AARHUS UNIVERSITY
HEALTH

Psychological stress and multimorbidity in general practice

PhD dissertation

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Faculty of Health

Aarhus University

2017

RESEARCH UNIT
FOR GENERAL PRACTICE
Aarhus

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Financial support:
This PhD project was supported by an unrestricted grant (grant number: R155-2012-11280) from the Lundbeck Foundation through Mental Health for Primary Care (MEPRICA) and by the Central Denmark Region Foundation for Primary Health Care Research. The Danish Health Profile 2010 was funded by the Capital Region of Denmark, Region Zealand, the Region of Southern Denmark, the Central Denmark Region, the North Denmark Region, the Danish Ministry of Interior and Health, and the Danish National Institute of Public Health at the University of Southern Denmark.

ISBN 978-87-90004-56-9.

ACKNOWLEDGEMENTS

It feels like forever since I was first introduced to the research community at the Research Unit for General Practice by Karen, my former neuroanatomy teacher, GP colleague, supervisor, and friend. Now, on the brink of submitting my PhD dissertation, which I wrote in this environment, I am very grateful to all the many people who have contributed, inspired, and supported me in achieving this goal. First of all, I would like to express my deep gratitude to my main supervisor, Mogens, for taking me under his wings from the very beginning and introducing me to the field of general practice epidemiology. Your always positive spirits, righteousness, and profound empathy for the weak patients have been inspiring. I would not have come this far without your great knowledge, enthusiasm, open-minded attitude, intellectual discussions, and kind and warm approach in every way. You have always been there and have dedicated your time to discuss my issues and concerns, big or small. You have been ambitious on my behalf, given me responsibility, put me in front, and shared your personal network with me. Yet, you have stressed the importance of maintaining the right work-life balance during my studies. You are probably the best supervisor you can get.

Going over things (once) again to ensure a deeper understanding of the data and the limitations of the applied methods and – above all – to produce high-quality research that we are proud to publish; these are codes of practice that I have learned from Morten, my co-supervisor and "statistician-in-chief". You have challenged my intellectual capacities and Stata skills, and your keen dedication to all my manuscripts, your phenomenal overview, and sparkling intellect have taken my education and research to another level, and for that I am so grateful. Thanks for all our fun talks, quirky comments, obscure literature references, and a tough morning run in Seattle.

Special and warm thanks go to you, Karen, my third supervisor, but you have just as much been a mentor through our shared professional path. You have always guided and supported me, first as a PhD student and now as a GP. Your mind-set encompasses both scientific evidence and a holistic patient-centred attitude; this has helped me remember both the patient and the GP perspective in the welter of statistical estimates.

I would also like to extend a great appreciation to the Lundbeck Foundation and the Foundation for Primary Health Care Research in the Central Denmark Region for believing in our research ideas and for funding my PhD project.

This research would not have been possible without the help from my many co-authors. You have contributed, commented, and encouraged me during the vast number of manuscript revisions, and I am truly indebted for your support.

During my PhD programme, I was lucky to visit Dimitry Davydow at the Department of Psychiatry and Behavioral Sciences at the University of Washington in Seattle. Thank you very much for your hospitality, enthusiastic support, idea sharing (including suggestions for hiking tours), and for helping me proceed with my research when things got a bit stuck.

My thanks also go to Solvej for prioritising mental health and supporting my research, to Bondo, Ovesen, and Heje for introducing me to modern general practice, and to the different GP clinics in Djursland that I have worked in, where multimorbidity and inequality in health seem to be obtrusively present in many consultations. Thank you for the clinical inspiration, which sparkled my interest in this field.

I wish to thank all my colleagues at the Research Unit for General Practice; you have helped and encouraged me a lot and, more importantly, you have contributed in making the research environment here very special. Thanks to Birthe for always providing friendly administrative support and to Lone for always finding the time to meticulously proofreading my English texts close to

deadlines. For spirit-lifting discussions, cheerful chats, laughs, and a beer now and then, I wish to thank all my office partners-in-crime and the young MEPRICAners. You have made it all so much more fun. Especially, my PhD colleagues and friends, Anette and Marie; it has been a great pleasure and privilege for me to do my PhD at the same time as you. I hope we can do more together in the future.

A warm and heartfelt gratitude goes to my family and friends: to my parents for fundamental values, for continuous and caring support, and for encouraging me to pursue my goals; to my brother, Thomas, and his family, for lots of fun, and to my parents-in-law for incredible help and support for our family, especially during the last part of my PhD. Finally, to my beloved and fantastic wife, Christina; I owe everything to you. You have made a tremendous effort to make our everyday life work in a time when we welcomed a new member of our family, built our own house, and I was writing my thesis. Thank you so much for taking care of me, for your never-ending support and love. Asta, you came out of nowhere in the middle of the PhD, and now you have really started to mark your presence; you give me so much fun and joy, and you make me remember what life is all about. We can split the computer screen between Peppa Pig and Stata anytime!

Skæring, May 2017

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PREFACE

MOTIVATION

The bio-psycho-social model is just about the same age as the author of this thesis. From the first day of my employment in a small-town general practice, my mentoring GP placed a small note with the ICD-10 criteria for depression in front of my keyboard, just to remind me that almost every aspect of disease may have a psychological dimension.

Over the years, my work experience has taught me that it can be a challenging task to maintain an overview of the treatment of complex patients. When I worked in the hospital, there was always a well-defined focus area or problem to handle, depending on the department. However, my focus is directed towards general practice, where we take pride in taking a broad perspective on the individual person's life in the treatment. In other words, we aim at taking a holistic approach, even though it can be difficult when schedules are tight, electronic medical record system are down, and multiple medical problems compete for focus. The general mental well-being is often overlooked when psychiatric disease is not present. Nevertheless, the mental well-being is essential for the patient's experience of health, motivation, and treatment.

The opportunity to explore the complex issues regarding the interplay between mental and physical health was, therefore, most welcome to me. In Denmark, unique data are available for research in this field. As I will soon be a GP, I was intrigued by the possibility to shed light on an issue that is increasingly relevant in our society; many people live with chronic diseases, and many feel mentally exhausted and stressed. Being able to place a small but important piece in the big puzzle of integrated mental and physical care was a great motivation for me. I hope that this research will contribute to directing more focus and eventually ensuring better care for the patients in general practice.

THE FOUR PAPERS OF THE THESIS

Study I:

Prior A, Fenger-Grøn M, Larsen KK, Larsen FB, Magtengaard KR, Nielsen MG, Christensen KS, Mercer SW, Vestergaard M. The association between perceived stress and mortality among people with multimorbidity: a prospective population-based cohort study. *Am J Epidemiol. 2016;184(3):199-210.*

Study II:

Prior A, Fenger-Grøn M, Davydow DS, Olsen J, Li J, Guldin M, Vestergaard M. Mental stress, multimorbidity and mortality: a population-based natural experiment using bereavement as an indicator of mental stress. *Under review, Psychological Medicine.*

Study III:

Prior A, Vestergaard M, Davydow DS, Larsen KK, Ribe AR, Fenger-Grøn M. Perceived stress, multimorbidity, and risk for hospitalizations for ambulatory care-sensitive conditions: a population-based cohort study. *Med Care. 2017;55(2):131-139.*

Study IV:

Prior A, Vestergaard M, Larsen KK, Fenger-Grøn M. Perceived stress, multimorbidity, and use of primary care health services. *Under review, British Journal of General Practice.*

OUTLINE OF THE THESIS

This thesis is based on research that was carried out during my research fellowship at the Research Unit for General Practice, Aarhus, Denmark in the *Mental Health in Primary Care* (MEPRICA) research group.

Chapter 1 of the thesis will introduce the research field of mental-physical multimorbidity in a primary care setting and describe different views on psychological stress. In **Chapter 2**, the research hypothesis and aims of the studies are stated. **Chapter 3** describes our study methodology, including the setting, data sources, study cohorts, and statistical analyses. The development process of the Danish Multimorbidity Index is also outlined here. **Chapter 4** presents the results of the studies in summary. Additional data on the cohorts and the Danish Multimorbidity Index is also supplied her. **Chapter 5** contains a general discussion of the methods used and a discussion of the validity and generalisability of the studies. In **Chapter 6**, the study results are discussed which leads on to a discussion of the underlying mechanisms. **Chapter 7** draws the main conclusion of the thesis, and **Chapter 8** describes clinical and public health implications, perspectives, and opportunities for future research.

References are placed in the end, followed by the **English and Danish summaries**, **appendices**, and finally **the four papers** of the thesis in full length.

LIST OF ABBREVIATIONS

ACSC: ambulatory care-sensitive condition

ATC: Anatomic Therapeutic Chemical classification

CI: confidence interval

CIP: cumulative incidence proportion

CPR: Civil registration number

DNHS: Danish National Health Survey

DNPR: Danish National Patient Register

GHQ: General Health Questionnaire

GP: general practitioner

HR: hazard ratio

ICD-10: International Classification of Diseases, version 10.

IRR: incidence rate ratio

NICE: National Institute for Health and Care Excellence

PSS: Perceived Stress Scale

QOF: Quality and Outcomes Framework

WHO: World Health Organization

CHAPTER 1:

INTRODUCTION

THE CHRONIC DISEASE EPIDEMIC

During the last century, several medical and societal advances have dramatically improved the health in the western world. Avoiding death from communicable diseases has increased the life expectancy for most people. However, prolonged life also means more time to accumulate chronic diseases, which are more prevalent than ever in the population.[1] Diseases are now generally diagnosed at an earlier age and in more early stages, but the consequences of chronic disease still threaten the quality of life and vitality. Improved medical treatment combined with the increased focus on risk factors for deterioration of chronic diseases, in particular life-style factors, have successfully reduced the mortality from the most common killers, such as cardiovascular diseases. However, mental health conditions have been on the rise for several years, and the World Health Organization (WHO) estimates that depression is now the leading cause of disability worldwide.[2] Hence, the consequences of mental health problems in a population with increasing numbers of physical conditions are major concerns in the healthcare systems worldwide.[3]

MULTIMORBIDITY: DEFINITIONS AND CONCEPTUALISATION

The concept of multimorbidity has gained increased attention as the demographic development and challenges of chronic disease have become more urgent for clinicians, researchers, and policy makers. Van den Akker et al. formally defines multimorbidity as "the co-occurrence of multiple chronic or acute diseases and medical conditions within one person."[4] Unlike the related concept of comorbidity, multimorbidity is not conditioned on the presence of an index disease.[4] Rather than focussing on one specific disease and its potentially course-altering comorbidities, the concept of multimorbidity embraces and articulates the full burden of disease in an individual (Figure 1).

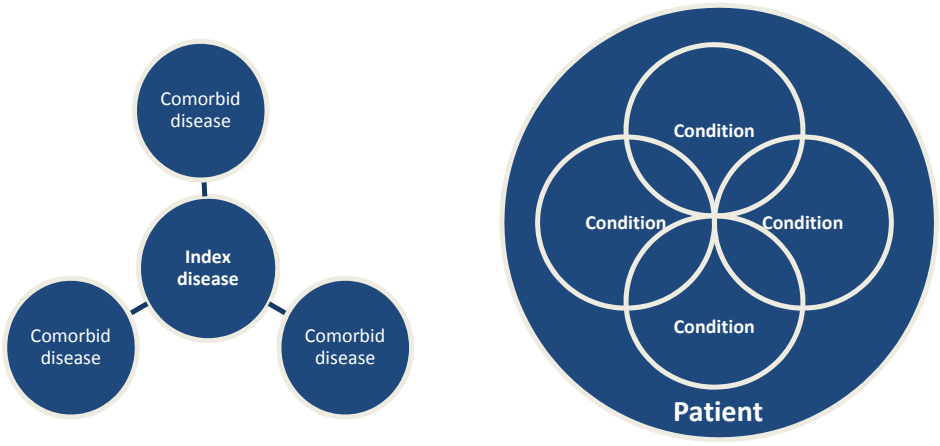

Figure 1. Comorbidity versus multimorbidity. Adapted from Boyd et al. 2010.[5]

The single-disease paradigm originates from the specialisation of medical treatment into subspecialties with a narrow focus on the pathology, treatment, and prognosis of diseases in one organ system. This tendency has been ongoing for decades, clinically, in medical education, and in research, and has led to great leaps in the treatment for the specific diseases. The problem is that an individual's health is more complex than the isolated course of single diseases. Even though vast evidence exists on comorbidities, only few studies have investigated the interaction between more than two diseases. Myriads of interactions occur between diseases, drugs, and psychological and social factors. Thus, from a generalist's perspective, the single-disease paradigm is too simple.

The multimorbidity paradigm aims to expand the narrow focus on single diseases to embrace all relevant diseases in an individual without an a priori ranking. However, this comes with several challenges: There is no full consensus on the definition of multimorbidity or on whether to include risk factors and/or symptoms in addition to diseases. The number and type of conditions to include under the concept vary, but certain diseases are recognised and recommended to be included when dealing with multimorbidity.[6] Most commonly,

multimorbidity is interpreted as "two or more" co-occurring (primarily chronic) conditions in the same person.[7,8]

Multimorbidity indices

To map and measure the concept of multimorbidity, several multimorbidity indices have been developed. They vary based on the available data sources, the scientific context, the outcomes they are validated to measure, and the target for their utilisation.[9] According to systematic reviews, studies have included from four to hundreds of diseases by using data obtained from e.g. surveys, medical records, and administrative health registers; these studies were primarily performed on background or primary care populations.[8,10,11] Due to the diversity in the multimorbidity literature, Diederichs et al. suggested a consensus list of 11 key diseases to be included in multimorbidity indices: cancer, diabetes mellitus, depression, hypertension, myocardial infarction, chronic ischemic heart disease, heart arrhythmias, heart insufficiency, stroke, COPD, and arthritis.[12]

Some indices use a disease count approach, whereas others put a statistical weight to each condition. These weights can reflect severity as measured by self-reported burden or predictive power of certain outcomes. The Charlson Comorbidity Index is the most widely used index which assigns weights to its 19 included diseases based on their ability to predict one-year mortality in inpatients.[13] Many indices, e.g. the Charlson Comorbidity Index and the Elixhauser Comorbidity Index, were developed using administrative diagnosis-based data.[14] The diseases listed in the Quality and Outcomes Framework (QOF) for practice reimbursement have also been used in research studies.[15] Pharmacy data can be used as a proxy for diseases according to the prescribed medication, and may be a powerful predictor of outcomes in primary care.[9,16,17] No generic

multimorbidity index using the comprehensive Danish health registers have been developed.

Epidemiology of multimorbidity

The Danish National Health Survey (DNHS) of 2010 reported an overall prevalence of multimorbidity of 33% based on a representative sample of the background population,[18] but estimates in different studies have shown great variation ranging from 13% to 95% (Figure 2).[8,10] The significant variation in multimorbidity prevalence is related to the choice of multimorbidity index or disease list, the data source, and the population under study.

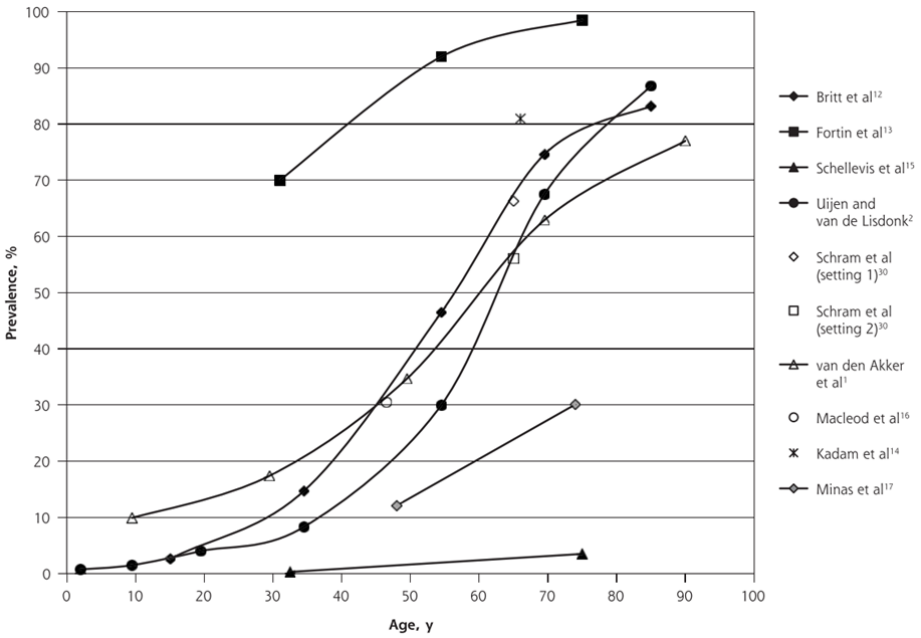

Figure 2. Prevalence of multimorbidity by age and study. From Fortin et al. 2012.[8]

The multimorbidity prevalence has been rising in primary care over the last twenty years, especially for those with severe multimorbidity, i.e. four or more

chronic diseases.[19] The strongest predictor of multimorbidity has been found to be age; it appears as an S-shaped form so the accumulation of diseases seems to level off at high ages (Figure 2).[10] Multimorbidity is thus not an issue solely for the oldest old. Barnett et al. found that the absolute number of persons with multimorbidity was higher among those under age 65 years than among those aged 65 years or more owing to the demographic composition.[20] Female sex and low socioeconomic status have also generally been associated with multimorbidity.[10]

MENTAL HEALTH AND MULTIMORBIDITY

The link between mental and physical health

The association between mental health and physical health is strong and well-documented. The WHO World Health Survey found significant co-occurrence of physical disease, depression, and anxiety across more than 40 countries.[21,22] The association with depression exists for many medical diseases, including cardiac disease, cerebrovascular and neurological diseases, diabetes and cancer.[23] In a Danish questionnaire-based health survey, all the 17 included somatic diseases were individually associated with an increased prevalence of psychiatric illness.[18] In Australian and Scotch cross-sectional studies, an approximately doubled risk of depression was found in persons with multimorbidity, depending on adjustments made, and there was a clear dose-response relation between the number of diseases and depression risk.[24,25]

Depression is the psychiatric disorder that has attracted the most attention in relation to physical illness owing to its high prevalence in the population. However, good evidence exists for severe mental illnesses as well. Patients with bipolar affective disorder and schizophrenia have been found to have a high risk of nearly all the somatic diseases listed in the Charlson Comorbidity Index, e.g.

diabetes, pulmonary disease, cardiovascular disease, liver disease, hemiplegia, and dementia.[26] In Scotch general practices, the risk of any mental condition has also been associated with the number of physical conditions; the risk rises by nearly a factor seven for those with five or more physical conditions. A total of 36% of persons with multimorbidity have mental-physical multimorbidity and most are younger than 65 years old.[20]

Risk factors and causal relations

Mental health, including childhood adversities[27] and negative life events,[28] is associated with an increased risk developing multimorbidity. Furthermore, factors associated with psychiatric illness such as unhealthy lifestyle, overweight, and socioeconomic position tend to play a role. [29,30] Evidence suggests that the relation between mental and physical conditions is bidirectional,[31] i.e. mental illness is both the cause and the consequence of physical disease. In a meta-analysis, the incidence of diabetes and depression was investigated; patients with diabetes had a 15% lifetime risk of incident depression, whereas patients with depression had a 60% risk of incident depression.[32] A similar bidirectional relation has been established for depression and myocardial infarction.[33] However, it has been debated whether the consequences of mental health are causal or due to confounding from the above mentioned factors. More confounder-robust studies on this issue are warranted.

Consequences of mental-physical multimorbidity

Poor mental health is an important prognostic factor in the course of physical disease. The presence of a psychiatric disorder generally doubles the risk of dying; this corresponds to an average of ten years of potential life lost, dependent of the type of disorder.[34] Moreover, the combination of mental and

physical health problems seems to impair the prognosis for a wide range of somatic diseases.[23] For example, the disease burden measured as the number of both physical and psychiatric diseases has been shown to have a dose-response impact on mortality in patients with diabetes.[35] Depression following myocardial infarction has been shown to be a poor prognostic sign and to increase both the risk of new cardiac events and death.[36]

A psychiatric disorder comes with a high relative risk of dying from unnatural causes, such as accidents and suicides not directly related to the physical health.[37] However, most deaths in absolute numbers are due to natural causes, i.e. related to physical diseases. For example, persons admitted with unipolar depression, bipolar affective disorder, and schizophrenia spectrum disorders have a two- to four-fold higher risk of dying from natural causes than the background population.[34]

Beside increased mortality and the impaired prognosis of physical health, the daily functioning and quality of life are heavily affected in the persons with multimorbidity.[38-40] Mental health problems in particular have a negative impact on quality of life.[41,42]

MEETING THE HEALTHCARE SYSTEM

Persons with multimorbidity have high healthcare utilisation,[43] but they face several challenges when being in contact with the healthcare system. Typical issues involve complicated and potential inappropriate patient pathways between the primary and secondary healthcare sectors, e.g. many referrals and re-referrals, conflicting treatment guidelines, polypharmacy, and other aspects of treatment burden.[3,44]

The patient and the GP

Persons with mental health problems and multimorbidity more often experience problems and hassles in health contacts. Poor communication with the general practitioner (GP), lack of information on diseases and treatment, and little time to discuss health problems are often reported by patients with multimorbidity, and these complaints are more frequent with a higher number of co-occurring diseases and symptoms of anxiety and depression.[45] Patients' self-management is challenged when treating multiple chronic conditions, and both the number of diseases and symptoms of mental health problems reduce self-management[46-49] and medical adherence.[31,50,51] In addition to the burden of mental and physical disease, persons with multimorbidity (and their relatives) have to manage the burden of treatment, i.e. demands from the healthcare system related to dosage of correct medication, coordination of appointments, and expected changes in health behaviour.[52]

Both mental health problems and multimorbidity are predictors of frequent attendance in general practice.[53-56] Nevertheless, the repeated contacts do not always guarantee an unproblematic course of treatment. A Danish survey has shown that GPs had difficulties allocating enough time to patients with multiple conditions, especially if the patient had psychiatric illness.[57] A meta-analysis suggested that mental-physical multimorbidity was associated with a high risk of poor quality of care and prescribing errors.[50] The presence of mental symptoms can overshadow physical symptoms, which may result in overlooked disease and delayed treatment.[58-60] The GP has a complex task in collecting knowledge, prioritising, and coordinating treatment.[44] The emergence of collaborative and integrated care models with the patient in the centre suggests a redefinition of the GP consultation in the direction of more focus on involving and empowering the patient to prioritise treatment; this new approach could be valuable for patients with complex mental-physical multimorbidity.[61,62]

Healthcare pathways

The risk of uncoordinated and fragmented care for multimorbid patients is high in modern healthcare for several reasons: complex disease history, reduced patient self-management, and limited GP resources. Additionally, the single disease paradigm is firmly integrated into the healthcare system, and the high degree of specialisation means that multimorbid patients must see several specialists separately. Consequently, persons with multimorbidity are more likely to be admitted to hospital for both acute and chronic conditions.[63-65] Furthermore, mental-physical multimorbidity increases the risk of less timely or inappropriate treatment pathways by a factor of two to three on recognised quality indicators, e.g. rate of rehospitalisation after hospital discharge, unplanned admissions, and emergency room contacts.[64,66]

An indicator aiming to capture primary care quality by assessing the rate of preventable hospitalisations is the concept of ambulatory care-sensitive conditions (ACSCs). By definition, these are conditions for which hospitalisations may be avoided if timely and appropriate care is given in primary care.[67] For example, if the patient with diabetes, the GP, and the community nurses cooperate well on the diabetes treatment, this should prevent hospitalisation for diabetes-related leg amputation; leg amputations are thought to be a consequence of suboptimal diabetes care. ACSC-related hospitalisations are estimated to cost 32 billion dollars annually in the US.[68] ACSC-related hospitalisation rates are increased by approximately 40% for depression, bipolar affective disorders, and schizophrenia compared to mentally healthy individuals even after adjusting for underlying physical conditions.[69,70]

PSYCHOLOGICAL STRESS

Psychiatric disorders are considered spectrum disorders. Stress symptoms are part of virtually all these conditions, but these symptoms are most directly seen in acute stress reactions, adjustment disorders, anxiety disorders, and post-traumatic stress disorders.[71] However, when the severity of symptoms is assessed to be below the specified cut-off values for diagnosis of psychiatric disease, the terminology becomes vaguer. Sub-threshold psychological stress (also referred to as mental stress, psychosocial stress, or work-related stress) is experienced by many people every day. Between 9% and 20% report high and/or frequent levels of psychological stress in questionnaire surveys, depending on the wording of the questions.[72-74]

Doctors have always listened to the patient's story and considered the psychological state of mind, which is in line with the bio-psycho-social approach to medicine,[75] but most doctors have concentrated on diagnosing and treating well-defined diseases. However, psychological stress has important consequences for the health and has also been linked to numerous diseases,[76] most importantly cardiovascular disease and metabolic syndrome,[77] in addition to increased mortality.[74,78] A report from the Danish Institute of Public Health stated that work-related stress accounted for 500,000 contacts to general practice, 30,000 hospital admissions, 1.5 million days of work absence annually, and a significant reduction in quality-adjusted life years.[72] In a study of Danish primary care, the second most common psychological reasons for requesting an encounter was acute or chronic stress, and additional psychosocial problems occurred more often when multimorbidity was present.[57,60]

The subjectivity of stress can impede the distinction between stress, other personal factors and attitudes, and health in general. Stress can also act as a marker for e.g. disease severity or burden, and causal inference is a challenging issue if no knowledge is available on confounding factors. However, if stress in

persons with multimorbidity does inflict some of the same adverse consequences as psychiatric illness, although possibly to a lesser extent, this would have considerable impact on the population level. Yet, no updated treatment or management guidelines for persons with stress exist in Danish primary care. Owing to the widespread prevalence of both psychological stress and multimorbidity in the population, more knowledge on the interplay between stress and physical disease is needed to improve treatment strategies, preventive interventions, and public health, especially in primary care.

