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CV

Michael Falk Hvidberg has around five years of previous non-academic experience working within the health-care sector regional administration of Northern Jutland. The work has been concentrated around the National Health Profiles, data management, health technology assessment and evaluation, patient satisfaction surveys, and administrative and political work. For example, the work of the National Health Profiles includes surveying the public health including developments in chronic conditions, several standardized quality of life measures, linking surveys and registers, and much more. The work has usually been a compulsory part of national agendas and thus carried out as part of the requirements of the Ministry of Health, Danish Regions, law and others.

Michael's work in academia has been a natural prolonging of his previous experience. This includes research into using registers defining a broad range of different chronic conditions based on, and in cooperation with, medical experts – and it includes the research of health-related quality of life and health economics. Moreover, Michael has a special interest in statistical methods, including complex regression modelling/econometrics such as mixed regression modelling, for example based on the health-related quality of life measure EQ-5D. In this regard, Michael has spent time abroad at Sheffield University and is still working together with one of the leading international researchers within the field, Monica Hernandez Alava, Senior Research Fellow in Econometrics, HEDS, ScHARR, Sheffield. Much of his work has also involved multifaceted and comprehensive data management combining numerous registers and surveys in SAS and STATA. Michael has produced several publications and given presentations at international conferences including the International Health Economics Association (IHEA) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Finally, Michael Falk Hvidberg teaches statistical methods and others at Aalborg University.

Michael Falk Hvidberg was awarded a master's degree in sociology with specialism in quantitative methods and surveys in 2007. Since his enrolment as a PhD fellow, Michael has been a member of the PhD cooperation board at the Faculty of Social Science, and the Union Board at the Faculty of Social Science (DJØF).

ENGLISH SUMMARY

In recent decades, there has been a shift in disease patterns towards chronic disease. Along with an ageing population, people live longer with chronic disease, including an often decreased health-related quality of life (HRQoL). The rising burdens of chronic conditions put economic pressures on the health-care system. For example, the increasing costs of medicine have resulted in layoffs for hospital staff. Several experts have forecasted that the rising budget burdens are not sustainable unless action is taken. Thus, there is a need for prioritization and health economic evaluation if existing universal health-care systems are to be sustained. However, there is a shortage of comparative data providing an overview of the burdens of chronic conditions in terms of both size and severity, and standardized data that can be used within health economic evaluation and other research, although reliable estimates and data are crucial for decision-makers making solid and lasting choices for future health care.

The current dissertation aims to support future health economic evaluation, decision-makers but also other health-care related research. This is done by providing a framework for identifying 199 chronic conditions within health registers (objective 1), which can be used for different outcomes and research areas. Moreover, the thesis provides prevalence estimates of chronic conditions (objective 2) in order to give estimates of the *size* of a problem. However, as size may not give any indication of the *severity* of a condition, estimates of HRQoL are crucial too. Thus, HRQoL based on EQ-5D 3L preference scores – which is the burden measure preferred within health economic evaluation – are calculated (objective 3) based on new, complex regression methods. Finally, a case example of HRQoL analytics of a *survey*-based chronic condition in contrast to register-based definitions is presented (objective 4).

Paper 1 contains a register-based catalogue of definitions for 199 chronic conditions and subgroups of conditions by medical assessment comprising if not all, then most chronic conditions (objective 1). To ensure inclusion of all conditions treated within the health-care system, ICD-10-based hospital discharge codes as well as medication ATC codes, services of general practitioners (GPs) and other variables were included.

A catalogue of 199 chronic condition prevalence rates is provided in paper 2 (objective 2) based on a point estimate from 2013. This provides the basic epidemiology of the burden, basically answering the questions: what's the *size* of the potential disease problems, and what are the different conditions like in comparison?

A catalogue of ICD-10-based EQ-5D 3L preference scores of 199 chronic conditions is provided in paper 3, including both unadjusted mean estimates and adjusted regression estimates (objective 3). This catalogue shed light on the severity, essentially answering the questions: which conditions have it worst, how bad is it, and what are the potential health gains? The regression estimates were provided in four models to accommodate different needs of health economic evaluation modelling including a fourth model with health risk, BMI, stress and social network. This especially enables health-care analysts to identify disparities and potential health gains within health inequalities. A technical guide on how to use the EQ-5D estimates and the four regression models is provided.

Finally, paper 4 shows the limitations of register-based approaches as not all conditions are reported or treated within the health-care system.

The results are expected to have several implications within priority settings. Overall, the estimates could help in setting priorities for resource allocation within health services, prevention and research in mainly two ways. First, the estimates of size and severity themselves may provide information that is useable in policy setting generating an awareness and overview of potential issues. Secondly, the estimates can be used in health economic evaluation to assist decision-makers in concrete resource allocation and prioritization. In regard to the first point, the results derived from estimates could potentially generate new policy dilemmas and priorities. For example, some cancers and heart conditions have comparatively high prevalence and mortality, but also relatively good HRQoL, while the conditions at the same time have high priority and high financing. On the other hand, several musculoskeletal- and psychiatric conditions have both relatively high prevalence and low HRQoL while they do not have the same priority and financing. Similar priority dilemmas can be found within the estimates. Moreover, the framework can be used for monitoring trends in population health as well as monitoring policies such as, for example, compulsory regional and local health agreements. However, in regard to the second point, the estimates themselves do not provide information about competitive alternatives or interventions and recommendations for decision-makers. Thus, using the estimates within cost-effectiveness analysis (CEA) is crucial, as described.

In summary, the dissertation delivers a register-based framework for identifying chronic conditions and complementing estimates of quantity/size (by prevalence) and severity (by EQ-5D HRQoL) for use in health economic evaluation and other research. Thus, the aim is not to provide any specific recommendations for decision-makers, but simply to provide the means for others to do so.

DANSK RESUME

I de seneste årtier er der sket et skifte i sygdomsmønstre således, at flere lever med en eller flere kroniske sygdomme. En aldrende befolkning, der lever længere med kronisk sygdom og for en stor dels vedkommende med nedsat helbredsrelateret livskvalitet (HRQoL). Den øgede kroniske sygdomsbyrde presser sundhedsvæsenet såvel i Danmark som internationalt. Flere eksperter understreger, at de stigende udgifter er ikke økonomisk bæredygtige med mindre de adresseres og håndteres. Således er der et behov for sundhedsøkonomisk evaluering og prioritering, hvis vestelige landes nuværende fri og skattebetalte sundhedssystem skal bestå. Samtidigt er der mangel på sammenlignelige data, som kan give overblik over kroniske lidelser og byrder, og som kan bruges i sundhedsøkonomisk evaluering, både hvad angår omfang (prævalens) og sværhedsgrad (HRQoL). Dette er tilfældet til trods for, pålidelige data er afgørende for, at beslutningstagere kan vurdere og lave solidt funderede prioriteringer.

Nærværende afhandling har bl.a. til formål at understøtte fremtidig sundhedsøkonomisk evaluering og beslutningstagere. Dette søges imødekommet ved at skabe et register baseret katalog af definitioner (framework), der identificerer 199 kroniske sygdomme (formål 1), som desuden kan kombineres med forskellige sundhedsbyrdemål. Endvidere estimeres prævalens af kroniske sygdomme (formål 2) for at give et estimat over *omfanget* af byrden. Ydermere, og da prævalens ikke giver en indikation af *sværhedsgraden*, målt som den oplevede helbredsrelaterede livskvalitet, af en kronisk sygdom, er HRQoL byrdemål også centralt. Formål 3 er således at give estimater af HRQoL baseret på EQ-5D 3L præference scores - som er det mest anvendte byrdemål inden for sundhedsøkonomisk evaluering - for de 199 kroniske sygdomme. Estimaterne er baseret på nye, komplekse regressions metoder. Endelig gives et case-eksempel på HRQoL analyse af en survey baseret kronisk sygdom i kontrast til register baserede definitioner (formål 4).

Artikel 1 præsenterer et katalog over register baserede definitioner for 199 kroniske tilstande og undergrupper baseret på medicinske vurderinger af, hvis ikke alle, så flest mulige kroniske sygdomme (formål 1). For at sikre, at alle sygdomme inkluderes, er både ICD-10 baserede hospitals koder samt medicin ATC-koder og tjenester af praktiserende læger (GP) med mere, medtaget.

Artikel 2 præsenterer et katalog over prævalens af 199 kroniske sygdomme (formål 2) baseret på et punkt estimat fra 2013. Dette grundlæggende epidemiologiske byrdemål besvarer essentielt: hvad er størrelsen af de potentielle sygdomsproblemer, og hvordan er de er i sammenligning?

Artikel 3 præsenterer et katalog over ICD-10 baserede EQ-5D 3L præferencer scores for 199 kroniske sygdomme, herunder både ujusterede gennemsnits estimater

og justerede regression gennemsnits estimater (formål 3). Dette kaster lys over sværhedsgraden af sygdomme og besvarer grundlæggende: hvilke sygdomme har det "værst", hvor slemt er det, og hvad er de potentielle sundhedsmæssige gevinster for de 199 sygdomme? De regression baserede estimater præsenteres i fire regressionsmodeller for at imødekomme forskellige behov for modellering i sundhedsøkonomisk evaluering, herunder særligt en fjerde model med følgende risikofaktorer, BMI, stress og socialt netværk. Dette giver mulighed for sundhedsøkonomer og forskere at identificere forskelle, sociale uligheder, potentielle sundhedsmæssige gevinster. Der er lavet en særskilt teknisk vejledning af, hvordan EQ-5D estimaterne og de fire regressionsmodeller kan bruges i sundhedsøkonomisk evaluering.

Artikel 4 illustrerer begrænsninger af at bruge registerdata til at identificere kroniske sygdomme, da ikke alle sygdomme er rapporteret i sundhedsvæsenet.

Resultaterne kan have flere anvendelser og implikationer indenfor sundhedsvæsnet. Samlet set kunne katalogerne assistere prioritering inden for sundhedsvæsenet, forebyggelse og forskning på primært to måder. Først og fremmest kan estimaterne over *omfang* og *sværhedsgrad* i sig selv generere bevidsthed og overblik over potentielle problemer til brug i prioritering. For det andet kan estimater anvendes i sundhedsøkonomisk evaluering og hjælpe beslutningstagere i ressource allokering og prioritering. I forhold til den første pointe, kan forhold afledt fra estimaterne potentielt set generere nye politiske dilemmaer og prioriteringer. For eksempel har flere kræftformer og hjerte sygdomme en forholdsvis høje forekomst og dødelighed, men også relativt fint / høj HRQoL, mens de på samme tid har høj prioritet og høj finansiering. På den anden side har flere muskel-skelet sygdomme- og psykiatriske sygdomme både relativ høj forekomst og lav HRQoL, mens de ikke har samme prioritet og finansiering. Lignende prioriterings dilemmaer kunne findes i kataloget blandt andre sygdomme. Derudover kan de register baserede definitioner bruges til at monitere tendenser i befolkningens sundhed og monitering af politikker som for eksempel obligatoriske regionale og lokale sundhedsaftaler. Imidlertid, jf. den anden pointe, giver estimaterne ikke i sig selv oplysninger om konkurrerende alternativer, interventioner og anbefalinger til beslutningstagere. Derfor er det centralt at bruge estimaterne indenfor cost-effektivitetsanalyse (CEA), som anbefalet.

Sammenfattende leverer afhandlingen en ramme for at identificere kroniske sygdomme via registrer; og den giver komplementerende estimater af disse kroniske sygdommes omfang (ved prævalens) og den sætter værdi på sværhedsgraden målt som HRQoL (ved EQ-5D) til brug i sundhedsøkonomisk evaluering og anden forskning. Således er formålet ikke at give nogen konkrete anbefalinger til beslutningstagere, men blot at levere redskaber for at andre kan komme med fremtidige anbefalinger.

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LIST OF ABBREVIATIONS

ALDVMM Adjusted Limited Dependent Variable Mixture Model (regression model)
BoD Burden of Disease
CBA Cost-benefit analysis
CPR Central Personal Register
COI Cost of Illness
DALY Disability-Adjusted Life Years
DRG Diagnosis-Related Groups
GBD Global Burden of Disease
GDP Gross Domestic Product
GLM Generalized Linear Model
EQ-5D EuroQoL 5 dimensions
EQ-5D-3L EuroQoL 5 dimensions, 3 levels of answers
EQ-5D-5L EuroQoL 5 dimensions, 4 levels of answers
HRQoL Health-Related Quality of Life
ICD-9 International Classification of Diseases 9th version
ICD-10 International Classification of Diseases 10th version
MI Multiple Imputation
NCD Non-communicable Diseases (or chronic conditions)
NDR North Denmark Region
NICE National Institute for Health and Care Excellence
NIHP National Institute of Public Health
NHP National Health Profiles
NPR National Patient Register
OLS Ordinary Least Squares (regression model)
RCT Randomized controlled trial.
SE Standard Error
SD Standard Deviations
SWB Subjective Well-being
TOBIT a censored regression model named after James Tobit (1958)
YLD Years Lived with Disability
YLL Sum of the Years of Life Lost
SR Self-reported
RR Register-reported
WTP Willingness to Pay
QALY Quality-Adjusted Life Years
QoL Quality of Life
QWB Quality of Well-being

LIST OF PUBLICATIONS

Paper 1 **Catalogue of 199 register-based definitions of chronic conditions.**
Michael Falk Hvidberg, Soeren Paaske Johnsen, Charlotte Glümer, Karin Dam Petersen, Anne Vingaard Olesen and Lars Ehlers
Scand J Public Health. 2016;44(5):462–79.

Paper 1b **Supplementary material: Process, content and considerations of the medical review and ratification regarding register-based definitions of chronic conditions Supplement to: Catalogue of 199 register-based definitions of chronic conditions.**
Michael Falk Hvidberg, Soeren Paaske Johnsen, Charlotte Glümer, Karin Dam Petersen, Anne Vingaard Olesen and Lars Ehlers
Scand J Public Health. 2016;44(5):462–79.

Paper 2 **Catalogue of prevalence rates and characteristics of 199 chronic conditions in a comprehensive nationwide register study.**
Hvidberg, M Falk, Johnsen, Soeren Paaske, Davidsen, Michael and Ehlers, Lars
Submitted.

Paper 3 **A national catalogue of 199 preference-based scores for ICD-10 based chronic conditions using DK, UK and US EQ-5D tariffs.**
Hvidberg, Michael Falk, Hernández Alava, Mónica, Davidsen, Michael, Petersen, Karin Dam, and Ehlers, Lars
Work in progress.

Paper 4 **The Health-Related Quality of Life for Patients with Myalgic Encephalomyelitis. Chronic Fatigue Syndrome (ME/CFS).**
Falk Hvidberg, Michael; Brinth, Louise Schouborg; Olesen, Anne V; Petersen, Karin D; Ehlers, Lars
PloS one, Vol. 10, Nr. 7, 01.2015, s. e0132421.

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The Danish National Health Survey 2010. Study design and respondent characteristics / Christensen AI1, Ekholm O, Glümer C, Andreasen AH, Hvidberg MF, Kristensen PL, Larsen FB, Ortiz, Juel K. Scand J Public Health. 2012 Jun;40(4):391–7. doi: 10.1177/1403494812451412.

Sundhedsprofil 2010: "Trivsel, sundhed og sygdom i Nordjylland" [Health profile 2010: " Well-being, health and disease in North Jutland"]. Source: http://www.rn.dk/Sundhed/Til-sundhedsfaglige-og-samarbejdspartnere/Folkesundhed/Sundhedsprofil/Undersoegelserne-2007-2013/Sundhedsprofil-2010

The development in body mass index, overweight and obesity in three regions in Denmark / Toft, Ulla; Vinding, Anker Lund; Larsen, Finn Breinholt; Hvidberg, Michael Falk; Robinson, Kirstine Magtengaard; Glümer, Charlotte. I: European Journal of Public Health, Vol. 25, Nr. 2, 2015, s. 273–278.

Related abstracts by the author:

Generating a set of preference-based EQ-5D index scores for chronic conditions using a percentage scale / Olesen, Anne Vingaard; Oddershede, Lars; Ehlers, Lars Holger; Hvidberg, Michael Falk; Petersen, Karin Dam. 2014. Abstract from 2014 iHEA World Congress, Dublin, Ireland.

Catalogue of EQ-5D Scores for Chronic Conditions in Denmark (abstract) / Hvidberg, Michael Falk; Petersen, Karin Dam; Ehlers, Lars Holger. I: Value in Health, Vol. 16, Nr. 7, 30.11.2013, s. A595.

Catalogue of EQ-5D Scores for Chronic Conditions in Denmark (poster) / Hvidberg, Michael Falk; Petersen, Karin Dam; Ehlers, Lars Holger. 2013. Poster session presented at ISPOR 16th Annual European Congress to be held 2–6 November 2013 at The Convention Centre Dublin in Dublin, Ireland.

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CHAPTER 1. INTRODUCTION

1.1. THE RISING BURDENS OF CHRONIC CONDITIONS

The burden of chronic conditions has been an important issue worldwide for years, for citizens, health-care providers, researchers and governments. The burden is considered a "rising" problem of "epidemic proportions" by the World Health Organization (WHO) that should and can be significantly reduced [1]. Studies show a global shift from communicable diseases to chronic diseases [2, 3] as well as varying burdens by chronic condition and country [1, 4–9]. These studies all depict major challenges for not only personal health but also societal development:

> "Noncommunicable diseases (NCDs[1]) are one of the major health and development challenges of the 21st century, in terms of both the human suffering they cause and the harm they inflict on the socioeconomic fabric of countries, particularly low- and middle-income countries. No government can afford to ignore the rising burden of NCDs. In the absence of evidence-based actions, the human, social and economic costs of NCDs will continue to grow and overwhelm the capacity of countries to address them…. The human, social and economic consequences of NCDs are felt by all countries but are particularly devastating in poor and vulnerable populations. Reducing the global burden of NCDs is an overriding priority and a necessary condition for sustainable development. As the leading cause of death globally, NCDs were responsible for 38 million (68%) of the world's 56 million deaths in 2012. More than 40% of them (16 million) were premature deaths under age 70 years…." WHO 2014 [5].

Although the WHO states that the burdens of chronic conditions in particular strike low- and middle-income countries, high-income countries like Denmark also have similar health-care issues on the horizon pressuring the health-care system [10]. Consequently, the Danish universal health-care model is also under pressure. For instance, in 2011, several Danish experts concluded that there were three major interrelated challenges in the health-care system: 1. the demographic development: ageing and more chronic patients; 2. a declining workforce; and 3. the fiscal sustainability of the universal health-care system [11]. Also, the demographic issues projected in the report are supported by the Danish Rational Economic Agents Model (DREAM). Projections from 2011 to 2100 show a 20 per cent increase in the

[1] "Noncommunicable – or chronic – diseases are diseases of long duration and generally slow progression." See: http://www.who.int/features/factfiles/noncommunicable_diseases/en/

total size of the future Danish population and a relative decrease in the workforce [12]. Moreover, the number of citizens over 65 and 80 years will double by 2035. Similar conclusions were drawn earlier by Eurostat for other high-income European countries, and for several countries even more explicitly [10]. This demographic tendency is particularly troubling because empirical studies have shown that the average public spending per citizen is considerably higher for these age groups [13]. Currently, around two persons support one person outside the legal occupationally active age[2]. However, by 2035 this number will increase to roughly four persons supporting three persons [11].

Obviously, there must be a balance between tax income and expenditures in order to maintain a sustainable health-care system. From 2000 to 2012, the Danish annual health-care spending of GDP increased from 8.7 to 11 per cent of GDP [4]. Yet, estimates are still debated due to different economic settlement methods, but in absolute numbers, the estimates varied from around 110 to 165 billion Danish crowns in 2012 [14, 15], including an approximately 50 per cent increase in hospital medical spending from 2009 to 2012 [16]. Of the total costs, the National Board of Health and others cite that chronic conditions possibly account for up to 80 per cent of all health-care expenditures [17, 18]. Another recent study from 2015 estimates total costs for approximately 20 selected conditions of 25.6 billion DK kr. annually in 2010–2012, though the inclusion of costs has several limitations [19]. And as this study does not include all chronic conditions, the numbers are without doubt much higher.

Adding the issues of demographic projections, increased life expectancy, healthy ageing, prices, wages and health-care productivity, several scenarios published by the Danish Economic Council show that the health-care expenditures are not sustainable unless some action is taken [20]. The Council's projected scenarios estimated an increase in expenditures ranging from 20 to 60 per cent up to 2050. Notably, a more recent publication found that an important contribution to increasing numbers was partly found to be the rise in chronic conditions [11].

In summary, the above issues highlight the need for prioritization within health care in order to ensure a sustainable health-care system, and the ability to handle an increasing number of chronic conditions with a smaller workforce to address the rising expenditures. For this, reliable methods and estimates for monitoring and evaluating chronic disease burden are crucial for health-care research and prioritization. It is within this context that this PhD thesis has been composed.

[2] The problem is further complicated due to potential future shortages of physicians and nurses [211], which in the Danish context is forecasted to be as high as 15–16 per cent of health-care personnel in 2020 [11], although other international estimates are more conservative [212].

1.2. HEALTH ECONOMIC EVALUATION AND PRIORITIZATION PER SE

Disease prevalence rates and cost of illness (COI) analysis have been the commonly used methods to illustrate the burden of disease, but also to some extent decision-making [21–23]. However, although informative, these methods are descriptive and do not provide an evaluation of interventions and alternatives, or any explicit recommendations; therefore, they are of little use for decision-making and prioritization of new technologies and resource allocation [21, 22]. For this, cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) are the better-suited and preferred methods within health economic evaluation as they relate health to costs and compare alternatives with recommendations [24, 25]. This is done using the incremental cost-effectiveness ratio (ICER), which measures effect against costs for different disease interventions [21]. The ratio is then compared to a predefined, normative willingness-to-pay threshold to decide whether the new intervention is cost-effective. This and CEA/CUA are described in more detail in chapter 2.

Several countries have institutions for health economic evaluation and prioritization of new technologies including new medications. One of the leading international institutions often mentioned is the National Institute of Clinical Excellence (NICE) in England. NICE is a decision unit that is independent of politicians, and that operates within a comprehensive framework of methods and requirements including the use of CEA/CUA and effect measures based on Quality-Adjusted Life Years (QALY) [26–28]. In 2006, 14 countries had different institutions and requirements for implementing new medications and technologies, including Denmark, Norway, Australia, Canada and England [29]. In 2016, 41 countries had pharmacoeconomic guidelines around the world, including South Africa, Egypt, Brazil, Cuba, Thailand, Israel, Taiwan, South Korea, Malaysia, China Mainland and several countries in Europe, among others [30].

The majority of new CEA are done in relation to new medications; hence, medication is particularly important within health economic evaluation/institutions – which is why NICE, for example, has comprehensive guidelines for evaluation [31, 32], although guidelines for all kinds of health technologies exist [28]. Moreover, rising costs of medicine in particular have been heavily debated worldwide in regard to how to handle this, whether the prices are set fair by the pharmaceutical companies, whether we should implement all new medicine even if the cost-effectiveness is low, and how to handle layoffs in hospitals in a Danish context due to rising medicine costs [16, 33–38]. A recent Health Technology Assessment (HTA) summarized several related issues also illustrating the public and political pressures on institutions as follows:

> "Organisations across diverse health care systems making decisions about the funding of new medical technologies face extensive

> stakeholder and political pressures. As a consequence, there is quite understandable pressure to take account of other attributes of benefit and to fund technologies, even when the opportunity costs are likely to exceed the benefits they offer. Recent evidence suggests that NICE technology appraisal is already approving drugs where more health is likely to be lost than gained. Also, NICE recently proposed increasing the upper bound of the cost-effectiveness threshold to reflect other attributes of benefit but without a proper assessment of the types of benefits that are expected to be displaced. It appears that NICE has taken a direction of travel, which means that more harm than good is being, and will continue to be, done, but it is unidentified NHS patients who bear the real opportunity costs." Claxton, 2015 [38]

Denmark has recently responded to these issues by making it compulsory to conduct CEA when new medicine is implemented in the future, even though the specific requirements are currently unclear and under development [39, 40]. Thus, authorities are increasingly resolving to carry out health economic evaluation, including the previously mentioned international accumulation of new guidelines in an attempt to meet the increasing need for prioritization and the rising burdens of health-care spending, and hence to regulate the monopoly and maximum costs of new medicine.

Where CEA can use different effect measures, CUA is based on one standardized effect measure, the Quality-Adjusted Life Years, which combines life years with health-related quality of life (HRQoL) most commonly based on the generic EQ-5D five-dimension health questionnaire (see chapter 2 for further details). This enables comparisons across different interventions and diseases. Notably, numerous effect and disease burden measures exist as well as other methods for health economic evaluation (again see chapter 2 for further details). What is important here is that CUA together with the QALY/EQ-5D is the preferred and most commonly used method within health economic evaluation, and is not dependent on a monetary evaluation of health from patients [24, 25]. Equally important in regard to the present thesis, the increasingly wide use of health economic evaluation and QALY founds a need for local EQ-5D preference scores of chronic diseases for use in CUA when modelling health scenarios.

1.3. STANDARDIZING HRQOL PREFERENCE SCORES FOR CHRONIC CONDITIONS – AND LIMITATIONS OF EXISTING RESEARCH

Even though CUA already uses a standardized effect measure (the EQ-5D), different EQ-5D-based studies of the same condition often give different HRQoL results; thus, comparisons of HRQoL estimates can still be difficult [41, 42]. Agreed, this is not surprising as different studies cannot be expected, for example, to use exactly the same sampling methods, regression or other methods, or to have exactly the same patient population etc. Nevertheless, when the industry or others provide documentation and CUA of new medicine, or treatments use estimates from existing literature, different studies and effect measures still enable selection of the effect results risking picking results that put the evaluated treatment into the best light – or publishing non-reliable results unintentionally.

Consequently, US and UK authorities have already called for standardized methods within CUA including an "*'off-the-shelf' catalogue of nationally representative, community-based preference scores for health states, illnesses, and conditions*" [41, 42]. In response, a local American catalogue of EQ-5D scores had already been published in 2005 based on approximately 140 chronic conditions within a single study and survey sample from 2000 to 2002, and later with UK EQ-5D preference values based on the same sample [43]. Notably, a few other single studies have also provided other local national EQ-5D preference catalogues, although for a much more limited number of chronic conditions [44–47].

Basing estimates on uniform methods/data was one of the key issues and reasons for recommending the catalogue in order to increase comparability and reduce the variability of existing estimates derived from different studies and methods; but also providing estimates that can be used without the burden of collecting primary data retrospectively when, for example, no other data exist [41, 42]. Thus, a standardized catalogue calculated based on a uniform methodology/data for all conditions enables impartial comparisons of severity (essentially revealing who has it worst) across conditions (although, naturally, with the limitations of the methodology and measures, but equal for all conditions). Moreover, the estimates enable the prevention and cure potentials of interventions within CUA to be modelled (see further description in chapter 5) [48, 49].

However, besides being based on older surveys from 2000 to 2002, the existing catalogues have several shortcomings. First, the regression methods are median

based, although health economists mostly use and prefer[3] means [24, 25]. Secondly, the regression method used might not be appropriate for handling the complex statistical distribution of the EQ-5D. Thirdly, the conditions are self-reported and based on the outdated International Classification of Disease Version 9 [50]. Fourthly, the studies could be improved by estimates of health risk factors, BMI, stress, social network and other variables of relevance for health economic evaluation and other research – and more conditions. This could further improve future analytics and shed light on unequal health characteristics, socio-economic determinants, associations and their strengths, not done before within a single study comprising if not all, then most chronic conditions. Finally, no catalogue of uniform Danish EQ-5D preference-based estimates exists of chronic conditions for use in health economic evaluation. Thus, there is room for further improvement and standardization of methods and estimates.

1.4. THE NEED FOR A STANDARDIZED FRAMEWORK FOR IDENTIFYING CHRONIC CONDITIONS

A "methodological framework" is defined in the present thesis as "appropriate data and transparent definitions or algorithms for identifying chronic conditions within these data".

Specific attention to the framework and methodology for identifying chronic conditions is critical. For example, the interpretation of burden estimates can be vastly "*misleading without transparent information about all the input data that informed the calculations*" [51]. Burden of disease measures often have a black box reputation because the reported results do not always include evidence about all the

[3] Notably, some health economists do also use medians, which statistically can be justified as the EQ-5D distribution is skewed [72], which is why the median might provide a statistically more accurate measure of the central tendency if needed. However, leading health economists argue that the mean is the "theoretically correct way to aggregate individual values, irrespective of the nature of distribution"… as "the mean reflects the people's intensity of preferences and follows conventional welfare concerns by addressing whether the total benefits to those who gain are greater than the sum of the benefits to those who lose from a policy change" [25]. Furthermore, studies have shown that median-based studies produce higher values for less severe conditions and lower values for more severe conditions compared to mean-based studies [213]. (However, the opposite association was found in paper 4, although this confirms that the mean and median produce different estimates [204].) As mean and median are different measures, and no absolute gold standard for choosing exists, the recommendations are to choose the measure based on a "prior philosophical position on how preferences should be aggregated" rather than intuition [25, 213].

epidemiological data – as well as assumptions about social value choices [51–53]. Invalid methods can result in biased results regarding the population's health status and, in the worst cases, lead to biased decisions and priorities [51]. Despite the importance, a relatively recent systematic review of general burden of disease studies showed a lack of methodological uniformity in the basic framework and data across studies:

> "However, large differences in used methodology exist between general burden of disease studies. Because of the methodological variation between studies it is difficult to assess whether differences in DALY estimates between the studies are due to actual differences in population health or whether these are the result of methodological choices. Overcoming this methodological rigor between burden of disease studies using the DALY approach is a critical priority for advancing burden of disease studies. Harmonization of the methodology used and high-quality data can enlarge the detection of true variation in DALY outcomes between populations or over time." Polinder et al. 2012 [53]

Thus, a new uniform framework for identifying conditions could potentially be used across different research fields and different measures of disease burdens.

In the US, a government report a few years back also called for more work allocating burden to specific diseases to avoid double counting etc., especially in regard to costs, but also deaths, utilization and other outcomes, and thus to enhance the accuracy of burden estimates for multiple diseases [54]. A new framework should naturally take this into account, including choosing appropriate data. Other COI studies have also recommended focusing on data and how to identify conditions as important issues [54–56].

In Denmark, the "calls" for using health-care data for monitoring chronic conditions, including using hospital discharge diagnosis, have been partly answered by Statens Serum Institute in regard to ongoing work on developing register-based definitions (framework) for a few selected conditions including diabetes, heart conditions, COPD, asthma, arthritis, osteoporosis, schizophrenia and dementia [57, 58]. However, this still does not include a comprehensive number of chronic conditions, or HRQoL burden measures. Likewise, various studies have tried applying big data based on registers to assess the burden of chronic disease [59–66]; nevertheless, the studies have typically only covered a few designated chronic conditions, thereby not using the full potential of existing data. To the best of the author's knowledge, no current register-based studies have explicitly aimed to present a uniform framework and methodology of register-based definitions on all chronic conditions in pursuit of comprising if not all, then most chronic conditions systemically. Notably, new problems arise in terms of when to include conditions

once comprising all and different register-based chronic conditions as they have diverse levels of chronicity as described later. This, for example, requires explicit judgment of how long a time each condition is included back in time from a time of interest (for example the survey time). To the best of the author's knowledge, this is not explicitly addressed or standardized within existing frameworks and research.

