously increasing, especially during the last 30 to 40 years [24, 25].

While the increase in life expectancy was first attributed to the decline of mortality risks of newborns and children, due to improvements in birth conditions, childhood nutrition, eradication of infectious diseases, etc., during the beginning and mainly the second half of the twentieth century mortality reductions in older ages started significantly contributing to life expectancy increase [26, 1], leading to the increase in the proportion of the elderly in the population over the years [27]. In Sweden, as in other Nordic countries, the number of individuals that live to celebrate their 100th birthday has increased considerably from 1969 to 2009 (a 9-fold increase for men and an 18-fold increase for women) [27, 28].

Figure 1: Record female life expectancy from 1840, with projections.
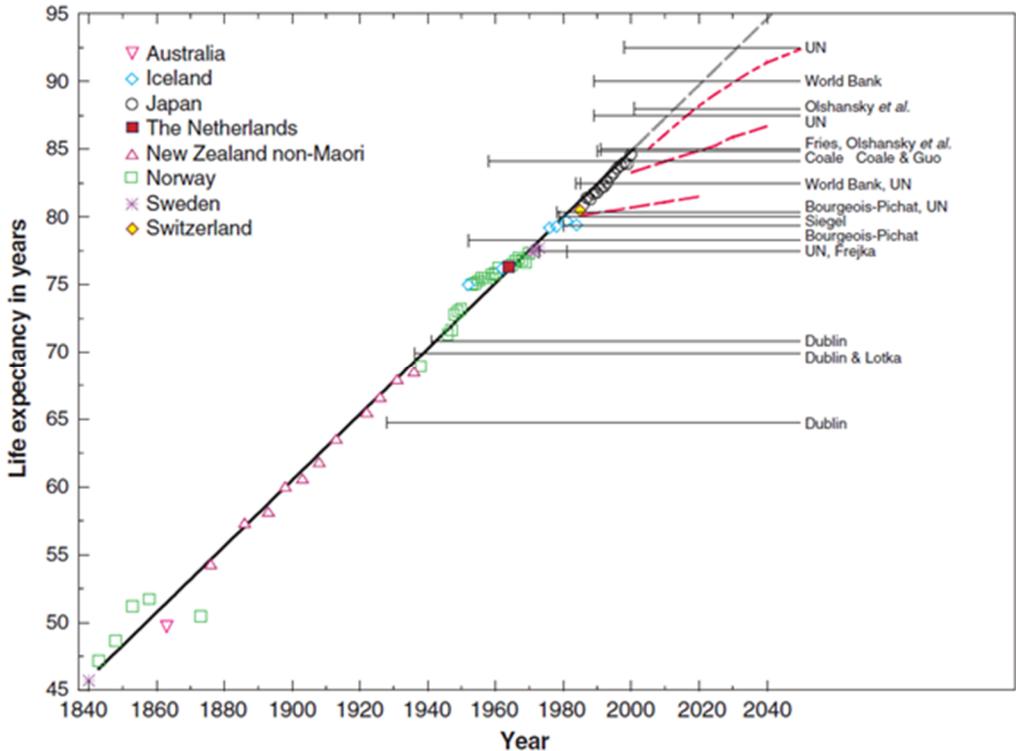
Source: Oeppen J and JW Vaupel JW [1]. Caption as stated in the source: "Record female life expectancy from 1840 to the present [suppl. table 2]. The linear-regression trend is depicted by a bold black line (slope = 0.243) and the extrapolated trend by a dashed gray line. The horizontal black lines show asserted ceilings on life expectancy, with a short vertical line indicating the year of publication (suppl. table 1). The dashed red lines denote projections of female life expectancy in Japan published by the United Nations in 1986, 1999, and 2001. It is encouraging that the U.N. altered its projection so radically between 1999 and 2001." [1]

The remaining life expectancy at the age of 60 and at the age of 65, which is defined as the average number of years a 60- and a 65-year-old person would be expected to live if the current mortality rates continue to apply, increased significantly over the years for men and women for all countries in Europe, the United States, Japan and Korea [25]. In Figure 2, the remaining life expectancy at the age of 65 from 1960 to 2013, for various countries, is displayed.

In Norway the remaining life expectancy at the age of 60 was 15.8 years in 1821 for women, and increased to 20.1 years in 1960 and 25.7 years in 2013; a smaller increase over time was observed for men for the same period (from 15.2 years in 1821 to 18 years in 1960 to 21.7 years in 2013) [29, 30]. Compared to the remaining life expectancy at the age of 60, the remaining life expectancy at the age of 65 increased more (percentage increase) from 1960 to 2013 for both Norwegian women and men (from 16.1 to 21.4 years for women and 14.5 to 18.5 years for men).

An analogous to Norway increase was estimated for Denmark [31, 25] and Iceland [25] from 1960 until 2013, for both the remaining life expectancy at the age of 60 and 65. In Sweden, the remaining life expectancy at the age of 60 increased from 19.3 and 17.3 years in 1960 to 25.7 and 22.9 years in 2013, for women and men respectively. Similarly with the other Nordic countries, the percentage of increase was even higher when the remaining life expectancy was calculated at the age of 65 (for both men and women) [25].

Since 1971, the Nordic country with the highest percentage of increase in the remaining life expectancy at 60 and 65 years of age was Finland; the increase was equivalent with the one observed for Japan over the same period, for both men and women and for both ages [*own calculations from data available online at the Organization for Economic Co-operation and Development (OECD)* [25]].

Assuming that health deteriorates with age, this demographic transition could possibly have an important impact on the proportion of individuals in the population that live "unhealthy", meaning with compromised health. Therefore, it is of high relevance the definition of health and how the health status of the elderly has changed over time, since with a higher number of individuals reaching older ages when severe diseases can occur, this can lead to extensive demand for healthcare resources [3-5]. However, when the ageing of the population is accompanied by improvements in health over time, such increased demand for healthcare resources may not necessarily occur.

Figure 2*: Remaining life expectancy at the age of 65, reported for the years 1960 to 2013, separately for a) men and b) women.*

A) Men
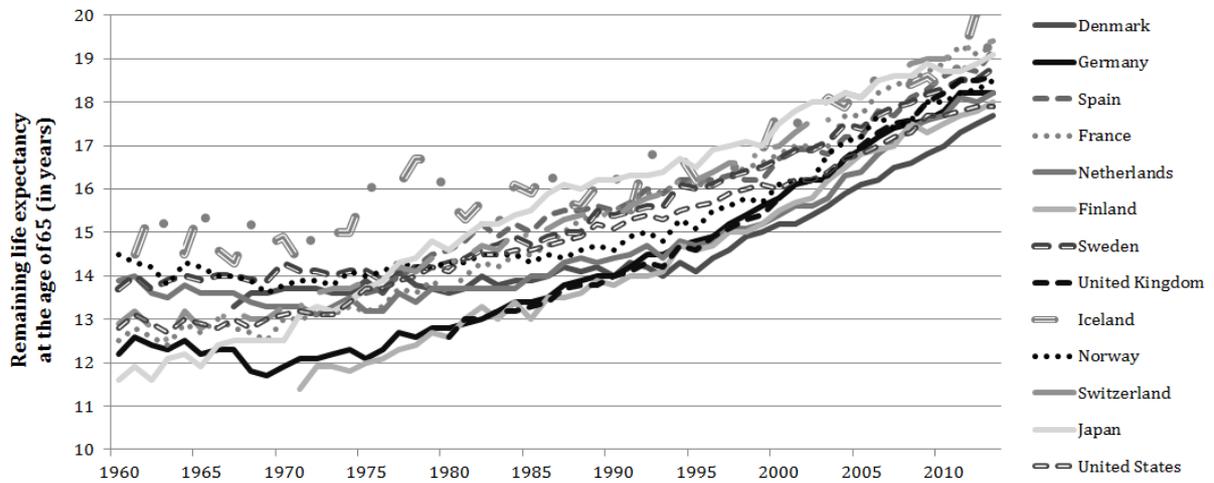
B) Women
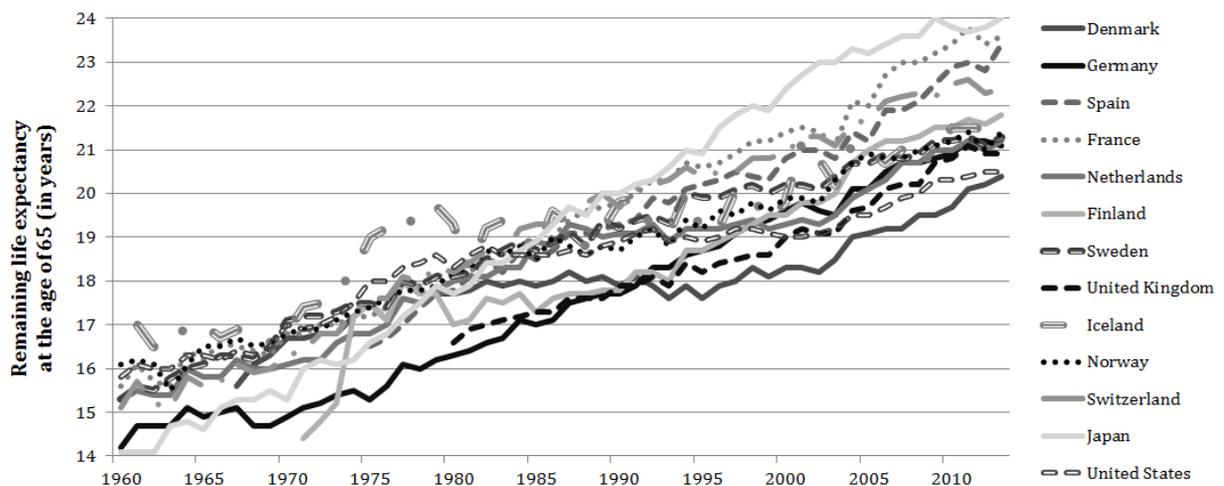
Source: OECD [25]; for missing data, the remaining life expectancy at the age of 65 was either not reported in the figure or the estimation of the previous year was assumed (Iceland, year 1979). Data were compared with information available at the Statistical Office of the European Communities (EUROSTAT) [32]; no numeric discrepancies were found in the remaining life expectancy at the age of 65, neither for men nor for women.