Defining and measuring psychological stress

In colloquial language, stress is used about being busy or under a lot of strain. Some call it "the new disease". Stress is also wrongly used interchangeably with mental illness, such as depression. The different understandings of the meaning of the word and the diverse concepts of stress have interfered with the science on the issue and kept physicians from taking an active share in managing stress.[79]

The original description of the stress syndrome is dedicated to Hans Selye (1907-1982). In a 1936 paper in Nature,[80] he observed stress effect in rats and distinguish between acute and chronic stress reactions. He later categorised stress as good (eustress) and bad (distress). Since then, stress research has branched out to physiology, neurology, psychiatry, psychology, sociology and philosophy. Several stress paradigms exists. The predominant paradigms and some measures of stress that we focus on in this thesis will be described below along with a unifying theoretical framework.

External stress

In this paradigm, stress is seen as the effect of external factors, i.e. stressors, on the individual. The focus is on the stressors and their magnitude and duration. Many different types of stressors exist and range from acute stressful events (e.g. natural disaster or assault), everyday life stressors (e.g. poor working conditions or noise pollution), to long-term stress exposure (e.g. consequences of handicap or chronic disease).[79] An early exponent of this paradigm was the work in 1967 by Holmes and Rahe, who developed *The Social Readjustment Rating Scale*.[81] They listed over 40 life events, such as marriage, retirement, being fired at work, and change of residence, according to how stressful they were perceived; the most stressful life event on their list was the death of a spouse. Research on the health consequences of losing a family member has been ongoing ever since.[82,83] The adverse health effects include psychiatric disease[84,85] and excess mortality, e.g. related to suicide and cardiovascular disease.[86-88]

Much research on work-related stress also falls under this paradigm because unhealthy factors in the physical and mental working environment can be improved. External stress is also the basis of post-traumatic stress disorder, which requires an acute traumatic event of catastrophic dimensions for the diagnostic criteria to be fulfilled.[71]

Appraised stress

In this paradigm, stress is an individual state. Subjective measures aimed at stress perception are preferred as opposed to an "objective" translation of a certain event presumed to be stressful. A growing understanding has emerged of differences in the stress perception among persons experiencing the same type of event, which has demanded a new stress paradigm as conceptualised by Lazarus and Folkman.[89] The primary focus is placed on the individual's ability to cope with both positive and negative life events; the balance between strains

resulting from perceived stressful events and coping mechanisms results in the amount of stress experienced. Coping mechanisms vary between individuals and may be more or less appropriate in a given situation.

Cohen developed the *Perceived Stress Scale* (PSS) in 1983. Since then, the PSS has been a widely used instrument for measurement of stress and has been translated into 25 languages.[90] The purpose of the scale was to measure global stress appraisal unrelated to specific life events or other external stressors. The original 14-item self-reported questionnaire was reduced to a 10-item version in 1988 and further validated.[91] This version was later translated into Danish.[91,92] The items concern the appraised level of stress, coping ability, and sense of control within the last month. The PSS has been thoroughly validated in different contexts[93,94] and is associated with physiological measures of stress, e.g. salivary cortisol response and cortical reactivity.[95,96]

Based on the original studies, the PSS measures an independent stress construct, which is different from e.g. depression scales.[90,91] The scale is not a diagnostic instrument as neither the single items nor the sum score are developed to fit the criteria of any ICD-10 diagnoses. No clinical meaningful cut-off values exist, so score comparison between samples or normative data is required.

Physiological stress

Selye observed that the autonomous body response to stress exposure was uniform, regardless of the stressor.[80] The science concerned with the biological aspects of stress also constitutes a paradigm of stress. It focuses on understanding the aetiology, the causal pathways, and investigating potential stress biomarkers and pharmaceutical intervention loci. The neuroendocrine stress response is mediated by the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis with various feedback mechanisms.[97] Released adrenaline and norepinephrine are responsible for the first acute

reaction giving rise to the "fight or flight" mode; the blood pressure rises, the heart rate goes up, and glucose is released for rapid muscular activity. Cortisol levels rise and interact with numerous biological systems to withstand the pressure, but this has the opposite and detrimental effect if the stress is prolonged. An important exponent for this is the immune system and the central nervous system, which are damaged by chronic stress. The acute stress response and the chronic stress response are hence very different biologically.

The approach in this paradigm is reductive, and the original research on stress hormones and the autonomous nervous system has been expanded by gene analyses, neural mapping techniques, and subcellular pathway research. However, the biological system is very complex, and no easily obtained or clinically relevant biomarkers of stress are available.

Allostatic load theory

The causal mechanism connecting body and mind responses to stress is complex and involves an interminable number of interacting factors, e.g. lifestyle choices, personality traits, and genetic, environmental, social, and behavioural factors. To synthesise this, the conceptual framework of allostatic load theory was created by McEwen in 1993.[76] Unlike physiological homeostasis that emphasises the static balance in body systems, allostasis is a dynamic adaption over time that absorbs and reduces exposures threatening the stability of the body.[98] If the adaptation fails, e.g. due to exhaustion from frequent stress, long-term stress (or failed stress shot-down response), or inadequate response to heavy stress, the allostatic load on the body follows. It wears down the body system over time with disease as a result.[76,99,100] The individual ability to adapt is partly genetic, partly influenced by environment, personality, social context, behaviour, and lifestyle. This implies that vulnerability to stress is related to the perception of

stressors as stressful in combination with preferred coping strategies when stress is experienced (Figure 3). Developmental exposures, major life events, and adverse social conditions can affect the neuroplasticity.[101,102] The allostatic load theory is based on the physiological paradigm of stress, but research in this field also recognises that psychosocial factors may influence allostasis. This has been operationalised in allostatic load indices, which incorporate biomarkers (e.g. glycosylated haemoglobin and high-density lipoprotein), anthropometrics (e.g. waist-hip ratio and body mass index), and clinical parameters (e.g. blood pressure and heart rate).[103,104]

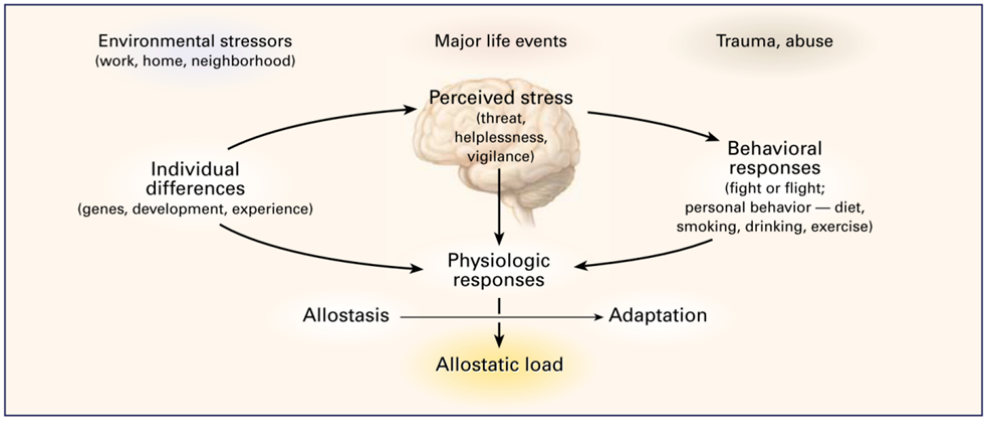

Figure 3. Concept of allostatic load. From McEwen 1998.[99]

There are reasons to believe that the causal pathways are shared for different mental burdens, whether recognised in the diagnostic system or not. The theoretical basis for the consequences of stress measured and understood outside the diagnostic system is established, and the close link to physical health makes it likely to affect the prognosis of persons with multimorbidity.

BACKGROUND AT A GLANCE

The prevalence of multiple co-existing diseases is increasing. Multimorbidity now affects one third of the population, and the multimorbidity paradigm has been put on the agenda. Mental health plays an important role for the physical health, and the consequences of psychiatric disease include impaired chronic care and excess physical morbidity and mortality. No agreement exists on the optimal multimorbidity measure, but numerous indices have been developed.

Psychological stress is common in the background population, but many symptoms fall under the threshold of psychiatric disease in the diagnostic system. Although stress is a common reason for visiting the GP, guidelines for stress management are still lacking. As for psychiatric illnesses, stress has been associated with poor outcomes of physical disease, but it has been questioned whether the association is causal. Little is known on the long-term consequences of stress and multimorbidity. Several stress paradigms exist; most are based on stress appraisal, external stressors, or physiological responses. Consequently, stress can be regarded and assessed in many different ways. Allostatic load theory aims to combine different aspects of stress in a general model of stress.

CHAPTER 2:

HYPOTHESIS AND AIMS

HYPOTHESIS

We hypothesised that high levels of psychological stress would increase the mortality, deteriorate the prognosis of physical disease, and complicate the chronic care in a primary care setting. An increasing number of physical and psychiatric conditions in the same person was expected to emphasize the effects of psychological stress on the course of chronic disease.

AIMS

The overall aim of this thesis was to determine how psychological stress may affect the prognosis of physical disease and the utilisation of primary healthcare while taking into account mental-physical multimorbidity.

Aim 1:

In study I, we aimed to investigate the association between perceived stress and all-cause mortality by accounting for multimorbidity, lifestyle, and socioeconomic factors.

Aim 2:

In study II, we aimed to explore whether external stress can affect mortality by using a natural experiment design in which bereavement served as a severe psychological stressor.

Aim 3:

In study III, we aimed to describe the association between perceived stress and potentially preventable hospitalizations by accounting for multimorbidity, predisposing conditions, and socioeconomic factors.

Aim 4:

In study IV, we aimed to investigate links between perceived stress level and primary care activities. Selected services related to mental health, chronic care management, and out-of-hours contacts were assessed.

CHAPTER 3:

MATERIALS AND METHODS

SETTING

The Danish healthcare system

Denmark is a nation of approximately 5.7 million citizens. The country is divided into five administrative regions and 98 municipalities. The regions fund the public healthcare system and have the overall responsibility for providing needed care. Denmark has a system of tax-financed universal healthcare, where the use of primary and secondary care services, including surgery and hospitalisation, are free of charge for all citizens. There is direct access to the GP, who acts as a gate-keeper to secondary care via referrals.[105] Patients must pay part of the expenses for medication and selected services, e.g. psychologists and physiotherapists after GP referral. Most Danish citizens are listed with a specific GP or GP clinic; only 2% have a special agreement with wider self-financed access to healthcare.[106] Up to 90% of the population see their GP at least once a year, and 90% of contacts are completed in primary care without further referral.

GPs are private contractors in the public health system and serve approximately 1600 patients each. The GPs are reimbursed partly on the basis of the size of the patient list (per-capita payment), partly on supplied services (fee-for-service).[105,106] In four of the five regions, GPs are also responsible for the coordination of the out-of-hours services (the Copenhagen Region provides its own service). All GPs in Denmark use electronic medical records, and the communication between GPs, specialists, hospitals, community nurses, administrative regions, and municipalities is electronic.

The Danish Civil Registration System and register-based research

Denmark has a long tradition of public registers. Historically, data on Danish residents have been recorded from 1924, but electronic registration was introduced in 1968 when the Civil Registration System was established.[107] All Danish citizens are assigned a unique 10-digit personal identification number at

birth; this number holds information on date of birth and sex in addition to a code that is specific to the individual. The personal identification number (CPR in Danish) follows the individual from cradle to grave and is rarely changed (only due to errors and similar), and no overlap exists.

The identification number is used in public registers, e.g. in relation to municipality, tax, education, employment, health, but also serves as an electronic identification tag in public surveys, banks and insurance companies. Public health registers include information on birth characteristics, biological specimens, hospital admissions (somatic and psychiatric), primary and secondary healthcare contacts, biobanks, redeemed prescriptions of medication, clinical databases, cause of death, and more.[108]

The unique identifier allows linkage of data at the individual level across public registers and public surveys, but such linkage must be approved by the Danish Data Protection Agency. Each request of data linkage for research purposes must first be reviewed to ensure anonymity for the individual. Data linkage across full registers requires anonymization of the CPR number and e.g. postal address. If full anonymization is guaranteed, individual consent is not required by Danish law. Linked datasets are commonly stored on secure serves at Statistics Denmark,[109] and researchers from authorised institutions may gain encrypted online access to datasets. Only data and computed estimates on an aggregated level must be downloaded and used for research publications.

This national resource of comprehensive and complete data has enabled large epidemiological studies over the years and has been referred to as "a cohort of an entire country."[110]

DATA SOURCES

The Danish Civil Registration System

The Danish Civil Registration System holds information on civil and vital status, family relations, address of residency, and migrations; it is updated on a daily basis.[107]

The Danish National Health Survey

The Danish National Health Survey (DNHS) 2010[111] supplied us with data for key variables in our research. The Danish regions, the National Institute of Public Health, and the Danish Health Authority together conducted a nationwide health survey in the spring of 2010. The aim of the survey was to describe the prevalence of disease and aspects related to health that were unavailable from the public health registers, e.g. health-related quality-of-life measures and lifestyle factors. The data was to be used for healthcare planning, research, and analyses of regional differences.

Sampling

The survey used a cross-sectional design with random sampling, which was intended to be representative on national, regional and municipal level.[111] Two levels of sampling were performed; at regional level and national level. The two samples were mutually exclusive. Certain rules applied regarding minimum sampling size for each municipality. Citizens aged 16 years or older living in Denmark were eligible for sampling. Participation was voluntary, and participants were guaranteed anonymity.

Survey questionnaire

A letter of invitation and an enclosed paper questionnaire was sent by postal mail to the sampled individuals. Alternatively, the questionnaire could be filled out online. A total of 52 core items were included in all survey questionnaires. Each region could also add items according to their interest. The core items included:

1. Age, sex, and native language.
2. *Short Form 12 Health Survey*, version 2:[112] health-related quality of life; physical and mental component summary scores.
3. 18 self-reported diseases and/or consequences of previous disease.
4. Smoking habits, including type and amount.
5. Alcohol habits, including type and amount.
6. Nutrition, including composition of food items and a score of healthy eating.
7. Physical activity level.
8. Height, weight, and body mass index.
9. Civil status, educational attainment, and employment.

Four of five regions and the national sample included *the Perceived Stress Scale* (PSS),[90] which was crucial for our studies of stress appraisal. Key variables for our research are described in detail in the section *Study cohorts and designs*.

Survey data

The questionnaires were collected from February 2010 onwards and response data from all participants had been obtained by 1 May 2010. A total of 298,550 citizens were invited to participate in the survey. The national sample included 25,000 citizens, and the rest was distributed across the regions. The overall response rate was 59.5%, resulting in complete or partly complete data from

177,639 participants; not all respondents filled out all the questionnaire items or errors occurred.

Survey respondents were linked to individual demographic data at Statistics Denmark.[109] Calibrated weights of the survey respondents were then calculated to account for differential non-response based on e.g. sex, age, marital status, educational level, income, and ethnicity, thereby ensuring that disease prevalence estimates would be representative of the background population.[111]

Danish health registers

Numerous public health registers have been used for the studies. Common to all these registers is the possibility to link data at the individual level through the CPR number. The registers also share the prospective and mandatory recording of data from e.g. Danish hospitals, primary care practices and pharmacies, and the availability of historical data. A short description of each register follows:

The Danish National Patient Register

The Danish National Patient Register (DNPR)[113] was established in 1977 and holds records of contacts to all Danish hospitals, including in-patient and out-patient visits (from 1995 onwards). The information is structured in administrative, procedural, and clinical data, e.g. diagnoses and surgical procedures. All hospital contacts are coded with one or more discharge diagnoses. Out-patient ambulatory contacts are coded with a contact diagnosis. The private healthcare sector also reports to the register. Contacts to psychiatric hospitals are less well recorded historically, and the Danish Psychiatric Central Register has been used in our research instead (see description below).

The current coding system of diagnoses in the DNPR is the WHO International Classification of Diseases, version 10 (ICD-10),[71] which has been applied since

1994. Until then, the ICD-8 was used as the ICD-9 was never implemented in Denmark.

The Danish Diabetes Register

The Danish Diabetes Register[114] was established in 2006 and compiles data on diabetes patients using a validated algorithm applied on data from other health registries. The presence of diabetes is based on in-patient and out-patient hospital diagnoses of type 1 or type 2 diabetes, registration of chiropody, repeated blood sugar measurements in primary care (at least five in one year or two per year in five years), or redemption of prescriptions for antidiabetic medication. Certain inclusion and exclusion rules apply. The register cannot distinguish between type 1 and type 2 diabetes.

The Danish Cancer Registry

The Danish Cancer Registry[115] was founded in 1942 and keeps records of cancer incidence and prevalence. It combines several sources of data, e.g. the NDPR and the Danish Pathology Register, and thus adds topography and morphology details and stages to cancer diagnoses. Currently, the ICD-10 diagnosis system (reconstructed back to 1978) and the *Tumour size/lymph Node/distant Metastasis* (TNM) staging system is used for information in this register.

The Danish Psychiatric Central Register

The Danish Psychiatric Central Register[116] supplements the DNPR with information on psychiatric diagnoses. Registration of psychiatric in-patient contacts began in 1938, and valid electronic records of every psychiatric hospital admission exists from 1970. Out-patient and psychiatric emergency room

contacts were added in 1995. Discharge and contact diagnoses have been coded using the ICD-10 system since 1995.

The Danish National Prescription Registry

All dispensed prescriptions from Danish pharmacies have been recorded in the Danish National Prescription Registry[117] since 1994. The patients identify themselves at the pharmacy counter using the CPR number or public health insurance card in order to redeem the prescription. The registry does not record prescriptions that are issued by a physician but never redeemed by the patient.

Beside the encrypted identity of the patient, the registry includes data on dispensing date and location, drug type, its pharmaceutical form, strength and package size, and prescriber's medical specialty. The drug type is coded using the Anatomical Therapeutic Chemical (ATC) classification system by the WHO Collaborating Centre for Drug Statistics Methodology.[118] Over-the-counter drugs sold at pharmacies and in retail shops are not recorded at the individual level.

The Danish National Health Service Register

The Danish National Health Service Register[119] holds information on activities in public primary healthcare and has been available for research purposes since 1990. Primary healthcare providers are contracted with the universal healthcare system and reimbursed for specific services listed in the contract and invoiced to the regional health administration. This includes GPs, practising physiotherapists, psychologists, dentists, chiropractors, chiropodists, medical specialists, and psychiatrists. The regional health administration forwards the service data to the Danish National Health Service register.

The register keeps information on the patient, provider, and service level. Patient data include patient identity, general practice provider number at which

the patient is listed, and the patient's health insurance group. The provider data includes provider number, provider type, and medical specialty. Recorded services are classified according to type of consultation (face-to-face, telephone, home visit, annual chronic care consultation, e-mail consultation, or out-of-hours services) and type of additional services, which depends on the specialty. In general practice, common additional services are blood samples, vaccinations, talk therapy, psychometric tests, and laboratory tests (e.g. blood sugar sampling, spirometry, ECGs, urine tests, and measurement of C-reactive protein).

The register only holds information on reimbursed services according to the contract. Therefore, no information is recorded on the reason for contact, diagnoses, content, or length of consultation. These data are often recorded in the GPs electronic medical record system, but they are not passed on to public registers. Some services are not publicly reimbursed, e.g. travel vaccination and documentation to insurance companies. Data on these services are thus not available in the register.

The Danish Register of Causes of Death

Records of death certificates have been collected since 1875 in Denmark.[120] The causes of death are classified according to WHO standards. The cause of death consists of contributing causes and an underlying cause coded using ICD-10 diagnosis codes. Since 2007, the registration of death certificate forms has been electronic, and the international standard for relations between medical conditions, the so-called automated classification of medical entities (ACME), has been applied to determine the hierarchy of contributing causes. The manner of death is recorded as natural, accident, violence, suicide, or uncertain. Additional information on the date and place of death, autopsy, and the physician issuing the death certificate is available from the register.

Statistics Denmark

Statistics Denmark (www.dst.dk/en)[109] is the official Danish statistics authority. The Statistical Yearbook has been published annually since 1896. Access to numerous national administrative registers of e.g. demographics, education, labour market affiliation, income, and other socioeconomic factors is available through the research portal of Statistics Denmark.[121,122] For our research, we obtained individual-level data on highest achieved educational attainment, occupational status, and ethnicity. Educational level was categorized according to the United Nations Educational, Scientific and Cultural Organization's (UNESCO) International Standard Classification of Education (ISCED).[123]

DEVELOPMENT OF THE DANISH MULTIMORBIDITY INDEX

Background

The comprehensive health registers compile historical and current data on diagnoses and drug use in the entire Danish population. Clinical databases keep detailed information on selected diseases. However, no register-based overview of multimorbidity on a national scale existed at the time of our research. Survey data were limited to samples of the population and by their self-report design. It was, therefore, important for us to establish a confident measure of multimorbidity that could be used in our research.

Development process

To achieve this, several challenges existed. Firstly, primary care diagnoses and reason-for-contact codes were not centrally registered and hence not obtainable. Secondly, no consensus on a reference multimorbidity index existed in the international literature.[12] Thirdly, many existing multimorbidity indices were not applicable on the available Danish register data.

To overcome these challenges, we decided to develop an algorithm that could combine hospital in-patient and out-patient diagnoses with redeemed drug prescriptions as a proxy for conditions commonly treated in primary care. This approach has been used previously and validated to specific aims, e.g. COPD and diabetes.[114,124] We also pre-specified some criteria that our multimorbidity index had to meet: The algorithm had to output an individual-level multimorbidity status at any given time in a format that would be comparable internationally and with long-term conditions relevant for primary care, i.e. they should be common in general practice with a high impact on public health and/or with a high impact on functional level and quality of life for the individual patient. Furthermore, good capture should be possible using the register data at hand.

Literature review

Systematic reviews of multimorbidity were studied and a literature search was performed to get an overview of existing multimorbidity indices, specifically indices applicable to Danish register data. Based on this, eight existing indices or methods were selected for further refinement, and the disease lists and definitions were compared across indices:

1. Danish National Health Survey 2010[111] disease list: 18 self-reported conditions based on the EUROHIS instrument developed by WHO's Regional Office for Europe for health surveys, including definitions of chronic diseases.
2. Diederichs et al.:[12] recommendation of 2011 on 11 diseases for multimorbidity indices based on a systematic literature review.
3. The Charlson Comorbidity Index:[13] This index is the most used comorbidity index and has been validated several times. It was developed for a hospital setting to predict one-year mortality, but has also been validated in primary care. Well-defined ICD-10 codes for use in Danish register research exist.

4. Elixhauser Comorbidity Index:[125] a widely used comorbidity measure based on administrative in-patient data. Includes 30 conditions.
5. Van den Bussche et al.:[126] study of 2011 on primary care claims data across Germany. This study included 46 conditions coded using the ICD-10 system.
6. Huber et al.:[16] study of 2013 on Swiss pharmacy claims data. The study assessed 22 chronic conditions in 1.3 million residents based on prescription data. All conditions were identified based on an algorithm using ATC drug codes.
7. Barnett et al.:[20] study of 2012 based on a Scottish primary care database of 40 long-term conditions. The index combined diseases in the QOF using READ codes of GP contacts with drug prescription data.

Other indices were considered (e.g. Adjusted Clinical Groups System, Chronic Disease Score, RxRisk and Cumulative Illness Rating Scale).[12,14] However, during the review process, we found that these indices were not thought to add extra dimensions, the data required for specified weights were not obtainable, or the diseases were already covered and defined by the selected indices.

Specifying the index conditions

For international comparability, we decided to base our multimorbidity index on the framework of the widely cited 2012 study by Barnett et al. in The Lancet.[20] The basis of this study was primary care, and its disease list reflected the common contact pattern of the background population which fulfilled our pre-specified criteria. Based on READ codes from the QOF for reimbursement, the diagnosis coding was not directly adaptable to Danish register data. We translated most READ codes from this index to ICD-10 diagnosis codes and ATC medication codes using conventions from the other selected indices. The ICD-10 and ATC manuals were reviewed for each translation for clinical meaningfulness.

