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A case study on osteoporotic fracture patients

Hansen, Louise

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THE IMPORTANCE OF EPIDEMIOLOGICAL PREDICTORS FOR HEALTHCARE COSTS FOR CHRONIC PATIENTS

A CASE STUDY ON OSTEOPOROTIC FRACTURE PATIENTS

BY
LOUISE HANSEN

DISSERTATION SUBMITTED 2016

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CV

Louise Hansen graduated from Aalborg University in 2012 with a master degree in Medicine with Industrial Specialisation. Her master thesis was written in collaboration with MSD Danmark and Peter Vestergaard and focused on the economic burden of osteoporosis. This project inspired her to work with osteoporotic patients, trying to improve the care these patients are offered following a fragility fracture, and subsequently resulted in her enrolment as a Ph.D. student on May 1st, 2013.

Especially the work with Danish registers and the application of these to health economic research has inspired most of her publications and, consequently, the work in this thesis. This work has resulted in presentations at several international conferences, including the 10th World Congress in Health Economics, ISPOR 17th and 18th Annual European Congress, and World Congress on Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases 2014 and 2015. Furthermore, Louise spent three months at the Garvan Institute in Sydney, Australia, where she worked alongside two of the leading researchers within osteoporosis and fragility fractures, Professor John A. Eisman and Associate Professor Jacqueline Center.

During her enrolment as a Ph.D. student, Louise has been a member of the Ph.D. Study Board at the Faculty of Social Science, the network of Ph.D. students at the Faculties of Social Science and Humanities (DELPHI), and the Academic Council at the Faculty of Social Science.

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SUMMARY

Healthcare systems around the world continue to see their expenditures increase, measured as a percentage of gross domestic product. Within health economics, the need for models that can predict healthcare costs is of substantial importance, as decisions to introduce as well as to decommission healthcare services are based on these. This dissertation is an attempt to highlight the importance of epidemiological factors for health economic research on chronic diseases. Hence, the research question of interest is: how do individual epidemiological and behavioural factors impact the healthcare utilisation of patients with a chronic disease, e.g. osteoporosis?

This dissertation proposes a framework for predicting healthcare utilisation which includes four steps: familiarisation with the study population, determining the appropriate resource use, determining which predictors are important to consider, and lastly choosing the most appropriate statistical model. This framework was developed as a result of five quantitative studies, of which four were based on patient specific data from registers, and one on cost of illness theory. The framework was applied for predicting the cost for all fractures patients in one year following the fracture, *i.e.* the fifth study included in this dissertation. This study showed that it is not only important to understand the population of interest, as this eases the subsequent identification of potential predictors, but also the healthcare system through which these patients are treated, as different resources were affected differently by the clinical and behavioural predictors included.

In conclusion, the results from this dissertation highlight the importance being familiar with the population of interest, identifying the relevant resources, including both epidemiological and behavioural predictors, when analysing outcomes from both an epidemiological and health economic perspective, and choosing the right statistical model to analyse all this with. Both health and social scientists interested in researching utilisation of healthcare should consider these four steps.

RESUME

Mængden af penge som bruges på sundhedsvæsner rundt om i verden er enorm, og på trods af adskillelige finanskriser, bliver den relative andel af vores forbrug på sundhed ved med at sige. Inden for sundhedsøkonomisk forskning er behovet for modeller som kan prædiktere sundhedsomkostninger stigende, fordi udbydere af sundhedsydelser i mange lande baserer deres beslutninger om at tilbyde eller afskaffe disse ydelser på sådanne modeller. Denne afhandling er en forsøg på at belyse vigtigheden af epidemiologisk forskning i forhold til sundhedsøkonomisk forskning af kroniske sygdomme. Forskningsspørgsmålet for denne afhandling er derfor hvordan individers epidemiologiske og adfærdsbestemte karakteristika har indflydelse på forbrug af sundhedsydelser for patienter med en kronisk sygdom, som eksempelvis knogleskørhed.

I denne afhandling præsenteres en model for hvordan forbrug af sundhedsydelser kan prædikteres. Denne model er baseret på erfaringer fra fem tilhørende kvantitative studier, hvoraf fire er baseret på individ data fra danske registre og et studie er baseret på cost-of-illness teori. I denne afhandling blev modellen testen på en population af danskere som pådrog sig et knoglebrud. Studiet viste at det var vigtigt ikke kun at have forståelse af populationen, som letter identifikationen af de efterfølgende prædiktorer men samtidig også opgørelsen af ressourcer for patientgruppen.

Overordnet viser afhandlingen, at kendskab til patientpopulationen, identifikation af relevante ressourcetræk for samme gruppe, inklusion af individers epidemiologiske og adfærdsbestemte karakteristika som prædiktorer til forbruget af sundhedsydelser, og valg af statistisk model, alle er vigtige parametre at afklare inden en model af forbrug af sundhedsydelser konstrueres. Dette gælder for såvel sundhedsvidenskabelige som samfundsvidenskabelige forskere.

LIST OF ABBREVIATIONS

BMD	Bone Mineral Density
CPR	Central Personal Register
DRG	Diagnosis Related Groups
DXA	Dual-energy X-ray Absorptiometry
GDP	Gross Domestic Product
GLM	Generalised Linear Model
ICD-10	International Classification of Diseases 10th version
NICE	National Institute for Health and Care Excellence
NPR	National Patient Register
SD	Standard Deviations

LIST OF INCLUDED PUBLICATIONS

Paper I **Subsequent fracture rates in a nationwide population-based cohort study with a 10-year perspective**

Louise Hansen, Karin D. Petersen, Stine A. Eriksen, Bente L. Langdahl, Pia A. Eiken, Kim Brixen, Bo Abrahamsen, Jens-Erik B. Jensen, Torben Harsløf, Peter Vestergaard
Osteoporosis International, 2015; 26(2): 513–9

Paper II **A health economic analysis of osteoporotic fractures: who carries the burden?**

Louise Hansen, Anne Sofie M. Mathiesen, Peter Vestergaard, Lars H. Ehlers, Karin D. Petersen
Archives of Osteoporosis, 2013; 8: 126

Paper III **Vitamin D and calcium deficiency are the main predictors for patients with osteoporosis to remain at high risk despite benefit of prior bisphosphonate treatment – a Danish case-control study**

Louise Hansen, Karin D. Petersen, Stine A. Eriksen, Fredrik Gerstoft, Peter Vestergaard
Submitted

Paper IV **Socioeconomic factor's influence on treatment patterns following an osteoporotic fracture**

Louise Hansen, Jacqueline Center, John Eisman, Matthew Tan Zhen-Wei, Peter Vestergaard, Karin D. Petersen
Manuscript

Paper V **The effect of socioeconomic status on healthcare-related costs accumulated one year after fracture**

Louise Hansen
Manuscript

Related papers by the author

The epidemiology of fractures in Denmark in 2011.
J. Driessen; L. Hansen; S. A. Eriksen; H. van Onzenoort; R. Henry; J. van den Bergh; B. Abrahamsen; P. Vestergaard; F. de Vries.
Osteoporosis International, 2016 [Epub ahead of print]

Fracture prevention programmes can reduce the number of subsequent fractures.
L. Hansen, P. Vestergaard, P.A. Eiken.
Ugeskrift for Laeger, 2015; 177: V05150451

Related abstracts by the author

Patients with osteoporosis who remain at high risk despite benefit of prior bisphosphonate treatment: a Danish perspective (P265).
L. Hansen, S.A. Eriksen, A. Krishna, A.D. Jørgensen, P. Vestergaard;
Osteoporosis International, 2014; 25 (Suppl2)

Descriptive study of renal impairment in patients with osteoporosis in Denmark (P307).
L. Hansen, S.A. Eriksen, A. Krishna, A.D. Jørgensen, P. Vestergaard;
Osteoporosis International, 2014; 25 (Suppl2)

Impact of Osteoporotic fractures on Quality of Life – design of a mapping study of QUALIOST to EQ-5D.
L. Hansen, P. Vestergaard, K.D. Petersen,
Value in Health, 2014; 17(7): A574–A575

Social inequality and hip fracture: secular trends in the Danish population.
N.C. Harvey, L. Hansen, A. Judge, M.K. Javaid, P. Vestergaard, C. Cooper, B. Abrahamsen.
Osteoporosis International, 2015; 26 (Suppl 1): 196

Health care costs in patients who became non-adherent during long-term oral bisphosphonate use (P602).
L. Hansen, A.D. Jørgensen, F. Gerstoft, A. Modi, P. Vestergaard;
Osteoporosis International, 2015; 26 (Suppl 1): 302

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CHAPTER 1.
INTRODUCTION

One of the biggest challenges for both economies and societies nowadays is the burden of patients suffering from one or more chronic diseases. Chronic diseases are the leading cause of death worldwide, but these are partially preventable through interventions aimed at modifiable risk factors such as tobacco and alcohol use, unhealthy diets, and physical activity. Thus, the United Nations has proposed a political declaration to prevent and control these non-communicable diseases [1]. In Denmark, an estimated one out of every three individuals is living with a chronic condition, and this has a significant effect on their quality of life. Thus, the potential to improve lives is immense, but, ideally, this should be accomplished without increasing healthcare budgets.

The epidemiological transition since 1900 has shifted the leading causes of death from microbial investigations and towards chronic diseases and resulted in decreased infant mortality and increased life expectancy [2]. In Denmark, the life expectancy at 60 years of age was 21 years for men and 24 years for women in 2012 (Statistics Denmark). The most recent World Health Statistics [3] showed that in high-income countries, including Denmark, life expectancy has increased by 4.8 years for men and 3.7 years for women since 1990. Furthermore, the number of Danish citizens above 65 years of age is expected to increase by 50% in the next 25 years, from 1 million in 2015 to 1.5 million by 2040. This change in population structure will inevitably increase the incidence rates of chronic diseases, resulting in a significant burden of highly prevalent diseases such as cardiovascular diseases, diabetes, cancers, and

osteoporosis. Individuals' self-care is becoming increasingly important within the healthcare system, as patients living with a chronic condition at a mild stage require less treatment. These patients are tossed between different sectors of the healthcare system, as the division of labour is often not specified in detail. Thus, an increased use of case management for chronic patients to support treatment across sectors has been observed since the turn of the century.

The amount of resources allocated to health care has increased substantially in the last decades – especially in the United States, where private health insurance dominates the market, and the total health expenditures accounts for approximately 17% of the gross domestic product (GDP). Within Europe, this number is substantially lower, but despite this constitutes close to 10% of GDP [3]. The increase in morbidity, combined with expensive treatments to target patients with chronic diseases will increase the total healthcare costs unless we can determine how to allocate resources more beneficially. Therefore, it is necessary to know how much in terms of costs these groups of patients accumulate regarding healthcare and if certain subgroups – e.g. lower socioeconomic groups – respond better to certain interventions, and thus accumulate fewer total health costs.

The organisation of healthcare systems is fundamentally different around the world, but can roughly be divided into three groups – the Beveridge model, the Bismarck model, and the market-oriented model [4]. The models are listed in order of expenditures per GDP with systems originating from the Beveridge model being the least expensive. Common to most systems, however, is the lack of a true market, with all the market failures that follow. In Denmark, the Beveridge model has been adopted, with taxes almost entirely financing the entire integrated healthcare system, with some fees required for dental treatments and pharmaceuticals.

