Doctoral theses at NTNU, 2021:105

Kristin Hestmann Vinjerui

Socioeconomic inequalities in multimorbidity and joint associations with mortality in a general population. The HUNT Study.

Doctoral thesis

Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Public Health and Nursing
Australian National University
ANU College of Health and Medicine
ANU Medical School

NTNU
Norwegian University of
Science and Technology

Kristin Hestmann Vinjerui

Socioeconomic inequalities in multimorbidity and joint associations with mortality in a general population. The HUNT Study.

Thesis for the Degree of Philosophiae Doctor

Trondheim, April 2021

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Public Health and Nursing

Australian National University
ANU College of Health and Medicine
ANU Medical School

NTNU
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the Degree of Philosophiae Doctor

Faculty of Medicine and Health Sciences
Department of Public Health and Nursing

Australian National University
ANU College of Health and Medicine
ANU Medical School

ISBN 978-82-326-6616-4 (printed ver.)
ISBN 978-82-326-5844-2 (electronic ver.)
ISSN 1503-8181 (printed ver.)
ISSN 2703-8084 (online ver.)

Doctoral theses at NTNU, 2021:105

Printed by NTNU Grafisk senter

Sosiale skilnadar i multimorbiditet og felles samanheng med død i ein ålmenn folkesetnad i Noreg

Sosiale skilnadar i helse, der menneskje med færre ressursar (typisk målt i utdanning, inntekt eller yrke) i gjennomsnitt har meir sjukdom og døyr tidlegare, har vore kjent over ti-år. Dette har vore mest studert for einskilde sjukdomar, medan pasientar i dag oftast har fleire, kroniske helseplager samtidig, *multimorbiditet*. Multimorbiditet aukar òg risiko for død, men alvorsgrad og kompleksitet i behandling vil variere med samansettinga av helseplager, samt personlege og sosiale forhold. Ein personleg faktor er å vera *skrøpeleg* (eng. *frail*)[1], eit svingande mål for biologisk alder kjenneteikna ved svekka fysiologiske reserver, nedsett funksjon og med auka risiko for komplikasjonar og død.[1, 2] Det er nyleg foreslått meir avanserte mål for multimorbiditet, med antatt auka alvorsgrad og utfordrande å behandle. Få har studert samspelet mellom personlege faktorar, sosial posisjon, multimorbiditet og samanheng med død. I denne avhandlinga undersøkte eg derfor førekomst og variasjon mellom sosiale lag, av ulike, avanserte mål for multimorbiditet (artikkel I og II) og felles samanheng med død (artikkel III).

Helseundersøkinga i Trøndelag 2006-08 (HUNT3) gav data om kroniske helseplager, nedsette funksjonar og død, samt yrkesgruppe som mål for sosioøkonomisk posisjon. Dei ulike måla for multimorbiditet varierte i total førekomst frå 18% til 63%. All multimorbiditet hadde høgare førekomst i lågare sosiale lag, blant kvinner og med aukande alder. Skilnadane i førekomst mellom sosiale lag, varierte med kjønn og alder, men var til stades frå ung vaksen til høg alderdom. Dødstala auka med talet på helseproblem og det var vekslande, men vedvarande skilnadar mellom sosiale grupper.

I ei norsk ålmenn folkesetnad, er sjølv avansert multimorbiditet vanleg, med ulik sosial fordeling gjennom heile vaksenlivet og sosiale skilnadar i død ved lik multimorbiditet. Denne kunnskapen viser at folkehelsearbeid mot sosiale skilnadar i helse framleis er aktuelt. Vidare kan ein anta at det er ei stor pasientgruppe som treng ei ålmenn tilnærming med personen i fokus, inkludert sosial samanvevnad. I Noreg har fastlegane ei nøkkelrolle i helsevesenet, denne ordninga bør prioriterast høgt òg framover.

Candidate:	Kristin Hestmann Vinjerui, MD
Department:	Department of Public Health and Nursing (ISM), Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU) ANU College of Health and Medicine, ANU Medical School, Australian National University (ANU)
Main supervisor:	Erik R Sund, PhD, Research scientist, HUNT Research Centre, NTNU
Co-supervisors:	Kirsty Douglas, MD, Professor, Academic Unit of General Practice, ANU Johan H Bjørngaard, Professor, ISM, NTNU Steinar Krokstad, MD, Professor, HUNT Research Centre, NTNU

Funding:	Faculty of Medicine and Health Science, NTNU The Liaison Committee for Education, Research and Innovation in Central Norway (Samarbeidsorganet) EPINOR - National research school in population based epidemiology

Contents

Acknowledgements

I am grateful to the Norwegian University of Science and Technology (NTNU) and Australian National University (ANU) for the opportunity to enter this joint PhD program, seated at the Department of Public Health and Nursing, Trondheim; HUNT Research Centre, Levanger; and the Academic Unit of General Practice, Canberra. I highly appreciate the general funding of this thesis by NTNU and support from the Liaison Committee for Education, Research and Innovation in Central Norway and the National research school in population based epidemiology to complete my research stay at ANU. I wish to thank the Psychiatric Department at Levanger Hospital, for flexibility in my final year of the thesis.

This thesis is based on vast data from the total county Trøndelag Health Study (The HUNT Study) which is a collaboration between HUNT Research Centre, Faculty of Medicine and Health Sciences, NTNU, Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. Of outmost importance for the excellence of the HUNT Study is the continuous support and contribution from the population of Nord-Trøndelag over more than four decades and the quality of management by the staff at the HUNT Databank and HUNT Biobank, a huge shout-out to all of you!

My supervisors have been a dream team; main supervisor researcher ER Sund, thank you for the continuous support on all platforms at all times and in all aspects of life; co-supervisor professor S Krokstad, thank you for opening doors to the research community, inspirational curiosity and for emphasizing the clear link of social epidemiology to clinical work; co-supervisor professor Johan Håkon, thank you for fundamental statistical support and methodological creativity; and co-supervisor professor KA Douglas, thank you for your patience and persistency with regards to the PhD program and research stay and attentive presence, guidance and care while at ANU. Co-authors PhD P Boeckxstaens and professor O Bjerkeset, thank you for valuable input on article I and II, respectively. Finally, with no official role, but of great value through all these years, professor L Getz, thank you for being my mentor, for introduction to multimorbidity and academia overall, for including me in side projects, acknowledging and challenging my knowledge.

In addition to senior researchers, I owe big thanks to fellow candidates and young researchers for academic, administrative and social support. The value of mentoring by those one step ahead, has been ground breaking to me, such as introduction to the international research community in multimorbidity. The greatest knowledge is shared knowledge and I will continue to strive to pay this forward. Thank you to everyone who has shared parts of my PhD journey from 2014 to 2020 in Trondheim, Levanger and Canberra.

I have worked on and off on this thesis over six years at in total five work places and wish to thank all colleagues for being supportive, inclusive and inspiring. Not to mention IT-personnel and librarians whose aid has been priceless.

Dear Sophia, friends are family we choose and you are my chosen twin. You mirror my core values, expand, reflect and act on them, which challenges me to reach further. You have travelled vastly, expanding my horizons and let me in on a parallel life in the USA. My greatest loss to the pandemic, is not being able to take part in your wedding. Who would have guessed your Mohawk punk a** would be seated in the manuscript editorial team of JAMA as I finalized my articles and thesis? Your writing assistance have truly helped make reviews a swift process and been invaluable in writing this dissertation.

My dear parents, thank you for endless love and the best start in life. To respect, care and demand fair chances for all, is in my blood. Raised by two teachers, I have associated learning with joy since probably day one and mom has shown me that learning can be a lifelong journey. Loving memories of my grandmothers who both dreamt of more education, has kept pushing me to pursue this PhD as well as striving to be a role model for all the children at Bright Future Pre-School in Ajumako-Techiman, Ghana. Education is the key to unleash the potential in every child, increase every person's life opportunities and strengthen local communities. I dedicate this thesis to Patrick Ankaii MacAidoo for decades of companionship in providing a health promoting and safe learning environment for hundreds of children in Techiman.

Finally, my dearest husband Lars, your love, support and challenge in the clinical, research and family life makes me stronger, wiser and more complete. I long to spend more time with you. Sine and Asta, you are both true miracles and endless sources of joy, I love you.

List of Publications

This thesis consists of 3 published articles, referred to later by their Roman numerals.

Article I: Vinjerui, K.H.; Boeckxstaens, P.; Douglas, K.A.; Sund, E.R.
Prevalence of multimorbidity with frailty and associations with socioeconomic position in an adult population: findings from the cross-sectional HUNT Study in Norway.
BMJ Open 2020, 10, e035070, doi:10.1136/bmjopen-2019-035070

Article II: Vinjerui, K.H.; Bjerkeset, O.; Bjorngaard, J.H.; Krokstad, S.; Douglas, K.A.; Sund, E.R.
Socioeconomic inequalities in the prevalence of complex multimorbidity in a Norwegian population: findings from the cross-sectional HUNT Study.
BMJ Open 2020, 10, e036851, doi:10.1136/bmjopen-2020-036851

Article III: Vinjerui, K.H.; Bjorngaard, J.H.; Krokstad, S.; Douglas, K.A.; Sund, E.R.
Socioeconomic Position, Multimorbidity and Mortality in a Population Cohort: The HUNT Study.
J Clin Med 2020, 9, doi:10.3390/jcm9092759

Acronyms and abbreviations

ANU	Australian National University
CI	Confidence interval
EGPRN	European General Practice Research Network
ESeC	European Socio-economic Classification
HUNT	The Trøndelag Health Study, former The Nord-Trøndelag Health Study (1984-2019)
HUNT1	The Nord-Trøndelag Health Study, survey 1 (1984-1986)
HUNT2	The Nord-Trøndelag Health Study, survey 2 (1995-1997)
HUNT3	The Nord-Trøndelag Health Study, survey 3 (2006-2008)
HUNT4	The Nord-Trøndelag Health Study, survey 4 (2017-2019)
ICD-10	The International Classification of Diseases, Tenth Revision
MAR	Missing at random
MCAR	Missing completely at random
MD	Doctor of Medicine
MNAR	Missing not at random
NICE	The British National Institute for Health and Care Excellence
NTNU	Norwegian University of Science and Technology
p.	page
WHO	The World Health Organization

List of Figures and Tables

Summary (English)

Background: Multimorbidity, the concurrence of multiple chronic conditions, is highly frequent. Varying definitions and measures of multimorbidity hamper comparability of research, which is exemplified with wide ranges of prevalence estimates but a steady association with mortality.

The complexity in the treatment and burden of multimorbidity are associated with the combinations of conditions, presence of associated health concepts, such as frailty, personal factors, and social context, such as biology, lifestyle, and living conditions. Frailty is a dynamic measure of biological age, with impaired function (physical, psychological, or social) and increased risk of adverse events including death. Social health inequalities, in which the burden of poor health and premature death is higher with lower socioeconomic position, is well-known worldwide, and multimorbidity is no exception, in that it occurs at higher rates at younger ages, and with more complex combinations of conditions in socioeconomically deprived groups.

There are few studies on complex measures of multimorbidity, suggested to detect those with increased care needs and severity and their association with socioeconomic position; there is also a research gap on the joint association of socioeconomic position and multimorbidity with mortality. Thus, the aims of this thesis are to describe the socioeconomic distribution of complex measures of multimorbidity (article I, article II, and supplemental analysis on writing this dissertation) and how socioeconomic position may modify the association of multimorbidity with mortality (article III) in an adult general population. Examining several multimorbidity measures in the same cohort makes possible a unique direct comparison of socioeconomic gradients in prevalence and joint associations with mortality.

Methods: The total county health survey Trøndelag Health Study 2006-2008 (HUNT3) provided data on chronic conditions, impairments, and mortality (until February 1, 2019), as well as socioeconomic position. Several multimorbidity measures were explored based on individual and organ system group counts and the presence of frailty. Socioeconomic

differences in prevalence were explored cross-sectionally, and joint association with mortality were explored prospectively.

Results: The overall prevalence varied by the complex measure of multimorbidity from 18% to 63%. All multimorbidity measures were more prevalent in the lower socioeconomic groups, in women, and with increased age but were common across age groups in both sexes. Socioeconomic inequalities in prevalence varied by sex and age but persisted from young adulthood to old age. Mortality increased by the number of conditions with varying but intact socioeconomic gradients, and relative mortality risk increased with the presence of multimorbidity and lower socioeconomic position.

Conclusions: Even complex measures of multimorbidity were common in the general population, with socioeconomic inequalities in prevalence throughout adulthood and socioeconomic inequalities in mortality across multimorbidity measures. The findings call for continuous public policy and public health to prevent socioeconomic inequalities in health. The magnitude of multimorbidity in all age groups suggest a demand for generalist and person-centered approaches that consider socioeconomic context in health care. In Norway, family doctors are in a unique position to offer continuous care, and this arrangement should be kept as a high priority. Future research on trajectories, associations with a variety of social determinants of health, health care utilization, and mortality would be relevant to enhance future prevention and management of multimorbidity.

1 Introduction

In this thesis, I have studied the socioeconomic distribution of several measures of multimorbidity and the joint association of socioeconomic position and multimorbidity with mortality in a general population. Social inequalities in morbidity and mortality, with the burden greater among those in lower social positions, is acknowledged worldwide.[3]

Multimorbidity, the concurrence of multiple chronic conditions of which none dominant,[4] is no exception, in that it occurs more often and at younger ages in socioeconomically deprived social groups. In addition, the complexity of multimorbidity, associated with combinations of conditions and personal factors,[5] such as living conditions, rises as socioeconomic position falls. Complexity affects the clinical challenge of multimorbidity management for both the individual and caregiver aided by single-disease guidelines in a fragmented health care system.[6] Multimorbidity is most commonly defined as 2 or more conditions. At this threshold, 1 of 3 people is identified as having multimorbidity globally,[7] and this percentage is 42% in Norway[8]; it has been shown to be associated with an increased risk of death.[9] There are few studies on more complex measures of multimorbidity and their association with socioeconomic position, as well as any joint outcome on mortality.

In Norway, Tomasdottir[10] explored multimorbidity prevalence and patterns in a life cycle perspective in the general-population Trøndelag Health Study (also known as the HUNT Study or HUNT) in her dissertation in 2017. Multimorbidity was defined as 2 or more chronic conditions. For future research, Tomasdottir suggested studying multimorbidity measures with increased specificity by socioeconomic position and expanding and making uniform the set of conditions from which to derive multimorbidity measures.

This thesis adds to the work of Tomasdottir,[10] in that I have accessed the same population cohort, increased the number of conditions studied, and operationalized several measures of multimorbidity suggested to reflect complexity and need for tailored care. I have explored the socioeconomic distribution of these and how socioeconomic position may modify these multimorbidity measures' association with mortality. The findings may increase the

background knowledge for public policy as well as informed public health interventions, health care organization, and clinical management of multimorbidity.

In the background section, I have highlighted how multimorbidity challenges clinical care and research, especially with respect to definitions, measures, and effects on prevalence studies. I have further explored the complexity of multimorbidity; highlighted structural theory as the framework of this thesis; and reviewed the status of research on multimorbidity determinants and association with mortality prior to my own studies. This lays the rationale for choice of measures and the overarching aim of the thesis that follows. In methods, I have elaborated on the population and variables studied and the statistical analyses. I have presented results by the main research aims, and in the discussion, I have recognized challenges in validity, compared the main findings internally and to relevant new literature, reflected on the constructed multimorbidity measures, and ended with suggestions of implications for the clinic, public health, and future research.

2 Background

2.1 The Norwegian context

To set the scene in which the research of this dissertation took place, Norway is a democratic, high-income country with general public responsibility for and universal access to health care, welfare, and education, financed through taxation. The health care system can be recognized as universal coverage with controlled access.[11] Firstly, the copayment at consultations in primary and specialist care is standardized, considered low,[12] and reimbursed on reaching a set threshold. Inpatient care in hospitals is free of charge. Secondly, since 2001, every individual has an assigned primary care family physician (general practitioner) and practically all use of specialist care services requires referral from primary care. Both the primary and specialist health care systems are mostly public.

The welfare regime model has social democratic characteristics.[13, 14] In particular, the National Insurance Scheme aims to contribute to equalization of income and living conditions over the individual person's life course and between groups of persons by providing financial security.[15] Education is similarly mostly public, free of charge, or low cost, including the tertiary level. Finally, employment rates, job security, and standards for health, safety, and the environment in the workplace are high.

Despite efforts to limit inequalities in access to health care and education, secure income, and maintain workplace safety, socioeconomic inequalities in health still exist in Norway. This has been termed *the Nordic paradox*.[16]

2.2 Multimorbidity

The health concept in focus of this thesis is copresence of several chronic conditions or health problems in an individual, introduced as multimorbidity. However, several terms are in use to describe this phenomenon (section 2.2.3). The collection of health problems will vary, and multimorbidity is thus a heterogenous health concept, which challenges management in both clinic and research (sections 2.2.2 and 2.2.3). Furthermore, numerous labels exist for health

problems, and to facilitate comprehension of the nuances between definitions (section 2.2.3.1), which affect the types of health problems included in multimorbidity measures (section 2.5), a short description follows.

2.2.1 Central health concepts

Health problems and *conditions* are synonymous broad terms for any worries with regards to health by the individual or health care professional,[17] such as disease (objective biological dysfunction[17]), risk factors (behavior, exposure, individual characteristic, or heredity, assumed prognostic for ill health outcomes and considered modifiable[17]), symptoms (individual perceived dysfunction[17]), symptom complexes (combinations of symptoms and objective findings[17]), impairment (objective loss of function of the mental, physiological, or anatomical kinds[17]) and disability (individual perceived activity limitation[17]).

Note, however, that many studies on multimorbidity use these terms, especially *condition* and *disease*, interchangeably. In this dissertation, I have sought to be consistent in the use of *condition* in the notion of multimorbidity. I have used *health problems* to describe additional or associated elements to multimorbidity.