2.3　THE HEALTH OF THE AGEING POPULATION

The health of the ageing population cannot be defined in one single way since morbidity, as well as the quality of life and psychosocial status of the elderly should be considered when investigating health changes in the population over time. The relevant literature, however, is rather inconclusive regarding the choice of the optimal way to define the health of the elderly with different methods being used by studies [8, 33, 34].

2.3.1　Self-reported disability and health status

Many studies have used disability and self-rated health information, e.g. individuals' general well-being, daily limitations, quality of life, etc. to define the health of the elderly, most probably due to the high cost of performance tests and biomarkers for the general health of the individual to implement [8, 35]. These studies either report the health status of the population at a certain point in time (cross-sectional information), or they follow-up individuals over time (re-measurement) in order to identify changes in the health of the study participants. They have used questionnaires, such as Self-Rated Health, Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (iADL), Global activity limitation indicator (GALI), EuroQol-5 dimensions, Short-Form 36, etc. when measuring limitations in the everyday life and quality of life of the elderly.

Such studies in Europe [36-60], US [61-66], and other parts of the world [67-75], have reported conflicting results regarding health trends among the elderly. In Sweden, older studies have indicated that disability and the prevalence of chronic health conditions increased over time for the elderly [76, 77], while recent studies reported stability or some decrease in disability over the years. Angelman et al. reported stable and/or decreasing trends in the prevalence of disability among the elderly for both men and women [36] while in the study by Sjolund et al. disability was found to be stable only for men [52].

As useful as it is defining health through self-reported disability and health status, when looking into disability changes over time as a way to define the health trends in the ageing population, limitations may occur since all self-reported measurements encompass a subjective element and, therefore, reporting may differ significantly, and without apparent reason, between different points in time and across different subgroups that participate in a study [35]. Another limitation is misreporting, which may occur especially when individuals are asked to remember during the past week/month/etc. if they have been able to, for example, get out of bed without help, needed to call a nurse, had pain in their back and for

how many days, and so on [6]. In addition, cultural differences across subgroups (endogenous and immigrant population in a country where the study is conducted), as well as the language barrier, when interpreting the questions, may enhance diverse reporting across subgroups. Given these limitations, this way of defining health may not be optimal when the purpose is to examine changes in the health of individuals over time.

2.3.2 Healthy or disability-free life expectancy

Some studies have measured the "average number of years individuals can spend without disability, if current mortality and disability rates continue to apply", which is called healthy life expectancy or disability-free life expectancy of the population. They measure disability through specific indicators, as described in the section before, constructing age-specific disability weights, and then they combine them with age-specific mortality information, in order to calculate how long individuals are expected to live free from disability [78].

Even if these studies use a similar method to look into health trends among the elderly, still, they report conflicting results across countries with similar lifestyles and levels of economic development [79-81, 27, 82-91, 44, 92-98, 49, 99, 100, 58, 101, 102], most probably due to the limitations imposed by the use of self-reported measurements to describe disability changes over time. Nevertheless, they point out that it is of relevance to know whether the health of the elderly has improved at a higher rate compared with life expectancy (compression of morbidity) [85, 103, 104, 98], at a similar rate (relative compression of morbidity) [103], or whether no health improvements have taken place over time despite increases in life expectancy, resulting in an expansion of morbidity over time for the elderly [105].

EUROSTAT measures the disability-free time at birth, at the age of 50, and 65 in the European population (EU 28 countries) from 2004 until 2013 [106]. According to published information, the time the elderly spend free from disability has been increasing over the years in parallel with life expectancy (Figure 3) [106]. In most of the Nordic countries some increase was reported for both genders over time in the remaining healthy life expectancy at the age of 65, while a decrease of this indicator of health was reported in Norway [106]. In Sweden, an increase was reported for both women and men, with healthy life expectancy at the age of 65 in 2013 being 13.8 years for women and 12.9 years for men [106]. These findings are confirmed by a recent Swedish study where the remaining healthy life expectancy at the age of 65 was shown to have increased between 1980 and 2010; the

increase was found to be more rapid compared to life expectancy improvements, suggesting in this way a compression of morbidity in the elderly population.

Figure 3: Remaining healthy life expectancy at the age of 65 across different countries in Europe, for a) men and b) women.

A) Men
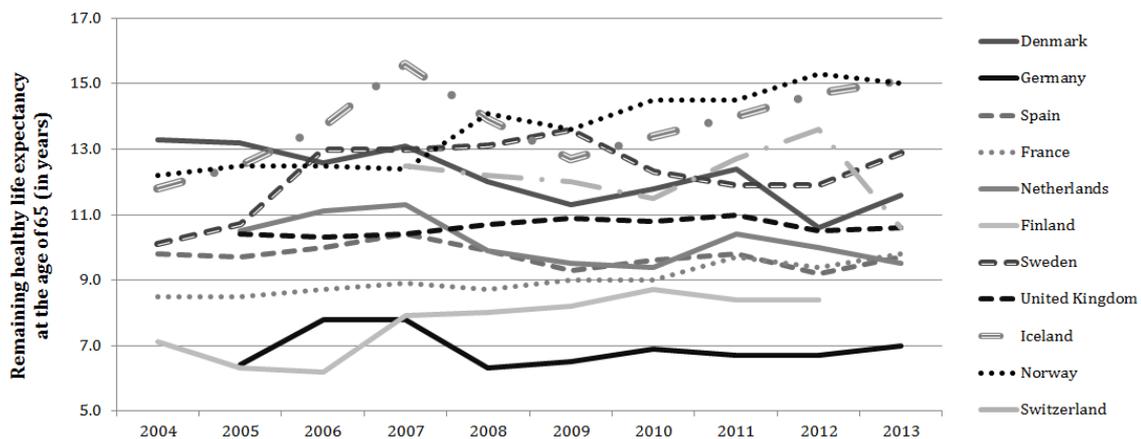
B) Women
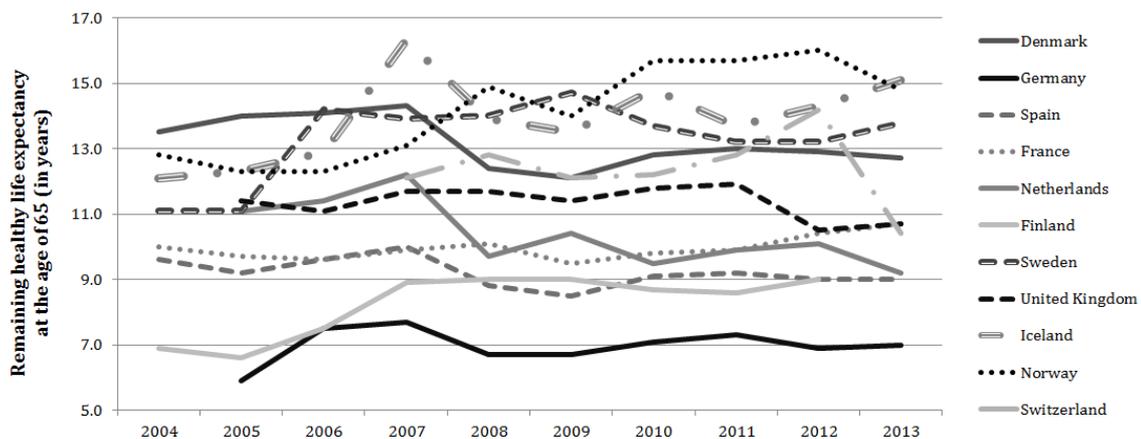
Source: Eurostat [106]; where data were missing, the remaining healthy life expectancy at the age of 65 was either not reported in the figure or the estimation of the previous year was assumed for the missing information (Iceland, year 1979)..