This dissertation is an attempt to highlight the importance of epidemiological factors for health economic research on chronic diseases. Within health economics, the need for models that can predict healthcare costs is of substantial importance as decisions to introduce as well as decommission healthcare services is based on these.

CHAPTER 2.
THEORETICAL FOUNDATION

2.1. MODELS OF HEALTHCARE COSTS

Econometric models of healthcare costs are used for many purposes, amongst others program and treatment evaluations [5] and analyses concerning the allocation of resources [6]. Modelling health costs, however, is not an easy task, as these exhibit characteristics that are difficult to replicate. Firstly, a significant proportion of individuals consume no healthcare resources, which leads to a substantial number of observations at zero. Within health economics, this is often handled using two-part or generalised Tobit models [7]. Secondly, when individuals consume health care services, a small minority consume a high proportion of the total costs, often due to clinical complications or comorbidities. The cost distributions, therefore, become skewed, kurtotic and heteroscedastic.

Traditional linear regression has been shown to perform poorly with respect to health costs [8], as ordinary least squares minimise prediction error and, because of the extreme values, this may result in the overfitting of data [7]. Some of the initially proposed methods for analysing healthcare costs with non-normal distributions focused on transforming data into more symmetric distributions. However, this results in regression models that cannot predict healthcare spending on the original cost scale [7]. Other transformation models, including the Box-Cox and semiparametric models, have since been proposed, but retransformation onto the original cost scale is still troublesome [7]. Another way to analyse these data is using nonlinear regression models, which assume a nonlinear relationship between predictors and the cost regression. One method for this is the generalised linear model approach, where prediction is performed on the original cost scale, while allowing

for heteroscedasticity. The limited number of pre-specified links and distributional families can, however, impose bias if these are incorrectly estimated [8]. Basu and Rathouz [9] proposed a more flexible version of the generalised linear model, called the extended estimating equations, and this has been shown to perform better than other models on most parameters [8].

Several studies have demonstrated that extended estimating equations provide the best fit for data within healthcare, but have simultaneously concluded that marginal effects were not significantly different than if less computationally difficult models were used, such as linear ordinary least square or gamma models with log link [8–10]. These results are, however, more pronounced in the younger adult population and for total costs compared with prescription drug expenditures [8]. Furthermore, previous studies have shown that patients with chronic conditions consume substantially more healthcare costs compared to matched controls [11,12]. Thus, it can be argued that results from other studies modelling healthcare costs from the general public cannot be directly transferred to patients with chronic diseases. For these reasons, caution is advised when modelling healthcare costs in older chronic populations.

The methods mentioned above only predict the conditional mean, and while this is an important feature, other aspects of the distribution might also be of importance [13,14]. For example, when a clinician is treating a patient, the decision is seldom based on 'the average benefit' but rather the potential to maximize the benefits to the individual, and even more so if the clinician believes that 'the average benefit' will cause harm to a particular patient [13]. In these cases, the econometric models of interest should predict the probability of high-end parameters or the entire distribution instead of predicting the conditional mean [15]. This could guide clinicians to recommend lifestyle changes that are not only beneficial from a clinical perspective but also from an economic one.

Healthcare costs are defined as "*the total expenditure, both public and private, on healthcare services*" [16]. These costs can be considered either from a country, group,

or individual perspective [16]. Between countries, variations exist with respect to what is regarded as a healthcare cost, and thus, discrepancies exist regarding whether or not to include items such as nursing home costs and other health-related social costs [17]. For the purposes of this dissertation and the appended papers, healthcare-related costs will be assessed using the costs of all hospital services, the costs of general practitioners and specialists, and the costs of prescriptions redeemed from any pharmacy. Ideally, over-the-counter medication and costs related to care outside the hospital should have been included as well.

When modelling healthcare costs, the perspective of the given analysis should be considered carefully. Most models within the existing literature utilise data from restrictive perspectives, such as costs related to pharmacies, hospitals or primary care physicians [8,15,18,19]. However, the models often attempt to estimate impact in a broader societal perspective [20]. Thus, separate models need to be fitted for different resources, or new models must be constructed to handle this.

Within the literature on models for healthcare costs, no studies have been identified discussing which explanatory variables to include to produce the best fitting model or whether the variables that are included are relevant with respect to the decision the given model should inform. However, from a health policy and clinical point of view, these things ought to be considered, as they could potentially affect the decisions that are made.

2.2. THE BEHAVIORAL MODEL AND SOCIOECONOMIC STATUS

One approach to explaining differences in utilization of healthcare costs is to investigate behavioural patterns. One theory for this is the behavioural model, which was developed in the late 1960s to explain why families use health services [21], and has since evolved to explain individuals utilization of health services [22]. The initial model suggested that the use of health services was a function of predisposing characteristics, enabling resources and needs [21], while later versions included factors explaining the health care system, the external environment, and personal

health practices [22]. The latest version, illustrated in Figure 1, is more dynamic and repeating in the explanation of the use of healthcare services, as this is a repetitive process throughout life, but also focuses on both the contextual and individual determinants of healthcare utilization [23].

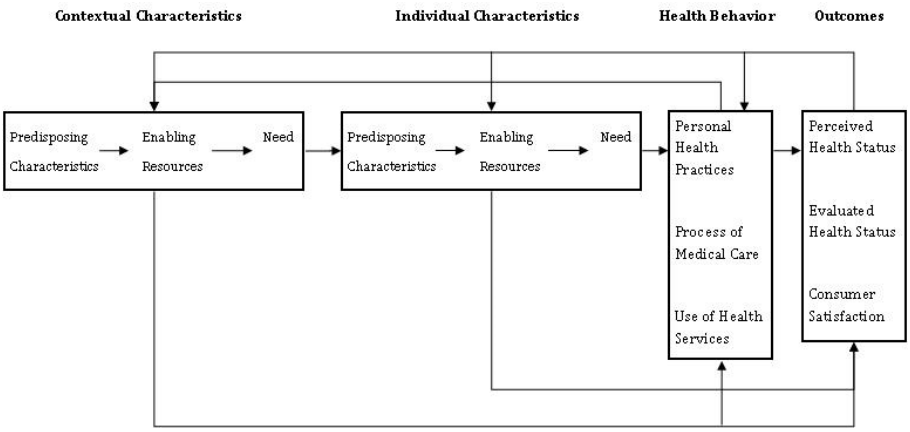

Figure 1 – Illustration of the behavioural model (phase 5) by Andersen [23].

The contextual characteristics are concerned with community age structure, the supply of medical personnel and facilities, and mortality, morbidity and disability rates. The individual characteristics encompass age, gender, insurance, income, and social structure. Health behaviour includes the use of health services, the patient's health practices and the interaction between providers and patients. Lastly, outcomes can be measured as effective and/or efficient access [22,23].

In continuation of the behavioural model, the social determinants of health consist of societal-level influences and individual-level risk factors [24] and include but is not limited to race/ethnicity, religion, socioeconomic status, sexual orientation, and disability [24,25]. Focusing on these will provide opportunities to improve the health of our society, but critics have argued that understanding and improving health require a focus directed at societies rather than individuals, and this may be difficult to achieve [24]. Therefore, it is important to change the view from investigating services for ill patients towards factors that can improve health [26].

One of the social determinants often investigated within epidemiological research is socioeconomic status, which can be defined as a "*measure of one's combined economic and social status and tends to be positively associated with better health*" [27]. Socioeconomic status is believed to influence health in three ways; in the ability to purchase treatment and health-promoting resources, through different socialisations of health habits between socioeconomic groups, and by health having an influence on socioeconomic status rather than vice versa [27]. Most classifications of socioeconomic status are primarily based on or include occupation as a factor by which to group individuals, e.g. Goldthorpe's class scheme [28]. However, these measures can be very problematic to apply on populations where the majority are elderly, and thus classified as pensioners. Thus, studies have reported on the individual variables that can be used to determine socioeconomic status when investigating this population [29–31]. In this thesis and the appended papers, socioeconomic status will be measured using the surrogate outcomes of highest completed education, personal income, marital status, and type of community living, as these represent potential confounder or effect modifiers for utilization of healthcare costs.

Within the Nordic countries, surrogate measures of socioeconomic status are routinely registered on a national level in registries. With the introduction of the civil registration system in 1968 it has been possible to conduct large population studies in Denmark [32] and since then the number of registers in Denmark has grown substantially. Research within this area continues to grow, and the term big data is now used to describe this phenomenon.

2.3. REGISTER-BASED RESEARCH AND STATISTICS

The theoretical framework of register-based research is still in the making, as the first paper on this topic was published in 1995 [33,34]. Since then some methodological papers in this area have discussed the use and quality of registry data for academic research. Compared to other surveys, register surveys are not embedded in a well-established methodological framework. Wallgren and Wallgren [35] introduced six

basic principles regarding preconditions and methodology for conducting good quality research on registers. These include the identity number, legal, transformation, system, consistency, and quality principles. These can be seen as the beginning of the development of a more generally accepted theory, and has led to the publication of the second edition of Wallgren and Wallgren's methodological book in 2014 [35], but this methodology is still in its early stage of development. One of the areas where a method has been proposed is for errors that occur in register-based research [36]. Where sampling errors is often used in sample surveys to assess the random errors that are unavoidable in any study [37], it is more appropriate to investigate the non-sampling errors within register surveys by identifying coverage errors between different registers [38]. Other non-sampling errors include linkage, differences between the purpose of collection and usage, control processes, missing data, and interest in specific registered data [36].

As register-based statistics originated from survey theory, much of the language to describe register-based research has been transferred from that theoretical framework. However, here is a need for a more register-specific terminology to separate these approaches and to develop a more comprehensive methodology [39].

> *A register is defined as a complete list of the objects in a population (e.g. all individuals in Denmark) including data on each object's identity, which makes it possible to update and expand the register with new variable values for each object*. [40] (p. 9)

This definition of a register is the one used in this thesis and embraces both administrative and statistical registers. Within register-based statistics, the term object is used to denote the entities included. This term differs from the sample survey terminology, where entities are referred to as subjects because of the active process of inclusion and the written/oral declaration of consent. The identity of objects included in a given register is determined using a unique identification number that never changes in order to avoid a breach of data. A register can only be considered as such if the identification number is present because it must be possible to update a register and this function disappears with the identification number. In Denmark the

unique personal identification number is called CPR-number and is provided to all persons who are born or take up permanent residence in Denmark [32].

The basis for most of the data collection is for administrative purposes, and, therefore, discrepancies arise between the needs of the researchers and the purpose of data collection, which is a crucial difference between register surveys and sample surveys [41]. In the latter case, the researcher is solely responsible for the selection of the study population, choice of study variables, and, therefore, the quality of the survey. Sample surveys, such as traditional epidemiological studies, furthermore, apply statistical inference, which cannot be applied to register surveys due to the massive number of observations and different sources of microdata. Thus, Wallgren and Wallgren introduced the system approach to accommodate these statistical challenges [39].