Nevertheless, some studies have attempted to comprise numerous chronic conditions in relation to different HRQoL measures such as, for example, the WHO Global Burden of Disease Studies (GBD) [2, 3, 6, 8, 67] (DALY) or Sullivan et al. [41, 42, 49] (the EQ-5D). Nevertheless, while the WHO studies are based on ICD-10 codes, unspecified data sources often vary across countries, why their use of data sources is at best unclear in the opinion of this author and naturally not uniform due to the different resources of the different countries. For example, studies have criticized and recommended methodological improvements [51, 53, 68, 69], and the authors of the GBD studies have recommended future use of hospital discharge and outpatient data [8]. But more importantly, the GBD studies lack a solution for how to include a substantial proportion of patients treated outside hospitals based on registers, and they do not provide a solution for how to treat the differences in chronicity across conditions and thus different inclusion times using register data. These issues need to be addressed transparently, which the current author intends to do within the present thesis.

Finally, the most comprehensive study in terms of number of included conditions actually using the EQ-5D is based on self-reported ICD-9 conditions (survey based), not the ICD-10 or doctor-reported register-based chronic conditions. For this, Danish national health registers containing diagnoses, medications and more can add the precision of ICD-10 doctor-reported diagnoses to the EQ-5D scores and other outcomes rarely seen, by combining survey data comprising the EQ-5D with national health registers from both private and public hospitals, and both primary and secondary sectors. Scandinavian national health registers have a long tradition of reporting different conditions and matters at the micro level. Although other countries have registers, the scope, comprehensiveness and population completeness are unique to Scandinavian countries:

> "The Nordic countries are world-famous within the research community for their ability to conduct register-based health- and welfare-oriented population studies. Legislation in most countries in the Nordic region allows researchers to carry out studies linking various registers by means of the individual personal identification number allocated to each person. This provides a unique source of data, which is invaluable for the public health community." Kamper-Jørgensen, 2008 [70]

Consequently, the use of several registers enables the incorporation of all types of nationwide-reported chronic conditions into a framework, with enhanced medical diagnostic precision, and without self-reported bias.

1.5. THE OBJECTIVES OF THE THESIS AND READING INFORMATION

The aims of the present thesis are to provide national standardized EQ-5D 3L health-related quality of life preference scores and prevalence rates of 199 chronic conditions, and to provide a transparent framework and method for identifying chronic conditions within public health registers. Altogether, the overall aim is to provide essential disease burden estimates and a new method for generating these estimates. This is done in order to support health economic evaluation, and epidemiological and other research. Thus, the aim is not to provide any specific recommendations for decision-making, merely the means for others to do so.

Initially, the main aim was to provide a catalogue of health-related quality of life (burden) estimates for health economic evaluation; yet this required register-based definitions (framework) of chronic conditions, which is also of epidemiological interest, which is why one of the first and most substantial parts of the thesis was to develop these in cooperation with medical and other specialists. Furthermore, health-care analysts, epidemiological and other researchers can benefit from prevalence (burden) estimates of chronic conditions, thus the thesis also provides estimates thereof. Therefore the thesis delivers estimates of both quantity (prevalence) and severity (HRQoL), which complement each other for use in health economic evaluation and other research.

Accordingly, the objectives of the PhD thesis are:

- *Objective 1:* To establish and present standardized register-based definitions of 199 medically reviewed chronic conditions.
- *Objective 2:* To estimate the population-based prevalence rates of the 199 chronic conditions.
- *Objective 3:* To establish and present a catalogue of Danish EQ-5D preference scores for 199 nationally representative chronic conditions.
- *Objective 4:* To present a case example of HRQoL analytics of a survey-based chronic condition and a case example of limitations of register-based definitions.

Background and reading information about objectives

As the basic methodological framework identifying all chronic conditions using register data was insufficient, one of the first and most important parts of the PhD study was to create reliable methodological, uniform definitions embracing all – or as many as possible – chronic conditions by clinical assessment (objective 1and paper 1). Thus, the methodological issues are thoroughly discussed. This is the foundation for the two catalogues of the selected burden estimates, but could also be used by other researchers and health-care professionals for other outcomes of interest, such as, for example, DALYs, mortality, incidence and life expectancy, among others [3].

A catalogue of prevalence estimates of chronic conditions (objective 2 and paper 2) provides the basic epidemiology of the burden, essentially answering the questions: how many are affected by the different conditions comparatively speaking, and how big (size) are the (potential) disease problems? Moreover, it provides new insights into the burden of chronic conditions based on data within an entire country not seen before. Furthermore, the prevalence study can be used for COI, and the framework can be used for monitoring disease prevalence by using the definitions in paper 1. However, prevalence data do not capture the burden of disease experienced by citizens in terms of lost health or differences in severity of the conditions [67]; hence, they are merely a measure of a potential problem. Neither do they provide useable information for health economic evaluation. Consequently, a second catalogue with severity outcomes is essential.

In this respect, the US and UK authorities have for a long time called for *uniform* measures for health economic evaluation and prioritization, including "off-the-shelf" catalogues of preference scores for health states [42]. The EQ-5D preference catalogue (objective 3 and paper 3) will shed light on which conditions have it worst based on the EQ-5D, and how bad it is, and thus what the potential health gains are. The discussion section will provide more details on the potential and practical use. Furthermore, the catalogue will be an improved version of existing research on several areas: improved regression modelling, more regression models, and the use of ICD-10-based conditions including health risk, BMI and social network, thereby constituting different methodological contributions to the field. Moreover, the estimates are intended for modelling within health economic evaluation as described elsewhere [41, 42, 49, 50]. Furthermore, the UK authorities require the EQ-5D to be used within all public health economic evaluation as the preferred measure [27] and it is the preferred measure among researchers within the field [24]. Thus, a catalogue of EQ-5D preference scores for 199 chronic conditions will meet several authorities' and researchers' needs and benefit future research, health economic evaluation and future prioritization. Also, we expect an EQ-5D preference catalogue to be of increasing importance in a Danish context, as, in

spring 2016, the Danish authorities decided that health economics evaluation is also required within prioritization of hospital medicine due to growing costs [39, 40].

Finally, the HRQoL case example of a survey-based chronic condition has two purposes (objective 4 and paper 4): first, to show a case example of how each condition could be analysed and presented; and secondly, it is also intended as a case example of the limitations of register-based definitions, as the condition is not representatively identified in registers even though it is a worldwide common condition. The case example is Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS).

The results and stages are described in more detail in chapter 3, while methods and process are described in detail in chapter 2.

CHAPTER 2. THEORY, METHODOLOGIES AND DEFINITIONS

2.1. THE BASICS, HISTORY, STRENGTH AND LIMITATIONS OF COST-OF-ILLNESS ANALYSIS AND HEALTH ECONOMIC EVALUATION

As the framework and estimates may be used for future cost-of-illness (COI) analysis and health economic evaluation, these methods are briefly introduced in the following. However, it is beyond the scope of this thesis to further address this comprehensive field in details as well as counteract the many theoretical limitations and discussions; therefore, the following is solely a limited introduction to the field that naturally can be explored further in references.

Cost-of-illness analysis

One of the first health evaluation methods, cost-of-illness (COI) analysis, appeared well before the mid-1960s and was the first method used within health-care assessment; COI measures the economic burden of illnesses for society and has been commonly provided by several countries as well as the US National Institute of Public Health, the World Bank and WHO, and researchers, although COI is debated [22]. The underlining assumption was that the economic costs of illness signified the potential economic benefits of a given health-care intervention if it eliminated the illness [22]. What COI does not do is provide an evaluation of the best alternatives to choose from as it does not provide information on the health-related burden or whether a condition can actually be cured or reduced by an intervention; thus critics say that it is little help to those taking decisions and ranking priorities [22]. As a consequence, COI is not considered a health economic evaluation by all [21], including by the definition below. Other so-called welfare economists criticize the lack of a theoretical foundation, while the human capital approach makes the criticism that costs of morbidity and mortality lack "the value people attach to their lives", e.i. lack of focus on potential growth, for example, based on personal earnings in relation to health [22].

Nevertheless, COI is a descriptive study and one type of burden measure among others that can provide information and input to decision-makers at different levels, yet is still used and recommended for use [23]. For example, COI may provide information on the highest expenditures and biggest potential gains for use within research priorities besides generating obvious awareness of the economic burden as costs matter [21]. Several methods and guidelines exist for providing COI and these are provided elsewhere [21, 22]. Although it is beyond the scope of the current

thesis to provide a comprehensive description and evaluation thereof, as well as other technical methods, COI can be estimated based on prevalence/incidence, top-down/bottom-up, retrospective versus prospective [22]. However, no real agreement exists: for example, Tarricone recommends a bottom-up approach, while Pedersen describes and uses a combined prevalence approach as the most common method [21, 22]. Nevertheless, what is important to mention in relation to this thesis is that it is possible to use prevalence studies for estimating COI.

Health economic evaluation methods

In line with the earlier described sparse societal resources, there is a need for assessing and choosing the best solution within health care, i.e. prioritization. In essence, this is what health economic evaluation is about: assessing the health-care inputs and outputs, costs and consequences, of activities [24]. Drummond et al. define health economic evaluation as:

> "The comparative analysis of alternative courses of action in terms of both their costs and consequences." Drummond et al. (2015) [24].

Two main types of health economic evaluation is often described in the literature: cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) [21]. Although not specified as CBA/CEA, some of the first CBAs and CEAs were done in the late 1960s [24]. From the 1970s, several new tools for health economic evaluation emerged, including the so-called Rosser Scale[4], and from the 1990s, the EQ-5D, as described later [25]. In contrast to COI, CBA and CEA evaluate different alternatives of interventions and provide a recommendation to decision-makers in order to get most value for money [21].

Cost-benefit analysis (CBA)

CBA measures all benefits in monetary terms. Monetary terms also include valuing, for instance, survival or health using money as the numéraire [25], for example the willingness to pay (WTP) different amounts for a pregnancy screening [21]. One advantage of CBA is its economic theoretical foundation and attempt to quantify the willingness to pay for health-care goods and services for society. On the other hand, there are practical difficulties to providing reliable estimates thereof as it can

[4] Rosser disability/distress scale: this was originally a measure of hospital output, which in the 1980s became the most widely used tool for deriving QALYs in the UK, but fell into disuse following the introduction of the EQ-5D and others. Basically, the survey measure has two dimensions, disability and distress, with a total of 29 health states. Originally, the measure was conducted by a clinical assessment, but it was also performed as a self-reported measure [25].

be difficult to monetize the value of health and life; moreover, valuing health in monetary terms clashes with the acceptance and norms within health-care. Additionally, market failure due to the complexity and asymmetric information about health and treatments within health-care systems makes such estimates difficult to obtain and should be used with caution [21].

The theoretical school behind CBA is closely related to welfare economics, often called welfarists. What matters to welfarists is measuring the social welfare, health or well-being *assessed by the individuals themselves*, as done in WTP, and less emphasis is laid on the problems of a non-functioning health-care market (asymmetric information and uncertainty of future health) and equity. Thus, welfarist benefits or social welfare are the sum of individual utility [25].

Cost-effectiveness analysis (CEA)

Since CBA (and COI) have met some criticisms and have practical issues regarding use within health economic evaluation, for instance equity issues of health-services and a nonfunctioning market, CEA is the most commonly used method. Within CEA, the benefits (effects) of an intervention are measured in natural units in comparison with the costs. Natural units may be life-years saved, mortality, morbidity, pain, "health", treatments avoided, illnesses avoided, high blood pressures avoided and others. Moreover, CEA measures the effect using the incremental cost effectiveness ratio (ICER) of two – or more – interventions as follows:

$$ICER = \frac{Effect\ new\ intervention - effect\ old\ intervention}{Costs\ new\ intervention - costs\ old\ intervention}$$

Because the many different effect measures make diverse ICERs and comparisons difficult, and since interpretation of the ICER[5] is crucial for the recommendation of alternatives, standardized generic health effect measures based on the QALY/EQ-5D have been developed for comparisons across conditions and treatments – the cost utility analysis (CUA) as a subgroup of CEA [25]. In essence, the QALY combines life-years, the HRQoL based on the EQ-5D and its five predefined health dimensions and the time into single value. The EQ-5D/QALY is described in more detail in a later section. Besides enabling comparisons, this also decreases the industry and others' chance of choosing the method – for example effect measure – that puts the treatment of evaluation in the best light or similar problems described

[5] Furthermore, new interventions are often more expensive, but with better effect. Thus, a crucial issue is where to set the threshold of how much society is willing to pay pr. increased effect (QALY). In the UK, the threshold is set at £20–30,000 pr. QALY, while other countries, including Denmark, do not have a threshold yet.

elsewhere [71]. For example, a treatment of diabetes may show a significant decrease in low blood sugars measurements and the number of injections needed, but not enough to generate a significant impact on the HRQoL based on generic measures. Yet, some disease-specific measures might show an impact, tempting medical companies to solely choose measures showing the impact at its best. Respectively, there may be technical reasons as the measure is not sensitive to the disease or effect, but it may also be that the effect is actually small on the HRQoL. CUA decreases this issue.

The theoretical foundation behind CEA and QALY is often mentioned as extra-welfarism. Extra welfarists challenge the welfarists' assumption that individuals necessarily are the best valuators of their own welfare, and benefits should be measured as the sum of individual utility; moreover non-health benefits can be left out as the objective of publicly funded health care is to improve population health [25]. Thus, within the extra welfarist perspective, benefits can be measured based on *population preferences* of different health states from a proxy (i.e. not directly patient valued) representative survey sample. Hence, "…the QALY is not a representation of individual utility, but a measure of health as a social desideratum" [25]. Notably, Brazier stresses that a welfarist interpretation of CEA would be to see the QALY as (substitute) representation of individual utility although not directly valued by patients themselves. Finally, an extra welfarist key issue is equity and is as such a response to the absence of a functioning market and to the welfare state's actual political and normative organization and distribution of health care without the concern of people's ability to pay for services.

The current thesis is implicit placed within the tradition of CUA and thus the extra welfarrist perspective as it aims to improve methods for future CUA. It is not the argument that CEA/CUA are without limitations as thoroughly described in the literature [21, 24, 25, 72], but the view of NICE and others is that CUA is probably the best alternative at this time for health economic evaluation and prioritization [21, 26, 27, 73].

2.2. THE BASICS OF QALY, EQ-5D, STRENGTHS AND LIMITATIONS

The concept of the QALY was initially introduced in 1968 in relation to a study of chronic renal failure; although the study did not use the phrase "QALY", the concept was the same [24]. The basic idea of the QALY, as previously mentioned, is that it combines both life-years and the HRQoL into a single measure. Therefore, it is not surprising that the concept was born in relation to chronic renal patients as they experience marked change in both HRQoL and life-years with and without treatment (see also Figure 2-1 for an example of QALY estimation with and

without treatment). Moreover, the increasing number of chronic conditions characterized by people who do not die immediately but live for several years within different health states has made the classic use of years of survival as the one single health measure outdated [21]. The QALY can be notated as follows, where H is the quality of health and Y is the years lived in the health state:

QALY = H * Y

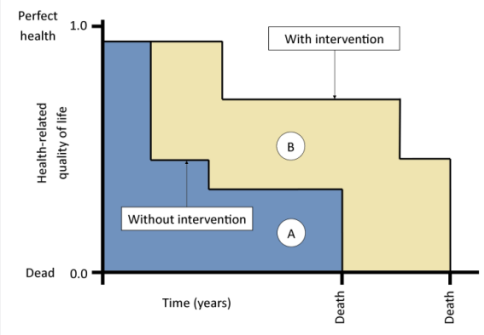

Figure 2-1. The QALY and interventions.

To estimate QALYs, it is necessary to represent the quality of health on a scale where full health and death are allocated values of 1 and 0, respectively, where 1 equals one year in perfect health and 0 death [25]. The most commonly used measured for this in health economic evaluation is the EQ-5D [21, 24, 25, 74] – a generic self-reported questionnaire transforming different dimensions of HRQoL into a single index score: the QALY weight or utility score (H). However, other measures can be used (see later description of QoL measures). The EQ-5D measures five dimensions of HRQoL: 1) mobility, 2) self-care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/depression. Each dimension has three (3L) or five (5L) levels of possible answers [75–77]. The answers of the three-level version – used in the present thesis – range from no problem to some problems and extreme problems [74, 76]. The five dimensions and corresponding three levels of the EQ-5D-3L have a total of 243 unique health states. These combinations of health states are transformed into a linear scale ranging from 0.624 to 1.000 based on the DK value set. The negative values represent health states worse than death. However, the way the index score is calculated is not trivial. First of all, the EQ-5D is preference based, i.e. the utility of the population. For Denmark, US and UK and other countries, the preferences are obtained based on national representative samples, not individual willingness to pay, for approximately 40–50 of the 243 health states of the EQ-5D using the so-called time trade-off method (TTO) [21, 78–80]. Naturally, only 40–50 health states are assessed as it is not practically possible to present all 243 health states to the respondents. Thus, the remaining health states are estimated based on advanced econometrics and regression

modelling. In essence, different health states, for example those with the answers "no problems" to mobility, self-care and anxiety/depression and "some problems" to the usual activates and pain dimension (1:1:2:2:1), are compared to a state of full health (1:1:1:1:1). The TTO exercise then assesses how much time spent in each of the health states makes the compared health states equally preferable [21]. Basically, it is the same choice that, for example, a cancer patient needs to make: how much extra survival time taking medication with side effects and reduced HRQoL is preferable to a shorter life in better health without side effects. The "choice" and preference of health states is the key and link to economic theory [21]. Other methods of valuing can be used, for example Standard Gamble (SG) or Person Trade-off, however it is beyond the scope of the present thesis to discuss this. Further reading and thorough descriptions of all valuation techniques can be found in references [21, 24, 25].

The construct validity, reliability and responsiveness of the EQ-5D have been investigated comprehensively [41]. Thus, some limitations related to the present thesis are well known: for example, the ceiling effects – as a large proportion indicates no problems at all (i.e. health state 11111) even though they have problems in other instruments [25] – and a lack of sensitivity of mild disease states in the 3L version in both general and disease-specific populations [27, 41, 81–83]. Consequently, the EQ-5D-3L might underestimate less severe conditions, but also to some extent overestimate more severe conditions. A newer systematic review regarding the responsiveness of the EQ-5D-3L, comprising 145 clinical studies and different conditions, found that 21 (45 per cent) of the examined conditions were responsive and could detect meaningful change in health. Another 27 conditions, or 48 per cent, had varied evidence. Finally, four conditions, or 7 per cent, were not found to be responsive to the EQ-5D-3L [81]. In addition, NICE has also identified trouble with the construct validity for the EQ-5D and a "weak" relationship with HRQoL for some forms of visual impairment, hearing loss and schizophrenia [27]. Paper 3 also discusses some of the well-known issues regarding the EQ-5D.

Notably, the 5L version of the EQ-5D was constructed in order to address ceiling effects [24, 84], although the current literature about whether this has succeeded is sparse, yet implications exist for eight chosen conditions for some ceiling improvement from 20 to 16 per cent on average [46]. Moreover, both the 3L and 5L have complex, multimodal distributions including gaps needing complex mixed regression modelling as most common regression models cannot handle these issues.

Finally, the EQ-5D is used in many countries and is, for example, required within health economic evaluation in the UK by the National Institute of Clinical Excellence (NICE) when making decisions about the use of new drugs, devices and prevention, among other things [24, 27, 41, 42]. In general, the QALY and the EQ-5D are the preferred HRQoL measures within health economic evaluation [24, 27].

In 2006, QALYs were also recommended as the preferred CEA measure in the US by the "Institute of Medicine (IOM) Committee to Evaluate Measures of Health Benefits for Environmental, Health, and Safety Regulation" – largely because of its ease of calculation and widespread use [85], but also as the QALY is considered useful for decision-making because the instrument reflects trade-offs (that people are willing to make) between quality of life and survival [54, 85].

In the Danish context, new principles for prioritization of hospital medication are under construct allowing for economic evaluation of new drugs in pursuit of ensuring "more value for money" [39, 40]. Although the details are still unknown, it is a possible first step towards a more systematic QALY-based health-care prioritization that has been debated for years.

2.3. DISEASE BURDEN MEASURES ACROSS TIME AND RESEARCH AREAS

Measuring disease burden is crucial for understanding chronic illness and the extent of issues, as well as prioritizing interventions; consequently, many measures have been developed over time [51]. This section describes the different disease burden measures in order to provide the reader with an overview of the history, uses, relationships and the state of the art across different research areas – and limitations. This will help the reader to put the used burden measures of the current thesis into the context of existing research and use. If the reader is already familiar with existing burden measures and limitations, this section can be skipped.

Naturally, there is no unambiguous definition of disease burden in the literature, and it is often defined broadly and comprises several different dimensions and measures [86]. Thus, within the present thesis, "disease burden" is likewise broadly defined as "the impact of a health problem measured using different indicators or disease burden measures".

One way of grouping disease burden measures is into three broad categories: Epidemiological Burden, Economic Burden and Quality of Life Burden [54]. Although not distinctly differentiated, this categorization is useful for illustrating the dependence and historical succession and development. For example, the Epidemiological Burden measures, such as prevalence, incidence, mortality, morbidity and life expectancy, can be seen to provide the building blocks and value of Economic Burden and Quality of Life Burden measures [54]. Furthermore, economic burden measures such as COI are based on epidemiological estimates such as prevalence and mortality, and Quality of Life measures such as QALY and disability-adjusted life-years (DALY) combine information about non-fatal health

outcomes and mortality describing population health. In what follows, the three groups of burden measures will be described.

Epidemiological burden

Epidemiology is defined as:

> "The study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems" [87].

Epidemiology has roots that go far back to the Greek physician Hippocrates (c. 460 – c. 370 BC), who was the first person known to have investigated the relationships between environmental influences and occurrence of disease [88]. In the late 19th and early 20th century, comparing subgroup population disease rates became common practice initially in order to control communicable disease, but later proved useful in linking environmental conditions to specific diseases [89]. Yet, modern quantitative methods studying population diseases, informing prevention and controlling efforts, are a relatively new discipline. For example, the Richard Doll and Andrew study of tobacco use and lung cancer in the early 1950s was one of the first to use long-term cohort studies, and established an association between smoking and lung cancer [89].

Epidemiologists distinguish between descriptive, analytical, theoretical and clinical branches of epidemiology [90]. Common descriptive epidemiological disease burden measures in the 21st century include prevalence, incidence, mortality, morbidity and life expectancy as mentioned, but also the Charlson Comorbidity Index, which combines mortality and comorbidity [91–93]. The initial use of population-based morbidity and mortality estimates gained momentum in the 1960s [94]. While prevalence measures the occurrence of a disease at a specific point in time, incidence measures new cases arising in a chosen period of time. Together, these two measures form the foundation for measuring disease occurrence and the overall scale of a health problem as well as the short-term population trends [54]. Mortality or mortality rate is often measured as the number of deaths by population or disease, per unit of time and scaled to the population. Life expectancy is defined as "the average number of years an individual of a given age is expected to live if current mortality rates continue to apply" [87]. It is common that the descriptive measures do not provide a measure of health-related *severity* experienced by the patients and do not provide any explicit information of the health-related quality of life, or differences therein between conditions. Neither do they address cause and effect. A limitation and challenge of existing prevalence estimates is not the calculation, but the underlying framework and methodology identifying the

conditions. For example, several studies have shown substantial prevalence differences between self-reported and register-identified conditions [60, 95, 96], although other studies show varying differences [97–105].

While descriptive epidemiological measures overall provide general statements on the occurrence of disease also using characteristics such as sex, age, class, occupation, race, calendar period and geographical localization, *analytical* epidemiology searches for causes and effect as well as classification, or outcome of disease [90]. The case of lung cancer and tobacco is a well-known example, along with survival analysis of any cancers; moreover, the randomized controlled trial (RCT) can be considered a specialized analytic epidemiology [90]. The used burden measures are excess risk, relative risk, odds ratio and population-attributable risk. It is outside the scope of the current thesis to explain these measures in detail (please see references for further details [54, 87, 89, 90]). One common challenge shared with other research areas is identifying cause and effect, more specifically attributing health outcomes to a single disease due to double counting because of high co-morbidity or multiple risk factors [90]. Yet, this is particularly a data problem depending on study or data possibilities, but certainly an issue to address within every framework identifying the conditions and other aspects of the study design, including handling competing risks statistically.

The last two branches, theoretical and clinical epidemiology, do not provide any explicit new disease burden measures. Theoretical epidemiology is based on and creates mathematical computer models to simulate disease occurrence, or the effect of preventive interventions; clinical epidemiology is applied to patients and clinical problems, not whole populations [90].

Within the three specified disease burden categories, epidemiological measures are the most explicit; moreover, they are also the foundation for developing economic and health quality measures [54, 106]. For instance, the prevalence is used to calculate aggregated costs and quality of life impacts on illness – and is as such a crucial measure of disease burden across disciplines. Nevertheless, a limitation of the epidemiological measures is that they cannot provide an overall measure of overall health status or change therein [54]. For example, if disease population prevalence indicators show a decline, but mortality rates are up, there is no way of concluding whether the population as a whole is better off or not. Consequently, various epidemiological measures function as health indicators, but shape the basis and complement higher aggregated population health measures such as the EQ-5D, Quality of Well-Being (QWB) or Subjective Well-being (SWB) [54, 107–109].

Economic burden

Economic burden of disease measures are commonly described in terms of health-care spending, both across time and at a single point in time [54]. Examples are the

health-care spending of GDP mentioned in section 1.1, but also the mean per capita spending is a classic macro-level economic burden measure. However, even though health-care spending accounts for a large proportion of the full burden of disease, other components, such as non-medical spending, of economic disease burden are of importance. In short, non-medical spending includes lost work days, impacts from increased morbidity or early mortality, and the effect on family members' employment situation – or patients' and family members' psychological well-being [54]. Through best practice, economic burden estimates endeavour to obtain the full burden of conditions – the "opportunity costs" of illness; this includes the value of both non-health and health outcomes foregone by a disease [54].

Economic burden of disease is often valued by COI as described earlier and its roots go back to the 1960s and beyond. However, some technical limitations and research trends have not been yet described, which is why this is done briefly here. Several studies have shown that costs vary extensively, even within the same disease [110–112]. Thus, over time, several attempts have been made to standardize COI. For example, in 1982, Hodgson and Meiners recommended including both direct and indirect costs in COI as well as six different points of best practice in how to apply costs [113]. Direct costs are defined as medical and non-medical spending on diagnosing, managing, treating and living with a disease, i.e. doctor visits, costs of transportation, family household expenditures etc. Indirect costs identify the productivity losses due to the lack of ability to work, but also psychosocial costs such as the "financial strain or uncertainty over a person's future health and well-being" [54].

Hundreds of COI studies exist and have estimated costs fully or partially within and for different conditions and often with different results [54]. In response, attempts at further standardization have included generating a national US catalogue of uniform estimates of direct and indirect costs for 75 diseases or risk factors in 2000 and 2006 [54, 114]. Moreover, newer research consensus guidelines standardizing disease cost estimation were created in 2009 based on a research workshop [115], while at the same time, the WHO also published their guidelines [116]. More guidelines exist (see, for example, this review [112]), but the important point here is simply that there are plenty of existing COI guidelines regarding estimating costs.

Nevertheless, the research focus in question has commonly been on how to account for costs, and less on identifying the conditions. Yet, the relevance of linking micro data of conditions to costs is recognized as a central challenge [56], as well as the importance of a standardized framework and methods for identifying conditions [54, 55]. However, none of these studies, to the best of the author's knowledge, provide a framework for using registers to do so and the challenges in doing so (see descriptions of challenges in the following sections).

CBA and WTP – also described earlier – are other measures of economic burden that are often closely related. A key advantage of the WTF method is that it is able to capture all the benefits of a disease prevention in a single measure, including the prevention of productivity loss and out-of-pocket medical spending, not to mention pain and suffering [54]. Nevertheless, besides the already mentioned limitations, CBA and WTP are more complex, costly and time-consuming than many other measures. Nevertheless, welfarist health economists (see appendices A–B) often prefer WTP, arguing that it is consistent with economic theory about maximizing personal utility [117].

Quality of life burden

HRQoL burden measures quantify a group's or person's self-reported perceived physical and mental health at a chosen point in time. Thus, these measures are not a proxy of either expert judgment or single measures like pain or motion [54]. HRQoL burden measures are needed to generate, for example, QALYs, and were in general intensively developed from the 1990s and beyond. Several HRQoL measures exist – from *disease-specific* to *generic* measures. Hundreds of disease-specific measures exist in all possible research areas, and are often used when generic measures are not evaluated to capture the condition's health states as desired (see, for example, Catquest, THI or ADDQoL used for measuring HRQoL in relation to cataracts, tinnitus and diabetes, respectively [118–120]. However, despite enhancing the precision of measuring precise aspects of a disease, the large variety of disease-specific measures has limitations. For example, within diabetes, a system review identified 31 different burden measures, and for vision-specific instruments, a review identified 32, often measuring different aspects [118, 119]. One obvious limitation is that it leaves a lot of room for researchers and the industry to choose the instrument that shows the largest improvement for a new treatment or drug. Moreover, comparisons across different conditions are difficult or even impossible in general with disease-specific measures, but also even within conditions unless exactly the same measures are used.

In contrast to disease-specific measures, generic HRQoL measures enable broad comparisons and evaluation of overall health across different domains or conditions. However, as several different generic and preference based HRQoL measures for QALY estimation exist, there is still some room for choosing the instrument that fits the condition best – or puts the treatment or drug in the best light. These instruments also have different dimensions, levels and measurements, although several overlap. For example, besides the EQ-5D already described, there is the Short Form 6D (SF-6D) and Health Utilities Mark (HUI). The SF-6D[6] is a

[6] The instrument was partly developed due to the popularity of the SF-36 in numerous studies, and the valuation is based on the standard gamble; as such, it ranges from 0 (death) to 1 (full health) and has a value of 0.3 as the lowest value. The SF-6D has trouble with floor

utility instrument with six dimensions that is based on 11 selected items from the SF-36 HRQoL questionnaire [121, 122]. The six dimensions relate to Physical functioning, Role limitation, Social functioning, Pain, Mental health and Vitality – all ranging from four to six levels of response describing 18,000 health states in total, of which 249 different health states were valued, and the rest were estimated using econometric modelling.

The HUI is currently in two versions, the HUI2 and HUI3 – also based on the scale of 0.0 (death) to 1.0 (perfect health) [24]. The HUI3 has eight health dimensions – Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain – with five or six response levels. There are 972,000 health states designated by the HUI3 in total. The HUI2 has seven dimensions: Sensation, Mobility, Emotion, Cognition, Self-care, Pain and Fertility. The valuation of the HUI is based on SG, and is not population preference valued in a Danish setting either. Notably, many other HRQoL preference-based instruments have been developed within the last few decades other than those referenced above, such as Quality of Well-being (QWB), 15D, AQoL, Rosser Classification of illness states and Index of Health-related Quality of Life [25]. Further reading regarding these HRQoL instruments can be found in references [24, 25, 74]. Several of the different preference-based HRQoL measures described earlier can be used to define the QALY.