The final choice of diseases for the Danish Multimorbidity Index was pragmatic and aimed at achieving the best possible capture in registers. The final list is shown in Table 1. Certain conditions were present in all the selected multimorbidity indices (e.g. diabetes, heart disease, chronic lung disease, and cancer). However, we removed conditions from the Barnett framework that did not fit our criteria (data availability or poor capture, e.g. dyspepsia, eczema, and learning disability) and added conditions from other indices that were clinically meaningful to primary care in Denmark (e.g. allergy and osteoporosis). Musculoskeletal diseases are very common and often only managed in primary care. Unfortunately, we had no valid data on these conditions. Consequently, we decided to keep the *painful condition* category from the Barnett study as musculoskeletal diseases are often treated with analgesics if they impair the daily functional level.

Risk factors with treatment potential were included, e.g. *hypertension* and *dyslipidaemia*. Due to the many medical indications of certain drugs, e.g. anti-hypertensives, the algorithm defined various rules that were applied to increase the certainty of a drug being prescribed on a specific indication (the coding definitions can be found in Appendix I). Conversely, we added a *psychological distress* category based on anti-depressive drug redemptions to capture mental conditions treated in primary care if no psychiatric secondary care diagnosis existed.

Time frames

Diagnosis and prescription time frames were added where appropriate to acknowledge that not all long-term conditions are truly chronic, and some can resolve spontaneously or be cured, e.g. some cancers and thyroid disorders. Consequently, changes in multimorbidity status could occur over time.

However, most conditions were treated as chronic, and a diagnosis of the condition counts from the first diagnosis date and onwards.

Repeated drug prescriptions (two redeemed prescriptions within the last year/ for *painful* condition; four redeemed prescriptions within the last year) were used to increase the specificity of the diagnosis and to heighten the likelihood of patient compliance; the GP would probably only re-prescribe drugs on the patient's request if the first package of drugs had been used.

Table 1. List of conditions in the Danish Multimorbidity Index

Category	Disease group
Circulatory system	Hypertension
	Dyslipidaemia
	Ischemic heart disease
	Atrial fibrillation
	Heart failure
	Peripheral artery occlusive disease
	Stroke
Endocrine system	Diabetes mellitus
	Thyroid disorder
	Gout
Pulmonary system and allergy	Chronic pulmonary disease
	Allergy
Gastrointestinal system	Ulcer/chronic gastritis
	Chronic liver disease
	Inflammatory bowel disease
	Diverticular disease of intestine
Urogenital system	Chronic kidney disease
	Prostate disorders
Musculoskeletal system	Connective tissue disorders
	Osteoporosis
	Painful condition
Haematological system	Anaemias
	HIV/AIDS
Cancers	Cancer
Neurological system	Vision problem
	Hearing problem
	Migraine
	Epilepsy
	Parkinson's disease
	Multiple sclerosis
	Neuropathies
Mental health conditions	Mood, stress-related, or anxiety disorders
	Psychological distress
	Alcohol problems
	Substance abuse
	Anorexia/bulimia
	Bipolar affective disorder
	Schizophrenia or schizoaffective disorder
	Dementia

Data extraction for the Danish Multimorbidity Index

Data for the condition-defining algorithm were extracted from three main registers: ICD-10 codes of physical diagnoses from the Danish National Patient Register, ICD-10 codes of psychiatric diagnoses from the Danish Psychiatric Central Register, and ATC drug codes from the Danish National Prescription Registry. Diagnoses were supplemented using two disease-specific registers to improve the capture: the Danish Diabetes Register and the Danish Cancer Registry (Figure 4). Full register data were available from 1 January 1995 to 1 January 2014, and the data extraction was limited to this time frame. Owing to the time frames in the condition definitions, a run-in period of two years was needed; this resulted in a fully functional multimorbidity index from 1 January 1997.

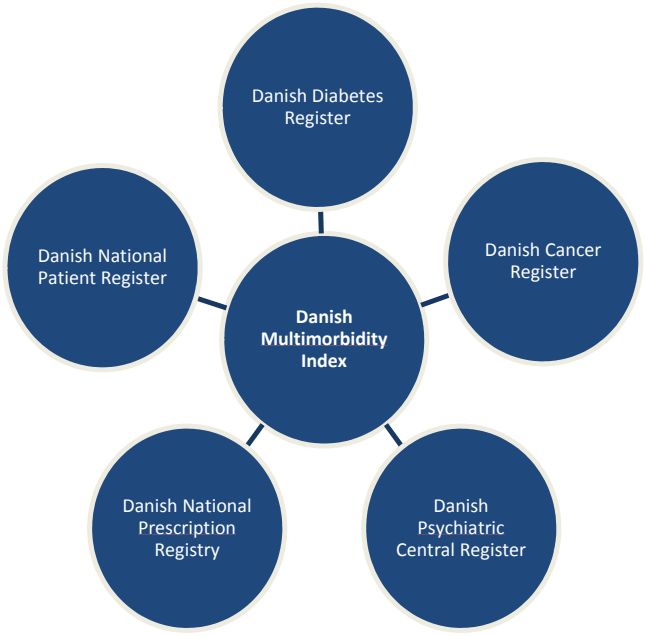

Figure 4. Data sources for the Danish Multimorbidity Index.

STUDY COHORTS AND DESIGNS

In this section, the different study designs, cohorts, exposures and outcomes will be described. An overview of the studies in this thesis can be found in Table 2.

Danish National Health Survey cohort

Studies I, II, and IV shared the same cohort of DNHS participants and were conducted as population-based cohort studies. They all included perceived stress and multimorbidity status as key independent variables, but they had different outcomes of interest.

Table 2. Overview of studies I–IV

	Study I	**Study II**	**Study III**	**Study IV**
Cohort	DNHS cohort	Bereavement cohort	DNHS cohort	DNHS cohort
Participants	118,410 survey respondents	389,316 bereaved persons + 1:5 matched references	118,410 survey respondents	118,410 survey respondents
Age (years)	25–100+	18–100+	25–100+	25–100+
Follow-up time (years)	~4	17	~4	1
Calendar time (years)	2010–2014	1997–2014	2010–2014	2010–2011
Stress measure	PSS	Spousal bereavement	PSS	PSS
Main outcome	All-cause mortality	All-cause mortality	ACSC-related hospitalisations	Primary care services
Data sources	DNHS and register data	Register data	DNHS and register data	DNHS and register data
Statistical analysis	Cox regression	Stratified Cox regression	Poisson regression	Negative binomial regression

Participants

The study cohort was defined on the basis of the random population sample from the DNHS 2010. The primary study population was survey respondents, but the dataset also included encrypted CPR numbers on survey non-respondents that were suitable for non-response analyses. We decided that persons under age 25 years would be of minor interest for the study of multimorbidity, so we included all persons aged 25 or older without any age maximum to have a broad age span. Furthermore, persons were only eligible if they had the opportunity to answer the perceived stress items in their survey questionnaire (PSS was included by four regions and in the national sample).

The survey data collection took several months. Some respondents emigrated from Denmark or died before the data collection was complete, and they were subsequently excluded from the study cohort. Among the survey respondents, some failed to fully complete the PSS questionnaire items on perceived stress. As this was a key measure for our research, they were excluded from the study cohort (Figure 5). The resulting cohort of survey respondents with full PSS data comprised 118,410 persons.

Register data on survey non-respondents were used for non-response analyses of the respective study outcomes.

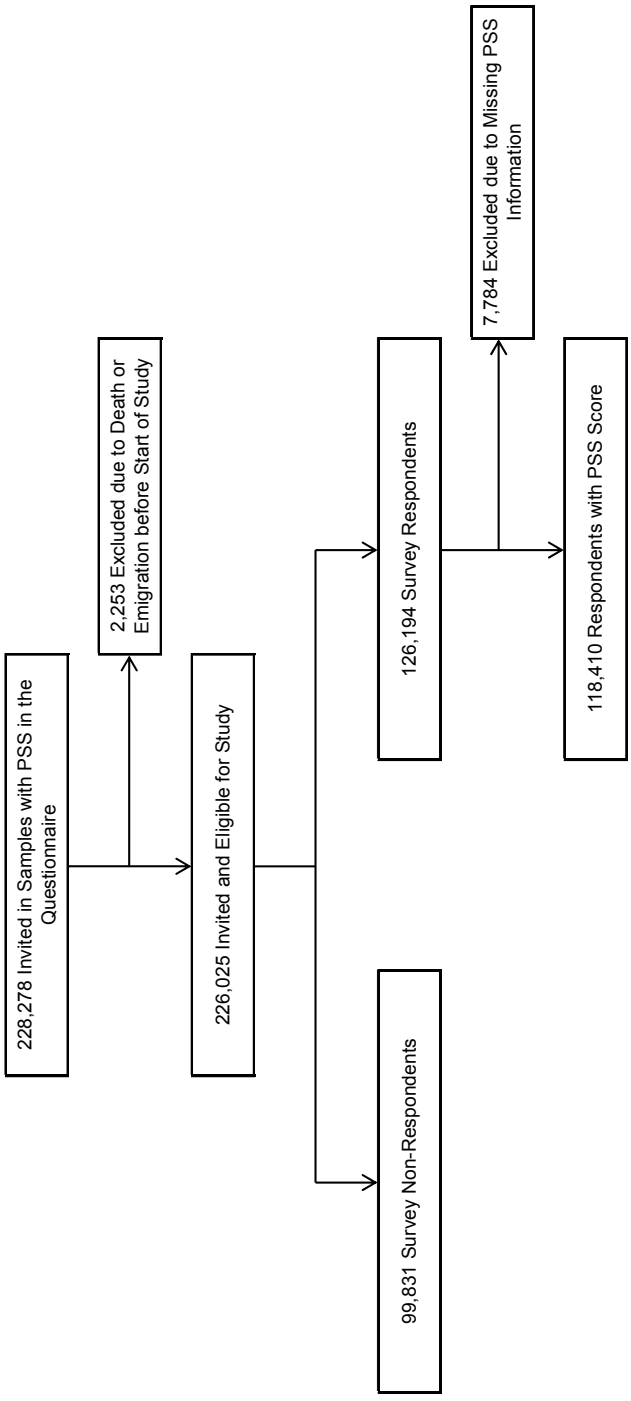

Figure 5. Flowchart of DNHS study participant for studies I, III, and IV.

Study designs

The overall study designs were follow-up studies with prospectively collected register data combined with survey data. For studies I and III, the cohort was followed from 1 May 2010 to 29 March 2014, which was the latest date with fully available register data. For study IV, the follow-up period was one year; from 1 May 2010 to 1 May 2011. The temporal resolution of censoring or events of interest was one day, except for general practice services in study IV which were registered weekly.

Exposure

Our main exposure in studies I, III, and IV was the PSS sum score obtained from the survey questionnaire (Danish and English versions in Appendix II) The ten Likert-type scale items (four items are positively stated, and six are negatively stated) were scored from 0 to 4, resulting in a total sum score of 0–40 accounting for the negatively stated items; a score of 40 indicates the highest level of perceived stress. The stress score was pragmatically divided into quintiles in accordance with previous literature[73,127] to assess dose-response and possible non-linear associations with outcomes.

Study I outcome

In study I, our outcome of interest was all-cause mortality. Information on each participant's vital status during follow-up and the date of death was obtained from the Civil Registration System.

Study III outcomes

In study III, we investigated the rate of potentially preventable hospitalisations. We used the standard definitions of ACSCs from the US Agency for Healthcare Research and Quality for 12 validated adult conditions.[67] For eight conditions, we used the original ICD-9 coding definitions translated into ICD-10 codes. For the remaining four ACSCs, ICD-10 codes from previous Danish register-based studies were applied.[70] Hospital discharge diagnoses were obtained from the DNPR. The resulting conditions for which hospitalisation rates were assessed were: diabetes with short-term complications, diabetes with long-term complications, uncontrolled diabetes, diabetes-related lower extremity amputations, chronic obstructive pulmonary disease exacerbation, adult asthma exacerbation, angina without procedure, congestive heart failure exacerbation, hypertension, appendicitis with perforation, bacterial pneumonia, and urinary tract infection. The latter three were considered *acute* ACSCs, whereas the rest were considered *chronic* ACSCs. Predisposing conditions for the chronic ACSCs were extracted from the Danish Multimorbidity Index (Appendix III). Secondary outcomes in study II were rehospitalisation for an ACSC within 30 days of discharge and 30-day post-discharge all-cause mortality.

Study IV outcomes

In Study IV, primary care activities were investigated, specifically mental-health related activities (GP talk therapy, psychometric testing, psychologist and psychiatrist visits after referral in addition to redeemed prescriptions of antidepressants, anxiolytics, and hypnotics), the use of chronic care services (annual chronic care consultations and diagnostic testing/monitoring of chronic diseases), and acute out-of-hours services (telephone, consultations, and home visits by GPs). The information on reimbursed services was obtained from the

National Health Service Register, and the information on redeemed prescriptions came from the Danish National Prescription Registry.

Other variables

Multimorbidity status was extracted using our multimorbidity index and categorised into groups by using disease counts. For adjustments, disease status was determined individually instead of by counts.

Survey variables that were thought to have confounding potential were selected for the analyses: lifestyle factors included physical activity (light intensity or no weekly activities, moderate intensity activities for at least 24 hours per week, hard intensity activities for at least 24 hours per week), alcohol use (drinks per week for men and women), smoking status (never smoker, former smoker, current smoker), diet score (unhealthy, medium, healthy), and body mass index (underweight < 18, normal weight 18–25, overweight 25–30, obese > 30). Socioeconomic factors obtained from the survey included employment status (employed or unemployed/students/retirees). Other socioeconomic factors were obtained from Statistics Denmark: cohabitation status (cohabitating or single), educational level (< 10 years, 10–15 years, > 15 years of education), and ethnicity (Danish, other western background, other).

Bereavement cohort

For Study III, we used an alternative to the self-reported stress measurement. As we shifted paradigm, we approached stress as the consequence of an external stressful life event in a natural experiment design. Bereavement was chosen as the stressor because of the supposedly high stress effect[81,86] and the high validity of the reporting of this event in registers, including well-defined timing.[107]

Participants and exposure

Using the information in the Civil Registration System on civil status, we identified all spouses residing in Denmark aged 18 years or older who had been bereaved from 1 January 1997 to 1 January 2014. This comprised our stress exposed cohort. We matched each bereaved person on sex and birth date with five randomly selected individuals to obtain a reference group; the matching was done on the day of bereavement, i.e. the death date of the spouse, defining the index date in that particular cohort stratum.

With age, a substantial part of the population experiences bereavement. Consequently, to maintain a natural background population and yet avoid mixing the exposed with the unexposed, we decided that reference persons could not have experienced bereavement within the past five years at the time of the matching. They were allowed to act as references again five years after bereavement. Reference persons could be selected by design as references for several bereaved persons if the matching criteria were fulfilled, but they were censored if they experienced bereavement themselves.

Study design

The bereavement study was performed as a population-based matched cohort study. Only prospectively recorded register-based information was used, and the follow-up time was up to 17 years.

Study III outcome

The primary outcome for the bereavement study was all-cause mortality, and the secondary outcome was mortality by natural causes. Death certificate data were obtained from the Civil Registration System and the Register of Causes of Death.

Other variables

Multimorbidity status, cohabitation status, and educational level were assessed on the index date, i.e. the day of bereavement/matching date, using the same methods and categorisations as in the survey-based studies. Cohabitation status was allowed to change during follow-up.

STATISTICAL ANALYSES

Details on the statistical analyses can be found in the manuscripts of studies I–IV. Here, we will present an overview of applied methods and considerations regarding the analyses.

Power calculations were performed prior to investigations. The results were reassuring; the statistical power of the rare outcome of death was above 90% if the hazard ratio was at least 1.15 for the most versus the least stressed persons.

Descriptive baseline statistics were produced for the study cohorts. Cumulative incidence proportions (CIP) of outcomes were calculated for the main outcomes in studies I, II, and IV as unadjusted absolute estimates. For the relative estimates, a suitable choice of regression model was made for each study depending on the outcome. In study I, a Cox proportional hazards model with age as the time axis was used to produce hazard ratios (HR) of all-cause mortality. In study II, a stratified Cox proportional hazards model with time since bereavement/matching as the time axis was used to account for matching strata in order to yield all-cause and cause-specific mortality HRs. Restricted cubic spline modelling of the relation between the PSS score and outcomes was used to assess potential non-linearity in studies I and III.[128] In study III, Poisson regression was used to produce incidence rate ratios (IRR) of ACSC-related hospitalisations. In study IV, negative binomial regression was used to produce IRRs of primary care services and psychotropic drug prescriptions. Robust

variance estimation was used to calculate 95% confidence intervals (CIs) to account for inter-individual heterogeneity. Person-time at risk was considered in all studies using information on vital status and emigration from the Danish Civil Registration System.

We calculated the excess number of outcomes associated with the stress exposure. This was done by multiplying the absolute estimate of the outcome of interest with the attributable fraction of the stress measure, e.g. for excess mortality: (number of deaths) × (HR–1)/HR.[129,130]

To assess the effect modification by mental-physical multimorbidity level, we stratified our models by disease count groups and/or psychiatric comorbidity. In the mortality studies, rescaling was performed for each multimorbidity group by risk-time weighted-average HRs to better represent the actual distribution of diseases within each group.

Missing values in our datasets (DNHS variables and educational attainment) were handled using multiple imputation. Missing values were often present on several variables so we utilised a chained equations model based on sequential multivariate regression. Ordinal logistic regression was used for categorical variables. All analysis parameters relevant to each study were part of the imputation model, including outcome variable and time variable. The adequate number of imputation sets was determined based on missing percentage, and the resulting estimates were combined using Rubin's rules.[131]

In studies I, III, and IV, survey non-response analyses were performed using register data only, and psychiatric illness was used as a proxy for the stress exposure when estimating the adjusted association with the respective study outcomes.

All *p*-values were two-sided. All analyses were performed using Stata 13.1 (StataCorp, College Station, TX).

ETHICS AND APPROVALS

All studies were based on de-identified register and survey data. Therefore, the individual patient consent was waived according to Danish law. The de-identified data with encrypted CPR numbers were securely stored on Statistics Denmark servers. Data access, data linkage, and investigations were approved by the Danish Data Protection Agency (file number: 2013-41-1719). The DNHS steering group supplied DNHS data and approved studies I, III, and IV.

CHAPTER 4:

RESULTS IN SUMMARY

In this chapter, the main results from the studies of this project are outlined. Additionally, unpublished data are presented on the PSS score distribution in the DNHS cohort and the descriptive statistics of the Danish Multimorbidity Index.

STUDY I

In the first study, the descriptive statistics of the DNHS cohort, including the Danish Multimorbidity Index algorithm and the baseline characteristics for the DNHS cohort, were presented along with the main study results on mortality associated with perceived stress. Supplemental data on the PSS distribution and psychiatric illness are presented here.

Description of the DNHS cohort

The histogram of the overall PSS scores of the DNHS respondents showed a right skewed distribution (Figure 6). The categorisation of the PSS score into quintiles yielded five groups of slightly unequal size due to discrete value cuts. Number of persons, PSS score range, and median values can be found in Table 3.

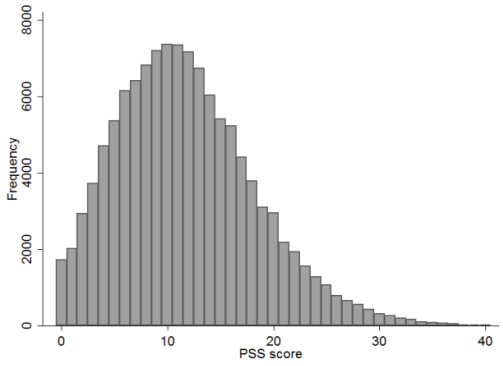

Figure 6. Histogram of Perceived Stress Scale (PSS) scores in the DNHS cohort

We found that female sex, low educational attainment, living alone, non-Danish ethnical background, and unhealthy lifestyle choices were associated with high levels of perceived stress (Table 3).

Psychiatric conditions recorded in the index were present for 8% of the study population and associated with high levels of perceived stress; subgroup histogram assessment of psychiatric illness presence showed that persons with psychiatric conditions generally had higher levels of perceived stress, but the curve was still bell-shaped with tails of both high and low PSS scores (Figure 7). A total of 50% of all with a psychiatric condition appeared in the highest PSS quintile. Still, as psychiatric conditions were not highly frequent, 79% of persons in the highest stress quintile had no recorded psychiatric diagnoses (Table 3).

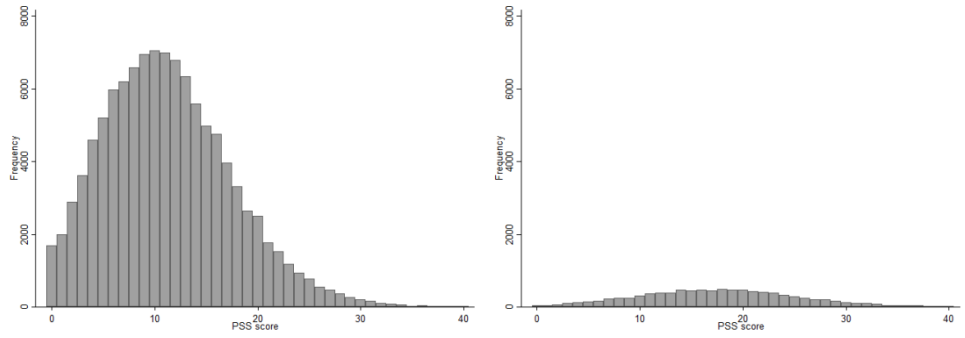

Figure 7. Histogram of Perceived Stress Scale (PSS) scores by presence of psychiatric illness

Table 3. Characteristics of DNHS cohort according to PSS score quintile

Characteristics[a]	Total no. (n=118,410)	Column %	PSS score quintile (row %) 1 (n=26,636)	2 (n=27,808)	3 (n=21,256)	4 (n=21,102)	5 (n=21,608)
PSS score median (range)			4 (0-6)	9 (7-10)	12 (11-13)	15 (14-17)	21 (18-40)
Age at baseline[b]							
25-34 years	13,881	11.7	17.9	23.7	19.5	18.9	20.0
35-44 years	22,673	19.1	20.9	24.5	18.9	17.2	18.4
45-54 years	25,272	21.3	22.9	24.3	18.2	16.8	17.9
55-64 years	26,610	22.5	25.5	24.0	17.3	17.0	16.2
65-74 years	19,982	16.9	25.8	22.9	17.1	18.2	15.9
≥75 years	9,992	8.4	16.8	18.4	16.5	21.7	26.6
Sex[b]							
Male	54,968	46.4	26.1	24.8	17.7	16.5	14.8
Female	63,442	53.6	19.4	22.3	18.1	19.0	21.2
Number of conditions[b]							
0	58,718	49.6	25.6	26.3	18.9	16.5	12.7
1	25,755	21.8	22.2	22.9	17.8	18.1	18.9
2	14,677	12.4	21.1	21.5	17.3	18.6	21.6
3	8,999	7.6	17.9	19.9	16.4	19.5	26.3
≥4	10,261	8.6	11.7	15.0	15.0	22.0	36.4
Any mental health condition[b]							
No	109,137	92.2	23.8	24.6	18.4	17.7	15.5
Yes	9,273	7.8	7.3	10.9	12.3	19.5	50.0
Physical activity							
Light or no weekly activity	16,818	14.2	13.1	16.2	15.2	20.4	35.1
Moderate activity ≥4 hours weekly	70,357	59.4	22.3	23.8	18.5	18.3	17.1
Hard activity ≥4 hours weekly	28,980	24.5	29.1	27.4	18.3	14.8	10.4
Missing	2,255	1.9	15.4	17.3	15.6	22.9	28.9
Alcohol habits[c]							
< 7 / < 14 units	76,894	64.9	23.9	24.8	18.4	17.2	15.7
7–14 / 14–21 units	15,768	13.3	24.0	24.4	18.8	17.7	15.2
> 14 / > 21 units	11,110	9.4	21.9	22.3	17.5	18.0	20.2
Missing	14,638	12.4	13.8	16.3	15.1	21.3	33.5
Smoking status							
Never smoker	50,386	42.6	24.7	24.8	18.1	17.1	15.3
Former smoker	38,812	32.8	22.9	24.0	18.4	17.8	16.9
Current smoker	27,012	22.8	18.4	20.5	17.1	18.9	25.1
Missing	2,200	1.9	14.6	20.7	15.9	21.6	27.1
Dietary habits							
Unhealthy	13,461	11.4	18.2	21.3	17.4	19.2	24.0
Medium	71,223	60.1	22.4	23.5	18.3	18.0	17.9
Healthy	29,854	25.2	25.5	25.2	17.6	16.4	15.2
Missing	3,872	3.3	16.2	18.2	15.6	21.0	28.9
Body mass index[d]							
Underweight (< 18 kg)	1,899	1.6	16.6	20.1	14.8	18.1	30.4
Normal weight (18-25)	55,295	46.7	23.4	24.2	18.3	17.5	16.6
Overweight (25-30)	41,957	35.4	23.5	24.1	18.0	17.6	16.9
Obese (> 30)	17,274	14.6	18.7	20.5	17.4	19.2	24.2
Missing	1,985	1.7	14.3	19.8	15.1	20.4	30.5
Working status							
Not working	45,573	38.5	19.9	20.0	16.3	18.8	24.9
Working	69,164	58.4	24.5	26.0	19.1	17.0	13.3
Missing	3,673	3.1	15.5	18.5	16.7	21.1	28.1
Education[a]							
< 10 years	26,626	22.5	16.9	19.3	16.8	20.8	26.2
10-15 years	57,108	48.2	22.3	24.3	18.6	17.8	17.0
> 15 years	32,392	27.4	27.9	26.0	17.9	15.3	12.9
Missing	2,284	1.9	14.5	16.2	16.0	20.1	33.2
Cohabitation status[a]							
Single	29,241	24.7	18.4	20.1	16.7	19.5	25.3
Cohabiting	89,169	75.3	23.8	24.6	18.4	17.3	15.9
Ethnicity[a]							
Danish	111,720	94.4	23.0	23.9	18.1	17.6	17.4
Other western background	3,258	2.8	20.1	19.9	17.0	19.8	23.2
Other	3,432	2.9	7.1	12.8	13.5	24.2	42.5

[a] Table shows data with missing values before multiple imputations. [b] Variables based on national registers (other variables based on survey). [c] Units per week for females/males. [d] Body mass index given as kg/m^2

Half of the population had no long-term conditions, 22% had one long-term condition, 12% had two, 8% had three, and 9% had three or more long-term conditions. A total of 29% of the population had multimorbidity according to the definition (Table 3). More details on the Danish Multimorbidity Index in general are described in *Descriptive statistics of the Danish Multimorbidity Index*.