Even if these studies estimating the healthy life expectancy trends provide useful and comparable results regarding the health of the ageing population, their main limitation lies within the use of self-reported information to define health, as mentioned previously; the disability weights that are used in the calculation of the healthy life expectancy are based on

self-rated health information. In addition, often there is a comparison of the healthy life expectancy between 2 or 3 calendar years, thus limiting the possibility to draw conclusions on the health evolvement of the population over a long period of time.

2.3.3 Morbidity from specific diseases

A different method to capture the health status of the elderly is by looking into morbidity, meaning the ill health of individuals, through the incidence of prominent diseases and survival after them. And rather than using self-reported data (e.g. self-reported information about chronic diseases), recorded admissions to hospital for specific diseases could be a good proxy to indicate the onset of severe morbidity. In this way, survival information after the disease can be collected as well. It is common in Nordic countries to conduct studies using information from national registers regarding time and cause for admission to hospital, re-admission, if surgery was performed, etc., time and cause of death after the disease, measuring in this way the morbidity onset and frailty in the population.

In Sweden, a number of such studies has been conducted over the years looking into the incidence of diseases among the elderly and survival after them, utilizing exclusively data from the National Patient Register, the Cause of Death Register, and/or other national and quality registers available in the country. For example, studies have looked into morbidity changes over time for stroke [107-114], myocardial infraction [115-124, 108, 125-128, 112, 129, 130], and hip fractures [131-146], which are prominent diseases among the elderly. Depending on the year the study was conducted, mainly downward trends in the incidence of these diseases have been observed.

Of course, even though such studies can overcome many of the limitations of self-rating one's health, on the other hand, this way of defining health is missing information regarding the subjective burden the disease has imposed on individuals, and how it has altered their quality of life. For example, even if the incidence of myocardial infraction has been decreasing over time, and survival rates after the disease have been improving, still it is not certain whether the disability imposed by the disease on individuals, leading to an extensive use of healthcare resources, has been improving as well.

The fact that survival rates may have been improving over time may be considered a good indicator of decreasing ill health, still, additional information of quality of life would be needed to complement the health status information for the ageing population and indicate whether the increase in life expectancy over time would lead to a compression or expansion of morbidity in the elderly.

3 AIM OF THE THESIS

The overarching aim of this PhD thesis was to explore whether the prolonged life of the older population in Sweden has been characterized by healthy or unhealthy years. By examining the trends in mortality and hospitalization rates due to any or specific diagnoses over time, and by comparing them with trends obtained from self-reported quality of life data, information regarding the overall health of the ageing population can be obtained.

More specifically, the aim of this PhD thesis work was:

- To investigate trends of the age at first hospital admission in relation to life expectancy trends of Swedish men and women above the age of 60.

- To investigate the risk of subsequent hospital admissions, relating them to the risk of a first hospital admission and the proportion of the never hospitalized, among men and women above the age of 60 in Sweden.

- To investigate changes in incidence, lifetime risk, and case fatality of hip fractures, among men and women above the age of 60 in Sweden.

- To investigate whether hospital admissions (seen as a marker for morbidity) are associated with changes in self-reported quality of life in men and women over the age of 65 who participated in the Stockholm Public Health Cohort

4 MATERIAL AND METHODS

Using the Total Population Register in Sweden, the entire population of 60-year-olds or over, living in Sweden since 1987 was defined as the study cohort for the first and third studies, while only the elderly living in Stockholm and Uppsala counties (60-year-olds and over) were chosen as the study cohort for the second study. They had to be living in Stockholm and Uppsala counties since 1972. The study cohort of the fourth study was defined using individuals living in Stockholm county (65-year-olds and over) who participated in the 2006 and 2010 Stockholm Public Health Cohort.

All four study cohorts were followed until the year 2010 in national registers in Sweden for hospitalizations and deaths. This information was linked to the study cohorts using an index number, unique for each individual, which was associated with the personal identification number (personnumer) that every person residing in Sweden bears. The creation of the index number for each individual in the registers and the linking procedure was done by Statistics Sweden. For studies included in this PhD thesis, only de-identified data were used (not possible to link the index number for each individual with his/her personal identification number).

4.1 SWEDISH NATIONAL REGISTERS

The National Board of Health and Welfare in Sweden (Socialstyrelsen), as well as Statistics Sweden (Statistiska Centralbyrån), hold a number of national registers that were used in this PhD thesis. National registers in Sweden were created for administrative purposes; researchers may apply to them for getting access to available data they need for studies.

4.1.1 Total Population Register

It exists since 1968, and was built based on the administrative data the Swedish tax authority (Skatteverket) stores. The Total Population Register contains the demographic information of the population in Sweden, such as the personal identification number (not available for the purposes of this PhD research), full name, address, citizenship, date of birth and death (where applicable), country of birth, date of emigration or immigration, etc. Since the year 1998 the marital status of individuals and an identifier for family relations has also been inserted in the register [147]. Information stored in this register is complete and only death dates for the very old were identified to be missing [148].

4.1.2 National Patient Register

The National Board of Health and Welfare started collecting hospitalization (in-patient care) information in Sweden during the 1960s, creating the National Patient Register (NPR). When the register started, it covered 6 of the 26 counties in the country, while it gradually reached national coverage in 1987. From 2001 the register contains outpatient visits as well (including day surgery and psychiatric care from private and public providers).

The NPR contains demographic information for each patient, as well as administrative information (e.g. date of admission to hospital and discharge, location of the hospital, etc.) and medical data (main and secondary diagnosis for hospital admission using the International classification of diseases (ICD) codes , external cause of injury or poisoning, and surgical procedures) [149]. The validity of the medical data that are included in the register is high, but differs across diagnosis [150].

4.1.3 Cause of Death Register

Until the year 2011, deaths occurring within or outside Sweden are reported, for all individuals that were registered in Sweden (as residents or citizens) at the time of death [151]. After the year 2012, all deaths (excluding still-birth) are reported in the register. The national coverage of mortality in the country started in 1961, while some historic data exist between 1952 and 1960 (the coverage of the country may vary during that period). The main and underlying diagnosed causes of death are reported using the International classification of diseases (ICD) codes [151].

The quality of this register is considered high, while some discrepancy may occur for few diagnoses of death and in the cases where there is no clear indication regarding the main or underlying diagnosis of death [150, 152].

4.1.4 Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

Given the fact that information regarding the migration or death of individuals may not be present for everyone in the population (especially for the very old), the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) [153] was used for the purposes of this PhD thesis to assert that individuals did live in Sweden the year before a hospitalization event or death occurred. This register includes annual income, pension and social transfer information for each individual residing in the country; therefore

individuals were followed over time in this register and were censored at the time when income information was missing.

4.2   THE STOCKHOLM PUBLIC HEALTH COHORT

The Stockholm Public Health Cohort was designed as a prospective study, comprising of the Stockholm County Council public health surveys of 2002, 2006, 2010 and 2014. A random sample of the population, 18 years old and above, living within the Stockholm county was invited to participate in the public health surveys – around 115 000 individuals have participated in the surveys and are part of this longitudinal study [154]. Participants have provided their informed consent to participate in the study and consented having their information from national registers in Sweden linked to the study. An approval by the ethics review board (Dnr 2010/1879-31/5; Dnr 2007/545-31) has been obtain before study commencement [154].

Participants that responded in the 2002 survey were then followed-up in 2007; those responding in 2007 were also followed-up in 2010. In 2006 a new wave of data collection has started, with a follow-up in 2010 of those that participated [155]. The latest survey has been sent out to participants in 2014 [154].

The collection of data was conducted using postal or more recently web-based questionnaires, including information regarding individual's physical and mental health, work and physical/psychosocial work environment, alcohol consumption, tobacco use, physical activity, etc. [154]. Additional information from registers has been also linked to the study.

4.3   STUDY-SPECIFIC METHODS AND STATISTICAL ANALYSIS

4.3.1 Study I

Life tables were constructed in order to obtain the remaining life expectancy, LE, after the age of 60, 70, 80, and 90, and the time from age 60, 70, 80, and 90 until first morbidity for each of the calendar years. The time between first morbidity and death was defined as the difference between the remaining LE and the time from the age of 60 until first morbidity.

First morbidity was defined as the first hospital admission after the age of 60 with a minimum duration of two nights. Both fatal and non-fatal events were taken into account. The International Classification of Diseases (ICD) 8, 9 and 10 was used to determine the causes of hospital admission. All causes were taken into account.