2.2.2 Challenges in clinical care

In Norway, as in other Western societies, there was a shift from acute infectious diseases dominating as morbidities and causes of mortality, to survival into older ages and accumulation of chronic diseases during the 1900s. The World Health Organization (WHO) considered chronic disease "the health care challenge of the 21st century," in 2002.[18](p. 11) This WHO report does not mention co-occurrence of chronic disease; however, this too has increased over the last decades,[19, 20] such that multimorbidity is considered the norm for individuals with chronic conditions.[21]

Reasons for overall increased survival in the last century are manifold. General living conditions has improved. Epidemiological research increasing knowledge of distribution and

determinants of individual diseases has guided development of efficient public health policies. At the same time, basic biomedical and clinical research has improved treatment of distinct diseases. This is reflected in the subspecialized health care of today, which is still in large part focused on acute care needs. Despite prior success, this single-disease acute care focus seems insufficient in the era of heterogeneous multimorbidity.

In fact, the fragmentation of health care and single-disease guidelines poses a safety threat to numerous patients with multimorbidity.[22] Through frequent contacts with health care services, coordination and continuation of complex management care are susceptible to failure; in addition, polypharmacy increases the risk of wrongful use and adverse interactions of medications. The insufficiency of single-disease guidelines to manage multimorbidity has been highlighted by many.[6, 23-26] A major concern is that the evidence is based on studies from which individuals with multimorbidity were excluded, and thus the use of single-disease guidelines in the context of multimorbidity is not evidence based.[6] Recommendations may be in opposition and harmful to the combinations of chronic conditions in multimorbidity.[6, 23]

As the scene was set for my thesis in 2014-2015, it was clear that many patients with multimorbidity would need individual, tailored care, beyond the sum of guideline components. General practitioners were encouraged to identify those with the greatest need of continuity of care and recommended to assign an appointed physician[6] and further aspire to a holistic approach, including the multiple conditions and integrating the person's biopsychosocial context.[23]

A personal goal for my research project, as a medical doctor with a strong heart for the best possible health for all, was for it to be of practical value for both clinical management and prevention of multimorbidity. A focus on identification, definition, and measurement of multimorbidity seemed to be at the core of good clinical care and necessary to enable further studies of the outcomes of multimorbidity to guide public health interventions.

2.2.3 Challenges in research

I have introduced the occurrence of several chronic conditions in an individual as multimorbidity. In fact, numerous terms exist to describe concurrence of multiple health problems.[27] The most common are *multimorbidity* and *comorbidity*, and the main difference is absence (multimorbidity) or presence (comorbidity) of an index disease of dominant focus.[27]

In research, these 2 terms have been inconsistently used over decades, and researchers have sought to clarify them on several occasions.[4, 28] One reason may be the lack of multimorbidity as a distinct index term in common research databases until 2018.[4] Another great challenge to multimorbidity research is the lack of a standard definition, which affects measures used and comparability of research on prevalence, determinants, and outcomes. The magnitude of the challenge is illustrated in a review of 165 articles in which 115 presented distinct definitions,[29] and the importance of clear description of definition, methods, and selection of conditions to facilitate comparison has been stressed.[30] A selected overview of definitions follows to highlight differentiation to the associated concept comorbidity and differences in requirements that guide measurement of multimorbidity.

2.2.3.1 Historical overview of definitions of multimorbidity

In 1970, Feinstein described the co-occurrence of several medical conditions and how this challenged research and clinical care. He named it *comorbidity* and defined it: "In a patient with a particular index disease, the term co-morbidity refers to any additional co-existing ailment."[31](p. 467) Thus, comorbidity puts 1 disease in the center and any other in association with that index disease. It was specified that clinical entities could include "non-disease," such as pregnancy and symptoms,[31] much like the term conditions as described in section 2.2.1.

In 1996, a review of empirical and theoretical articles from 1966 to 1994 by van den Akker et al[28] stated that comorbidity came to have plural interpretations since it originated 26 years earlier.[28] The review sought to clarify the distinction between a focus on an index disease or not. The concept *multimorbidity* was first introduced and seemingly exclusive to research in

Germany from 1976 to 1990.[32] Brandlmeier in 1976 (as cited in van den Akker et al in 1996[28] (p. 67)), proposed multimorbidity as "the co-occurrence of several chronic or acute diseases." Van den Akker et al[28] suggested continuous use of comorbidity as defined by Feinstein[31] in 1970, while introducing a definition of multimorbidity as "the co-occurrence of multiple chronic or acute diseases and medical conditions within one person."[28](p. 69) This definition differs from Feinstein's comorbidity, in that *multiple* states an unspecified plurality; it adds the requirement of duration of disease, but does not specify the timespan of *chronic* (section 2.5) and *acute*; *patient* is replaced with *person*, which implies a shift in focus from disease to person. The definitions similarly use the terms *clinical entity* and *medical conditions*, which implies a broad perspective on health problems to include (section 2.5).

In 2008 The World Health Organization (WHO) declared multimorbidity as being "affected by two or more chronic health conditions simultaneously."[33] (p. 8) In comparison with the definition by van den Akker et al[28] a decade earlier, the WHO's definition is more specific; the threshold of multiple is set to 2 or more; it emphasizes long-term duration, as it omits *acute from the* definition, and it implies *condition* to be an umbrella term, because it omits diagnosis. The report did not define chronicity.

In 2013, the European General Practice Research Network (EGPRN) criticized the multimorbidity definition by the WHO for using the term *condition*. They found clarification necessary for it to be useful in research and clinical practice.[32] The EGPRN did a review on definitions, measures, and criteria of multimorbidity. This guided the creation of a broad definition of multimorbidity, including modifiers and outcomes:

> "Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor.
>
> "Any biopsychosocial factor, any somatic risk factor, the social network, the burden of diseases, the health care consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity).
>
> "Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty."[32](p. 323)

As expected, the EGPRN definition differentiates between and ranks disease higher than other conditions, in that a chronic disease is required to further establish multimorbidity. This may resemble the concept of an index disease in comorbidity, and the major consequence is that sole risk factors cannot constitute multimorbidity. The EGPRN acknowledges both acute and chronic diseases as elements of multimorbidity, in line with the definition by van den Akker et al[28] in 1996 and opposed to the WHO definition. The EGPRN definition equates multiple to 2 or more conditions, as did the WHO definition. The EGPRN definition explicitly encompasses the holistic view on multimorbidity and the patient by including biopsychosocial factors, such as somatic risk factors, sociodemographic characteristics, psychosocial conditions, and individual beliefs.[32] Finally, the EGPRN views symptoms as potential modifiers of multimorbidity and multimorbidity as a precursor to disability and frailty.[32] (Frailty is further discussed in section 2.6.)

In 2013, there was another systematic review on definitions of multimorbidity in Canada by Almiral and Fortin,[27] who focused on linguistic similarities in current definitions. More than 9 of 10 definitions complied with 2 overarching phrasings, and the reviewers suggested the following refinement: "Multiple co-occurring chronic or long-term diseases or conditions, including both physical and mental diseases, and none considered as index disease."[27](p. 8) Compared with the definition suggested by van den Akker et al[28] in 1996, the Almiral and Fortin multimorbidity definition combining 2 high-frequent in use definition phrasings similarly does not specify the meaning of *multiple* and includes diseases and conditions as separate entities. Further, it differs in that it omits a definition of acute and does not specify multimorbidity occurring within 1 person. The review does not specify duration of chronic or any distinction between chronic and long term. Most notably, the definition equates inclusion of somatic and mental diseases and makes the exclusion of an index disease explicit.

Definitions guide the operationalization of a construct, which makes it possible to measure and study its outcomes. To conclude, by 2015, the definitions of multimorbidity were numerous. However, most include a quantitative threshold from which to identify multimorbidity, and qualitativeelements (duration and types of conditions) to guide selection

criteria of inclusion of health problems to study. A further introduction to these elements follows in section 2.3 and section 2.5.

2.3 Measures of multimorbidity

In search of a proper measure of multimorbidity to detect individuals with complex conditions and presumably burdened in a general population, I initially studied 4 reviews extensively: Diederichs et al (2011),[34] Fortin et al (2012),[35] Huntley et al (2012),[36] and Willadsen et al (2016).[29] Appendix 8.1 presents details of; search period; number of included articles; aims; inclusion criteria; reported findings on definitions, measures, and settings; selection criteria; number and types of conditions; and recommendations by the authors. Note that these reviews used the terms *condition* and *disease* interchangeably, naturally with the exception of the review on types of conditions.[29]

With regards to definition, 3 reviews defined multimorbidity with multiple equated to 2 or more,[29, 34, 35] while 1 did not determine a threshold.[36] Three recommended no change to the definition, [34-36] while 1 suggests using the definition by the EGPRN.[29]

The overall recommendation of measure is that choice needs to fit available data and outcomes of interest.[36] The reviews highlight 2 main approaches to measure multimorbidity: weighted indices or disease count. Weighted indices are developed in and meant for use in subpopulations, to prognosticate a certain outcome by use of medical records, administrative databases, or patient self-reports.[34] Such indices would not fit the general population health data I had available, and I will not explore weighted measures further. Disease count, a simple, unweighted sum of conditions from a total set of conditions, is the dominant multimorbidity measure[29, 34-36] and 2 or more conditions the most common threshold.[29, 34-36] Disease count reproduces anticipated associations with sociodemographic characteristics and health outcomes and can prognosticate health care utilization and mortality as well as more sophisticated measures.[36] One review suggested investigating both 2 or more conditions and 3 or more conditions as thresholds, to help detect differences in age distribution.[35]

The reviews did not suggest any specific setting or data source as superior, but most multimorbidity research is conducted in the general population,[29] and self-report is the typical data source.[34, 35] One review recommend the use of multiple data sources;[35] however, in larger samples, unweighted disease counts based on self-reports are suggested as justified.[35] Two reviews suggested a set number of conditions[34, 35] for increased societal relevance[34] or limiting variance in prevalence and increasing comparability between studies.[35] These and further findings and recommendations from the reviews are included in section 2.4 and section 2.5.

2.4 Elements that influence prevalence and age distribution of multimorbidity

To assess the outcomes of multimorbidity, it is necessary to obtain proper prevalence estimates. The most common measure, disease count, yield vast variations in prevalence.[35] Even in the same age groups, multimorbidity prevalence ranges from 3.5% to 98.5%[35]; in the same setting, from 12.9% to 95.1%.[37] Variation in operationalization of multimorbidity explains most of the discrepancy. Specifically, the number of conditions in the total set,[35, 36, 38] the threshold to identify multimorbidity,[35, 36, 38] and the level of differentiation of conditions[36, 38] are important. These factors also affect the age distribution. One article elegantly examined the outcome of altering these elements on prevalence and age specificity in 1 cohort.[38]

Prevalence increases by the total number of conditions under study.[30, 38] and the set of conditions may vary from 4 to 147 to an open list (an infinite or indeterminate number).[29] At a threshold of 2 or more individual chronic conditions, 12 highly frequent conditions[35] identify a reasonable proportion of all multimorbidity in the complete set of 452 conditions (C. Harrison, [PhD], written communication, October 24, 2017).[38]

Prevalence decrease as a threshold to identify multimorbidity increase. An increased threshold is furthermore suggested to be of greater clinical relevance.[35, 38] At a threshold of 3 or more conditions, the proportion detected by the set of 12 highly prevalent conditions were

insufficient, and the authors[38] suggest researchers include all chronic conditions to obtain proper prevalence estimates.

Prevalence decrease with lower differentiation, because the grouping of conditions results in fewer total units.[30, 38] It is most common to differentiate conditions in single, rather than grouped, units,[34, 35] but sets of conditions may also be mixed.[34] Conditions categorized by separate organ systems produced comparable prevalence estimates at identical thresholds.[38] At a threshold of 2 conditions or more, prevalence estimates were comparable regardless of level of differentiation, while at a threshold of 3 conditions or more, comparability of prevalence measures required conditions to be of equal distinction.[38] Two of the organ system categorizations were based on major disease classification systems in primary and specialist health care, and this may systematize and simplify data collection.[38] Furthermore, conditions in separate organ systems will likely affect the complexity of multimorbidity and be of clinical value, as discussed in section 2.6.

Prevalence of all measures of multimorbidity increase with age. Onset and growth of multimorbidity is delayed by increasing the threshold[35, 38] and additionally by grouping entities,[38] which thus increases age specificity.

2.5 Selection criteria to inclusion of health problems in measures of multimorbidity

While most definitions of multimorbidity contains qualitative elements to guide selection of conditions, the main lead factors being chronicity and condition, few studies explicitly state selection criteria for inclusion to the total set of conditions.[29, 34-36] Proposed requirements to selection of chronic conditions are duration,[18, 34, 35] requiring medical care, [18, 34, 35, 39, 40] severe effects on the individual,[34, 35, 39] and high prevalence.[34, 35, 39] The WHO include both duration and medical care to define chronic conditions.[18] Duration is an obvious component of chronicity; however, in a major review, [29] less than one-third of the studies quantified duration, and of those who did, length ranged from historical to months or years.[29] Furthermore, 1 in 5 studies included the severity of the conditions, which varied from self-

report to staging of disease.[29] Instead of requiring the severity of each condition, some argue that the multimorbidity measure may imply a total severe outcome through an increased threshold[35, 36, 38] and grouping by organ system.[38]

There are opposing views on the selection of highly frequent conditions. Some argue high prevalence will increase clinical and societal relevance of the multimorbidity measure,[34, 35] while others claim this approach may corrupt the true prevalence, in that a large number of people suffer from less common conditions[30] and undermine the norm in multimorbidity, which is multiplicity.[41, 42] To obtain proper prevalence estimates for multimorbidity measures with suggested greater outcomes and clinical relevance, an expanded set of conditions is necessary compared with only highly frequent conditions.[38]

The terms used for health problems (section 2.1.1) vary between definitions and measures of multimorbidity.[34-36] This affects types of conditions selected, as well as the total number. In a review of 115 multimorbidity measures, 100% included diseases, 85% risk factors, and 62% symptoms.[29] Risk factors, while possibly asymptomatic and not causing impairment, may still increase health care utilization and cause treatment burden and thus be a relevant chronic condition. Symptoms may be viewed as modifiers of multimorbidity[32] that affect total patient complexity or are included in the measure,[40] which may strengthen the person focus[29] and clinical relevance[29] in assessments of multimorbidity.

2.6 Multimorbidity, burden and complexity

In the history of multimorbidity, it was early noted that multimorbidity is more than the sum of its parts.[42] The complexity in multimorbidity is associated with both the conditions and the person which entails them.[5, 43, 44] This is reflected in the definition of multimorbidity by the EGPRN,[32] and 1 way to visualize the interplay is presented in Figure 1.

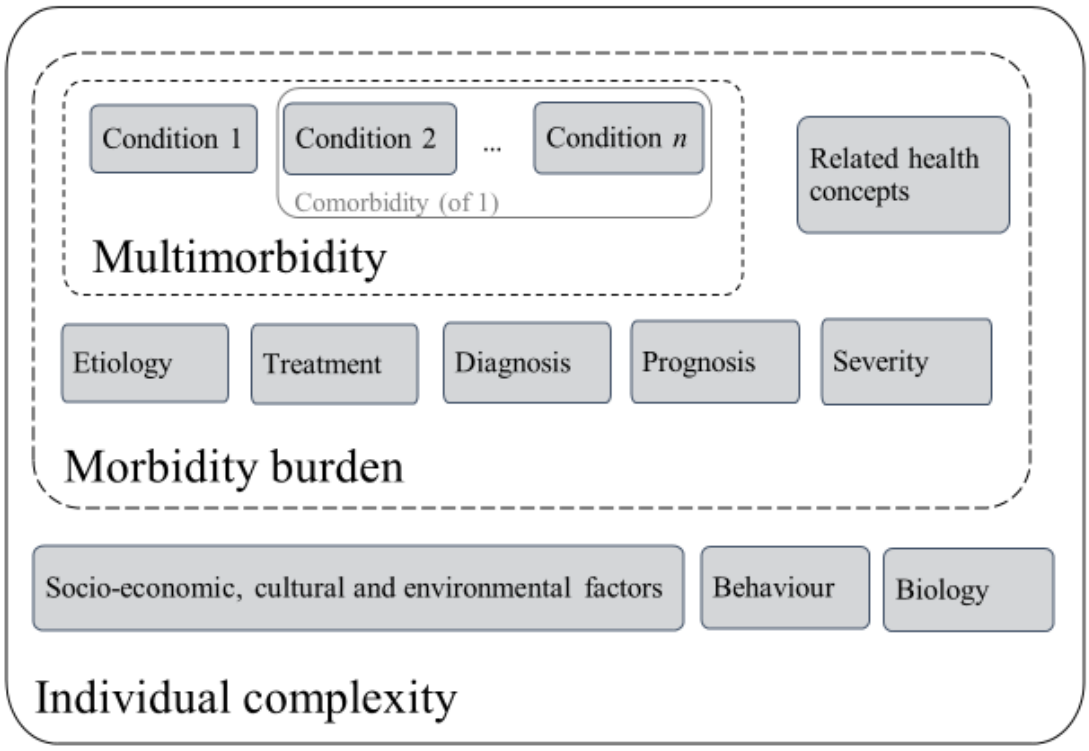


Figure 1. Comorbidity constructs, adapted from Safford et al[43] *and Valderas et al.*[5]

Figure 1 illustrates the demarcation of comorbidity and multimorbidity; how multiple health conditions are at the heart of morbidity burden's further complexity, which is associated with combinations of conditions; their severity; interactions in risk factors and management; association with prognosis; and diagnosis of other conditions and presence of other health problems (eg, frailty). Final individual complexity arises from modification of the aforementioned and fixed biological factors, as well as lifestyle, living conditions, and overarching social, economic, cultural and political context, also known as *social determinants of health*[45] (as further discussed in section 2.8.2).