Furthermore, in the early 2000s, two HRQoL instruments were created for use in America, one measuring the amount of time for which people are unhealthy, the "healthy days measures[7]" for both mental and physical health [123], while the Health and Activity Limitation Index (HALex) was created based on a self-assessment of health and "limitations of five activities of daily living" from the US National Health Interview Survey (see details in reference [124]).

Another kind of QoL measure is the Health-Adjusted Life Years (HALYs); these measures combine the impacts of disease mortality and HRQoL [125]. Historically, the HALYs were generated in order to improve epidemiological mortality measures and provide information about the severity of a health state or condition; this development occurred along with a decline in mortality rates, increasing life expectancies and a change from infectious disease towards (increasing) chronic disease, making mortality rates inaccurate as a population burden of disease measure [86]. The QALY, described earlier and thus not described in detail here,

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effects, which is why a second version is under development [24]. Besides the SF-6D and SF-36, there is also a shorter version called the SF-12 with eight dimensions [25, 121]. Only the SF-6D can be used for QALY estimation, but it is not population preference valued in a Danish setting.

[7] See http://www.cdc.gov/hrqol/hrqol14_measure.htm

and DALY are two common examples of HALYs; moreover, they also both depict the burden of disease within a single number on a scale from 0 to 1.0. The DALY is a part of the Global Burden of Disease Studies (GBD), one of the most comprehensive attempts made to create a framework of disease burden measures (also including prevalence) and estimates of disease burden for hundreds of conditions and risk factors with widespread use [54]. The understanding of burden of disease has in fact increasingly been associated with the GBD [86], although numerous other measures exist as stated earlier. The GBD study was started at the request of the World Bank in collaboration with the WHO in the early 1990s, and the first of several studies was published in 1993 based on data from 1990, while the latest study is from 2010 published in 2015 [3, 7, 94]. The aims of the GBD were originally:

> "To facilitate the inclusion of nonfatal health outcomes in debates on international health policy, to decouple epidemiological assessment from advocacy so that estimates of the mortality or disability from a condition are developed as objectively as possible", and "to quantify the burden of disease using a measure that could be used for cost-effectiveness analysis" [125, 126].

However, in recent times, the Global Burden of Disease Studies have not been officially directed at local health economic evaluation, as the later studies carefully state that the aim is to provide "essential input into global, regional and national health politics" [2, 7, 127, 128]. In particular, other studies criticize the lack of local estimates for use in national resource allocation and prioritization, and stress the need for national or subnational estimates [51].

One DALY can be seen as one year *lost* in healthy life due to death or disability, but is, however, rather complex in construction [86]. It is crucial to point out that while DALY assign disability scores to *diseases* (weighted by age stratum), QALY assign disability scores to *health states* (not weighted by age stratum/others) [54]. Moreover, the disability weights were initially created based on expert opinion – not population HRQoL preferences like the QALY; the argument was that self-assessments of health constituted a particular problem when comparing internationally, because different populations have different attitudes about desired health [54, 129]. This approach generated some critics [130], especially in regard to the lack of a theoretical foundation – the legitimacy of using the estimates for societal prioritization as the estimates did not reflect the population preference in trade-off between life and QoL – for use in health economic evaluation, which was one of the WHO original aims; thus, this was later given up and the disability weights were later generated by *global* population preferences based on a mean of several countries and regions [24, 25, 131]. This was done as DALYs are aimed at

comparing on a global scale in contrast to the QALY; yet, critics[8] argue that the DALY is too inaccurate for *local* or country-specific CEA [7, 9, 130].

In more detail, the DALY is attributable to specific illnesses, and for a certain population, equal to the sum of years of life lost (YLL) and years of life lived with disability (YLD), hence DALY = YLL + YLD [7, 9, 127, 128]. YLLs are calculated by multiplying the average life expectancy at the age of death (L) by the number of deaths for a given cause (N), hence YLL = L x N [126, 129]. YLD "multiplies the number of disability cases (I) by the average duration of the disease (L) and by a weighting factor (DW) that reflects the severity of the disease", hence YLD = I x L x DW [54, 129].

So, what are the limitations and potentials for improvement of the GBD framework? First of all, much has already been done to improve the DALY calculation as mentioned – including methods handling large amounts of missing data and strengthening varying data sources [3, 131, 132]. However, Murray et al., among others, suggests further use of data-related improvements, for example ICD-10 codes and hospital discharge records [8]:

> "Hospital discharge data and outpatient data coded to ICD-10, despite issues of selection bias, have proven to be very useful in the assessment of the burden from many conditions; wider and more systematic collation of this data especially at the unit record level would be extremely useful." The Lancet, 2012 [8]

Moreover, the use of HRQoL measures has also been recommended as a supplement by the authors of the GBD:

> "Broader use of functional health status instruments such as SF-12 in surveys or in health service settings that also provide reliable diagnoses would strengthen the analysis of many conditions, including mental and behavioral, musculoskeletal, neurological, chronic respiratory, and diabetes." The Lancet, 2012 [8].

Notably, this methodological recommendation is broadly consistent with earlier recommendations and issues within COI and health economic evaluation regarding the basic issues of data and a framework identifying conditions used for different

[8] In addition, several studies have shown differences in costs across countries – in terms of actual costs, records and estimating costs – making transferability of results from health-care valuations problematic [21]; moreover, the HRQoL population-based preference values and clinical practice vary across countries.

burden estimates. Naturally, burden of disease estimates are only as good as the data and underlying methodology. Different data and methods naturally provide different burden estimates; also, different studies are often measured partially. Even the GBD studies consist of multiple and varying data sources and different data collection methods all put together using complex statistical methods [3, 131, 132]. Thus, these studies often show substantial differences in burden estimates within the same condition as mentioned. Therefore, there is room for improvement with a transparent standardized, uniform framework for identifying multiple conditions within health-care data; and for catalogues of uniform estimates of HRQoL and prevalence of multiple conditions for use in health economic evaluation, among others.

The present thesis focuses on two crucial burden of disease measures: prevalence and HRQoL based on the EQ-5D.

2.4. THE ERA OF BIG DATA – POTENTIALS, RECOMMENDATIONS AND DEFINITIONS: MAKING USE OF DATA

As pointed out earlier, proper (use of) data is crucial for valid estimates of the different outcomes used for health economic evaluation. But equally important, the use of data could also generate several societal potentials.

In "An OECD horizon scan of megatrends and technology trends in the context of future research policy", the OECD and the Danish Ministry of Higher Education and Science describe megatrends as 10–20-year slow-moving trends with a socio-economic impact, and technologies of societal importance from a research perspective [133]. One important recommendation is actual monitoring of diseases and shifting perspective to a preventive set-up, and interestingly in regard to this PhD, focusing on quality of life and health record systems is an important tool in addressing health-care challenges too:

> "Big data analytics may trigger some substantial changes in healthcare systems by enabling a shift from a reactive set-up that focuses on disease to a preventive setup that focuses on quality of life and well-being (OECD, 2013d). Sharing health data, through electronic health record systems, for example, can increase efficient access to healthcare and provide novel insights into innovative health products and services (OECD, 2013e). Diagnosis, treatment and monitoring of patients may become a joint venture of analytical software and physicians. Clinical care may even become preventive in nature as big data analytics help discover pathologies before symptoms occur. On top of open research data, the connection of smart applications through the Internet of Things

> (IoT) will enable the gathering of a wealth of health-related records, being self-reported or automatically tracked, on both sick and healthy people. New potential clinical trial participants will be more easily in reach. Broad data on exposures, outcomes and healthcare utilisation could be put together with deep clinical and biological data, opening new avenues to advance common knowledge, for instance on ageing-related diseases, or to support interdisciplinary research, for instance on combined effects of cure and care (Anderson and Oderkirk, 2015)…" OECD, 2016 [133]

In essence, HRQoL estimates of disease burden could possibly fuel societal trends towards prevention and thus better health if monitored continuously, especially if at the same time, in the author's opinion, explicitly combined with already existing prevention politics and new measurable goals based on the very same data (prevention potentials are indirectly described in chapter 5 in regard to introduction to use the HRQoL estimates within health economic evaluation).

The WHO has also recommended more automated use, reliable estimates and monitoring of conditions and risk factors within health care [1]. In short, there is no lack of recommendations for using big data within health care from global and leading institutions; moreover, in response, this PhD provides a register-based framework for monitoring chronic disease.

Notably, in a Danish context, "big data" is not really a new term. Danish researchers have been exercising "big data analytics" for several decades using unique Danish registers or large nationwide surveys. Thus, even though the term is getting increasingly popular, it may seem "old news" for some. However, in the author's opinion, the term "big data" is still justified as an umbrella for a trend of expanding data to different areas, for example social media and consumer data. But also, the size of data is increasing within existing areas, such as health care, for example, in terms of variables for monitoring, for example, organizational goals of treatments, health improvements or patient satisfaction. In this context, the need for big data analytics for making sense and optimal use of data is increasing, as the increasing data sources generate new possibilities used in combination. Moreover, existing data could still be used further, including combining data sources, as done within this PhD.

Within the present thesis, big data are defined as population register data and/or survey data of a minimum of 50,000 respondents collected continuously. However, we will not use the term "big data" further, as the term does not add any precision to the term "data" here, but is merely a broad definition comprising all kinds of data.

2.5. REGISTERS AND POTENTIALS – WHEN IDENTIFYING CONDITIONS

The registers included in the current thesis are mainly used for identifying chronic conditions. Scandinavian countries have a long tradition of reporting different conditions, treatments and others at the micro level in national health registers. The Danish tradition goes back to the 18th century with the Danish Twin Registry, Danish Registry of Cerebral Paresis and more [134] – and even longer if you include church birth registers.

Register data are usually collected for public administration such as management and claims, control functions and surveillance [135]. There are several advantages to register-based studies. First, the data are already collected, continuously collected and thus cost-effective and easily accessible. Secondly, registers contain doctor-reported diagnoses and medicine, among other things, and despite limitations such as selection bias, they do not, for example, have recall bias or have trouble with non-responders. Also, advantages are large study size and population coverage as well as reduced likelihood of differential misclassification [136]. Although another advantage is the lack of bias due to non-responders [135], this only partly applies when combining survey and register data, as done in paper 3.

Another advantage is that register data are updated yearly, comes with affiliated quality declarations, undergo ongoing quality testing by full-time employees for the full Danish population and therefore have no missing values on a comprehensive variety of variables. Accordingly there's no response due to misinterpretation of questions, wrong check marks, perhaps half-true or missing answers whenever the reason is that the respondent, for example, does not know, forgets or will not answer etc. The register data are created from identical criteria for each variable and are not dependent or subject to individual bias.

Register data are collected population wide full scale since registrations are mandatory be law. Data are collected from, for example, the National Board of Health, but also IRS (income and occupation etc.) or when citizens record addresses and other mandatory information at the city hall etc. Furthermore, educational institutions automatically record when a citizen has finished his or her education, the hospital record birth date etc. All these data are mandatorily reported to Statistics Denmark by the responsible public data controller who revived or created the data.

Table 2-1 shows the size of some essential included register data from current studies. In 2014, there were more than 21.4 million contacts with hospitals, private specialists and GPs.

Table 2-1. Contacts with hospitals, GPs and specialized doctors, Denmark, 2009–2014

	2009	2010	2011	2012	2013	2014
Public and private hospitals and clinics – all	**7,496,098**	**7,738,695**	**8,007,830**	**8,297,679**	**8,534,966**	**8,591,692**
- hospitalizations	1,157,172	1,197,206	1,207,761	1,239,128	1,245,161	1,279,051
- outpatients	6,338,926	6,541,489	6,800,069	7,058,551	7,289,805	7,312,641
GPs – all contacts	**11,640,041**	**11,733,941**	**11,877,864**	**11,337,669**	**11,447,165**	**11,132,224**
- Consultations	5,021,894	5,004,369	5,127,817	5,067,024	5,110,388	5,006,647
- Home visits	374,106	349,744	343,489	341,321	338,568	275,156
- Phone consultations	4,408,531	4,310,533	4,337,740	4,248,743	4,191,013	3,903,992
- Email consultations	653,114	796,298	967,353	1,114,465	1,254,979	1,402,561
- Consultations, prevention	1,182,396	1,272,997	1,101,465	566,116	552,217	543,868
Private specialist doctors (e.g. eye, ear, skin, obstetrics) – all	**1,512,219**	**1,544,877**	**1,580,607**	**1,608,411**	**1,643,575**	**1,681,555**

Source: Statistics Denmark 1/3/2016, http://www.statistikbanken.dk/

While all diagnoses of hospital in- and outpatients are reported in registers, this is not the case for GP and private specialists. To ensure inclusion of these chronic conditions also treated in the primary sector, the study included several other registers including medication and GP health services. These registers are summarized in chapter 3.

2.6. DEFINING CHRONIC CONDITIONS AND CHALLENGES

A key point of the PhD is defining chronic conditions as it set out the foundation. The literature and authorities have several, although similar, suggestions for definitions of chronic conditions. For example, the WHO defines a chronic disease as:

> "Noncommunicable – or chronic – diseases are diseases of long duration and generally slow progression. The four main types of noncommunicable diseases are 1. cardiovascular diseases (like heart attacks and stroke), 2. cancer, 3. chronic respiratory diseases (such as chronic obstructed pulmonary disease and asthma) and 4. diabetes. [137] See: http://www.who.int/features/factfiles/noncommunicable_diseases/en/index.html

In this context, "chronic" is not defined as (definitely) not curable, but "only" as a disease of long duration, slow progression and non-communicable. Moreover, chronic conditions are specified to a limited number of disease areas.

The Danish National Board of Health defines a chronic disease as follows, and though similar, some differences exist:

> 2005: "Chronic disease has one or more of the following characteristics: The disease is persistent, has permanent consequences, due to irreversible changes, requires a lengthy treatment and care and/or a special rehabilitation" [18].

> 2012: "Chronic disease is defined by the Board of Health as a 'disease that has a long-term course or is constantly recurring' [64].

Although not explicitly contradictory, the definitions do vary. For example, the 2005 definition is more explicit in terms of persistence and permanence. In contrast, the 2012 definition does not stress "permanent", but only refers to the condition as being "long-term". However, the National Board of Health emphasizes that the definition is not well defined [64]. Yet, similarly to the WHO definition, a disease is long-term and being cured is not ruled out, therefore the health state is not infinite. This is important as many chronic conditions either reoccur periodically (like allergies, among others) or can be partly cured, "put to sleep" (for example HIV), or even cured in the long term as new technologies emerge (for example ulcers).

The above definitions, however, are too unspecific to be used in register research. They lack a more specific time frame for inclusion/exclusion of conditions. This is especially important as different chronic conditions can have a different "long-duration" or "long-term" course, and since "chronic", despite the mainstream use of the word, in reality might not be life-long as indicated above. Furthermore, none of the definitions actually define whether the condition requires treatment or not, or has any influence on health, although this is implied. This is, however, clearer in this definition by Hwang et al., which is the definition the current study is based upon:

> "We defined a person as having a chronic condition if that person's condition had lasted or was expected to last twelve or more months and resulted in functional limitations and/or the need for ongoing medical care" [41, 138, 139].

First of all, the definition includes a time frame in contrast to other definitions. Secondly, "disease" is interchanged with "condition" unlike the previous definitions. Although the two words are often used interchangeably, the term "condition" is preferred as it is considered to be more closely connected to a "state of health", which might change in line with real-life chronic conditions, unlike a classic understanding of disease that historically originates from communicable disease. This is important as the focus is on a wide range of illnesses, where some perhaps do not necessarily have a long duration and are relatively easily cured or have health state changed (such as "glaucoma", "cataract", "gastric ulcer", "renal/ureteral calculus", "cholelithiasis" and more). However, it is recognized that the term "condition" might be unclear in regard to some "health conditions" such as overweight and alcohol dependency, which are actually also defined within the ICD-10 coding system. As such, overweight and alcohol dependency are excluded as chronic conditions (see supplementary material of reference [140]).

Although the Hwang et al. definition includes the necessary "minimum inclusion time" that is universal for every chronic condition (minimum 12 mouths' duration), it does not have a "maximum inclusion time", which is also needed in register research. A maximum inclusion time is less important within self-reported conditions, where a person has started having a condition at the specific survey time. If the condition usually lasts longer than 12 months, then it is present and chronic if self-reported. However, in register research, there is not a respondent statement of conditions, but often a random report of conditions across different times. As a survey is combined with register-based conditions, it is essential to know if a condition identified, for example, once in a register 10 years back in time is still present at the time of the *survey*. This is the "maximum inclusion time", and is crucial in order to ensure a correlation between the condition and the HRQoL. As the maximum inclusion times differ across conditions, no existing definition comprises the precision and definition needs of register research. Thirdly, the definition opens to include several medications and treatment registers as it also comprises "medical treatment".

All the presented approaches have a rather broad definition of chronic conditions. Hwang et al.'s definition is used to *select* which overall conditions are to be included as *chronic conditions*, as it comprises most operational dimensions also corresponding to the used registers, for example the use of medicine, but the definition is modify by adding maximum inclusion times to fit the challenges of using ICD-10 diagnoses and register data. In this respect, it is the intention to provide a new framework of differential inclusion times including clinical suggestions of individual maximum inclusion times for each of the 199 identified chronic conditions for future use in research and by health-care professionals. This is presented in the results section and represents a methodological contribution of this PhD thesis as, to the best of the author's knowledge, it has not been done before.

As ICD-10 diagnosis codes only exist within secondary care, the main challenge, for those chronic conditions only treated in primary care, is to include using registers other than the NPR as the aim is to capture a representative disease population. However, we expect that many chronic patients treated in primary care are also treated in secondary care at some time and thus reported with a diagnosis at some time, and for many more severe and common conditions such as heart conditions and cancers, they are mainly reported and diagnosed in secondary care. So how big is the problem really? It depends on the condition and severity. In general, less severe conditions are treated in primary care and thus many most likely would not be considered chronic according to the overall definition, although more than half of all contacts are within primary care as seen in Table 2-1.

Yet, less severe cases of chronic lung diseases, such as COPD, type 2 diabetes and others, are treated in primary care, while other less severe eye and ear diseases are treated by private specialists without reporting diagnoses. Consequently, we used the previously mentioned medication and service registers to identify these. The extent and differences in prevalence between only using NPR diagnosis codes and several registers are shown for some conditions in section 4.2 and paper 1B.

CHAPTER 3. DATA AND METHODS

3.1. THE REGISTERS

The Danish National Registers contain various high-quality microdata for the entire Danish population. All registers contain a unique 10-digit personal identification number (the CPR number) for each individual. This allows record linkage at the individual level of data across time from complete national registers used in the current study. Naturally, this use is regulated by law, and therefore the current PhD received permission from the Danish Data Protection Agency to link the survey data with relevant register data using the Statistics Denmark "researcher service" (The project number is 702835, with permissions given in autumn 2012 and later , learn more at http://www.dst.dk/en/TilSalg/Forskningsservice.aspx). This is a user platform providing relevant register data and the statistical packages SAS and STATA all managed on Statistics Denmark's secured servers from a secured remote desktop, so confidentiality is ensured.

The following registers were included:

- The National Patient Register (NPR) [141]
- The Danish Psychiatric Central Research Register (PCRR) [142]
- The National Health Service Register (NHSR) [143]
- The Danish National Prescription Register (DNPR) [144]
- The Danish Civil Registration System (CRS) [145]
- The Population's Education Register (PER) [146]
- The Income Statistics Register (ISR) [147]

The Danish National Patient Register (NPR) [50, 140, 141, 148]. The NPR contains data on diagnoses, patient types, treatments, surgeries, dates and more from all public and private nationwide hospital treatments. This is reported for every patient contact at the individual level, and comprises in- and outpatients and emergency patients [141]. However, diagnoses of emergency patients were excluded from the current study as the validity thereof was not shown adequately [149, 150]. The register was initially established in 1977 for administrative use, although it has progressively been used for research. From 1994, the use of ICD-10 codes was employed with more than 22,000 different codes [141], and one year later, somatic, psychiatric and emergency patients were included in the register. Finally, from 2003 private hospitals and private clinics were integrated in the NPR as a result of the upcoming of private health care in Denmark. The NPR is founded on the attending doctor's diagnosis reports and is reported at discharge for each patient. The reporting to the NPR is mandatory by Danish law, and is collected on a daily

basis on data servers. Further data descriptions can be found at: http://www.dst.dk/da/TilSalg/Forskningsservice/Data/Andre_Styrelser.aspx

The Danish Psychiatry Central Research Register (PCRR) [142]. The PCRR was employed to increase the accuracy of psychiatric diagnoses from the NPR. It was first founded in 1938, and was made national in 1969. The PCRR comprises data on nationwide psychiatric in-, out and emergency patients' ICD-10 diagnoses at Danish psychiatric hospitals from 1995 [142]. As with the NPR, the data are reported by the attending physicians, and include information about diagnoses, discharges, dates, places of treatment and types of referral, among other things. Further data descriptions and documentation can be seen here: http://www.kea.au.dk/file/Psykiatriske%20Centrale%20Forskregister/VARIABESKRIVELSE%202011.pdf

The National Health Service Register (NHSR) [140, 143, 151]. The NHSR was first compiled in 1984 and contains information regarding services of publicly funded primary care health professionals including data about all GPs, dentists, medical specialists, psychologists, physiotherapists, chiropractors and chiropodists. The NHSR is used for economic settlement of the provided services with the government, and is reported electronically every week through the physicians' invoices to the Regional Health Administration and later the National Board of Health [143]. The NHSR was integrated into the present study to link services (e.g. lung tests, diabetes tests, blood samples, different laboratory tests, referrals to specialists and more) to diagnoses and conditions where possible. See further data documentation and descriptions at: http://www.dst.dk/en/Statistik/dokumentation/documentationofstatistics/health-insurance-statistics

The Danish National Prescription Register (DNPR) [140, 144, 152]. The DNPR contains data on all non-hospital-prescribed medicine for all Danish citizens at an individual level; the register was established in 1994. All medications are reported using the Anatomical Therapeutic Chemical (ATC) classification system; moreover, the register includes date and from 2003 partly indication codes providing information on the conditions treated with the drugs. Notably, the DNPR does not provide data on drugs dispersed at hospitals and over-the-counter (OTC) drugs. The validity of the register is heightened as all Danish pharmacies are required by law to electronically report dispensed prescriptions to the Danish Medicines Agency. High-quality data are ensured as all drug packages have a drug article number matching a labelled barcode, which is why inter/intra-observer bias and information bias are unlikely to occur. Naturally, this does not ensure or report consumption of the drugs (primary non-compliance); hence the DNPR is a surrogate measurement of the patient's actual ingestion of the drug [144]. Within the current study, the DNPR is used to link specific drugs to specific conditions among patients treated in the primary care sector. Further data descriptions can be

found at:
http://www.dst.dk/da/TilSalg/Forskningsservice/Data/Andre_Styrelser.aspx

The Danish Civil Registration System (CRS) [140, 145, 153]. The CRS includes the names, gender, age/birth dates, residence, ethnicity and more of all persons alive and living in Denmark. The entire Danish population aged 16 or more totalled 4,555,439 inhabitants on 1st January 2013. The CRS was established in 1968, while information on ethnicity, immigrants and their descendants was first recorded from 1991. See more details about the CRS at:
http://www.dst.dk/da/Statistik/dokumentation/Times/cpr-oplysninger.aspx and
http://www.dst.dk/Site/Dst/SingleFiles/kvaldeklbilag.aspx?filename=611d9cb3-442d-42b8-9b68-e27950059130Immigrants_and_Descendants_2016

The Population's Education Register (PER) [146]. The PER contains a variety of individual-level information about education, type and name, enrolment, time of enrolment, length, and most importantly highest completed educational level and time thereof. An eight-digit code enables transformation into the International Standard Classification of Education (ISCED). The register only provides information about education of more than 80 hours' duration authorized by the Danish Ministry of Education. The register was started in 1977, although several data breaks and changes exist [146]. See also:
http://www.dst.dk/da/Statistik/dokumentation/Times/uddannelseregister

The Income Statistics Register (ISR) [147]. The ISR was first established in 1970 and contains more than 160 variables including salaries, capital income, taxes, entrepreneurial income, private pension contributions, public transfer payments, payouts and socio-economic status [147]. In the current study, we use the family equalized income variable provided by Statistics Denmark. See:
http://www.dst.dk/da/TilSalg/Forskningsservice/Dokumentation/hoejkvalitetsvariable/personindkomster.aspx and
http://www.dst.dk/da/Statistik/dokumentation/Times/moduldata-for-indkomst--forbrug-og-priser/famaekvivadisp.aspx and
http://www.dst.dk/da/Statistik/dokumentation/Times/personindkomst/socio02.aspx

3.2. CURRENTLY USED DEFINITION OF CHRONIC CONDITIONS

For completeness, as mentioned earlier, the current study is based upon the following definition of chronicity by Hwang et al.:

> "We defined a person as having a chronic condition if that person's condition had lasted or was expected to last twelve or more months and resulted in functional limitations and/or the need for ongoing medical care." Hwang et al., 2001 [41, 138, 139]

Another challenge is time, as previously mentioned, as chronicity varies across conditions, and since the definition does not account for the maximum inclusion times needed using registers (as we look back in time from the survey time). Therefore, the following four inclusion categories were created to comprise the different levels of chronicity across conditions on average:

1. **Category I:** Stationary to progressive chronic conditions (no time limit equals inclusion time going back from the time of interest, for as long as valid data were available. In the current study, this starting point was defined by the introduction of the ICD-10 diagnosis coding in Denmark, in 1994);
2. **Category II:** Stationary to diminishing chronic conditions (10 years of register inclusion time, to the time of interest);
3. **Category III:** Diminishing chronic conditions (5 years of register inclusion time, to the time of interest); and
4. **Category IV:** Borderline chronic conditions (2 years of register inclusion time, to the time of interest).

Source: adapted from Hvidberg et al. [140], see http://sjp.sagepub.com/content/early/2016/04/19/1403494816641553.full

These four categories were applied to all registers and conditions. The full medical categorization of all conditions into one of the four categories is found in paper 1.

3.2.1. PANEL OBJECTIVES, PROCESS AND MEDICAL RATIFICATION

Two kinds of definitions were created: complex definitions, including several registers as this was considered medically necessary in order to capture the full disease population, and simple conditions solely using NPR diagnosis register data. In practice, existing literature also formed and inspired some of the suggested definitions as described in paper 1/1B [140].

A medical expert panel was established in order to categorize, review and ratify the register-based definitions. The objectives of the expert panel were as follows:

- "Selecting the ICD-10 codes of chronic conditions
- Ensuring grouping of the chronic conditions into clinically meaningful groups
- Ratifying the four overall inclusion times and assigning one of the four inclusion times to each of the chronic conditions
- Assessing conditions in need of complex definitions, reviewing and ratifying these"

Source: adapted from Hvidberg et al., supplementary material page 3 [140], see http://sjp.sagepub.com/content/44/5/462

In order to archive consensus over the objectives, the panel process seen in Table 3-1 – in part inspired by the Delphi method [154] – was carried out:

Table 3-1. The process

I.	**The panel of medical experts**: A medical panel of seven doctors, including a "core panel" of two doctors from the co-authors of the manuscript. The corresponding author acted as coordinator of the process.
II.	**Process and rounds**: The rounds were performed bilaterally, by meetings, phone and email, between the coordinator and each expert. When conducted by personal meeting or phone, the main conclusions were incorporated into the manuscript for the next round, or for the external doctors not among the authors, and also by a separate summary thereof by email. The contributions of the external experts were, however, finally reviewed and approved by the authors. At least six full rounds were carried out (many more if bilateral email correspondence and other communications are included).
III.	**Personal meetings**: Three bilateral personal meetings were carried out with the corresponding author and with Søren Paaske Johnsen, Ib Rasmussen and Martin Bach Jensen, respectively, as well as email correspondence including a summary of the discussed conclusions.
IV.	**Conference calls/email**: Several conference calls were held with Charlotte Glümer, Søren Paaske Johnsen, Ib Rasmussen, John Hyltoft and Kaare Dyre Palnum, as well as email correspondence including a summary of the discussed conclusions either in the form of a separate summary or by incorporation into the manuscript.
V.	**Questions**: A core of systematic questions were asked for each meeting or contact, including the option of further discussion and comments.
VI.	**Anonymity**: Anonymity, as in the traditional Delphi method, was only partially ensured as the corresponding author handled the comments bilaterally, and by incorporating the comments into the manuscript mostly with anonymity. However, all participants knew each other by name, and some named comments for discussion were also implemented in the manuscript if asked for.
VII.	**Time of process**: The process started in late 2013 and finished in early 2016.

Source: adapted from Hvidberg et al., supplementary material page 3 [140], see http://sjp.sagepub.com/content/44/5/462

The contents of the process and steps are further described in more detail in the supplementary material of paper 1 [140].

3.3. THE SURVEY SAMPLES

The Danish National Health Profiles (NHP) are a comprehensive nationwide survey with a total of 298,550 invited citizens conducted to moniter/survey public health every fourth year [155–159]. The survey includes questions on health-related quality of life, health behaviour, morbidity, consequences of illness, social relations, socio-demographic characteristics and more.

The NHP contained six mutually exclusive random subsamples: one in each of the five Danish regions (see Figure 3-1) and one national random sample sampled by the National Institute of Public Health (NIPH). All regional samples were further subsampled – or stratified – by municipalities, with a minimum of 2000 individuals included, while the NIPH's national data were not subsampled. Some regions, including the North Denmark Region (NDR), have chosen to include more than the minimum requirement of 2000 individuals to enable more detailed geographic analysis in larger municipalities.

The survey data were collected from February to April 2010/2013, sampled from the Danish Civil Registration System, which is a national register of the entire population. A simultaneous mixed-mode approach was used to collect the data for all six samples. All included individuals received a letter of introduction that briefly described the voluntariness, purpose and content of the survey. The included individuals were invited to either fill in an enclosed paper questionnaire or complete a web questionnaire using a unique user name. A minimum of two postal reminders in all samples were used; further details of the samples and data collection can be found in reference [155].