Given that no data were available for hospital admissions before 1987, a transition period had to be applied in order to ensure that the time from age 60 until the first admission to the hospital was not confounded by the existence of a previous hospitalization. A period of seven years was chosen, by comparing the age-specific occurrence of first morbidity using the longest possible follow up period, 23 years (from 1987 to 2010), and by restricting the follow up to 7 years (from 2003-2010). However, first morbidity events were still overestimated for the beginning of the period. To account for this, age-specific correction factors, derived when comparing first morbidity using the longest vs. the shortest follow-up time, were applied on the years 1995-2010, even if after 2003 no real effect was seen from the difference in follow up time.

4.3.2 Study II

Building on the knowledge obtained from the first study, the change in the risk of subsequent morbidity events over time among the elderly was quantified and compared to the change in the risk of a first morbidity event and the proportion of those never having been hospitalized.

A hospital admission due to any cause, with a minimum duration of two nights, was chosen to represent the morbidity event. The first, second, and third morbidity events after the age of 60 were analyzed; a minimum of 91 days was chosen to be the time separating the morbidity events. No transitory period was used in this study since the follow-up of individuals in the NPR was longer compared to study I, started in 1972, thus accounting for a possible overestimation of first morbidity during the first years of follow-up in NPR.

The age-specific risk of being admitted to hospital for the first, second, and third time after the age of 60 was compared over time with a discrete time logistic model, applying a complementary *loglog* link to obtain the relative risk measurement [156]. With this model, the average annual change over all ages, stratified in nine different age groups (60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94, 95-99, and 100+), and in four different time periods (1972-1980, 1981-1990, 1991-2000, and 2001-2010) was calculated. Then, the annual change in the risk was estimated by subtracting the relative change from one (1-RR). For all morbidity events, the model was adjusted for the age at first hospitalization, while for the second and third events the time since the previous event occurred was also accounted for.

In order to calculate the proportion of non-hospitalized men and women over time at a given age, a Kaplan-Meier estimator was used [157]. Five different birth cohorts, 1912, 1916, 1920, 1924, and 1928 were analyzed and the proportions of non-hospitalized individuals were compared for six ages; 70, 75, 80, 85, 90, and 95 years old.

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4.3.3 Study III

This study focused on one single diagnosis, hip fractures, investigating changes over time in the incidence, lifetime risk, and survival after the disease. Hip fracture incidence was estimated using hospital admissions for hip fractures, either as main or secondary cause, based on the National Patient Register (NPR) [149] (International Classification of Diseases (ICD) codes: ICD-9 820. ICD-10 S72 excluding codes S72.3, S72.4, and S72.9). An admission to hospital due to a hip fracture event that had a minimum duration of one night was chosen for the analysis. Hip fracture cases without an overnight stay were not included (n=4 426). The follow-up in the NPR commenced in 1987; a 7-year disease-free period for individuals entering the study population was applied, as for study I.

The lifetime risk of a first hip fracture after the age of 60 was calculated using multiple decrement period life table methodology, with death being the only competing risk [158]. The age-specific case fatality, i.e. mortality among cases, was defined as death of any cause within 3 months (91 days) and within one year (365 days), respectively, of admission to hospital for the first hip fracture.

Similarly to study II, the relative change over time in the incidence and case fatality was quantified using a discrete time logistic model with a *cloglog* link [156]. The age at first hip fracture (treated as a categorical variable) was used as a time-varying predictor of the outcome in the regression models. The percentage (%) of annual change in risk was estimated by subtracting one from the relative change (RR-1).

4.3.4 Study IV

In this study, the effect a hospital admission has on an individual's health-related quality of life (HRQoL), measured using a utility score, was investigated. Utilizing the Stockholm Public Health Cohort and data available in 2006 and 2010 for individuals 65 years old and above, utility was estimated using the EuroQol 5D (EQ5D) instrument [159]. This is a non-disease specific instrument focusing on five dimensions: mobility, self-care, usual activities, pain, and anxiety/depression. Each question has three possible distinct responses: "no problems…", "some problems…", and "I am unable to…". The combination of the five dimensions with the three-level responses gives 243 possible health states, which can be transformed into a utility value, a number ranging from 0 to 1, with 1 indicating perfect health. The transformation was performed using the special weights that are specific for the EQ5D health states and are derived from a normal population in UK [160].

Baseline demographic characteristics were collected for all individuals in order to determine whether there were important differences in age, proportion of females, education and health status (% of hospitalizations) for those that responded to the 2010 follow-up survey vs. non-responders. Individuals with missing information on the EQ5D questions in 2006 or 2010 and all individuals with a hospitalization prior to the study initiation were excluded from the analysis.

The main outcome measured was the change in utility between 2006 (baseline) and 2010 (follow-up) due to one or more hospitalizations for any cause and/or for specific causes. A hospitalization for at least one night was chosen to avoid including admissions for only suspected illness.

The association between the change in utility and hospitalizations was studied using descriptive statistics (two-way associations) and linear regression, where it was possible to control for several covariates that could influence the observed crude associations [161].

4.4 SENSITIVITY ANALYSIS

4.4.1 Studies I and II

In order to explore the impact of three of the most important causes of death and hospital admissions of older individuals, analyses were made where hospitalizations related to CVD (1), neoplasms (2), and mental, behavioral and neurodevelopmental disorders (including dementia and Alzheimer's disease) – applicable only for study II (3) - were removed one at a time. ICD codes were used to identify and exclude the relevant hospital admissions.

The minimum duration of hospital admission was also altered from two nights to one and then to three nights to see if that had any impact on the trends. In addition, in the second study, the impact of the minimum transition time from first to second and from second to third hospital admission was tested by running the analysis with 365 days as a minimum time apart between the events.

4.4.2 Study IV

In order to determine whether the change in utility after hospitalization(s) was influenced by excluding individuals with a hospitalization prior to 2006, and whether the relatively short follow-up of individuals would influence the study outcome, the same analysis was conducted utilizing another (similar) study cohort with a longer follow-up (from 2002 to 2010), which was derived from the Stockholm Public Health Cohort as well.

4.5   ETHICS APPROVALS

For studies I, II, and III, an ethics approval was obtained from the Regional Ethics Committee in Stockholm, Dnr 2011/136-31/5. For the last study of this PhD thesis work, study IV, the relevant ethics approvals that were obtained are the following: Dnr 2011/136-31/5, Dnr 2012/978-32, and Dnr 2013/1828-32.

5 SUMMARY OF THE RESULTS

In this PhD thesis it was found that along with the increase in remaining life expectancy at the age of 60, first overall morbidity after the age of 60, as measured by a hospital admission, was postponed over the years from 1995 to 2010 to higher ages in Sweden, for both men and women.

The time from the first to subsequent overall morbidity, again measured using hospital admissions, has also been prolonged, suggesting that the population is getting older, but not more fragile over time. The time between the age of 60 and the occurrence of the first morbidity increased over the years more than the time between the first and second morbidity. From then on, the time from second to third morbidity increased even less.

The findings regarding overall morbidity in relation to mortality changes over time in Sweden were confirmed when looking into a specific cause of morbidity as well, namely hip fractures. The incidence of hip fractures decreased over time for both men and women and for most ages after 60. However, survival after the first hip fracture did not improve over time for the elderly in Sweden, a result that may be surprising when knowing how the overall health of the elderly has been improving over time.

On the other hand, according to the last study of this PhD thesis, a hip fracture is a severe condition leading to a decrease in the overall quality of life of individuals, possibly accounting for no improvements in survival rates being observed. Regarding the impact of the overall morbidity on the quality of life of individuals, multiple hospitalizations for any cause have resulted in a deterioration of the quality of life, for both men and women.

 A summary of the results deriving from each study is presented below.

5.1 STUDY I

As it was previously mentioned, in this study individuals aged 60 and above, living in Sweden in 1987, were followed over time in the National Patient Register and in the Cause of Death Register for hospitalizations and deaths. The time until first morbidity, as measured by their first admission to the hospital, regardless of the diagnosis, was estimated for the years 1995-2010. In addition, the time from the age of 60 until death (remaining life expectancy, LE) and the difference between these two measurements was also estimated.

It was found that the time from the age of 60 to first hospital admission has been prolonged over time, indicating a postponement of first morbidity to higher ages between 1995 and 2010. Such a postponement has also been observed for the age of death, since the remaining life expectancy at 60 increased over time, for both men and women in Sweden. A compression of morbidity was visible over time for the oldest men and women, in which group the remaining life expectancy was almost stable over the years, while the time to first morbidity has been prolonged. For 60- and 70-year-old women and the 70-year-old men, remaining LE and the time to first morbidity increased at a similar pace, which suggests a relative compression of morbidity. For the 60-year-old men, the remaining LE started to increase after 2003 at a slightly higher pace compared to the time to first morbidity, implying a possible expansion of morbidity (Figure 4).