In 2016, the British National Institute for Health and Care Excellence (NICE) published a guideline[40] on assessment and management of multimorbidity, which follows this broad approach to complexity. While simply defining multimorbidity as 2 or more individual chronic conditions, NICE recommended initiation of comprehensive, integrated care in

patients with increased complexity in either conditions (severity or discordant interactions), treatment regime (multidisciplinary or cross-sectorial), or personal context (frailty or psychosocial factors).[40]

Complexity of conditions rise in association with their etiology and treatment, described by the terms concordant conditions, which appear similar in origin and share risk factors and management requirements, while discordant conditions seem unrelated, do not share predisposing factors, and require different approaches to treatment.[46] Examples of concordant multimorbidity is coronary artery disease and diabetes, in which both conditions will benefit from physical activity. Examples of discordant multimorbidity are chronic obstructive pulmonary disease and diabetes, where use of steroids to alleviate respiratory symptoms will elevate blood glucose levels, exacerbating diabetes. Thus, discordant conditions may compete for treatment or recommendations for 1 condition may be harmful for a discordant condition. Discordant multimorbidity will likely involve several medical disciplines and require more health care resources.[38, 40] Furthermore, complexity rise with the severity of the individual conditions; some argue an elevated threshold to identify multimorbidity will reflect overall severity.[35, 36, 38] Conditions in separate organ systems are often discordant, and this assumption combined with increased threshold, was suggested by Harrison et al in 2014 to capture multimorbidity expected to require tailored care. They named the measure *complex multimorbidity* and defined it as "the co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition."[38] (p.8)

The multimorbidity burden rise in presence of other health problems, such as frailty, which is a dynamic state of multicausality involving loss of function across biopsychosocial domains that increase the likelihood of adverse events.[47] Multimorbidity and frailty are recognized to overlap and considered interconnected.[48-51] Frailty can be determined a personal characteristic[5, 40, 44] reflecting biological age[52-54] that contributes to an individual's complexity of condition, and it is of great clinical value, regardless of chronological age.[40] Frailty, like multimorbidity, is a heterogenous concept, which I have explored in the following section.

2.7 Frailty

2.7.1 Definitions and models of frailty

Definitions and subsequently operationalizations of frailty are manifold. One literature review in combination with opinion of experts, recommended definitions of frailty to support a holistic view of the person and suggested, "Frailty is a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes."[47](p. 342) Three common approaches to measure frailty are the frailty phenotype,[55] the frailty index[54] and multidimensional models.[47]

In 2001, the frailty phenotype[55] was established as a distinct clinical syndrome from disability and comorbidity. The frailty phenotype emphasizes the biophysical domain in observing 5 characteristics: weight loss, fatigue, muscle weakness, low physical activity, and slow walking speed. Persons presenting 3 or more criteria are identified as frail. This measure requires a clinical examination.

Also in 2001, an accumulation of deficits model was developed, as a frailty index[54] that calculates a ratio of the number of health deficits in a given person from a complete set of deficits under study, and the resulting proportion indicates a likelihood of nonspecific frailty.[56] In contrast to the frailty phenotype, the frailty index is inseparable from morbidity and disability, in that symptoms, signs, paraclinical abnormalities, diseases, and disabilities can all be included.[57] In 2008, the original authors suggested a standard operationalization of the frailty index, requiring a minimum of 30 health deficits to be assessed[57] that cover multiple domains. Thus, any medical record data[57] with variables on cognitive, mental, physical, natural functions, dependency, and social resources[58] can help provide a frailty index ratio.

The third approach is to identify frailty by use of questionnaires and self-reports. Similar to the frailty index, commonly used scales require loss of function in multiple domains to identify individuals with frailty,[59, 60] and a general term is multidomain or multidimensional

models of frailty. [60, 61] In contrast with the frailty index, scales will have a fixed set of less than 30 deficits in at least 3 domains.[60]

2.7.2 Measures of frailty, effect on prevalence, recommendations, and associations

The different frailty models capture different aspects, identify different populations, and subsequently result in varying prevalences.[60, 62] In a comparison of 35 frailty measures of all 3 models, identifying frailty dichotomously was common[60] and resulted in higher prevalence than continuous measures.[60] To increase accuracy of prevalence estimates, the authors[60] recommended multidimensional measures. The researchers concluded that prevalence studies using different frailty measures were incomparable.[60] Other reviews have pooled prevalence calculations of frailty and estimated a prevalence of 12% with the frailty phenotype and 16% with other measures of frailty in the middle-aged and older adult general population.[63]

Despite heterogeneity of frailty measures, frailty prevalence is higher among women[59, 60] and increases with age[59, 60] and lower socioeconomic position.[64, 65] Multidimensional frailty scales share the ability to show associations with mortality among those 50 years and older.[59] Frailty is associated with multimorbidity and mortality from middle age onward.[66]

2.8 Social inequalities in health

Social inequalities in health is a very broad concept and can be defined as "any type of persistent and important differences in aggregated health between social positions in the same social structure(s)".[67](p.8) Social inequalities in health are studied on group level (section 2.8.3) and inequalities in health is a consistent finding for nearly all health outcomes for all measures of social position. A common indicator pertains to the socioeconomic stratification of society and in particular socioeconomic inequalities in health form a gradient in which every step up the affluence or status ladder decreases the chances of poor health and premature mortality.[3, 45] Multimorbidity is no exception, because it occurs at higher rates and in younger ages in socioeconomically deprived groups (section 2.9.2) but has an additional dimension compared with other health outcomes, in that the complexity of multimorbidity rises with lower socioeconomic position[5, 21] (section 2.6) as well. Multimorbidity is a generic

measure of health, which makes it particularly suitable to study how social factors affect distribution in the population. In what follows, I have introduced terms for social differences in health, theory, framework, and suggestions of causal pathways, as well as how to measure and report these differences.

2.8.1 Health inequality and health inequity

There are 2 major terms to describe disparities in health. In 1992, the WHO declared health inequity to define avoidable and unfair health differences,[68] while health inequality may describe mere arithmetic differences.[68] In 2008, a WHO report emphasized the amendable structural drivers of health inequalities between social groups, thus defining social health difference inequities per se.[3] However, others have defined social inequalities and inequities in health to similarly describe systematic differences in health between populations by fundamental social structures.[69] The ambiguity and perhaps linguistic challenge, in that the Norwegian language does not offer nuances between these terms, has led to the use of the term *health inequalities* in this thesis.

2.8.2 Theory, framework, and suggested explanations

Theories to explain possible connections between social factors and social group differences in health are manifold.[70-72] A simple distinction can be made between causative explanations, which suggest affiliation in a social group to cause poor health, and selection explanations, which suggest that poor health causes downward social mobility (also known as *reverse causation*). The considered effects of social structures on social groups and their health is clear from the distinction of terms on health disparities (section 2.8.1). This is in line with what can be called *structural theory*[70] or *social production of disease*,[72] which emphasizes the effects of the overarching social, economic, cultural, and environmental structures on living conditions throughout life and consider skewed distribution of income, power, access to services, and freedom of choice to cause accumulation of differential health hazards and explain health inequalities between social groups. The structural theory encompasses some former theories of material deprivation (physical health risks and resources), psychosocial factors (psychological reactions to social experiences), biological risk factors, and lifestyle

risk factors (as discussed below), and view these rather as partial explanations also affected by fundamental structural contexts. The structural theory is a major theory in social epidemiology and the framework for this dissertation.

Structural theory is heavily based on the concept of social determinants of health, which was introduced by the WHO in Europe in 1991 as a layered model of originally termed *main influencers on health*, visualized in figure 2.[45]

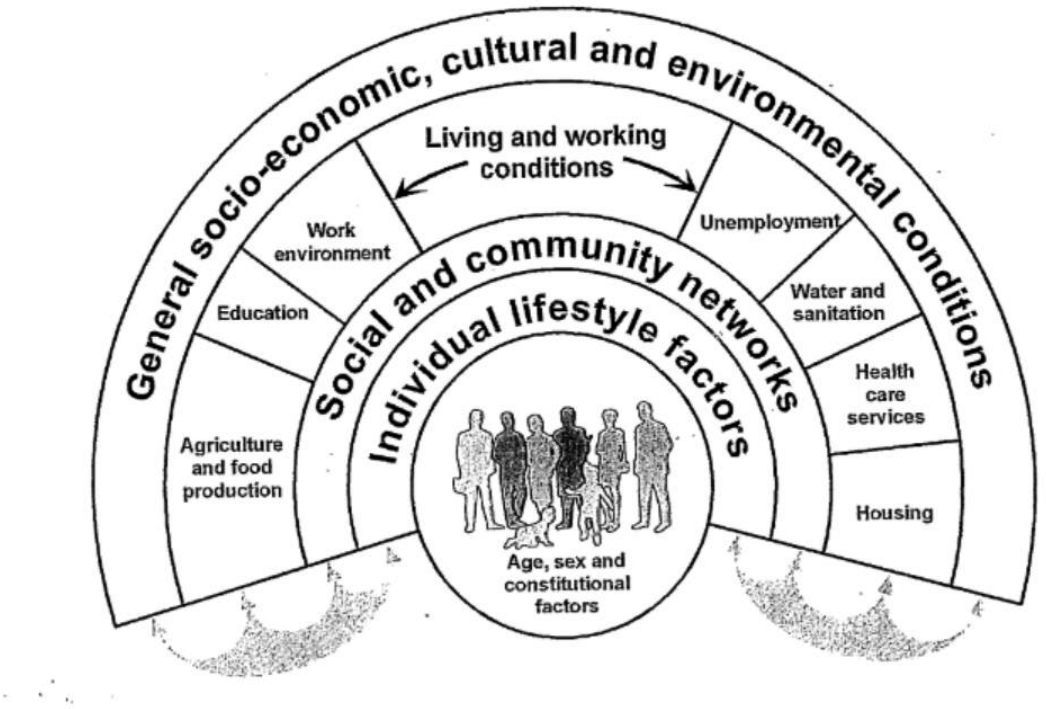


Figure 2. Social determinants of health.[45]

The model is later known as the social determinants of health. It illustrates pathways and elements through which the determinants act and how to politically amend these.[45] The inner core of the model are personal factors, such as age, sex, and genes, while lifestyle, network, living conditions, and overarching structures of social, economic, cultural, legal, and political conditions can be modified through interplay between all levels and increasingly by political actions.[45] Whereas the inner circle has been considered fixed and not politically amendable,

concepts of embodiment[69] and allostasis[73] challenge this and are further discussed in closing remarks on possibilities for future research (section 6.5.3). Furthermore, the authors have acknowledged that health behaviors, originally termed *individual* lifestyle factors, such as smoking, alcohol consumption, diet, and physical activity, are socially patterned, and restriction of choice may depend on socioeconomic position.[45] The model does not illustrate an exact timeline, but the inner core presents people at different life stages, and the report highlights the cumulative and dynamic effects of these conditions from a life course perspective.[45]

In 2008, the WHO commission on social determinants of health put emphasis on the role of the top 2 layers, structural determinants and conditions in daily life, throughout life, as causes of a major part of social health inequalities.[3] The authors viewed the next 2 modifiable layers, social support and behavioral options, to interact on the vulnerability of social groups to poor health.[3] Thus, the structural theory has had a strong position in the WHO over decades, together with the lifecycle approach, which simply put is to acknowledge that health status at 1 point reflects both former and current conditions.[69]

Figure 3 adds to the layered social determinants of health model as it attempts to visually depict the causal pathways through which social position and health are associated.

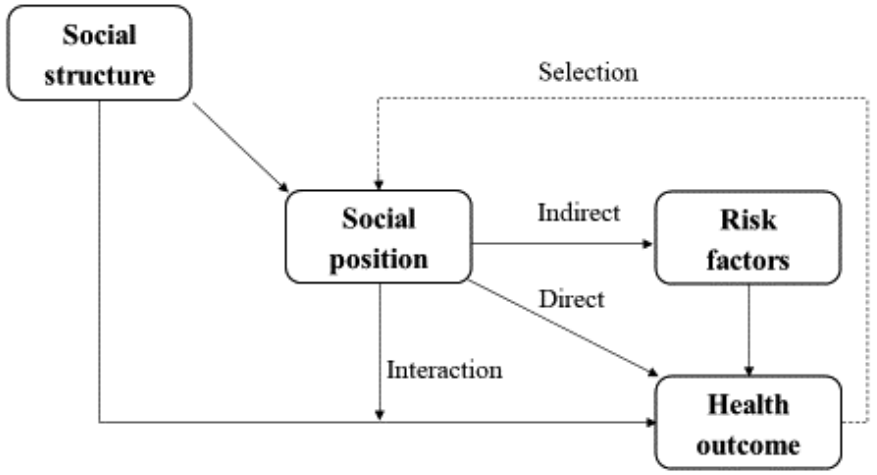


Figure 3. A generic causal model for social health inequalities, translated with the permission of JG Mæland, (Professor), in written communication, April 27, 2020.[74]

Social position reflects that individuals can be categorized in social groups along several axes, such as constitutional or socioeconomic factors (section 2.8.3), which most often have an implicit hierarchical structure with consequences of skewed distribution of and access to resources. The figure illustrates 5 pathways: (1) a direct effect from social structure to health outcome; (2) an interaction in which a social position modifies the effect of social structures; (3) a direct effect of social position on health outcome; (4) an indirect effect, such as a social group-dependent exposure to risk factors and subsequently on health; and (5) the selection effect or reverse causality, in which health determines social position.[74] Any of the social determinants of health as shaped by social position can be investigated along these pathways.

To illustrate, a present structural challenge facing nations worldwide is the coronavirus disease 2019 pandemic and subsequent major lockdown of society, which affect all but some social groups (and nations) more than others.[75, 76] The major advice to individuals involves proper hygiene, social distancing, and (in certain settings) face masks. The overall risk of exposure to the virus varies with structural conditions, such as a national coordinated strategic plan for surveillance, testing, tracing, individual quarantine, and eventually lockdown.

Exposure to the virus will vary with social position, directly as living area may affect access to and income the affordability to buy soap, hand sanitizers, and face masks. Social position will interact with the structural measures as for instance type of work will affect the opportunity to isolate using home office or require continuous close contact with numerous people. Finally, in the case of a family member with the virus, the type of housing will impact the possibility to isolate oneself, an example of how social position may indirectly increase risk of exposure in certain social groups.

2.8.3 Indicators of socioeconomic position

To study social health inequalities, social epidemiology classifies individuals in groups according to numerous social markers, such as age, sex, ethnicity or socioeconomic conditions. Only the latter of these is modifiable, of which some measures, their qualities, and potential explanations have been further explored. Overall terms for social groups are social class, socioeconomic status, and socioeconomic position. Social class reflects an economic relationship between people, typically manifested in labor or ownership.[69] Socioeconomic status primarily determines material resources, and researchers suggest avoiding this term.[69] Socioeconomic position is a broader concept, encompassing prestige, material resources, and social resources,[69] and has been used throughout this dissertation.

Individual measures of socioeconomic position are education, income, wealth, and occupation. Education can be a simple self-reported measure; exclusion of individuals and reverse causation is rare. It is most often a stable measure that associates with life opportunities for work and income. Education reflects health literacy, which may have an indirect effect on health.[77]

Income and wealth may be sensitive to self-report, such that it may necessitate more research resources to obtain valid data. The measures exclude few people, but reverse causality is likely, especially for income, which is dynamic, while wealth is the accumulation of income over time. Income and wealth affect overall living conditions, indirectly affecting health.[77]

Occupation is easy to obtain by self-report, but the measure may exclude those without employment and those working without contracts.[77] Reverse causality is likely. Occupations may not be clearly defined and have a less clear hierarchy compared with education, income, and wealth. Different classification schemes have been developed to assign socioeconomic position based on occupations.[78] An example is the European Socioeconomic Classification (ESeC),[79] which is based on occupation (grouped according to similarities in skill level and specialization)[80] and additional information on employment status and size of organization.[79] Limitations in use of a social class scheme, is that relevant occupations and work relations change over time and it needs to be updated regularly.[77-79] Occupation can directly affect health through biopsychosocial work exposures and indirectly, through general associations to intellectual assets, income, material resources, and social position.[77]

In sum, several indicators of socioeconomic position can identify existing health differences in cross-sectional studies.[81] However, all indicators act through both overlapping and unique pathways and will associate differently with health outcomes.[81, 82] In this thesis, education and income would require linkage to other data sources; thus, an occupation-based socioeconomic classification was used, since the data were available from the questionnaires and up-to-date with ESeC.

2.8.4 Measuring socioeconomic differences in health

One may report socioeconomic differences in health on an absolute or relative scale. In general, absolute measures are differences in occurrence, and relative measures are ratios of occurrence.[83] Several measures exist on both scales, and no measure is considered superior. It is recommended to present socioeconomic health inequalities with both absolute and relative measures.[84]

2.9 Previous research on multimorbidity prevalence, determinants, and association to mortality

This thesis has aimed to explore the complexity of multimorbidity and the individual and its joint association with prevalence and mortality. Before commencing the studies, the

knowledge on associations of multimorbidity with sociodemographic determinants and mortality were as follows.

2.9.1 Measures of multimorbidity and prevalence

Multimorbidity prevalence varies, because of discrepancy in methods (section 2.4). In reviews of multimorbidity measured as a threshold of 2 conditions or more, prevalence ranged from 12.9% to 95.1% in general practice[37] and from 3.5% to 98.5%[35] within the same age group. In the second review,[35] the prevalence estimates varied no less with an increased threshold to 3 conditions or more.[35] In 1 cohort, prevalence for individual entities decreased from 47.4% to 33.8% with an increased threshold from 2 conditions to 3 or more.[38]

I did not find reviews on the measure of complex multimorbidity. One study reported complex multimorbidity in 27.4% of a cohort in general practice and estimated a general population prevalence of 17.0%.[85] Overlap and coexisting multimorbidity and frailty was scarcely explored. One review reported a pooled prevalence of 16% for multimorbidity of 2 conditions with a concurrent frailty phenotype.[50]

In the general population in Norway, multimorbidity at a threshold of 2 conditions or more has been identified in 28% of the population via registry data[86] and 42% via self-reported data.[8] In individuals aged 60 to 69 years, 47.8% met the requirements of complex multimorbidity in self-reported data.[87] The clinical relevance of multimorbidity and frailty has been explored in elderly age groups in Norway,[88, 89] but no study was found on the prevalence of joint multimorbidity and frailty.