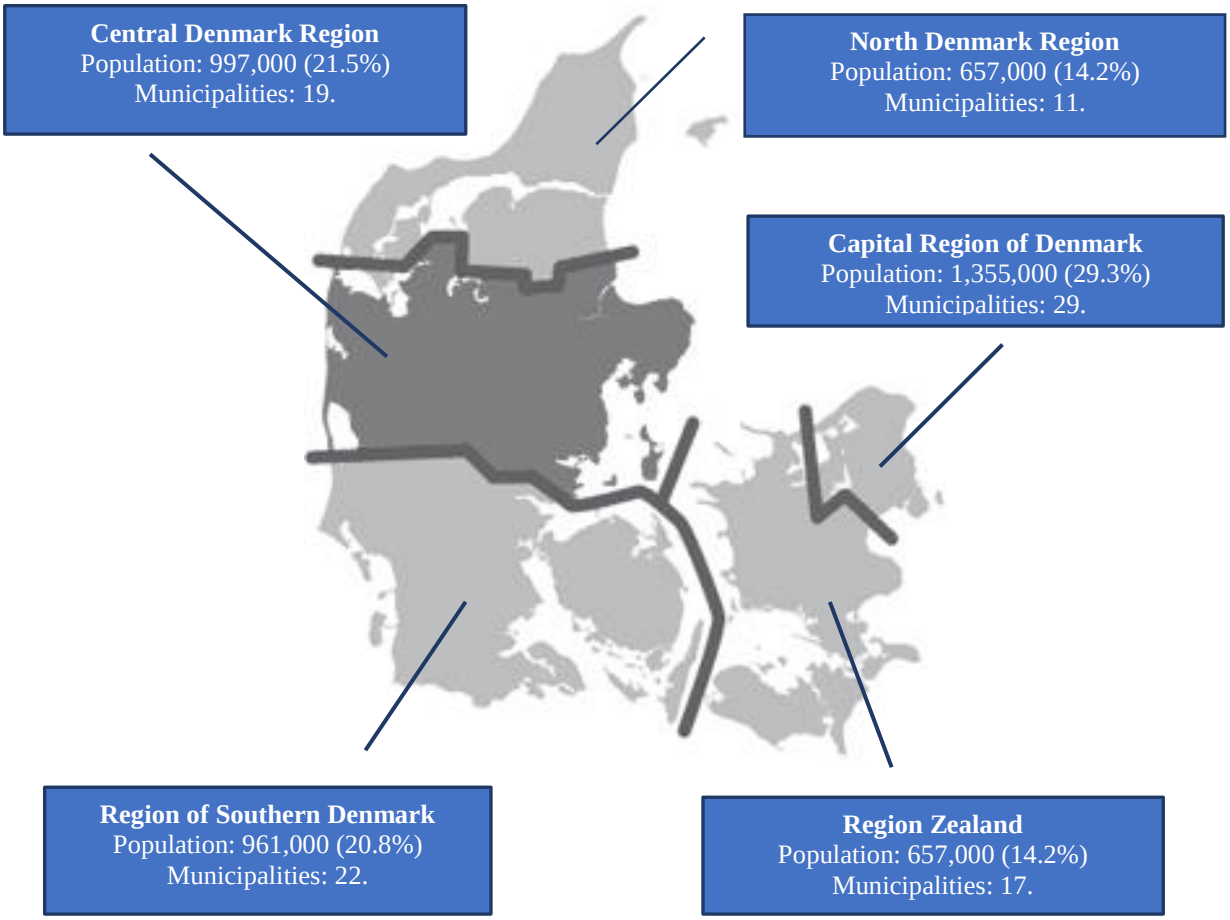

Figure 3-1. Map of Denmark and the municipalities. Source: adapted from A.I. Christensen et al., Figure 1 [155].

3.3.1. THE QUESTIONNAIRE

The *standard* questionnaire included 52 core questions identical for all six samples. In addition, every region or NIPH can include extra unique questions of interest besides the identical 52 core questions [155]. The extra survey questions differ, but relevant for this study, we used the full Cohen's Perceived Stress scale (10 questions) and the five EQ-5D questions version 2. Only the NIPH and NDR have included the EQ-5D besides the core questions.

Table 3-2. Summary of questionnaire core questions

Topics	**Indicators**
Socio-demography	Marital status, cohabiting status, number of children in the household, education and occupation
Quality of life and health	Stress (three questions from the Perceived Stress Scale) and the 12-item Short-Form Health Survey v2 (SF-12 v2).
Anthropometry	Self-reported weight and height
Diet	Food frequency and self-rated dietary habits
Smoking	Smoking frequency and smoking quantity
Alcohol	Alcohol consumption – quantity and frequency, type of alcoholic beverages, binge drinking and CAGE-C
Physical activity	Leisure time physical activity and self-rated physical condition
Health promotion and prevention	Readiness for health behaviour change (physical activity, weight, diet, smoking, alcohol), help and support for smoking cessation
Social relations	Contact with family, friends, colleagues or fellow students in leisure time, neighbours, people from the Internet, social support, help with practical problems, loneliness
Morbidity, symptoms and contact with health services	Long-standing illness, specific diseases (asthma, allergy, diabetes, hypertension, heart attack, angina pectoris, stroke, chronic obstructive pulmonary disease, osteoarthritis, rheumatoid arthritis, osteoporosis, cancer, migraine, transient mental disorder, persistent mental illness or disorder, back disorder, cataract, tinnitus), pain or discomfort (pain or discomfort in the shoulder or neck, pain or discomfort in the back or lower back, pain or discomfort in the arms, hands, legs, knees, hips or joints, fatigue, headache, sleeping problems or insomnia, melancholy/depression or unhappiness, anxiety/nervousness/restlessness or apprehension) and contact with the general practitioner
Absence from work	Absence due to illness, discomfort or injury

Source: adapted from A.I. Christensen et al. [155], Table I.

3.3.2. THE SAMPLES IN COMPARISON AND DIFFERENCES IN HRQOL

The included data used for estimating EQ-5D-based HRQoL in paper 3 consist of three survey samples, one sample from 2010 from the NIPH and two samples from the NDR from 2010 and 2013, with a total of 56,988 respondents. The EQ-5D was not present in the NIPH sample from 2013 or in other regional samples. Naturally, this asymmetric national sample constitutes challenges in pursuit of creating nationally representative estimates. Consequently, a comprehensive summary of the samples and differences is provided in what follows.

All invited individuals within samples were randomly chosen, aged 16 years or older and resident in Denmark on 1st January 2010 or 2013. The rather large sample size was needed to be able to create reliable estimates of the 199 chronic conditions. However, since the samples were stratified in different geographic sections (including municipalities), and since the NDR is over-represented, the responses have several different sampling probabilities, making national representativeness a challenge. These statistical challenges and solutions are addressed later in detail in regard to the use of weights and regression. Notably, all NDR estimates in Table 3-3 are nationally standardized by age, gender and education, as done in paper 3, to be as close as possible to national estimates.

The small NIPH NDR 2010 sample of 1,646 respondents actually differs slightly from the other NDR samples, by not only having the highest mean EQ-5D of all regions, but also differences in gender, education and age. These differences also persisted without standardization of the two NDR samples, and the socio-economic status levels were very different' as seen in Table 3-4. In comparison, other studies showed mostly worse health in the NDR in most different health measures compared to other regions [156–159].

Another issue was the three-year time differences between samples. In line with previous studies, samples across time were combined in order to increase the sample size [41, 43]. This could constitute a problem if any medical advancement, public health programmes or changed societal conditions, such as the labour market, impacted on and changed the HRQoL. Yet, there were no overall indications thereof, as the EQ-5D mean difference across the 2010 and 2013 sample was relatively small.

In conclusion, the NDR and NIPH national differences in the EQ-5D mean were small and almost identical – especially in an international context – and although partly significant, this is not surprising due to the large samples.

Table 3-3. Respondent characteristics of the included samples (NDR and NIPH) sorted by regions

	NDR 2013: North Denmark Region	NDR 2010: North Denmark Region	NIPH 2010: North Denmark Region	NIPH 2010: Central Denmark Region	NIPH 2010: Region of Southern Denmark	NIPH 2010: Capital Region of Denmark	NIPH 2010: Region Zealand	NIPH 2010 combined sample	All samples combined	Full population* 1/1/2010
Initial sample (n)*	35,700 / 33,911**	35,700	2.693	5,630	5,502	7,693	3,549	25,000	96,400 / 94,611**	4,46,0874
Valid responses, n (%)*	20,220 (56.6%)	23,392 (65.5%)	1,646 (61.1%)	3,567 (63.4%)	3,415 (62.1%)	4,385 (57.5%)	2,152 (60.6%)	15,165 (60.7%)	58,777 (61.0%)	n/a
Valid responses after removal of duplicate respondents, n (%)*	18,431 (54.4%) **	23,392 (65.5%)	1,646 (61.1%)	3,567 (63.4%)	3,415 (62.1%)	4,385 (57.5%)	2,152 (60.6%)	15,165 (60.7%)	56,988 (60.2%)	n/a
Datacollectionmethod, n (%)										
Internetsurvey*	8,165 (40.4%)	2.329 (10.0%)	488 (29.6%)	1,154 (32.3%)	1,058 (31.0%)	1,459 (33.3%)	643 (29.9%)	4,802 (31.7%)	12,969 (23.0%)	n/a
Paper based survey*	12,055 (59.6%)	21,063 (90.0%)	1,158 (70.4%)	2,413 (67.7%)	2,357 (69.0%)	2,926 (66.7%)	1,509 (70.1%)	10,363 (68.3%)	43,481 (77.0%)	n/a
Mean age at time of response [CI] (SE; SD)	47.8 [47.5-48.1] (0.171; 19.02)	47.5 [47.2-47.8] (0.148; 18.66)	48.2 (0.148) (18.91)	47.8 (0.509) (19.15)	46.3 (0.337) (19.04)	48.9 (0.302) (18.13)	46.3 (0.436) (18.18)	47.6 [47.3-47.9] (0.1653; 18.77)	47.6 [47.4- 47.8] (0.093; 18.79)	47,4 [n/a] (n/a; 18,73)
Gender, men (%)[CI]	49.2 % [48.4-50.1]	49.2 % [48.5,50.0]	52.0 %	48.4 %	50.3 %	48.16 %	48.5 %	49.1 % [48.3-50.0]	49.2 % [48.7-49.7]	49,2 % [n/a]
Education										
No education/training	5,645 (30.8%)	7,916 (34.2%)	524 (33.9%)	1,002 (30.6%)	1,060 (33.6%)	1,024 (23.2%)	663 (30.1%)	4,428 (29.5%)	17,989 (31.9%)	1,421,594 (33.3%)
Short education	8,653 (47.2%)	10,544 (45.6%)	754 (48.7%)	1,551 (47.3%)	1,498 (47.5%)	1,969 (44.6%)	1,131 (51.4%)	7,049 (46.9%)	26,246 (46.5%)	1,955,082 (45.8%)
Middle education - bachelor etc.	2,898 (15.8%)	3,167 (13.7%)	203 (13.1%)	485 (14.8%)	459 (14.5%)	790 (17.9%)	307 (13.9%)	2,296 (15.3%)	8,361 (14.8%)	3,984,088 (14.2%)
High education - master degree etc.	1,127 (6.2%)	1,498 (6.5%)	66 (4.3%)	239 (7.3%)	140 (4.4%)	630 (14.3%)	99 (4.5%)	1,254 (8.3%)	3,879 (6.9%)	284,012 (6.7%)
Current Health state:										
11111 (perfect health)	8,069 (43.8%)	10,678 (45.7%)	773 (48.3%)	1,571 (46.1%)	1,410 (43.0%)	2,188 (47.2%)	990 (44.1%)	6,933 (45.7%)	25,680 (45.1%)	n/a
Only one level 2 item	4555 (24.7%)	5712 (24.4%)	384 (24.0%)	878 (25.8%)	835 (25.4%)	1,100 (23.8%)	539 (24.0%)	3,738 (24.6%)	14,005 (24.6%)	n/a
Several level2s, no level 3	4466.7 (24.2%)	5459.7 (23.3%)	334 (20.9%)	751 (22.0%)	813 (24.7%)	1,067 (23.1%)	564 (25.1%)	3,529 (23.3%)	13,456 (23.6%)	n/a
At least one level 3 item	1258 (6.8%)	1630.7 (7.0%)	88 (5.5%)	188 (5.5%)	219 (6.7%)	256 (5.5%)	156 (7.0%)	908 (6.0%)	3796.5 (6.7%)	n/a
Mean EQ-5d (SE) [CI]	0.849 (0.0017) [0.845-0.852]	0.852 (0.0015) [0.849-0.855]	0.8675 (0.0093)	0.8613 (0.0066)	0.8466 (0.0073)	0.8638 (0.0055)	0.8465 (0.0088)	0.857 (0.0016) [0.853-0.860]	0.852 (0.0009) [0.850-0.854]	n/a
Mean EQ-5d: Men (SE)	0.868 (0.0022)	0.869 (0.0021)	0.8826 (0.0064)	0.8768 (0.0046)	0.8583 (0.0052)	0.8772 (0.0039)	0.8656 (0.0060)	0.871 (0.0023)	0.869 (0.0013)	n/a
Mean EQ-5d Women (SE)	0.829 (0.0025)	0.835 (0.0021)	0.8512 (0.0070)	0.8468 (0.0049)	0.8346 (0.0053)	0.8513 (0.0040)	0.8286 (0.0066)	0.842 (0.0024)	0.835 (0.0013)	n/a

Source: National Health Profiles 2010,2013 [155, 157–159], Statistics Denmark data extraction.
non-weighted/standardized if indicated by. Otherwise weighted/ standardized. All samples and population data have solely included residents age 16-100+. All estimates are complete cases only.
**Numbers after removal of duplicates respondents/included from 2010 samples.

Table 3-4. Population, samples by regions and their responses in comparison

	Denmark population 2010 %	NIPH complete sample	All samples combined	NDR population 2010 %	NDR 2013: North Denmark Region	NDR 2010: North Denmark Region	NIPH 2010: North Denmark Region	NIPH 2010: Central Denmark Region	NIPH 2010: Region of Southern Denmark	NIPH 2010: Capital Region of Denmark	NIPH 2010: Region Zealand
Total, N/n	4,460,874	15,165	56,988	475,637	18,431	23,392	1,646	3,567	3,415	4,385	2,152
Gender											
Men	49.2	49.1	50.8	49.9	49.2	50.0	52.1	48.4	50.3	48.2	48.5
Women	50.8	50.9	49.2	50.1	50.8	50.0	47.9	51.6	49.7	51.8	51.5
Age											
16–24 years	13.6	13.5	13.7	13.9	14.2	13.9	15.2	14.6	12.1	13.8	11.8
25–34 years	14.9	14.8	14.7	13.5	14.3	13.5	12.6	15.7	12.8	18.6	10.3
35–44 years	18.0	18.0	17.6	16.6	16.7	16.7	17.2	19.3	17.4	18.0	17.3
45–54 years	17.1	17.2	17.3	17.5	17.6	17.6	17.0	16.7	19.5	15.6	17.9
55–64 years	16.2	16.2	15.9	16.9	15.3	16.9	18.1	15.5	16.9	14.7	18.3
65–74 years	11.6	11.6	11.9	12.1	12.7	12.2	10.8	10.5	11.1	11.4	14.9
75+ years	8.7	8.7	8.8	9.5	9.3	9.3	9.2	7.7	10.2	7.9	9.5
Education											
Missing	4.3	3.8	3.8	3.8	2.9	3.3	3.3	3.8	3.8	4.7	2.1
No education / training, *ref.*	31.9	28.2	30.2	36.6	29.2	34.2	32.8	29.4	32.3	22.1	29.5
Short education	43.8	45.5	45.2	43.5	46.5	44.9	47.1	45.5	45.6	42.5	50.4
Middle education – bachelor	13.6	14.8	14.4	12.1	15.5	13.3	12.7	14.2	14.0	17.1	13.7
Higher education – master's degr.	6.4	7.7	6.5	4.0	5.9	4.4	4.1	7.0	4.3	13.6	4.4
Family Equalized Income											
< 100.000 kr. (< £9,500)	8.2	7.0	6.6	6.6	6.1	6.8	7.4	7.3	6.3	8.6	4.3
100,000-199,999 kr. (£9,500–£19,000)	42.5	41.9	42.8	40.4	39.1	46.3	45.0	43.5	43.8	37.7	43.2
200,000–299,999 kr. (£19,000–£28,500)	34.5	35.8	36.0	36.0	37.1	35.4	35.9	36.4	36.7	34.1	36.9
300,000–399,999 kr. (£28,500–£38,000)	10.7	11.4	10.8	12.1	13.0	8.8	8.4	9.8	10.2	13.9	12.3
400,000+ kr. (£38,000+)	4.1	3.9	3.7	4.8	4.7	2.8	3.3	3.1	3.0	5.7	3.3
OECD poverty											
OECD poverty, family income	8.1	7.0	6.4	7.7	5.5	6.8	7.3	7.3	6.3	8.5	4.3
Socio-economic grouping											
Retired, age	18.2	18.6	19.1	19.7	20.3	19.9	18.3	16.8	19.8	17.2	22.6
Retirement (pre-senior retirement)	3.0	3.3	3.5	3.6	3.2	4.0	4.4	3.2	3.5	2.2	4.7
Early retirement, health	5.2	4.6	4.6	5.3	4.7	4.6	4.3	4.6	6.4	3.7	3.9
Seekleave, other leave etc.	1.1	1.0	1.2	1.3	1.3	1.2	1.3	1.2	0.6	0.9	1.0
Unemployed, social benefits	2.3	1.7	1.8	2.1	1.8	1.7	2.1	1.7	1.7	1.9	1.3
Unemployed min. 6 months	1.3	1.2	1.5	1.5	1.7	1.5	1.8	1.1	1.1	1.2	1.2
In training, education	6.3	7.1	7.8	6.5	9.0	7.3	7.8	7.8	7.0	6.9	6.4
Employed	58.3	59.2	57.8	56.4	55.8	57.2	56.2	60.6	56.8	62.3	56.6
Others not in workforce	4.2	3.3	2.7	3.6	2.2	2.6	3.8	3.0	3.2	3.8	2.3
Family type											
Married couples	51.0	52.9	53.6	53.3	52.4	55.5	57.4	53.0	56.8	46.4	57.1
Registered partners	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.3	0.1
People living togehter	5.1	4.3	5.1	5.6	5.4	5.1	6.0	4.4	3.6	3.9	4.9
Cohabiting couples	8.9	8.8	9.2	9.4	9.4	9.1	7.6	9.7	8.7	9.4	7.4
Single (incl. non-resident children)	34.9	33.8	31.9	31.6	32.6	30.2	28.9	32.9	30.8	39.9	30.5

Source: National Health Profiles 2010, 2013 and national population registers 2010/2013. Sample percentages are weighted, but not nationally standardized so as to enable regional comparisons. UK currency estimates are rounded and calculated based on DK/UK rates of 16-03-2016.

3.4. STATISTICAL ANALYSIS

3.4.1. REGRESSION MODELLING – THE ALDVMM

The problem with the EQ-5D arises from its highly skewed, non-normal distribution and its several gaps [50]. Of particular concern is the fact that the EQ-5D generates 243 discrete values, and has varying and several numbers of classes and a high mass of 1 (ceiling effect), as seen in Figure 3-2. This creates a problem for the estimations of most regression models, as the majority will estimate values in the gap from 0.838 (DK) to 1, while others do not estimate negative values or even non-existing values above 1. Hence, the EQ-5D is defined as a limited dependent variable as it's restricted and is not higher than 1 or lower than -0.624 (DK). So far, no real agreement exists on which regression model is best suited for the EQ-5D [50]. Therefore, we tested and compared conventional regression mean models such as OLS and TOBIT with the ALDVMM in paper 2.

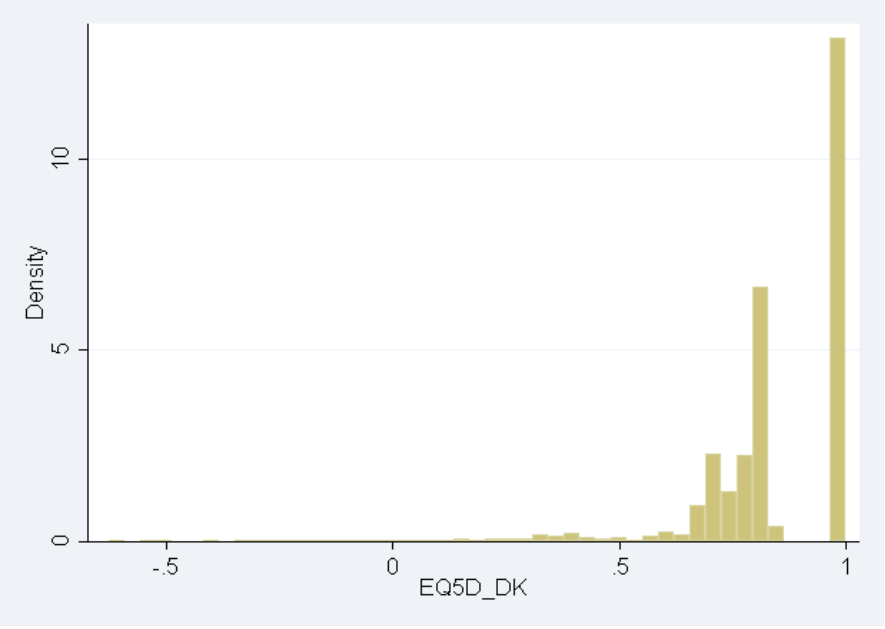

Figure 3-2. Histogram of the EQ-5D, National Health Profiles 2010/2013. Source: adapted from Hvidberg et al. [50].

The ALDVMM is intended to handle the distribution(s) of the EQ-5D instrument; recent studies have found the ALDVMM superior to other regression models traditionally used [160–163].

The ALDVMM is founded on two innovations reflecting the key structures of the distinctive EQ-5D distribution [160]. The first innovation is managing the problems arising from a limited dependent variable such as the EQ-5D with a gap with no values from 0.838 to 1 based on the DK EQ-5D value set. This is done assuming y_i is 1 when the latent variable y^*_i is greater than the last discrete value (0.838) before 1 and equal to y^* – thereby forming a new distribution. The second innovation uses the first innovation, the adjusted, limited dependent variable distribution, within a mixture model, with c components. Therefore, the ALDVMM treats the EQ-5D like a flexible number of identified c components unique to each EQ-5D distribution that is used to form a new density. Thus, in contrast to the majority of other mean regression models, the ALDVMM is not linear between variables. Further details can be found in references [160, 163].

Moreover, mixture models such as the ALDVMM are not as easy to use as other traditional regression models. One reason for this is the existence of numerous local maxima located in each c component that need to be identified for the likelihood function. It cannot be assumed that the reliable model has been found solely by running the ALDVMM program in STATA: "*To identify the global maximizer, at the very least, it is important to try different sets of random starting values and to select the solution with the highest likelihood function*" [163]. Therefore, it is essential to have hands on and manually start with a minor number of covariates as well as components when fitting mixture models, and then use each model as a stepping stone to generate models with more covariates and components. Consequently, the ALDVMM requires extensive effort, consideration and documentation. Details from regression modelling of the present study can be found in paper 2.

3.4.2. WEIGHTING AND NON-RESPONSE

The three samples had *multidimensional* weights computed by Statistics Denmark taking both sampling designs and non-response into account [164]. The weights were computed using GLM regression and auxiliary variables from national population registers. A unique personal identification key (CPR) of all invited persons was used to combine survey and register data [155]. However, because the two NDR samples resemble around two-thirds of the samples, but only one tenth of the country's population, the two NDR samples were further standardized by national gender, age and educational levels [165]. This was done by combining the standardization with the existing multidimensional weights by Statistics Denmark.

Principle and the auxiliary variables used

The basic principle in multidimensional weighting is to divide the population into a given number of *separate* tables which are all recreated in calculations. For example, gender and age are calculated in one table and geography is calculated separately in another table. This way you avoid having to include all variables in every stratum/table. Here, Statistics Denmark has chosen and done the computations based on the sample's original stratification design (regions, municipalities etc.) and iterative tests of main effects and interactions with auxiliary variables in different tables and combinations for best model fit [164].

The multidimensional weights were computed based on register information about *sex, age, region, municipality of residence, income, highest completed educational level, ethnic background, marital status, occupational status, owner/tenant status, hospitalization in 2007 (yes/no), number of visits to the general practitioner in 2007 and thus important scientist inquiry protection* – for all individuals living in Denmark on 1st January 2010/2013 [155].

But why choose exactly these variables? Accounting for all for non-response would require that we know the precise information on non-response for every variable in the survey. Since we do not have this as register information, we use auxiliary variables from registers that we know are well correlated *with* crucial survey variables and usually important.

Choosing auxiliary variables and final model

First the correlations between non-responders and as many register variables as possible are identified using logistic regression with response/non-response as dependent variable. Significant variables indicate explanatory power with non-response, and non-significant ones are deselected.

Secondly, four separate general linear regression models are run with the *survey variables* considered most important, as dependent variables (=responses, here "prolonged illness", self-rated health, BMI and smoking) with *all* register variables as covariates. Here the best correlations once again are identified and used to help in choosing the best auxiliary variables.

On the basis of an evaluation of all models, the final auxiliary variables for the weight computation are chosen iteratively, namely non-significant variables are rejected in securing best model fit; however, a sudden experience in modelling is required and used. The final models with main effects and interaction are shown in Table 3-5 for the two different weights provided:

Table 3-5. Weight 1: Non-response model used in regression, gi (individually)

Sample	Models used in weight estimation
NIPH	GP-visit*hospitalization*age*gender Socioeconomic status*familytype*income*region Ethnicity*home-owner*moved GP-visit, hospitalization, age, socioeconomic status, familytype, gender, income, ethnicity, region.
NDR	GP-visit* age*gender familytype*income GP-visit, hospitalization, socioeconomic status, familytype, income, ethnicity, municipalities. Gender* municipalities, age* municipalities

Source: Adapted from Mejldahl [164], page 1.

The fundamentals of the multidimensional weights

The sample weights are computed using generalized regression estimator (GREG) as the multidimensional approach of choice, which underlined makes it possible to use many more different background variables in the estimation of the weight than a traditionally "after stratification[9]" approach [164]. First, the chosen auxiliary variables are used to estimate a chosen dependent variable, y, in a regression model, for example GLM:

$$y_k = \beta_1 x_{1k} + \beta_j x_{jk} + e_k$$

The choice of y is actually not of importance for estimating the weight, but the x_1-x_j's are [166], though it is presumed – and tested – that y and x's are well correlated [164]. Hence the *generalized regression estimator* (GREG) can be written as:

$$\hat{Y} = \sum_{i=1}^{n} \frac{N}{n} * g_i * y_i$$

[9] A traditional and simple "*after stratification*" approach is to calculate weights using typically gender, age (for example 5 age intervals) and geography (here 5 regions or 11 municipalities). For every one of the strata combinations (for example 2*5*5 = 50 strata) the *design weight (*N/n) is calculated (N = total population size in strata and n = sample responses in strata). The problems emerge when more variables are added, for example just five income intervals (2*5*5*5 = 250) add 5 times more cell combinations. This can make the estimation more unreliable due to the risk of cells with 0 observations and as a consequence quickly requiring larger samples [166]. Thus, there is a limitation to the number of explanatory variables that can in fact be included before the model gets unreliable [214]. Increasing the number of explanatory variables would in fact enrich the precision of the weights – so-called *multidimensional estimation* – reducing skewness in non-response as well as reducing random sample error, making it a worthy method to correspond to the increasing non-response [164, 166].

where y_i is the i'th individual, (N/n) is the design weight that adjusts for the stratification, and (gi) is a regression estimate that adjusts for non-response. The main point and difference from traditional post-stratification weights is that the gi and the design weight are independent of each other, making it possible to include many more auxiliary variables in the estimation of the non-response.

The design weight (N/n) depends only on population size (N) and the responders in the sample (n) and is usually used to compensate for disproportionate stratification – as here where subsampled by municipalities – or over/under-sampling of specific cases. Remember that the minimum requirements were 2000 individuals per municipality for each of the five regions regardless of the population size of the municipality and that most regions, including the NDR, have chosen to include more than 2000 individuals; in addition there are a different number of individuals included for most municipalities. As a consequence, the included individuals have asymptotic probability extractions in municipalities as well as regions. The design weight corrects this so that the sample is weighted to correctly represent the entire Danish population (NIPH sample) or region (NDR sample etc.). The weights total the number of responses in each sample.

The other component (gi) of the weight adjusts for non-response using regression based on information from the chosen auxiliary variables (see Table 3-5).This correction is of course done to compensate for the fact that persons with certain characteristics are not as likely to respond to the surveys; in fact, the experience is that increasing the number of social factors in particular – rather than demographic factors – significantly impacts on the non-response correction [166].

Table 3-5 shows the final model with the chosen (also social) auxiliary variables, interactions and main effects for the gi. Notice that geography in terms of regions and municipalities is included, adjusting correctly in different subsamples and geographic areas. The gi's purpose is to reduce uncertainty (standard errors) as well as eventual skewness (bias) due to non-responses. Following that, the weight for the i'th individual can be written as:

$$v_i = \frac{N}{n} * g_i$$

The weights total the sample size. For further details and reading see [164, 166, 167].

3.4.3. MISSING DATA

Missing values have the potential to undermine the outcomes of research and recommendations in, for example, clinical studies or health economic evaluation. This is a common and unavoidable problem that is often ignored or overlooked in

the medical literature and health economic evaluation, although flexible methods exist to deal with problems caused by missing data [50, 168, 169].

In this PhD's paper 2, missing values were imputed using auxiliary data from national registers and surveys. This was done for education, partnership, children and income. As the used register variable of education had missing values, the education survey variable was used to impute the missing values. For partnership and children, the survey variables were preferred, and the register variables were used to impute missing values. The advantages are that these imputed values are truly based on true known data about the respondent, not a regression estimated probability as in a multiple imputation (MI) approach. The results are seen in Table 3-6 and further programming details can be found in the supplementary material of paper 3.

Table 3-6. Missing values of the EQ-5D and the covariates of the three combined samples of paper 3

	Missings in samples before imputation		**Missings in samples after imputation**	
	n	*Per cent*	*n*	*Per cent*
EQ-5D utility score	**1,372**	**2.4**	**1,372**	**2.4**
- EQ-5D: Mobility	659	1.2	659	1.2
- EQ-5D: Self-care	723	1.3	723	1.3
- EQ-5D: Usual activities	772	1.3	772	1.3
- EQ-5D: Pain/discomfort	798	1.4	798	1.4
- EQ-5D: Anxiety/depression	884	1.5	884	1.5
Gender	0	0	0	0
Age at 1st January 2010 or 2013	0	0	0	0
Ethnicity	0	0	0	0
Partnership in 2010 or 2013	846	1.5	0	0.0
Children living at home at age 15 or below in 2010 or 2013	2,654	4.7	698	1.2
Education on October 2010 or October 2013	1,233	2.2	297	0.5
Family income in the last of calendar year 2009 or 2012	1	0.0	0	0.0
All 199 conditions in 2010 or 2013	0	0.0	0	0.0
Sample variable	0	0.0	0	0.0
Total missing accumulated – regression models 1–3 paper 3	**4,913**	**8.6**	**2,263**	**4.0**
Social networks – loneliness	992	1.7	992	1.7
Cohen's Perceived Stress Scale	2,794	4.9	2,794	4.9
BMI	1,956	3.4	1,956	3.4
Smoking	1,171	2.1	1,171	2.1
Alcohol intake	4,860	8.5	4,860	8.5
Exercise	1,608	2.8	1,608	2.8
Fruit intake	1,497	2.6	1,497	2.6
Total missing accumulated - regression model 4 paper 3	**13,120**	**23,0**	**12,943**	**22.7**

Source: adapted partly from Hvidberg et al. [50]. Data source: National Health Profiles 2010, 2013. n=56,988.

As the chronic conditions and other variables were based on registers, we had no missing values within these variables. The disadvantage of our approach, however, is that we cannot impute values of EQ-5D and other survey variables as no auxiliary register variables exist. The gold standard would be to apply MI chained equations [168] – besides the imputation based on the auxiliary information. Nevertheless, due to the fairly low number of missings in the EQ-5D score and as the ALDVMM function did not support MI, we exchanged the advantages of MI of the remaining survey variables for the advantages of model estimation precision using the ALDVMM. All missing values of the independent survey variables were included with a separate dummy. Consequently, all study estimates in paper 3 had 2.4 per cent missing values due to the missing values of the dependent variable EQ-5D, and linear estimates of stress and BMI could not be calculated due to the inclusion of the dummy variables.