An increasing number of persons were assigned to the highest PSS quintiles as the number of co-existing conditions rose, and the relation was near-linear up to at least nine co-existing conditions (Figure 8).

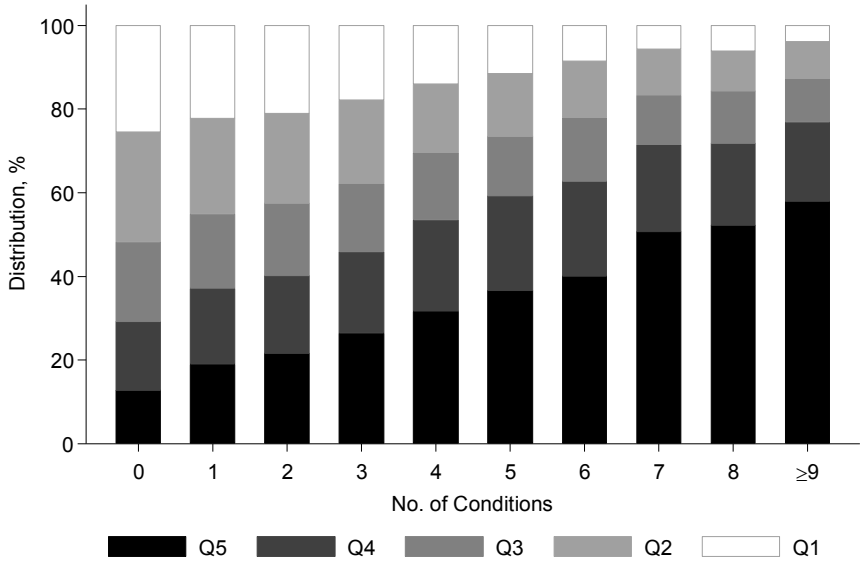

Figure 8. Distribution of PSS quintiles by number of co-existing conditions (white bar = lowest stress quintile (Q1); black bar = highest stress quintile (Q5)).

DNHS non-respondent characteristics

The overall response rate was 56%. Baseline characteristics of non-respondents differed from respondents; they were more often male, in the youngest or oldest age groups, and had more conditions from the multimorbidity index, both psychiatric and physical conditions (Table 4).

Table 4. DNHS respondents and non-respondent characteristics

	Respondents[a] (n=126,194)		Non-respondents (n=99,831)	
Characteristic	Number	Row %	Number	Row %
Response rate (%)		55.8		44.2
Age				
25-34 yrs	14,356	47.8	15,668	52.2
35-44 yrs	23,448	52.5	21,177	47.5
45-54 yrs	26,244	56.1	20,563	43.9
55-64 yrs	27,970	61.5	17,541	38.5
65-74 yrs	21,793	64.9	11,773	35.1
>75 yrs	12,383	48.6	13,109	51.4
Sex				
Male	57,946	52.3	52,891	47.7
Female	68,248	59.2	46,940	40.8
Chronic conditions				
0	61,102	55.4	49,259	44.6
1	27,296	58.1	19,674	41.9
2	15,958	57.9	11,586	42.1
3	9,948	56.5	7,659	43.5
≥4	11,890	50.5	11,653	49.5
Any mental health condition				
No	115,992	57.2	86,641	42.8
Yes	10,202	43.6	13,190	56.4
Education				
<10 yrs	29,974	48.3	32,025	51.7
10-15 yrs	59,968	57.9	43,652	42.1
>15 yrs	33,534	66.2	17,099	33.8
Missing	2,718	27.8	7,055	72.2

[a]Survey respondents with missing data on the Perceived Stress Scale score included.

Perceived stress and mortality

We registered 4,229 deaths among the 118,410 survey participants during the nearly four years of follow-up. The relative risk of dying rose with increasing PSS score to an adjusted HR of up to 2.5 for those with the highest scores (Figure 9). A dose-response pattern was evident with no obvious lower threshold. When we compared the lowest and highest stress quintiles, the most stressed had an unadjusted mortality HR of 2.95 (95% CI, 2.68–3.25). When we adjusted for multimorbidity, socioeconomic factors, and lifestyle, the HR was 1.45 (95% CI, 1.30–1.61).

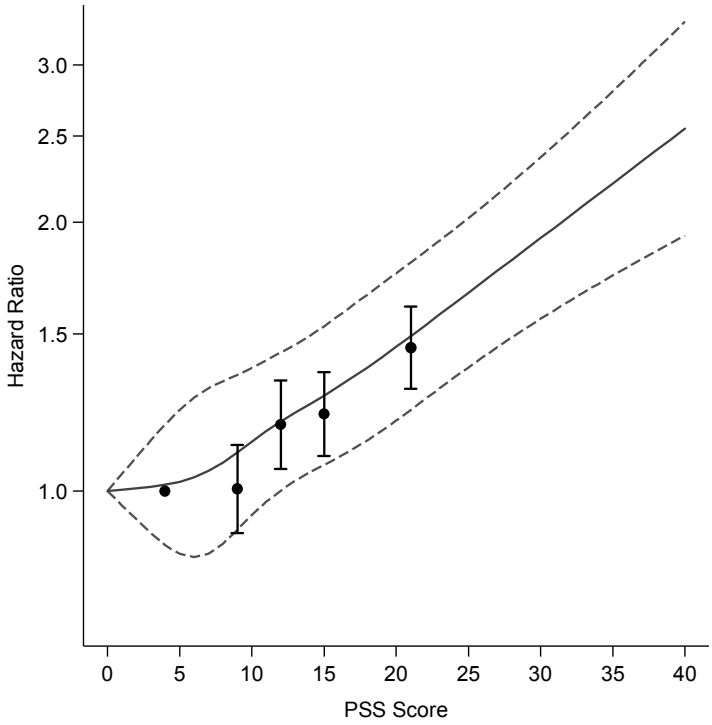

Figure 9. Adjusted mortality hazard ratios by PSS score (full line with dashed 95% CI) and by quintiles (circle and 95% CI bars placed at the median score within the quintile)

Multimorbidity accounted for a substantial amount of deaths, but perceived stress had an independent effect on death within each multimorbidity group. When we compared absolute and relative estimates of death, between 1.1% and 1.7% died (CIPs) had died in the group with none or one long-term condition, corresponding to a HR of 1.51 (95% CI, 1.25–1.84) between the lowest and highest stress quintile. For those with four or more conditions, the corresponding CIP for the lowest and the highest stress quintile were 11% and 23%, respectively, corresponding to a HR of 1.43 (95% CI, 1.18–1.73) (Table 5). For those without multimorbidity, high stress was estimated to account for 69 deaths in the study cohort. For those with four or more conditions, 255 deaths were associated with high stress. The combined risk by PSS quintile and

multimorbidity level when accounting for disease composition is shown in Figure 10.

When we stratified by presence of psychiatric conditions, the dose-response relation between PSS quintile and mortality was robust for those without psychiatric conditions, but not for those with psychiatric conditions. More excess deaths were associated with high levels of perceived stress (328 deaths) than with psychiatric conditions (240 deaths). Non-response analyses showed comparable results for respondents and non-respondents.

Table 5. Mortality hazard ratios for PSS quintiles stratified by multimorbidity status in various adjusted models

			Crude model[a]		Fully adjusted model[b]			
No. of conditions and PSS score quintile	**Deaths**	**CIP**	HR	95% CI	HR	95% CI	*P*-value trend	Excess deaths associated with stress[c]
0—1 conditions								
1	223	.011	1	reference	1	reference	<0.0001	reference
2	218	.010	1.10	0.91-1.32	1.06	0.88,1.28		12
3	171	.011	1.23	1.01-1.50	1.13	0.93,1.38		20
4	188	.013	1.43	1.18-1.74	1.19	0.98,1.45		30
5	205	.017	2.16	1.79-2.62	1.51	1.25,1.84		69
2—3 conditions								
1	225	.048	1	reference	1	reference	<0.0001	reference
2	222	.045	1.00	0.83-1.20	0.95	0.79,1.14		-12
3	230	.057	1.34	1.11-1.61	1.19	0.99,1.43		37
4	285	.063	1.39	1.16-1.65	1.15	0.97,1.38		37
5	456	.082	2.19	1.86-2.57	1.39	1.18,1.64		128
≥ 4 conditions								
1	134	.111	1	reference	1	reference	<0.0001	reference
2	190	.124	1.12	0.90-1.40	1.01	0.81,1.26		2
3	230	.150	1.38	1.12-1.71	1.21	0.98,1.50		40
4	403	.179	1.62	1.34-1.98	1.26	1.04,1.54		83
5	849	.228	2.36	1.96-2.83	1.43	1.18,1.73		255

[a]Adjusted for age and sex.

[b]Further adjusted for 39 conditions, lifestyle, and socioeconomic factors, and a *P*-value for test of trend between PSS quintiles and mortality rate within each multimorbidity group.

[c]Absolute number of deaths associated with being in a PSS quintile above one within a multimorbidity group.

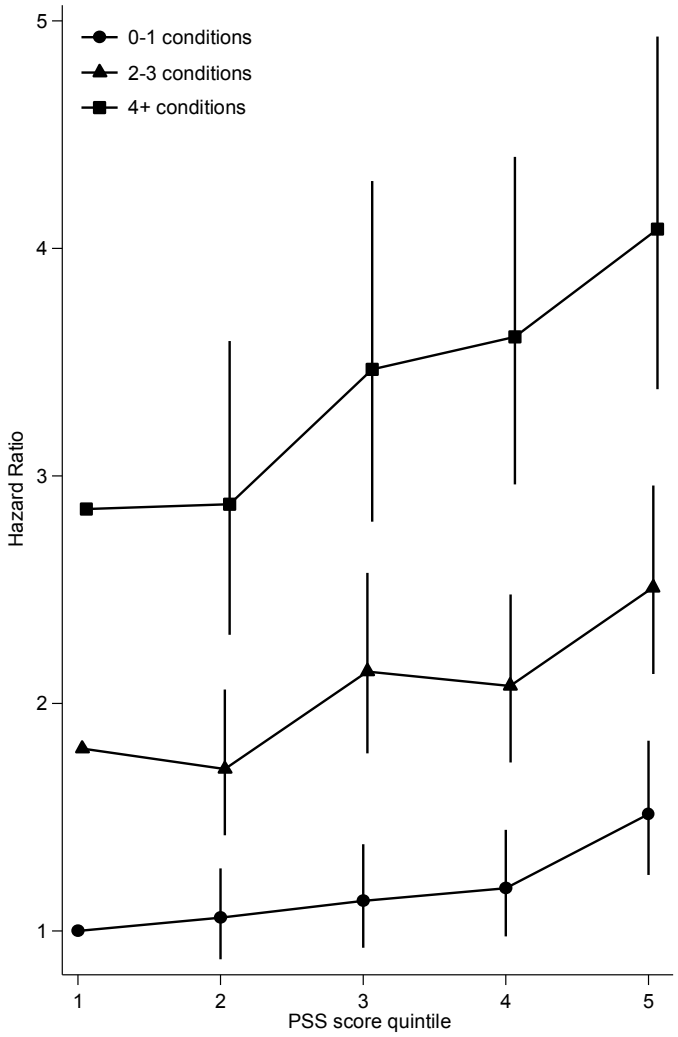

Figure 10. Mortality hazard ratios for mortality according to multimorbidity status and PSS quintile.

STUDY II

In this study, we identified nearly 400,000 persons who had experienced spousal bereavement over a period of 17 years. The bereavement cohort consisted of more women than men and most bereaved persons were elderly (Table 6). Matched reference persons were generally similar to bereaved persons at baseline.

The relative mortality attenuated with the time since bereavement. During the first month, the mortality HR was 2.50 (95% CI, 2.37–2.63) for the bereaved persons versus reference persons after adjusting for multimorbidity, but it attenuated to a HR of 1.34 (95% CI, 1.32–1.37) at one to two years after bereavement. The mortality HRs and the accompanying excess deaths associated with bereavement remained fairly stable at this level during the whole follow-up period of up to 17 years (Table 7).

The background relative risk of dying after bereavement was higher for persons with multimorbidity than for those without (Figure 11). The excess mortality associated with bereavement rose with increasing number of physical conditions; 1.33 (95% CI, 1.08–1.58) deaths per 1000 persons-months were associated with bereavement for those without any physical conditions, whereas the corresponding number of bereavement-associated deaths were 7.00 (95% CI, 6.13–7.87) for those with three or more physical conditions.

Even though the relative risk of dying from unnatural causes was high shortly after bereavement (first-month suicide: HR 33.97, 95% CI 21.71–53.14), most deaths after bereavement (96%) was attributed to natural causes, such as exacerbation of chronic disease. Unexpected spousal death, i.e. no severe chronic illness was present in the year preceding the loss, or younger age, i.e. under 65 years, seemed to be associated with especially high mortality rates in the bereaved individuals.

Table 6. Characteristics of the bereavement cohort

	Bereaved individuals		References
	Number	Col %	Col %
Age group, years			
18-40	12,450	3.2	3.2
40-60	75,158	19.3	19.3
60-80	216,660	55.7	55.7
≥80	85,048	21.8	21.8
Sex			
Women	260,562	66.9	66.9
Men	128,754	33.1	33.1
Cohabitation, status			
Bereaved	389,316	100.0	0.0
Single	0	0.0	37.5
Married/cohabitating	0	0.0	62.5
Educational level			
<10 years	175,753	45.1	40.9
10-15 years	122,575	31.5	32.1
>15 years	38,485	9.9	13.4
Missing	52,503	13.5	13.6
Calendar period			
1997-2002	123,511	31.7	31.7
2002-2007	115,028	29.5	29.5
2007-2012	108,982	28.0	28.0
2012-2014	41,795	10.7	10.7
Physical conditions, number			
0	150,064	38.5	39.5
1	101,041	26.0	25.6
2	64,745	16.6	16.3
≥3	73,466	18.9	18.6
Psychiatric disorder, status			
No	353,654	90.8	91.9
Group 1[a]	26,959	6.9	5.7
Group 2[b]	8,703	2.2	2.3

[a] Mood or anxiety disorders, alcohol or substance abuse, or anorexia/bulimia
[b] Bipolar affective disorders, schizophrenia, or dementia

Table 7. All-cause mortality for bereaved individuals versus couples by time since bereavement

		Model 1[a]		Model 2[b]		
Time since bereavement	CIP [c]	HR	95% CI	HR	95% CI	Excess mortality rate with 95% CI (deaths per 1000 person-months)[e]
0-1 month	5.1	2.47	(2.35,2.60)	2.50	(2.37,2.63)	3.12 (2.86, 3.38)
1-2 months	8.4	1.61	(1.52,1.71)	1.54	(1.45,1.63)	1.18 (0.99, 1.37)
2-3 months	11.7	1.62	(1.53,1.72)	1.58	(1.48,1.68)	1.19 (0.99, 1.40)
3-6 months	20.6	1.47	(1.42,1.53)	1.42	(1.37,1.47)	0.89 (0.75, 1.03)
6-12 months	37.7	1.43	(1.39,1.47)	1.38	(1.34,1.42)	0.81 (0.72, 0.90)
1-2 years	70.7	1.37	(1.34,1.40)	1.34	(1.32,1.37)	0.74 (0.68, 0.80)
2-5 years	167.2	1.35	(1.33,1.37)	1.31	(1.29,1.32)	0.71 (0.67, 0.75)
5-10 years	326.6	1.38	(1.37,1.40)	1.33	(1.31,1.35)	0.87 (0.82, 0.92)
10-17 years	605.9	1.40	(1.37,1.42)	1.34	(1.32,1.36)	1.12 (1.02, 1.21)

[a] Matched on sex and date of birth, adjusted for single status.
[b] Further adjusted for 39 mental and physical conditions and educational level.
[c] Cumulative incidence proportion (CIP) for bereaved individuals at the end of the respective time interval per 1000 persons
[d] Mortality rate for bereaved individuals in the respective time interval per 1000 person-months
[e] Mortality rate for bereaved individuals × (adjusted HR - 1) / adjusted HR – the proportion of deaths that theoretically could be avoided if the risk in the bereavement group equalled that of the reference group.

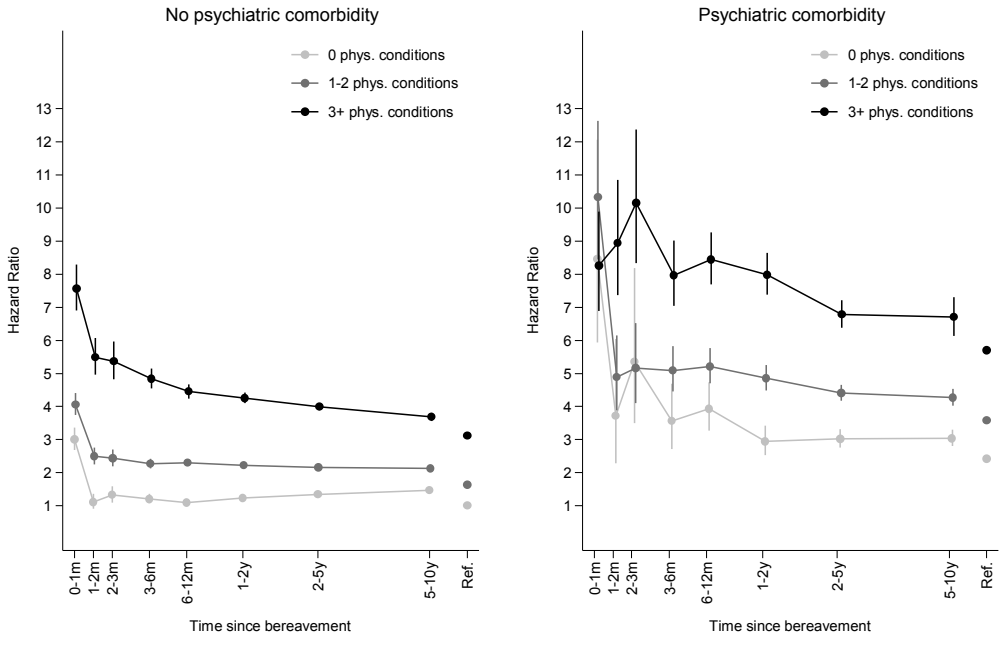

Figure 11. Adjusted all-cause mortality hazard ratios for bereaved individuals versus couples by the time since bereavement and mental-physical multimorbidity

STUDY III

During the nearly four years of follow-up, we identified 9,382 hospitalisations for ACSCs. The hospitalisations were distributed among 6,127 persons out of the 118,410 persons followed. We saw a dose-response relationship between perceived stress and the risk of ACSC-related hospitalisations, with a potential threshold at a PSS score of approximately 10 (Figure 12). When we compared the highest with the lowest PSS quintiles, the IRR of any hospitalisation for an ACSC was 2.13 (95% CI, 1.91–2.38) after adjusting for sex, age, and predisposing conditions. When we further adjusted for mental-physical multimorbidity and socioeconomic factors, the association attenuated to an IRR of 1.48 (95% CI, 1.32–1.67).

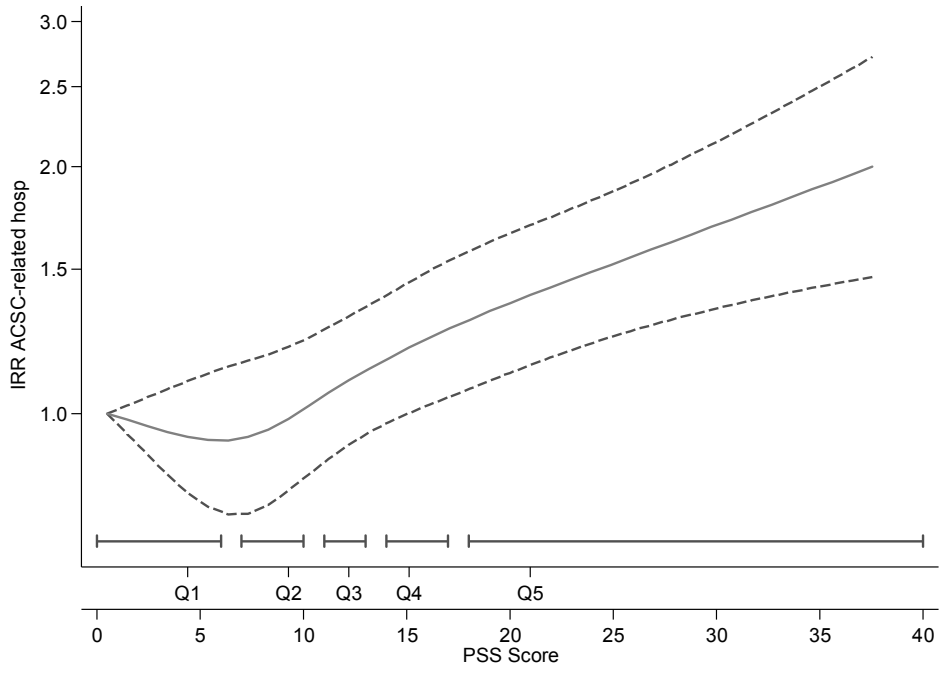

Figure 12. IRR of ACSC-related hospitalisations by PSS score.

A total of 18% of ACSC-related hospitalisations could be attributed to stress, and 36% of all ACSC-related hospitalisations occurred in persons in the highest PSS quintile. The association between high level of perceived stress and ACSC-related hospitalisation was significant for all ACSCs, except for circulatory conditions and perforated appendicitis after adjustments (Table 8). Perceived stress was associated with ACSC-related hospitalisations in both persons with and without multimorbidity. Persons with psychiatric comorbidity had a nearly 50% higher risk of these hospitalisations. Non-response analyses did not affect the conclusions.

The risk of rehospitalisation for an ACSC within 30 days of discharge after an initial ACSC-related hospitalisation tended to be higher for those with high stress levels, but this was not statistically significant in the fully adjusted model (IRR 1.26; 95% CI, 0.79–2.00).

In total, 11% of those in the lowest PSS quintile and 18% of those in the highest PSS quintile died within 30 days of the first ACSC-related hospitalisation, corresponding to a post-admission mortality HR of 1.43 (95% CI, 1.13–1.81).