2.9.2 Sociodemographic determinants of multimorbidity

Reviews and cohort studies generally report multimorbidity to be more common in women[19, 37, 90] and increase with age[19, 37, 90, 91] and with lower socioeconomic position.[19, 37, 91] However, the association of sex and multimorbidity may depend on included conditions.[37, 92] Furthermore, most people with multimorbidity are young and middle-aged,[21, 91] and aging of

society cannot alone explain the increasing trend of multimorbidity.[20] In lower socioeconomic groups, multimorbidity occurs at a younger age,[21, 93] and rates of multimorbidity are consistently higher throughout adulthood.[21, 93] Complexity of multimorbidity increases with lower socioeconomic position, with higher cooccurrence of discordant, mental, and somatic conditions.[21, 93, 94] Studies in Norway reproduce these associations, because multimorbidity is reported to be higher in women,[8, 86, 95] to increase with age[8, 86] and with lower socioeconomic position.[86]

All of these associations are shown for multimorbidity measured as 2 or more chronic conditions. Measured at a threshold of 3 conditions or more plus complex multimorbidity, increase with age is less steep.[35, 38] Further associations to sex and socioeconomic position for these measures or concurrent multimorbidity and frailty were not detected prior to my studies.

2.9.3 Multimorbidity, mortality, and modification by socioeconomic position

A review of 26 cohort studies established that all multimorbidity measures associated with mortality risk.[9] The magnitude of the association was greater with a threshold of 3 or more individual conditions and less for continuous measures of multimorbidity.[9] The relation was weaker in population studies and with broader adjustment by sociodemographic factors.[9] The review could not pool effects with regards to sex or frailty.[9]

Few studies have explicitly studied the association of multimorbidity with mortality across socioeconomic strata.[96-99] Two studies explored several multimorbidity measures.[97, 98] The measures of multimorbidity and indicators of socioeconomic position varied, as did the reported modification of associations to mortality from stable,[98] to reduced,[97] to nonexistent[99] across socioeconomic strata. Sex differences in the associations of multimorbidity to mortality varied from being present[96, 98] to reported absent.[97, 99]

In Norway, no studies on the association of multimorbidity with mortality as a primary outcome was detected. Complex multimorbidity was associated with all-cause mortality in people aged 60 to 69 years, adjusted for sociodemographic characteristics.[87]

2.10 Summary of background, research gaps and opportunities

Multimorbidity is the new norm and a challenge to individual health care personnel and organizations and researchers. The complexity depends on the cooccurring conditions and individual factors reflected in the social determinants of health. Social health inequalities are timeless and omnipresent, and multimorbidity is no exception. However, associations vary, and there is a lack of studies on socioeconomic differences in the prevalence of more complex measures of multimorbidity and their possible joint outcome on mortality, both internationally and in Norway.

Suitable multimorbidity measures to explore complexity of conditions could be an increased threshold of 3 or more individual conditions, possibly composite with organ system grouping of entities (complex multimorbidity), or a combination of the most commonly studied multimorbidity, defined by a threshold of 2 single conditions, and a complicating context, such as frailty.

In Norway, the dissertation by Tomasdottir[10] explored multimorbidity defined as 2 or more chronic conditions in the general-population Trøndelag Health Study (HUNT). For future research, Tomadottir suggested studying multimorbidity measures with increased specificity, explicitly mentioning *complex multimorbidity*, and studying these by socioeconomic position. The complex multimorbidity measure requires a broad inclusion of conditions to obtain proper prevalence estimates, and this thesis adds to the work by Tomasdottir et al, as I use the same population cohort to expand and make uniform the set of conditions and operationalize several measures of multimorbidity suggested to be of increased complexity and need of tailored care.

The clinical challenge has recently given rise to multimorbidity guidelines.[40, 100] The relevance of single-disease guidelines is thoroughly explored in HUNT data,[101] and it had seemed to be a useful follow-up to investigate how a multimorbidity guideline would fit the general population.

This thesis has aimed to fill a research gap on possible socioeconomic differences in prevalence of complex measures of multimorbidity and their combined associations to mortality. The findings ought to have societal relevance, increasing the background knowledge for informed public health interventions, health care organizations, and clinical management of multimorbidity.

3 Aims

This thesis overarching aim was to describe the socioeconomic distribution of several complex measures of multimorbidity and how socioeconomic position may modify the association of multimorbidity to mortality in an adult general population. The research questions were:

How does prevalence of multimorbidity with frailty vary with socioeconomic position?	Article I
How does prevalence of complex multimorbidity vary with socioeconomic position?	Article II
How does socioeconomic position modify the association of multimorbidity to mortality?	Article III

4 Population and methods

4.1 The Trøndelag Health Study

The counties of Nord- Trøndelag and Sør-Trøndelag merged in 2018, and the largest general population cohort study in Norway changed its name to The Trøndelag Health Study (HUNT). Prior to 2019, this total county health survey invited all adults 20 years and older who were registered as living in Nord-Trøndelag county. There have been 4 waves of cross-sectional data collections, in 1984-1986, 1995-1997, 2006-2008, and 2017-2019, called the HUNT1, HUNT2, HUNT3 and HUNT4 surveys, respectively. HUNT1 screened for tuberculosis and further focused on hypertension, diabetes, and quality of life. The scope has since expanded with more than 5000 variables covering a broad range of topics. A biobank was established in HUNT3. Description of cohort profiles, data collection procedures, and nonparticipants have been published for HUNT1,[102] HUNT2,[103] and HUNT3,[104, 105] and a cohort profile is currently being prepared for HUNT4.

This thesis uses data from HUNT3, which invited 93860 community-dwelling citizens to participate. The major parts of HUNT3 are the main questionnaire sent by mail invitation and handed in on attendance at a screening station in their local municipality, where participants took part in an interview, and clinical measurements and biological samples were taken. A second questionnaire, which was sex-specific and age-specific, was handed out at the screening station and returned by prestamped mail.[104] Details on the HUNT Study are available at https://www.ntnu.edu/hunt/about-hunt. Questionnaires are in appendix 8.2.

4.2 Study population

In total, 50807 of 93860 individuals (54.1%) completed the main questionnaire, fulfilling the criteria of general participation.[104] All studies required complete participation in the major parts of HUNT3 to obtain all possible conditions and classifiable occupational data to assign socioeconomic position. The prevalence studies (article I and II) excluded participants younger than 25 years, to avoid misclassifications in socioeconomic position. The cohort study (article III) focused on the age group 35 to 75 years, omitting younger age groups

because of expected low statistical power and the higher age range to minimize a bias toward healthy older adults. Article III furthermore required registry data on mortality status, which was complete. Figure 4 depicts the sampling process for all articles.

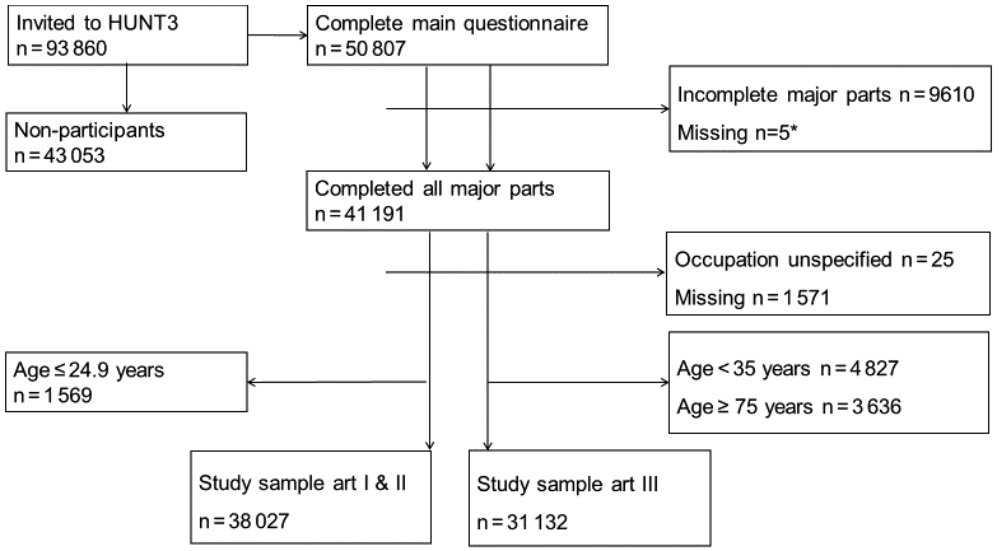


Figure 4. Flowchart for sample selection; inclusion and exclusion criteria, and missing data.

*In article I and II, I reported data missing on participation (n=4) and age (n=1). In article III, 1 person was missing data on mortality status. This is more likely because of retracted consent by these individuals (oral communication, HUNT Databank).

4.3 Study variables

4.3.1 Registry variables

4.3.1.1 Sociodemographic variables

Sex and age were regarded as confounders (section 6.2.2) in all articles and are provided by the HUNT Databank. Sex is derived from the personal identification number. Age at participation, a continuous variable rounded to 1 decimal, was used in articles I through III, and dates of birth, truncated to month and year, were used in article III.

4.3.1.2 All-cause mortality

All-cause mortality was the primary outcome in article III. The Norwegian National Population Registry reports regularly to the HUNT Databank with the statuses alive, emigrated out of the country, or dead for its cohort, linked on an individual level and with no loss to follow-up. The last update from the National Registry and end of follow-up was February 1, 2019.

4.3.2 Multimorbidity

In articles I and II, multimorbidity was the outcome variable, and in article III, it was an independent variable measured at baseline. First, I have presented the definition and selection criteria for the complete set of conditions used to derive all multimorbidity measures. Secondly, I have described operationalization of the separate multimorbidity measures for each article.

4.3.2.1 Definition and selection criteria

Multimorbidity was defined as "multiple co-occurring chronic or long-term diseases or conditions, including both physical and mental diseases, and none considered as index disease."[27] (p.8)

Chronicity was specified as a condition lasting at least 3 months, with severe impact, or requiring health care management. Information on some of these factors were available for 32 conditions, either from the raw data or implicit by construction (table 1). In the absence of information, chronicity was determined by lead author K.H. Vinjerui, MD, and co-author S. Krokstad, MD, professor. Types of conditions included were diagnoses, symptoms, and risk factors requiring treatment.

4.3.2.2 The complete set of conditions

Chronic conditions totaled to 51, and all but 3 were individual entities. Details of operationalization for each condition, references on validity and nonparticipant studies are provided in appendix 8.3. Table 1 summarizes construction, chronicity, and severity for each condition, furthermore types of conditions and grouping by organ system, and finally operationalization of frailty dimensions. In short, 26 conditions were dichotomous self-reported variables, 23 conditions were constructed from several variables by main author K.H. Vinjerui, and 2 conditions were generated by the HUNT Databank. The 51 conditions were categorized according to 14 *ICD-10* chapters reflecting organ systems, by use of the Norwegian Directorate of eHealth online search engine[106] on February 1, 2017. Four frailty dimensions were created from 6 variables on impairments, details are in article I.

Table 1. The set of conditions by type, organ systems and frailty dimensions

	Op.	51 chronic conditions		14 organ systems		4 frailty dimensions
		Diagnosis	1	Neoplasms	1	General
1		Angina pectoris	1.1	**Cancer**	1.1	Self rated health: "poor" or "not so good"
2		Ankylosing spondylitis	2	Blood/immune mechanism	2	Mental
3		Asthma	2.1	**Sarcoidosis**	2.1	Anxiety or
4		Cancer	3	Endocrine/nutritional/metabolic	2.2	Depression or
5		Cataract	3.1	Obesity	2.3	Both anxiety and depression
6	C	Chr. bronchitis/emphysema/COPD*	3.2	Hypercholesterolemia	3	Physical
7	C,S,c	Chr. headache, other	3.3	**Diabetes**	3.1	Chr. illness/injury impair daily life function and
8		Diabetes	3.4	Hypothyroidism		moderate or severe impairment in
9		Epilepsy	3.5	Hyperthyroidism	3.2	motor ability/vision/hearing
10		Fibromyalgia	4	Mental/behavioural	4	Social
11	C,S	Gastro-oesophageal reflux disease	4.1	Alcohol problem	4.1	Physical/emotional problems limit usual socializing:
12		Glaucoma	4.2	**Depression****		"much" or "not able to socialize"
13		Hand eczema	4.3	Anxiety		
14		Heart failure	4.4	Insomnia		
15		Hyperthyroidism	5	Nervous system		
16		Hypothyroidism	5.1	**Epilepsy**		
17		Kidney disease	5.2	Migraine		
18		Macula degeneration	5.3	Chr. headache, other		
19	S,c	Migraine	6	Eye/adnexa		
20		Myocardial infarction	6.1	Cataract		
21		Osteoarthritis	6.2	Macula degeneration		
22		Osteoporosis	6.3	Glaucoma		
23		Other heart disease*	7	Ear/mastoid		
24		Psoriasis	7.1	**Hearing impairment**		
25		Rheumatoid arthritis	8	Circulatory system		
26		Sarcoidosis	8.1	Hypertension		
27		Stroke/brain haemorrhage*	8.2	**Angina pectoris**		
		Symptoms	8.3	**Myocardial infarction**		
1	c	Alcohol problem	8.4	**Heart failure**		
2	S,db	Anxiety	8.5	**Other heart disease***		
3	C,c	Chr. widespread pain	8.6	**Stroke/brain haemorrhage***		
4	S	Dental health status	9	Respiratory system		
5	S,db	Depression	9.1	**Chr. bronchitis/emphysema/COPD***		
6	C,S,c	Hearing impairment	9.2	**Asthma**		
7	C,S,c	Insomnia	10	Digestive system		
8	C,c	Irritable bowel syndrome	10.1	Dental health status		
		Local musculoskeletal pain/stiffness:	10.2	Gastro-oesophageal reflux disease		
9	C,c	Neck	10.3	Irritable bowel syndrome		
10	C,c	Upper back	11	Skin/subcutaneous tissue		
11	C,c	Lower back	11.1	**Hand eczema**		
12	C,c	Shoulder	11.2	**Psoriasis**		
13	C,c	Elbow	12	Musculoskeletal/connective tissue		
14	C,c	Hand	12.1	**Rheumatoid arthritis**		
15	C,c	Hip	12.2	**Osteoarthritis**		
16	C,c	Knee	12.3	**Ankylosing spondylitis**		
17	C,c	Foot/ankle	12.4	**Fibromyalgia**		
18	S,c	Menopausal hot flashes	12.5	**Osteoporosis**		
19	S,c	Nocturia		Local musculoskeletal pain/stiffness:		
20	S,c	Prostate symptoms	12.6-	Neck or upper back or lower back		
21	S,c	Urine incontinence		or shoulder or elbow or		
		Risk factors	-12.14	hand or hip or kne or foot/ankle		
1	S,c	Hypercholesterolemia	13	Genitourinary system		
2	S,c	Hypertension	13.1	**Kidney disease**		
3	S,c	Obesity	13.2	Urine incontinence		
			13.3	Prostate symptoms		
			13.4	Menopausal hot flashes		
			14	Symptoms/signs/laboratory		
			14.1	Nocturia		
			14.2	**Chr. widespread pain****		

Abbreviations table 1: Op., operationalization; C, raw data on chronicity; S, raw data on severity or through construction; c, constructed from ≥ 1 question; db, constructed by HUNT Databank; chr., chronic; COPD, chr. obstructive pulmonary disease; *, group variable; **bold**, variable in sensitivity analysis article II; **, alternative variable used in sensitivity analysis article II.

4.3.2.3 Operationalization of multimorbidity in article I

In article I, a combined construct of multimorbidity and frailty was explored. Frailty was operationalized separately from multimorbidity, as a multidimensional concept. By qualitative judgement of available data in HUNT3, 6 variables on impairments were clustered in general, mental, physical, and social dimensions, as presented in table 1 and in detail in article I. Two dichotomous measures were created by combining occurrence of at least 2 of 51 conditions, plus impairment in at least 1 of 4 dimensions of frailty, and at least 3 of 51 conditions, plus impairments in at least 2 of 4 dimensions of frailty.

4.3.2.4 Operationalization of multimorbidity in article II

Article II explored complex multimorbidity.[38] *ICD-10* chapters reflected organ systems as presented in table 1. Chapters were counted once if affected by 1 or more chronic condition and complex multimorbidity was constructed as a dichotomous variable, including as cases those having conditions in at least 3 of 14 organ systems. In a sensitivity analysis, complex multimorbidity was derived from the main questionnaire only (Table 1). This totaled to 22 conditions categorized in 12 organ systems.

4.3.2.5 Operationalization of multimorbidity in article III

Article III investigated 5 multimorbidity measures. Three were categorical: at least 3 of 51 individual conditions, complex multimorbidity, and multimorbidity with frailty (at least 2 of 51 conditions plus impairment in 1 of 4 dimensions); and there were two continuous measures: individual and organ systems disease counts. Organ systems disease count was used in sensitivity analyses.

4.3.3 Socioeconomic position

In article I and II, an indicator for socioeconomic position, occupational group, was the main independent variable. In article III, occupational groupings were explored as an effect modifier.

Occupational data in HUNT3 were free-text answers to "What is/was the title of your main occupation?" asked at the screening stations, subsequently manually categorized corresponding to Standard Classifications of Occupations by Statistics Norway,[80] which is based on the International Standard Classification of Occupations-88.[107] The classifications categorize occupations on skill level and specialization and does not imply any social, occupational position.[80] For this purpose, occupations linked to the individual were allocated according to the simplified, 3-class version of the ESeC scheme.[79] Details are provided in appendix 8.4. In the articles, the classes were labelled high, middle, and low occupational groups. In this dissertation, occupational group has been replaced with socioeconomic position (section 6.2.2.4).

4.4 Statistical analysis

4.4.1 Overview of statistical models

In this thesis, I used regression models, which is a family of statistical techniques that can model and analyze the association between 1 or more measured factors (independent variables) and a single outcome (dependent variable). These techniques can describe associations or predict values, isolate the effect of a single variable, or understand multiple variables. The type of outcome (ie, the measurement level for the outcome) guides which method to choose, although there are situations in which the outcome may be analyzed with different models.

Logistic regression was applied in all 3 articles. Logistic regression models are appropriate when investigating the association between a binary outcome and independent variables. Results may be presented in various forms, as explained in detail for the articles below. There

are no distributional assumptions for the logistic regression model,[108] but other assumptions may apply (independent observations, no severe collinearity, linearity between continuous variables, and the log odds).

Article III also included survival time data, which I have investigated with Cox proportional hazards regression models in addition to logistic regression models. Cox regression models analyze the association of time with an event and 1 or more independent variables as relative hazards.[109] Results are estimates of hazard ratios, which are ratios of the hazard rates, the instantaneous rate of event at time *t*, of individuals with exposure compared with those without exposure. The Cox regression model does not estimate the underlying hazard function but assumes that the hazard ratio is constant (proportional) over time.