Making quality improvements and editing registers for register surveys is more complicated than for sample surveys, as both base registers and all linked registers need to be assessed, and thus, changes in these affect more than just the current register survey [39]. The strengths and weaknesses of register surveys have been extensively described elsewhere [39,41,42]. Some of these arguments can introduce both strengths and weaknesses, e.g. when data is collected independently of the research question. Recall bias and subject influence on the diagnostic process is reduced but can result in unavailable or inaccurate data for the purpose of the study. Often data collection within registers is complete and thus entire population studies for both rare diseases and exposures are possible at a fraction of the cost compared to if traditional epidemiological studies were to investigate the same issue. However, another implication is when researchers identify missing data. This type of missing data can be difficult to explain, lead to the incorrect interpretation of results, and can lead to under-coverage [41].

Missing values within registers are different from those in sample surveys and must be handled accordingly. That is, only objects with a contact to the hospital will be recorded in National Patient Register (NPR) and thus, if combined with other

registers, any variables originating from the NPR will produce missing values if this object has never been in contact with a hospital. One method to handle this in a sample survey is to impute missing values[43], but this would produce wrong values for register surveys, and thus, the imputed values should be zero in such cases.

The use of administrative registers on their own may limit the producible results, but, as described in Wallgren and Wallgren [39], the integrated register system where different registries are linked through the use of personal identification numbers enables more comprehensive analyses that benefit from the qualities that each registry provides.

2.3.1. THE INTEGRATED REGISTER SYSTEM

Administrative data may originate from different sources and hence different registers. Combining these creates a system of coordinated statistical registers – *i.e.* the integrated register system [44]. The advantage of working in one system is good coverage and consistency, given that the six basic principles are followed [44]. The integrated register system used for this thesis comprised data from the National Patient Register (NPR), Civil Registration System, National Prescription Registry, Register of Cancer, The National Health Insurance Service Registry, Register on Causes of Death, and Population's Education Register. Table 1 includes more details about the different registers.

Name of register	Translated name	Content	Year of registration
Centrale person register	Civil Registration System	Information on residence and relationships of all citizens	1974 - present
Dødsårsagsregisteret	Cause of Death Register	Information on causes of death based on death certificates	1970 - present
Lægemiddelstatistik-registeret	National Prescription Registry	Information on dispensed prescription drugs	1994 – present
Landspatientregisteret	National Patient Register	Information on diagnoses and operations performed at hospital	1976 - present
Skatteregisteret	Tax registry	Information on taxable incomes	1980 - present
Sygesikringsregisteret	The National Health Insurance Service Register	Information on providers, health services and citizens receiving primary health care treatment	1990 - present
Uddannselsesregisteret	Population's Education Register	Information on citizens approved educations	1973 - present

Table 1 –Details about the registers included in the integrated register system. Additional information is available from Statistics Denmark and The Danish Health Data Authority.

Throughout this dissertation, the variables with the highest quality of information were chosen for analysis. Statistics Denmark introduced high-quality variables to their registers in 2006, with detailed information and documentation for all high-quality variables. For these variables, descriptions of the period of application, contingent data breaches, data quality assessment, and topic clusters exist. Today, more than 700 variables are included in this quality assurance initiative, including diagnosis of action at the hospital (NPR) and highest completed education (Population's Education Register). Within the ten topic clusters, this dissertation primarily relied on the social relations and health, education, personal finance, and population variables.

2.4. THE RESEARCH QUESTION

This dissertation will attempt to highlight the importance of epidemiological factors for health economic studies on chronic diseases. As presented in the theoretical framework, previous research on models to predict healthcare costs are only concerned with a limited amount of epidemiological knowledge. Policy makers and clinicians are, however, often more interested in which predictors influence specific outcomes. In the ensuing parts of this dissertation, the chronic disease osteoporosis will be the case considered, as this is a highly prevalent disease, which results in increased morbidity and mortality for those affected. Furthermore, this results in different utilisations of healthcare services because of its complexity.

The appended papers should not be considered as the outcome of the research question, but merely supporting arguments. The research question addressed in this thesis is:

How do individual epidemiological factors impact the healthcare utilisation of patients with a chronic disease, e.g. osteoporosis?

CHAPTER 3.
OSTEOPOROSIS – A CHRONIC DISEASE

Osteoporosis is one of the biggest public health concerns, that has increased concurrently with the increasing length of life of the population. Osteoporosis in itself is not easily detected, and thus many patients remain undiagnosed. In 2010, the estimated prevalence of osteoporosis was 27.6 million individuals in a population of 400 million, solely in the European Union [45]. Fragility fractures are the main consequences resulting from osteoporosis, with an estimated 3.5 million incident fractures occurring in the European Union in 2010 [45], and these fractures have been shown to increase both morbidity [46] and mortality [47]. In Denmark a fracture of the femoral neck is the 14th most common diagnosis for patients admitted to hospital and accounts for 2% of all admissions. Furthermore, a fracture of lower end of the radius is the 7th most common reason for an outpatient visit and 5th for emergency room contacts [48]. Thus, this disease constitutes a substantial part of healthcare costs, with an estimated economic burden of the illness and the resulting fractures in the European Union of €37 billion in 2010, and this is expected to increase by 23% in 2025 entirely due to changes in the population demographic [45].

Osteoporosis was defined as "*a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk*" in 1991 by 14 leading experts [49]. Many countries worldwide have adopted another criterion for diagnostic purposes, which defines osteoporosis as "*a bone mineral density (BMD) that lies 2.5 standard deviations (SD) or more below the average value for young healthy women*" [50] – a measure that is referred to as a T-score. However, the clinical definition necessitates

a Dual-energy X-ray Absorptiometry (DXA) scanner to diagnose osteoporosis, and these are primarily located in specialist clinics.

Bone fragility is a multifactorial disease, where both genetics and environmental factors influence an individual's risk of fracture. Age and gender are the two most important risk factors for osteoporosis and thus fragility fractures. The gender difference is evident in that the disease predominately affects women, with approximately 40% of postmenopausal women and 15% of men above 50 years of age expected to fulfil the diagnostic criterion [51]. Oestrogen deficiency after menopause results in more bone resorption than bone formation, and together with lower peak BMD could explain why women after the age of 50 sustain two-thirds of all incident fractures [52].

Even though the incidence rate of hip fractures has continuously decreased since 2001 [53], the number of hip fractures is not going decline as rapidly, and is even expected to increase in Europe in the future, given the changing population demographic [54].

3.1. OSTEOPOROTIC FRACTURES

The variation in fracture incidence rates across the world has been well investigated [55], with European countries, and, in particular, Scandinavian countries, having the highest hip fracture rates in the world. A 10-fold difference in the age-standardised rate of hip fractures can be observed across the world and exceeds the within country difference between genders [55]. This difference between countries could be explained by the correlation between hip fracture probability and both latitude and gross domestic product (GDP) [56]. The proposed reasons for these findings were less sun exposure and thus lower levels of Vitamin D, and decreased physical activity with increasing socioeconomic status.

There has been some dispute about which fractures should be included in the definition of osteoporotic fractures, but the most recognized method is to include all fractures arising from low trauma injuries, such as tripping over the doorstep.

Therefore, almost all hip, vertebral, and wrist fractures occurring after the age of 50 will be considered low-energy fractures and thus osteoporotic [57]. The risk of sustaining a fracture as a woman is almost double that for men; however, this varies within different fracture sites[58]. Other fractures, such as ankle, face, finger, toe, and foot, are still not consistently included when discussing osteoporotic fractures [59], because these kinds of fractures occur more seldom than hip, vertebral and wrist fractures and have therefore not been shown to be more prevalent in osteoporotic patients compared to the general population [60].

Future studies on osteoporotic fractures should investigate other fracture groups; such as the humerus, tibia, and proximal radius/ulna, and not merely group these as "other fractures". Despite the lack of focus on these, studies have shown that these are also signs of osteoporosis based on BMD [60]. Many of these fractures are observed less frequently than hip, vertebral, and wrist fractures [58], which is why a possible approach could be to utilise national patient registers where fractures are registered. For example, a humerus fracture is considered an osteoporotic fracture; it is very frequently observed [45] but not grouped separately as hip or forearm fractures are (e.g. [61]). Also, the long-term consequences of fractures should be investigated more thoroughly, as most studies are terminated before there have been five years of follow-ups, and thus, the effect of future fractures in the following decade remains unclear.

This thesis distinguishes between two kinds of subsequent fracture types: recurrent fractures – *i.e.* where index and subsequent fractures were of the same type – and second fractures – *i.e.* where index and subsequent fractures were of different types. This is based on the assumption that the bone in which the original fracture occurred must be porous and, thus, be more likely to break again compared to other bones in the individual's body. However, the NPR does not register whether a fracture occurs in the right or left extremity. Therefore, data on recurrent fractures might be second fractures if *e.g.* the index fracture occurred in the left humerus and the recurrent fracture occurred in the right humerus.

3.2. CLINICAL MODIFIABLE RISK FACTORS FOR OSTEOPOROTIC FRACTURES

Non-pharmaceutical interventions for the prevention of osteoporosis focus on modifiable risk factors, as illustrated in Figure 2. Vitamin D and calcium deficiency are some of the most significant nutritional risk factors to consider for osteoporosis and fragility fracture prevention, as they influence the bone mineralization. Supplementing these is more efficient if these are supplied together compared to separately [62]. Poor nutrition can furthermore lead to low body mass index, which is another well-established risk factor [63], which also increases the risk of fracture, most likely due to the diminished body weight at fragile sites of the body. Another risk factor to consider is physical activity, which prevents bone loss and increases BMD, thus improving balance and coordination, and furthermore reduces the risk of falling and thereby fracturing a bone [64]. Smoking influences the risk of fracture and has an independent, dose-dependent effect on bone loss, which increases the risk of hip fracture by up to 40% [65]. This effect is, however, reversible, as no significant difference in BMD has been shown between former and non-smokers, but a significantly lower BMD has been shown in current smokers compared with non-smokers [65]. Additionally, alcohol is a risk factor that influences both BMD and risk of fracture because it affects both the skeletal fragility and increases the risk of falling as a result of intoxication [66,67]. Lastly, use of glucocorticoids has been shown to increase the possibility of fracture both for intermittent and prolonged use [68]. Educating patients in osteoporosis using multifaceted group education can impact the patients' engagement in the management of their disease [69]; however, it has limited or no effect on the behaviour of patients in regards to clinical risk factors [70].