Testing and exploration of the missingness function of the EQ-5D was done by logistic regression. This could not rule out a possible missing at random (MAR) pattern [50]. Combined with the relatively high number (22.7 per cent) of accumulated missing values from health risk factors, stress and loneliness, and the lack of a possibility of linear estimates of BMI and stress within current model, it is recommended that future studies incorporate MI and chained equations along with the ALDVMM. Notably, a full imputation model was applied in paper 4 using OLS regression.

Therefore, a chained MI model was actually created, although it could not be applied using the ALDVMM. For future use, we briefly describe the model in accordance with recommendations in the following [168, 169]:

An MI chained equation model for future use

To avoid analytic bias, (almost) all applied variables from the main analysis were included in the chained MI model. However, to make the MAR assumption most plausible, further possible variables related to missingness were incorporated [168, 169], based on the initial descriptive missingness analyses. This included the five EQ-5D domains separately (ordinal), variability of samples (nominal), gender, age (in interaction with gender and age splined to account for non-linear correlations), ethnicity (nominal), education (ordinal), children below 15 years of age living at home (or not), in a relationship or not, family equalized income (continuously), often lonely or not, socio-economic status (five categories, nominal), Cohen's Perceived Stress Scale (10 dimensions, ordinal), BMI (continuous), smoking daily, binge drinking (five categories, ordinal), exercise as recommended or not, fruit intake as recommended or not, self-reported health (five dimensions, ordinal), long-standing illness or not, and finally, 18 self-reported dichotomous conditions from the original survey. A trade-off was applied between the number of included variables and having a functioning MI model [168], which is why the 215 chronic

conditions were not included. Instead, the 18 broadly defined self-reported conditions comprising many of the same register-based conditions were included to ensure some estimation based on chronic conditions in the model.

The MI was computed with 20 imputations, each of which had 20 iterations. RSEED was set to 1978. All imputation was done with the survey weights incorporated [170, 171]. The EQ-5D score from the five imputed domains was finally obtained using the MI PASSIVE function. There were no reported problems of perfect prediction or non-convergence.

Since there were different missing values for different samples, the three samples were added in the Stata "by" option to impute the samples separately and correct for different missingsness. Thus, the samples were treated as recommended for different "treatment arms" [168].

For sensitivity analysis and validation, the observed and imputed values for the chosen variables/conditions as well as the overall mean should be compared. Furthermore, a complete case model (CCA), a crude imputation model and an extreme case model (with different extremes such as 0.25, 0.5, 0.75 and 1 of the EQ-5D imputed for all missing values) could also be compared to the final imputation model.

3.4.4. WEIGHTING AND IMPUTATION – THE DIFFERENCES IN OVERVIEW

Figure 3-3 shows the entire sample, non-responders, responders and the relationship between weighting and imputation. Weighting and imputation are separate but complementary methods.

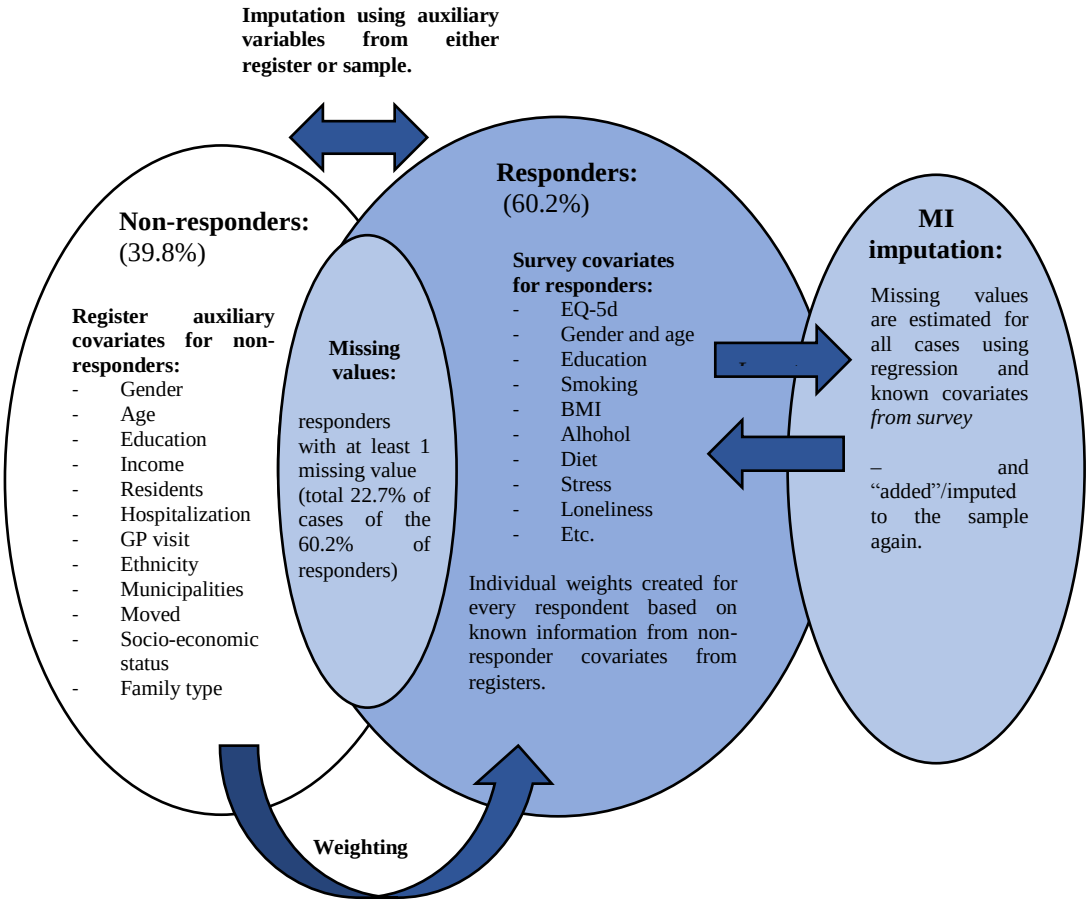

Figure 3-3. Non-responders, responders, weighting and imputation.

3.4.5. DATA MANAGEMENT AND DATA ANALYSIS

Primary data management

All primary data management of survey and register variables, including programming of the defined chronic conditions, was done in SAS 9.4 by the author. Different MACRO programming was done to make smother and smaller programs, but even so the total programming comprises more than 200 pages.

Data analysis

Population-based frequencies of the conditions were outputted from SAS using the TABULATE function, and prevalences were calculated in Microsoft Excel 2010 – and likewise for the survey non-response estimates.

All other data analysis, including mean estimation, regression modelling and imputation, was mainly done in Stata 14 using the svy, svy set, means, sum, logistic, regress, regress, TOBIT, aldvmm, predict, margins and estimates functions. See papers for more details regarding each paper.

All data analysis and data management were done on Statistics Denmark remote research servers.

CHAPTER 4. RESULTS AND SUMMARIES OF PAPERS

4.1. OBJECTIVE 1: TO ESTABLISH REGISTER-BASED DEFINITIONS OF CHRONIC CONDITIONS

4.1.1. BACKGROUND AND PURPOSE

No single framework or definitions exist for identifying all ICD-10-based chronic conditions with the use of big data in respect of public national health-care registers and ICD-10 codes. Thus, the potentials uncovering the different burdens of most possible chronic conditions are not yet unleashed.

In short, the purpose of this study was to medically review, identify and discuss a comprehensive range of register-based definitions of chronic conditions and the challenges and pitfalls while defining chronic conditions with the use of several registers in combination. The aim was to include all ICD-10-based chronic conditions based on the definition and by evaluation and opinion of the involved medical experts. However, as this includes expert opinions, the included conditions are not absolute, but open for discussion. In essence, this study aims to create a methodological framework of definitions for future use with different outcomes of interest when exploring chronic conditions. As such, this study is a thesis contribution to one solution for "making sense" of the big health-care data in regard to chronic disease.

Purpose in summary:

- to medically review, identify and discuss a comprehensive range of register-based definitions of chronic conditions and the challenges and pitfalls when defining chronic conditions with the use of registers
- to create a methodological framework of definitions for future use by others with different outcomes of interest when exploring chronic conditions

4.1.2. SUMMARY AND RESULTS OF PAPER 1: THE REGISTER-BASED DEFINITIONS

The register-based definitions were defined based on data from nationwide Danish public health-care registers, and internationally recognized classification systems such as the ICD-10 and ATC.

A medical review of the chronic conditions was carried out as described in the previous methods section and in the paper. One hundred and ninety-nine chronic conditions and subgroups were identified and defined. One of the innovations is the four clinical and differentiated inclusion time categories into which all of the medically identified chronic conditions were divided. The results can be seen in paper 1. The definitions were defined based on ICD-10 and ATC codes, but also GP services and others from several registers.

One of the important challenges was how to identify conditions where no ICD-10 codes exist as some conditions were treated outside hospitals where no diagnosis codes were reported. This was partly solved by including multiple registers such as prescribed medications and using general practitioners' services and others used for treating chronic conditions. This was done for 35 conditions based on a medical assessment. Table 4-1 shows selected differences between solely using ICD-10 codes and the importance of using multiple registers to ensure the validity of the definitions; for example, the prevalences range from approximately 3 to 23 times difference, underlining the importance of using multiple registers for some conditions. Future studies should further validate the definitions based on, for example, comparison with medical records.

The study provides a medically reviewed catalogue of register-based definitions of 199 chronic conditions for use in research and health-care planning within different areas of interest. The paper includes a thorough discussion of strengths, challenges and pitfalls, and is, to the best of the author's knowledge, the largest collection of definitions currently compiled in a single study based on a uniform methodology.

Table 4-1. Examples of impact using complex algorithms

Cond. no.	Condition	ICD-10 code/definition	Category	Full population estimates for Denmark	
				N	*Per cent*
-	Hypertensive diseases*	I10–I15	Cat. III	316,037	6.9
21	Hypertensive diseases [c]	I10–I15 and/or prescribed medicine	Cat. III	1,060,043	23.3
-	Ulcers*	K25–K27	Cat. IV	6,702	0.1
28	Ulcers [c]	K25–K27 and/or prescribed medicine	Cat. IV	157,379	3.5
-	Psoriasis*	L40	Cat. I	15,232	0.3
29	Psoriasis [c]	L40 and/or prescribed medicine	Cat. I	65,469	1.4
-	Depression*	F32, F33, F34.1, F06.32	Cat. III	91,534	2.0
12	Depression [c]	F32, F33, F34.1, F06.32 and/or prescribed medicine	Cat. III	454,933	10.0
-	Bipolar affective disorder*	F30–F31	Cat. II	6,427	0.1
11	Bipolar affective disorder [c]	F30–F31 and/or prescribed medicine	Cat. II	22,669	0.5
-	ADHD*	F90	Cat. I	15,453	0.3
14	ADHD [c]	F90 and/or prescribed medicine	Cat. I	42,908	0.9

* Not complex defined condition. [c] Complex defined condition. Full Denmark population estimates based on a sample of N = 4,555,439 citizens aged 16 or more on 1st January 2013.

Source: adapted from Hvidberg et al., supplementary material [140], see http://sjp.sagepub.com/content/44/5/462

4.2. OBJECTIVE 2: TO ESTIMATE THE POPULATION-BASED PREVALENCE RATES OF THE 199 CHRONIC CONDITIONS

4.2.1. BACKGROUND AND PURPOSE

So far no studies have provided prevalence estimates comprising most possible chronic conditions within a single study based on an entire country's population. Yet, in Denmark, the prevalence of a few conditions ranging from approximately 4 to 18 are continuously monitored by the government and the NIPH and others – but using different methods and thus yielding different results [57, 58, 60, 64, 95, 96, 155–157]. Moreover, existing studies show that up to 40–50 per cent of the population have one or more chronic conditions or long-standing illness [60, 156], but studies show varying prevalence and do not include all chronic conditions. Thus, there is a need for reliable estimates based on uniform methods showing the basic epidemiology of chronic disease.

In this section, we provide population estimates of the basic epidemiology: the prevalence of selected estimates of the 20 most prevalent of the 199 chronic conditions. The full prevalence catalogue of all 199 conditions can be found in

paper 2 in the appendix. Furthermore, the population estimates are compared to the samples in paper 3 for the 20 most prevalent conditions.

There are two main purposes. First, the full population-based prevalence estimates are crucial, as described earlier, as an epidemiological measure of disease burden, as well as being useable for COI, and a source of new basic knowledge in general. Secondly, the comparison of the population estimates to the samples in paper 3 (indirectly) gives insights into the representativeness of the samples in paper 3 (unique survey sample response rates for all 199 conditions are also provided in appendix A for the interested reader). This enables the reader to identify problematical conditions and qualify discussion on the reliability of the conditions/results of objective 3.

Purpose in summary:

- to create estimates of basic epidemiological disease burden: estimate full population prevalence of the 199 chronic conditions (paper 2)
- to compare population prevalence to the survey sample/survey response used for EQ-5D preference scores in order to give insights into the representativeness and sample bias of the survey sample in paper 3

4.2.2. SUMMARY AND RESULTS OF PAPER 2: NATIONAL PREVALENCE RATES – AND COMPARISONS TO SAMPLES IN PAPER 3

Besides estimating the prevalences of the 199 chronic conditions, the aim of paper 2 was to summarize characteristics in regard to gender and age, and regional differences among the 199 chronic conditions. The comparison to the sample in paper 3 is not a part of paper 2 and is solely done in the thesis.

The study population in paper 2 was set to all 4,555,439 Danish resident citizens aged 16 or more on 1st January 2013. We used several different national registers from 1994 to 2012, including the NPR, using the ICD-10 diagnosis codes of all private and public hospitals' in- and outpatients as well as prescription medicine, GP services and others as described earlier.

A total of 65.6 per cent of the nationwide population aged 16+ had one or more chronic condition. The most prevalent diseases are found among diseases of the circulatory system, diseases of the respiratory system, diseases of the musculoskeletal system and connective tissue and endocrine, nutritional and metabolic diseases, while cancers, for example, only account for a small fraction compared to each of the latter mentioned disease groups. The sample prevalence

estimates are in general fairly close to the national population prevalences, although there are small variations for some conditions and disease groups.

To the best of the author's knowledge, paper 2 provides the most wide-ranging catalogue of prevalence rates and characteristics established on a national population yet made. The prevalence rates and characteristics of the 199 chronic conditions provide fundamental information for future estimates of the basic epidemiological burden of disease for use in economic, aetiological and other research, and in health-care planning in general.

The sample estimates are included in order to discuss these briefly later.

Table 4-2. The 20 conditions with the highest population-based prevalence

Cond. no.	Conditions	ICD-10	Population		Survey samples	
			N	*Per cent*	*n*	*Per cent*
79	Hypertensive diseases [c]	I10–I15	1,060,046	23.3	23,826	25.2
105	Respiratory allergy [c]	J30, except J30.0	841,685	15.4	15,689	16.6
33	Disturbances in lipoprotein circulation and other lipids [c]	E78	652,242	14.3	15,083	15.9
183	Depression [c]	F32, F33, F34.1, F06.32	454,933	10.0	9,096	9.6
105A	Chronic lower respiratory diseases c	J40–J43, J47	418,120	9.2	8,402	8.9
109	Asthma, status asthmaticus [c]	J45–J46	361,129	7.9	7,134	7.5
29	Diabetes type 2 [c]	E11	242,177	5.3	5,641	6.0
108	Chronic obstructive lung disease (COPD) [c]	J44, J96, J13–J18	216,184	4.7	4,303	4.5
127	Gonarthrosis [arthrosis of the knee]	M17	178,811	3.9	4,021	4.3
122A	Inflammatory polyarthropathies and ankylosing spondylitis [c]	M05–M14, M45	165,944	3.6	3,265	3.5
165	Osteoporosis [c]	M80–M81	158,813	3.5	3,060	3.2
112	Ulcers [c]	K25–K27	157,379	3.5	4,113	4.3
42	Migraine [c]	G43	149,866	3.3	3,007	3.2
80A	Ischaemic heart diseases	I20–I25	139,173	3.1	3,286	3.5
26	Diseases of the thyroid [c]	E00–E04, E06, E07	131,908	2.9	2,422	2.6
48	Mononeuropathies of upper limbs	G56	122,395	2.7	2,270	2.4
124	Inflammatory polyarthropathies – except rheumatoid arthritis [c]	M074–M079, M10–M14, M45	115,945	2.5	2,402	2.5
91	Atrial fibrillation and flutter	I48	112,342	2.5	2,582	2.7
126	Coxarthrosis [arthrosis of the hip]	M16	104,115	2.3	2,316	2.4
128	Arthrosis of first carpometacarpal joint and other arthrosis	M18–M19	91,101	2.0	1,616	1.7
-	**Having at least one chronic condition**	**n/a**	**2,989,441**	**65.6**	**38,590**	**67.7**

Source: partly adapted from paper 2. [c] Complex defined condition. All estimates are non-weighted.

Table 4-3. The 20 conditions with the lowest population-based prevalence

Cond. no.	Conditions	ICD-10	Population		Survey samples	
			N	*Per cent*	*n*	*Per cent*
34	Cystic fibrosis [c]	E84	947	0.02	8	0.01
166	Osteoporosis in diseases classified elsewhere	M82	1,007	0.02	30	0.03
30	Diabetes, others [c]	E12–E14	1,117	0.02	27	0.03
139	Dermatopolymyositis	M33	1,137	0.02	25	0.03
140	Systemic sclerosis	M34	1,675	0.04	20	0.02
168	Disorders of continuity of bone	M84	1,865	0.04	53	0.06
58	Disorders of the choroid and retina	H31–H32	1,900	0.04	60	0.06
55	Corneal scars and opacities	H17	2,173	0.05	68	0.07
83	AMI complex/other	I23–I24	2,969	0.07	45	0.05
20	Haemolytic anaemias	D55–D59	3,055	0.07	38	0.04
138	Systemic lupus erythematosus	M32	3,376	0.07	57	0.06
164	Fibromyalgia	M797	3,399	0.07	45	0.05
141	Kyphosis, lordosis	M40	4,160	0.09	86	0.09
2	Human immunodeficiency virus [HIV] disease	B20–24	4,229	0.09	39	0.04
110	Bronchiectasis	J47	4,362	0.10	78	0.08
40	Demyelinating diseases of the central nervous system	G36–G37	4,571	0.10	91	0.10
1	Chronic viral hepatitis	B18	4,584	0.10	49	0.05
4	Malignant neoplasms of digestive organs	C15–C17; C22–C26	4,839	0.11	111	0.12
13	Malignant tumour of the male genitalia	C60, C62–C63	5,194	0.11	88	0.09
107	Emphysema	J43	5,557	0.12	143	0.15
-	**Having at least one chronic condition**	**n/a**	**2,989,441**	**65.62**	**38,590**	**67.7**

Source: partly adapted from paper 2. [c] Complex defined condition. All estimates are non-weighted.

Table 4-4. Prevalence of the overall disease groups

Conditions	**ICD-10**	**Population**		**Survey samples**	
		N	*Per cent*	*n*	*Per cent*
B – Viral hepatitis and human immunodeficiency virus [HIV] disease	B18, B20–B24	8,813	0.2	31	0.1
C – Malignant neoplasms	C00–C99; D32–D33; D35.2–D35.4; D42–D44	229,331	5.0	3,072	5.4
D – *In situ*, benign and neoplasms of uncertain or unknown behaviour and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D00–D09; D55–D59; D60–D67; D80–D89	116,560	2.6	1,314	2.3
E – Endocrine, nutritional and metabolic diseases	E00–E14; E20–E29; E31–35; E70–E78; E84–E85; E88–E89	877,433	19.3	12,888	22.6
G – Diseases of the nervous system	G00–G14; G20–G32; G35–G37; G40–47; G50–64; G70–73; G80–G83; G90–G99	561,054	12.3	6,698	11.8
H – Diseases of the eye and adnexa and diseases of the ear and mastoid process	H02–H06; H17–H18; H25–H28; H31–H32; H34–H36; H40–55; H57; H80,H810; H93, H90–H93	448,176	9.8	6,578	11.5
J – Diseases of the respiratory system	J30.1; J40–J47; J60–J84; J95, J97–J99	1,210,598	26.6	17,647	31.0
I – Diseases of the circulatory system	I05–I06; I10–28; I30–33;I36–141; I44–I52; I60–I88; I90–I94; I96–I99	1,254,427	27.5	14,516	25.5
K – Diseases of the digestive system	K25–K27; K40, K43, K50–52; K58–K59; K71–K77; K86–K87	329,337	7.2	4,617	8.1
L – Diseases of the skin and subcutaneous tissue	L40	65,469	1.4	747	1.3
M – Diseases of the musculoskeletal system and connective tissue	M01–M25: M30–M36; M40–M54; M60.1–M99	1,032,808	22.7	13,588	23.8
N – Diseases of the genitourinary system	N18	20,162	0.4	238	0.4
Q – Congenital malformations, deformations and chromosomal abnormalities	Q00–Q56; Q60–Q99	124,898	2.7	1,351	2.4
F – Mental and behavioural disorders	F00–99	683,194	15.0	6,353	11.1
Having at least one chronic condition	**n/a**	2,989,441	65.6	38,590	67.7

Source: partly adapted from paper 2. All estimates are non-weighted.

4.3. OBJECTIVE 3: TO ESTABLISH EQ-5D-3L PREFERENCE SCORES FOR 199 CHRONIC CONDITIONS

4.3.1. BACKGROUND AND PURPOSE

As the costs and individual burdens of chronic conditions are increasing, the development of tools and reliable estimates for prioritization is essential to maximize the utility of societal resources. Furthermore, there is a need for standardized disease burden measures identifying the conditions with the greatest need and potential for improving HRQoL. For this, the use of the EQ-5D is desired as the EQ-5D and the QALY are the preferred disease of burden measures within health economic evaluation and are recommended by American and British authorities [24, 27, 42, 85]. However, existing estimates are often measured partially, and results thus vary across studies within the same condition. Therefore, there is a need for further standardization of estimates in order to decrease the variability of estimates and provide researchers with a uniform, reliable tool.

Although older, standardized preference catalogues of multiple conditions exist, and the current research aims to improve existing research by using doctor-reported ICD-10 conditions, for more conditions, with new more precise regression methods that are mean based, as preferred within health economic evaluation [25] in contrast to existing catalogues, and by adding new variables such as stress, social network, BMI and behavioural risk factors of importance in health economic evaluation.

The main purpose of paper 3 was to create a catalogue of EQ-5D 3L preference scores for 199 nationwide representative chronic conditions for use within future health economic evaluation.

However, a crucial part of the methodological debate from the literature including paper 1 has been differences in results between self-reported and register-based conditions. The current data provide a unique opportunity to qualify this debate further by comparing HRQoL between self-reported and register-based conditions from exactly the same sample. Therefore, we also provide new estimates thereof not presented in the papers for discussion.

Moreover, an important underlining issue is the reliability and representativeness of the samples, as this naturally impacts on the reliability of the estimates, since the study is based on three asymmetric samples: one for the whole of Denmark and two for the North Denmark Region. Thus, a short summary of prevalence and survey-response differences is presented in the following.

Main purpose in regards to thesis:

- to create an improved catalogue of EQ-5D preference scores for 199 Danish nationally representative chronic conditions for use in future health economic evaluation

Subpurposes within the thesis:

- to present and compare HRQoL (and prevalence) across self-reported and register-based conditions for discussion
- to briefly summarize the main results of prevalence rates and survey response rates across conditions for discussion

4.3.2. SUMMARY AND RESULTS OF PAPER 3: EQ-5D PREFERENCE-BASED SCORES

The 199 defined and identified register-based chronic conditions were combined with the Danish National Health Profile Surveys including the EQ-5D. Three survey samples from 2010 and 2013 with a total of 56,988 respondents were included and combined with registers comprising their chronic conditions using a unique personal identification number (CPR). A total of seven registers were included comprising the conditions with the use of ICD-10 diagnosis codes, medications, GP services and others within the period 1994–2013.

The EQ-5D index scores for all conditions were obtained by incorporating DK national tariffs (UK and US tariffs are planned for later). In contrast to existing research, the current catalogue uses mean scores and is based on the ALDVMM.

The unadjusted EQ-5D preference scores and adjusted ALDVMM regression estimates of 199 conditions were calculated and presented in Table 4-6 shows the 20 conditions with the worst HRQol. Four regression models, all with the EQ-5D as the dependent variable, were introduced to accommodate different health evaluation requirements: model 1 adjusted for all conditions; model 2: adjusted for the conditions gender and age and the accumulated number of co-morbidities; model 3: model 2 + education, partnership, children, income and ethnicity; and finally model 4: model 3 + behavioural risk factors, BMI, stress and social networks (see paper 3 for all unadjusted and full regression estimates of all 199 conditions).

Overall, conditions within mental and behavioural disorders, diseases of the nervous system, diseases of the musculoskeletal system and connective tissue, and endocrine, nutritional and metabolic diseases showed some of the lowest HRQoL (see Table 4-7) This also applies for the adjusted regression estimates in paper 3.

Paper 3 is, to the best of the author's knowledge, the largest study in terms of the wide-ranging number of chronic conditions, the sample size and the uniform methodology. The study is the first of its kind to use doctor-reported ICD-10 chronic conditions, new regression methods designed to handle the EQ-5D and nationally representative adjusted *mean*-based EQ-5D preference scores of the 199 chronic conditions. The catalogue of preference scores will assist and be useful to international researchers and health-care analysts, without the costs and burden of primary data collection. In contrast to existing studies, the estimates can also – to some extent – model different severities of conditions and thus different levels of potential health gains. The study provides new insights into potential health gains and differences in HRQoL within an unprecedented number of conditions as well as health risks.

Table 4-5. Frequency and percentages of the five dimensions of the EQ-5D based on the three samples. Weighted and complete cases

		Mobility		**Self-Care**		**Usual Activities**		**Pain/Discomfort**		**Anxiety/Depression**	
		n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
No	NIPH 2010	12,694	(84.8%)	14,315	(95.6%)	11,396	(76.2%)	8,307	(55.5%)	11,737	(79.0%)
problems	NDR 2010	19,303	(83.4%)	21,963	(94.9%)	17,411	(75.3%)	12,546	(54.3%)	18,225	(78.9%)
	NDR 2013	15,501	(83.3%)	17,579	(94.9%)	13,777	(74.3%)	9,821	(53.0%)	14,524	(78.3%)
	Combined	**47,499**	**(83.8**%)	**53,858**	**(95.0**%)	**42,585**	**(75.2**%)	**30,675**	**(54.2**%)	**44,486**	**(78.7**%)
Some	NIPH 2010	2,239	(15.0%)	579	(3.9%)	3,130	(20.9%)	6,178	(41.3%)	2,892	(19.5%)
problems	NDR 2010	3,764	(16.3%)	1,051	(4.5%)	4,849	(21.0%)	9,714	(42.0%)	4,522	(19.6%)
	NDR 2013	3,034	(16.3%)	852	(4.6%)	4,158	(22.4%)	7,999	(43.2%)	3724	(20.0%)
	Combined	**9,038**	**(15.9**%)	**2,484**	**(4.4**%)	**12,139**	**(21.4**%)	**23,893**	**(42.2**%)	**11,140**	**(19.7**%)
Extreme	NIPH 2010	40	(0.3%)	77	(0.5%)	427	(2.9%)	474	(3.2%)	236	(1.6%)
problems	NDR 2010	74	(0.3%)	131	(0.6%)	861	(3.7%)	867	(3.7%)	342	(1.5%)
	NDR 2013	66	(0.4%)	112	(0.6%)	611	(3.3%)	711	(3.8%)	305	(1.6%)
	Combined	**180**	**(0.3**%)	**321**	**(0.6**%)	**1,899**	**(3.4**%)	**2,052**	**(3.6**%)	**882**	**(1.6**%)
	Total combined	**56,717**	**(100%)**	**56,663**	**(100%)**	**56,622**	**(100%)**	**56,620**	**(100%)**	**56,508**	**(100%)**

Source: adapted from paper 3, supplementary material. Source: National Health Profiles 2010, 2013. All estimates are non-weighted.

Table 4-6. The 20 conditions with the lowest EQ-5D-based HRQoL, unadjusted

Cond. no.	Condition	ICD-10 code	n	Unadjusted EQ-5D
34	Cystic fibrosis [c]	E84	4	0.303
140	Systemic sclerosis	M34	13	0.432
164	Fibromyalgia	M797	36	0.49
160	Rheumatism, unspecified	M790	113	0.515
176	Dementia [c]	F00, G30, F01, F02.0, F03.9, G31.8B, G31.8E, G31.9, G31.0B	179	0.546
188	Post-traumatic stress disorder	F431	73	0.557
36	Systemic atrophies primarily affecting the central nervous system and other degenerative diseases	G10–G14, G30–G32	70	0.583
52	Cerebral palsy and other paralytic syndromes	G80–G83	113	0.60
185	Phobic anxiety disorders	F40	78	0.611
145	Other inflammatory spondylopathies	M46	62	0.618
151	Dorsalgia	M54	621	0.619
125	Polyarthrosis [Arthrosis]	M15	169	0.629
146	Spondylosis	M47	924	0.629
186	Other anxiety disorders	F41	226	0.631
147	Other spondylopathies and spondylopathies in diseases classified elsewhere	M48, M49	483	0.633
166	Osteoporosis in diseases classified elsewhere	M82	16	0.636
106	Bronchitis, not specified as acute or chronic, simple and mucopurulent chronic bronchitis and unspecified chronic bronchitis	J40–J42	182	0.641
190	Dissociative (conversion) disorders, somatoform disorders and other neurotic disorders	F44, F45, F48	170	0.644
96	Sequelae of cerebrovascular disease	I69	513	0.645
97	Atherosclerosis	I70	397	0.645
194	Specific personality disorders	F602, F604–F609	363	0.645
149	Other intervertebral disc disorders	M51	501	0.646

Source: adapted from paper 3. [c] = complex defined conditions. All estimates are weighted.

Table 4-7. The EQ-5D-based HRQoL based on disease groups

Condition	ICD-10 code	n	Unadjusted EQ-5D
B – Viral hepatitis and human immunodeficiency virus [HIV] disease	B18, B20–B24	31	0.760
C – Malignant neoplasms	C00–C99; D32–D33; D35.2–D35.4; D42–D44	2,947	0.78
D – *In situ*, benign and neoplasms of uncertain or unknown behaviour and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D00–D09; D55–D59; D60–D67; D80–D89	1,254	0.744
E – Endocrine, nutritional and metabolic diseases	E00–E14; E20–E29; E31–35; E70–E78; E84–E85; E88–E89	12,412	0.783
F – Mental and behavioural disorders	F00–99	6,106	0.703
G – Diseases of the nervous system	G00–G14; G20–G32; G35–G37; G40–47; G50–64; G70–73; G80–G83; G90–G99	6,698	0.747
H – Diseases of the eye and adnexa and diseases of the ear and mastoid process	H02–H06; H17–H18; H25–H28; H31–H32; H34–H36; H40–55; H57; H80,H810; H93, H90–H93	6,309	0.779
I – Diseases of the circulatory system	I05–I06; I10–28; I30–33;I36–141; I44–I52; I60–I88; I90–I94; I96–I99	16,990	0.783
J – Diseases of the respiratory system	J30.1; J40–J47; J60–J84; J95, J97–J99	14,087	0.81
K – Diseases of the digestive system	K25–K27; K40, K43, K50–52; K58–K59; K71–K77; K86–K87	4,462	0.744
L – Diseases of the skin and subcutaneous tissue	L40	722	0.789
M – Diseases of the musculoskeletal system and connective tissue	M01–M25: M30–M36; M40–M54; M60.1–M99	13,163	0.755
N – Diseases of the genitourinary system	N18	224	0.698
Q – Congenital malformations, deformations and chromosomal abnormalities	Q00–Q56; Q60–Q99	1,323	0.814
All	-	**55,616**	**0.852**

Source: adapted from paper 3. All estimates are weighted.