I have conducted all analyses in articles I, II, and III separately for women and men. Table 2 summarizes similarities and differences in methods of this thesis articles.

Table 2. Overview of methods in thesis

	Article I	Article II	Article III	Supplemental analysis
Type of study	Cross-sectional	Cross-sectional	Prospective	Cross-sectional
Data	HUNT3	HUNT3	HUNT3 All-cause mortality	HUNT3
Sample size	38027	38027	31132	38027
Inclusion criteria	Complete major parts Occupational data Age ≥ 25 years	Complete major parts Occupational data Age ≥ 25 years	Complete major parts Occupational data 35 ≤ Age ≤ 75 years Mortality data	Complete major parts Occupational data Age ≥ 25 years
Outcome(s)	2+ ind. MM & 1+frailty 3+ ind. MM & 2+frailty	Complex MM	All-cause mortality	3+ ind. MM 2+ ind. MM & 1+frailty 3+ ind. MM & 2+frailty
Prognostic factors	Occupational group Age Sex	Occupational group Age Sex	Occupational group Age Sex 3+ ind. MM Complex MM 2+MM & 1+ frailty Individual DC Organ system DC	Occupational group Age Sex
Statistical methods	Logistic regression	Logistic regression	Logistic regression Linear regression Cox regression	Logistic regression

Abbreviations: 2+ ind. MM & 1+frailty, at least 2 individual conditions plus 1 dimension of frailty; 3+ ind. MM & 2+frailty, at least 3 individual conditions plus 2 dimensions of frailty; Complex MM, at least 3 conditions in 3 organ systems; 3+ ind. MM, at least 3 individual conditions; DC, disease count.

4.4.2 Statistical analyses in articles I and II

Logistic regression models were fitted to study associations between occupational groups and the presence of the categorical multimorbidity measures, multimorbidity with frailty (article I), and complex multimorbidity (article II). Final models included an interaction term between occupational group and age, which implies multiplicative statistical interaction, that the association with exposure on outcome varies by a third variable.[110] Results were presented as prevalence differences, the difference in mean predicted probability and prevalence ratios, the ratio between the mean predicted probabilities.[111]

In article II, age was in addition entered as restricted cubic splines in the models to explore and visually present the differential associations between age and complex multimorbidity in each occupational group. Restricted cubic spline transformation of continuous, prognostic variables increases the flexibility in estimating a smooth shape of the regression function by use of piecewise polynomials.[112] The estimated prevalence of complex multimorbidity was presented with 95% CIs.

4.4.3 Statistical analyses in article III

Logistic regression models were fitted to analyze the association between chronic disease count and occupational group with 10-year all-cause mortality, adjusted for age and stratified by sex. The number of individual chronic conditions was entered as restricted cubic splines and estimations for women and men separately from each model at age 60 years were combined in a graph showing estimated mortality as proportions with 95% CIs by number of individual chronic conditions. To assess interaction on an additive scale, linear regression models with sandwich standard errors were specified.[113, 114]

The association between multimorbidity and occupational group and time to mortality was analyzed with Cox proportional hazard models with a constructed variable of combinations of multimorbidity and occupational group stratified by sex and with age as time scale until either the date of emigration, all-cause mortality, or the end of follow-up (February 1, 2019), whichever came first. Results were reported as hazard ratios with 95% CIs, visually presented in forest plots.

4.4.4 Sensitivity analysis

In article II, a sensitivity analysis investigated how number and types of conditions may affect associations with age, sex, and occupational group. In article III, a sensitivity analysis investigated how level of differentiation of conditions, grouped by organ system in contrast with individual entities, may affect associations with mortality by age, sex, and occupational group.

4.4.5 Supplemental statistical analysis to complement thesis

Article III introduced the categorical multimorbidity measure of 3 or more individual conditions. To complement the thesis, descriptive analysis of this measure was performed in the larger study sample of articles I and II. Furthermore, to supplement the visual presentation in article II, the procedure was repeated for 3 or more individual conditions and the combined measures of multimorbidity with frailty in article I.

4.5 Missing data

Missing occupational data was the main criteria disqualifying participants from the studies. Mechanisms for missing data can be associated with the missing data (missing not at random [MNAR]), associated with the observed data (missing at random [MAR]), or not associated with the observed or missing data (missing completely at random [MCAR]). Several statistical methods can manage missing data. Complete case analysis is proper, given assumption of data being MCAR, which does not bias results, and is a reasonable approach when the discarded cases represent a small proportion of the entire dataset.[115] Assuming data are MAR, different statistical methods will make use of incomplete data, whereas assuming data are MNAR, sensitivity analyses are recommended.[116]

In all studies in this thesis, less than 5% were missing occupational data, justifying complete case analysis. However, occupational data can be MNAR, since multimorbidity may cause inability to work, which results in underestimated socioeconomic gradients. Occupational data could be MAR, since missingness was associated with age and sex, and thus conservative effect estimates can be expected in older women. Management of missing data for each 51 conditions in the multimorbidity measure is given in appendix 8.2.

4.6 Ethics

HUNT3 data was collected prior to this thesis. Participation in HUNT3 was voluntary, and written consent was obtained.[104] Common to all tests, findings in HUNT3 may have false-

positive results and cause unnecessary worry, or false-negative results, which may delay diagnosis of health problems. About 10% of the participants were advised to consult their primary physician based on management of abnormal findings determined prior to the data collection. Overall, the Regional Committee for Medical and Health Research Ethics in Norway regard the benefits of HUNT to outweigh any potential disadvantage for individual participants. The HUNT data is shared only after studies are approved by the Regional Committee and the current thesis holds project no. 2014/2265. Furthermore, the studies are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[117]

5 Results – overview of articles

Three articles covered the overarching aims of this thesis. Articles I and II and supplemental analyses explored the socioeconomic distribution of in total 4 dichotomous measures of multimorbidity cross-sectionally. I have reported the results jointly for a complete and comparable presentation of all categorical multimorbidity measures studied in this dissertation. Article III investigated the association between multimorbidity and mortality and assessed how socioeconomic positions modified these associations. I have summarized the results on mortality for each analytical model.

5.1 The socioeconomic distribution of complex measures of multimorbidity

The prevalence studies included 38027 of 50807 (74.8%) of the HUNT3 participants, 49.5% in the low and 23.6% in the high socioeconomic group. The overall prevalence estimates of the different measures of multimorbidity in this population cohort are listed in table 3.

Table 3. Frequency and prevalence of complex measures of multimorbidity

Article	Multimorbidity	Frequency	Total	Prevalence
I	2+ ind. MM & 1+ frailty	14860	38027	39.1%
	3+ ind. MM & 2+ frailty	6640	38027	17.5%
II	Complex MM	20385	38027	53.6%
III	3+ ind. MM	23755	38027	62.5%

Abbreviations: 2+ ind. MM & 1+frailty, at least 2 individual conditions plus at least 1 dimension of frailty; 3+ ind. MM & 2+frailty, at least 3 individual conditions plus at least 2 dimensions of frailty; complex MM, at least 3 conditions in 3 organ systems; 3+ ind. MM, at least 3 individual conditions.

Prevalence of all the measures of multimorbidity increased with lower socioeconomic position, higher age, and female sex, but multimorbidity was common across age groups in both sexes. Figure 5 (women) and figure 6 (men) are complementary to the articles, a presentation of the differential association between age, socioeconomic position, and estimated prevalences of the categorical multimorbidity measures with 95% CIs in the age range 25 to 100 years (section 4.4.5).

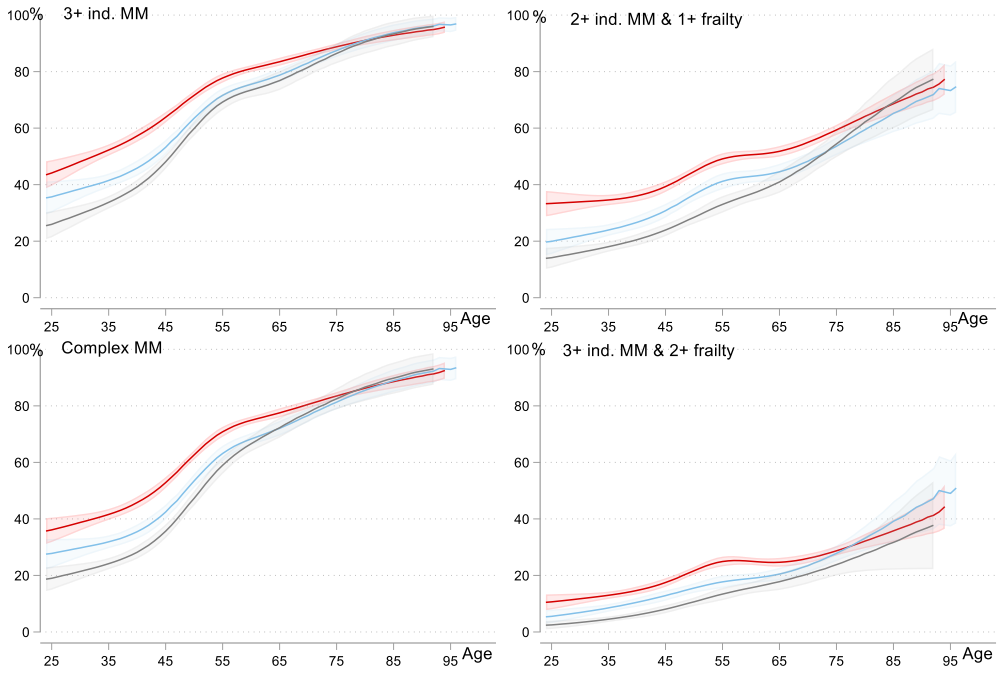


Figure 5. Estimated prevalence (%) with 95% CIs by age and socioeconomic position for women [a]

Abbreviations: 2+ ind. MM & 1+frailty, at least 2 individual conditions plus at least 1 dimension of frailty; 3+ ind. MM & 2+frailty, at least 3 individual conditions plus at least 2 dimensions of frailty; complex MM, at least 3 conditions in 3 organ systems; 3+ ind. MM, at least 3 individual conditions.

[a]Red indicates low socioeconomic position; blue, middle socioeconomic position; and grey, high socioeconomic position. Y-axis: predicted prevalence (%), x-axis age (years).

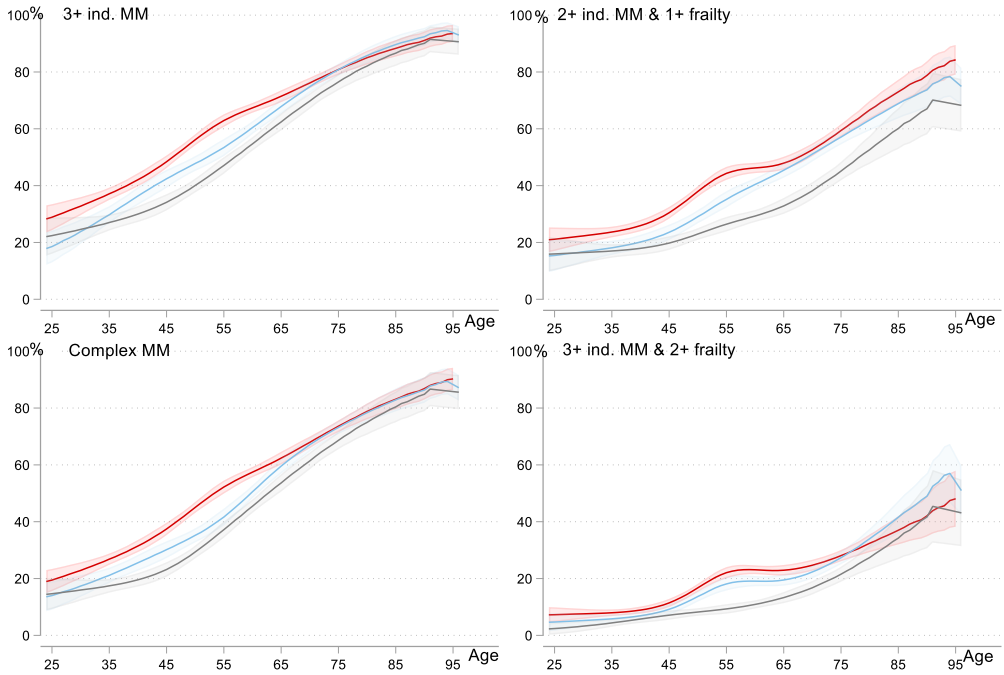


Figure 6. Estimated prevalence (%) with 95% CIs by age and socioeconomic position for men[a]

Abbreviations: 2+ ind. MM & 1+frailty, at least 2 individual conditions plus at least 1 dimension of frailty; 3+ ind. MM & 2+frailty, at least 3 individual conditions plus at least 2 dimensions of frailty; complex MM, at least 3 conditions in 3 organ systems; 3+ ind. MM, at least 3 individual conditions.

[a]Red indicates low socioeconomic position; blue, middle socioeconomic position; and grey, high socioeconomic position. Y-axis: predicted prevalence (%), x-axis age (years).

For all dichotomous measures of multimorbidity, absolute and relative socioeconomic inequalities in prevalence varied by sex and age but were consistent in both sexes until elderly age ranges. In article II, a sensitivity analysis in which complex multimorbidity was derived from fewer conditions, resulted in similar trends in socioeconomic gradients, but the effect sizes were overall smaller and socioeconomic differences in younger age groups were not detectable.

5.2 The association of socioeconomic position and multimorbidity with mortality

The final population cohort study included 31132 of 50807 HUNT3 participants (61.3%) followed for a mean (SD) of 11.1 (1.5) years. At baseline, 49.0% were assigned low and 24.1% high socioeconomic positions. Descriptively, disease count, prevalence of multimorbidity and mortality were higher in the lower socioeconomic group. Table 4 summarizes the total number of deaths, mortality by socioeconomic position, and mortality in those with multimorbidity at baseline.

Table 4. Number of deaths and mortality by socioeconomic group and multimorbidity

	Deaths	Total	Proportion
Cohort	2254	31132	7.2%
Socioeconomic position			
High	373	7501	5.0%
Middle	571	8370	6.8%
Low	1310	15261	8.6%
Multimorbidity			
3+ ind. MM	1795	19409	9.2%
Complex MM	1642	16546	9.9%
2+ ind. MM & 1+ frailty	1312	11861	11.1%

Abbreviations: 3+ ind. MM, at least 3 individual conditions; complex MM, at least 3 conditions in 3 organ systems; 2+ ind. MM & 1+frailty, at least 2 individual conditions plus 1 dimension of frailty.

In logistic regression analysis, mortality increased by number of chronic conditions and socioeconomic gradients varied but were consistent. There was a tendency toward a stronger association between disease count and mortality in men with low socioeconomic position. A sensitivity analysis with multimorbidity measured as an organ system disease count confirmed the associations and revealed greater socioeconomic differences in the risk of death in both sexes. Cox regression analysis showed that the relative risk of death increased similarly with lower socioeconomic position and the presence of any multimorbidity. Overall, the risk of death was more than 2-fold in the lower socioeconomic group with all measures of multimorbidity compared with the reference category for both women and men.

6 Discussion

6.1 Summary of findings

The overall aims were to describe socioeconomic inequalities in prevalence of various complex measures of multimorbidity and study the joint association between socioeconomic position and multimorbidity with mortality in a general population.

Even complex measures of multimorbidity were common in the general population, from 17.5% with at least 3 individual conditions plus at least 2 dimensions of frailty to 62.5% with at least 3 individual conditions. The number of chronic conditions and prevalence of dichotomous multimorbidity measures were higher with lower socioeconomic position. Prevalence increased with age and was higher in women but common across age groups in both sexes. Absolute and relative socioeconomic inequalities in prevalence varied by sex and age but persisted, to diminish only in elderly age ranges in women.

Overall, mortality was higher in lower socioeconomic groups. Mortality increased by disease count with varying but persistent socioeconomic gradients. The increase in mortality was greater by count of organ systems than individual conditions, and the socioeconomic gradients were greater in men. Mortality risk increased similarly with presence of any categorical multimorbidity and lower socioeconomic position.

6.2 Methodological considerations

Epidemiologic studies produce estimates of unknown true results. Article I and II are cross-sectional prevalence studies, in which exposure and outcome are assessed simultaneously and the association of temporality between the two cannot be determined.[118] Thus the prevalences are estimates of a true frequency, and the socioeconomic gradients are descriptive. In article III, the cohort was followed up over 11 years. This prospective design allows for an examination of temporal associations in which the results will be estimates of associations of

unknown true magnitude. Elements regarding accuracy and generalizability of these estimates are discussed below, as well as general strengths and limitations of this thesis.

6.2.1 Random error and precision

Random error may be understood as the role of chance in the data, but preferably it is viewed as unexplained variability in unknown causes of the outcome that are not yet explicitly accounted for.[119] Random error leads to imprecision of the estimate, which can be expressed by reporting confidence intervals. Imprecision affects the reliability and reproducibility of the measure. Random error decrease with larger samples.

In this thesis, the samples are overall large; however, stratification, which may better describe the characteristics that affect associations, reduce the sample size in the subgroups and imprecision rises. In articles I and II, the number of individuals stratified by socioeconomic position, sex, age, and outcomes were still in hundreds or thousands, and one may assume high precision. In article III, the original sample was smaller, the outcome less prevalent, and the results more imprecise.

6.2.2 Systematic error and internal validity

Validity is whether a measure truly indicates what it intends to measure. Internal validity concerns validity of inferences made in the source population, which can be distorted by systematic errors, such as confusion of associations (confounding), bias in participant selection, or mismeasurement of study variables.[120] Such systematic errors deviate results in a directed, nonrandom manner. Confidence intervals of the estimate do not account for systematic error, nor does increase of sample size reduce systematic error.

6.2.2.1 Confusion of associations with confounding

The magnitude of association estimates may shrink or increase by confusion of associations by a third, extraneous factor.[120] A confounder is separately associated with the exposure and outcome under study and is not in the causal pathway between exposure and outcome nor a consequence of the outcome.[121] The bias of confounders is limited by statistical methods, such as adjustment or stratification.[83] In this thesis, age and sex are confounders in all articles and managed accordingly (section 4.4).