Table 8. Incidence rate rations of ACSC-related hospitalisations by PSS quintile and ACSC subgroup

			Model adjusted for age, sex, follow-up time, and ACSC predisposing conditions		Model further adjusted for socioeconomic factors[a]		
ACSC Outcome	PSS quintiles	No. ACSC-H	IRR	95% CI	IRR	95% CI	Excess ACSC-Hs associated with stress[b]
Overall	1	1,241	1	Reference	1	Reference	Reference
	2	1,417	1.08	(0.96,1.20)	1.02	(0.91,1.14)	28
	3	1,362	1.25	(1.12,1.40)	1.13	(1.01,1.26)	157
	4	1,979	1.50	(1.34,1.68)	1.27	(1.13,1.42)	421
	5	3,383	2.13	(1.91,2.38)	1.48	(1.32,1.67)	1,097
Chronic ACSC groups:							
Diabetes-related conditions	1	49	1	Reference	1	Reference	Reference
	2	59	1.10	(0.67,1.79)	0.96	(0.58,1.57)	-2
	3	82	1.94	(1.23,3.04)	1.57	(1.00,2.48)	30
	4	95	1.80	(1.15,2.80)	1.31	(0.84,2.05)	22
	5	218	3.48	(2.31,5.26)	1.78	(1.16,2.73)	96
Chronic lung conditions	1	138	1	Reference	1	Reference	Reference
	2	211	1.41	(0.92,2.15)	1.22	(0.81,1.86)	38
	3	214	1.70	(1.12,2.57)	1.35	(0.89,2.05)	55
	4	378	2.36	(1.56,3.56)	1.69	(1.11,2.57)	154
	5	827	4.13	(2.72,6.27)	2.18	(1.42,3.34)	448
Circulatory conditions	1	513	1	Reference	1	Reference	Reference
	2	500	0.91	(0.77,1.08)	0.89	(0.76,1.05)	-62
	3	503	1.13	(0.96,1.34)	1.06	(0.90,1.24)	28
	4	612	1.15	(0.97,1.36)	1.05	(0.88,1.25)	29
	5	841	1.29	(1.09,1.52)	1.07	(0.91,1.27)	55
Acute ACSC groups:							
Perforated appendicitis	1	33	1	Reference	1	Reference	Reference
	2	19	0.56	(0.32,0.99)	0.55	(0.31,0.97)	-16
	3	28	1.09	(0.65,1.83)	1.03	(0.61,1.73)	1
	4	27	1.05	(0.62,1.76)	0.92	(0.55,1.55)	-2
	5	33	1.27	(0.77,2.09)	0.94	(0.53,1.66)	-2
Pneumonia	1	335	1	Reference	1	Reference	Reference
	2	418	1.30	(1.10,1.54)	1.14	(0.96,1.34)	51
	3	360	1.46	(1.22,1.74)	1.15	(0.97,1.37)	47
	4	578	2.12	(1.80,2.49)	1.40	(1.19,1.65)	165
	5	953	3.53	(3.02,4.11)	1.62	(1.37,1.90)	365
Urinary tract infection	1	173	1	Reference	1	Reference	Reference
	2	210	1.20	(0.95,1.51)	1.06	(0.84,1.33)	12
	3	175	1.26	(0.99,1.60)	1.03	(0.81,1.30)	5
	4	289	1.86	(1.50,2.32)	1.33	(1.07,1.65)	72
	5	511	3.17	(2.59,3.88)	1.58	(1.28,1.95)	188

ACSC-H: ACSC-related hospitalisation.

[a] Education, ethnicity, cohabitation status, and employment status.

[b] No. ACSC-H × (IRR-1)/IRR

STUDY IV

During the study year, over a million primary care services were recorded and more than 85,000 drug prescriptions for psychotropic drugs were redeemed in the study population. Perceived stress level at baseline was associated with most primary care activities after adjusting for age, sex, mental-physical multimorbidity, lifestyle, and socioeconomic factors. Among those in the lowest PSS quintile, 77% had a GP daytime consultation during the year. The corresponding number was 89% for those in the highest PSS quintile, which corresponded to an IRR of 1.28 (95% CI, 1.25–1.30) when adjusting for sex, age, multimorbidity, socioeconomic factors, and lifestyle. The IRR for GP out-of-hours services was 1.47 (95% CI, 1.51–1.68).

High stress levels were particularly associated with high relative use of mental health related services after adjustments (e.g. an IRR of 4.96 [95% CI, 4.20–5.86] for GP talk therapy and an IRR of 4.62 [95% CI, 4.03–5.31]) for antidepressant prescriptions) (Table 9). In absolute terms, psychotropic medication, e.g. antidepressants, were more often used than talk therapy (CIP 22% versus 7%) among the highly stressed. This pattern was more pronounced when the underlying number of physical conditions rose (Figure 13).

The use of all chronic care services, i.e. annual chronic care consultations and chronic disease monitoring tests (except home blood pressure measures), generally increased with perceived stress level (Table 10). Even though the absolute number of chronic care services rose consistently with multimorbidity level, the association with chronic care services use across the PSS quintiles attenuated and disappeared when the number of coexisting physical conditions increased (Figure 13). The opposite was true for out-of-hours services that increased with both multimorbidity and stress level.

Excluding persons with known psychiatric illness did not affect the conclusions.

Table 9. Cumulative incidence proportions and incidence rate ratios of mental health related primary care activities according to PSS quintile.

Primary care service	PSS quintile	CIP_{1y} (%)	95% CI	IR	Crude IRR	Adj. IRR*	95% CI
Talk therapy by GP	1	1.1	(1.0,1.2)	0.02	1	1	Reference
	2	1.7	(1.5,1.8)	0.03	1.48	1.38	(1.15,1.65)
	3	2.2	(2.0,2.4)	0.04	2.01	1.72	(1.43,2.06)
	4	3.1	(2.9,3.3)	0.06	2.76	2.38	(1.99,2.83)
	5	6.8	(6.5,7.2)	0.15	6.90	4.96	(4.20,5.86)
Psychometric tests	1	1.2	(1.1,1.3)	0.02	1	1	Reference
	2	1.8	(1.6,1.9)	0.02	1.38	1.26	(1.06,1.51)
	3	2.5	(2.3,2.7)	0.04	2.04	1.75	(1.46,2.10)
	4	3.2	(2.9,3.4)	0.05	2.82	2.16	(1.82,2.56)
	5	6.6	(6.2,6.9)	0.10	5.96	3.68	(3.11,4.35)
Psychologist services	1	0.4	(0.4,0.5)	0.02	1	1	Reference
	2	0.7	(0.6,0.8)	0.04	1.57	1.49	(1.08,2.05)
	3	1.2	(1.0,1.3)	0.06	2.54	1.99	(1.47,2.69)
	4	1.5	(1.4,1.7)	0.08	3.53	3.07	(2.26,4.16)
	5	3.3	(3.1,3.6)	0.21	8.69	6.49	(4.90,8.58)
Psychiatrist services	1	0.2	(0.1,0.3)	0.01	1	1	Reference
	2	0.3	(0.3,0.4)	0.02	2.17	1.96	(1.16,3.32)
	3	0.5	(0.4,0.6)	0.03	3.20	1.92	(1.07,3.46)
	4	0.9	(0.8,1.0)	0.06	6.86	4.61	(2.77,7.69)
	5	3.7	(3.4,4.0)	0.24	28.74	13.26	(8.33,21.09)
Antidepressant prescriptions	1	2.6	(2.4,2.8)	0.10	1	1	Reference
	2	3.7	(3.5,3.9)	0.16	1.55	1.28	(1.09,1.49)
	3	5.7	(5.4,6.0)	0.25	2.37	1.84	(1.58,2.16)
	4	8.6	(8.2,9.0)	0.40	3.85	2.35	(2.04,2.71)
	5	21.5	(20.9,22.0)	1.21	11.63	4.62	(4.03,5.31)
Anxiolytic prescriptions	1	1.5	(1.4,1.7)	0.03	1	1	Reference
	2	2.0	(1.8,2.2)	0.05	1.61	1.53	(1.29,1.83)
	3	2.8	(2.6,3.0)	0.08	2.59	2.02	(1.67,2.44)
	4	4.1	(3.8,4.4)	0.13	4.27	2.56	(2.16,3.03)
	5	9.4	(9.0,9.8)	0.46	14.52	4.73	(4.03,5.54)
Hypnotic prescriptions	1	3.4	(3.2,3.6)	0.08	1	1	Reference
	2	4.3	(4.0,4.5)	0.11	1.39	1.34	(1.18,1.51)
	3	5.3	(5.0,5.6)	0.16	2.03	1.67	(1.47,1.89)
	4	6.6	(6.3,7.0)	0.22	2.77	1.83	(1.61,2.07)
	5	11.0	(10.6,11.5)	0.50	6.32	2.93	(2.59,3.31)

PSS: Perceived Stress Scale. CI: Confidence interval. CIP_{1y}: Cumulative incidence proportion at one year (in %). IR: Incidence rate. IRR: Incidence rate ratio.

*: adjusted for sex, age as 10-year age bands, presence of each of the 39 psychiatric and physical conditions in the multimorbidity index, socioeconomic factors, and lifestyle on index date.

Table 10. Cumulative incidence proportions and incidence rate ratios of general primary care and chronic care services according to PSS quintile.

Primary care service	PSS quintile	CIP_{1y}(%)	95% CI	IR	Crude IRR	Adj. IRR*	95% CI
Spirometries	1	2.6	(2.4,2.8)	0.03	1	1	Reference
	2	3.0	(2.8,3.2)	0.04	1.15	1.12	(1.00,1.25)
	3	3.0	(2.8,3.3)	0.04	1.14	1.06	(0.94,1.19)
	4	3.6	(3.4,3.9)	0.05	1.40	1.17	(1.04,1.32)
	5	4.4	(4.1,4.6)	0.06	1.67	1.16	(1.03,1.31)
Blood sugar measures	1	13.9	(13.5,14.3)	0.21	1	1	Reference
	2	13.7	(13.3,14.1)	0.21	1.02	1.02	(0.97,1.07)
	3	14.7	(14.2,15.2)	0.23	1.08	1.05	(0.99,1.10)
	4	16.3	(15.8,16.8)	0.27	1.26	1.09	(1.04,1.15)
	5	18.4	(17.8,18.9)	0.30	1.44	1.12	(1.06,1.18)
ECGs	1	7.4	(7.1,7.7)	0.08	1	1	Reference
	2	7.7	(7.4,8.0)	0.09	1.03	1.05	(0.99,1.12)
	3	8.0	(7.6,8.4)	0.09	1.10	1.08	(1.02,1.16)
	4	9.2	(8.9,9.6)	0.11	1.29	1.17	(1.09,1.25)
	5	9.6	(9.3,10.1)	0.11	1.32	1.14	(1.07,1.22)
Home blood pressure measures	1	5.2	(4.9,5.5)	0.07	1	1	Reference
	2	5.2	(5.0,5.5)	0.07	0.99	1.05	(0.96,1.14)
	3	5.3	(5.0,5.6)	0.07	1.01	1.04	(0.95,1.14)
	4	5.6	(5.3,6.0)	0.08	1.11	1.10	(1.00,1.20)
	5	5.2	(4.9,5.5)	0.07	0.97	1.02	(0.93,1.13)
Annual chronic care consultations	1	18.1	(17.6,18.5)	0.31	1	1	Reference
	2	17.9	(17.5,18.4)	0.31	1.01	1.02	(0.97,1.06)
	3	18.7	(18.2,19.2)	0.33	1.09	1.04	(0.99,1.10)
	4	21.0	(20.4,21.5)	0.39	1.27	1.09	(1.04,1.14)
	5	23.8	(23.2,24.4)	0.47	1.53	1.22	(1.16,1.29)
Out-of-hours contacts	1	14.2	(13.8,14.7)	0.21	1	1	Reference
	2	16.1	(15.7,16.5)	0.25	1.16	1.07	(1.02,1.13)
	3	17.4	(16.9,18.0)	0.28	1.32	1.13	(1.07,1.19)
	4	19.7	(19.1,20.2)	0.33	1.57	1.22	(1.16,1.29)
	5	26.1	(25.6,26.7)	0.54	2.57	1.47	(1.39,1.55)
Daytime consultations	1	77.4	(76.9,77.9)	3.22	1	1	Reference
	2	79.9	(79.4,80.4)	3.46	1.07	1.04	(1.02,1.06)
	3	82.1	(81.6,82.6)	3.82	1.18	1.10	(1.07,1.12)
	4	84.7	(84.2,85.2)	4.45	1.38	1.18	(1.16,1.20)
	5	88.7	(88.3,89.2)	5.50	1.71	1.28	(1.25,1.30)

PSS: Perceived Stress Scale. CI: Confidence interval. CIP_{1y}: Cumulative incidence proportion at one year (in %). IR: Incidence rate. IRR: Incidence rate ratio.

*: adjusted for sex, age as 10-year age bands, presence of each of the 39 psychiatric and physical conditions in the multimorbidity index, socioeconomic factors, and lifestyle on index date.

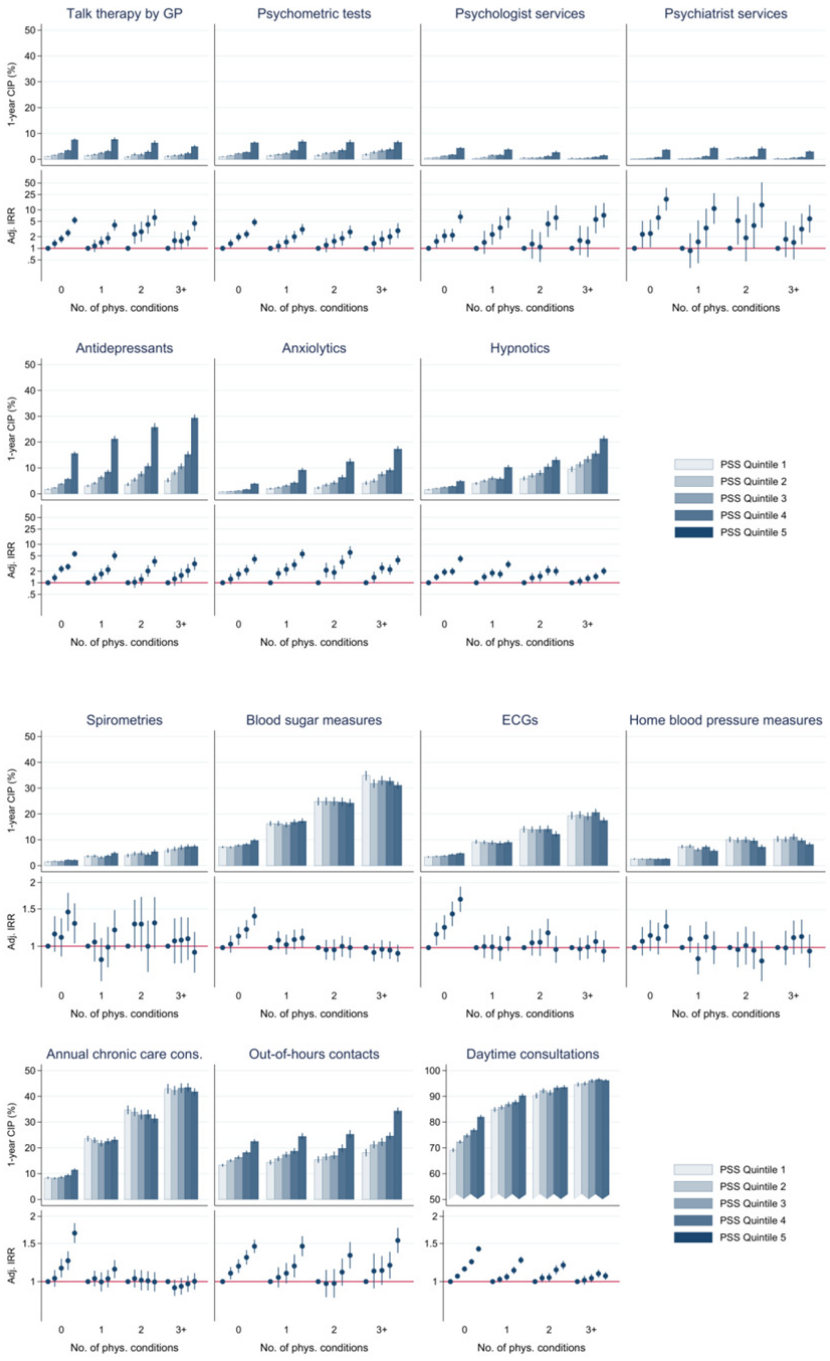

Figure 13. Cumulative incidence proportions and incidence rate ratios of primary care activities according to PSS quintile and number of physical conditions.

DESCRIPTIVE STATISTICS OF THE DANISH MULTIMORBIDITY INDEX

The Danish Multimorbidity Index was developed and used for all the studies of this thesis. The index was applied on the DNHS and bereavement cohorts to extract multimorbidity status for the follow-up periods. However, the dataset comprises the whole Danish population from age 18 years and over. The full population prevalence for each of the 39 conditions as defined by the algorithm on 1 January 2014 is shown in Table 11. According to the index, 55% had no long-term conditions, 20% had one, 11% had two, and 15% had three or more long-term conditions. Thus, 45% had at least one long-term condition and 26% had multimorbidity. Psychiatric illness was present in 8% of the population. Detailed sex- and age-group separated tables can be found in Appendix IV.

The calculated prevalence rates were compared with the prevalence rates reported in the study by Barnett et al. of Scottish general practices in 2007, the Danish National Health Survey of 2013, and the Global Burden of Disease study of 2015 for Denmark (Appendix IV).[18,20,132]

Table 11. Disease prevalence according to the Danish Multimorbidity Index

		Prevalence		
		Total	Men	Women
		N=4,368,069	N=2,146,403	N=2,221,666
Category	Disease group			
Circulatory system	Hypertension	19.6%	18.1%	21.1%
	Dyslipidaemia	7.9%	7.5%	8.2%
	Ischemic heart disease	3.5%	4.3%	2.7%
	Atrial fibrillation	2.5%	2.9%	2.1%
	Heart failure	1.1%	1.4%	0.8%
	Peripheral artery occlusive disease	1.9%	2.2%	1.7%
	Stroke	2.6%	2.8%	2.5%
Endocrine system	Diabetes mellitus	6.5%	6.7%	6.3%
	Thyroid disorder	3.0%	1.0%	5.0%
	Gout	1.0%	1.5%	0.5%
Pulmonary system	Chronic pulmonary disease	4.4%	3.8%	4.9%
and allergy	Allergy	2.3%	1.8%	2.7%
Gastrointestinal	Ulcer/chronic gastritis	1.9%	1.9%	1.8%
system	Chronic liver disease	0.8%	0.9%	0.7%
	Inflammatory bowel disease	1.1%	1.0%	1.2%
	Diverticular disease of intestine	1.8%	1.6%	2.0%
Urogenital system	Chronic kidney disease	0.7%	0.8%	0.6%
	Prostate disorders	2.4%	4.7%	0.1%
Musculoskeletal	Connective tissue disorders	2.0%	1.2%	2.8%
system	Osteoporosis	3.0%	0.9%	4.9%
	Painful condition	4.0%	2.8%	5.3%
Haematological	Anaemias	1.5%	1.1%	1.8%
system	HIV/AIDS	0.1%	0.1%	0.1%
Cancers	Cancer	3.0%	2.9%	3.2%
Neurological	Vision problem	5.0%	4.0%	6.1%
system	Hearing problem	5.3%	5.7%	5.0%
	Migraine	1.0%	0.3%	1.7%
	Epilepsy	0.8%	0.8%	0.8%
	Parkinson's disease	0.2%	0.2%	0.2%
	Multiple sclerosis	0.3%	0.2%	0.4%
	Neuropathies	1.0%	0.9%	1.1%
Mental health	Mood, stress-related, or anxiety			
conditions	disorders	1.8%	1.4%	2.1%
	Psychological distress	4.7%	3.2%	6.1%
	Alcohol problems	0.6%	0.9%	0.4%
	Substance abuse	0.3%	0.4%	0.2%
	Anorexia/bulimia	0.1%	0.0%	0.2%
	Bipolar affective disorder	0.4%	0.3%	0.5%
	Schizophrenia or schizoaffective			
	disorder	0.6%	0.7%	0.5%
	Dementia	0.6%	0.5%	0.7%

CHAPTER 5:

DISCUSSION OF METHODS

STUDY METHODOLOGY

PSS as a measure of psychological stress

Several measures of stress appraisal have been developed over the years, but they have different focuses.[133] The choice of using the PSS instead of other stress or stress-related instruments (e.g. the General Health Questionnaire [GHQ]) in our studies was partly pragmatic; the decision to include the PSS in the DNHS was taken by the steering group behind the national surveys before our research questions were developed. Fortunately, this meant that PSS data were available for a large cohort with sufficient follow-up time at the time of our studies, which allowed us to examine rare outcomes, e.g. mortality or small subgroups. The PSS was found very suitable for our study aims; it is fairly general and free of context, and is recommended for use in both healthy and ill populations.[133] In addition, it seems to be constant over longer periods of time.[134] The PSS has been psychometrically tested and has shown good properties on internal consistency reliability and test-retest reliability in several studies (Cronbach's alpha and correlations coefficients > 0.70).[93] In our study population, Cronbach's alpha was 0.88. Exploratory and confirmatory factor analyses have been performed and suggest that both a one- and two-dimensional (positive and negative stress dimensions) structure exists.[93,94] We used the PSS as originally intended; as a one-dimensional scale of stress.

The stress construct measured by the PSS is thought to be independent, but several studies have shown that it overlaps with other constructs.[90,91,93] The PSS moderately correlates with measures of depression and anxiety symptoms, e.g. the Beck Depression Inventory (BDI-II: r=0.67),[135] the Hospital Anxiety and Depression Scale (HADS-T: r=0.72),[136] and the GHQ (GHQ-12: r=0.59–0.61).[137,138] This is not surprising as altered stress perception is part of several psychiatric syndromes. The PSS provides a broader assessment of mental health than clinical instruments developed to screen or diagnose (probable) depression and

anxiety disorders. Clinicians may, therefore, not know how to interpret it intuitively, and it is more difficult to operationalise in terms of caseness as there is no cut-off value. However, it was not the purpose of our research to validate the PSS as a clinical instrument, but rather to focus on psychological stress below the threshold for psychiatric disease in the background population.

Bereavement as a measure of psychological stress

Bereavement was used as a proxy for psychological stress based on literature suggesting that it is extremely stressful to lose a spouse, but also because spousal loss is independent of the bereaved person's own health status.[81,86] Furthermore, it is an event that occurs frequently and is fairly easy to measure using the Danish Civil Registration System. However, it is not certain that this widowhood effect on mortality is attributable to psychological stress alone. The social and economic setting, nature of the relationship, years together, time in life, acute or expected death, etc. may also influence how bereavement affects a person.[139-144] The social and economic position of the bereaved person is affected too, and the effect of widowhood may change over time from acute grief and depression to social isolation. Yet, studies suggest that the effect of bereavement is not caused by selection, for instance by couples sharing socioeconomic background, lifestyle, risk attitudes, or access to healthcare,[145] and this indicates a causal effect.

ACSC as an indicator of quality of care

In study III, we focused on preventable hospitalisations to investigate the ability of the healthcare system to handle persons with high perceived stress levels, particularly the crossing between primary and secondary care sectors. After reviewing different measures of suboptimal health care, such as emergency

admissions or rehospitalisations, we chose to utilise the concept of ACSCs. The included conditions vary,[146] but we used the standard list from the US Agency for Healthcare Research and Quality.[67]

The justification of ACSCs as indicators of healthcare is based on a preventive treatment potential in primary care. For the patient to be admitted, there should be a relevant exacerbation or progress of disease, a GP who reasons that hospitalisation is best for the patient, access to a hospital department, and a consenting patient. These requirements are partly influenced by the patient-GP relationship regarding chronic care over time, e.g. early prevention, adequate chronic care consultations, and treatment adherence, but the natural history of the disease plays a role; some deterioration of chronic disease is bound to happen even if the definition of the ACSCs takes this into account.[67,146]

The Danish Multimorbidity Index and the multimorbidity paradigm

The Danish Multimorbidity Index was developed primarily to supply the variables of multimorbidity in our studies. The index was strongly inspired by existing indices for comparability and has been reviewed locally by epidemiologists and clinicians at the Research Unit for General Practice, Aarhus, and externally by international collaborators. In addition, it has undergone peer-review before publication. However, no formal validation process has been performed due to the lack of a gold standard and the massive scale of data; chart reviews of 39 conditions on the whole population are beyond the scope of this PhD. However, prevalence estimates of the chronic conditions with large public health impact (e.g. cancer, diabetes, ischemic heart disease, COPD, and mental disorders) in the Danish Multimorbidity Index are comparable to national and international estimates. Yet, variation exists due to differences in the definitions of diseases, the available data, and the population under study. In study I, a

number of sensitivity analyses were performed to benchmark the results using the new multimorbidity index against other measures of multimorbidity, i.e. self-reported diseases, raw disease count, and the weighted Charlson Comorbidity Index score, and the results were consistent.

The general idea behind the multimorbidity paradigm is that seeing the whole patient is more than seeing all of his or her individual diseases separately. In other words, having multiple conditions is more complex than just the sum of the individual diseases. However, for practical reasons, multimorbidity is often reduced to "having two or more conditions" from a certain list in research, which does not reflect the complexity of the concept. Logically, if the list of diseases is long, the risk of being multimorbid is higher.[12] This standard approach often results in heterogenic groups of persons with multimorbidity. Admittedly, fully characterising and categorising persons with complex mental and physical disease history is difficult. Two very different approaches to incorporating the complexity of multimorbidity are using advanced statistical cluster analyses of diseases[147-150] and comprehending multimorbidity through qualitative research.[151-153] We chose a conventional epidemiological approach and based our disease list on previous research regarded relevant to primary care. Statistically, we countered heterogeneity in multimorbidity groups by weighting estimates by the actual individuals in the groups and adjusted estimates by the diseases individually instead of using disease counts.