4.3.3. DIFFERENCES IN HRQOL (AND PREVALENCE) OF SELF-REPORTED AND REGISTER-BASED CONDITIONS – AND INDIRECT SAMPLE MEASURES OF REPRESENTATIVENESS

For later methodological discussion, additional results are presented in regard to differences in HRQoL and prevalence rates between self-reported and register-based conditions based on the EQ-5D. The estimates are all based on exactly the same samples giving a unique opportunity for comparisons, but only for 18 self-reported conditions; also, some limitations exist due to a lack of diagnostic precision with the self-reported conditions due to broadly defined disease categories, which is why the register-reported conditions in some cases have more diagnoses reported.

For most conditions, the mean age of the self-reported (SR) conditions is lower than that of the register-reported conditions (RR), except for some chronic lower respiratory diseases, and to some extent cancers and diabetes.

However, the age differences are not necessarily reflected in differences in the HRQoL. For example, asthma and allergies have a similar HRQoL, which is barely significantly different even though sample size are rather high. The same applies for diabetes, high blood pressure, heart attack and stroke. Moreover, the HRQoL is barely significantly different for arthrosis, migraine or common headaches – even though n and age are different between SR and RR.

Relatively large, mostly significant differences in HRQoL, and partly for age and n, exist for most heart conditions (except heart attack and high blood pressure), lung diseases, rheumatoid arthritis, cancers, herniated or other back conditions, mental illness, cataracts and to some extent osteoporosis and tinnitus.

Table 4-8. The unadjusted EQ-5D-3L-based HRQoL and prevalences of self-reported conditions and register-based conditions in comparison

Cond. no.	Conditions	ICD-10	Per cent	n	Mean age	Mean age SD	Mean EQ-5D	EQ-5D SE
n/a	SR – Asthma		6.3	3,523	46.4	19.3	0.781	0.0047
108	RR – Asthma, status asthmaticus	J45–J46	7.4	4,107	52.3	19.4	0.779	0.0042
n/a	SR – Allergies		16.3	9,077	42.8	16.9	0.835	0.0023
103	RR – Respiratory allergy	J30, except J30.0	17.6	9,792	50.2	18.3	0.819	0.0024
n/a	SR – Diabetes all types		5.1	2,814	62.3	15.0	0.751	0.0053
28	RR – Diabetes type 1	E10	0.5	284	45.1	15.7	0.801	0.0154
29	RR – Diabetes type 2	E11	5.8	3,253	65.6	13.2	0.752	0.0048
n/a	SR – High blood pressure		20.3	11,299	62.8	13.8	0.785	0.0023
76	RR – Hypertensive diseases	I10–I15	26.1	14,504	64.8	14.0	0.776	0.0021
n/a	SR – Heart attack		1.1	624	66.9	13.3	0.663	0.0122
77	RR – Heart failure	I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9	0.7	369	72.4	13.8	0.678	0.0151
n/a	SR – Angina		1.9	1,051	60.7	17.5	0.653	0.0103
79	RR – Angina pectoris	I20	2.3	1,253	66.3	11.6	0.725	0.0078
78	RR – Ischaemic heart diseases	I20–I25	3.6	2,017	67.9	12.0	0.719	0.0066
n/a	SR – Stroke (hjerneblødning)		1.4	759	64.8	15.5	0.628	0.0117
92	RR –Stroke	I60, I61,I63–I64, Z501 (rehabilitation)	1.5	812	68.6	13.2	0.707	0.0093

n/a	SR – Chronic bronchitis		4.6	2,545	61.5	16.0	0.695	0.0059
104	RR – Chronic lower respiratory diseases	J40–J43, J47	9.1	5,046	55.0	17.3	0.782	0.0036
105	RR – Bronchitis, not specified as acute or chronic, simple and mucopurulent chronic bronchitis and unspecified chronic bronchitis	J40–J42	0.3	182	67.3	12.3	0.641	0.0292
106	RR – Emphysema	J43	0.1	76	62.9	12.4	0.706	0.0266
107	RR – Chronic obstructive lung disease (COPD)	J44, J96, J13–J18	4.4	2,435	61.3	17.7	0.733	0.0060
n/a	SR – Arthrosis		21.4	11,918	61.8	14.3	0.725	0.0023
n/a	RR – Arthrosis	M15–M19	8.3	4,589	64.2	14.1	0.739	0.0037
n/a	SR – Rheumatoid arthritis		5.5	3,044	58.0	15.8	0.674	0.0051
122	RR – Inflammatory polyarthropathies and ankylosing spondylitis	M05–M14, M45	3.6	2,008	60.3	15.8	0.726	0.0057
n/a	SR – Osteoporosis		3.3	1,832	69.7	13.2	0.678	0.0071
165	RR – Osteoporosis	M80–M81	3.3	1,817	71.8	11.0	0.710	0.0066
n/a	SR – Cancers all		2.5	1,408	63.2	14.4	0.734	0.0073
	RR – Malignant neoplasms disease group C (all)	C00–C99; D32–D33; D35.2–D35.4; D42–D44	5.3	2,947	64.9	14.6	0.780	0.0045
n/a	SR – Migraine or common headache		13.6	7,579	44.1	15.9	0.755	0.0031
42	RR – Migraine	G43	3.7	2,042	47.1	13.8	0.747	0.0035
43	RR – Other headache syndromes	G44	0.3	143	44.8	14.4	0.700	0.0265
n/a	SR – Temporary mental illness		8.7	4,859	45.3	17.4	0.672	0.0038
n/a	SR – Long-lasting mental illness		3.8	2,113	44.1	17.2	0.625	0.0066
n/a	SR – Both temporary and long-lasting mental illness		9.9	5,669	44.9	17.5	0.674	0.0036
n/a	RR – Mental and behavioural disorders disease group F	F00–F99	11.0	6,106	50.7	18.5	0.703	0.0037
n/a	SR – Herniated or other back conditions		13.1	7,280	52.8	15.9	0.705	0.0030
n/a	RR – Diseases of the musculoskeletal system and connective tissue, disease group M	M01–M25: M30–M36; M40–M54; M60.1–M99	23.7	13,163	57.0	17.6	0.755	0.0023
n/a	SR – Cataracts		3.8	2,113	71.7	13.1	0.727	0.0064
57	RR – Diseases of the eye lens (cataracts)	H25–H28	1.7	928	73.5	11.7	0.761	0.0086
n/a	SR – Tinnitus	-	10.3	5,721	55.3	16.7	0.799	0.0031
73	RR – Tinnitus	H931	0.6	350	63.6	13.3	0.776	0.0139

SR=self-reported, RR=register-reported. All estimates are weighted. Data source: National Health Profiles 2010, 2013. n=56,988.

As seen in the previous section, most of the register-based survey prevalence estimates are fairly close to national population prevalence estimates (see Table 4-2 to Table 4-4 and appendix A for all sample prevalences). However, within "Endocrine, nutritional and metabolic diseases" and "Diseases of the respiratory system", the sample prevalences are slightly higher for the population estimates. On the other hand, prevalences of "Diseases of the circulatory system" and "Mental and behavioural disorders" are slightly lower than those of the population prevalences. All in all, the sample prevalences are slightly higher than the population estimates by around 2 percentage points, from 65.6 to 67.7 per cent.

Comparing the SR prevalences to the RR prevalences (see Table 4-8) shows that eight of the 18 conditions have either slightly higher or much higher SR than RR prevalences (heart failure, rheumatoid arthritis, arthrosis, migraine or common headache, cataracts, tinnitus and partly the two times mental illness). Migraine or common headache, arthrosis, cataracts and tinnitus all have much higher prevalences defined as more than twice the size of the compared estimate.

Prevalences of osteoporosis and stroke are almost the same for SR and RR.

The rest, eight of the 18 conditions, have higher or much higher RR prevalence including diseases of the musculoskeletal system and connective tissue, cancers, lung conditions, high blood pressure and diabetes, while asthma and allergy have close to the same estimates, although slightly higher RR prevalence.

Possible non-response bias could be indicated by differences in survey response across conditions. The survey data give a unique possibility of estimating survey responses for each condition as we also have the non-respondents' register-based chronic conditions of all the respondents from the invited sample.

Appendix A shows all survey response rates of the sample. The survey response ranges from 18.9 (mental retardation) to 82.2 per cent (fibromyalgia). Interestingly, mental conditions top the list of the 20 conditions with the lowest survey response (ranging from 18.9 to 45.4 per cent), but also other common stigmatizing conditions such as HIV and hepatitis are among the 20 conditions with the lowest survey response. On the other hand, other severe conditions such as fibromyalgia and systemic lupus erythematosus have the highest survey response, although the majority of the conditions with the highest survey response are less severe conditions. Notably, the survey response rates of the variable measuring the number of co-morbidities as an indicator of disease severity are fairly constantly within 2–5 co-morbidities, but lower for conditions with 0–1 condition, and only marginally lower for 6–7+ comorbidities.

4.4. OBJECTIVE 4: TO PRESENT A CASE EXAMPLE OF HRQOL ANALYTICS OF A SURVEY-BASED CHRONIC CONDITION AND LIMITATIONS OF REGISTER-BASED DEFINITIONS

4.4.1. BACKGROUND AND PURPOSE

Often, HRQoL estimates of chronic conditions are presented based on one condition and one single study, and thus not one study comprising 199 conditions as in paper 2. In contrast to existing papers, a case example based on the condition myalgic encephalomyelitis (ME)/chronic Fatigue Syndrome (CFS) was included. This allows exemplification of the state of the art of detailed HRQoL analysis in comparison to paper 2 and some limitations of register-based conditions.

ME/CFS is a severe and widespread illness affecting 0.2 to 0.4 per cent of different populations [172]. The primary purpose of paper 4 was to estimate EQ-5D-3L HRQoL scores with Danish time trade-off values. The secondary aims were to explore whether the results were influenced or not by other conditions using regression, to compare the results to 20 other conditions and to display ME/CFS patient characteristics for use in medical practice.

Purpose in relation to the thesis:

- to show a case example of HRQoL analytics of a chronic condition
- to discuss and identify the limitations of other papers in relation to register-based conditions based on the case

4.4.2. SUMMARY AND RESULTS OF PAPER 4: HRQOL FOR PATIENTS WITH ME/CFS

The study identified several interesting methodological aspects. Although the condition is common worldwide and severe, it cannot be identified using registers, although you would expect a complex and severe condition to be diagnosed and reported at hospitals within the ICD-10 coding system. There may be several reasons for this, as discussed in the paper. Consequently, this condition can only be identified by self-reported conditions or by a medical screening of patients using the ICD-10 and the newest clinical diagnostic criteria at this time. Notably, the study used a rather controversial approach as the sample was based on all members of the Danish ME/CFS Patient Association in 2013 (n=319). Thereof, 105 ME/CFS patients gave valid responses to the questionnaire, including the EQ-5D. Issues of sampling methods were discussed in the paper.

Unadjusted EQ-5D-3L mean and median scores were calculated. The means of the condition were compared to the Danish population mean and to the mean of 20 other conditions. Moreover, adjusted OLS regression estimates were calculated, adjusted for gender, age, educational level and co-morbidity of 18 self-reported conditions.

The unadjusted EQ-5D-3L HRQoL mean score of ME/CFS was 0.47 [0.41–0.53], while the population mean was 0.85 [0.84–0.86]. The unadjusted median was different to the mean – 0.584 [0.53–0.64] compared to a population median of 0.824 [0.82–0.83]. Thus, the medians of conditions were significantly higher than the mean estimates. Furthermore, the mean-based regression disutility estimates were calculated as being -0.29 [-0.21–0.34] for ME/CFS patients. The characteristics of ME/CFS patients were different from the national population in regard to gender, relationship, employment etc.

Moreover, the EQ-5D-based HRQoL of ME/CFS was not only significantly lower than the population mean, but also the lowest of all the compared conditions. The adjusted regression analysis confirmed that poor HRQoL of ME/CFS was distinctly different from, and thus not a proxy of, an impact from other included conditions. Nevertheless, further studies are required to exclude the possibility of selection bias of the study.

4.5. SUMMARY

In paper 1, a framework of register-based definitions was defined based on a medical assessment, existing research and seven different registers comprising 199 conditions and subgroups thereof. Thirty-five conditions and subgroups had complex definitions compiled using the different registers in combination in order to ensure the best possible inclusions of the conditions by medical assessment. The definitions can be used by other researchers and health-care professionals for measuring different outcomes of interest using big data. In the current PhD, the framework of definitions was the basis used for the outcomes in papers 2 and 3.

In paper 2, prevalence rates and characteristics of the 199 conditions were presented based on the nationwide population of 4,555,439 Danish citizens aged 16 and older on 1st January 2013. Seven different national registers from 1994 to 2012 were used. A total of 65.6 per cent of the national population had one or more chronic conditions, and the most prevalent conditions were found within diseases of the circulatory system (I), diseases of the respiratory system (J), diseases of the musculoskeletal system and connective tissue (M) and endocrine, nutritional and metabolic diseases (E). While the prevalences provide important basic epidemiological burden estimates, another aim was to compare the prevalences of the population to the sample of paper 3 in order to assess the reliability thereof. In

general, the sample prevalence estimates are, overall, fairly simular to the national population prevalences, though small differences exist across some conditions and disease groups.

While paper 2 provides the basic prevalences of the objective sizes of the conditions, paper 3 generates estimates of the severity and subjective EQ-5D HRQoL burden of disease mean estimates for the 199 chronic conditions, and is thus complementary to paper 2. The study was based on the Danish National Health Profile Surveys, including the EQ-5D, from 2010 and 2013 with a total of 56,988 respondents. The survey combined with registers containing information about the chronic conditions for each respondent using a unique personal identification number (CPR). One hundred and ninety-nine chronic conditions had EQ-5D index scores calculated and presented. Both unadjusted and adjusted estimates were calculated. The adjusted estimates were based on the ALDVMM designed to handle the skewed distribution of the EQ-5D and mean-based contrary existing research. Four regression models and new variables – behavioural risk factors, BMI, stress and social networks – were introduced to accommodate different health evaluation requirements for future use in health economic evaluation. Generally, chronic conditions within mental and behavioural disorders (F group), diseases of the nervous system (G group), diseases of the musculoskeletal system and connective tissue (M group), and endocrine, nutritional and metabolic diseases (E group) had some of the lowest HRQoL.

Finally, paper 4 is a case example of HRQoL analytics of a single chronic condition, in contrast to paper 3. The paper also discussed and identified limitations of register-based conditions based on the case and literature. The unadjusted HRQoL EQ-5D-3L-based mean score for ME/CFS patients was 0.47 [0.41–0.53], compared to the Danish population mean of 0.85 [0.84–0.86]. Moreover, the adjusted mean-based regression disutility estimates for ME/CFS patients were -0.29 [-0.21–0.34]. The ME/CFS patient characteristics were dissimilar to the national population regarding gender, relationship, employment etc. Additionally, the EQ-5D-based HRQoL of ME/CFS patients was the lowest of all the compared conditions within the study. The adjusted regression model confirmed that the poor HRQoL of ME/CFS patients was markedly different from, and not a proxy of, any possible impact from other embraced conditions. The study also found that the ME/CFS patients, although a common condition, cannot be identified based on registers. The possible reasons were discussed in the paper; however, consequently, this is an example of a condition that can only be identified by using a medical screening of patients or by self-reported conditions as done in the study. Nonetheless, further studies are necessary to exclude possible study selection bias.

CHAPTER 5. DISCUSSION AND PERSPECTIVES

5.1. IMPACTS OF METHODS – AND THE SAMPLES

Methods matter: The impact on HRQoL and prevalence of different methods

The validity, pros and cons of register-based methods and data are discussed in detail in paper 1, and thus not discussed here. Yet, the empirical grounds for related discussion are expanded within the current thesis. Moreover, it is not the intention to provide a detailed statistical analysis of overlapping conditions like other studies [95, 173], but merely to generate further input to the discussion by illustrating the overall differences between each method (see results of Table 4-8).

In line with earlier studies [57, 58, 60, 64, 95, 96, 155–157], the present study has shown that different study methods yield different results in regard to both prevalences and HRQoL (see Table 4-8). However, most existing HRQoL studies are based on single conditions using one sampling method (SR or RR). Thus, the current study is, to the best of the author's knowledge, one of the first to show that even within the same sample, there are differences in HRQoL for some conditions depending on both SR and RR. Notably, other studies have already shown differences in prevalences, as also identified here [60, 95, 96]. Hence, the current thesis further supports the argument that a uniform, transparent methodology and appropriate data are of great importance to the validity of the results, and for accessing the validity and statistical uncertainties, and to the decision-makers, so that decisions are made based on the most solid grounds possible within health care.

There may be several reasons for the differences. At an aggregated level, some conditions may be either treated in primary care and still not reported or self-treated and thus not reported. SR might also include special kind of patients: not severe enough or wanting medical treatment, but still severe enough to have an impact on HRQoL. However, possible reasons are mainly speculation, as the thesis do not provide empirical evidence on explanations and can thus only theorize about explanations.

In detail, the results of the current thesis also indicate that some conditions are more exposed to differences than others. First of all, the differences vary between HRQoL and prevalence depending on methodology, i.e. SR and RR conditions. For example, there are no real differences in SR and RR prevalences of stroke and osteoporosis, while the same conditions all have different HRQoL. On the other hand, there are no real differences in SR and RR HRQoL for hypertension, heart

attack, arthrosis, migraine and to some extent tinnitus, while their prevalences all differ.

In regard to HRQoL, differences between SR and RR estimates exist among heart conditions such as angina, stroke, lung diseases, rheumatoid arthritis, osteoporosis, cancers, mental illness, back conditions, cataracts and to some extent tinnitus. For these conditions, except for tinnitus, the HRQoL RR estimates are lower than those of the SR conditions, and at the same time, the RR disease populations are mostly older too. However, there do not seem to be any systemic shared explanations across disease areas for the differences as they cover many different disease groups, except perhaps that most of the conditions are either mostly severe or multifaceted. Thus, the reliability of these SR conditions could be questioned due to possible patient or recall bias increased by the complexity of the conditions. Furthermore, it is recognized that the SR conditions might lack the precision to fully enable comparability due to the broadly defined conditions within the questionnaire, such as, for example, lung diseases, mental illness, cancers and back conditions. Nevertheless, the SR HRQoL estimates for cataracts might be preferred as the register data are known to be limited due to treatment outside hospitals and limited medical data thereof. Finally, it is worth mentioning that less severe and common conditions such as allergies, asthma, migraine and to some extent tinnitus do not show significant differences in HRQoL estimates between SR or RR conditions.

In regard to prevalence, the differences between SR and RR estimates primarily exist among hypertension, heart attack, angina, lung conditions, arthrosis, rheumatoid arthritis, osteoporosis, cancers, migraine, cataracts and tinnitus. Again, it is hard to identify any systemic differences across disease areas. Nevertheless, hypertension, angina, lung conditions, osteoporosis and cancers have considerably higher prevalence estimates for RR conditions, while asthma, allergies, diabetes and stroke have borderline higher prevalence for RR conditions. The higher prevalence could indicate that the RR conditions capture more of the less severe patients among, for example, angina, stroke, lung diseases, cancers, back conditions, as, for example, these conditions also have better HRQoL than could be expected from less severe patients (see Table 4-8). However, arthrosis, rheumatoid arthritis, migraine, cataracts and tinnitus all have higher SR prevalence. These conditions have in common that they include a broad range from severe to less severe patients that are not necessarily treated or treatable (except for cataracts) or perhaps self-treated. Moreover, especially for arthrosis and rheumatoid arthritis, the medication is often used for several diseases or bought as OTC drugs. Consequently, the conditions are not all register reported and several have difficulty being identified solely based on registers.

So, there are differences, but what methodology, SR or RR, to use and when? First of all, it depends on the purpose. If the study needs the precision of doctor-reported diagnosis or ICD-10-based conditions then the RR conditions should be the main

choice as this precision is not provided in most SRs. On the other hand, if the purpose is to get an *overall* and broad estimate for use in public health research, SR might be the appropriate choice – especially in the case of migraine, tinnitus, rheumatoid arthritis, cataracts and arthrosis. On the other hand, the large differences among, for example, cancers could indicate some SR recall bias or respondent confusion regarding their own illness as SR is around half the size of RR, and we do not expect the large differences in prevalence to be caused by register error. Moreover, the SR HRQoL is significantly lower than that of the cancer RR conditions, thereby indicating that the RR conditions actually capture more less severe cancers than the SR conditions. This also applies to other only severe and complex conditions including hypertension, angina and ischaemic heart diseases, chronic lung diseases, diseases of the musculoskeletal system and connective tissue, and to some extent heart attack and mental illness.

In addition, the SR HRQoL is noticeably lower for many severe conditions such as heart conditions and lung conditions, but also arthrosis, rheumatoid arthritis and osteoporosis, which cannot solely be explained by higher RR prevalence (with relatively more less severe conditions to increase the HRQoL). There may be a correlation between SR conditions and identifying those with lower HRQoL. One explanation might be that SR better includes those with actual functional limitations of a disease than RR conditions, which use medically defined inclusion times that may not suit every individual. But it could also be that the less severe patients have not self-reported the condition even though it exists.

On the other hand, some SR conditions might still not be accurately captured compared to the definition of chronic conditions, as they could include more conditions that do not have any real "functional limitations" due to the illness or "ongoing need for medical care" identified in the registers, for example arthrosis, cataracts or tinnitus. It could be argued that conditions with functional limitations or ongoing need for medical care most likely would, at some point in time, be reported in registers when people seek health care when the "limitations" become functional – although it is recognized that some treated patients might not be reported or identified even so (for example arthrosis, cataracts, migraine and tinnitus, as discussed in paper 1).

In summary, the best suited method depends on purpose, data possibilities *and* the condition. Moreover, it should also be evident that there might be several possible, sometimes contradicting explanations for the differences from methodology. The current study cannot provide definite explanations, but merely identify differences and theorize about explanations. Within the literature, the two discourses, the SR and RR, are usually compared, divided and disputed, yet it is often implied that RR is the gold standard [97–104, 174–176] – except for in the GBD studies, which mix different data sources and methodologies within and across countries [3, 126, 131, 132, 177]. Notably, this is most likely needed within the GBS as uniform data

quality is difficult to obtain across countries with very different resources, data infrastructures and populations. However, an SR and RR combined methodology within Western countries could possibly improve, despite not being doctor reported, the validity for some RR conditions not identified properly in registers such as migraine, tinnitus, rheumatoid arthritis and to some extent arthrosis ("to some extent" as many do not have any functional limitations due to the disease, which is why there is a risk of over-reporting). It was also showed that the disputed condition ME/CFS was not identified properly within registers, perhaps due to cultural medical differences and diagnostic practices across countries. Therefore, ME/CFS and other disputed or stigmatized conditions might benefit from a combined methodological approach, if possible and economically feasible, until other medical diagnostic practices materialize in register reports. Nonetheless, an expert review should identify further conditions at risk of not being reported. In the author's opinion, a mixed approach might be a lesser evil and complementary for the conditions that are known not to be properly RR reported, although it may be argued that this is done at the cost of losing full uniformity of methodology. On the other hand, severe conditions such as cancers, heart and most lung diseases, mental illness and others are for the most part recommended used based on RR definitions as long, when detailed diagnosis is needed, as many patients most likely cannot identify the correct diagnosis.

Response rates – and the impact on samples

The knowledge of differences in survey response rates across conditions could indirectly give an *indication* of the reliability of the conditions' estimates. However, no gold standard exists for good response rates, although an acceptable response rate as a rule of thumb is usually set at around at least 50 per cent [178, 179]. In theory, a response rate of 20 per cent may give just as reliable estimates as a response rate of 90 per cent if the samples are equally distributed across the "true" disease population.

Nevertheless, it cannot be ruled out that conditions with relatively low survey response rates have different and possibly lower HRQoL than those of the estimated results in paper 3, as the strongest patients responded to the survey. Several survey response rates differ widely across conditions (see appendix A for an overview of all survey response rates across conditions). This might indicate that low response rates are correlated with higher disease severities, such as, for example, mental conditions that have low HRQoL. However, only 27 out of 199 conditions have lower than 50 per cent response rates, most of which are mental conditions. In general, most conditions have relatively high response rates, indicating above average reliability in regard to the rule of thumb of a 50 per cent response rate. Yet, some response rates also indicate possible issues with mental conditions within surveys and that the HRQoL thereof might be even lower. This also applies to several other disease areas with low response rates.

As the survey response rate is only an indication of possible non-response bias, further studies are needed on specific possible indications as no real evidence exists in regard to implications between the size of the response rate and non-response bias. Ideally, each response (disease) population of the sample should be compared with the full populations' socio-.economic and other variables in order to assess the reliability fully. However, this comprehensive work is beyond the scope of the present thesis and has therefore not been done.

5.2. INTRODUCTION TO USING THE EQ-5D PREFERENCE SCORES WITHIN CUA, STRENGTHS AND LIMITATIONS

The main advantage of an "off-the-shelf" catalogue of preference scores for health states is its uniform methodology ensuring standardized estimates free of different biases across studies – besides being easily and cost-effectively accessible. As such, any advantages as well as disadvantages in terms of validity and reliability derived from the study design apply to all estimates and conditions, and will also apply to any future CEA/CUA and research studies based on these estimates. In addition, the catalogue eliminates the need to search for and combine different estimates from different studies and different, possibly not comparable study methods.

Overall, the EQ-5D-3L preference catalogue sheds light on which patients and conditions fare worst, how severe each conditions is, and what the potential health gains are if the illness is eradicated or its start delayed. The improves existing catalogues in several areas: new regression modelling which respects the characteristics of EQ-5D-3L, different specifications and models for analysts to choose from for health economic evaluation, and finally the use of ICD-10-based doctor-reported conditions, added variables of health risks, BMI, and quality social network in regard to loneliness constituting several new opportunities and methodological contributions to the research field. However, there is one limitation in particular:

> "If the goal is to estimate the impact of treatment intervention on *disease severity* within specific study populations, primary data collection of preference-based HRQoL scores in a randomized controlled trial (RCT) may be more appropriate. On the other hand, the estimates in this catalogue may be preferable for simulating the impact of postponing, preventing or curing chronic conditions. This is particularly true of measuring the effectiveness of interventions in the community where nationally representative estimates are important or where primary data collection may not be feasible." Sullivan et al. [49]

Modelling disease severity of special interest could constitute a problem as the register definitions do not have any clinical differentiated disease severities defined. In addition, many RCTs target specific disease populations, for example GOLD classification 1–4 of COPD, which is why the estimates of the catalogue may not be appropriate as the study population of the current study is defined as a nationally representative sample of chronic conditions, not specific subgroups thereof. However, if the relevant conditioning variables are in one of the four regression models which characterize the disease population of interest, then the analyst can condition on them and get different estimates of the effects similar to the specific disease population using the ALDVMM. When the covariates are set to different values, they would output different marginal effects unlike the linear regression for which the marginal effect will be the same regardless of the group you are looking at. Naturally, this approach assumes that the effect is the same as clinical defined groups based on the conditioning variables. Future research could investigate this assumption further. Moreover, other solutions using the different components of the regression model exist for modelling disease severity using the catalogue as described later. Finally, several other useful possibilities exist, including "simulating the impact of postponing, preventing or curing chronic conditions".

Existing literature has already described modelling within health economic evaluation in detail, and therefore the following descriptions of how to model and use the estimates are not designed as a replacement for the existing literature, but as a supplement that is also partly inspired by referenced studies [41, 42, 49, 50].

Material provided for CUA – and comments on modelling for future users

For complex, non-linear modelling, Excel and Stata .ster files containing full parameter estimates and covariance matrices of regression models 1-4 will be provided and should be used by experienced health economist modellers and statisticians. Please bear in mind that present author is not among this group of people; nevertheless, the following illustrations are intended as an introduction and may still provide useful information and inspiration for future modellers.

The parameter estimates allow the computation of the effects of different chronic conditions (singly or jointly) on EQ-5D-3L. The covariance matrix of the estimated parameters is required by analysts to undertake Probabilistic Sensitivity Analysis (PSA) (current version may be provided to the ph.d committee on request). The effects in complex models, i.e. models with comorbidities and/or use of additional covariates, should be predicted with programming in Excel or Stata based on the formula for the EQ-5D prediction provided on page 739 in reference [163].

In the future - when final validated - the Excel and stata .ster files will most likely be published on the http://www.dchi.aau.dk/forskning/web-ressources/ website along with an interactive online calculator. This work is currently still in progress. The calculator will expectedly be based on the formula for the EQ-5D prediction

provided in reference as mentioned [163]; it will enable the modeller to get an estimate of the specific health status needed from each of the four regression models.

Up until now, EQ-5D preferences catalogues have usually been modelled *additive* [41–43, 49]. That is, the change in EQ-5D-3L of developing two chronic conditions simultaneously is assumed to be the sum of developing each of the two chronic conditions in isolation. For additive or single condition modelling and comparisons, the regression based disutility's provided within paper 3 may be sufficient. Also, an example of an additive model is provided in appendix B). Yet, multimorbidity and complex modelling of several covariates is in reality properly not linear, why additive models most likely are wrong reflections of disease burden.

This issue has been discussed in the literature [46, 180–189] and has been shown that in general the estimated change in EQ-5D-3L when using the separate estimates additively is too large. One of the reasons might be that the two diseases might share some common effects and by adding them up there is double counting. Thus, for years, researches have sought methods to handle and incorporate comorbidity or "joint health states" in models (for example additive, multiplicative, best-of-pair, worst-of-pair, minimum and adjusted decrement estimator methods have been proposed) [181, 186]. The non-linear and different properties of the ALDVMM along with the study-data containing the 199 chronic conditions within a single study provides new powerful possibilities for more precisely identifying and estimating joint health states uniquely contrary other single or even other multi condition studies as they do not comprise the same number of conditions.

Modelling impact/cure for an explicit condition

The marginal disutility regression estimates in paper 3 represent the average across the population of each individual's marginal decrement in EQ-5D-3L preference scores for each condition after controlling for co-morbidity, gender, age and so forth, depending on the regression model of choice. In addition to the previous example, a cure for a condition is thus equivalent to the marginal disutility of the regression estimates. A simple model of a cure for ulcers, for example, may be modelled as an decrease in the EQ-5D preference score of -0.0289 (based on regression model 2 of paper 3), and standard errors can be used to calculate 95% confidence intervals for use in the probabilistic sensitivity analysis [49]. However, for more complex models with for example more comorbidities, the modeller will need use the excel or Stata .ster files later provided on the webpage, which has all parameter estimates and the full variance covariace matrix for proper sensitivity analysis.