6.2.2.2 Selection bias and non-participation

Selection bias is associated with the sample under study, either from the procedure to select participants or by factors that affect study participation.[122] As estimates in the study are conditioned on participation, the observed associations may be confounded by factors that determine participation as well as outcome.[120]

The HUNT Study invites participants broadly. Participation depends on self-selection and in HUNT3, on the possibility to attend a screening station, an absolute requirement to be registered as participant.[104] Overall participation was 54.1% (50807 of 93860 individuals invited). Reasons reported for nonparticipation were largely "not having had time" (53.7%), while a small proportion reported being "too ill" (3.7%).[105] Still, one can expect healthy participant bias, which may skew the data and result in underestimated associations.

Participation in HUNT3 was lower among men, the age groups younger than 40 years and older than 80 years,[104] and lower socioeconomic groups.[105] Noneligibility in the 3 studies excluded more individuals who were young and in lower socioeconomic positions, while most missing data on socioeconomic position were older women. Conservative outcome estimates can be expected in men, the lower and higher age ranges (especially in older women), and lower socioeconomic groups.

6.2.2.3 Mismeasurement and information bias

Outcome estimates will be biased if information and measures collected about and from study participants, on confounders, exposure, or outcome are incorrect.[121] In particular, differential misclassification is wrongful placement of people under study in categorical variables that are associated with exposure or outcome, which may cause bias of outcome estimates in either direction.[121]

In this thesis, age and sex, confounders in all articles, and the outcome all-cause mortality (article III), are registry data linked to the individual and are complete and considered accurate. Differential misclassification can occur in allocating individuals in socioeconomic position and identifying individuals as cases (or not) of the dichotomous multimorbidity measures. Below, I have discussed the validity of occupational group as an indicator for socioeconomic position and general aspects of the multimorbidity measures. A further discussion on the set of conditions and multimorbidity constructs compared with recent literature follows in section 6.4.

6.2.2.4 Validity of indicator for socioeconomic position

Occupation is a common and recognized measure of socioeconomic position. In the cross-sectional studies (articles I and II), multiple measures can detect socioeconomic gradients, if such exist,[77] while temporal associations and mechanisms to explain these in the cohort study (article III) will vary with measure of socioeconomic position.[81, 82]

I used an up-to-date, validated, occupation-based socioeconomic class scheme suitable for international comparison.[79] The HUNT3 study provided occupational data only, which allows for allocation in a simplified ESeC scheme, which has 79.7% agreement with the original classification.[79] The major redistribution occurs from higher to lower categories.[79] In my studies, the scheme was further collapsed to a 3-class version, which slightly improved the aforementioned misplacement, but some dilution of outcome estimates can be expected.

In the articles, the terms *high*, *middle*, and *low occupational groups* replaced the original terms *salariat*, *intermediate*, and *working class*,[79] respectively, emphasizing occupation as basis for placement in ESeC. While ESeC states to be a socioeconomic class scheme, occupation is a comprehensive measure encompassing education, income, and resources.[77] Therefore the broader term *socioeconomic position* is used in this dissertation to emphasize the generalizability of the findings.

In articles I and II, younger participants may systematically be misclassified with lower socioeconomic position, assuming that the highest level of occupation may not yet be obtained. This can dilute the outcome estimates of lower socioeconomic position. Raw data excluded those never having worked and may not represent current socioeconomic context, which probably underestimate socioeconomic gradients in all the studies.[123]

6.2.2.5 Validity of multimorbidity

At the start of this thesis project, there was no gold standard definition or measure of multimorbidity, nor were there recommendations on setting and data source. There were some suggestions on selection criteria for conditions, types, and the total number of conditions to include in studying multimorbidity. Updated literature continues to encourage clear statements of methodology,[4, 124, 125] the study of validated multimorbidity measures,[124] and investigations of the validity of each included condition.[125]

This thesis complies with former and recent literature, in that I have presented definitions of multimorbidity, selection criteria (including chronicity) and operationalization of each condition (appendix 8.3). As most multimorbidity research, the studies in this thesis are conducted in the general population[29] and based on self-report, the most common data source.[34, 35] In larger samples, such as HUNT3, unweighted disease count based on self-report were suggested to be justified,[35] and multimorbidity measures based on disease counts were considered valid in a recent review of studies of multiple outcomes or populations.[124] Disease count reproduces anticipated associations with sociodemographic characteristics and health outcomes and anticipate mortality as well as more sophisticated measures.[36] Validity studies

on most conditions are available in appendix 8.2. Some are general validity studies, other cover several variables in the HUNT Study historically, and there is a selection of validity studies on conditions in HUNT3. These conditions are varyingly considered valid,[126-128] or to overestimate[126, 127] or underestimate[129] outcomes, and few report stratified socioeconomic, age, or sex differences.[127]

Self-report is susceptible to report bias, which is a concern to the associations studied if there are systematic differences in reporting between socioeconomic groups, age groups, and sexes. The nonparticipant study after HUNT3 detected that participants reported more symptoms, while nonparticipants and data from general practitioners confirmed more diseases.[105] The disagreement varied by age, sex, and condition and was not studied by socioeconomic position.[105] The difference in symptoms and disease may partly be explained by symptoms not leading to help seeking, or on seeking health care, more specific diagnosis may have replaced symptoms. Other studies on general populations comparing self-report and administrative data found trends towards the underreporting of chronic conditions by lower socioeconomic groups.[130, 131] The subtle differences in occurrence of diseases and symptoms between participants and nonparticipants is likely not causing any large bias in the results of the multimorbidity measures studied in this thesis. Overall, one may assume underreporting by lower socioeconomic groups, which will underestimate the associations to socioeconomic position.

There is still a lack of consensus on number of conditions required to produce valid prevalence estimates of multimorbidity.[125] For comparability, recent reviews suggest using previously published sets of conditions if they are similar in setting and outcome.[125, 132] I extracted all conditions in HUNT3 to provide a valid prevalence estimate of complex multimorbidity.[38] The set of conditions in this dissertation expand on and made uniform the previous list created by Tomasdottir et al in this cohort.[8] The conditions are limited to those collected for the general health survey and the questions on morbidities in HUNT3 are heterogeneous. As opposed to proposed limitations in the articles, most of the conditions had information on chronicity. Nearly all included conditions were individual conditions but with

various levels of detail. There was for instance 1 variable on cancer, whereas local chronic pain was detailed to 9 locations. Types of conditions are discussed in section 6.4.

6.2.2.6 Validity of frailty measure

There is no consensus on a superior frailty measure. It is common to modify assessment of frailty to fit available data.[62]

This thesis investigated frailty as a separate but associated concept to multimorbidity, of which only the multidimensional model would fit the data and purpose. The validity of each frailty variable in HUNT3 were not explored, but multidimensional frailty measures are shown to increase accuracy in prevalence estimates and recommended by a recent comparative study of frailty models.[60] The measures in this thesis are comparable in number of domains and threshold to common multidimensional scales.[59]

In HUNT3, the questions on functional deficits vary in timespan, which may affect the likelihood of reporting. Dichotomous frailty measures may overestimate prevalence,[60] and based solely on self-report, overestimation may be higher in women.[133]

6.2.3 External validity

External validity concerns the transferability of inferences to populations beyond the people studied.[120] The HUNT Study with its total county approach still lacks major cities, has a low prevalence of immigrants (2.4%[134] vs national 9.2%[135]), and has slightly lower educational level[136] and median income[137] than the Norwegian mean, while participants in HUNT3 had higher socioeconomic position than their nonparticipating counterparts.[105] Participants have lower mortality than nonparticipants,[105] but the trends in life expectancy in Nord-Trøndelag follows that of Norway in general.[138] Bearing in mind self-selection and likely healthy participant bias, the HUNT Study is considered to be representative for Norway overall.[103] Health trends in the cohort follows that of Western high-income countries,[139, 140] and in

particular, socioeconomic differences in health has been comparable with those of other Northern European countries.[141]

6.2.4 Summary of methodological considerations

Summarized, these methodological considerations indicate that estimates in articles I and II will have good precision but likely be conservative in the extremes of the age range. Article III will have less precise estimates and likely be conservative in women of older ages. In all articles, one may expect underestimation of associations in the lower socioeconomic groups and men. The results will be transferable to Norway and Northern European countries.

6.2.5 Strengths and limitations

A strength of this dissertation is that data and methods on multimorbidity, frailty, and social health inequalities meet the standards of studies on these topics. Multimorbidity methodology is transparent and detailed to accommodate comparability.[4, 21, 30, 124, 125] I have investigated the socioeconomic distribution of several measures of multimorbidity,[125] in the same cohort, which offers a unique opportunity for direct comparison of prevalence values, sociodemographic gradients, and the joint association of socioeconomic position and multimorbidity measures with mortality. I have reported absolute and relative measures of socioeconomic differences in prevalence and associations with mortality.[84] I have compared mortality with reference groups that may have some morbidities.[9] Stratification by sex and socioeconomic position can clarify characteristics useful to inform future interventions.

The overall limitations in the studies are that all the multimorbidity measures are based on counts and not types of conditions, which may vary with socioeconomic positions. This heterogeneity may bias estimates in either direction. Plural indicators of socioeconomic position on individual or household level would have benefitted this thesis. With regard to article III, when assessing prospective health outcomes, weighted multimorbidity measures are recommended[125]; however, this was not possible to construct with the data available. The duration of exposure of multimorbidity prior to HUNT3 may vary by socioeconomic group, and using only 1 measure of baseline health status may underestimate socioeconomic

gradients.[9] The number of deaths are relatively few, yielding imprecision in estimates and limiting the interpretation of the results.

6.3 Discussion of findings

6.3.1 Comparison of the socioeconomic distribution of complex measures of multimorbidity

6.3.1.1 Socioeconomic differences in prevalence of multimorbidity with frailty

Because of differences in methodology, directly comparable studies and results are few. Since the completion of article I, I have not identified studies on the association of sociodemographic variables with multimorbidity with frailty.

Three cohort studies have investigated socioeconomic position, multimorbidity, frailty, and associations with mortality.[66, 99, 142] These report the overall prevalence of more than 2 chronic conditions of multimorbidity with the frailty phenotype and are thus not directly comparable with the measure of multidimensional frailty in article I.[60]

The worker cohort study reported prevalence of multimorbidity and frailty separately.[99] Differences in prevalence values of both varied with indicators for socioeconomic position and were higher in men. In contrast, I have reported higher prevalence of the joint measure in women. Multimorbidity may be underestimated in a healthy worker sample,[99] and frailty may be overestimated as threshold for identification were less than originally proposed.[99, 142] The worker sampler were homogenous, as only 13.0% (835 of 6425) were classified in the low occupational group, and men constituted 71.2% (4577 of 6425) of the sample, which may partly explain differences in socioeconomic gradients to article I.

The most comparable study in terms of setting and multimorbidity measure[66] to article I, reported 7.3% (11865 of 161576) with at least 2 of 39 individual chronic conditions and unidimensional frailty, while I identified 39.1% (14860 of 38027) with a minimum of 2 of 51

conditions of multimorbidity and a minimum of 1 of 4 dimensions of frailty. Higher prevalences of each measure and thereby overlap is as expected, since this thesis's multimorbidity measures were derived from larger sets of conditions and plural dimensions of frailty.

The conclusion from article I remain unchanged. Variable prevalence and association with determinants are likely explained by methodological differences.

6.3.1.2 Socioeconomic differences in prevalence of complex multimorbidity

Since the submission of article II, the measure complex multimorbidity has been investigated in comparison with a threshold of 2 or more individual chronic conditions[143, 144] and disability[143] in a cross-sectional study of full-time farmers (18 to 59 years old) in Brazil[144] and 7 repeated cross-sectional studies of a middle-aged and older adult population cohort in England.[143]

The Brazilian study included 20 chronic conditions categorized in 8 organ systems. Socioeconomic position was explored as education, income, and land ownership. Overall prevalence of complex multimorbidity was 16.7% (132 of 790), which increased with age but not lower socioeconomic position or female sex, in contrast with article II. In addition to differences in methodology, nonexistent socioeconomic gradients could be attributable to homogeneity of the sample, in that lower socioeconomic groups encompassed nearly 90% of the participants. Indifference to sex data is explained by low access to local health care.[144]

In England, there were 25 chronic conditions categorized in 8 organ systems and proxy variable for socioeconomic position was household wealth quintile. Age-standardized prevalence of complex multimorbidity increased from 12.2% in 2002 to 21.1% in 2015. At each point, prevalence increased by age and was higher in women and in groups with more deprived, as in article II. However, the increase in prevalence of complex multimorbidity from 2002 to 2015 was greater in men than women. Similar to findings in article II, age and

socioeconomic position interacted into elderly age ranges. Complex multimorbidity captured greater inequalities into higher age groups compared with 2 or more individual conditions.[143]

The complex multimorbidity measure in this dissertation is derived from a larger set of individual chronic conditions and categorized in more organ systems compared with these studies and identified a higher prevalence of complex multimorbidity, as expected. The sociodemographic gradients are of greater interest than the exact prevalence estimates. In particular, the English repeated prevalence studies with consistently directed sociodemographic gradients support the findings in article II.

6.3.1.3 Sociodemographic differences in distribution of several measures of multimorbidity in the same cohort

Investigating a variety of multimorbidity measures in 1 cohort allows to directly compare socioeconomic and demographic prevalence distribution. I performed supplemental analysis (section 4.4.5) and created a complementary visual display (section 5.1) to highlight this purpose on writing the dissertation. The differential association of age, socioeconomic position, and estimated multimorbidity prevalence of the categorical measures show that 3 or more individual conditions yield the highest prevalence estimates in all socioeconomic groups at all ages. Complex multimorbidity compresses the prevalence estimates, and growth by age is less steep. Lower prevalence values and less increase by age are even more pronounced for the multimorbidity measures, including frailty. In common, all the multimorbidity measures presented larger socioeconomic position prevalence differences among young women and among middle-aged people of both sexes. Furthermore, socioeconomic position prevalence differences diminished in older adult women while still being present in men at 80 years of age for all multimorbidity measures. Multimorbidity with frailty captured the greatest socioeconomic gradients in old age. Sensitivity analyses revealed that a higher number of conditions studied, detected greater socioeconomic position differences in younger age groups (article II).

6.3.2 Comparison of the impact of socioeconomic position and multimorbidity on mortality

Since submission of article III, I have not detected new studies exploring the joint association of socioeconomic position and multimorbidity with mortality. In article III, the results were compared with 4 studies, 2 population cohorts that measured multimorbidity as disease counts (range, 0 to ≥4)[97, 98] and 1 population cohort[96] and 1 worker cohort,[99] which measured multimorbidity as 2 or more of 30 and 9 individual chronic conditions, respectively.

Compared with these studies, the findings in article III reproduced a larger mortality risk with increasing disease counts in men.[98] Modification by socioeconomic position in the association between multimorbidity and mortality in men only, is in line with previous findings showing that only men with multimorbidity having persistent differences in survival according to socioeconomic position.[96]

When exploring a greater range of individual conditions, I found increased mortality with consistent socioeconomic group gradients with increasing disease counts, as opposed to formerly described stable[98] or decreased[97] socioeconomic gradients with higher disease counts. Also, in contrast with diminished socioeconomic gradients in mortality in the presence of dichotomous measures of multimorbidity and frailty,[99] results in article III suggested intact socioeconomic position gradients in mortality in the presence of all categorical measures of multimorbidity. Methodological differences will partly explain differences in the associations of socioeconomic position and multimorbidity with mortality.

6.3.2.1 Differences in socioeconomic position interaction with several multimorbidity measures on mortality in the same cohort

Investigation of various measures of multimorbidity in 1 cohort offers a unique opportunity for direct comparison of the joint association of socioeconomic position and multimorbidity measures with mortality. Sensitivity analysis revealed that count of organ systems compared with individual conditions, confirmed statistical interactions in men and revealed greater

socioeconomic differences in mortality in both sexes (article III). This may be explained by increased number of affected organ systems, implying discordance, which is associated with lower socioeconomic position.[21, 93, 94]

The relative risk of death increased similarly with lower socioeconomic position and with prevalence of multimorbidity for all categorical measures of multimorbidity. A former review established that all multimorbidity measures are associated with mortality risk,[9] and thus reproduction of association to mortality for all created multimorbidity measures in this dissertation suggest that they are valid measures of multimorbidity.

6.3.3 Potential explanations of socioeconomic differences in prevalence of multimorbidity and joint associations to mortality

This thesis reveals that there are persistent socioeconomic differences in prevalence of multimorbidity and socioeconomic position modifies multimorbidity's association with mortality. In the framework of the social determinants of health and life course perspectives, these social health inequalities are understood to occur as socioeconomic groups experience and interact with social structures that determines an unequal distribution of power, access, and resources that fundamentally affect conditions of everyday life and result in skewed health hazards accumulated throughout life.[3]

Because occupation is the indicator for socioeconomic position in this thesis, it is possible to point out some specific explanations for the reported social health differences. Following the generic model in figure 3 (section 2.8.2), occupation may affect health through several mechanisms; directly, through exposure to toxic hazards[81] or demanding physical requirements,[77] which tend to cluster in lower occupational groups[3]; indirectly, through intellectual assets and health literacy, income, and material resources[77]; interaction with overall socioeconomic structures, where lower occupational groups are likely to be more greatly affected by financial crises and increased unemployment; and finally, through reverse causality, where current health will affect access to job opportunities. There is also selection into occupations, based on childhood socioeconomic positions, individual education, and

health, such that occupational health inequalities can largely be a reflection of this selection.[145] The bidirectional association of health and work may explain quite large socioeconomic group prevalence differences in younger women, while survival bias explains diminishing socioeconomic group prevalence differences in older ages.

6.4 Reflections on multimorbidity, complexity, and constructs

The definition of multimorbidity, inclusion of conditions, and choice of complex measures of multimorbidity were up to date with research as of December 2017. Since submission of articles I and II, there has been published a systematic review of systematic reviews of definitions and measures of multimorbidity[124] and a report on multimorbidity and priorities for global health research[146] with suggestions on definitions and measures, as well as a commentary that differentiates multimorbidity, comorbidity, and associated concepts[4] and another review on multimorbidity measures only.[125] In light of these new studies, I have reflected on the overall set of conditions, complexity, and the constructed multimorbidity measures.