Figure 4*: Remaining life expectancy (LE) at the age of 60 and time to first morbidity (time to first hospital admission) after the age of 60 from 1995 to 2010, for a) men and b) women.*

A) Men
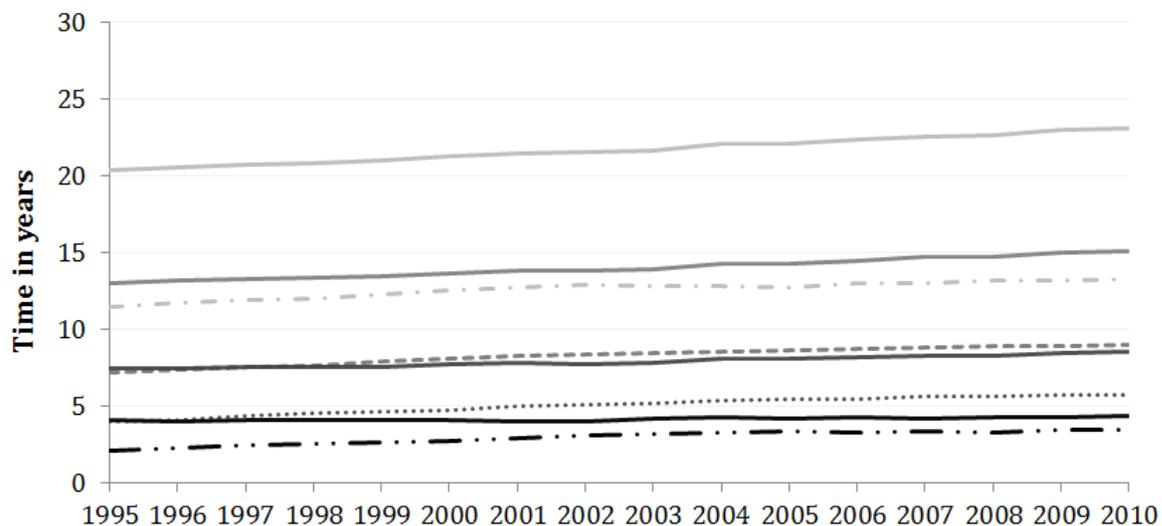
B) Women
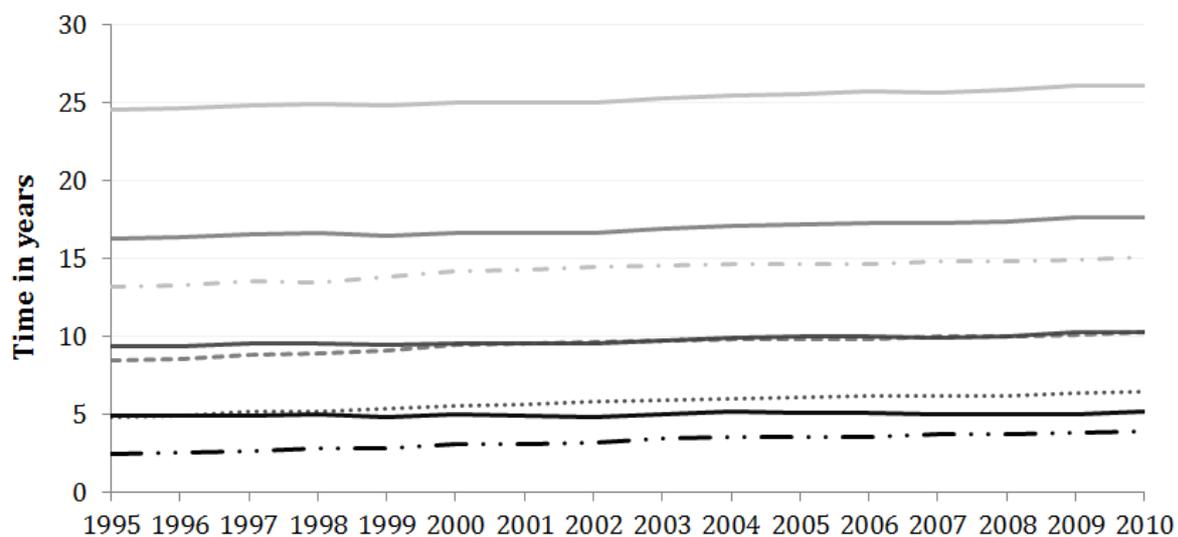
—— Age 60, Remaining LE	–·– Age 60, Time to first hospital admission
—— Age 70, Remaining LE	·--- Age 70, Time to first hospital admission
—— Age 80, Remaining LE	······· Age 80, Time to first hospital admission
—— Age 90, Remaining LE	·— Age 90, Time to first hospital admission

Source [148]

5.2   STUDY II

The postponement of the age of first morbidity over time, and the fact that other studies have shown that survival after many diseases improved over the years in Sweden, could lead to a more fragile population. If such is the case, time to subsequent morbidity could decrease over time. Alternatively, the overall trend of improved health could continue after the first morbidity, also prolonging the time to subsequent one. Therefore, the focus of this second study was on trends in subsequent morbidity, measured again using hospital admission as a proxy, among men and women in Sweden above the age of 60, relating them to first morbidity and the proportion of individuals never having been hospitalized. To answer the study question, individuals living in Stockholm and Uppsala counties in 1972 were followed in the National Patient Register and the Cause of Death Register for hospital admissions and deaths between 1972 and 2010.

Results indicate no evidence for the hypothesis that the postponement of severe morbidity to higher ages renders the population more fragile; hence the risk of subsequent morbidity events would decrease over time. On the contrary, the risks of being hospitalized both for the first and the second time after the age of 60 have decreased by about 9% per decade for men as well as for women on average. For the third admission to hospital, the reduction in this risk was slightly lower, 8% and 6% per decade for men and women respectively. Improvements were observed mainly for individuals below the age of 90 and up to the year 2000.

5.3   STUDY III

The next step after the second study was to look into a specific disease prominent among the elderly, that is hip fractures, and examine whether the observed positive trends for overall health would still hold.

Therefore, this study examined the incidence and lifetime risk trends of hip fractures, as well as time trends of survival after the first hip fracture, in the elderly, 60 years old and above, living in Sweden since the year 1987.

It was found that the age-specific hip fracture incidence decreased between 1995 and 2010 in all ages up to 94 years, by 1% per year on average. The lifetime risk remained almost stable, between 9 and 11% for men, and between 18 and 20% for women. No significant improvements over time were observed regarding the 3-month and 12-month survival, neither for men nor for women (Figure 5).

Figure 5*: Hip fracture incidence, lifetime risk, and case fatality at 3 and 12 months trends from 1995 to 2010, summary measures (results for men and women are presented together).*
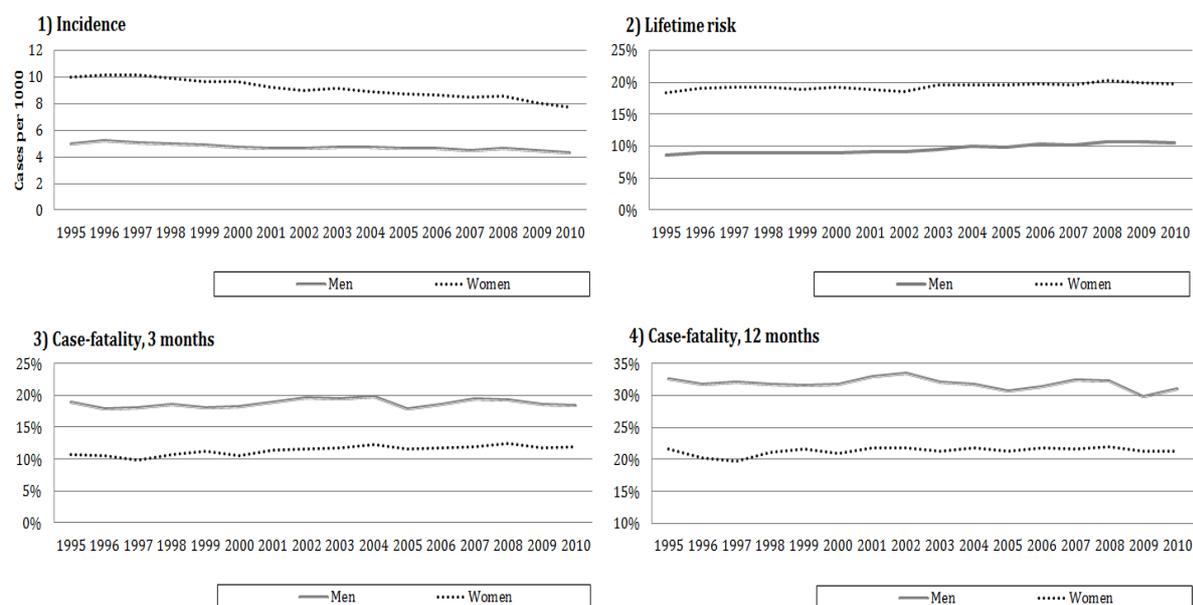
Source [136]

5.4 STUDY IV

This study focused on linking the morbidity definition that used in this PhD thesis with self-reported quality of life information, examining in this way whether the health improvements observed previously for the Swedish ageing population still hold, regardless of the morbidity definition used.