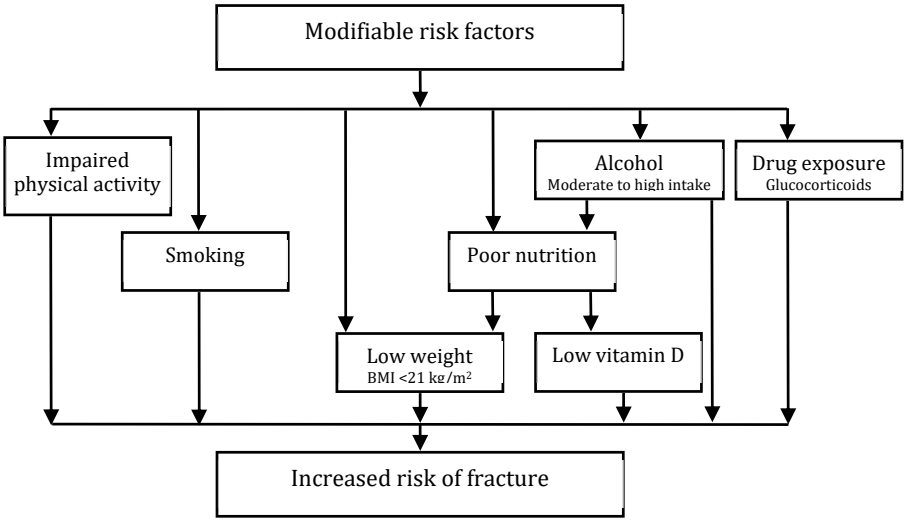

Figure 2 – Simplified illustration of fracture risk due to modifiable risk factors, adapted from Abrahamsen *et al.* [70] and reproduced with permission of Nature Publishing Group.

Despite the potential effect of these modifiable risk factors on the risk of future fractures, not all patients will benefit from lifestyle changes because non-modifiable risk factors such as gender and age together with race/ethnicity and genetic predisposition are as or more important risk factors for osteoporotic fractures. Thus, pharmaceutical interventions are still needed to prevent future fragility fractures.

3.3. TREATMENT AND MANAGEMENT

In Denmark, the Danish Endocrine Society has composed the national guidelines for treatment of osteoporosis. They recommend performing biochemical tests and a DXA scan for all patients presenting with a low-energy fracture in order to diagnose osteoporosis. Patients already receiving anti-osteoporotic medication are routinely scanned every 2–3 years to investigate whether the medication has an effect [71].

General practitioners are only allowed to prescribe anti-osteoporotic medication for patients if at least one of four pre-defined criteria is fulfilled. These include, among others [72]:

- Persons with x-ray verified low-energy fracture of the hip and/or spine. A spine fracture is defined as:
    - Reduction in height of >20% of the anterior vertebral compared to posterior height
    - Reduction in height of >20% at any site, compared to the above or below vertebrae
- Persons with at least one risk factor for the development of osteoporosis, and with a BMD measurement in the hip and/or spine with T-score < -2.5 SD.
- Persons with T-score <-4.0 SD without simultaneous risk factors.
- Persons in current or scheduled systemic glucocorticoid treatment (equivalent to >5 mg of prednisolone per day for three months or more; or intermittent use with a total use for more than three months within one year) with a BMD-measurement in the hip and/or spine where the T-score is <-1.0 SD.

The risk factors comprise, but are not limited to, genetic predisposition, body mass index < 19 kg/m^2, previous fractures, osteogenesis imperfecta, menopause before 45 years of age, systemic treatment with glucocorticoids, smoking, excess alcohol consumption, and patients at increased risk of falling.

In Denmark, the bisphosphonate alendronate is the first choice of pharmaceutical therapy for all patients, unless the general practitioner can argue otherwise. Thus, alendronate is used to treat nine out of ten Danish osteoporotic patients [73]. Several systematic reviews and meta-analyses have been published on the clinical effects, and side-effects, of anti-osteoporotic medications, and, in particular, bisphosphonates [61,74–94]. These show that all bisphosphonates significantly reduce the risk of vertebral fractures and zoledronate and alendronate minimize the possibility of hip fractures. However, treatment with a bisphosphonate is not without risks, as severe atrial fibrillation, stroke [78,88] and atypical femur fractures [74,77,85] are occasionally reported with use of bisphosphonates.

Most publications reporting the effects of anti-osteoporotic medications originate from those randomised controlled trials mentioned above, where the population and compliance can be investigated in more detail. The effectiveness in the entire

population using anti-osteoporotic medications, which in 2014 constituted approximately 100,000 Danish citizens [95], has not been reported to the same extent. Particularly, given the low persistence and diversity observed in this patient group [96,97]; future studies on improving the outcome for osteoporotic patients should consider this.

3.4. HEALTHCARE COSTS AND OSTEOPOROSIS

Most health economic analyses on osteoporosis or osteoporotic fractures are economic evaluations based on cohort models, where mean costs are used to predict the cost-effectiveness of two or more alternatives. The most comprehensive of these publications was conducted by the National Institute for Health and Care Excellence (NICE), which investigated the secondary prevention of fragility fractures in postmenopausal women. The results showed that pharmaceutical treatments were cost-effective for women aged 65 or older with confirmed osteoporosis, for women aged 60–64 with confirmed osteoporosis and with one clinical risk factor, and for women aged 55–59 with confirmed osteoporosis and two or more clinical risk factors [98]. The treatment was only cost-effective as a first-line use for alendronate and not for other bisphosphonates [98].

Patients with multiple chronic conditions, such as many osteoporotic patients, show many varying patterns for healthcare cost distributions because their healthcare utilisation is influenced by many different factors and not necessarily concerned with one specific condition [99]. Thus, merely analysing the mean cost of a population might reveal incorrect results, because the effects observed are not caused by the disease, but may be the results of unobserved variables. Furthermore, it can be difficult to differentiate healthcare utilisation in countries where payments are aggregated, such as using diagnosis-related group (DRG) tariffs. Patients may be admitted with a broken bone, and this might be caused by osteoporosis, but if the patient simultaneously had diabetes and suffered from hypoglycemia at the time of the fracture, then the actual cause of the fracture might not be recorded, and thus future research using these data would produce erroneous results.

Studies have shown that the average utilization of healthcare-related resources differs substantially between different groups of fracture patients, which underscores the need for differentiating on this when performing economic evaluations [54,100,101]. Borgström *et al.* [100] showed that patients with hip fractures accumulated significantly more costs for inpatient care compared to vertebral and wrist fractures, whereas wrist fracture patients accumulated more for the costs of outpatient care. Additionally, costs associated with community care were significantly higher for vertebral fracture patients compared to patients with hip fractures, and almost non-existent for wrist fracture patients. Hiligsmann *et al.* [101] demonstrated that the level of compliance with anti-osteoporotic medications was significantly associated with the total cost, as the cost of medicines increased with increasing medication possession ratio, and this consequently lowered the cost of the disease. Lastly, age and gender also significantly influences the average total cost for osteoporotic hip fracture patients [54] and thus differentiating between groups of patients is necessary from a health economic perspective. Decision makers should, however, be aware that these results might not be directly transferable to their setting, as the average cost of treatment may vary depending on which treatment regime is offered and the organisation of the healthcare system.

The effect of modifiable risk factors, such as obesity, smoking, and excess alcohol consumption, on the utilisation of healthcare mimic that on health, *i.e.* obesity has the most effect on the outcome [102]. Data on these are, however, not routinely recorded in registers, and thus controlling for these in the major population-based studies is difficult.

3.5. SOCIOECONOMIC STATUS AND OSTEOPOROSIS

When looking at socioeconomic variables and their association with the utilisation of healthcare in general, studies have shown that higher education increases the number of visits to a general practitioner, and most significantly for women. Widowed/divorced women have a tendency to increase their number of visits, whereas single men have significantly fewer visits. Furthermore, higher income

decreases the number of visits to a general practitioner. This picture slightly changes when looking at the utilisation of specialists, where higher education and income significantly increases the number of visits. Furthermore, living in a rural community also increases the number of visits to a specialist [103]. These associations are, however, influenced by the contextual characteristics of the healthcare system, particularly the type and organisation. Thus, associations observed in American studies are probably not generalizable to a Danish setting.

Few studies have investigated the association between different socioeconomic variables and utilisation of healthcare for osteoporotic patients [104,105]. Both studies have focused either on a limited part of the services utilised for osteoporosis and furthermore only investigated one surrogate measure of socioeconomic status – income. More research is needed to determine if the socioeconomic status is associated with the amount of utilisation of healthcare services for osteoporotic patients, but more interestingly how big these associations are, and if these can be used for improving treatment regimes. The combination of epidemiological and health economic research traditions could improve the knowledge on which policy makers make decisions on where to allocate resources.

A few studies have been published on the associations between epidemiological outcomes and socioeconomic status, and these results might likewise be replicable for health economic outcomes, as an increased incidence of epidemiological outcomes would increase the utilisation of healthcare services. A review of the literature on socioeconomic status and osteoporotic fractures found eleven studies of sound quality that investigated the association between these [106]. In particular, the studies looked at income, education, occupation, type of residence, and marital status. The studies found no significant evidence for any association between increased fracture risk and education or income, while marriage was correlated with a decreased risk of fracture. The generalizability of these studies is, however, limited by the varying methods used for measuring the different variables of socioeconomic status and fractures. Furthermore, the generalizability of these associations across different

population is also troublesome, as the effect of low socioeconomic status would affect health differently. No previous studies have investigated the combined effect of socioeconomic status on the rate of death following a fracture. Some studies have shown that some variables, such as marital status [107] and residence [108], affect mortality, but without controlling for other socioeconomic variables, it is hard to determine if this effect is truly caused by e.g. marriage or if the observed effect is merely a moderate of other causes. Future research should investigate if the same tendencies for clinical outcomes can be observed with respect to outcomes of health utilisation.

CHAPTER 4.
CONTRIBUTIONS FROM THIS THESIS

When performing research, it is important to understand both the setting in which it is conducted, and the methods applied. The researchers who investigate the models of healthcare costs extensively and in-depth are primarily trained as economists or biostatisticians and only later acquire some knowledge about healthcare research. This becomes very apparent when dissecting the models proposed for predicting the costs of healthcare, as these very often contain very limited if any information about the included predictors for these models. The reason for this is most likely the theoretical appreciation common to social sciences, which is different from the methodology applied to health sciences. This produces research that is innovative and advanced regarding methodology but which lacks application potential, as these results tends to be written off by clinicians. On the other hand, when researchers within the health sciences produce research on healthcare utilisation they tend to focus more on choosing the accurate predictors and making sense of the possible interactions between these, in order to yield results that can be generalised and inform future decisions. This produces research that is often used as the basis for decisions, as clinicians trust the results from their peers but lack the understanding of how costs behave in economic models and lack understanding of how predictors depend on characteristics of the national/regional health care system. This may lead to erroneous conclusions and the introduction of health services under false pretences. Thus, there is a need for more joint venture research between these two sciences, as this could potentially combine the best of both worlds.

4.1. THE POPULATION

Osteoporosis is the chronic disease investigated throughout this thesis. To make any predictions about the amount of healthcare utilisation, the population investigated must be characterised. As described in the previous chapter, patients suffering from osteoporosis are not easily detected, and thus, the clinical manifestations of osteoporotic fractures are often investigated instead.

In the first paper included in this thesis [53], the osteoporotic fracture population was investigated from an epidemiological perspective in order to understand the 10-year effect of a fracture on the risk of future fractures and death. The results showed that fractures in other areas, such as the humerus, lower leg, and femur, were as likely to be associated with subsequent fractures as typical osteoporotic fractures. Furthermore, the results showed that appendicular fractures were more often linked to proximal fractures of the same limb, compared to other fractures. This can be seen in Table 2. The conclusion was that recurrent fractures constituted the most significant associations between the index and subsequent fractures and that fractures of the distal parts of the extremities often resulted in subsequent proximal fractures of the same extremity.