Modelling an average population with one given condition – baseline

On the other hand, the unadjusted EQ-5D mean scores reflect not only the chronic condition, but also the impact of co-morbidities, age, gender and other characteristics of the Danish disease population. The unadjusted EQ-5D preference mean score may be used for modelling a baseline for the average disease population. For example, a baseline score for an average population with ulcers can be modelled as 0.707 (=the unadjusted utility), and the impact of a cure for the disease population can be calculated as 0.7359=0.707+0.0289. However, please bear in mind that using the margin dy/dx function in Stata, the combined disutilities of the ALDVMM components are actual calculated as marginal effect for the whole population (all n of sample) with ulcer rather than the marginal effect for the smaller population with ulcers. This technical detail is little known although the margins command is widely used. However, the results are still comparable to other estimates based on the margins command commonly used.

Modelling different severities of conditions

Previous preference catalogues have been criticized for missing preference values by level of condition severity, which in particular constitutes a problem as many treatments or interventions mainly move patients from moderate to mild health states [48, 50]. However, when primary data collection is not feasible, and even though the register-based definitions or EQ-5D estimates do not incorporate specific clinical disease severity, the estimates may be used to model severity if some assumptions are made. For modelling different severities of the average disease population baseline, the different EQ-5D estimates of the 25^{th} or 75^{th} percentile of the condition of interest can be used to represent either a worse or better health condition (can be found in appendix to paper 2). Naturally, these estimates also reflect the differences in co-morbidities, age, gender and other (also unobserved) characteristics associated with differences in severity of the disease population. A similar approach can be taken using the adjusted regression estimates when modelling disease severity by assuming, for example, that a 50 per cent increase or decrease in marginal decrement reflects the impact of severe or mild disease on, for example, rheumatoid arthritis [49]. A mild case of rheumatoid arthritis could be modelled as 0.725 (=0.710 + 0.5*0.0297), and a severe case could be modelled as 0.696 (=0.710 - 0.5*0.0297). 0.710 is the unadjusted mean of rheumatoid arthritis, and 0.0297 the adjusted disutility of ALDVMM model 2– all based on the estimates of paper 3.

However, a third and new possibility for modelling disease severity exists in the form of the ALDVMM regression model as it provides marginal estimates of the identified components for every chronic condition. This can be done as each component represents different areas, with low/high scores, of the EQ-5D distribution. Thus, each component can be seen as a different severity of a

condition, with the lowest numbered components as the most severe cases on average – although a statistically identified severity can still not be compared with a clinically defined disease severity. Nevertheless, this approach is at least as feasible as the previously mentioned ways to adjust severity using the catalogue, and perhaps better, as the components are not arbitrary cut points, but identified from the distribution of the actual EQ-5D preference scores. For example, modelling not a cure but an impact in moving from a severe to a milder health state of, for example, COPD or sclerosis could be done by subtracting the estimates of, for example, component 1 from component 2. A move from a moderate health state to the mildest health state of a condition could be modelled using the marginal disutility of component 2 subtracted from the estimate of component 3, if the model has three components. The difference is the potential gain of the move from one health state to another. The baseline disease population could be modelled as the unadjusted average of the condition of interest subtracted from the difference in marginal disutility of the chosen components. However, as always, the choice should be clear and thoroughly discussed using appropriate sensitivity analysis. In summary, the different identified ALDVMM components may provide new possibilities and level of detail to previous catalogues that can be used for modelling different disease severities or subgroups.

The four different regression model/estimates – and recommendations for use

An essential improvement to existing catalogues is the extra added regression models and estimates. The different models and disutility estimates are made to accommodate different needs within health economic evaluation. For example, NICE recommends/requires adjustment of gender and age (similar to regression model 2 of the current study), while existing catalogues by Sullivan et al. adjust for co-morbidities, gender, age, education, income, ethnicity, socio-economic status and family size (equal to regression model 3 of the current study). Moreover, some health economics evaluators may prefer an estimate only adjusted for co-morbidities as their first choice when modelling (equal to regression model 1 of the current study). Finally, new analytic possibilities arise from adding new variables to model 3 such as health risks, BMI, stress and social network as these variables – as seen earlier – have a major impact on the HRQoL and could thus be important for future studies and modelling (equal to regression model 4 of the current study). Notably, the choice of regression model estimates should be thoroughly discussed and documented by future users, and it is recommended that estimates of other models are presented and used for sensitivity analysis in order to avoid the risk of choosing a model that suits the desired results best.

Thus, the different models reflect different health economics modelling needs – and the regression model and coherent estimates should therefore be used according to specific needs and possible government or other requirements for the study of interest. However, multiple estimates increase the risk of confusion and possible

"bias selection" in order to provide the most positive results of interest. Consequently, the minimum requirement should be to:

- clearly present which regression model and coherent estimates are used,
- clearly argue for the choice in a transparent manner,
- presenting a sensitivity analysis using the other regression estimates.

Further requirements and guidelines for regression modelling can be found in references [190–192]. Although the choice of regression model/estimates depends on the study of interest and government regulations, a few recommendations are provided in regard to present thesis:

The estimates of *regression model 1* should be chosen when the population of interest needs to correspond to the national disease population only adjusted for co-morbidities – as the estimates reflect the disutility of the chronic condition of interest including effects of age, gender and all other characteristics of the disease population. It is expected to be of interest for the majority of health economics evaluations.

The estimates of *regression model 2* should be chosen when the population of interest needs to correspond to the national disease population *adjusted* for co-morbidities, gender and age, but all other disease population characteristics still need to be comprised in estimates (such as BMI, income, education and other covariates). This might be of importance when analysing and comparing different conditions adjusted for these basic covariates in order to compare and identify which condition has the most health gain, or when it is necessary to identify the "clean" effect from one condition of interest "free" (adjusted) of only gender and age differences, for example, an RCT. This might also be of interest when comparing an RCT population of interest to a national population. Finally, model 2 (or 1) should be used when the study is aimed at NICE or other government agencies with similar requirements or just in general recommended in order to keep the models simple and adjusted only for the most basic variables in order to include and reflect most characteristics of the chronic condition of interest.

The estimates of *regression model 3* should be chosen when the population of interest needs to correspond to the national disease population *adjusted* for co-morbidities, gender, age, family equalized income, education, ethnicity, partnership and children living in household, but all other disease population characteristics still need to be comprised in estimates. As such, this model is suitable when the purpose is to analyse different impacts of classic socio-economic equality, or model different patient populations of interest according to specific socio-demographic distributions of interest.

The estimates of *regression model 4* should be chosen when the population of interest needs to correspond to the national disease population *adjusted* for the variables of model 3 and social network, stress, BMI, smoking, exercise, and alcohol and fruit intake. This model is suitable when the purpose is to analyse different impacts of classic socio-economic equality, and other aspects of health inequality such as social health risks, network and stress. These estimates enable further modelling in order to create different patient populations of interest based on known disease populations within RCT or other studies.

Mixing estimates of the different models within the same study, HTA or similar, is not recommended as it is not consistent. Finally, please note that regression models and estimates may change in final versions of paper 3, and, therefore, should only these final estimates be used in future CUA.

5.3. IMPLICATIONS OF USE IN PRIORITY SETTING, STRENGTHS AND LIMITATIONS

Honeycutt et al. pinpoint eight different potential uses of burden of illness measures in general (see Figure 5-1) [54]. In the following, this framework is used for placing the potentials of the current thesis in a broader policy context. The grey highlighted text in Figure 5-1 indicates topics in which the thesis is expected to be of use to the author.

1. **Setting Priorities for Resource Allocation**
    a. Health services
    b. Prevention
    c. Research
2. **Monitoring and Evaluating Policy**
    a. Cost-effectiveness analysis (CEA) of individual interventions
    b. Monitoring performance of health systems
3. **Monitoring Population Health**
4. **Identifying Disparities**
5. **Understanding the Burden of Morbidity and Assessing Morbidity/Mortality Trade-offs**
6. **Budgeting for Future Health Expenditures**
7. **Improving Measurement of National Income and Inflation**
8. **Identifying Opportunities for International Development**
    - Technology transfer to low-income nations
    - Neglected diseases
    - Reductions in burden may increase human capital formation

Figure 5-1. Potential uses of burden of illness measures. Source: adapted from Honeycutt, 2011 [54].

Setting priorities for resource allocation

In general, burden of illness measures can play a role in *setting priorities for resource allocation* solely by identifying diseases with considerable needs for medical care and preventable risk factors [54] (although it can be debated whether resource allocation can be properly done without CEA/CUA). For this, epidemiological prevalence measures of size and HRQoL burden measures such as the QALY and EQ-5D of the current thesis can play an important role. Moreover, the burden estimates of the current thesis can in combination complement each other and give birth to policy setting dilemmas. For instance, it may not be the most prevalent conditions or the conditions with the highest mortality that have the worst HRQoL severity. Or it might be that the most prevalent and severe conditions are neglected and need decision-makers' attention. For example, one of the most important insights from the GBD studies in 2004 was that depression was the third leading cause of burden worldwide based on DALYs, even though it did not rank among the 20 most mortal conditions measured in life years lost [193].

Similar dilemmas derived from *estimates* of the current thesis could potentially generate new policies and priorities (obviously, this also requires solid public debate and presentation of results to health care professionals, decision makers and politicians besides a publication of a single thesis). For instance, cancers (combined) and several heart conditions have relatively high prevalence and mortality, but for many of these conditions, the HRQoL is relatively high too[10]. At the same time, these conditions already have high priority among politicians, and within research and the health-care system, including relatively high financing. This issue, "the injunction to rescue identifiable individuals in immediate peril, regardless of the cost", is discussed in the literature under the name "rules of rescue" [194].

On the other hand, there are several other conditions, such as musculoskeletal and psychiatric conditions, that have both relatively high prevalence and low HRQoL and at the same time do not have the same priority setting or financing. The comprehensive number of conditions and results from the current thesis puts this dilemma into a new perspective. Yet, future studies should generate QALYs and thus include mortality in the equation. Nevertheless, the results might still outline a historical division between easily understandable, often physical and highly mortal conditions that currently have high political priority, and more complex, often less mortal conditions with relatively lower HRQoL. In essence, this is also a classical dilemma and a trade-off between mortality and QoL.

[10] Notably, there may be an impact of mortality on HRQoL as the survivors might be the strongest patients. Thus, future conclusions should be based on studies using the QALY so that mortality is included too.

Whereas the priority setting for health-care services may frequently focus on treatments for particular illnesses, the priority setting for *prevention* frequently focuses on specific, modifiable risk factors such as those used within the present study described in chapter 3, Table 3-2. In contrast to existing EQ-5D catalogues, the current study includes risk factors, but also stress, social networks and other variables essential for providing estimates for use in prevention and calculating the potentials of prevention. However, ideally, risk factors should methodically be linked to specific conditions and their consequences using, for example, attributable fractions or similar methods when the estimate of risk factors etc. is needed for a specific disease [54, 195]. However, this is not done, despite the fact that the catalogue provides estimates of risk factors adjusted for all chronic conditions that can be used for modelling prevention potentials. Yet, it cannot be ruled out – as we have not done any regression interactions due to the large number of conditions/variables – that estimates from interactions between risk factors etc. and conditions vary across conditions. Future studies should explore this, but also conduct analysis of which conditions/co-morbidities may cluster and provide interactions that influence results. Nevertheless, there is a trade-off between complexity and keeping it simple; and increased complexity does not necessarily provide more useful estimates.

Although understanding the burdens of illness, including the size and severity, is an inescapable first step in generating priorities, "these measures alone do seldom provide enough information to make informed resource allocation decisions" [54]. For example, they say little about whether there are currently obtainable interventions that can treat the illness, the cost of interventions, or how much of the burden can be reduced by the interventions. Therefore, it is crucial to understand that burden estimates in general, and those of the present thesis in particular, are an initial starting point, and thus are means for others to generate actual health economic evaluations for decision-making:

Monitoring and evaluating policy and monitoring population health

Burden of illness measures can also be used to monitor and evaluate health policies. For instance, combining burden measures with information about interventions, costs and outcomes may be used to evaluate interventions in CEA [54]. Specifically, the preference scores can be used in CEA/CUA as described in the previous section.

Changes in burden of diseases measures at the aggregate level and/or for specific illnesses may be tracked over time to identify whether the general performance of the health-care system is improving or adjustments to policies are required. For this, the framework of definitions for the 199 chronic conditions can be used in combination with any burden measure of interest collected at the micro level. In particular, the framework could be used for monitoring the prevalence/incidence

rates or EQ-5D of the 199 chronic conditions over time, and thus whether these burdens are decreasing. Moreover, the prevalence rates (and the register framework in a Danish setting could be used for identifying individual costs linked to diseases) of the current thesis can be used for generating cost-of-illness (COI) estimates in future studies to inform decision-making and monitor health-care expenditures of chronic conditions as mentioned earlier. Combined, the estimates, prevalence, EQ-5D/QALY and costs could be used for discovering whether changes in health-care spending correspond to changes in burden estimates over time.

More specifically in a Danish context, burden of disease estimates could also be used for monitoring the results of national and local health agreements and policies. Since the structural reforms in 2007, local regional governments and municipalities have been obligated to generate agreements on interventions to improve public health [196, 197]. However, the indicators used for monitoring the health policies are mostly organizationally minded and less patient and health related:

- Prevention of hospitalizations among the elderly
- Acute medical short-term admissions
- Acute admissions among adult COPD patients
- Acute admissions among adult citizens with type 2 diabetes
- Acute somatic readmissions within 30 days
- Acute somatic readmissions within 30 days among adult COPD patients
- Acute somatic readmissions within 30 days among adult citizens with type 2 diabetes
- Acute psychiatric short-term admissions
- Acute psychiatric readmissions within 30 days
- Finishing days (somatic)
- Finishing days (psychiatry)
- Waiting for general rehabilitation
- Rehabilitation plans for general rehabilitation

Source: Danish National Board of Health and Health Data Agency, 2015 [198, 199].

There might be several reasons why these measures are not directly health-related burden measures. First, it may be difficult (or risky politically) to generate policies that can actually improve health burdens significantly in the eyes of the public at an aggregate level. Secondly, and more importantly in this regard, the policies may not in their *current* form be able to actually generate measurable improvements on health, thus leaving less meaning and incitement measuring policies at an aggregate level. In addition, it may be technically difficult to *link* numerous and often not evidence-based policy initiatives to changes in burden measures. However, this is an opportunity to generate operational measurable policies aimed at improving QoL; for example, political goals regarding health status or prevalence could be set

based on specific burden measures known to be sensitive to the interventions of the policy. Thus, there is the potential for implementing burden measures such as the EQ-5D, QALY, SF-12 and prevalence or other burden measures – such as those of the National Health Profiles described in chapter 3.

Identifying disparities

Many health policies aim to decrease health inequalities, including the above-mentioned health agreements[11]. Health equity, not to be confused with equal access and use of health services [11], has also been a research concern for years with numerous, comprehensive publications including several initiated by the government [18, 19, 60, 96, 156, 157, 159, 200–203].

Inequality is important within health economic evaluation because the potentials for health gains are often found within the disparities. Epidemiological inequalities have for a long time focused on life expectancy, mortality, prevalence and incidence etc., as well as inequalities within socio-demographic variables such as gender, age, ethnicity, education, income, geography, work status, family status etc. in relation to different burden outcomes such as HRQoL, stress, QWB, morbidity and health risk, among others. For example, self-rated health is valued as being relatively less good for single, early-retired people and others outside the labour force, and people with only a primary education, but similar tendencies exist within other outcomes including diseases, lost life-years and mortality etc. [19, 156]. However, estimates have not been accessible within existing EQ-5D preference score catalogues for health economic evaluation.

Thus, the present catalogue of EQ-5D preference scores generates new possibilities for modelling health inequalities within health economic evaluation, as described in more detail in the previous section, as the catalogue provides numerous new variables used for identifying health inequalities. As all the variables, including conditions, socio-demographics, health risk etc., are estimated within a single regression analysis, it is possible, in contrast to most other studies, to compare the size/strength of HRQoL differences and identify the highest disparities and inequalities across variables. Besides confirming the patterns of classic socio-

[11] "Order on health coordination and health agreements. Order No. 1569 of 12.16.2013 Applicable. §4. The Regional Council and local councils in the region enter into a health agreement for the discharge of duties in the health field. The health agreement must include both citizens with somatic and mental illnesses. PCS. 4. The health agreement shall, as appropriate, be based on the following cross-cutting themes: division of work and cooperation, including knowledge sharing and health counselling between sectors, coordination of capacity, the involvement of patients and families, **health equity**, documentation, research, quality and patient safety." Source: https://www.retsinformation.dk/forms/R0710.aspx?id=160777

demographic determinants, stress and loneliness in the current EQ-5D preference catalogue are two major determinants of HRQoL that might impact on future research and priority settings. In the author's opinion, the main contribution to existing research is the precision of comparability from estimates due to the uniform single-study-based methodology and comprehensive number of variables and conditions.

Moreover, paper 2 provides some information about health inequalities among the 199 chronic conditions based on cross-sectional analysis using a few socio-demographic variables besides prevalence estimates.

Understanding the burden of morbidity and assessing morbidity/mortality trade-offs

HRQoL measures may provide perspective on the trade-off between mortality and morbidity in policy settings by quantifying the role of morbidity [54]. For instance, in line with the example of depression within the GBD studies, there are examples of disease burdens that have relatively low mortality and severe HRQoL, which is naturally not discovered using mortality measures alone. The current catalogue of EQ-5D scores will be of assistance in quantifying the role of morbidity in health economic evaluation from more ICD-10-based conditions than in any other previous studies.

Budgeting for future health expenditures and neglected diseases

Economic burden measures such as COI or health-care service expenditures, specific treatments, medication or others of interest may be combined with epidemiological and public health trends in risk factors and socio-demographics. This may prove useful in predicting future health-care expenditures, including disparities within subgroups, at a national and local level [54]. However, the use of the current thesis is limited in terms of providing these economic estimates, although the framework of definitions for chronic conditions provides a basis for future studies generating COI estimates and estimating costs of chronic conditions using registers. Moreover, the National Health Profiles may provide estimates of trends for health risks and socio-demographics for the prediction of future health trends.

Finally, the catalogue of both EQ-5D and prevalence scores could be used for identifying neglected diseases – to some extent – by comparing the prevalence and HRQoL of current catalogues in combination as mentioned earlier. Neglected diseases could have low prevalence and low HRQoL, for example fibromyalgia, or even high prevalence and low HRQoL, such as several mental and musculoskeletal diseases not commonly prioritized as mentioned. Within resource allocation, there may be a tendency to focus on common illnesses with high prevalence and severe burdens; yet, this is an oversimplification as rare illnesses may collectively have

large burdens [54]. Critical use of the burden estimates in the present thesis should account for this so that rare diseases still receive resources.

However, an example of a neglected and common disease not captured within the register framework is ME/CFS in paper 4. As such, a crucial limitation of the framework of definitions could be the clinical culture, disease complexity and disagreements in aetiology and treatment preventing even common diseases from being reported (and treated) in registers [204].

5.4. FUTURE RESEARCH EXPLORED AND SUMMARIZED

Although suggestions for future research are continuously being noted, suggestions are summarized and some new ones are described here.

Exploring multi-morbidity of utility estimates

Though chronic conditions or long-term disorders are a major challenge for health care, "health systems are largely configured for individual diseases rather than multimorbidity… Better understanding of the epidemiology of multi-morbidity is necessary to develop interventions to prevent it, reduce its burden, and align health-care services more closely with patients' needs" [205, 206]. Multi-morbidity is also important as it puts a large burden on patients; but also since it reflects the reality of actual disease better than a single-view focus on disease whenever it is within research, hospitals or the health-care system in general.

Little is known about estimating or combining utilities for comorbid (or 'joint') health states when the only data the analyst has access to the utilities of each condition from separate studies. Several joint health state prediction models have been suggested (for example, additive, multiplicative, best-of-pair, worst-of-pair, minimum and adjusted decrement estimator methods as mentioned earlier etc.), but no general consensus has been reached [181, 186]. From a statistical point of view, the multiplicative model recommended by Ara and Brazier [186] may be the best practical approximation, but not necessarily in line with actual data and reality. However, paper 3 of present study is not linear, nor multiplicative, but actually incorporates multi-comorbidity in the utility estimates in better alignment with the data due to the unique properties of the ALDVMM regression model; in addition, the enhanced possibilities in regard to multi-morbidity is facilitated by the fact that as much as 199 conditions and subgroups are uniquely included within a single study. These improvements are significant as the results may provide a solution to issues of multi-morbidity.

Future studies should explore the properties of comorbidities and their utility estimates of paper 3, and, if possible, identify systemic patterns or different clusters of conditions and their relationships to a get better understanding hereof. If possible, they could suggest new and differentiated joint health state prediction models based on the findings (may for example be done by simulation based on the earlier mentioned Stata .ster file). The inclusion of all the conditions within a single study gives future studies a unique opportunity as many other "joint health states" studies are based on a limited number of conditions often from different studies. Although it may be difficult to identify general patterns given the large number of combinations of the different sets of comorbidities, future studies might identify some patterns within large clusters of for example chosen common diseases.

The register-based definitions of 199 chronic conditions

In general, the register-based framework of 199 conditions can be applied onto an unlimited number of outcomes, including costs, HRQoL and others also mentioned below, as long as the conditions of interest are linked at the micro level to the outcome of interest. Moreover, the framework of definitions can be used by everybody, including health-care administrators within hospitals and governments, and insurance registers, as long as the data contain the ICD-10 codes, medication ATC codes and other variables defined within the framework. Therefore, there is an almost unlimited number of future studies derived from the framework.

Future studies should further validate the register-based definitions based on, for example, comparisons with medical records. This is crucial since there are known diagnostic issues and controversies affected diagnostics such as, for example, shown within depression or similar conditions such as ME/CFS as mentioned [204, 207].

Future studies could also explore clusters of conditions using the registers, in order to support for example prevalence and incidence studies in regards to the importance of multi-comorbidity as mentioned.

Finally, future studies could explore the possibilities and implications of combining SR and RR methods for identifying chronic conditions. For which conditions could this be beneficial or otherwise? Some register conditions are known for not providing valid prevalence estimates, such as diseases like cataracts and tinnitus, for example, which is why there may be some precision to gain for some conditions. The current study has already shown that the two often competing methods may complement each other in certain areas, and that RR-based conditions also have limitations like SR, although the use of SR conditions depends on the purpose of the study and the need for precise diagnosis etc.

Monitoring trends in disease prevalence and incidence

Future studies could explore *trends* in prevalence – and incidence – rather than the single-point estimate of prevalence provided here, using the register-based framework of 199 chronic conditions. However, these studies should also take the growing number of diagnoses ("diagnostic inflation") into account and explore whether this is a result of more disease or changes in diagnostic practices or the increasing productivity of country-specific diagnostics, as well, in contrast, possible under diagnosis of some diseases as debated [208–210]. Although the debate has been especially strong within the psychiatric field, an initial test of nationwide somatic ICD-10 codes also revealed an increasing number of somatic conditions by year.

Identifying and monitoring trends in costs and COI

Moreover, future studies could use the register-based framework for identifying the costs of health-care treatments and services by chronic condition.

Future studies could use the prevalence rates of the current study for generating COI [21]. Another approach for generating COI estimates is to use the register framework to identify individual costs and link them to diseases at the micro level within national registers or insurance data that contain the same data and variables defined within the framework. This will most likely enhance precision, but may require some work.

Monitoring trends within costs and COI for chronic conditions could inform decision-makers, but also be of interest to researchers making recommendations and forecasting health-care expenditures or disease burdens.

Generating ratios of costs and EQ-5D/QALY – cost pr. perfect health or QALY

One simple use of the framework and estimates is dividing the mean cost of a condition over (preferable adjusted) EQ-5D essentially generating mean cost pr. perfect health of each condition for comparison. This would improve the information of traditional COI - expectably easier to generate than CEA as many health care professionals have information on costs – although not a CEA. Future studies could generate national ratios, as well is this might be done by health-care professionals in local municipalities where cost, but not HRQoL, are usually known. However, it is recommended that future studies also explore implications of use for decision makers as it is not a traditional CEA comparing alternatives and interventions; and that were applicable, QALYs are used instead of preference scores. This approach might provide a simply, quick overview with more information for policy and decision makers than common practice.

Improvement of EQ-5D HRQoL estimates and QALY

Future studies could explore the effects of regression interactions between risk factors etc. and conditions, as well as interaction with clusters of multi-morbidities that may influence results. Previous reference studies have recommended that complex epidemiological methods are used for linking conditions and health risk etc. [54] This could also be done in cohesion with reviewing the framework of definitions. There may be different pathways and methods both overlapping and accounting for this.

Future studies could also generate a catalogue of QALYs for the 199 conditions, thereby including mortality in the equation of the burden estimate.

Finally, future studies might incorporate multiple imputations and chained equations along with the ALDVMM as this cannot be done at the present time. However, the gains thereof may be limited, although it cannot be ruled out that it may have a smaller impact on regression model 4, that is the model with the most missing.

5.5. EPILOG

The thesis provides a standardized, transparent framework of definitions and estimates for use in future health economic evaluation and other research. It embraces new complex methods and data, setting new boundaries for use in for example regards to the comprehensive number of medical defined chronic conditions, as well as the new regression methods expanding the boundaries of classic additive and multiplicative regression models including handling comorbidities within complex econometric modelling. However, the methods and estimates are not without limitations as thoroughly discussed; thus future research will most likely explore and address these in more detail by for example validating the medical defined register based definitions as suggested. Moreover, most work from the thesis lies ahead, as the thesis merely provide a framework and estimates for future use in several research areas; and as seen in previous sections, the possible use is wide reaching far beyond this thesis.

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APPENDICES

Appendix A. Conditions and survey responses

Table 5-1. The 20 conditions with the lowest survey response

Cond. no.	Condition	ICD-10 code	n invited survey	Survey response, per cent
196	Mental retardation	F70–F79	244	18.9
176	Dementia [c]	F00, G30, F01, F02.0, F03.9, G31.8B, G31.8E, G31.9, G31.0B	876	23.9
197	Disorders of psychological development	F80–F89	164	28.0
177	Organic, including symptomatic, mental disorders	F04–F09	506	34.6
1	Chronic viral hepatitis	B18	49	34.7
180	Schizophrenia [c]	F20	413	35.4
2	Human immunodeficiency virus [HIV] disease	B20–24	39	35.9
178	Mental and behavioural disorders due to use of alcohol	F10	1,068	37.0
181	Schizotypal and delusional disorders	F21–F29	555	38.0
184	Mood (affective) disorders	F340, F348–F349, F38–F39	118	38.1
198	Hyperkinetic disorders (ADHD) [c]	F90	518	38.2
188	Post-traumatic stress disorder	F431	199	38.7
199	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	F91–F99	637	39.9
179	Mental and behavioural disorders due to psychoactive substance use	F11–F19	940	40.4
182	Bipolar affective disorder [c]	F30–F31	322	42.5
67	Blindness and partial sight	H54	138	42.8
36	Systemic atrophies primarily affecting the central nervous system and other degenerative diseases	G10–G14, G30–G32	171	44.4
193	Emotionally unstable personality disorder	F603	257	44.7
52	Cerebral palsy and other paralytic syndromes	G80–G83	265	45.3
189	Reactions to severe stress and adjustment disorders	F432–F439	868	45.4

[c] Complex defined condition. All estimates are non-weighted.

Table 5-2. The 20 conditions with the highest survey response

Cond. no.	Condition	ICD-10 code	Invited survey, n	Survey response, per cent
164	Fibromyalgia	M797	45	82.2
138	Systemic lupus erythematosus	M32	57	80.7
77	Other specified disorders of ear	H938	480	75.6
71	Other diseases of the inner ear	H83	1,254	73.3
69	Otosclerosis	H80	230	73.0
8	Malignant melanoma of skin	C43	318	72.3
14	Malignant neoplasm of prostate	C61	643	71.4
129	Acquired deformities of fingers and toes	M20	892	71.4
167	Adult osteomalacia and other disorders of bone density and structure	M83, M85, except M833	852	71.4
125	Polyarthrosis [Arthrosis]	M15	246	71.1
102	Varicose veins of lower extremities	I83	718	71.0
76	Tinnitus	H931	1,134	70.4
10	Malignant neoplasm of breast	C50	1,015	70.0
19	*In situ* neoplasms	D00–D09	426	69.7
132	Internal derangement of knee	M230, M231, M233, M235, M236, M238	189	69.3
110	Bronchiectasis	J47	78	69.2
113	Inguinal hernia	K40	714	69.0
73	Other hearing loss and other disorders of ear, not elsewhere classified	H910, H912, H913, H918, H930, H932, H933	176	68.2
40	Demyelinating diseases of the central nervous system	G36–G37	91	68.1
159	Other enthesopathies	M77	235	68.1

All estimates are non-weighted.