The Stockholm Public Health cohort was used for our study; individuals aged 65 years or older who responded in the 2006 and 2010 surveys and had utility information (measured using the EQ5D questionnaire) were included in the study. Using a linear regression, the change in health-related quality of life (HRQoL) was associated with a hospitalization due to any or specific causes; this change was further adjusted for the following covariates: age in 2006, education, maximum number of hospitalization events, time since last hospitalization, and baseline utility.

Our results showed an additional decrease between 1% and 6.5% in utility (HRQoL) for individuals with any-cause morbidity, while this decrease reached 10% for morbidity from hip fractures, compared to those individuals without any morbidity event, between 2006 and 2010. The decrease was observed for both men and women and for all ages, while it was mainly related to multi-morbidity rather than to an only-one-time event. The decrease in

utility could be explained by the increase in moderate, and in cases severe, mobility problems, followed by an increase in moderate and/or severe problems concerning self-care, usual activities, pain, and anxiety/depression problems.

6 DISCUSSION

This PhD thesis looks into the health of the ageing population in Sweden, in relation to mortality and quality of life, attempting to shed light on the question whether the overall health and quality of life of the elderly has been improving over time in parallel with mortality reductions. The main hypothesis has been that the elderly in Sweden do live longer over time, most probably due to lifestyle changes and preventive medicine advances, which leads to the postponement of prominent diseases and severe morbidity to higher ages, compressing the time they spend in ill health.

The four studies that are part of this thesis were conducted to answer different aspects of the main question posed; study I focused on the changes in the time individuals 60 years and older spend in "good health", i.e the time they are free from severe morbidity, measured by hospital admissions, and how this time relates to improvements in remaining life expectancy over time. The findings of the first study were complemented by the results of the second and fourth studies, examining whether the health of individuals was compromised after their first morbidity event, thus entering a phase of their life characterized by poor health and low quality of life.

The third study included in this PhD thesis focuses on one specific health condition, hip fractures, which is prominent among the elderly in Sweden, aiming to examine whether the conclusions drawn from the first two studies regarding the overall health and mortality of the population still hold while focusing on only one disease. The last study of this PhD thesis, study IV, connects the severe morbidity with its impact on the quality of life of individuals, thus examining how the definition of morbidity used in this PhD thesis, that is hospital admissions, relates to the quality of life of individuals.

6.1 MAIN FINDINGS AND COMPARISON WITH OTHER STUDIES

From the first and second studies of this PhD thesis, it was found that the elderly in Sweden, both men and women, do live longer over time. The remaining life expectancy at the age of 60 has increased substantially, approximately 3 years for men and 2 years for women between 1995 and 2010. In addition, the time from the age of 60 until they experience their first hospital admission, and the age at which subsequent morbidity occurs, has been rising over time [26, 148]. In favor of these findings speaks the decrease of the incidence of serious public health problems, such as myocardial infarction and stroke [124, 108, 111, 117, 125,

130], as well as hip fractures, as indicated by the third study of this PhD thesis [162] and previous studies [131-146].

For the very old men and women in Sweden minimal or no morbidity improvements were found, though, no deterioration in their health was found either [26], which is in line with the development of death rates of Swedish centenarians [28, 163]; the death rates for ages 100 years and older appeared to have been stable between the years 1969 and 2008, while for younger ages a continuous reduction has been observed [28, 163].

There are a couple of Swedish studies, however, which reached different conclusions regarding the changes in overall morbidity in Sweden, namely a worsening of old people's health status over time [76, 77]. These studies used a different methodology to define morbidity, mainly relying on self-reported health indicators. More recent studies confirm that there has been at least stability, with downward trends, in disability and morbidity among the elderly in Sweden [36, 52].

However, when studies mainly measure health by looking into specific (self-reported or observed) disease occurrence, by relating the age-specific decrease of disease incidence with the overall increase in the life expectancy of the population, this methodology, can underestimate the health improvements over time. As seen from the third study of this PhD thesis, describing the hip fracture trends in the Swedish population, the incidence of a disease has to decrease considerably and for all ages, in order to compensate for the increase in the number of old and very old individuals in the population over time. When assuming no increase in the number of the elderly over time (holding the life expectancy of the population at the levels of the initial measurement), the lifetime risk of the disease (disease occurrence) can decrease over time even with small improvements in its incidence.

In addition to the lifetime risk of hip fractures, in the third study of this PhD thesis the incidence and survival from hip fractures have been examined. Decreasing age-specific incidence trends of hip fractures in ages up to 94 years in Sweden were found, which constitute similar to other studies findings in Sweden and for other countries in Scandinavia [131-146]. In the latest study conducted about Sweden, however, incidence trends were presented for very large age groups 65-79 and 80+ years of age [142]. Since the risk of hip fractures increases with age [164, 165] and life expectancy has increased over the same period [148], it is difficult to disentangle effects among the old in such broad age groups. Therefore, this study contributes to the existing literature by presenting decreasing incidence trends in 5-year-age groups and for all ages up to 95+ years.

The focus of the fourth study was to describe the association between hospitalizations with the change in the quality of life of individuals, also looking into factors influencing this association. Results indicate no clear association between the first any-cause hospitalization and a decrease in quality of life for men and women. This may come as a paradox, bearing in mind that hospitalizations for the ageing population may lead to long-term disability and, therefore, a reduction in the general well-being of individuals. However, it is in line with study II indicating no accumulation of frailty after a hospitalization leading to subsequent ones [26].

Multiple hospitalizations, on the other hand, indicating a multi-morbidity status, did result in a decrease in quality of life, a finding that was confirmed previously [166-172]. In Sweden, a study by Gimby et al. in 1997, found HRQoL decrease in multi-morbidity among 76 year-old individuals living in Göteborg [166]. Another study, involving 85-year-old individuals residing in Linköping, Sweden, revealed that those hospitalized at least once 12 months prior to the study had significantly more quality of life problems compared to individuals who had not been hospitalized [167].

6.2   INTERPRETATION OF THE FINDINGS

6.2.1 Postponement of morbidity and mortality

Survival improvements have been found over time among the elderly in Sweden, which are attributed to the decrease in the occurrence of prominent diseases among them, for instance cardiovascular problems, as well as to the lower case fatality after severe morbidity.

Regarding the postponement of first and subsequent morbidity to later stages in life, measured using hospital admissions as a proxy, this contradicts the idea that after retirement, around the age of 60, the health condition of individuals deteriorates significantly, to the extent that they need extensive healthcare and medical support. The results of the studies also indicate that the ageing process may not necessarily be genetically pre-programmed in our body but external, environmental, factors are potentially able to influence the overall health of individuals. So, when overall reducing the risk factors leading to ill health of the population by better controlling over time serious diseases in a primary care setting, through prevention medicine, better access to care, advanced medical treatments, etc., improvements in the morbidity levels, as well as survival after prominent diseases can be observed over time for the elderly in Sweden.

The reduction in the annual risk of the first and subsequent hospital admissions among the elderly in Sweden was mainly evident during the decades of the 1980s and 1990s; no clear improvements were observed for the most recent decades (2000s and 2010s). This finding may be attributed to a temporal stagnation of morbidity improvements, not affecting the overall trends when allowing for longer follow up in the next decades. It may, however, also be a sign of a real stagnation of improvements. The effect of a single (period-) factor, such as the increase in elective surgery among the elderly in Sweden, could be responsible for the stagnation observed (causing the number of hospital admissions to rise); however, such procedures constitute a minor part of all hospital admissions in Sweden therefore their impact on the general morbidity trends of the elderly population should be minimal.

6.2.2 Morbidity compression and frailty hypothesis

Comparing improvements in the first morbidity after the age of 60 with mortality reductions over time, a compression or relative compression of morbidity was evident from the first study of the thesis, mainly for younger individuals (up to 80 years of age). For the very old, no significant improvements in mortality have been noted over time; however, morbidity has been postponed to even higher ages for this group of individuals, too [148]. Moreover, even though the first morbidity event has been occurring in later stages in the life of the elderly in Sweden, this has not rendered individuals more fragile over time, also extending the time to second or third morbidity event over time, thus contradicting the frailty hypothesis according which ageing is linked to the deterioration of the health status of individuals. In fact, as indicated by the second study of this PhD thesis, the age-specific annual risk of a second and third any-cause morbidity event was also reduced from 1995 to 2010 for both men and women up to ages of 90 years.

On the other hand, the findings of the third study in a way confirm the frailty hypothesis, since they do not speak in favor of improvements in survival from hip fractures over time for the elderly in Sweden. For other prominent conditions though, such as myocardial infraction and stroke, an improvement in survival over time has been observed for this population [108], indicating that hip fractures probably comprise a special category.