INTERNAL VALIDITY

Selection bias

Selection bias affecting the study estimates may arise if study participation is associated with the exposure (here: psychological stress) and the outcomes of interest. However, if participation is only associated with the exposure or the outcome, the estimates tend to be biased towards the null hypothesis.

Participants for our cohort studies were sampled from the target population (all adult Danish citizens). As all Danish citizens are registered in the Civil Registration System, we experienced no loss to follow-up in any of our studies. We thus had full information for all individuals during the time under study (time at risk). If participants left the country or died, this would be registered on a daily basis, and such person would no longer contribute to the study with person time.

Danish National Health Survey cohort

The initial selection of participants for the DNHS cohort (studies I, III, and IV) was based on two steps. The first step was the sampling mechanism applied for the invitation to participate in the nationwide study. The second step was the voluntary return of the completed survey questionnaire. To achieve the best possible representation of the sampled population on both a local and national scale, different sized sub-samples were drawn randomly from all municipalities.[111] The random sampling process on a national level should avoid selection bias on this first step. However, it is important to note that the Region of Southern Denmark chose not to include the PSS in their questionnaire, which was an eligibility criterion for study participation. Citizens from the Region of Southern Denmark were only included in our studies via the national sample questionnaire that did include the PSS, but this resulted in a much smaller

fraction of participants from this region. Apart from reducing the sample size, we do not consider this to be problematic as the overall composition of citizens in this region resembles that of the other Danish regions.

The survey response rate was 56% in our eligible population. Response rates of this size must be expected in large nationwide surveys, and our initial power calculations took this into account. This magnitude of non-response could introduce bias if systematic differences were found between respondents and non-respondents, and the epidemiological criteria of associations with exposure and outcome were fulfilled. Being aware of this potential issue, the survey data administrators at the National Institute of Public Health calculated a calibrated weight to each survey participant to counter the differential non-response.[111] This was useful for disease prevalence estimates that should be generalisable to the target population. Due to some of our statistical methods (e.g. multiple imputations) and other outcome measures than prevalence, we approached the differential non-response actively by other means: As we knew the CPR number of all randomly invited non-respondents, we used register data to characterise non-respondents and to perform non-response analyses in all our survey-based cohort studies.

Because our main exposure was self-reported stress, we had no means to access this in the non-respondents. However, we studied the association between psychiatric illness (i.e. a register-based proxy of psychological stress) and our outcomes separately for respondents and non-respondents in study I, III, and IV. The results revealed that respondents and non-respondents had comparable relative risks of outcomes when using the stress proxy and adjusting for obtainable register variables, e.g. multimorbidity status and socioeconomic factors which were also used in the main analyses. In the analysis of ACSC-related hospitalisations, we also applied inverse probability weighting of the non-respondents' characteristics with the same confident result (see full

articles/supplementary materials of studies I, III, and IV for estimates and further details).

Bereavement cohort

Study II was purely register-based, and the data on both exposure (bereavement) and mortality had high validity. However, details on relationships beyond that of spouses, registered partners, and cohabitating persons are not available, so persons living together as partners in unconventional ways may not be registered as such, and some partner deaths may thus not have been be captured. This problem is assumed to be small and would tend to bias mortality estimates against the null hypothesis.

With certain reservations, we conclude that the effect of selection bias on estimates were minimal and conservative; they only tended to blur the true associations and did not cause considerable problems in our studies.

Information bias

Information bias arises if misclassification of exposure, outcome, or confounding control variables occur in the study. All data on variables in our studies were obtained from either nationwide registers or the DNHS, both of which have different strengths and weaknesses.

Information from Danish registers

Danish registers are valuable to epidemiological research owing to their prospective recording of data independently of the research questions at hand. This ensures that any misclassification is inherently non-differential, i.e. a true effect can be overlooked, but an observed effect cannot be dismissed as due to

information bias. When relying on data that are primarily collected for administrative and clinical purposes, the data quality is paramount.

Danish register data are generally of high quality and have been validated several times.[108] The data from the Civil Registration System on e.g. sex, age, and vital status are regarded as virtually flawless, whereas the validity of e.g. hospital diagnoses and cause-specific mortality may be improved.[108,113,120] The validity of the data on educational attainment is high for birth cohorts from 1945 onwards, but it was lower before 1945.[121] Data from Statistics Denmark on educational attainment and civil status are updated annually, which could lead to misclassification. For instance, a man who is divorced and whose ex-wife dies within the same year may be considered bereaved. This is a misclassification by definition (the person was single at the time of the event). Still, the emotional relationship does not necessarily end on the day of the divorce, and the man may experience stress in relation to losing his ex-wife anyway.

Our primary source of data for study IV was the Danish National Health Service Register. Being private contractors paid by the public health system, all provided GP services are recorded in this register for remuneration purposes. This means that reporting is incentivised economically and thus of good validity. A contract-based specific list describes which services are eligible for remuneration, but the list does not reflect all aspects of practice work. Thus, uncertainties with the GPs on which services to charge for and differences in reporting habits between GP clinics remain.[119] Registrations are collected on a weekly basis so the exact date of the service is not known; we only know that it occurred during a specific week. Non-GP primary care services are also assessed in this study, e.g. psychological services after referral. These publicly reimbursed referral-based services are probably well recorded, but they include only a fraction of the psychologist services offered to patients in general. Some

persons receive psychologist treatment privately, via health insurances, or through public programmes outside the healthcare system.

Information on multimorbidity

When classifying persons with disease using register data, several risks of misclassification exist. The multimorbidity algorithm captured a number of hospital-diagnosed diseases by combining various registers. We had no way to determine disease stage or severity outside the ICD-10 diagnostic system. The debut of many diseases is initially indistinct with increasing symptom burden. The effects of the diseases on the individual may occur before the actual diagnosing, or the diagnosis is established in primary care but is not recorded in registers and thus cannot be captured. Information on when diseases are not affecting the person anymore is hard to obtain. The diseases included in the Danish Multimorbidity Index are long-term diseases with supposedly prolonged effects on the individual, but time limitations (e.g. when controls or treatment appears to have stopped) are incorporated in the disease-defining algorithm to account for the temporal factor.

An important limitation is the lack of a primary care diagnosis register. Misclassification may occur because the multimorbidity index algorithm cannot capture all relevant diseases that are primarily managed by GPs. Efforts have been put into designing rules of the algorithm that capture the diagnoses based on treatment in primary care via prescriptions (e.g. diabetes-specific medication) to achieve better capture. The data quality on redeemed prescriptions is high, and all Danish pharmacies are covered.[117] However, no information is available on actual treatment adherence or the indication for prescribing the medication; this is based on assumption. For certain drug categories, the indications can be very broad. For example, analgesics are indicated in numerous diseases and are thus very unspecific. Acknowledging this, we defined a disease category based

on the symptoms of pain instead of on an anatomical or physiological entity to capture e.g. musculoskeletal diseases that were not categorised elsewhere. We wanted to include depression and anxiety disorders, which are often treated with antidepressants, but these also have broad indications for use, and we had to categorise them, rather unspecifically, as psychological distress (not to be confused with psychological stress). Even so, some misclassification may occur because neurological pain is also treated with antidepressants. Conditions diagnosed by a GP but not medically treated were obviously not included (e.g. diabetes without medical treatment). However, there seems to be good accordance between prevalence estimates of high impact diseases from the multimorbidity index and acknowledged disease estimates, which speaks against a high degree of misclassification.

Self-reported information from the DNHS

The information obtained through a questionnaire is influenced by the respondent's (knowingly or unknowingly) interpretation of the question, personal beliefs and factual knowledge on the issue. The ability to measure perceived stress is dependent on the subjective feeling of stress and can hardly be misclassified as such. However, the construct validity determines whether the instrument is good at measuring what it is supposed to measure, e.g. stress appraisal.

Answering questions rely on memory. Misclassification may thus occur if the memory is biased by exposure and outcome, namely recall bias.[129] In our survey-based studies, all self-reported variables were assessed at baseline or start of follow-up so outcomes were separated in time from these variables; potential misclassification would hence be non-differential. We expect recall bias to be minimal as participants were specifically asked about e.g. stress level within the last month, drinking within the last week, or current smoking habits.

Self-reported diseases among patients may not always agree with a physician's view on diseases or understanding of what constitutes a disease or a risk factor for disease. A self-report approach could help capture more diseases, but possibly with lower specificity. Misclassification dependent on other self-reported variables may occur. We decided to rely on the registers as diagnoses recorded here were authorised by physicians. Sensitivity analyses comparing outcomes adjusted for self-reported versus register-based diagnoses were conducted in study I with concurring results.

Self-reported lifestyle factors should generally be interpreted with caution, but they are important to consider and are not obtainable from registers. Alcohol consumption may be underreported[154] and physical activity overreported. This misclassification is thought to be non-differential and valid for adjusting comparisons between groups. Lifestyle items also had the highest number of missing information, and multiple imputations were used to avoid excluding all persons with just a single missing variable.

Confounding

Confounding is the mix-up of effects and can impede the estimation of the true associations between exposure and outcome if confounding is not controlled. In an epidemiological sense, a variable is a confounder if it is associated with the exposure and affects the outcome, and not solely a mediator of the association.[129]

Observational studies are prone to confounding, especially if the causal relations under study are complex. Unlike randomised controlled trials, in which potential but unmeasured confounding factors are thought to be randomly distributed between groups, observational studies rely on the best possible information on confounders. If this is not fully achieved, residual confounding

may occur and lead to both overestimation and underestimation of the studied associations.

DNHS cohort studies

Combining register-based and survey data at the individual level gave us a unique dataset with information on many potential confounders. We were able to control for key demographic and socioeconomic factors, detailed health information from the multimorbidity index, and lifestyle factors. Being able to control for these potential confounders was important because perceived stress is associated with many of these personal and health- related factors that could also affect the outcome.[73] Even with a wide range of study variables, more unmeasured factors could interact in the complex associations studied, which could have resulted in residual confounding. Additionally, as described earlier, misclassification may challenge controlling for confounding from known variables.

Bereavement cohort study

The bereavement cohort was observed in a natural experiment of imposed stress, which is otherwise difficult to perform in an ethically sound way (e.g. in randomised controlled trials) if the stress is supposed to be severe and persistent over a long period of time. The cohort was followed from back in time (1997) and forward. The natural experiment design can be justified because all register data were prospectively collected completely independent of the research question and cohort members. As the data collected from natural experiments are independent and longitudinal by design, they potentially allow for better causal inference than survey data as these can be confounded by the participant. However, residual confounding cannot be completely avoided as the restrictions

and firm control of parameters in intervention trials is not possible in the real world.[155]

In study II on bereavement, we used matching as initial confounding control. The resulting analysis effectively controls for the matching variables (birthdate and sex). We subsequently adjusted for multimorbidity status and socioeconomic factors in the multivariate analysis. Relying solely on registers meant that information on lifestyle factors was unobtainable, but these could be intermediate variables that should not be adjusted for (see *Intermediate variables* below).[129]

Multimorbidity adjustment

Information on 39 mental and physical conditions was included from a wide range of disease categories and body systems. Multimorbidity was considered both as a stratification variable and an adjustment variable. Residual confounding could arise if a simple disease count measure was used for adjustment because diseases affect the outcomes differently. The approach of individual condition adjustment improved this by introducing an ad-hoc weight related to the outcome of interest. Another approach is using multimorbidity indices with predefined weights, such as the Charlson Comorbidity Index, but weights are often calculated in distinct populations for the purpose of selected outcomes. Hence, the adjustment effect may vary depending on the outcome.[12]

The stratification by multimorbidity level was based on disease count, which categorised persons with the same number of diseases, but not the same composition of diseases. Diseases may cluster resulting in a tendency for multiple diseases to occur at the same time, e.g. within the metabolic syndrome domain. To account for this, risk-time weighted (to account for the number of persons) average risks (to account for the composition of diseases) were calculated for each multimorbidity group.

Psychiatric conditions

A special focus was put on psychiatric conditions as confounders of the observed associations of psychological stress. In the DNHS and bereavement study cohorts, the prevalence of persons with psychiatric conditions was around 8%. Although this is a minority, their psychological stress levels were supposed to be high and could potentially drive the observed associations. Therefore, sensitivity analyses were performed in all studies by stratification or restricting the analyses to include only persons without psychiatric illness. The main findings were robust for the population without psychiatric disorders.

Intermediate variables

It is important to note that one should not blindly adjust for all available variables at hand. Adjustment variables should be selected before the study is conducted and should be based on a priori knowledge of the causal relations.[129] Intermediate variables (i.e. variables that are part of the causal pathway from exposure to outcome) should not be adjusted for as this would underestimate the true association.[129] In our studies, lifestyle factors may be intermediate variables; a classical example is work-related stress leading to increased alcohol drinking that leads to liver disease, hospitalisation, and premature death. If this is the true causal path of events, alcohol consumption should be left out of the analysis. Another example is disease emerging during follow-up as a consequence of stress that eventually may lead to death. The actual circumstances and role in the causal interplay are, however, very hard to determine for all variables, and various assumptions must be made. In all studies, we controlled for confounders in steps, starting with fairly crude models and adding potential confounders to the analysis. The most adjusted

estimates are often presented as main results because they are more conservative estimates, although more true estimates may lie in other models.

Statistical precision and methods

Precision

The large cohort sizes ensured that the potentially small effects of stress after efficient control for confounders could be detected without losing too much statistical precision.

In all performed studies, the overall estimates had high precision with fairly narrow confidence intervals. Stratified analyses reduced the precision for subgroups that came out small, e.g. persons in the fifth PSS quintile with low educational level and four or more health conditions. The matching in study II was a way to effectively control for confounders and still retain high statistical precision.

Multiple imputations

By default, regression analysis will exclude all study subjects with missing information on just a single variable. With the large number of variables, especially in the DNHS cohort studies, a substantial part of the study population (and all their information) would be omitted from the analyses. To include the largest possible mass of information, we used multiple imputations to obtain the statistically most probable value when information was missing. This has been shown to be a statistically sound and more efficient approach than conducting complete-case analysis if certain criteria are fulfilled; most importantly, information has to be missing at random and is yet conditional on the observed information (if information is missing completely at random, estimates would be unbiased, but this is rarely the case). [131,156-158] This is a plausible approach in our

survey-based studies, where answers in different categories may be correlated, whereas "missingness" is random. We included all analysis parameters in the imputation model as previously recommended to obtain unbiased results.[131] The complete-case sensitivity analyses in our studies did not differ substantially from the analyses using multiple imputations. In study II, education was the only variable with missing information, and the main analysis was a complete-case analysis.

PSS parameterisation

The choice of categorising the PSS score into quintiles was based on convention and previous literature on adverse outcome, especially for the 20% most stressed.[73,127] However, the PSS in itself suggests no such subdivision, and no clinical threshold or specific condition demands a certain diagnostic cut-off value.[90]

Using the PSS sum score as a linear predictor would assume a linear relationship between perceived stress and outcome, which may be too simplistic. Instead of grouping the 20% highly stressed from the rest by dichotomisation, quintiles of the score allowed us to assess a potential dose-response relationship between perceived stress and outcomes. In studies I and III, we further applied restricted cubic splines to assess the functional form of the association over the full range of the PSS scores. These results supported the general findings, even though the confidence limits were wide.

Regression models

The choice of regression models was based on the outcome, but this choice also reflected tradition and more practical issues. For all studies and regression models, time-at-risk was accounted for to avoid immortal-time bias,[159] but it was

accounted for in different ways depending on the type of regression used. The Cox proportional hazards model used in studies I and II is commonly applied in time-to-event analysis and does not require specification of the underlying hazards. The assumption of proportional hazards was checked using log-log plots. For the count measures, two different approaches were used: Poisson regression and negative binomial regression. Negative binomial regression is an extension of the classical Poisson regression that accounts for over-dispersed count outcome variables. In study IV, this was efficiently applied to primary care service data. However, in study III, negative binomial regression models failed to converge for several ACSC outcomes. We used Poisson regression instead, and the estimates were virtually the same for the converged outcomes that we could compare with (unpublished data).

Excess risk

Presenting excess risks associated with a certain exposure or other measures related to attributable fractions is a challenging issue as many pitfalls in the interpretation and of correct use exist.[129,130] Attributable fractions are based on a counterfactual approach, where a causal assumption is made: that the exposure is fully responsible for the observed effect after adjustments and that removing the exposure would fully relieve the persons from the adverse outcome associated with the exposure. This is obviously not always the case, but it estimates the potential size of the effect in absolute terms and the potential implications for public health.

EXTERNAL VALIDITY

Generalisability

The population-based design with random sampling and large study cohorts should guarantee a high degree of national representativeness; participants were of both sexes, adults of all ages, healthy and sick, from all socioeconomic classes, and from all parts of Denmark. The vast majority of study participants were ethnic Danes.

For the DNHS cohort, the invited sample was representative of the Danish adult background population.[111] Nevertheless, differences between respondents and non-respondents existed, and fewer were sampled from the Region of Southern Denmark. However, non-response analyses did not show marked differences in the main study estimates when comparing respondents and non-respondents in studies I, III, and IV; this speaks in favour of good external validity.

The bereavement cohort consisted primarily of middle-aged and older persons. Bereavement was most common in these age groups, and the reference persons were matched on birth date and sex. However, a sensitivity analysis showed a strong effect of bereavement in both the younger and the older study population. Bereavement is a severe life event that generally inflicts a lot of stress, but generalisation to all severe life events may be problematic. The generalisation of bereavement as a measure of stress has been discussed in the *Study methodology* section.

Stress is a widely accepted concept, but cultural differences exist. The PSS has been translated into numerous languages from all the major language groups, and the underlying stress construct is used worldwide. If the observed effects of psychological stress on mortality are causal, we would expect our results from studies I and II to be widely generalisable, at least in a western population.

The findings on healthcare utilisation in studies III and IV are dependent on the structure and the accessibility of the healthcare system. The setting in Denmark with universal and free healthcare and hence unlimited access to the GP and hospitals may affect the results and reduce the generalisation to countries with other healthcare systems, e.g. insurance-based healthcare. The results on ACSC-related hospitalisations and the use of primary care services are likely to be generalised to countries with a similar primary care system and a strong gatekeeper function, e.g. countries in Northern Europe and Scandinavia.

CHAPTER 6:

DISCUSSION OF RESULTS

RESULTS IN GENERAL

In this thesis, we found significant associations between the level of psychological stress and three investigated factors: death, potentially preventable hospitalisations, and primary care utilisation. Multimorbidity aggravated adverse outcomes, especially in absolute terms. Multimorbidity was accounted for in the best way possible, and much effort was put in meticulous control of potential confounding variables although residual confounding cannot be excluded.

To the best of our knowledge, these are the first population-based longitudinal studies to include comprehensive data on mental-physical multimorbidity in the examination of psychological stress.

Here, study-specific findings are discussed and compared with the existing literature in the field. Additionally, the possible mechanisms behind the presented findings and potential causality issues are discussed.

STUDY-SPECIFIC RESULTS

Study I

All-cause mortality was the main outcome of interest in this study. This specific outcome was chosen to establish a link between the subjective measure of perceived stress and an indisputable hard endpoint with strong impact on public health. Being a rare outcome, this tested the overall impact of the exposure and the power of both the cohort and the multimorbidity index.

The mortality estimates attenuated in the four analysis models, which indicates that confounding by adjustment variables was likely. The fully adjusted estimates became statistically insignificant for lower values of the PSS (quintile one and two), although the trend remained significant. The identified dose-

response relationship suggests that an underlying mechanism exists and that the observed association is not purely seen by chance. Formal additive and multiplicative interactions between the PSS and multimorbidity level were tested and found insignificant. However, such tests require large amounts of data, and the study may have been underpowered to show this. In the stratified and rescaled analyses, it was clear that mortality was affected independently by multimorbidity burden and PSS level. Still, high perceived stress affected persons with multimorbidity more in absolute terms. Excess deaths associated with perceived stress rose with multimorbidity level. Such numbers should be interpreted with caution, as also described earlier, because other factors that have not been accounted for could play an important role for the overall mortality in those with multimorbidity, e.g. social network and treatment adherence. The association between PSS score and mortality may also be explained by confounding, e.g. if the PSS score is merely a marker of disease severity.

Our findings are in line with previous studies of self-reported mental health and mortality, e.g. using the GHQ.[78,160-163] The items of the GHQ give a general impression of psychological distress with a particular focus on symptoms of depression and anxiety, whereas the PSS have a more global focus on stress. The referenced studies had limited information on mental-physical multimorbidity, but they all included data on cause-specific mortality. Ad-hoc or single item measures of stress perception and mortality are generally ambiguous.[164,165] Stress has also been shown to reduce mortality, but this was probably related to confounding.[166] The increased mortality associated with stress is also consistent with studies on psychiatric stress-related disorders, e.g. post-traumatic stress disorder.[167]

Study II

The aim of study II was to use another scientific perspective on psychological stress and relate it to the same endpoint as in study I: mortality. We found bereavement to be associated with acutely increased mortality after the loss, but the increased mortality remained elevated for the entire study period of 17 years. Extensive literature on spousal bereavement and mortality exists.[86,87,142] The mortality of the bereaved has been shown to be high in both the short and the long term,[87,142,143,168] but attenuating over time[87] as also confirmed by our findings.

Pre-bereavement health has been investigated before,[141] but it has not been investigated as extensively as in this study, where both mental and physical health is considered. The cause of death was mostly found to be natural, which was probably related to exacerbation of chronic disease, although we found a noticeably high relative risk of unnatural deaths, e.g. suicide, which is also in line with previous studies.[169] Physical health and socioeconomic factors have been examined as potential mediators of the widowhood effect, but this cannot fully explain the effect.[141,143]

Compared with study I, the information on the timing of the exposure is potentially better. Even if the PSS measures the stress level within the last month, it is unknown whether the stressed situation is new or has been there for a long period of time. Even though the impact on spouses and caregivers may precede the actual bereavement,[170,171] the day of the event is well recorded, and the time-dependent effect found in study II supports this.

Study III

The risk of ACSC-related hospitalisations rose with increasing stress levels in a dose-response relation, not unlike what was found in the mortality studies.

Additionally, the prognosis after hospitalisation was impaired with higher stress-associated 30-day mortality after admission. We were able to adjust for underlying and predisposing conditions, socioeconomic status, and lifestyle; the resulting decrease in risk supported that confounding or mediation was present. If persons with mental health problems have more physical health problems, the background rate of ACSCs is higher, but this should be well accounted for by using the multimorbidity index of predisposing conditions in the analysis.

Many factors must be accounted for when interpreting perceived stress as a cause of ACSC-related hospitalisations. The patient's socioeconomic position[172] and lifestyle[173,174] in addition to motivation, resilience, and self-efficacy regarding treatment[175] are all factors that highly affect the appraised stress level. The GP may react in response to this with a lower threshold for admitting the patient to the hospital. Importantly, this may be the most clinically appropriate thing to do. Some or all of this can explain the observed link between perceived stress and the high ACSC-hospitalisation rates, but it is difficult to disentangle what are the most important contributors based on the available data. Interestingly, stress seems to affect a broad range of ACSCs; acute and chronic, highly severe and less severe. If perceived stress is merely a marker of disease severity, this may also explain the association between stress and ACSC-related hospitalisations, but this cannot be deducted from the register or survey data.

Existing literature has shown a strong link between mental illness, e.g. depression, bipolar affective disorder, dementia, schizophrenia, and hospitalisations for ACSCs. [69,70,176-178] Studies have primarily been based on administrative data, although some self-reported data, e.g. self-reported health status, have been used for adjustment. To our knowledge, perceived stress has not previously been investigated in relation to ACSC-related hospitalisations.

Study IV

Study IV showed an overall increase in the primary healthcare utilisation associated with perceived stress; this remained significant after adjusting for the most obvious confounders, i.e. mental and physical conditions that understandably would lead to increased visit frequency. Existing literature suggests that multimorbidity,[56,126] mental illness, [53,179] and psychosocial factors,[180-182] including stress, predict a high frequency of contacts with the GP. Gili et al.[54] compiled many of these factors in a model and found that both mental and physical health affect healthcare consumption, which is in accordance with our results. Our study adds to the literature a more comprehensive take on multimorbidity and extends our knowledge in this field by investigating several specific primary care services that have not previously been investigated in a longitudinal study design.

Even though the dose-response pattern of the PSS score applied to all mental health related services, psychotropic treatment was dominant in absolute terms compared with GP talk therapy and psychologist visits. It is worth noticing that although persons with diagnosed psychiatric illness were accumulated in the fifth PSS quintile, most persons in this quintile did not have any psychiatric diagnosis. This should be kept in mind when interpreting the results. It is also important to remember that we did not obtain information on psychologist services or other therapeutic services that were paid for outside the public healthcare system; these may account for a substantial part of all psychotherapy given.