Recent literature emphasizes that no individual condition holds priority in multimorbidity,[4, 146] which strengthens the holistic focus, encompassing complexity of multimorbidity and the individual. The term *condition* can seem to narrow down, in that symptoms[4, 124] and risk factors[4, 124, 146] are explicitly excluded. Others recognize that historically, there is a precedent that multimorbidity measures more than diseases.[124] The most common threshold measure of multimorbidity is still 2 or more individual chronic conditions.[4, 124] The global report suggests making future research uniform by defining multimorbidity at this threshold,[146] while others suggest investigating increased thresholds,[4, 124] as well as continuous disease counts.[4] There are new and more clear suggestions to report risk factors, lifestyle, behaviors, and associated concepts separately[146] and study multimorbidity holistically by investigating determinants, effect modifiers, association with social factors[4, 124] and functions, such as frailty and disability,[4, 146] and total association with outcomes, such as mortality.[124] This is in contrast to earlier views on how to implement the holistic perspective in research, in that some proposed

to include biopsychosocial elements[32] and loss of function[40] in the definition and measure of multimorbidity.

I believe this thesis fit well with recent suggestions on exploration of the holistic and complex nature of multimorbidity. The studies have investigated several continuous and categorical operationalizations of multimorbidity in the framework of social health determinants, recognized to increase complexity of multimorbidity, in 1 cohort. Furthermore, article III investigates the total joint association of socioeconomic position and multimorbidity measures with mortality in a subsample of the same cohort.

In this dissertation, a broad inclusion of conditions, regardless of individual prevalence, was inspired by a focus on the nonspecific nature of multimorbidity.[30, 41] I have considered symptoms and risk factors (requiring medical care) relevant to patient and management[29, 40] and included them in the set of conditions. The demarcation between lifestyle factors, such as use of alcohol, associated with health outcomes, and their inclusion (or not) as a risk factor or their clinical manifestation as a disease, will depend on the data available and purpose of study. It is possible to argue that this thesis's inclusion of symptoms and risk factors, ignorant to prevalence, and the lack of complete information on chronicity in all individual conditions yield multimorbidity measures of smaller burdens. Instead of narrowing the inclusion of conditions on these terms, I have chosen to investigate the burden of multimorbidity by various operationalizations and through these measures' sociodemographic gradients and associations with mortality.

Reflecting on the multimorbidity measures explored, I aimed to study measures implying increased complexity and thus did not investigate prevalence and associations with mortality of 2-condition multimorbidity only. In hindsight, this could have been performed for the purpose of comparability with standard multimorbidity research. On writing the thesis, I have repeated the statistical analysis of estimated prevalence in article II for all categorical measures to enhance internal comparison.

The lack of comparable studies with the joint multimorbidity and frailty measure (articles I and III) likely reflects an unsettled research approach to these connected measures. While some call for research on epidemiology and pooled effects,[52] others recommend keeping the terms separate and rather explore their association.[124, 146] To comply with both perspectives, it would have been possible to investigate the determinants of each measure separate, as well as jointly in articles I and III.

Both multimorbidity and frailty are considered indicators of biological age,[52, 54] in which multimorbidity reflects dysfunctions surpassing a clinical threshold, whereas frailty can include both clinical and subclinical measures[52, 54] and reflect the multidimensional loss of function with biological age.[51] A recent dissertation[147] exploring health inequalities in multimorbidity and functional limitation suggested complex multimorbidity, which indicates the ways multiple organ systems are affected to better capture the multidimensional assets of biological aging than multimorbidity measured as individual conditions. While I have included complex multimorbidity foremost as a measure to indicate increased complexity of conditions (section 2.6) because of assumed discordance,[38] the associations of discordant multimorbidity with lower socioeconomic position[21, 93, 94] and complex multimorbidity as a suggested favorable indicator for biological age point at additional explanatory mechanisms for social health inequalities, further explored in section 6.5.3.

In article II and III, the outcome of grouping entities in organ systems were explored. Individual conditions varied on the level of detail in HUNT3 and may be subject to more reporting bias,[34] while by grouping the conditions by organ system, the measure becomes more uniform and valid. Recently, complex multimorbidity has been shown to capture greater socioeconomic inequalities into older age groups compared with 2-condition multimorbidity.[143] In this thesis, estimated prevalence values of organ system complex multimorbidity compared with a threshold of 3 individual conditions compromised prevalence values overall and had less increase in prevalence with age. The socioeconomic distribution varied by age and sex for both measures, and there was no obvious difference in magnitude of socioeconomic gradients. In article III, the joint associations of socioeconomic position and presence of 3 individual conditions vs conditions in 3 organ systems with mortality was similar.

Continuous measures of multimorbidity were only explored in studying the joint association of socioeconomic position and multimorbidity with mortality (article III). Here, continuous measures seem superior to categorical measures in detecting socioeconomic gradients, which may reflect loss of information by dichotomization.[148] Furthermore, a disease count by organ system revealed greater socioeconomic gradients than a count of individual conditions, which, as mentioned, may be explained by the former measure being more likely to reflect increased discordance associated with lower socioeconomic position.

6.5 Implications for the clinic, public health, and future research

This thesis reveals that a high proportion of the general population is identified with multimorbidity of assumed increased complexity. There are persistent socioeconomic differences in prevalence and modification of the association of multimorbidity with mortality by socioeconomic position. The estimates are likely conservative, especially in lower socioeconomic groups. Notwithstanding methodological limitations , the findings are uniform and should guide management of multimorbidity in the clinic, public health, and future research.

6.5.1 Implications for clinical, policy, and public health management of multimorbidity

Multimorbidity and social context need increased attention in the education of health care workers and clinical care. Guidelines on management of multimorbidity are emerging,[100, 149, 150] and organization of health care is commonly suggested to facilitate person-centered, coordinated generalist care.[6, 22, 40] In Norway, assigned family doctors play a key role in managing individuals with multimorbidity. Electronic journal systems should offer technological support to identify patients with multimorbidity in both primary and specialist health care.

Preventing socioeconomic differences in multimorbidity and mortality ought to be a priority for public policy, and in public health, interventions will need to be both universal and targeted throughout the life course.[151] In particular, these studies highlight occupational differences, which emphasize the importance of job security and standards for health, safety, and environment in this sector.

6.5.2 Future research, exploring multimorbidity concepts

There are initiatives to uniform multimorbidity research, in terms of definitions, suggested sets of conditions, operationalizations of multimorbidity and reporting of results, such as reporting health-associated concepts (frailty and disability) separately. I will strongly recommend future multimorbidity researchers to use resources available at The International Research Community on Multimorbidity.[152]

Measures of multimorbidity will continuously need to fit data and outcome of interest. This thesis has broadly included conditions to study multimorbidity as a generic concept and highlight upstream socioeconomic factors influencing the development of a range of conditions. Studying multimorbidity patterns and highly prevalent individual conditions may highlight more biologically precise, immediately socially stratified risk factor pathways. I view these approaches as complementary.

As generic measures, I recommend that future research explores multimorbidity at threshold of 2 or more and 3 or more individual conditions to comply with former research and highlight organ systems counts as a valuable multimorbidity measure onwards, as they may be more robust to report bias, have higher age specificity, and offer advanced capability to detect socioeconomic gradients. In addition to categorical measures, continuous measures of multimorbidity should be investigated.

6.5.3 Future research, exploring potential explanations to social differences in multimorbidity

As stated, this thesis studied multimorbidity as a generic concept in the framework of structural theory; however, only occupation indicated socioeconomic position and structural health determinants, and the life course perspective was not emphasized. Possibilities for future investigation of these are highlighted.

With regards to a life course perspective, frailty and recently complex multimorbidity has been suggested indicators of biological age. The socioeconomic gradient in health, where morbidities (and multimorbidity) accumulate and mortality occurs at earlier chronological age in socioeconomically disadvantaged groups, may be viewed as premature biological aging. Embodiment describes this sociobiological interaction and refers to how people incorporate the material and social world in which they live, from conception to death.[69] This accumulation of experiences occurs across multiple systems in the body affecting allostasis, which is a theory to describe how the body functions maintain stability through adaptability to the physical and social environments throughout life.[73] Allostatic overload denotes accumulation of prolonged strain, such that the capacity to adapt is overstretched, dysregulation occurs, and vulnerability to development of clinical dysfunction and diseases in multiple organ systems increases,[10, 153] which is equal to the measure of complex multimorbidity. Corrupt allostasis may be a common biological mechanism, an indicator of biological age, underlying various multimorbidity. Several biomarkers can reveal subclinical dysregulation in (for instance) hormones, neuroendocrine, immune, and metabolic systems.[153] In connection with this thesis, allostatic overload biomarkers fit with the biologic components of individual complexity (figure 1; section 2.6) and the inner circle of social determinants of health (figure 2, section 2.8.2). Including parameters of allostatic overload in studying trajectories of complex multimorbidity may be valuable to detect vulnerable subgroups. Furthermore, biological findings may ease and strengthen communication with the public and policy makers.

In the HUNT Study, Tomasdottir et al's articles highlighted the theory of allostasis and how adverse life experiences in children and adults broadly affect biology and may explain the

development of complex co-occurring conditions.[8, 10, 154, 155] They thus explored multimorbidity from the life course perspective but did not study the outcome of socioeconomic position or other social determinants of health.

The broader impact of social determinants of health, including material, psychosocial, and behavioral factors, has been jointly examined in Singer's recent dissertation on health inequalities in multimorbidity in England.[147] Furthermore, Singer has developed a theoretical framework for a life-course model to integrate social determinants of health in exploring possible pathways to multimorbidity, which is suggested to be useful to assessing other multifactorial and cumulative health outcomes, such as frailty and allostatic load.[147] In the HUNT Study, a comprehensive investigation of social determinants of health to explain socioeconomic differences in mortality but not multimorbidity has been studied via data from HUNT2 (1995-1997).[156] Overall, a broader inclusion of social determinants of health in investigating social differences in multimorbidity and mortality is rare.

This thesis builds on Tomasdottir et al's work in the HUNT Study population cohort, in that it adds to and makes uniform the set of conditions included to create new measures of multimorbidity, with suggested increased specificity and complexity, and exploring these by socioeconomic position and the joint association with mortality. However, the life course perspective, exploration of sociobiological interaction, and further social determinants of health were not explored. Thus, there is a research gap in the Norwegian population that implements life course, allostasis and broader models of social determinants of health and associations with trajectories of multimorbidity and mortality. Data from the HUNT Study is suitable for such comprehensive study and would add to existing studies on HUNT data. I would consider it a golden opportunity to show the great value of this repeated population health survey, as well as an opportunity to collaborate across research groups and disciplines.

7 Conclusion

This dissertation investigated the socioeconomic distribution in prevalence of several complex measures of multimorbidity, suggesting detecting individuals requiring tailored care, and the joint association of socioeconomic position and multimorbidity with mortality in a general population. Overall, these complex measures of multimorbidity are common, socioeconomic differences in prevalence persist throughout adulthood, and there are continuous socioeconomic inequalities in mortality across multimorbidity measures.

The findings imply a need for public policy and public health to focus on prevention of socioeconomic inequalities in health in general, which would likely affect the prevalence of multimorbidity and overall mortality. In health care, the magnitude of multimorbidity in all age groups suggests a demand for generalist and person-centered approach, including socioeconomic context. This needs to be reflected in health care organizational structure, treatment guidelines, and general medical education. In Norway, individually assigned family doctors are in a unique position to offer such care continuously, and this arrangement should be kept high in priority. Future research on trajectories of multimorbidity, association with biological markers and a variety of social determinants of health, health care utilization, and mortality could enhance future prevention and management of multimorbidity.

8 Appendix

8.1 Table A1. Multimorbidity measures; details of reviews, results and recommendations

Reviews	Diederichs et al, 2011	Fortin et al, 2012	Huntley et al, 2012	Willadsen et al, 2016
Basic study details				
Years included	1960 to 2009	1970 to 2012	Inception to 2009	Inception(?) to 2013
No. of articles	39	21	194 on 184 distinct studies	163
Aim	Overview: selection criteria, data source, no. and types of diseases included; methods: study population used to develop indices; weighting methods applied in indices	Identify and compare studies reporting MM prevalence; suggest method aspects to consider in such studies	Identify measures of MM and burden suitable for use in primary care and general population; investigate their validity on anticipated associations with sociodemographic characteristics/process measures/health outcomes	Examine how MM is defined: what diseases, risk factors, and symptoms are included in the definition?
Inclusion criteria (No. of articles)	Studies that analyze the "impact of MM on different outcomes specifically in the general population" (21); methods studies concerned with "development of weighted MM indices" (18)	Describe prevalence of MM or report results that allow its calculation; studies conducted in primary care (18), general population (12), or both (1)	Studies on measures of MM and associations to sociodemographic characteristics/process measures/health outcomes; comparing measures; demonstrating reliability; quantitative studies in primary care or general population	Empirical articles that contain a MM definition
Multimorbidity (No. of articles)				
Definition	"The coexistence of ≥2 chronic diseases" in the same individual	"Multiple coexisting chronic diseases"; by review: ≥2 CIRS (1); ≥2 chronic diseases (20)	"Co-occurrence of multiple diseases or medical conditions within 1 person"	"The coexistence in one patient of two or more concurrent chronic conditions (eg, diseases, risk factors, or symptoms)"; by review: individual constructed definitions (115); morbidity indices (30); lack info (21)
Measure	Disease count	General population; disease count (12 of 13); primary care: disease count (8 of 9), plus ≥3 or ≥4 (7); CIRS (1)	17 measures, based on diagnosis (13) or medication (4); most common: disease count (98 of 194); 5 MM indices (96)	Not specified (55); disease count, ≥2 (61); disease count with several cutoffs (13); disease count, ≥3 (11); disease count, ≥1 (4); MM indices (19)

Table A1 continued	Diederichs et al, 2011	Fortin et al, 2012	Huntley et al, 2012	Willadsen et al, 2016
Setting (No. of articles)				
Population	General population	General population; national random sample (8 of 13); geographical cohort (4)	Primary care(76); general population(108)	General population(68); primary care(41); specific databases(26); specialist health care(16); mixed(11)
Data source	Self-report (17 of 21); physical report and/or medical records (3); mixed (1)	General population: self-reports (9); mixed (1); clinical exams (1); pharmacy data (1); primary care: all patients (6); medical records (7)	Disease count; medical records, physician reports, self-reports	Self-reports (56); mixed (44); registries (36); medical records (22)
Conditions (No. of articles)				
Selection criteria	16 of 39 with explicit criteria: 13 association with mortality (4), function (3), or health (3); prevalence (7); other indices (4); treatment required (3)	"The definition of a chronic condition varied among studies, and the importance or severity of the disease was usually not specified."	Disease count: Chronic, rarely defined	Specified duration(32 of 115); included severity(25); great heterogeneity in those terms
Pool	Range: 4 to 102 (majority 6 to 25); mean, 18.5; median, 14	General population; range, 7 to 22; mean, 12; median, 12; primary care; range, 5 to 185 or open list	Disease count: range, 9 to 35	Range, 4 to 147
Types	17 most common: 13 individual diseases, 2 grouped diseases, and 2 functional impairments	≥50 or open list (5); 13 grouped diseases (1)	Individual or grouped conditions, diseases, or health problems	Diseases (115); top 3: diabetes, stroke, cancer, (individual or grouped); risk factors (98); top 3: hypertension, osteoporosis, hypercholesterolemia, (individual); symptoms (71); top 3: back pain, visual impairment, urinary incontinence, (individual).

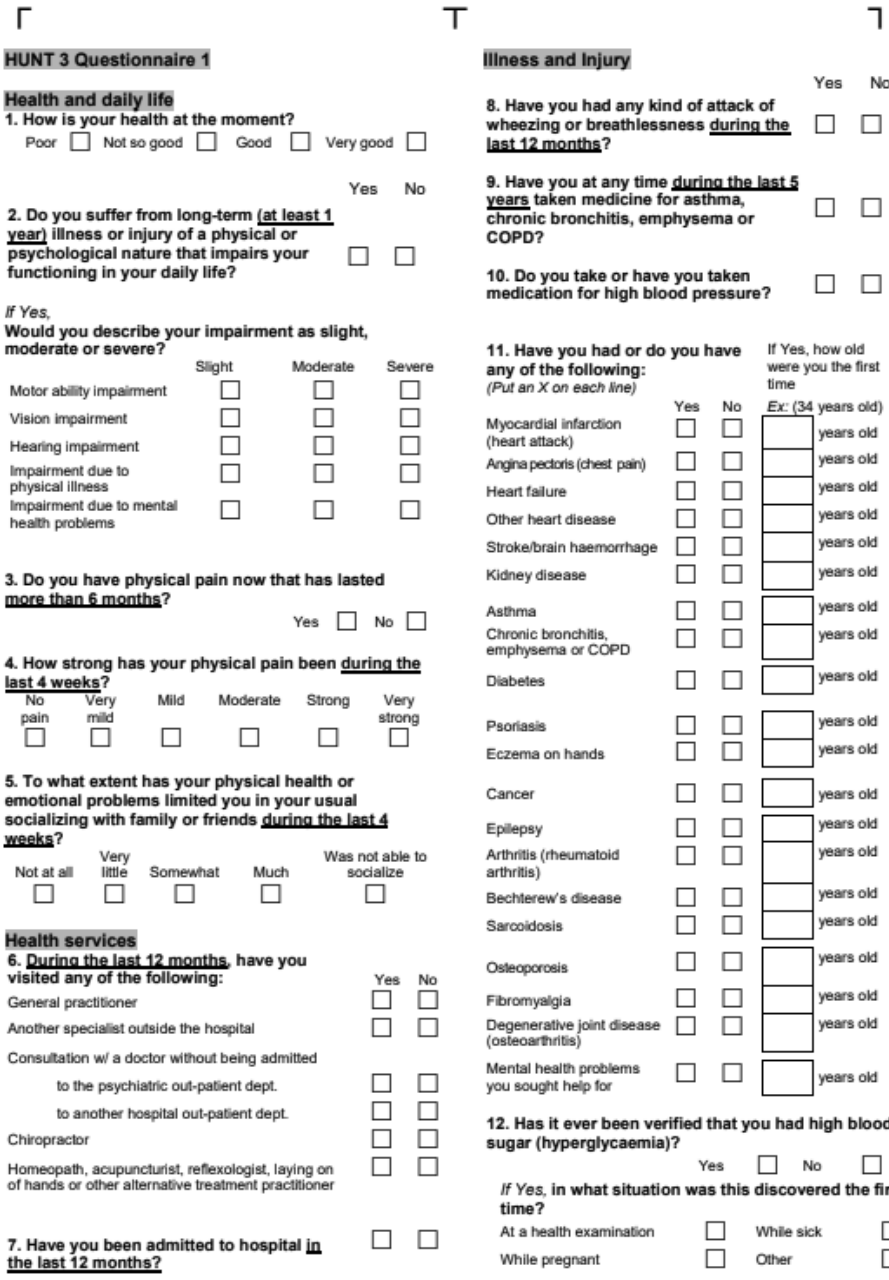
Table A1 continued Conclusions or suggestions	Diederichs et al, 2011	Fortin et al, 2012	Huntley et al, 2012	Willadsen et al, 2016
	Define chronic diseases by long duration, requirement of continuing treatment, severe effects on affected people, high prevalence in those >65 y; include 11 specific diseases based on German context, adding as appropriate	Use both ≥2 and ≥3 as a measure; use multiple data sources; large samples with no other data justify using unweighted self-reports; selection criteria should include effect or burden prevalence; include	Choose MM measure based on; data available, outcome of interest. Use disease count if cross-sectional. Pro: associate with sociodemographics and health outcomes (health care use, mortality); most common, multiple data sources, associates/predicts as good as sophisticated methods. Con: very heterogene (lack selection criteria)	Use 2013 EGPRN definition; symptoms and severity increase clinical relevance

Abbreviations: No., number; MM, multimorbidity; CIRS, Cumulative Illness Rating Scale (a MM index)

8.2 HUNT3 Questionnaires, English version

8.2.1 Main questionnaire:

https://www.ntnu.edu/c/document_library/get_file?uuid=129b68c3-520c-457f-8b98-02c49219b2ee&groupId=140075



HUNT 3 Questionnaire 1

Health and daily life

1. How is your health at the moment?

Poor ☐ Not so good ☐ Good ☐ Very good ☐

	Yes	No
2. Do you suffer from long-term (at least 1 year) illness or injury of a physical or psychological nature that impairs your functioning in your daily life?	☐	☐

If Yes,
Would you describe your impairment as slight, moderate or severe?