The lack of hip fracture survival improvements could be attributable to a high risk profile for other severe comorbidities, such as cardiovascular diseases, subsequent fractures, infections, malignancies, etc. In fact, mortality changes in comorbid conditions over time could influence the hip fracture survival trends. However, in the third study the causes of death within a period of 3 months and 1 year after the first hip fracture were examined, and no

changes were found in the composition of the underlying causes of death over time. Therefore, there is no evidence supporting this alternative hypothesis. It is probably that the lack of improvements observed could be related to the severity of the fracture itself or other factors, such as delay in surgery [135], or shortening of length of stay in hospital after the fracture [173].

6.2.3 Morbidity and quality of life

From the first three studies that are part of this PhD thesis it is evident that the health of the ageing population has been improving over time for both men and women in Sweden. The fourth study that has been conducted strengthens this conclusion, indicating that the health-related quality of life (HRQoL) does not decrease after one hospitalization.

Study IV enables the connection of morbidity, measured by the number of hospitalizations in older ages, with the change in HRQoL, thus allowing combining information both from recorded and self-reported measurements regarding the health of elderly Swedish population. Its distinct advantage lies with the use of registry data to collect hospitalization information; not relying on the study participants to collect information on the exposure eliminates the possible misreporting of past events.

The study's findings speak in favor of the non-accumulation of frailty in the population after one morbidity event. However, when looking into multi-morbidity, three or more hospitalization events during a determined amount of time, a decrease in HRQoL was observed for both men and women. Therefore, hospital admissions, as well as their cause and frequency over time, could be a useful marker for the advent of a period of life with compromised quality of life, rendering them a plausible measure of morbidity.

6.3 GENERAL METHODOLOGICAL CONCERNS

There are some methodological concerns about the particular studies comprising this PhD thesis, related to the definition of morbidity using hospital admissions as a proxy, the definition of the time individuals are morbidity-free, the availability of data from national registers in Sweden, and the way quality of life measurements were used in order to describe the time individuals live with compromised health.

6.3.1 Hospital admission as a proxy for morbidity

In this PhD thesis morbidity is captured using hospital admissions. Therefore, a morbidity event presented in studies I, II, and IV constitutes a hospital admission for any cause, with a

specific length of stay. This definition ensures that any health-altering condition requiring a hospitalization is considered in the analysis; it is dependent, though, on healthcare changes occurring in Sweden between 1987 and 2010, namely the shift from inpatient to outpatient care for certain diseases, the shortening of the length of stay in the hospital over the years, [174, 175] and the reduction in the number of hospital beds [176].

Over time in Sweden the treatment of certain minor conditions, such as eye diseases, has changed from in- to outpatient care. This change could in theory create a bias related to the comparability of annual hospitalization rates; a decrease over the years in the probability of getting hospitalized for these minor conditions could falsely indicate that morbidity has been postponed to higher ages, while in fact hospitalizations simply do not appear in the data. Such a bias, however, would not be expected to be large, due to the fact that very few diagnoses previously treated only with inpatient care, are now treated solely in an outpatient setting. Our data indicate that cardiovascular diseases and neoplasms are the two main causes of all admissions to hospital for the elderly in Sweden, followed by injury, poisoning and certain other consequences of external causes (ICD 10 codes: S00-S99 and T00-T98, ICD 9 codes: 800-999), diseases of the musculoskeletal system and connective tissue (ICD 10 codes: M00-M99, ICD 9 codes: 710-739), and diseases of the digestive system (ICD 10 codes: K00-K93, ICD 9 codes: 520-579). All these conditions are exclusively treated in an in-patient setting.

Moreover, the fact that some diseases are better monitored in primary/outpatient care nowadays in Sweden compared to 20 years ago (e.g. high blood pressure), therefore delaying admission to inpatient care, indicates a population that has postponed severe illness, strengthening in this way our hypothesis and conclusions regarding the postponement of severe morbidity to higher ages in line with mortality reductions.

Regarding the length of stay in hospital in Sweden, this has decreased in the last 20 years [30], while hospitalizations have become more frequent. This fact is also supported by a Danish study for the oldest-old, comparing hospitalizations in the cohort of 1895 with the cohort of 1905. The younger cohort went through more frequent hospital admissions but had shorter length of hospital stay [177]. However, such a change would only pose a limitation and possible bias for the results of this PhD thesis if the definition of hospitalization were based on particularly lengthy hospital stays. To overcome this limitation, a hospital admission for any cause had to have a minimum duration of 2 days in the first study of this thesis, and one day for the rest of the studies. This duration is the minimum required so that suspected illness is differentiated from actual diseases altering the health of individuals.

In addition, first and subsequent morbidity events had to be apart for a predetermined amount of days in study 2, in order to ensure that the transition from longer to shorter and more frequent hospitalizations would not be responsible for the observed morbidity trends. Nevertheless, since the assumptions for the minimum length of stay in the hospital and the way first and subsequent hospitalizations are differentiated could be considered arbitrary, lacking medical reasoning, a sensitivity analysis was performed in all studies, altering them; still, no changes in the conclusions drawn from each study could be decided based on the sensitivity analysis findings, revealing that these assumptions most probably do not constitute a source of bias.

Another important structural change concerning healthcare in Sweden is with regards to the number of hospital beds; a decrease in the number of beds has been observed since 1987 [176]. This change is probably one of the reasons why the length of hospital admission has also decreased over time. Regarding the decrease in the number of hospital beds, this could be a possible source of bias for the studies, even though it is mainly a consequence of a more efficient healthcare [176], not necessarily affecting the likelihood of getting admitted to hospital. Still, if the probability for being admitted to hospital has decreased over time, the postponement of any cause morbidity, and/or hip fracture incidence, to higher ages could be partly explained by this change.

Finally, the existence of home care programs in Sweden, having been designed to enable the elderly to live an independent life [178], could explain part of the shift in all-cause morbidity to higher ages, since elderly individuals receiving home care may not be admitted to hospital for conditions that can be monitored through home care services. However, based on the studies conducted within this PhD thesis regarding the all-cause morbidity trends, it is difficult to evaluate how much the effect of such programs on trends would be.

6.3.2 Definition of being morbidity-free

In this thesis, the time individuals are free from morbidity is related to the time they are free from hospitalizations, as a consequence of defining morbidity through hospital admissions. Therefore, diseases that would be treated by a general practitioner or specialist in a primary care setting, would not be captured in this definition. This, however, does not constitute a limitation for the studies conducted. The definition of morbidity, and as a consequence, being morbidity-free, only refers to conditions altering significantly and in cases permanently the health status of the elderly, in other words it refers to severe morbidity, not temporary states of illness. Since the aim was to study the change from "good" to compromised health, which

can be accomplished when looking into hospitalizations, especially for prominent diseases such as myocardial infraction and cancer, this definition was necessary to ensure that morbidity events are properly described.

If the individual visits her/his general practitioner for a minor, easily treatable condition, this may temporality take her/him out of the "good health" status, but soon enough full health will be re-obtained, unless her/his health condition worsens, forcing an admission to hospital, which is the event captured in all four studies. Therefore, being hospitalization-free could, in the end, be translated into being free from long-term, burdening, morbidity.

Regardless of the definition of morbidity though, limitations appeared when defining the morbidity-free time as a consequence of the availability of data in the National Patient Register (NPR), that is the source of hospitalization information. NPR acquired national coverage in Sweden in 1987, which means that no information for all hospitalizations in the country was available prior to that year, thus not being able to observe the full health history of the study cohort. Therefore, additional assumptions, such as the disease-free period that was applied in all three studies, plus the weights used in the first study, were made to ensure that only morbidity-free individuals enter the follow-up and if they occur a hospitalization this would in fact be considered the first morbidity event.

6.3.3 Identifying disease-specific morbidity using register data

In the third study of this PhD thesis, hip fracture incidence trends were studied; for the purpose of this study the National Patient Register (NPR) in Sweden was used to identify morbidity from hip fractures. Such a choice was not arbitrary, but was based on the methodologies and data sources of previous studies in Sweden that describe the change over time in the panorama of this disease. Still, as valid a choice as it may appear, it may raise methodological concerns when considering the coverage of the population in the NPR regarding this condition, and the quality of the diagnosis described in the NPR, used in order to define hip fracture events in the third study.

As mentioned above, since the NPR first had national coverage in 1987, additional assumptions had to be made in order to ensure that the first hip fracture case was not a re-occurrence of a hip fracture event. In addition, hip fracture morbidity was defined in the same way as all-cause morbidity, i.e. requiring a minimum length of stay in hospital. This assumption actually strengthened the incidence estimations rather than posed a limitation, since merely any suspected hip fracture cases were included in the analysis.