The interplay between perceived stress level and multimorbidity was particularly interesting. When we compared those with multimorbidity to those without, a lower percentage of persons with multimorbidity received talk therapy, whereas the opposite was true for psychotropic medication. This pattern attenuated in the adjusted IRRs.

The lack of association between perceived stress and chronic care services for those with multimorbidity was noteworthy and contrasted the pattern in all mental health related services, daytime consultations, and out-of-hours contacts. If perceived stress is a marker of disease severity in those with multimorbidity, more chronic care services would be expected (or at least considered to be appropriate). The observed indifferences may indicate suboptimal primary care, or it could be that those with the highest levels of stress and multimorbidity are more frequently managed in secondary care, e.g. outpatient clinics due to the complexity of their disease(s), which could result in fewer chronic care services from the GP. The high use of out-of-hours services, which is often regarded as less appropriate in relation to chronic care, could suggest that stressed persons with multimorbidity may receive suboptimal chronic care.

THE STRESS MECHANISM

In this thesis, psychological stress has been approached from different angles or paradigms, including the related differences in methodology. The strength and weaknesses have been discussed, which leads on to an overall discussion of the findings and the mechanisms behind them: Is the relation between psychological stress and the observed outcomes part of a causal chain? If stress is modifiable, interventions may be designed to alleviate the stress and optimise the healthcare. Causal inference should not be taken lightly and should definitely not be based on observational studies alone. However, in the following discussion of our findings, we will dive into some of the aspects related to causation as originally proposed by Hill: The observed association should be consistent, strong, specific, timely appropriate, biologically plausible, and preferably be confirmed by experiments.[129,183]

Consistency and strength

Regardless of paradigms, methods, and outcomes, we consistently found psychological stress to be a prognostic factor. This is also in line with the majority of the literature. For the adjusted estimates, a 30–50% increase in the relative measures of risk associated with high stress levels seemed to be the overall magnitude of effect; this was found for all-cause mortality (both PSS and bereavement-associated, except for the first month after bereavement), ACSC-related hospitalisations, and both daytime and out-of-hours contacts to the GP.

Across studies, we found that the underlying risk of the investigated outcomes increased with increasing numbers of co-existing conditions. Formal multiplicative and additive interaction between multimorbidity status and stress levels was tested, but these links were not found statistically significant. Still, in absolute terms, more adverse outcomes were associated with psychological stress for those with multimorbidity.

The strength of the observed association is affected by the underlying degree of stress impact. Personal resilience opposing stress is incorporated in the PSS; the personal situation should be regarded as stressful, but the coping mechanisms should be exhausted before stress would be reflected in the PSS. This is not the case with bereavement, where the event is assumed to be so stressful that stress is perceived by most people. The level of stress obviously depends on the situation, the relationship, and many other things. The PSS score cannot be fully separated from the burden of disease and adverse lifestyle choices, whereas bereavement is independent of multimorbidity because the underlying event occurs in another person. However, both methods of measuring stress yielded similar multimorbidity-graded responses on mortality.

Specificity

It is important to establish that the exposure was in fact psychological stress, but measuring stress specifically and avoiding any confounding is inherently difficult. Our efforts to achieve rigorous control of confounding factors have been discussed. The natural experiment may be a more robust design in this way and is better than self-reported data to infer causality. However, the limitation of residual confounding needs to be stated again here.

Acute and chronic stress affects the body biologically in very different ways, and it is important to understand what has been measured in our studies. The PSS is based on experiences during the last month, but it reveals no information about recent stressful or relieving events or whether the stress level has been high for several years. Literature suggests that the score is relatively constant over time.[134] The bereavement proxy of stress may yield better temporal information as the stress level is thought to peak at the time of the bereavement. Our study suggests that the experience of bereavement has both acute and long-term effects, but stress levels may very well be elevated before the time of the spousal loss. With the resolution of time and the level of detail available, we cannot firmly conclude whether the associations could be due to biologically acute or chronic stress reactions, but we tend to think that chronic stress is the predominant reason.

Temporality

Independent of the characteristics of the stress exposure, cause and effect can only be established if the outcome comes chronologically after the exposure. Otherwise, reverse causation may occur. This is ensured by the prospectively recorded and timely precise register data and several years of follow-up. When assessing stress level at one point in time only, outcomes that are not too distant

in time could be a more plausible consequence of the outcome as the stress level may change over time.

Biologic gradient and plausibility

Dose-response patterns between perceived stress and all main outcomes were observed. The highest and most reliable estimates were found for the fifth stress quintile. Nevertheless, assessment of the functional form using restricted cubic splines did not reveal a sharp threshold for the effect at this spot; rather, a near-linear association was present. Previous literature has used the fifth quintile as an arbitrary cut-off value, but we find no solid justification for this. We had no way to grade the stress exposure from the bereavement. Still, if the assumption about a peak in stress at the time of the bereavement holds, the attenuation of stress over time is reflected by the observed attenuation of mortality risk, and this may be regarded as a temporal dose-response pattern.

Ongoing research in many biological, psychological, and medical fields aims to establish links between mental and physical health. We approached our research questions by using two paradigms of the understanding of stress, but we had no access to biomarkers of stress that could have supplemented our research from a third perspective. Our findings are in line with allostatic load theory, which is an example of theoretical framework that combines the processes leading from the perception of stress, over neural processing to the derived effect of stress on body organs and physical health.[76] In this context, there is no substantial difference between subjective symptoms of stress and subjective symptoms that combined constitute a syndrome defining a psychiatric disorder. Symptoms of various psychiatric disorders are experienced by many people (but to a lesser degree than in the case of an actual disorder). The clinical thresholds for disease are defined by the consequences that the individual psychiatric disorder may have. Our findings suggest that also sub-threshold psychological stress is

associated with an impaired prognosis, and sensitivity analyses differentiating between persons with psychiatric disease and persons without supported this.

Experiment

The scope of this PhD did not allow experimental investigation of interventions targeting stress and multimorbidity. Nevertheless, based on our findings, such interventions are intriguing and warranted. This will be discussed later in the *Implications* section.

CHAPTER 7:

MAIN CONCLUSION

MAIN CONCLUSIONS

The main conclusion of the thesis is that psychological stress was consistently found to be associated with adverse health outcomes and was also related to potential suboptimal healthcare when accounting for mental and physical multimorbidity. The Danish Multimorbidity Index was developed to support this, and the developed index was found viable to use.

Our two approaches to stress, self-reported perceived stress and bereavement as a proxy for stress, both showed a significantly increased mortality rate of about 40% for those with high stress levels, regardless of underlying multimorbidity status. However, most stress-associated deaths in absolute numbers occurred in persons with multimorbidity, especially severe multimorbidity. Being in the highest stress quintile without a diagnosed psychiatric illness was comparable to actually having a psychiatric illness in terms of relative mortality, but more excess deaths occurred in persons with high perceived stress than in those with psychiatric illness. Owing to our different approaches and study designs, we cautiously suggest that there may be a causal relation between psychological stress and mortality. The underlying mechanism is not fully understood.

Little is known about how to treat stress and no guidelines exist in Denmark. Yet, stressed persons in our studies were generally high users of primary care services, and most persons saw their GP regularly. In the primary care services related to mental health, we found a treatment preference of psychotropic medication over talk therapy. Among those with multimorbidity, high stress was associated with a care pattern for chronic care, which could be interpreted as less timely appropriate, e.g. relatively few preventive chronic care consultations and more acute out-of-hours contacts. In continuation hereof, persons with high stress levels were exposed to more potentially preventable hospitalisations and higher post-hospitalisation mortality. This may reflect suboptimal primary care, but it could also be due to interacting factors in the

patient, GP, and healthcare system. Suboptimal chronic care may thus play a role in explaining the increased mortality rate.

CHAPTER 8:

IMPLICATIONS, PERSPECTIVES, AND FUTURE RESEARCH

IMPLICATIONS AND PERSPECTIVES

Psychological stress is a popular concern, as also witnessed by the numerous referrals in the media and the big market for stress-relieving self-help literature. Everyone has a personal understanding of the word, but it is generally recognised that stress is bad for the health. Psychological stress is not a disease per se; it is rather seen as a risk factor. However, it has direct consequences for the health, and the potential of being modifiable makes it attractive for early prevention. This could be a task for the healthcare system if targeted attempts to prevent chronic disease follow. The increasing focus on stress and health has engaged policy-makers and has had a major impact on the economy as several initiatives have been launched to investigate better stress management, especially for work-related stress and faster returns to the job market.

Still, over-medicalisation of a perfectly natural phenomenon such as stress has the potential of labelling the many thousands of people who "only" feel stressed as sick (by referring to their condition as new "disease"), and such stigmatization may not be in the interest of society or the medical profession. Should persons with stress then be encouraged to see a psychologist or treated with antidepressants to alleviate the stress? Organisations similar to patient associations have already emerged for stress-affected people. A natural continuation of the discussion on medicalisation is the general debate on when and where to use screening programs. Many self-screening instruments for stress exist online, and the question is: Should the GP screen patients for stress systematically or opportunistically, or not at all? This is probably not yet a clinically relevant decision to make as no validated screening instrument for stress currently exists in clinical practice, and no protocolled treatment is recommended. This might also be unethical, at least when considering the prevailing criteria for screening.[184]

An increasing focus has been directed towards the consequences of multimorbidity and (with it) the understanding of mental health as an important risk factor. This development emerged from studies showing a strong link between psychiatric disorders and physical health. "No health without mental health" is now the mantra.[3] Still, multimorbidity research needs more large longitudinal and intervention studies to provide a better understanding of multimorbidity and to further develop the concept.[185,186] Interventions aimed at improving the outcomes for patient with multimorbidity have so far only shown modest effects, but the evidence is better when targeting mental-physical multimorbidity.[186] The topic has been debated in several leading medical journals,[3,187-190] and guidelines on treatment of multimorbidity have started to emerge, e.g. from NICE, which also incorporate psychiatric disorders.[191] Hopefully, multimorbidity models will develop and become more comprehensive to better reflect its inherent complexity (and not just a count of diseases) and guide clinicians in the treatment choices and thus improve the prognosis of the individual patients.

The link between stress and multimorbidity could substantiate efforts to treat stress more seriously in medicine. Persons affected by stress are sitting in every waiting room and in every hospital department, but the vast majority of clinicians do not consider stress. To the best of our knowledge, our studies are the first to place the long-term prognosis of psychological stress in a multimorbidity context. Patients with multimorbidity are under great stress from multiple symptoms, treatment burden, and low functional levels, and mental well-being in this patient group is consequently pivotal. From a public health perspective, many more are affected by some kind of stress than psychiatric disease. We believe that it is important to focus on mental health below the threshold for psychiatric disease because there might be a potential for early prevention. If counter-stress measures or better care management are

effective tools, a substantial number of deaths and costly hospitalisations may be avoided.

Stress interventions

Our studies are not the first to show that stress has consequences, but there has been an ongoing discussion on whether confounding factors such as lifestyle and physical health were the real cause of the problem. Our methods were methodologically strong regarding the causal interpretation, and the findings supplemented each other despite limitations in different methodological approaches. This further supports the argument for stress-alleviating intervention studies.

Two main approaches to stress intervention can be taken. You can concentrate on reducing the individual's perceived level of stress to improve the quality of life, the self-management of the chronic disease, and perhaps the allostatic load. Alternatively, you can try to accommodate the healthcare system to better embrace poor mental health below the threshold for psychiatric disorders and to facilitate the way through the system for persons with stress and multimorbidity.

Stress-alleviating interventions

Stress reduction can be achieved by removing the stressors, e.g. sick leave from a stressful work, but this can have both social and economic drawbacks and may not always be feasible. Some emotional stressors, e.g. family problems, are not easily removed or tend to return. Instead, improved coping or resilience could relieve symptoms. Serenity has been sought through religious practices, meditation, psychotherapy, alcohol, and iatrogenic treatment, e.g. anxiolytic medication. Lifestyle changes, such as increased physical activity, may reduce

the feeling of stress and improve the outcome of physical disease.[192,193] Such changes should be highly motivated to be accomplished, which can be difficult when there is limited mental energy. Cognitive behavioural therapy is recognised, well documented, and a popular tool among most psychologists and GPs.[194] Problem-solving therapy is a more pragmatic approach that aims to help the patient set goals, prioritize efforts, observe progress, and thereby obtain overview and stress relief.[195] Mindfulness-based stress reduction therapy (MBSR), which was originally developed by Jon Kabat-Zinn in 1979, has recently gained popularity. The methods of the eight-week program are inspired by Buddhism and have been clinically investigated in persons with e.g. post-traumatic stress disorder, anxiety disorder, or depression.[196,197] The mindfulness method has also been applied in persons with chronic diseases, but treatment effects have been modest, and high adherence to the time-consuming program is required.[198,199] However, policy-makers seem to have appreciated mindfulness as also indicated in the report *Mindful Nation UK* and by the implementation in the NICE guidelines.[200]

Collaborative and integrated care

Almost every healthcare professional meets patients with stress, but the focus on stress is primarily concentrated in general practice, occupational medicine, and social medicine as well as among psychologists. Mental health nurses and psychiatric specialists are also important, but their role is mostly limited to psychiatric patients in the Danish healthcare system. Naturally, limited resources are available to the healthcare system; this calls for a continuous prioritising of efforts and treatment offers. In a healthcare system with GPs serving as gatekeepers, it might be rational to manage stress-related health issues in primary care (where most chronic care is also performed) in order to reduce fragmentation and costs.[43,201,202] However, increased sharing of

knowledge and expertise across specialties (e.g. internal medicine and psychiatry) may be desirable for the benefit of the individual patient with mental-physical multimorbidity.[203,204]

Collaborative care models, where e.g. a nurse acts as case manager to coordinate the care between primary care and psychiatric specialists, have aimed to achieve this. The case manager can also offer conversational therapy and support for the patient as well as help with the medication. Collaborative care has shown good evidence for mental health problems, e.g. anxiety and depression,[205] including sub-threshold depression.[206] If such competencies are gathered and constitute an integrated part of the primary care practices, this is referred to as integrated care (even though the distinction between collaborative and integrated care is not consistently used).[62] These care models have been evaluated for use in chronic care when treating persons with mental-physical multimorbidity. In particular, coordinated treatment of depression and chronic physical conditions, e.g. diabetes and cardiovascular disease, has shown to improve the quality of life and depression scores. However, the effect sizes were small, the health outcomes and the health utilisation remained virtually unchanged, and the long-term prognosis is unknown.[186,207-210]

Another (less integrated) way for GPs to collaborate on patients with multimorbidity is through the multimorbidity clinics that exist a few places in Denmark. Patients with multimorbidity, including those with mental conditions, can be referred to these hospital-based outpatient clinics for a multi-specialty one-day assessment of their case with a comprehensive plan for prescribing/unprescribing, further examinations, and treatment suggestions. In this way, the GP retains the treatment responsibility and the continuity of care for the patients, but they receive specialty support for complicated treatment decisions.

Patient-centred care

The GP has a pivotal role in managing patients with mental-physical multimorbidity. The bio-psycho-social approach to medicine is a core value, which is essential to achieving both mental and physical well-being.[75] Continuity of care is a classic virtue in general practice, which may reduce both elective and acute admissions and has been found important in preventing hospitalisation for ACSCs.[211,212] The knowledge of the individual patient's life and health over time is important in understanding the patient's perspective. For the person with multimorbidity, the GP can do much to improve the mental well-being simply by keeping the patient's perspective on the treatment. The complexity of handling and living with multimorbidity, the stressful burden of symptoms and treatment, and the lack of evidence-based answers to these complex health issues in the current guidelines have turned the attention to the patient-doctor relationship. Patient-centred care is about empowering the patient to more actively participate, prioritise, and determine the level of care, which in combination is intended to provide a more holistic view on the patient's situation.[61,213] An empathetic and trusting dialogue with the GP enables the patient to take informed decisions on care, to continuously assess the progress, and to select the most important focus areas. A conceptualisation of this shared decision-making between the patient and the GP is the Ariadne principles in which the repeated setting of realistic treatment goals is central.[214] Strengthening the patient-centred care in general practice could become very valuable for patients with psychological stress, who may feel derailed and incapable of managing their physical health problems. Studies exploring the effects of a patient-centred approach combined with complex whole-system interventions are well underway.[210,215]

FUTURE RESEARCH

The knowledge base on mental-physical multimorbidity is sparse, but growing. However, little is known on psychological stress, and how it should be managed in primary care specifically in relation to chronic care. Is stress a modifiable risk factor? Is stress alleviation feasible? Can better stress management improve the long-term outcomes? These are some of the questions that remain unanswered. Large observational studies and intervention trials are needed to supply evidence for future treatment strategies and health policies.

Future studies may aim to develop validated stress instruments for general practice and to test their predictive capabilities in relation to health service utilisation, quality of care, and long-term prognosis. Comprehensive descriptive studies on persons with multimorbidity in Denmark and their pathways through the healthcare system are lacking. Additionally, better knowledge on markers of poor outcomes, e.g. perceived stress, is needed for stratification of care in a healthcare system with limited financial resources.

The overall organisation of primary care is shifting towards larger units and clusters of practices, and the consequences of this should also be investigated; potential advantages could be more local resources to deal with mental-physical multimorbidity (e.g. better time allocation and more psychological treatment offers), and increased care coordination, but this could also affect the continuity of care negatively.

Intervention studies may investigate stress-alleviating interventions, e.g. problem-solving therapy or mindfulness methods for persons with chronic disease and stress, or other aspects of poor mental health. Such treatment offers could be based in general practice, where the integration of chronic care is optimal, but the sessions could be led by psychologists or specially trained nurses if GP resources are sparse. A systematic implementation of patient-

centred care principles or further exploration of the adherence to the Ariadne principles in primary care could also be interesting topics in relation to patient-reported outcomes, quality of care, and long-term prognosis.

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ENGLISH SUMMARY

Background

The number of persons living with multiple chronic conditions (multimorbidity) is rising owing to prolonged life and improved medical treatment. In this context, attention to mental health is essential; psychiatric illness has been associated with impaired quality of chronic care and poor prognosis of physical diseases, including increased mortality. However, little is known on the physical consequences of sub-threshold psychological stress, which is more common than psychiatric disorders in the background population and is highly prevalent in persons with multimorbidity. Additionally, stress is a common reason for contacting the general practitioner (GP), and yet no guidelines for management and treatment exist.

Aims

The aim of this thesis was to investigate the consequences of psychological stress on the health while taking into account mental-physical multimorbidity, i.e. the associations between perceived stress and mortality, hospitalisations for ambulatory care sensitive conditions (ACSC), and primary healthcare service use. Furthermore, we aimed to explore the impact of bereavement, a highly stressful life event, on mortality.

Methods

Four nationwide cohort studies were performed. The Danish National Health Survey 2010 supplied data on perceived stress and lifestyle. Data on socioeconomic factors, the outcomes and the cohort of bereaved individuals were obtained through Danish national health registers. The Danish Multimorbidity Index was developed based on diagnoses and prescription data and supplied data on multimorbidity.

Results

We found that high levels of perceived stress were associated with a 30–50% increase in all-cause mortality, ACSC-related hospitalisations, and both daytime and out-of-hours contacts to the GP after adjustments. Bereavement was also associated with a long-term mortality increase of 40%. In absolute terms, stress was associated with more adverse outcomes among those with multimorbidity, and the combination of stress and multimorbidity seemed to result in less timely chronic care.

Conclusions and perspectives

Psychological stress was consistently found to be associated with adverse health outcomes and potentially suboptimal healthcare. The link between stress and multimorbidity could substantiate the efforts to develop management guidelines for primary care, stress-targeted interventions, and to accommodate the healthcare system to better embrace poor mental health below the threshold for psychiatric disorders. More research on interventions targeting stress and multimorbidity are warranted.

DANSK RESUME

Baggrund

Flere og flere mennesker lever i dag med flere samtidige kroniske sygdomme (multisygdom) som følge af længere levetid og forbedret medicinsk behandling. Det mentale helbred spiller i denne sammenhæng en væsentlig rolle. Psykisk sygdom er blevet forbundet med forringet behandlingskvalitet af kronisk sygdom og dårligere prognose for fysisk sygdom, herunder øget dødelighed. Alligevel ved vi meget lidt om, hvilke fysiske konsekvenser det kan have at lide af psykisk stress, som ikke berettiger en egentlig psykiatrisk diagnose. Stress ses oftere end psykisk sygdom i befolkningen og forekommer særligt hyppigt hos personer med multisygdom. Stress er også en udbredt kontaktårsag hos den praktiserende læge, men der findes endnu ingen officiel kliniske vejledning til behandling af stress i dansk almen praksis.

Formål

Formålet med denne afhandling var at undersøge, hvilke helbredsmæssige konsekvenser psykisk stress kan få, når der tages højde for mental-fysisk multisygdom. Sammenhængene mellem selvopfattet stress og dødelighed, potentielt forebyggelige hospitalsindlæggelser og brugen af serviceydelser i den primære sundhedssektor undersøges. Derudover undersøges, hvordan tabet af en nærtstående – som er en meget stressende livhændelse – påvirker dødeligheden hos de efterladte.

Metoder

Fire landsdækkende kohortestudier blev gennemført. Den Nationale Sundhedsprofil 2010 leverede data om selvopfattet stress og livsstil. Data om socioøkonomiske faktorer, studiernes udfald og kohorten af efterladte kom fra danske nationale sundhedsregistre. Det Danske Multimorbiditetsindeks, som blev udviklet på baggrund af registrerede diagnoser og recept-data, leverede data om multisygdom.

Resultater

Vi fandt, at et højt niveau af selvopfattet stress var forbundet med en stigning på 30-50 % for overordnet dødelighed, potentielt forebyggelige hospitals-indlæggelser og antallet af kontakter til den praktiserende læge – både i og uden for den normale åbningstid selv efter justering for multisygdom. Tab af ægtefælle var også forbundet med en stigning i dødeligheden over længere tid på 40 %. I absolutte tal var stress forbundet med flere negative behandlings-udfald hos individer med multimorbiditet, og kombinationen af stress og multisygdom synes også at være forbundet med mindre rettidig kroniker-omsorg.

Konklusion og perspektiver

Psykisk stress havde en negativ indvirkning på helbredet og syntes også at være forbundet med dårligere kronikeromsorg. Denne nye viden om sammenhængen mellem stress og multimorbiditet kan understøtte udvikling af retningslinjer på området samt målrettede interventioner til forebyggelse af stress i almen praksis. Derudover kræver det tilpasninger, hvis man fremover skal sikre, at sundhedsvæsenet skal kunne støtte de mange mennesker med dårligt mentalt helbred, som ligger under de normale grænseværdier for psykisk sygdom. Fremtidig forskning bør derfor undersøge, hvilke interventioner der vil kunne imødegå både stress og multimorbiditet.

APPENDIX I

THE DANISH MULTIMORBIDITY INDEX CODING DEFINITIONS

Danish Multimorbidity Index coding definitions

Category	Disease group	Origin[a]	Coding definition[b]	Diagnosis codes (ICD-10)	Diagnosis time frame	Drug codes (ATC)	Prescription time frame
Circulatory system	Hypertension	a, b	Diagnosis AND/OR prescriptions of antihypertensives, if not ischemic heart disease or heart failure (or kidney disease: only diuretics)	I10-I13, I15	Ever	C02, C04, C07, C08, C09, C03	Twice last year
	Dyslipidaemia	b	Diagnosis AND/OR drug prescription for lipid-lowering drugs if not ischemic heart disease.	E78	Last two years	C10	Twice last year
	Ischemic heart disease	a, b	Diagnosis AND/OR prescription for antianginal drug	I20-I25	Ever	C01DA	Twice last year
	Atrial fibrillation	a, b	Diagnosis	I48	Ever		
	Heart failure	a, b	Diagnosis	I50	Ever		
	Peripheral artery occlusive disease	a, b	Diagnosis	I70-I74	Ever		
	Stroke	a, b	Diagnosis	I60-I64, I69	Ever		
Endocrine system	Diabetes mellitus	a, b	Diagnosis AND/OR prescription of antidiabetics	E10-E14	Ever	A10A, A10B	Twice last year
	Thyroid disorder	a, b	Diagnosis AND/OR prescription of thyroid therapy drugs	E00-E05, E061-E069, E07	Last two years	H03	Twice last year
	Gout	b	Diagnosis	E79, M10	Ever		
Pulmonary system and allergy	Chronic pulmonary disease	a, b	Prescription for obstructive airway disease drugs			R03	Twice last year
	Allergy	b	Prescription for non-sedative antihistamines AND/OR nasal antiallergics			R06AX, R06AE07, R06AE09, R01AC, R01AD	Twice last year
Gastrointestinal system	Ulcer/chronic gastritis	a, b	Diagnosis	K221, K25-K28, K293-K295	Ever		
	Chronic liver disease	a, b	Diagnosis	B16-B19, K70-K74, K766, I85	Ever		
	Inflammatory bowel disease	a, b	Diagnosis	K50-K51	Ever		
	Diverticular disease of intestine	a, b	Diagnosis	K57	Ever		
Urogenital system	Chronic kidney disease	a, b	Diagnosis	N03, N11, N18-N19	Ever		
	Prostate disorders	a, b	Diagnosis AND/OR prescription of prostate hyperplasia therapy drugs	N40	Ever	C02CA, G04C	Twice last year
Musculoskeletal system	Connective tissue disorders	a, b	Diagnosis	M05-M06, M08-M09, M30-M36, D86	Ever		
	Osteoporosis	b	Diagnosis AND/OR prescription for osteoporosis drugs	M80-M82	Ever	M05B, G03XC01, H05AA	Twice last year
	Painful condition	a, b	Repeated prescriptions of analgesics			N02A, N02BA51,N02BE, M01A, M02A	Four times last year

Danish Multimorbidity Index coding definitions (cont.)