Table 5-3. All 199 conditions and survey response

Cond. no.	Condition	ICD-10 code	n	Per cent of sample	Per cent *Survey response*	Per cent *Non-response*
	B – Viral hepatitis and Human immunodeficiency virus [HIV] disease	**B18, B20–B24**	**88**	0.2	**35.2**	**64.8**
1	Chronic viral hepatitis	B18	49	0.1	34.7	65.3
2	Human immunodeficiency virus [HIV] disease	B20–24	39	0.1	35.9	64.1
	C – Malignant neoplasms	**C00–C99; D32–D33; D35.2–D35.4; D42–D44**	**4,695**	8.2	**65.4**	**34.6**
3	Malignant neoplasms of other and unspecified localizations	C00–C14; C30–C33; C37–C42; C45–C49; C69; C73–74; C754–C759	421	0.7	61.0	39.0
4	Malignant neoplasms of digestive organs	C15–C17; C22–C26	111	0.2	61.3	38.7
5	Malignant neoplasm of colon	C18	421	0.7	65.6	34.4
6	Malignant neoplasms of rectosigmoid junction, rectum, anus and anal canal	C19–C21	290	0.5	63.4	36.6
7	Malignant neoplasm of bronchus and lung	C34	305	0.5	54.4	45.6
8	Malignant melanoma of skin	C43	318	0.6	72.3	27.7
9	Other malignant neoplasms of skin	C44	219	0.4	60.3	39.7
10	Malignant neoplasm of breast	C50	1,015	1.8	70.0	30.0
11	Malignant neoplasms of female genital organs	C51–C52; C56–C58	183	0.3	62.8	37.2
12	Malignant neoplasm of cervix uteri, corpus uteri and parts unspecified	C53–C55	234	0.4	63.7	36.3
13	Malignant tumour of the male genitalia	C60, C62–C63	88	0.2	63.6	36.4
14	Malignant neoplasm of prostate	C61	643	1.1	71.4	28.6
15	Malignant neoplasms of urinary tract	C64–C68	272	0.5	64.0	36.0
16	Brain cancer [c]	C71, C75.1–C75.3, D33.0–D33.2, D35.2–D35.4, D43.0–D43.2, D44.3–D44.5 (brain). C70, D32, D42 (brain membrane). C72, D33.3–D33.9, D43.3–D43.9 (cranial nerve, spinal cord)	335	0.6	63.9	36.1
17	Malignant neoplasms of ill-defined, secondary and unspecified sites, and of independent (primary) multiple sites	C76–C80, C97	580	1.0	58.1	41.9
18	Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	C81–C96	359	0.6	61.8	38.2
	D – *In situ*, benign and neoplasms of uncertain or unknown behaviour and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	**D00–D09; D55–D59; D60–D67; D80–D89**	**2,252**	4.0	**58.3**	**41.7**
19	*In situ* neoplasms	D00–D09	426	0.7	69.7	30.3
20	Haemolytic anaemias	D55–D59	38	0.1	52.6	47.4
21	Aplastic and other anaemias	D60–D63	343	0.6	51.0	49.0
22	Other anaemias	D64	964	1.7	51.0	49.0
23	Coagulation defects, purpura and other haemorrhagic conditions	D65–D69	358	0.6	63.7	36.3
24	Other diseases of blood and blood-forming organs	D70–D77	140	0.2	59.3	40.7
25	Certain disorders involving the immune mechanism	D80–D89	165	0.3	65.5	34.5
	E – Endocrine, nutritional and metabolic diseases	**E00–E14; E20–E29; E31–35; E70–E78; E84–E85; E88–E89**	19,758	34.7	65.2	34.8
26	Diseases of the thyroid [c]	E00–E04, E06, E07	2,422	4.3	64.9	35.1

27	Thyrotoxicosis [c]	E05	1,216	2.1	61.0	39.0
28	Diabetes type 1 [c]	E10	456	0.8	63.2	36.8
29	Diabetes type 2 [c]	E11	5,641	9.9	60.4	39.6
30	Diabetes others [c]	E12–E14	27	0.0	66.7	33.3
31	Disorders of other endocrine glands	E20–E35, except E30	423	0.7	61.0	39.0
32	Metabolic disorders	E70–E77; E79–E83; E85, E88–E89	386	0.7	60.1	39.9
33	Disturbances in lipoprotein circulation and other lipids [c]	E78	15,083	26.5	66.7	33.3
34	Cystic fibrosis [c]	E84	8	0.0	50.0	50.0
	G – Diseases of the nervous system	**G00–G14; G20–G32; G35–G37; G40–47; G50–64; G70–73; G80–G83; G90–G99**	**10,900**	19.1	**61.4**	**38.6**
35	Inflammatory diseases of the central nervous system	G00–G09	135	0.2	51.1	48.9
36	Systemic atrophies primarily affecting the central nervous system and other degenerative diseases	G10–G14, G30–G32	171	0.3	44.4	55.6
37	Parkinson's disease [c]	G20, G21, G22, F02.3	1,268	2.2	50.6	49.4
38	Extrapyramidal and movement disorders	G23–G26	172	0.3	64.5	35.5
39	Sclerosis	G35	257	0.5	63.0	37.0
40	Demyelinating diseases of the central nervous system	G36–G37	91	0.2	68.1	31.9
41	Epilepsy [c]	G40–G41	1,272	2.2	48.5	51.5
42	Migraine [c]	G43	3,007	5.3	67.9	32.1
43	Other headache syndromes	G44	253	0.4	56.9	43.1
44	Transient cerebral ischaemic attacks and related syndromes and vascular syndromes of brain in cerebrovascular diseases	G45–G46	1,019	1.8	63.5	36.5
45	Sleep disorders	G47	710	1.2	65.5	34.5
46	Disorders of trigeminal nerve and facial nerve disorders	G50–G51	337	0.6	63.2	36.8
47	Disorders of other cranial nerves, cranial nerve disorders in diseases classified elsewhere, nerve root and plexus disorders and nerve root and plexus compressions in diseases classified elsewhere	G52–G55	182	0.3	62.6	37.4
48	Mononeuropathies of upper limbs	G56	2,270	4.0	66.3	33.7
49	Mononeuropathies of lower limbs, other mononeuropathies and mononeuropathy in diseases classified elsewhere	G57–G59	319	0.6	62.7	37.3
50	Polyneuropathies and other disorders of the peripheral nervous system	G60–G64	501	0.9	61.5	38.5
51	Diseases of myoneural junction and muscle	G70–G73	92	0.2	60.9	39.1
52	Cerebral palsy and other paralytic syndromes	G80–G83	265	0.5	45.3	54.7
53	Other disorders of the nervous system	G90–G99	479	0.8	56.2	43.8
	H – Diseases of the eye and adnexa and diseases of the ear and mastoid process	**H02–H06; H17–H18; H25–H28; H31–H32; H34–H36; H40–55; H57; H80,H810; H93, H90–H93**	**10,393**	18.2	**63.3**	**36.7**
54	Disorders of eyelid, lacrimal system and orbit	H02–H06	390	0.7	67.7	32.3
55	Corneal scars and opacities	H17	68	0.1	52.9	47.1
56	Other disorders of cornea	H18	214	0.4	63.1	36.9
57	Diseases of the eye lens (cataracts)	H25–H28	1,559	2.7	62.3	37.7
58	Disorders of the choroid and retina	H31–H32	60	0.1	61.7	38.3
59	Retinal vascular occlusions	H34	212	0.4	58.0	42.0
60	Other retinal disorders	H35	1,416	2.5	56.1	43.9
61	Retinal disorders in diseases classified elsewhere	H36	313	0.5	57.8	42.2
62	Glaucoma [c]	H40–H42	1,536	2.7	58.4	41.6
63	Disorders of the vitreous body and globe	H43–H45	219	0.4	62.6	37.4

64	Disorders of optic nerve and visual pathways	H46–H48	128	0.2	58.6	41.4
65	Disorders of ocular muscles, binocular movement, accommodation and refraction	H49–H52	466	0.8	63.5	36.5
66	Visual disturbances	H53	651	1.1	57.5	42.5
67	Blindness and partial sight	H54	138	0.2	42.8	57.2
68	Nystagmus and other irregular eye movements and other disorders of eye and adnexa	H55, H57	130	0.2	62.3	37.7
69	Otosclerosis	H80	230	0.4	73.0	27.0
70	Ménière's disease [c]	H810	212	0.4	67.9	32.1
71	Other diseases of the inner ear	H83	1,254	2.2	73.3	26.7
72	Conductive and sensorineural hearing loss	H90	945	1.7	62.9	37.1
73	Other hearing loss and other disorders of ear, not elsewhere classified	H910, H912, H913, H918, H930, H932, H933	176	0.3	68.2	31.8
74	Presbycusis (age-related hearing loss)	H911	2,573	4.5	61.3	38.7
75	Hearing loss, unspecified	H919	1,781	3.1	67.2	32.8
76	Tinnitus	H931	1,134	2.0	70.4	29.6
77	Other specified disorders of ear	H938	480	0.8	75.6	24.4
	I – Diseases of the circulatory system	**I05–I06; I10–28; I30–33;I36–141; I44–I52; I60–I88; I90–I94; I96–I99**	**27,842**	48.9	**63.4**	**36.6**
78	Aortic and mitral valve disease [c]	I05, I06, I34, I35	699	1.2	63.9	36.1
79	Hypertensive diseases [c]	I10–I15	23,826	41.8	63.4	36.6
80	Heart failure [c]	I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9	688	1.2	55.7	44.3
80.5	Ischaemic heart diseases	I20–I25	3,286	5.8	64.1	35.9
81	Angina pectoris	I20	1,926	3.4	67.6	32.4
82	Acute myocardial infarction and subsequent myocardial infarction	I21–I22	856	1.5	59.6	40.4
83	AMI complex/other	I23–I24	45	0.1	66.7	33.3
84	Chronic ischaemic heart disease	I25	2,056	3.6	63.0	37.0
85	Pulmonary heart disease and diseases of pulmonary circulation	I26–I28	292	0.5	56.2	43.8
86	Acute pericarditis	I30	96	0.2	56.3	43.8
87	Other forms of heart disease	I31–I43, except I34–I35 and I42	152	0.3	56.6	43.4
88	Atrioventricular and left bundle branch block	I44	341	0.6	56.3	43.7
89	Other conduction disorders	I45–46	235	0.4	57.9	42.1
90	Paroxysmal tachycardia	I47	970	1.7	64.0	36.0
91	Atrial fibrillation and flutter	I48	2,582	4.5	60.3	39.7
92	Other cardiac arrhythmias	I49	669	1.2	65.8	34.2
93	Complications and ill-defined descriptions of heart disease and other heart disorders in diseases classified elsewhere	I51–52	85	0.1	63.5	36.5
94	Stroke	I60, I61,I63–I64, Z501 (rehabilitation)	1,577	2.8	54.5	45.5
95	Cerebrovascular diseases	I62, I65–I68	329	0.6	56.5	43.5
96	Sequelae of cerebrovascular disease	I69	1,126	2.0	48.7	51.3
97	Atherosclerosis	I70	774	1.4	54.5	45.5
98	Aortic aneurysm and aortic dissection	I71	197	0.3	62.4	37.6
99	Diseases of arteries, arterioles and capillaries	I72, I74, I77–I79	227	0.4	63.9	36.1
100	Other peripheral vascular diseases	I73	670	1.2	60.4	39.6
101	Phlebitis, thrombosis of the portal vein and others	I80–I82	766	1.3	59.5	40.5
102	Varicose veins of lower extremities	I83	718	1.3	71.0	29.0
103	Haemorrhoids [c]	I84	1,628	2.9	66.5	33.5
104	Oesophageal varices (chronic), varicose veins of other sites, other disorders of veins, non-specific lymphadenitis, other non-infective disorders of	I85–I99 , except I89 and I95	258	0.5	58.1	41.9

	lymphatic vessels and lymph nodes and other and unspecified disorders of the circulatory system					
	J – Diseases of the respiratory system	**J30.1; J40–J47; J60–J84; J95, J97–J99**	**23,217**	40.7	**62.5**	**37.5**
105	Respiratory allergy [c]	J30, except J30.0	15,689	27.5	64.1	35.9
106A	Chronic lower respiratory diseases [c]	J40–J43, J47	8,402	14.7	62.1	37.9
106	Bronchitis, not specified as acute or chronic, simple and mucopurulent chronic bronchitis and unspecified chronic bronchitis	J40–J42	332	0.6	59.0	41.0
107	Emphysema	J43	143	0.3	55.9	44.1
108	Chronic obstructive lung disease (COPD) [c]	J44, J96, J13–J18	4,303	7.6	59.1	40.9
109	Asthma, status asthmaticus [c]	J45–J46	7,134	12.5	59.5	40.5
110	Bronchiectasis	J47	78	0.1	69.2	30.8
111	Other diseases of the respiratory system	J60–J84; J95, J97–J99	413	0.7	54.5	45.5
	K – Diseases of the digestive system	**K25–K27; K40, K43, K50–52; K58–K59; K71–K77; K86–K87**	**7,793**	13.7	**59.2**	**40.8**
112	Ulcers [c]	K25–K27	4,113	7.2	56.9	43.1
113	Inguinal hernia	K40	714	1.3	69.0	31.0
114	Ventral hernia	K43	219	0.4	61.6	38.4
115	Crohn's diease	K50	335	0.6	63.9	36.1
116	Ulcerative colitis	K51	583	1.0	65.7	34.3
117	Other non-infective gastroenteritis and colitis	K52	417	0.7	53.2	46.8
118	Irritable bowel syndrome (IBS)	K58	924	1.6	63.2	36.8
119	Other functional intestinal disorders	K59	1,020	1.8	55.2	44.8
120	Diseases of liver, biliary tract and pancreas	K71–K77; K86–K87	495	0.9	56.6	43.4
	L – Diseases of the skin and subcutaneous tissue	**L40**	1,152	2.0	64.8	35.2
121	Psoriasis [c]	L40	1,152	2.0	64.8	35.2
	M – Diseases of the musculoskeletal system and connective tissue	**M01–M25: M30–M36; M40–M54; M60.1–M99**	**21,155**	37.1	**64.2**	**35.8**
122	Infectious arthropathies	M01–M03	166	0.3	61.4	38.6
122A	Inflammatory polyarthropathies and ankylosing spondylitis [c]	M05–M14, M45	3,265	5.7	63.8	36.2
123	Rheumatoid arthritis [c]	M05, M06, M07.1, M07.2, M07.3, M08, M09	1,426	2.5	66.8	33.2
124	Inflammatory polyarthropathies – except rheumatoid arthritis [c]	M074–M079, M10–M14, M45	2,402	4.2	63.7	36.3
125	Polyarthrosis [arthrosis]	M15	246	0.4	71.1	28.9
126	Coxarthrosis [arthrosis of hip]	M16	2,316	4.1	65.8	34.2
127	Gonarthrosis [arthrosis of knee]	M17	4,021	7.1	66.9	33.1
128	Arthrosis of first carpometacarpal joint and other arthrosis	M18–M19	1,616	2.8	65.8	34.2
129	Acquired deformities of fingers and toes	M20	892	1.6	71.4	28.6
130	Other acquired deformities of limbs	M21	432	0.8	66.4	33.6
131	Disorders of patella (knee cap)	M22	864	1.5	58.1	41.9
132	Internal derangement of knee	M230, M231, M233, M235, M236, M238	189	0.3	69.3	30.7
133	Derangement of meniscus due to old tear or injury	M232	762	1.3	67.2	32.8
134	Internal derangement of knee, unspecified	M239	592	1.0	65.5	34.5
135	Other specific joint derangements	M24, except M240–M241	100	0.2	58.0	42.0
136	Other joint disorders, not elsewhere classified	M25	311	0.5	62.7	37.3
137	Systemic connective tissue disorders	M30–M36, except M32,M34	755	1.3	64.0	36.0
138	Systemic lupus erythematosus	M32	57	0.1	80.7	19.3
139	Dermatopolymyositis	M33	25	0.0	60.0	40.0
140	Systemic sclerosis	M34	20	0.0	65.0	35.0
141	Kyphosis, lordosis	M40	86	0.2	64.0	36.0

142	Scoliosis	M41	300	0.5	56.7	43.3
143	Spinal osteochondrosis	M42	130	0.2	53.1	46.9
144	Other deforming dorsopathies	M43	444	0.8	64.4	35.6
145	Other inflammatory spondylopathies	M46	117	0.2	53.8	46.2
146	Spondylosis	M47	1,522	2.7	63.1	36.9
147	Other spondylopathies and spondylopathies in diseases classified elsewhere	M48, M49	762	1.3	65.7	34.3
148	Cervical disc disorders	M50	207	0.4	64.3	35.7
149	Other intervertebral disc disorders	M51	779	1.4	66.1	33.9
150	Other dorsopathies, not elsewhere classified	M53	146	0.3	64.4	35.6
151	Dorsalgia	M54	1,060	1.9	60.4	39.6
152	Soft tissue disorders	M60–M63, except M60.0	256	0.4	54.7	45.3
153	Synovitis and tenosynovitis	M65	407	0.7	67.3	32.7
154	Disorders of synovium and tendon	M66–68	386	0.7	62.4	37.6
155	Soft tissue disorders related to use, overuse and pressure	M70	278	0.5	65.1	34.9
156	Fibroblastic disorders	M72	792	1.4	67.4	32.6
157	Shoulder lesions	M75	1,393	2.4	66.3	33.7
158	Enthesopathies of lower limbs, excluding foot	M76	180	0.3	62.2	37.8
159	Other enthesopathies	M77	235	0.4	68.1	31.9
160	Rheumatism, unspecified	M790	177	0.3	66.1	33.9
161	Myalgia	M791	197	0.3	55.8	44.2
162	Other soft tissue disorders, not elsewhere classified	M792– M794; M798–M799	133	0.2	66.9	33.1
163	Other soft tissue disorders, not elsewhere classified: pain in limbs	M796	419	0.7	62.1	37.9
164	Fibromyalgia	M797	45	0.1	82.2	17.8
165	Osteoporosis [c]	M80–M81	3,060	5.4	62.8	37.2
166	Osteoporosis in diseases classified elsewhere	M82	30	0.1	56.7	43.3
167	Adult osteomalacia and other disorders of bone density and structure	M83,M85, except M833	852	1.5	71.4	28.6
168	Disorders of continuity of bone	M84	53	0.1	54.7	45.3
169	Other osteopathies	M86–M90	293	0.5	57.0	43.0
170	Other disorders of the musculoskeletal system and connective tissue	M95–M99	403	0.7	63.8	36.2
	N – Diseases of the genitourinary system	**N18**	425	0.7	56.0	44.0
171	Chronic renal failure (CRF) [c]	N18	425	0.7	56.0	44.0
	Q – Congenital malformations, deformations and chromosomal abnormalities	**Q00–Q56; Q60–Q99**	**2,212**	3.9	**61.1**	**38.9**
172	Congenital malformations: of the nervous, circulatory, respiratory system; cleft palate and cleft lip, urinary tract, bones and muscles, other and chromosomal abnormalities not elsewhere classified	Q00–Q07; Q20–Q37; Q60–Q99	1,452	2.5	61.0	39.0
173	Congenital malformations of eye, ear, face and neck	Q10–Q18	330	0.6	62.4	37.6
174	Other congenital malformations of the digestive system	Q38–Q45	142	0.2	57.0	43.0
175	Congenital malformations of the sexual organs	Q50–Q56	333	0.6	60.4	39.6
	F – Mental and behavioural disorders	**F00–99**	**12,769**	22.4	**49.8**	**50.2**
176	Dementia [c]	F00, G30, F01, F02.0, F03.9, G31.8B, G31.8E, G31.9, G31.0B	876	1.5	23.9	76.1
177	Organic, including symptomatic, mental disorders	F04–F09	506	0.9	34.6	65.4
178	Mental and behavioural disorders due to use of alcohol	F10	1,068	1.9	37.0	63.0
179	Mental and behavioural disorders due to psychoactive substance use	F11–F19	940	1.6	40.4	59.6
180	Schizophrenia [c]	F20	413	0.7	35.4	64.6
181	Schizotypal and delusional disorders	F21–F29.	555	1.0	38.0	62.0

182	Bipolar affective disorder [c]	F30–F31	322	0.6	42.5	57.5
183	Depression [c]	F32, F33, F34.1, F06.32	9,096	16.0	52.8	47.2
184	Mood (affective) disorders	F340, F348–F349, F38–F39	118	0.2	38.1	61.9
185	Phobic anxiety disorders	F40	167	0.3	47.9	52.1
186	Other anxiety disorders	F41	485	0.9	48.9	51.1
187	Obsessive compulsive disorder (OCD) [c]	F42	150	0.3	47.3	52.7
188	Post-traumatic stress disorder	F431	199	0.3	38.7	61.3
189	Reactions to severe stress and adjustment disorders	F432–F439	868	1.5	45.4	54.6
190	Dissociative (conversion) disorders, somatoform disorders and other neurotic disorders	F44, F45, F48	332	0.6	53.9	46.1
191	Eating disorders	F50	89	0.2	60.7	39.3
192	Behavioural syndromes associated with physiological disturbances and physical factors	F51–F59	98	0.2	59.2	40.8
193	Emotionally unstable personality disorder	F603	257	0.5	44.7	55.3
194	Specific personality disorders	F602, F604–F609	772	1.4	47.9	52.1
195	Disorders of adult personality and behaviour	F61–F69	276	0.5	46.0	54.0
196	Mental retardation	F70–F79	244	0.4	18.9	81.1
197	Disorders of psychological development	F80–F89	164	0.3	28.0	72.0
198	Hyperkinetic disorders (ADHD) [c]	F90	518	0.9	38.2	61.8
199	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	F91–F99	637	1.1	39.9	60.1
				0.0		
	Having no chronic conditions		32,818	57.6	56.1	43.9
	Having 1 chronic condition		18,551	32.6	62.2	37.8
	Co-morbidity: 2 conditions		12,224	21.5	64.0	36.0
	Co-morbidity: 3 conditions		9,181	16.1	63.9	36.1
	Co-morbidity: 4 conditions		6,435	11.3	63.7	36.3
	Co-morbidity: 5 conditions		4,581	8.0	63.5	36.5
	Co-morbidity: 6 conditions		3,286	5.8	61.0	39.0
	Co-morbidity: 7 or more conditions		7,535	13.2	58.0	42.0
	One or more chronic condition(s)		61,793	108.4	62.5	37.5
	Samples:			0.0		
	Sample: NIPH 2010		25,000	43.9	60.7	39.3
	Sample: North Denmark Region 2010		35,700	62.6	65.5	34.5
	Sample: North Denmark Region 2013		33,911	59.5	54.4	45.6
	Gender:			0.0		
	– Women		47,188	82.8	63.7	36.3
	– Men		47,406	83.2	56.8	43.2
	Age:			0.0		
	16–24 years		12,533	22.0	48.5	51.5
	24–34 years		10,338	18.1	52.8	47.2
	35–44 years		14,843	26.0	58.1	41.9
	45–54 years		17,238	30.2	62.8	37.2
	55–64 years		16,830	29.5	68.0	32.0
	65–74 years		12,962	22.7	70.5	29.5
	75+ years		9,850	17.3	55.2	44.8
	Education:					
	– No education/training		28,527	50.1	53.3	46.7
	– Students or in training		7,698	13.5	65.3	34.7
	– Short education		39,438	69.2	63.3	36.7
	– Middle education – bachelor etc.		11,639	20.4	72.4	27.6
	– High education – master degree etc.		4,362	7.7	70.4	29.6
	– Missing.		2,947	5.2	10.1	89.9
	Ethnicity:(no non-response ethnicity of sample 3)					
	– Danish		74,153	130.1	73.6	26.4
	– Other Western		2,178	3.8	53.7	46.3
	– Non-Western		2,800	4.9	44.4	55.6

Family Equalized Income:				
< 100,000 kr. (< £10,000)	6,171	10.8	40.7	59.3
100,000–199,999	41,162	72.2	55.7	44.3
200,000–299,999 kr. *(£20,000–£29,999)*	33,578	58.9	65.5	34.5
300,000–399,999 kr. *(£30,000–£39,999)*	10,079	17.7	69.9	30.1
400,000+ kr. *(£40,000+)*	3,570	6.3	69.9	30.1
Partnership:				
– Having a partner	44,184	77.5	64.9	35.1
– Not married /not in a relationship	50,371	88.4	56.2	43.8
Children at home:				
– No children at home	64,007	112.3	65.9	34.1
– Having children living at home under 15	16,023	28.1	88.1	11.9
– Missing	14,581	25.6	4.8	95.2

[c] = complex defined conditions. All estimates are non-weighted. Conditions marked ‘A, overlap with other conditions and are thus not counted twice [140].

Appendix B. Example of additive modelling of an intervention for CUA

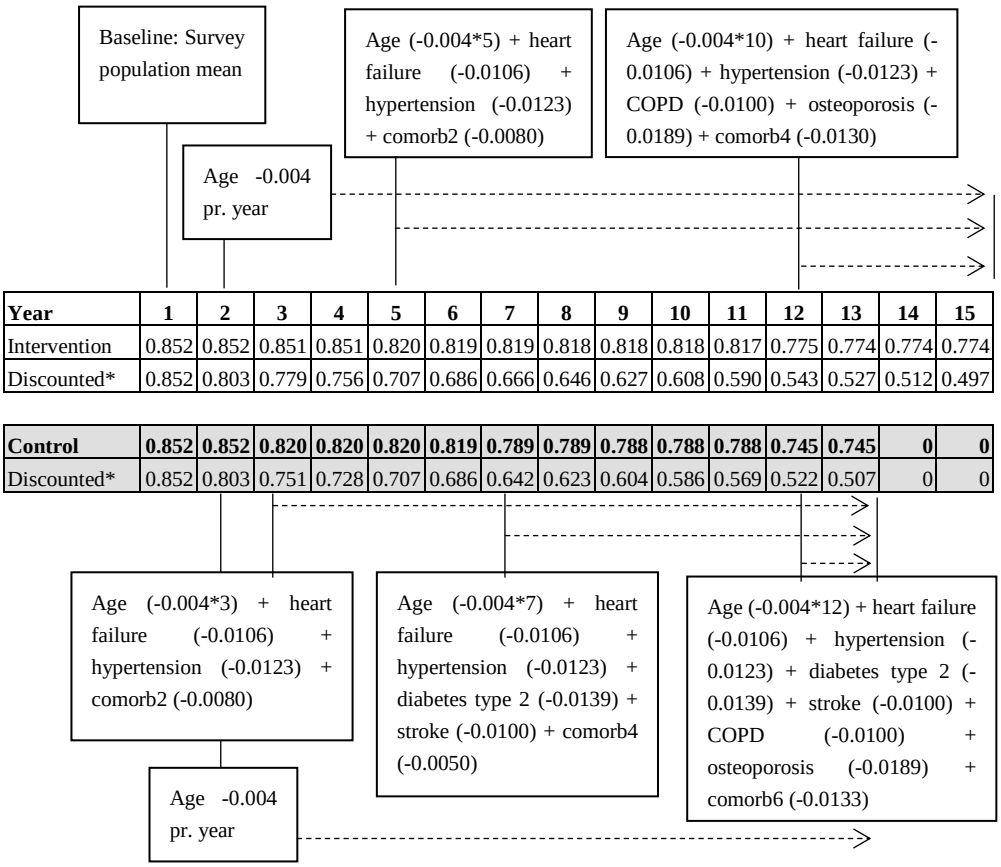
The following example is a more simple, traditional *additive* modelling and is not recommended for use in future CUA, as the ALDVMM is able to model non-linear relationships reflecting the relationships of covariates more precisely thus unfolding the potentials of the results better. However, the additive example is included to give an understanding of the use of the estimates usually done and directly related to the EQ-5D estimates provided within paper 3 - and for comparative reasons with Sulivan et al. and others using additive regression modelling [41–43, 49].

Notably: experienced modellers should use the "Excel" and Stata ".ster" files with full parameter estimates and covariance matrices of regression model 1-4 to model non-linear models of specific needs for use in CUA rather than additive linear models.

Additive modelling an intervention to prevent/postpone heart failure

The aim in this example is to model the effectiveness in QALYs of an intervention (for example, doctor-prescribed exercise or new medicine) that postpones the occurrence and development of heart failure and co-morbidities compared to an identical control group. In the control group, the patients develop heart failure and hypertension in year 3, diabetes type 2 and stroke in year 7, COPD and osteoporosis in year 12, and die in year 14. The intervention delays and changes the progression as the heart failure – and hypertension – is first added after five years, and only COPD and osteoporosis are added after 12 years. The first modelling step is to determine the baseline. In our example, the population mean has been used, but you could also argue that if/as the population is at high risk, the 25 unadjusted percentiles of the population mean could have been used [43]. Although this value is arbitrary, it may be assumed that it reflects the lower health-related quality of life of the heart failure population or other chronic conditions. Another solution to setting the baseline, however, could be to use the unadjusted preference scores of the co-morbidity variable similar to the condition of interest; for example, if the condition of interest has on average 3.7 co-morbidities, the baseline could be equal to a co-morbidity of 4 or 0.789. Moreover, all conditions are mapped based on the adjusted regression estimates seen in paper 3, regression model 2. Notably, which regression model estimates are used depends on the purpose of the study and variables needed.

In the example, the QALY of the intervention group is 12.2 (9.8 discounted) and that of the control group 10.4 (8.6 discounted), or 1.8 (1.2 discounted) QALYs gained by the intervention.



Year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Intervention	0.852	0.852	0.851	0.851	0.820	0.819	0.819	0.818	0.818	0.818	0.817	0.775	0.774	0.774	0.774
Discounted*	0.852	0.803	0.779	0.756	0.707	0.686	0.666	0.646	0.627	0.608	0.590	0.543	0.527	0.512	0.497

Control	**0.852**	**0.852**	**0.820**	**0.820**	**0.820**	**0.819**	**0.789**	**0.789**	**0.788**	**0.788**	**0.788**	**0.745**	**0.745**	**0**	**0**
Discounted*	0.852	0.803	0.751	0.728	0.707	0.686	0.642	0.623	0.604	0.586	0.569	0.522	0.507	0	0

Figure 5-2. Example of modelling a treatment and control with heart failure.

* Discounted at 3 per cent per year (value/1.03^t), where t = number of years. Arrow indicates from when and how long time that each disutility from condition, age or other is included and counted in.

Table 5-4. Extracts of the EQ-5D regression estimates of paper 3 - used in the example

			Unadjusted EQ-5D scores			**ALDVMM model 2: Reg. adjusted EQ-5D scores**		
			n	*Score*	*SE*	*disutility*	*sig*	*SE*
183	Depression [c]	F32, F33, F34.1, F06.32	4,619	0.686	0.0043	-0.0723	*	0.0027
29	Diabetes type 2 [c]	E11	3,253	0.752	0.0048	-0.0139	*	0.0029
108	Chronic obstructive lung disease (COPD) [c]	J44, J96, J13–J18	2,435	0.733	0.0060	-0.0100	*	0.0033
112	Ulcers [c]	K25–K27	2,245	0.707	0.0061	-0.0289	*	0.0033
79	Hypertensive diseases [c]	I10–I15	14,504	0.776	0.0021	-0.0123	*	0.0019
80	Heart failure [c]	I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9	369	0.678	0.0151	-0.0106		0.0087
94	Stroke	I60, I61,I63–I64, Z501 (rehabilitation)	812	0.707	0.0093	-0.0166	*	0.0064
165	Osteoporosis [c]	M80–M81	1,817	0.710	0.0066	-0.0189	*	0.0038
123	Rheumatoid arthritis [c]	M05, M06, M07.1, M07.2, M07.3, M08, M09	919	0.710	0.0088	-0.0297	*	0.0051
	Age pr. year		N/a	N/a	N/a	-0.0004		0.0003
	Having 1 chronic condition		11,303	0.882	0.0016	-	-	-
	Co-morbidity: 2 conditions		7,657	0.848	0.0023	-0.0080	*	0.0030
	Co-morbidity: 3 conditions		5,698	0.820	0.0030	-0.0050	****	0.0039
	Co-morbidity: 4 conditions		3,959	0.789	0.0035	-0.0130	*	0.0050
	Co-morbidity: 5 conditions		2,805	0.754	0.0047	-0.0113	***	0.0066
	Co-morbidity: 6 conditions		1,915	0.732	0.0061	-0.0133	***	0.0079
	Co-morbidity: 7 or more conditions		4,143	0.641	0.0048	-0.0191	**	0.0091
	All	-	**55,616**	0.852				

***** p<0.01. ** p<0.05 *** p<0.1 ***** p<0.2.

Appendix C. Paper 1: Catalogue of 199 register-based definitions of chronic conditions

(See separate document or http://sjp.sagepub.com/content/44/5/462)

Appendix D. Paper 1B: Supplementary material: Process, content and considerations of the medical review and ratification regarding register-based definitions of chronic conditions. Supplement to: Catalogue of 199 register-based definitions of chronic conditions

(See separate document or http://sjp.sagepub.com/content/44/5/462)

Appendix E. Paper 2: Catalogue of prevalence rates and characteristics of 199 chronic conditions in a comprehensive nationwide register study

(See separate document)

Appendix F. Paper 3: A national catalogue of 199 preference-based scores for ICD-10 based chronic conditions using DK, UK and US EQ-5D tariffs

(See separate document)

Appendix G. Paper 4: The Health-Related Quality of Life for Patients with Myalgic Encephalomyelitis. Chronic Fatigue Syndrome (ME/CFS)

(See separate document or http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0132421)

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