Concerning the quality of the hip fracture diagnosis in the NPR, previous studies have shown that the disease codes entered in the NPR system by the treating nurses/surgeons are, in the majority of the cases, accurate, correctly indicating the existence of a hip fracture [179]. Nonetheless, the diagnosis of a hip fracture is obtained after a physical examination to the patient and an X-Ray, strengthening in this way its accuracy. However, the sequence in which the hip fracture diagnosis would appear in NPR, along with the other co-morbid conditions a patient has, may not be a standardized practice among physicians. Therefore, when looking into the changes in the first hip fracture event over time, it was crucial to ensure that all possible events would be captured, regardless of the position of the event (first or subsequent diagnosis registered in the NPR). For this reason, main or secondary hip fracture diagnosis was used in the analysis, as opposed to using only the main diagnosis indicating a hip fracture event.

6.3.4 Defining and measuring health-related quality of life

In the fourth study of this PhD thesis, the change in health-related quality of life (HRQoL) was estimated in association with morbidity, measured using hospital admissions as a proxy (in line with the previous three studies). It was defined using a utility index as a proxy, which was obtained from the EuroQol 5 dimensions (EQ5D) questionnaire. EQ5D is a common, multiple times validated for many languages and cultures, questionnaire [159]. Even though it is a generic instrument, it is able to capture change in many diseases [180], among the elderly as well [181], and it has shown to be able to predict morbidity and mortality [182]. In this study, all individuals with hospitalization events prior to 2006 when the study was commenced were excluded to ensure that the outcome of the study would not be influenced by the presence of previous hospitalizations and thus violate the causal pathway of hospitalization and change in HRQoL.

However, its main limitation lies with its ability to capture only long-term, rather permanent disability, but not periodical, since the period individuals reported their discomfort, pain, mobility, and mental health problems, was for "the past week". Therefore, it is expected that exposure (hospitalizations in this case) leading to long-term disability could be more strongly associated with the outcome of the study, which was the change in HRQoL. This limitation was also identified in a previous Swedish study, conducted in 1997 in Göteborg; the researchers have found that HRQoL, mainly the emotional and social dimensions, were not much influenced by morbidity until the amount of disability accumulated by individuals in the study was significant [166].

In the fourth study of the thesis, given that only two time-measurements of HRQoL were available in the data (start of the study, 2006, and then 4-years after, 2010), it was not possible to overcome the limitation of possibly only capturing temporary disability. In addition, the change in HRQoL for each individual may have been influenced by the time since the last hospitalizations parameter (even if the linear regression models counts for this bias). Had we had more systematic measurements of HRQoL, then a more significant association between HRQoL and hospitalization could have been observed.

Moreover, the interpretation of the size of the change in HRQoL, in association with hospitalizations, was not straightforward. The utility index used as a proxy of the HRQoL could not reveal what the consequences of an e.g. 3% decrease in utility would be for the health of individuals. To overcome this limitation, additional analysis aimed to better describe the change in HRQoL, using the five dimensions of health available from the EQ5D questionnaire; still, the interpretation of the importance of the change remained rather unclear.

6.4   ETHICAL CONSIDERATIONS

In this PhD thesis, individuals' demographic, health and death information available in the Swedish national registers has been used. Such data constitute personal sensitive data according to the Personal Information Act (PUL 1998, Sections 3 and 13) [183] and even though access is prohibited, an exception can be made for research that is of public interest to be performed, e.g. potentially beneficial results leading to disease prevention (PUL 1998, Section 18 [183]). The databases containing the information were linked using individuals' personal identification number (personnumer). The linkage was conducted by Statistics Sweden and the researchers involved in the studies only received anonymized data, without having access to the original data containing the personal identification number of individuals. Information could potentially have become more "identifiable" if it would have been linked to e.g. birth register and multigenerational register (access to date and place of birth and who the parents are); however, none of the researchers involved in the studies conducted within the framework of this PhD thesis had any interest in de-identifying the individual information, hence such attempts have not been made.

Individuals participating through the registers in this study were not asked for their informed consent for the use of their data, which may be in contrast with the fundamental statements of the Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" [184] and the PUL 1998, Section 10 [183]. However, in the same statement is is

also mentioned that informed consent should be obtained when it is possible - but in the case of Register Based research using large national registers it is not feasible to ask every single individual in the registers for their consent to participate. Despite this limitation, data holders (the National Board of Health and Welfare in Sweden in this case) require that information about the study be published on their webpage so that it is accessible to the general public.

Furthermore, the data used in this PhD thesis have been archived according to the Archiving Law in Sweden [185, 186], safely stored in a secure server at the Institute of Environmental Medicine, Karolinska Institutet, and only the researchers having worked with these data were allowed to access the material. Last but not least, no deletion of the original data has or will occur.

7 CONCLUSIONS

The four studies conducted within this PhD thesis were aimed to answer the question whether morbidity has shifted to higher ages in line with mortality reductions among the elderly in Sweden.

The main finding was that the time individuals over the age of 60 spend in "good" health (without a hospital admission or a hip fracture), has been improving over time, suggesting a compression or relative compression of morbidity in Sweden over the years. In addition, frailty does not seem to have increased over time, neither have any significant quality of life reductions due to morbidity occurred, at least not severe ones, which implies that the overall health of the elderly in Sweden has been improving over time.

The improvements in health that were observed could have resulted from the reduction in the incidence of prominent diseases among the elderly, such as cardiovascular conditions and hip fractures. Lifestyle changes and living conditions among the elderly, as well as the re-organization of healthcare in Sweden over the past 20 years, aiming to improve disease prevention, may be the underlying mechanism of this positive change in health.

Future research could focus on the implications of the changes observed within the framework of this thesis, investigating healthcare initiatives that could lead to further morbidity reductions.

8 SAMMANFATTNING PÅ SVENSKA

I Sverige, liksom i de flesta andra länder, har medellivslängden ökat markant under hela 1900-talet. De senaste decennierna har ökningen i medellivslängd nästan uteslutande skett som en följd av sjunkande dödlighet i högre åldrar. Förbättringar i livslängd beror antingen på att sjukdomar förskjuts uppåt i åldrarna, dvs. att vi blir friskare, och/eller att vi överlever våra sjukdomar i högre utsträckning. Den övergripande frågeställningen i denna avhandling har varit huruvida hälsan hos den åldrande befolkningen i Sverige har ökat i samma utsträckning som livslängden. Detta har studerats med hjälp av nationella register över Sveriges befolkning (studie I till III) samt i den fjärde studien med hjälp av survey-data från Stockholms folkhälsokohort tillsammans med registerdata över sjukhusinläggningar.

I studie I undersöktes hur tiden från 60 års ålder fram till första sjukhusinläggning, som en proxy för sjuklighet, har förändrats över tid och om denna eventuella förskjutning är i paritet med den ökade livslängden. Resultaten visade att tid till första sjukhusinläggning efter 60 år har förskjutits mot högre åldrar, i linje med dödligheten. I studie II undersöktes om detta gällde även för upprepade sjukhusinläggningar. Om tiden till första inläggning förskjutits mot högre åldrar skulle det kunna vara så att tiden till andra eller tredje inläggning inte har förbättrats, pga att individer är äldre och därmed mer sköra vid sjukdom. Våra resultat visade emellertid att så inte var fallet, även tid till andra och tredje inläggning har förskjutits mot högre åldrar, för både män och kvinnor och för de flesta åldrar.

I studie III valdes en specifik diagnos ut för at studera äldres hälsa, höftfrakturer. Förändring i incidens, överlevnad och livstidsrisk beräknades för män och kvinnor från 60-99 år för perioden 1995 till 2010. Resultaten visade att incidensen av höftfrakturer har minskat över tid för män och kvinnor upp till 94 år. Däremot observerades inga förbättringar i överlevnad eller i livstidsrisk.

Eftersom registerinformation om sjukhusinläggningar och diagoser inte kan fånga upp hela sjukdomspanoramat gjordes i studie IV en analys över hur sjukhusinläggning påverkar hälsorelaterad livskvalitet, mätt med EQ5D-index. Individernas hälsorelaterade livskvalitet mättes vid en tidpunkt, 2006, och individerna följdes därefter upp med avseende på sjukhusinläggning. Efter 4 år mättes deras hälsorelaterade livskvalitet igen och en skattning gjordes i vilken grad sjukhusinläggning predicerade en negativ förändring i livskvalitet. Resultaten visade att endast en sjukhusinläggning inte resulterade i någon försämrad livskvalitet. Upprepade inläggningar och inläggningar för specifika diagnoser gav däremot en viss försämring av livskvaliteten.

Sammanfattningsvis så visar resultaten i avhandlingen på en viss komprimering av sjukligheten i den äldre befolkningen. Tiden i livet fram till första sjukhusinläggning och första höftfraktur har förskjutits mot högre åldrar. Samtidigt har detta inte lett till att tiden till andra eller tredje inläggning har förkortats. Förbättringar i livsstil och preventiva åtgärder har troligen bidragit till dessa förbättringar.

9 ACKNOWLEDGEMENTS

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