Surveys investigating incidence rates for fractures in such detail as this study are very rare because it is very time-consuming to do so and it is often impossible to recruit the population needed for traditional epidemiological studies. Thus, register surveys can facilitate more knowledge being gained concerning untraditional fracture types, for which little is known.

Furthermore, the results from the first paper [53] suggest that e.g. when modelling the cost of healthcare utilisation, it is important to consider the history of the individual, as this could affect the outcome later on as patients with previous fractures are likely to experience more expensive fractures in the following decade.

Table 2 - Gender-stratified 10-year subsequent fracture incidence in per cent, for both men and women

Index fracture	Subsequent fracture							
	Lower leg	Femur (non-hip)	Hip	Pelvis	Vertebral	Forearm	Humerus	Any
Men								
– Lower leg	21.1	2.5	8.7	0.9	2.8	6.8	10.3	62.0
– Femur	10.3	20.2	17.0	3.2	3.2	9.1	9.0	64.8
– Hip	3.9	5.0	33.8	1.8	3.1	5.4	14.1	56.1
– Pelvis	5.0	3.3	21.2	9.4	5.0	7.2	15.8	55.0
– Vertebral	5.0	2.3	15.0	1.9	20.2	4.8	17.0	52.3
– Forearm	4.8	1.4	10.7	1.9	3.1	14.5	13.3	41.7
– Humerus	5.6	2.5	16.5	2.4	3.7	8.6	26.9	55.7
Women								
– Lower leg	21.4	3.5	12.5	2.1	2.9	14.4	8.1	60.8
– Femur	8.7	20.2	20.5	4.0	3.0	10.5	11.9	65.8
– Hip	6.1	8.4	40.3	5.7	4.7	14.3	9.4	82.1
– Pelvis	8.1	6.6	29.5	11.7	7.1	16.4	15.6	81.4
– Vertebral	6.2	4.5	25.9	8.8	17.6	16.1	10.0	81.9
– Forearm	6.1	2.5	19.3	2.9	3.6	24.8	9.9	65.3
– Humerus	7.4	4.0	26.3	4.2	5.4	22.5	23.8	84.8

4.2. DIFFERENT SECTORS – DIFFERENT COSTS

After identifying the population of interest, the researcher investigating the utilisation of healthcare, should determine which parts of the healthcare sector are being utilised by this patient group and whether these are important to consider in the analysis. As described previously (Chapter 2 - Models of healthcare costs) most studies on models of healthcare costs focus on very narrow cost perspectives, such as only hospitalisation or pharmaceutical costs.

In the second paper included in this thesis [109], the cost of osteoporosis and osteoporotic fractures were investigated. This was estimated at €1.6 billion in 2011 [109], of which the municipalities carried the biggest burden for ensuring rehabilitative care after the patients had been discharged from the hospital. Figure 3 is an illustration of the share each payer identified in the model carries and shows that the municipalities pay more than half of the total costs.

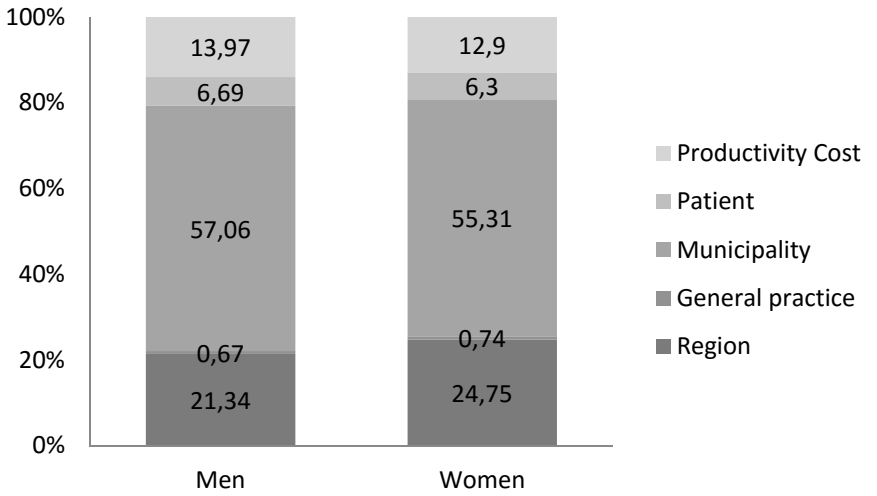

Figure 3 - Total accumulated costs with the simplified osteoporotic Markov model stratified into payers. Results are presented as a percentage of the total costs [109].

This study was among the first to illustrate the enormous resource burden for osteoporotic patients that lie outside the healthcare system. The proportion of costs

associated with community care has previously been estimated substantially lower [100]. In other countries, where municipalities are not responsible for rehabilitative care as in Denmark, this burden would most likely fall on the patients. Additionally, this study adopted a very broad societal perspective, and thus the burden for Denmark appears much larger than for other countries that are very similar. The yearly costs related to osteoporosis in the European Union have previously been estimated at €37 billion, where incident fractures represent 66% of these costs [45]. If, instead, the expenses of the individual states are compared, with respect to e.g. the cost of hip fractures, then the result of the present study is lower compared to other previously published estimates [100,110]. Thus, future studies investigating health economic aspects of osteoporosis or osteoporotic fractures should consider adopting a broader societal perspective, as substantial costs are located outside the healthcare system.

Future studies trying to predict the cost of healthcare utilisation for a chronic disease should carefully consider which perspective to adopt, based on what decision the authors are interested in informing. With the accumulation of costs from different sectors, it is possible that the cost distributions will result in even more skewedness, heteroscedasticity, and fewer individuals with zero costs.

4.3. CHOOSING APPROPRIATE CLINICAL PREDICTORS

Following the choice of population and costs, the researcher should consider which variables could potentially explain the variations in healthcare costs. Here the researcher should consider whether he or she believes that all individuals within the population are truly from the same population, and thus have covariates that behave similarly across the range of the outcome. To explain the behaviour of healthcare cost accumulation, the clinical predictors are of particular relevance. As emphasised in the presentation of the case of osteoporosis, variables such as anti-osteoporotic medications, modifiable risk factors, and previous fractures all influence the clinical outcome of the disease and therefore potentially the healthcare utilisation.

Through the work on the third paper included in the thesis, which investigated the clinical risk factors that predicted which osteoporotic patients, who despite compliance to medication, continued experiencing fractures, the literature was searched for which clinical risk factors might affect the outcome for this patient group. Unfortunately, many of the *a priori* variables, mostly related to modifiable risk factors are not routinely registered in the Danish registers, the data source of four of the five studies included in this dissertation. This includes information about alcohol and tobacco use, body weight, nutrition, and physical activity – *i.e.* all but the use of medication from Figure 2.

Several comorbidities that have previously been linked to osteoporosis were identified. These included anorexia nervosa, asthma, celiac disease, chronic obstructive pulmonary disease, dementia, hyperparathyroidism, inflammatory bowel disease, lactose intolerance, lupus, renal disease, rheumatoid arthritis, and stroke. There is a potential influence from these with regards to exacerbating osteoporosis, and hence a possible increase in healthcare utilisation.

4.4. CHOOSING APPROPRIATE BEHAVIORAL PREDICTORS

The first and third paper only utilised the clinical subset of the integrated register system [53]. Thus, a substantial, and previously unutilised, part of this system might provide other variables that could explain the difference in utilisation of healthcare.

Of the different behavioural variables that could potentially influence healthcare utilisation, as presented in Andersen's behavioural model (Figure 1), demographic and social characteristics were of particular interest in the fourth paper. This fourth study investigated the influence of socioeconomic status on two epidemiological outcomes, as several papers have suggested this might have an influence, but without coming to any definitive conclusions. The predictor variables investigated were education, income, marital status, and type of community residence. Furthermore, this paper differentiated between fracture groups, whereas the previous literature had investigated osteoporotic fractures in general or only the major osteoporotic fractures.

The predictor variables chosen were easily identifiable within the Danish registers for all objects, with the exception of education for a very specific subgroup. The mechanisms for these 'missing' values were investigated, and this was primarily present for women born before 1960. The probable reason for this is the Population Education Register was introduced in the 1970s – shortly after the civil registration number. Attempts have been made to update the information for objects with completed education before the introduction, but a substantial amount of missing values is still observed [111]. Instead of performing a complete case analysis, a new category called "missing values" was added to all four socioeconomic variables to control for any missing observations.

The results showed a clear relationship between both outcomes and socioeconomic status. Decreased rate of death was significantly associated with living with a spouse and higher income quintiles for all thirteen fracture groups. Furthermore, there was a tendency towards decreased rate of death being associated with higher education, but only significantly for the forearm, distal forearm, hand and foot fractures. Lastly, the results did not indicate any association between rural/urban living and rate of death. A decreased rate of subsequent fracture was often associated with living with a spouse and remote residence, however, not to the same extend as for rate of death. In conclusion, low socioeconomic status was associated with both increased risk of subsequent fracture and post-fracture mortality. Therefore, these variables might potentially also influence the utilisation of healthcare.

4.5. THE IMPACT OF CLINICAL AND BEHAVIORAL PREDICTORS ON UTILISATION OF HEALTHCARE SERVICES

The fifth paper aimed to demonstrate the importance of including clinical and behavioural predictors for the utilisation of healthcare services across all thirteen groups of fractures.

4.5.1. METHODOLOGY

The previously investigated predictor variables were combined with healthcare-related costs from general practices, hospitals, and pharmacies, and this resulted in the fifth paper. Even though the second paper showed that social care cost – *i.e.* services provided by the Danish municipalities – would account for the largest healthcare utilisation for osteoporotic fracture patients, object-specific costs were not available from the integrated register system utilised, and, hence, this utilisation could not be included in this study.

The thirteen fracture groups previously identified (paper IV) constitute the population used for this article. The socioeconomic status variables (paper IV) and the clinical risk factors (paper III and paper IV) were included if relevant and correlated with healthcare-related costs. Comorbidities affecting mortality were incorporated using the updated Charlson Comorbidity Index Score [112].

The study was designed as a three-part model, however without an attempt to combine the three components. A logistic regression model was fitted for the zero cost objects in the study, and generalised linear models (GLM) for the remaining two components. The model's assumptions for logistic regression model were tested using locally weighted scatterplot smoothing, standardized Pearson residuals, and the Hosmer-Lemeshow goodness of fit test[113]. The model's assumptions were assessed with a link test, Park test and modified Hosmer-Lemeshow test[114]. Robust variance estimates were used to avoid overdispersion.

In this dissertation, hip fractures will be used to demonstrate the model, but results for all thirteen fracture groups are presented in the manuscript for the fifth paper. The crucial difference between the thirteen groups was the amount of accumulated costs and hence different cut-off points between the second and third components.

Hip fractures

The density of the observed 1-year accumulated healthcare-related costs is illustrated in Figure 4. The first component included zero cost objects, the second component

included objects with accumulated healthcare-related costs amounting to no more than €7000, and the third and final component included objects with accumulated healthcare-related costs amounting to €7000 or higher. The cut-off point at €7000 was chosen as this separates the two distinct distributions seen in Figure 4.