Category	Disease group	Origin[a]	Coding definition[b]	Diagnosis codes (ICD-10)	Diagnosis time frame	Drug codes (ATC)	Prescription time frame
Hematological system	HIV/AIDS	b	Diagnosis	B20-B24	Ever		
	Anaemias	b	Diagnosis	D50-D53, D55-D59, D60-D61, D63-D64	Last two years		
Cancers	Cancer	a, b	Diagnosis	C00-C43, C45-C97	Last five years		
Neurological system	Vision problem	a, b	Diagnosis	H40, H25, H54	Ever		
	Hearing problem	a, b	Diagnosis	H90-H91, H931	Ever		
	Migraine	a, b	Diagnosis AND/OR prescription of specific anti-migraine drugs	G43	Last two years	N02C	Twice last year
	Epilepsy	a, b	Diagnosis AND prescription of anti-epileptics	G40-G47	Ever	N03	Twice last year
	Parkinson's disease	a, b	Diagnosis	G20-G22	Ever		
	Multiple sclerosis	a	Diagnosis	G35	Ever		
	Neuropathies	b	Diagnosis	G50-G64	Last two years		
Mental health conditions	Mood, stress-related, or anxiety disorders	a, b	Diagnosis	F32-F34, F40-F48	Last two years		
	Psychological distress	a, b	Prescription of antidepressants if not other mental disorder			N06A	Twice last year
	Alcohol problems	a, b	Diagnosis	F101-F109	Last two years		
	Substance abuse	a, b	Diagnosis	F11-F16, F18-F19	Last two years		
	Anorexia/bulimia	a	Diagnosis	F50	Last two years		
	Bipolar affective disorder	a, b	Diagnosis AND/OR prescription of lithium salts	F30-F31	Ever	N05AN	Twice last year
	Schizophrenia or schizoaffective disorder	a, b	Diagnosis	F20, F25	Ever		
	Dementia	a, b	Diagnosis AND/OR prescription of anti-dementia drugs	F00-F03, F051, G30	Ever	N06D	Twice last year

Abbreviations: ICD-10, International Classification of Diseases, version 10; ATC, Anatomical Therapeutic Chemical Classification System; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

[a]ICD-10 diagnosis code recorded or redeemed prescription of ATC-coded drug registered within defined time frames (time range: 1995-2010) in national health registers (the Danish National Patient Register, the Danish Diabetes Register, the Danish Cancer Register, the Danish Psychiatric Central Register, and the Danish National Prescription Registry.)

[b]a: Barnett, b: Other index (Van den Bussche, Huber, Charlson, and/or Elixhauser)

APPENDIX II

DANISH AND ENGLISH VERSIONS OF THE PERCEIVED STRESS SCALE

Dagligdagens stress

17. Spørgsmålene drejer sig om din oplevelse af belastende eller stressende situationer inden for *den seneste måned*.

(Sæt ét X i hver linje)	Aldrig	Næsten aldrig	En gang imellem	Ofte	Meget ofte
Hvor ofte er du blevet bragt ud af ligevægt over noget, der skete uventet?	☐	☐	☐	☐	☐
Hvor ofte har du følt, at du var ude af stand til at kontrollere de vigtige ting i dit liv?	☐	☐	☐	☐	☐
Hvor ofte har du følt dig nervøs og stresset?	☐	☐	☐	☐	☐
Hvor ofte har du følt, at du var i stand til at klare dine personlige problemer?	☐	☐	☐	☐	☐
Hvor ofte har du følt, at tilværelsen formede sig efter dit hoved?	☐	☐	☐	☐	☐
Hvor ofte har du oplevet, at du ikke kunne overkomme alle de ting, du skulle?	☐	☐	☐	☐	☐
Hvor ofte har du været i stand til at håndtere dagligdagens irritationer?	☐	☐	☐	☐	☐
Hvor ofte har du følt, at du havde styr på tingene?	☐	☐	☐	☐	☐
Hvor ofte er du blevet vred på grund af ting, du ikke var herre over?	☐	☐	☐	☐	☐
Hvor ofte har du følt, at problemerne hobede sig op, så du ikke kunne magte dem?	☐	☐	☐	☐	☐

PSS

INSTRUCTIONS:

The questions in this scale ask you about your feelings and thoughts during THE LAST MONTH. In each case, please indicate your response by placing an "X" over the circle representing HOW OFTEN you felt or thought a certain way.

	Never	Almost Never	Sometimes	Fairly Often	Very Often
	0	1	2	3	4
1. In the last month, how often have you been upset because of something that happened unexpectedly?	○	○	○	○	○
2. In the last month, how often have you felt that you were unable to control the important things in your life?	○	○	○	○	○
3. In the last month, how often have you felt nervous and "stressed"?	○	○	○	○	○
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	○	○	○	○	○
5. In the last month, how often have you felt that things were going your way?	○	○	○	○	○
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	○	○	○	○	○
7. In the last month, how often have you been able to control irritations in your life?	○	○	○	○	○
8. In the last month, how often have you felt that you were on top of things?	○	○	○	○	○
9. In the last month, how often have you been angered because of things that were outside your control?	○	○	○	○	○
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	○	○	○	○	○

APPENDIX III

LIST OF CHRONIC ACSCS AND PREDISPOSING CONDITIONS

List of chronic ACSCs and predisposing conditions

Chronic ACSC Outcome	ACSCs included in group[a]	ACSC-predisposing medical comorbidity from Danish Multimorbidity Index
Diabetes-related conditions	Diabetes (with short-term complications)	Diabetes mellitus
	Diabetes (uncontrolled (without short-term or long-term complications))	Diabetes mellitus
	Diabetes (with long-term complications)	Diabetes mellitus
	Amputations (diabetes-related)	Diabetes mellitus
Chronic lung conditions	COPD exacerbation	Chronic pulmonary disease
	Adult asthma exacerbation	Chronic pulmonary disease
Circulatory conditions	Angina	Ischemic heart disease
	CHF exacerbation	Heart failure
	HTN	Hypertension Ischemic heart disease
		Heart failure
		Stroke
		Peripheral artery occlusive disease

Abbreviations: ACSC: ambulatory care-sensitive conditions. COPD: chronic obstructive pulmonary disease. CHF: chronic heart failure. HTN: hypertension.

[a] For definitions, see Davydow DS, Ribe AR, Pedersen HS, et al. Serious Mental Illness and Risk for Hospitalizations and Rehospitalizations for Ambulatory Care-sensitive Conditions in Denmark: A Nationwide Population-based Cohort Study. *Med Care* 2016; 54: 90-97

APPENDIX IV

PREVALENCE OF CONDITIONS IN THE DANISH MULTIMORBIDITY INDEX BY SEX AND AGE GROUP AND PREVALENCE COMPARISONS

Prevalence by sex - the Danish Multimorbidity Index (adults>18yrs by 1 January 2014)

	Overall		Sex			
		N=4,368,069	Female	N=2,221,666	Male	N=2,146,403
Disease group	%	n	%	n	%	n
Hypertension	19.6%	857,557	21.1%	469,311	18.1%	388,246
Dyslipidaemia	7.9%	344,191	8.2%	182,377	7.5%	161,814
Ischemic heart disease	3.5%	151,232	2.7%	59,166	4.3%	92,066
Atrial fibrillation	2.5%	110,080	2.1%	47,191	2.9%	62,889
Heart failure	1.1%	46,610	0.8%	17,633	1.4%	28,977
Peripheral artery occlusive disease	1.9%	84,396	1.7%	37,244	2.2%	47,152
Stroke	2.6%	114,843	2.5%	54,691	2.8%	60,152
Diabetes mellitus	6.5%	283,921	6.3%	139,834	6.7%	144,087
Thyroid disorder	3.0%	131,034	5.0%	110,039	1.0%	20,995
Gout	1.0%	43,962	0.5%	11,021	1.5%	32,941
Chronic pulmonary disease	4.4%	191,648	4.9%	109,605	3.8%	82,043
Allergy	2.3%	98,609	2.7%	59,849	1.8%	38,760
Ulcer/chronic gastritis	1.9%	81,346	1.8%	40,500	1.9%	40,846
Chronic liver disease	0.8%	34,523	0.7%	15,679	0.9%	18,844
Inflammatory bowel disease	1.1%	49,187	1.2%	27,242	1.0%	21,945
Diverticular disease of intestine	1.8%	78,510	2.0%	44,798	1.6%	33,712
Chronic kidney disease	0.7%	29,454	0.6%	12,642	0.8%	16,812
Prostate disorders	2.4%	102,703	0.1%	1,784	4.7%	100,919
Connective tissue disorders	2.0%	86,836	2.8%	61,387	1.2%	25,449
Osteoporosis	3.0%	129,869	4.9%	109,696	0.9%	20,173
Painful condition	4.0%	176,292	5.3%	116,984	2.8%	59,308
Anaemias	1.5%	63,751	1.8%	39,490	1.1%	24,261
HIV/AIDS	0.1%	4,375	0.1%	1,181	0.1%	3,194
Cancer	3.0%	132,860	3.2%	70,085	2.9%	62,775
Vision problem	5.0%	220,359	6.1%	135,301	4.0%	85,058
Hearing problem	5.3%	232,380	5.0%	110,130	5.7%	122,250
Migraine	1.0%	45,478	1.7%	38,004	0.3%	7,474
Epilepsy	0.8%	34,596	0.8%	17,224	0.8%	17,372
Parkinson's disease	0.2%	9,175	0.2%	3,992	0.2%	5,183
Multiple sclerosis	0.3%	13,937	0.4%	9,578	0.2%	4,359
Neuropathies	1.0%	42,880	1.1%	23,891	0.9%	18,989
Mood, stress-related, or anxiety disorders	1.8%	76,926	2.1%	47,716	1.4%	29,210
Psychological distress	4.7%	205,168	6.1%	136,596	3.2%	68,572
Alcohol problems	0.6%	28,037	0.4%	8,977	0.9%	19,060
Substance abuse	0.3%	12,254	0.2%	3,874	0.4%	8,380
Anorexia/bulimia	0.1%	4,729	0.2%	4,492	0.0%	237
Bipolar affective disorder	0.4%	17,885	0.5%	10,617	0.3%	7,268
Schizophrenia or schizoaffective disorder	0.6%	27,495	0.5%	11,649	0.7%	15,846
Dementia	0.6%	27,526	0.7%	16,485	0.5%	11,041
Disease count=0	55.2%	2,410,347	51.7%	1,149,559	58.7%	1,260,788
Disease count=1	19.6%	855,701	21.2%	469,985	18.0%	385,716
Disease count=2	10.6%	464,155	11.5%	254,765	9.8%	209,390
Disease count=3+	14.6%	637,866	15.6%	347,357	13.5%	290,509
Any psychiatric condition	8.2%	358,536	9.8%	218,384	6.5%	140,152

Prevalence by age groups - the Danish Multimorbidity Index (adults>18yrs by 1 January 2014)

	Age groups													
	18-29ys	N=802,489	30-39ys	N=663,700	40-49ys	N=799,856	50-59ys	N=734,633	60-69ys	N=692,354	70-79ys	N=437,864	80+ys	N=237,173
Disease group	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Hypertension	0.5%	4,063	2.3%	15,471	8.0%	63,657	20.5%	150,823	36.7%	254,285	50.7%	222,131	62.0%	147,127
Dyslipidaemia	0.1%	1,031	0.7%	4,317	2.6%	20,913	8.3%	60,930	17.1%	118,340	22.3%	97,766	17.2%	40,894
Ischemic heart disease	0.1%	692	0.4%	2,595	1.4%	11,389	3.6%	26,358	6.1%	42,452	9.0%	39,349	12.0%	28,397
Atrial fibrillation	0.1%	622	0.3%	1,674	0.6%	4,525	1.4%	10,162	3.7%	25,780	7.8%	34,254	13.9%	33,063
Heart failure	0.0%	189	0.1%	437	0.2%	1,678	0.6%	4,536	1.6%	10,732	3.3%	14,330	6.2%	14,708
Peripheral artery occlusive disease	0.1%	915	0.2%	1,514	0.5%	4,232	1.3%	9,627	3.2%	21,822	6.1%	26,919	8.2%	19,367
Stroke	0.1%	1,190	0.4%	2,583	0.9%	7,103	2.0%	14,774	4.0%	27,719	7.3%	32,037	12.4%	29,437
Diabetes mellitus	0.9%	6,900	1.9%	12,503	3.4%	26,975	6.4%	46,887	11.3%	78,003	16.3%	71,173	17.5%	41,480
Thyroid disorder	0.5%	4,261	1.5%	10,036	2.2%	17,630	3.4%	24,891	4.4%	30,409	5.7%	25,098	7.9%	18,709
Gout	0.0%	239	0.1%	898	0.4%	3,198	1.0%	7,237	1.8%	12,569	2.7%	11,856	3.4%	7,965
Chronic pulmonary disease	1.6%	13,229	2.1%	13,912	2.9%	23,502	4.4%	31,992	6.4%	44,503	9.3%	40,524	10.1%	23,986
Allergy	0.9%	7,095	1.4%	9,065	2.0%	16,276	2.8%	20,395	3.4%	23,506	3.5%	15,357	2.9%	6,915
Ulcer/chronic gastritis	0.2%	1,838	0.6%	4,044	1.1%	8,710	1.8%	13,496	2.8%	19,358	4.3%	18,757	6.4%	15,143
Chronic liver disease	0.2%	1,918	0.6%	4,030	0.8%	6,539	1.2%	8,581	1.2%	8,250	0.9%	3,991	0.5%	1,214
Inflammatory bowel disease	0.7%	6,017	1.2%	8,135	1.3%	10,298	1.2%	8,939	1.2%	8,002	1.1%	4,996	1.2%	2,800
Diverticular disease of intestine	0.0%	163	0.1%	896	0.6%	4,445	1.5%	10,858	3.0%	20,560	5.2%	22,562	8.0%	19,026
Chronic kidney disease	0.2%	1,314	0.2%	1,595	0.3%	2,610	0.5%	3,367	0.9%	5,928	1.7%	7,548	3.0%	7,092
Prostate disorders	0.0%	130	0.0%	329	0.2%	1,458	0.9%	6,922	3.9%	27,122	8.7%	38,164	12.0%	28,578
Connective tissue disorders	0.9%	7,387	1.0%	6,785	1.3%	10,777	1.8%	13,206	2.6%	17,952	4.0%	17,711	5.5%	13,018
Osteoporosis	0.1%	603	0.2%	1,163	0.4%	3,237	1.7%	12,695	5.1%	35,575	9.4%	41,060	15.0%	35,536
Painful condition	0.2%	1,988	1.1%	7,120	2.3%	18,178	4.0%	29,657	5.7%	39,258	8.7%	38,267	17.6%	41,824
Anaemias	0.2%	1,805	0.4%	2,965	0.7%	5,821	1.0%	7,421	1.7%	11,770	3.3%	14,654	8.1%	19,315
HIV/AIDS	0.0%	191	0.1%	768	0.2%	1,567	0.2%	1,131	0.1%	545	0.0%	148	0.0%	25
Cancer	0.2%	1,899	0.6%	4,060	1.2%	9,381	2.6%	19,189	5.7%	39,677	8.8%	38,327	8.6%	20,327
Vision problem	0.2%	1,474	0.3%	1,714	0.6%	4,565	1.7%	12,605	5.7%	39,277	16.3%	71,295	37.7%	89,429
Hearing problem	1.1%	8,981	1.2%	7,940	1.9%	15,201	3.5%	25,677	7.2%	49,764	13.6%	59,715	27.4%	65,102
Migraine	0.4%	3,470	0.9%	6,219	1.6%	12,596	1.8%	12,880	1.0%	7,210	0.6%	2,529	0.2%	574
Epilepsy	0.5%	4,221	0.7%	4,318	0.8%	6,031	0.9%	6,383	0.9%	6,431	1.1%	4,627	1.1%	2,585
Parkinson's disease	0.0%	35	0.0%	70	0.0%	196	0.1%	667	0.3%	2,014	0.8%	3,535	1.1%	2,658
Multiple sclerosis	0.1%	664	0.3%	2,041	0.4%	3,406	0.5%	3,658	0.4%	2,846	0.2%	1,079	0.1%	243
Neuropathies	0.3%	2,501	0.7%	4,674	0.9%	7,373	1.3%	9,578	1.2%	8,584	1.5%	6,542	1.5%	3,628
Mood, stress-related, or anxiety disorders	2.3%	18,694	2.2%	14,425	1.9%	15,006	1.7%	12,125	1.1%	7,958	1.0%	4,587	1.7%	4,131
Psychological distress	1.6%	12,649	3.3%	21,657	4.5%	35,720	5.6%	41,152	6.0%	41,784	6.8%	29,985	9.4%	22,221
Alcohol problems	0.2%	1,689	0.4%	2,599	0.7%	5,761	1.1%	7,909	1.0%	6,633	0.6%	2,831	0.3%	615
Substance abuse	0.6%	4,839	0.4%	2,761	0.3%	2,230	0.2%	1,384	0.1%	623	0.1%	268	0.1%	149
Anorexia/bulimia	0.4%	2,859	0.2%	1,157	0.1%	469	0.0%	150	0.0%	64	0.0%	22	0.0%	8
Bipolar affective disorder	0.2%	1,746	0.4%	2,457	0.4%	3,299	0.5%	3,711	0.5%	3,640	0.5%	2,095	0.4%	937
Schizophrenia or schizoaffective disorder	0.6%	5,011	0.8%	5,507	0.8%	6,299	0.7%	5,479	0.5%	3,489	0.3%	1,316	0.2%	394
Dementia	0.0%	64	0.0%	104	0.0%	337	0.2%	1,145	0.4%	3,049	1.6%	7,168	6.6%	15,659
Disease count=0	86.4%	693,146	78.5%	521,223	67.7%	541,605	50.0%	367,239	30.3%	209,568	14.9%	65,267	5.2%	12,299
Disease count=1	11.1%	89,312	15.9%	105,829	20.9%	167,323	25.8%	189,592	26.3%	182,377	21.0%	92,041	12.3%	29,227
Disease count=2	2.0%	16,026	3.9%	26,104	7.2%	57,452	13.0%	95,652	19.2%	132,828	21.3%	93,252	18.1%	42,841
Disease count=3+	0.5%	4,005	1.6%	10,544	4.2%	33,476	11.2%	82,150	24.2%	167,581	42.8%	187,304	64.4%	152,806
Any psychiatric condition	5.1%	41,299	6.7%	44,263	7.6%	60,981	8.8%	64,845	8.8%	60,740	10.2%	44,748	17.6%	41,660

Prevalence comparisons - the Danish Multimorbidity Index

Danish Multimorbidity Index (2014) (a)		Barnett et al. (2007) (b)		Friis et al. (2013) (c)		Global Burden of Disease (2015) (d)	
Disease group	%	Disease group for comparison	%	Disease group for comparison	%	Disease group for comparison	%
Hypertension	19.6%	Hypertension	13.4%	Hypertension	18%		
Dyslipidaemia	7.9%						
Ischemic heart disease	3.5%	Coronary heart disease	4.7%	Myocardial infarction (Angina pectoris: 2%)	1%	Ischemic heart disease	2.5%
Atrial fibrillation	2.5%	Atrial fibrillation	1.4%			Atrial fibrillation and flutter	1.1%
Heart failure	1.1%	Heart failure	1.1%				
Peripheral artery occlusive disease	1.9%	Peripheral vascular disease	1.3%			Peripheral artery disease	4.3%
Stroke	2.6%	Stroke & TIA	2.1%	Stroke	2%	Cerebrovascular disease	0.6%
Diabetes mellitus	6.5%	Diabetes	4.3%	Diabetes	5%	Diabetes mellitus	7.1%
Thyroid disorder	3.0%	Thyroid disorders	4.1%				
Gout	1.0%					Gout	1.0%
Chronic pulmonary disease	4.4%	COPD (Asthma currently treated: 6.0%)	3.2%	COPD (Asthma: 7%)	4%	Chronic obstructive pulmonary disease	4.8%
Allergy	2.3%			Allergy	21%		
Ulcer/chronic gastritis	1.9%	Treated dyspepsia	4.5%			Peptic ulcer disease	1.7%
Chronic liver disease	0.8%	Chronic liver disease (Viral hepatitis: 0.1%)	0.1%			Cirrhosis and other chronic liver diseases	0.1%
Inflammatory bowel disease	1.1%	Inflammatory bowel disease	0.6%			Inflammatory bowel disease	0.4%
Diverticular disease of intestine	1.8%	Diverticular disease of intestine	1.9%				
Chronic kidney disease	0.7%	Chronic kidney disease	1.9%			Chronic kidney disease	7.3%
Prostate disorders	2.4%	Prostate disorders	0.9%			Benign prostatic hyperplasia	3.3%
Connective tissue disorders	2.0%	Rheumatoid arthritis, other inflammatory polyarthropathies & systematic connective tissue disorders	3.4%	Rheumatoid arthritis	6%		
Osteoporosis	3.0%			Osteoporosis	3%		
Painful condition	4.0%	Painful condition	7.2%				

Cont.

Prevalence comparisons - the Danish Multimorbidity Index (cont.)

Danish Multimorbidity Index (a)		Barnett et al. 2012 (b)		Friis et al. 2016 (c)		Global Burden of Disease (d)	
Disease group	%	Disease group for comparison	%	Disease group for comparison	%	Disease group for comparison	%
Anaemias	1.5%						
HIV/AIDS	0.1%					HIV/AIDS	0.2%
Cancer	3.0%	New diagnosis of cancer	2.5%	Cancer	3%	Neoplasms	4.4%
Vision problem	5.0%	Blindness & low vision (Glaucoma: 0.9%)	0.5%				
Hearing problem	5.3%	Hearing loss	3.4%			Age-related and other hearing loss	18.1%
Migraine	1.0%	Migraine	0.6%	Migraine/recurrent headache	14%	Migraine	16.5%
Epilepsy	0.8%	Epilepsy (currently treated)	0.8%			Epilepsy	0.4%
Parkinson's disease	0.2%	Parkinson's disease	0.2%			Parkinson disease	0.1%
Multiple sclerosis	0.3%	Multiple sclerosis	0.2%			Multiple sclerosis	0.2%
Neuropathies	1.0%						
Mood, stress-related, or anxiety disorders	1.8%	Anxiety & other neurotic, stress related & somatoform disorders	3.2%				
Psychological distress	4.7%	Depression	8.2%	(Mental disorders)	10%	Depressive disorders	5.0%
Alcohol problems	0.6%	Alcohol problems	2.4%			Alcohol use disorders	1,4%
Substance abuse	0.3%	Other psychoactive substance misuse	2.4%			Drug use disorders	0.9%
Anorexia/bulimia	0.1%	Anorexia or bulimia	0.3%			Eating disorders	0.2%
Bipolar affective disorder	0.4%	Schizophrenia (and related non-organic psychosis) or bipolar disorder	0.7%			Bipolar disorder	0.8%
Schizophrenia or schizoaffective disorder	0.6%	Schizophrenia (and related non-organic psychosis) or bipolar disorder	0.7%			Schizophrenia	0.3%
Dementia	0.6%	Dementia	0.7%			Alzheimer disease and other dementias	1.6%

a: Health register data (diagnoses and prescriptions), 2014, 4,37 million persons (whole population), age:18+ yrs, 39 conditions

b: General practice READ codes, 2007, 1,75 million patients from Scottish practices, age: 0-85+ yrs, 40 conditions.

Ref: Barnett et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. Lancet. 2012;380(9836):37-43, Supplementary Table S1

c: Danish National Health Survey, 2013, 162,000 randomly sampled persons, age: 16+ yrs, 17 self-reported conditions.

Ref: Friis et al. A National Population Study of the Co-Occurrence of Multiple Long-Term Conditions in People With Multimorbidity, Denmark, 2013. Prev Chronic Dis 2016;13:150404

d: Global Burden of Disease algorithm on available Danish data, 2015, whole population, age:0-85+, selected diseases

Ref: Global Burden of Disease Study 2015 (GBD 2015) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2016. Available from http://ghdx.healthdata.org/gbd-results-tool