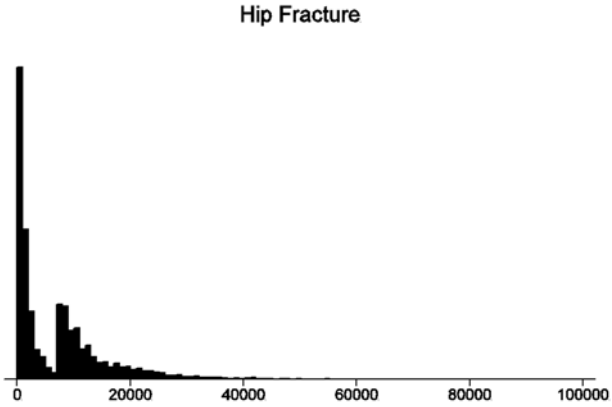

Figure 4 – Cost distribution of 1-year accumulated healthcare-related cost (€) for hip fracture objects 2008-9 (zero-costs excluded).

A logistic regression model was chosen for the first component, a GLM with identity link and a gamma distribution for the second component, and a GLM with square root link and inverse Gaussian distribution for the third component. The goodness of fit and Wald tests were used to verify the model assumptions for the logistic regression, and these were not violated. Both GLMs passed the linktest, but in regards to the choice of variance function the deviance residuals and Park test were not in agreement for the second component. In the end, the gamma distribution was chosen, because the residuals were normally distributed using normality plots.

4.5.2. RESULTS

Across all thirteen fracture groups, more than one-third of objects had previously collected a prescription of glucocorticoids, more than one-third had previously experienced a fracture, and null-cost objects had a significantly higher mortality in

the year after fracture. A diagnosis of excessive alcohol consumption was found in 10–15% of objects and 5–10% had a diagnosis or pharmacy prescription relating to smoking. Generalising results from the regression analyses, costs accumulated in the year before fracture had no influence on which objects accumulated costs or not in the year after a fracture. Age, gender and glucocorticoid use was significantly associated with utilisation of healthcare services for all three components across all fracture groups. Socioeconomic status variables only had a sporadic significant effect on healthcare-related costs. Any presence of comorbidities, measured by the Charlson Comorbidity Index Score, was the variable that had the largest influence on whether objects (regardless of fracture group) accumulated healthcare-related costs. Female gender and living with a partner appeared as the most salient characteristics holding down the accumulation of costs. When objects (regardless of fracture group) accumulated costs, high income was the variable that reduced the accumulation of healthcare-related costs the most. Use of medication for alcohol addiction or smoking cessation, on the other hand, were the factors most likely to result in excessive accumulation of healthcare-related costs. These results can be found in the fifth paper that is included in this dissertation.

Results for hip fracture patients showed that null-cost objects were significantly older, more often male, had higher Charlson index scores, were previously treated with anti-osteoporotic medication, live alone, and live in urban communities, see Table 3. As described above, the presence of comorbidities was the variable that increased the probability of accumulating costs the most and female gender and living with a partner also here decreased the likelihood of accumulating costs (component 1). When objects did accumulate healthcare-related cost, they would either end up in the second or third component. The GLM model for the second component showed that increasing healthcare-related costs was significantly associated with lower age, a higher Charlson Index Score, current/previous anti-osteoporotic medication use, smoking-related diagnosis, glucocorticoid use, and urban living (Table 3). For this component, income decreased the accumulation of costs the most, whereas anti-osteoporotic medication and use of glucocorticoids increased accumulation the most.

For the third component, *i.e.* objects with higher healthcare-related cost, increasing healthcare-related cost was significantly associated with higher ages, higher Charlson index scores, smoking-related diagnosis, alcohol diagnosis, glucocorticoid use, lower income, and urban living (Table 3). Again, income decreased the accumulation of costs the most, but here living in an intermediate municipality had the largest marginal effect on the accumulation of healthcare costs.

Despite the very significant results observed for both clinical and socioeconomic predictors in the previous paper, this was not as evident in this analysis, which sparked curiosity whether this was a result of the accumulation across different types of costs.

Table 3 – Results from regression models for estimation of the influence of clinical and socioeconomic status variables on total accumulated costs one year after a hip fracture.

Hip fracture	**Component 1 (Odds Ratio)**	**Component 2 (average marginal effects)**	**Component 3 (average marginal effects)**
Age	*1.047	* -4.69	*30.90
Gender, female	*0.426	-37.71	-131.92
Charlson index score			
• 1-2	*1.744	*202.00	*805.08
• 3+	*3.166	43.00	*1859.54
Anti-osteoporotic medication			
• Current	1.063	*243.64	362.03
• Ever	*1.742	*277.17	8.51
Smoking-related diagnosis	0.824	*219.14	*1826.26
Alcohol diagnosis	1.030	-34.67	*1510.77
Glucocorticoids	0.875	*329.91	*1365.81
Previous fracture	0.814	50.61	297.88
Education			
• Secondary	0.929	22.97	122.33
• Higher	0.869	52.70	459.98
Income			
• 2nd Quintile	0.819	-114.66	* -833.39
• 3rd Quintile	0.721	-82.25	-550.20
• 4th Quintile	0.815	13.07	-465.78
• 5th Quintile	0.698	-92.06	* -1155.68
Marital status, with partner	*0.713	49.87	-200.73
Rural/urban living			
• Rural	1.523	101.79	477.33
• Intermediate	*1.705	39.51	*1937.64
• Urban	*1.988	*149.33	*1490.97
Cost one year before fracture	1.000	*0.01	*0.09

* $p<0.05$

Charlson index score: no comorbidities are baseline. Anti-osteoporotic medication: never treated is baseline. Education: basic education is baseline Income: 1st Quintile is baseline. Rural/urban living: rural is baseline.

4.5.3. SUBANALYSIS OF DIFFERENT COSTS

A sub-analysis of all three cost components – *i.e.* costs from secondary care, costs from the redemption of prescription medication, and costs from primary care – was carried out in order to identify if this significantly influenced the conclusion regarding the effect of socioeconomic and clinical predictor variables on healthcare-related expenditures. For the costs of secondary care, a square root link and inverse Gaussian family GLM were fitted, for the costs of prescription medication an identity link with poisson family GLM was fitted, and for the costs of primary care, a log link with gamma family GLM was fitted.

Null-cost objects (component one)

The subdivision into cost categories significantly influenced the results both for null-cost objects and those who did accumulate costs following a hip fracture (see Table 4, Table 5, and Table 6). For null-cost objects, clinical predictors significantly increased the risk of not accumulating secondary care costs, with the exact opposite tendency observed for medication and primary care costs. For both medication and primary care, null-cost objects were significantly more likely to live alone, whereas this had no effect on the cost of secondary care. Also, null-cost objects in regards to medication and primary care were significantly more often urban community residents, but this variable had no effect on null-cost objects for the cost of secondary care. Higher income quintiles reduced the likelihood of belonging to the null-cost object group with respect to both medication and primary care but increased the likelihood with respect to secondary care. Education was not significant for any group of costs in regards to null-cost objects. The driving predictors for the accumulation of healthcare-related costs were a smoking-related diagnosis and higher income with respect to secondary care, whereas living in an intermediate municipality was the predictor that drove objects towards not accumulating costs. Equivalent to primary care and medication costs, the presence of comorbidities drove the model for objects to accumulate costs the most, whereas female gender was the driving force in decreasing the accumulation of costs.

Objects' accumulated costs (component two)

With respect to objects' accumulated costs, higher education and living with a partner increased the costs of primary care significantly, but neither had any effect on the costs of medication or secondary care. Both urban communities and lower income increased the accumulation of costs for secondary care, but neither of these influenced the costs of medication or primary care. Clinical predictors significantly increased the accumulation of costs with respect to both secondary care and medication but had less effect on primary care costs. The driving predictor for primary care and medication costs to increase was the use of smoking cessation drugs, whereas alcohol diagnosis and presence of comorbidities were the driving force in decreasing the accumulation of primary care costs, and higher education was likewise for medication costs. For the cost of secondary care, the presence of comorbidities and living in an intermediate or urban municipality were the main predictors. In this subgroup, higher income was the driving force in decreasing the accumulation of secondary care costs.

Table 4 – Results from regression models for estimation of the effect of clinical and socioeconomic status variables on accumulated costs from secondary care one year after a hip fracture

Cost of secondary care, €	**Component 1 (Odds Ratio)**		**Component 2 (average marginal effects)**	
Age	**1.006**	**[1.002; 1.011]**	**44.02**	**[17.80; 70.24]**
Gender, female	0.967	[0.895; 1.046]	-251.01	[-728.31; 226.30]
Charlson index score				
• 1-2	0.925	[0.849; 1.008]	**547.40**	**[26.51; 1068.3]**
• 3+	1.106	[0.948; 1.289]	**1642.91**	**[433.22; 2852.60]**
Anti-osteoporotic medication				
• Current	**1.125**	**[1.009; 1.255]**	198.27	[-457.00; 853.55]
• Ever	1.099	[0.928; 1.300]	-64.49	[-1044.18; 915.21]
Smoking-related diagnosis	**1.211**	**[1.057; 1.389]**	**1714.92**	**[784.87; 2644.96]**
Alcohol diagnosis	0.906	[0.805; 1.020]	**1600.83**	**[803.83; 2397.83]**
Glucocorticoids	0.953	[0.887; 1.025]	**981.97**	**[548.97; 1414.97]**
Previous fracture	0.954	[0.887; 1.025]	77.53	[-352.18; 507.25]
Education				
• Secondary	1.069	[0.987; 1.158]	157.67	[-306.56; 621.90]
• Higher	1.061	[0.934; 1.206]	415.87	[-361.19; 1192.93]
Income				
• 2nd Quintile	1.033	[0.914; 1.168]	-560.75	[-1266.69; 145.19]
• 3rd Quintile	**1.134**	**[1.000; 1.285]**	-290.87	[-1051.10; 469.37]
• 4th Quintile	**1.144**	**[1.011; 1.295]**	-519.42	[-1261.09; 222.24]
• 5th Quintile	1.131	[0.998; 1.281]	**-984.50**	**[-1688.20; -280.80]**
Marital status, with partner	1.009	[0.923; 1.103]	-44.59	[-572.63; 483.45]
Rural/urban living				
• Rural	0.959	[0.852; 1.080]	361.14	[-254.61; 976.88]
• Intermediate	0.876	[0.767; 1.000]	**1623.35**	**[867.28; 2379.42]**
• Urban	0.977	[0.870; 1.096]	**1121.73**	**[500.49; 1742.97]**
Cost one year before fracture	0.999	[0.999; 1.000]	**0.08**	**[0.06; 0.11]**

Table 5 - Results from regression models for estimating the effect of clinical and socioeconomic status variables on accumulated costs from redemption of prescription medication one year after a hip fracture

Cost of medicines, €	**Component 1 (Odds Ratio)**		**Component 2 (average marginal effects)**	
Age	**1.020**	**[1.012; 1.030]**	**1.56**	**[0.47; 2.64]**
Gender, female	**0.460**	**[0.395; 0.535]**	11.93	[-10.56; 34.42]
Charlson index score				
• 1-2	**1.864**	**[1.588; 2.187]**	**76.84**	**[47.01; 106.67]**
• 3+	**3.164**	**[2.483; 3.986]**	**93.16**	**[23.11; 163.21]**
Anti-osteoporotic medication				
• Current	0.980	[0.769; 1.249]	-1.20	[-37.17; 34.77]
• Ever	1.329	[0.953; 1.854]	47.76	[-6.89; 102.41]
Smoking-related diagnosis	**0.707**	**[0.518; 0.965]**	**117.76**	**[71.23; 164.29]**
Alcohol diagnosis	0.968	[0.759; 1.234]	**41.47**	**[8.11; 74.83]**
Glucocorticoids	**0.772**	**[0.663; 0.899]**	**72.40**	**[49.83; 94.97]**
Previous fracture	**0.842**	**[0.723; 0.980]**	6.49	[-13.98; 26.97]
Education				
• Secondary	0.994	[0.848; 1.166]	16.21	[-7.88; 40.31]
• Higher	0.882	[0.675; 1.152]	-20.14	[-52.73; 12.44]
Income				
• 2nd Quintile	1.014	[0.799; 1.287]	10.68	[-25.01; 46.37]
• 3rd Quintile	**0.620**	**[0.478; 0.806]**	15.09	[-20.94; 51.13]
• 4th Quintile	0.778	[0.606; 1.000]	31.17	[-12.59; 74.93]
• 5th Quintile	0.833	[0.652; 1.066]	-5.21	[-39.17; 28.74]
Marital status, with partner	**0.810**	**[0.676; 0.970]**	0.44	[-28.11; 28.99]
Rural/urban living				
• Rural	1.258	[0.953; 1.661]	12.66	[-17.45; 42.77]
• Intermediate	**1.627**	**[1.211; 2.185]**	-7.35	[-41.29; 26.58]
• Urban	**1.751**	**[1.344; 2.282]**	25.32	[-5.09; 55.75]
Cost one year before fracture	0.999	[0.999; 1.000]	**0.68**	**[0.66; 0.71]**

Table 6 - Results from regression models for estimation of the effect of clinical and socioeconomic status variables on accumulated costs from primary care one year after a hip fracture

Cost of primary care, €	**Component 1 (Odds Ratio)**		**Component 2 (average marginal effects)**	
Age	**1.042**	**[1.035; 1.049]**	**2.09**	**[0.72; 3.46]**
Gender, female	**0.525**	**[0.471; 0.587]**	-2.62	[-30.81; 25.57]
Charlson index score				
• 1-2	**2.204**	**[1.969; 2.468]**	-19.83	[-49.44; 9.80]
• 3+	**4.956**	**[4.166; 5.895]**	-22.28	[-77.68; 33.10]
Anti-osteoporotic medication				
• Current	0.925	[0.783; 1.093]	**42.48**	**[10.95; 74.00]**
• Ever	1.216	[0.959; 1.541]	56.29	[-6.03; 118.61]
Smoking-related diagnosis	1.003	[0.820; 1.226]	**90.65**	**[40.20; 141.10]**
Alcohol diagnosis	0.986	[0.822; 1.182]	-29.12	[-68.48; 10.25]
Glucocorticoids	**0.898**	**[0.807; 0.998]**	**79.20**	**[55.90; 102.50]**
Previous fracture	**0.888**	**[0.799; 0.988]**	-12.42	[-36.29; 11.44]
Education				
• Secondary	0.960	[0.855; 1.078]	**34.08**	**[7.70; 60.45]**
• Higher	0.855	[0.700; 1.046]	**80.22**	**[37.17; 123.26]**
Income				
• 2nd Quintile	1.053	[0.886; 1.251]	6.17	[-35.25; 47.60]
• 3rd Quintile	**0.679**	**[0.565; 0.816]**	4.63	[-35.71; 44.97]
• 4th Quintile	**0.743**	**[0.618; 0.892]**	33.61	[-6.84; 74.06]
• 5th Quintile	**0.725**	**[0.603; 0.872]**	29.04	[-10.83; 68.91]
Marital status, with partner	0.880	[0.769; 1.007]	**66.85**	**[37.14; 96.56]**
Rural/urban living				
• Rural	1.148	[0.960; 1.373]	17.35	[-18.64; 53.33]
• Intermediate	**1.250**	**[1.026; 1.521]**	-5.96	[-46.77; 34.85]
• Urban	**1.267**	**[1.066; 1.506]**	23.00	[-11.66; 57.66]
Cost one year before fracture	**0.999**	**[0.999; 0.999]**	**0.54**	**[0.49; 0.59]**

4.6. RECOMMENDATIONS FOR PREDICTING THE EFFECT OF EPIDEMIOLOGICAL FACTORS ON HEALTHCARE COSTS

Through the dissertation and the appended papers, four preliminary steps are recommended before building a regression model that can predict the effect of epidemiological factors on healthcare expenditures. These are based on knowledge from both the social and health sciences, which emphasizes the importance of interdisciplinary research.

Firstly, the researcher should become familiar with the population of interest, as this will ease the subsequent steps. This should at least include a review of the epidemiological literature and ideally an epidemiological study of the particular population of interest. Furthermore, these identifications will facilitate hypothesis generation for which predictors could potentially influence the utilisation of healthcare costs, as knowledge about the population will guide the *a priori* selection of variables for further investigation.

Secondly, economists and clinicians should jointly determine the appropriate resource use and hence which costs to include in the study. When investigating chronic diseases where different parts of the health sector are utilised, this steps becomes crucial, as the omission of one or more sectors could influence the results. Additionally, the choice of the time horizon for the analysis should be carefully considered and based on knowledge about the population. Despite its importance, this part was not investigated during this thesis, as costs were limited to four years of observations.

Thirdly, all important predictors should be jointly determined by both economists and clinicians. For clinical predictors, this identification is most easily facilitated by investigating the risk factors for clinical events related to the chronic disease of interest, e.g. future fractures for osteoporosis. These factors will often be potential confounders for both the clinical outcomes and healthcare expenditures. Additionally, behavioural predictors of importance should be identified as these

could potentially confound the utilisation of health services. One method to identify these by is using a theoretical model, such as the behavioural model applied in this study. The proposed mechanisms for health behaviour will moderate the utilisation and are therefore important to consider when predicting healthcare costs.

Fourthly, consideration of the most appropriate statistical model is important for the results of the analysis, as the initial theoretical review found that the choice of the econometric model could potentially affect the result of the analysis. As shown in the fifth paper, behavioural and clinical predictors had a different effect on the outcome depending on which sector the expenditures originated in. This emphasises the importance of the second and fourth steps of the model, as erroneous conclusions may be drawn if narrow perspectives are chosen.

The associations between the different aspects of the prediction model and application of results from the different papers appended to this dissertation are graphically presented in Figure 5.

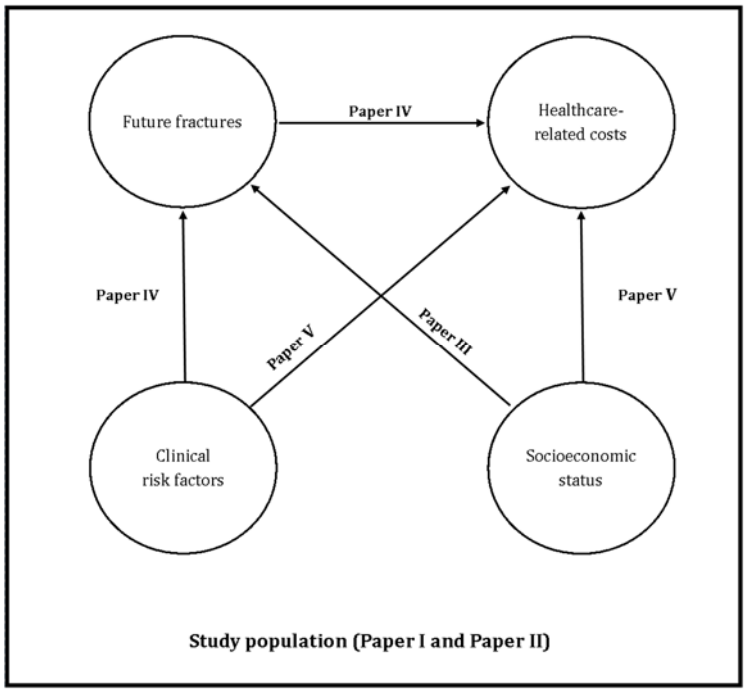

Figure 5 – Summary of results. A schematic representation of the association between socioeconomic status and clinical risk factors for future fractures and accumulation of healthcare-related costs as outcomes within an osteoporotic population.

CHAPTER 5. IMPLICATIONS AND FUTURE RESEARCH

When life expectancy increases by as much as what has been observed in the last century, the incidence of different diseases shifts. An increase in diseases such as diabetes, chronic heart disease, and osteoporosis has been observed during the same period and may be a result of this. Research within the health sciences has discovered many new drugs that have also contributed to the increase in life expectancy. Whereas people died from diabetes up until the 1920s, today they can live an almost symptom-free life due to the discovery of insulin. Despite the obvious advantages of an aging population, the concomitant diseases that follow with older age significantly worsen the health outcomes. This dissertation has attempted to emphasise the need for knowledge from the traditional health sciences to inform economic models for healthcare utilisation. The combination of theoretical frameworks across these different fields of research could produce research that borrows the best of both worlds. The proposed four-step model comprises one possible strategy for this. As illustrated through the papers appended to this dissertation, the choice of population, perspective, predictors, and statistical model is important when estimating the conditional mean healthcare costs for fracture patients. The results of this dissertation may be based on osteoporotic fractures, but nothing suggests that these steps would be any different for other chronic diseases. Applying this to another population, *e.g.* diabetics, could be interesting in order to verify this.

Defining the population of interest is the crucial first step to emerge from this dissertation. One of the key results of this thesis was the identification of the wider fracture population. Future analyses were the cost of osteoporotic fractures are

included should consider the difference in cost accumulation across different groups of fractures and would be well advised not to group these together as "other fractures." As illustrated in both the dissertation and the appended papers, a vast diversity exists between the different fracture groups and a number of different outcomes. The morbidity and mortality following a fracture are significantly different between groups, and this affects the influence of different predictors' effect on these outcomes. This is most likely due to differences in the individuals' demographic characteristics, and, as a result, grouping very diverse fracture groups such as ankle and humerus fractures into one will most likely result in insignificant associations. Exploring the true effects is difficult in a smaller population where fractures are observed in fewer numbers, and hence, population studies utilising data from national registers could elucidate the true effect.

Previous studies, e.g. Seeley *et al.* [115], have shown a fracture of the humerus, especially of the proximal location, to be osteoporotic and associated with low bone mass. Despite the acknowledgement of this, most recent clinical studies with osteoporotic fractures as endpoints concentrate on hip, vertebral, and non-vertebral fractures [61]. The specification of the additional fracture groups will add to the knowledge about health behaviour for fracture patients and allow for potential differentiations to be made between individuals who experience a fracture. Another important finding from the first paper was the increased rates of subsequent a fracture at proximal sites compared to the index fracture. In particular, lower leg fractures resulting in subsequent hip fractures and wrist fractures resulting in humerus fractures were as high in fracture rates as some second fracture rates. Cuddihy *et al.* [116] found the 10-year subsequent fracture rate to be 55% following a forearm fracture and that the risk of humerus fractures, in particular, increased, which supports the argument from the first paper, that distal fractures can predict future proximal fractures in the same extremity. This knowledge is important also from an economic perspective, as health expenditure accumulation is influenced by an individual's history with the healthcare system and risk factors for future events. This association between the accumulation of costs and knowledge about previous fractures was

confirmed in the fifth paper with respect to both medication and primary care costs, where a previous fracture was found to increase the likelihood of accumulating costs (component one). Further, it could be speculated that this association would be even more pronounced for social costs, as previous fractures would likely lead to a higher rate of absence from work and decreased productivity, and, hence, further productivity loss. Additionally, it is possible that previous fractures could result in increased need for assistive devices and lead to greater use of nursing homes and/or respite care.

The second step was to identify the appropriate perspective and thus the relevant resources for the analysis. Within the literature on health economics, the textbooks stress the importance of there being sufficiently broad perspectives for informing decisions [20], whereas the applied research focuses on narrow perspectives [8,15,18,19]. This can affect the result of the analysis of healthcare utilisation if *e.g.* social care was omitted from analyses of an osteoporotic population, as the second paper in the thesis showed that this could constitute more than half of all costs. Furthermore, if results from such narrow perspective analyses are used as the basis for decisions, this may lead to erroneous conclusions being drawn, as these could shift the recommendation in decision analytical models. Furthermore, this step also emphasises choosing the appropriate time horizon for the analyses. In the fifth paper this was, however, limited to a one-year perspective due to a lack of data, but ideally future research should investigate this over a longer time period, as this could potentially also affect the results.

Choosing the accurate predictors for healthcare utilisation is another crucial element. From a clinical framework, it is well documented that different risk factors and the patient's history is decisive for the clinical outcome and thus healthcare utilisation. This is also evident from the behavioural model, where health outcomes are determined by personal health practices, the process of medical care, and the use of personal health services, which is also influenced by the contextual characteristics and individual characteristics. The epidemiological studies conducted in relation to

this thesis, and similar publications from experts within the field of osteoporosis, have documented the importance of identifying clinical predictors both when investigating clinical outcomes as well as costs, as these have a significant effect on the outcome of interest. But clinical risk factors are not the only factors that influence the outcome for osteoporotic patients. Previous studies have shown that socioeconomic variables, such as income, have a significant influence on the rate of future fractures and mortality [29,30,108,117–121]. However, these have primarily focused on hip, vertebral, and wrist fractures, whereas the fourth paper in this thesis shows that these associations are seen across a wide range of fracture groups. This emphasises the need to consider predisposing individual characteristics of health behaviour. When looking at behavioural factors, which have been investigated using socioeconomic status, in particular, as predictors, the same certainty in the effect on a given outcome has not been demonstrated as with clinical predictors. Only a few studies have been identified that investigate the effect socioeconomic predictors have on both epidemiological outcomes as well as costs. Furthermore, the behavioural factors are more difficult to measure and hence incorporate into prediction models.

Some of the included elements in the behavioural model, though important to generally consider, are less important to investigate when considering the case of osteoporosis in a Danish setting. However, if these results were to be generalised, factors pertaining to both the individual's and the healthcare service's - such as health policy, financing, and the organisation - could potentially be quite different and thus affect the use of healthcare services.

Furthermore, the application of the behavioural model is only one method to control for societal and behavioural factors that might influence the results of the analyses. Other, both more and less complicated, models exist and could potentially have been utilised instead. The memory or feedback mechanism essential to the behavioural model was only incorporated through the variables of previous fracture, chronic conditions, and to some extent previous years' utilisations of healthcare services. This is not sufficient, as the model includes a lot of other feedback that contributes to the

current health status, and future models for prediction of healthcare utilisation should consider other ways or other types of models that could integrate some memory, such as discrete event simulations within decision analytic models.

The results from the fifth paper highlight the necessity of understanding the process of medical care and the organisation of the healthcare system. Only investigating the healthcare expenditures from an accumulated costs perspective would hide the true effects of the different predictors on the utilisation of healthcare services. The effects observed for accumulated costs changed significantly for the sub-analysis on individual cost categories. Leal *et al*. [104] has previously investigated the predictors of one-year hospitalisation costs following a hip fracture and found that gender, age, income, and Charlson Comorbidity index score were significantly associated with this outcome. The fifth paper attempted to demonstrate this relationship in all thirteen fracture groups using a larger set of socioeconomic variables. However, no generalizable association between health care utilisation and socioeconomic status was observed. Future research on this area could focus on understanding the association between different socioeconomic variables in relation to epidemiological outcomes and higher costs. And specifically which of these predictors have the largest effect on the outcome, as this might be of interest to policy makers.

However, future research is advised for understanding the effect of behavioural predictors, and especially socioeconomic status, on the utilisation of healthcare costs. Results from both this thesis and previous studies indicate that the true connection between these has yet to be identified. This could include studies where different and other surrogate variables for socioeconomic status are investigated. Perhaps individual income is not as good a predictor as the accumulated income of the family, or education might be an inferior predictor compared to the designation of occupation. This leads to the consideration of structural conditions, as the behavioural model suggests that contextual characteristics influence individual ones. Hence, socioeconomic status could be investigated from a contextual perspective as well –

i.e. income might be less influential on the outcome if the healthcare system is organised in a particular way.

Lastly, the proposed model emphasises that taking steps to ensure that the most appropriate statistical model is used is important for the results of the analysis. When investigating the predictors for healthcare utilisation and incorporating elements from both health and social sciences, it is important to acknowledge the previous research from these fields. Not only must social scientists familiarise themselves with epidemiological results that could be of importance to the study they are about to conduct, but researchers within the health sciences should also consider the theories of how healthcare costs behave and how these are best modelled. Hence, the fourth step of the proposed model from this dissertation emerges. Researchers within the social sciences have acknowledged that traditional and easy computational statistical models for continuous outcomes, such as ordinary least squares regression analysis, are not adequate when studying healthcare costs. Instead, they propose more complex models that can handle most of the difficulties that arise with healthcare costs. This acknowledgement should be recognised by health scientist when using such models. This observation is supported by the results from the fifth paper, where the accumulation of all healthcare-related costs generated unusual distributions, which lead to the three-part regression model. Furthermore, the sub-analysis revealed that the included predictors behaved very differently and often in opposite ways between different types of healthcare costs. Hence, an ordinary least squares analysis of these accumulated costs would have led to an erroneous conclusion about the effect of predictors on the utilisation of healthcare costs.

Four of the five appended papers to this dissertation are based on data from registers and hence are grounded in register-based statistics. The quality and generalizability of different registers have often been discussed, primarily because the populations which these are based on are limited to certain groups within society. In healthcare systems based on the Bismarck model, it can be almost impossible to collect data for the entire population, as sickness funds and insurance companies are often

contributors of data to these registries. However, problems may also arise for systems based on the Beveridge model. In the United Kingdom the Clinical Practice Research Datalink is only able to collect data from volunteering general practices, and though the study population is representative of the entire population, only 6.9% of all residents are included in this database [122]. However, within the Scandinavian countries and especially Denmark, registers enable research using the entire population as the sample. These studies are not limited by which subjects are willing and able to participate. Furthermore, register-based research facilitates the investigation of effectiveness rather than efficacy, which would be the result of clinical trials. These results could then inform decision models on treatment of e.g. osteoporotic fractures, but using other effect measures than health-related quality of life. One of the challenges with register-based research in Denmark is the restrictions placed by Statistics Denmark, in terms of the re-identification of objects and data use. Despite this, a few studies have been able to investigate the coverage and quality of data from different Danish registers [123,124].

All five papers included in this thesis have used the arbitrary exclusion criterion for objects younger than 50 years of age. This was based on the assumption that bone mass is primarily constructed during the first two decades of life, after which it deteriorates and should not become fragile enough to break until after the age of 50 from a low-energy trauma [125]. However, it could be argued whether this criterion should be lowered. A study, based on the same integrated register system utilised for this thesis, showed that the incidence of major osteoporotic fractures increased from the age of 40 [126].

A limitation of the fifth paper is that results cannot be used to generate the average cost of different fractures, as results were divided into three separate models for no costs, low costs, and high costs. The combination of these models could facilitate more specific modelling approaches for results from economic evaluations. This could be an issue for further research. Additionally, the data utilised for this last paper is not ideal for hospital costs, as these are based on diagnosis-related tariffs, which

are generalised tariffs applied for similar diagnoses at different hospitals. This eases the budget strain and makes easier the account management from an organisational perspective, but will dilute the results with respect to true healthcare expenditures.

The choice of statistical model for the fifth paper was not challenged by other statistical models, despite the knowledge that extended estimating equations might produce superior results compared to the generalised linear models used in the paper. However, the scope of the paper was not to identify the model of best fit, and, as the previous literature has shown no significant difference in the marginal effects between the models, this limitation was not investigated further.

A cautious interpretation of the results from the fifth study is advised, as these are to some extent affected by survivorship bias. The detailed results showed that objects that accumulated zero costs in the year after a fracture were significantly more likely to die during the follow-up period. The average healthcare expenditure per patient would consequently be estimated too high if only objects with accumulated costs were considered, as has routinely been shown in other studies.

In conclusion, this dissertation has focused on the impact of different epidemiological predictors on the utilisation of healthcare cost for the population of patients who have suffered an osteoporotic fracture. The results from this highlight the importance being familiar with the population of interest, identifying relevant resources, including both epidemiological and behavioural predictors when analysing outcomes from both an epidemiological and health economic perspective, and choosing the right statistical model to analyse all this with. Both health and social scientists interested in researching the utilisation of healthcare should consider these four steps.

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SUMMARY

Healthcare systems around the world continue to see their expenditures increase, measured as a percentage of gross domestic product. Within health economics, the need for models that can predict healthcare costs is of substantial importance, as decisions to introduce as well as to decommission healthcare services are based on these. This dissertation is an attempt to highlight the importance of epidemiological factors for health economic research on chronic diseases. Hence, the research question of interest is: how do individual epidemiological and behavioural factors impact the healthcare utilisation of patients with a chronic disease, e.g. osteoporosis? This dissertation proposes a framework for predicting healthcare utilisation which includes four steps: familiarisation with the study population, determining the appropriate resource use, determining which predictors are important to consider, and lastly choosing the most appropriate statistical model. This framework was developed as a result of five quantitative studies, of which four were based on patient specific data from registers, and one on cost of illness theory. The framework was applied for predicting the cost for all fractures patients in one year following the fracture, i.e. the fifth study included in this dissertation. This study showed that it is not only important to understand the population of interest, as this eases the subsequent identification of potential predictors, but also the healthcare system through which these patients are treated, as different resources were affected differently by the clinical and behavioural predictors included. In conclusion, the results from this dissertation highlight the importance being familiar with the population of interest, identifying the relevant resources, including both epidemiological and behavioural predictors, when analysing outcomes from both an epidemiological and health economic perspective, and choosing the right statistical model to analyse all this with. Both health and social scientists interested in researching utilisation of healthcare should consider these four steps.

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