	Slight	Moderate	Severe
Motor ability impairment	☐	☐	☐
Vision impairment	☐	☐	☐
Hearing impairment	☐	☐	☐
Impairment due to physical illness	☐	☐	☐
Impairment due to mental health problems	☐	☐	☐

3. Do you have physical pain now that has lasted more than 6 months?

Yes ☐ No ☐

4. How strong has your physical pain been during the last 4 weeks?

No pain	Very mild	Mild	Moderate	Strong	Very strong
☐	☐	☐	☐	☐	☐

5. To what extent has your physical health or emotional problems limited you in your usual socializing with family or friends during the last 4 weeks?

Not at all	Very little	Somewhat	Much	Was not able to socialize
☐	☐	☐	☐	☐

Health services

6. During the last 12 months, have you visited any of the following:	Yes	No
General practitioner	☐	☐
Another specialist outside the hospital	☐	☐
Consultation w/ a doctor without being admitted		
to the psychiatric out-patient dept.	☐	☐
to another hospital out-patient dept.	☐	☐
Chiropractor	☐	☐
Homeopath, acupuncturist, reflexologist, laying on of hands or other alternative treatment practitioner	☐	☐
7. Have you been admitted to hospital in the last 12 months?	☐	☐

Illness and Injury

	Yes	No
8. Have you had any kind of attack of wheezing or breathlessness during the last 12 months?	☐	☐
9. Have you at any time during the last 5 years taken medicine for asthma, chronic bronchitis, emphysema or COPD?	☐	☐
10. Do you take or have you taken medication for high blood pressure?	☐	☐

11. Have you had or do you have any of the following:
(Put an X on each line)

	Yes	No	If Yes, how old were you the first time *Ex:* (34 years old)
Myocardial infarction (heart attack)	☐	☐	☐ years old
Angina pectoris (chest pain)	☐	☐	☐ years old
Heart failure	☐	☐	☐ years old
Other heart disease	☐	☐	☐ years old
Stroke/brain haemorrhage	☐	☐	☐ years old
Kidney disease	☐	☐	☐ years old
Asthma	☐	☐	☐ years old
Chronic bronchitis, emphysema or COPD	☐	☐	☐ years old
Diabetes	☐	☐	☐ years old
Psoriasis	☐	☐	☐ years old
Eczema on hands	☐	☐	☐ years old
Cancer	☐	☐	☐ years old
Epilepsy	☐	☐	☐ years old
Arthritis (rheumatoid arthritis)	☐	☐	☐ years old
Bechterew's disease	☐	☐	☐ years old
Sarcoidosis	☐	☐	☐ years old
Osteoporosis	☐	☐	☐ years old
Fibromyalgia	☐	☐	☐ years old
Degenerative joint disease (osteoarthritis)	☐	☐	☐ years old
Mental health problems you sought help for	☐	☐	☐ years old

12. Has it ever been verified that you had high blood sugar (hyperglycaemia)?

Yes ☐ No ☐

If Yes, **in what situation was this discovered the first time?**

At a health examination ☐ While sick ☐

While pregnant ☐ Other ☐

Injuries

13. Have you ever had:

	Yes	No	If Yes, how old were you the **first** time *Ex: (34 years old)*
Hip fracture	☐	☐	☐ years old
Fractured wrist/forearm	☐	☐	☐ years old
Fracture/compressed dorsal vertebrae?	☐	☐	☐ years old
Whiplash	☐	☐	☐ years old

Illness in immediate family

14. Do your parents, siblings or children have, or have they had, the following illnesses? *(one X per line)*

	Yes	No	Don't know
Stroke or brain haemorrhage before the age of 60	☐	☐	☐
Myocardial infarction (heart attack) before the age of 60	☐	☐	☐
Asthma	☐	☐	☐
Allergies/hay-fever/nasal allergies	☐	☐	☐
Chronic bronchitis, emphysema or COPD	☐	☐	☐
Cancer	☐	☐	☐
Mental health problems	☐	☐	☐
Osteoporosis	☐	☐	☐
Kidney disease (not kidney stone, urinary tract infection, urinary incontinence)	☐	☐	☐
Diabetes	☐	☐	☐

15. Have your parents' siblings, your cousins or either of your grandparents been diagnosed with diabetes (type 1 or type 2)?

Yes ☐ No ☐

How do you feel?

16. In the last two weeks, have you felt: *(one X per line)*

	No	A little	A good amount	Very much
Confident and calm	☐	☐	☐	☐
Happy and optimistic	☐	☐	☐	☐
Nervous and restless	☐	☐	☐	☐
Troubled by anxiety	☐	☐	☐	☐
Irritable	☐	☐	☐	☐
Down/depressed	☐	☐	☐	☐
Lonely	☐	☐	☐	☐

17. Has anyone at any time in your life tried to oppress, degrade or humiliate you over an extended period of time?

Yes ☐ No ☐

Lifestyle

Smoking

	Yes	No
18. Did any of the adults where you grew up smoke indoors?	☐	☐
19. Did your mother smoke when you were growing up?	☐	☐

20. Do you smoke? *(Put an X in only one box)*

- **No**, I have never smoked ☐
  *If you never smoked, skip to question **22***
- **No**, I quit smoking ☐
- Yes, cigarettes occasionally (parties/vacation, not daily) ☐
- Yes, cigars/cigarillos/pipe occasionally ☐
- Yes, cigarettes daily ☐
- Yes, cigars/cigarillos/pipe daily ☐

21A. Answer this if you smoke daily now or previously smoked daily:

1. **How many cigarettes do/did you usually smoke daily?** ☐ Cigarettes pr day
2. **How old were you when you started smoking daily?** ☐ years old
3. **If you previously smoked daily, how old were you when you quit smoking?** ☐ years old

21B. Answer this if you smoke/previously smoked occasionally, but not daily:

1. **How many cigarettes do/did you usually smoke in a month?** ☐ Cigarettes pr mo.
2. **How old were you when you started smoking occasionally?** ☐ years old
3. **If you previously smoked occasionally, how old were you when you quit?** ☐ years old

22. Do you use, or have you used snuff?

No, never	☐	Yes, occasionally	☐
Yes, but I quit	☐	Yes, daily	☐

*If you answered No, never, skip to question **23***

If Yes,

How old were you when you began using snuff?

☐ years old

How many portions snuff do/did you use a month?

☐ Portions snuff a month

If you use(d)/smoke(d) both cigarettes and snuff, which did you begin with first?

Snuff	☐	About the same time (within 3 months)	☐
Cigarettes	☐	Don't remember	☐

Did you begin using snuff to try to quit or cut down on smoking?

No ☐

Yes, to quit smoking ☐ Yes, to cut down on smoking ☐

Diet

23. How often do you normally eat these foods?
(one X on each line)

	0-3 times a month	1-3 times a week	4-6 times a week	Once a day	Twice or more a day
Fruits, berries	☐	☐	☐	☐	☐
Vegetables	☐	☐	☐	☐	☐
Chocolate/candy	☐	☐	☐	☐	☐
Boiled potatoes	☐	☐	☐	☐	☐
Pasta/rice	☐	☐	☐	☐	☐
Sausages/hamburgers	☐	☐	☐	☐	☐
High-fat fish on bread or for dinner (salmon, trout, herring, mackerel, haddock)	☐	☐	☐	☐	☐

24. Do you take the following dietary supplements?
(One X for each supplement)

	Yes, daily	Occasionally	No
Cod-liver oil	☐	☐	☐
Omega-3 capsules	☐	☐	☐
Vitamins and/or minerals	☐	☐	☐

25. How <u>many glasses</u> do you usually drink of the following? ½ litre = 3 glasses (one X on each line)

	Seldom/ never	1-6 gl. a week	1 gl. a day	2-3 gl. a day	4 gl or more a day
Water, Farris, etc.	☐	☐	☐	☐	☐
Whole milk (sweet/sour)	☐	☐	☐	☐	☐
Other milk (sweet/sour)	☐	☐	☐	☐	☐
Soda/juice w/sugar	☐	☐	☐	☐	☐
Soda/juice w/out sugar	☐	☐	☐	☐	☐
Juice or nectar	☐	☐	☐	☐	☐

26. How many cups of coffee do you drink a day?
(write 0 if you do not drink coffee/tea daily)

	Boiled coffee	Other coffee	Tea
Number of cups			

27. How many cups of coffee do you drink in the evening (after 6pm)?

Number of cups ☐

Alcohol

28. About how often in the last 12 months did you drink alcohol? *(do not include low-alcohol beer)*

4-7 times a <u>week</u>	☐	About once a <u>month</u>	☐
2-3 times a <u>week</u>	☐	A few times a <u>year</u>	☐
About once a <u>week</u>	☐	Not at all the last <u>year</u>	☐
2-3 times a <u>month</u>	☐	<u>Never</u> drink alcohol	☐

29. Did you drink alcohol during the last 4 weeks?

Yes ☐ No ☐

If Yes,
Did you drink so much that you felt very intoxicated (drunk)?

No ☐ Yes, 1–2 times ☐ Yes, 3 times or more ☐

30. How many glasses of beer, wine or spirits do you usually drink <u>in the course of two weeks</u>: *(do not include low-alcohol beer, write 0 if you do not drink alcohol)*

	Beer	Wine	Spirits
Number of glasses			

31. How often do you drink <u>5 glasses or more</u> of beer, wine or spirits in one sitting?

Never ☐ Monthly ☐ Weekly ☐ Daily ☐

Exercise

By exercise we mean going for walks, skiing, swimming and working out/sports.

32. How often do you exercise? *(on the average)*

Never ☐
Less than once a week ☐
Once a week ☐
2-3 times a week ☐
Nearly every day ☐

33. If you exercise as often as once or several times a week: How hard do you exercise? (average)

I take it easy, I don't get out of breath or break a sweat ☐
I push myself until I'm out of breath and break into a sweat ☐
I practically exhaust myself ☐

34. For how long do you exercise each time?(average)

Less than 15 minutes ☐ 30 min -1 hour ☐
15-29 minutes ☐ More than 1 hour ☐

35. Do you have at <u>least 30 minutes</u> of physical activity daily at work or in your leisure time?

Yes ☐ No ☐

36. About how many hours do you sit during a normal day? *(include work hours and leisure time)*

☐ hours

Employment

37. If you have had paid or unpaid employment, how would you describe your job? *(One X only)*

- Work that mostly involves sitting *(ex: desk work, assembly worker)* ☐
- Work that requires much walking (*ex: clerk, light industry worker, teacher*) ☐
- Work that requires much walking and lifting (*ex: mail carrier, nurse, construction worker*) ☐
- Heavy physical labour (ex: *forester, farmer, heavy construction worker*) ☐

Height/Weight

38. About how tall were you at age 18?

☐☐☐ cm Don't remember ☐

39. About how much did you weigh at age 18?

☐☐☐ kg Don't remember ☐

40. Are you satisfied with your weight now?

Yes ☐ No, don't weigh enough ☐ No, weigh too much ☐

41. Have you tried to diet in the last 10 years?

No ☐ Yes, a few times ☐ Yes, many times ☐

42. Do you weigh at least 2 kg less than you did 1 year ago?

Yes ☐ No ☐

If Yes, **what is the reason for this?**

Dieting ☐ Illness/stress ☐ Don't know ☐

Serious events in the last 12 months

43. Has a member of your immediate family died? *(Child, spouse/partner, sibling or parent)*

Yes ☐ No ☐

44. Have you been in imminent mortal danger because of a serious accident, catastrophe, violent situation or war?

Yes ☐ No ☐

45. Has your relationship with your spouse or long-term partner ended?

Yes ☐ No ☐

46. If you answered Yes to one or more of the above questions (43, 44 or 45), how much have you reacted to this in the last 7 days?

Not at all ☐ Moderate amount ☐

A little ☐ Very much ☐

Childhood – When you were 0-18 years old

47. Who did you grow up with?

Mother ☐ Other relatives ☐

Father ☐ Adoptive parents ☐

Stepmother/ stepfather ☐ Foster parents ☐

48. Did your parents leave each other, or get a divorce, when you were a child?

No ☐

Yes, before I was 7 years old ☐ Yes, when I was 7-18 years old ☐

49. Did either of your parents die when you were a child?

No ☐

Yes, before I was 7 years old ☐ Yes, when I was 7-18 years old ☐

50. Did you grow up with pets?

No ☐

Yes, cat ☐ Yes, dog ☐ Yes, horse ☐ Yes, other animal ☐

51. How much milk or yoghurt did you usually drink?

Seldom/ never	1-6 glasses pr. week	1 glass pr. day	2-3 glasses pr. day	More than 3 glasses pr. day
☐	☐	☐	☐	☐

52. Did you grow up on a farm with farm animals? Yes ☐ No ☐

53. When you think about your childhood, would you describe it as:

Very good ☐ Average ☐ Very difficult ☐

Good ☐ Difficult ☐

In General

54. Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied? *(One X only)*

- Very satisfied ☐
- Satisfied ☐
- Somewhat satisfied ☐
- A bit of both ☐
- Somewhat dissatisfied ☐
- Dissatisfied ☐
- Very dissatisfied ☐

8.2.2 Age-differentiated and sex- differentiated questionnaire:

https://www.ntnu.edu/c/document_library/get_file?uuid=35ae2816-4155-4b64-a259-770946fa46d4&groupId=140075

Dear HUNT participant

Thank you for taking part in this health study. We ask that you complete this questionnaire. Though some of the questions are similar to questions you have previously answered, it is important that you answer all the questions. The information will be used in research and preventative health care. Researchers will only have access to anonymous information; this means that the information cannot be traced back to the individual participants.

Please complete the questionnaire and send it in as soon as possible. Postage is paid.

Date completed 20

Housing and Friends

Who do you live with? *(One or more Xs)*

- No one ☐
- Parents ☐
- Spouse/partner ☐
- Other people over 18 years old ☐ ☐
- Other people under 18 years old ☐ Number of people under 18 ☐

Are there any pets in your home?

No ☐

Yes, cat ☐ Yes, dog ☐ Yes, other animals w/ fur/birds ☐

Do you have friends that can help you when you need them? Yes ☐ No ☐

Do you have friends that you can speak to confidentially? Yes ☐ No ☐

Your Surroundings (neighbourhood/group of farms)

I feel a strong sense of community with the people who live here *(One X)*

Strongly agree	Somewhat agree	Not sure	Somewhat disagree	Strongly disagree
☐	☐	☐	☐	☐

We do not trust each other here *(One X)*

Strongly agree	Somewhat agree	Not sure	Somewhat disagree	Strongly disagree
☐	☐	☐	☐	☐

People like living here *(One X)*

Strongly agree	Somewhat agree	Not sure	Somewhat disagree	Strongly disagree
☐	☐	☐	☐	☐

Physical Activity

How much of your leisure time have you been physically active in the last year? *Weekly average for the year. Commute counts as leisure time.*

	Hours a week			
	None	Less than 1	1-2	3
Low physical activity *no sweat, not out of breath*	☐	☐	☐	☐
Vigorous physical activity *sweat, out of breath*	☐	☐	☐	☐

How many hours in total are you in front of a computer screen? *(Write 0 if you don't use a computer)*

Work ☐ hours Leisure ☐ hours

How many hours do you watch TV/video/DVD daily?

- Less than 1 hour ☐ 4-6 hours ☐
- 1-3 hours ☐ More than 6 hours ☐

Culture/Life Philosophy

How often in the last 6 months have you been to: *(One X per line)*

	More than 3 x /mo.	1-3 x /mo	1-6 x /6 mos.	Never
Museum/art exhibition	☐	☐	☐	☐
Concert, theatre, film	☐	☐	☐	☐
Church/chapel	☐	☐	☐	☐
Sports event	☐	☐	☐	☐

How many times in the last 6 months have you participated in the following: *(One X per line)*

	More than 1x /week	1x /week	1-3x /mo.	1-5x /6 mos.	Never
Association or club meeting/activity	☐	☐	☐	☐	☐
Music, singing, theatre	☐	☐	☐	☐	☐
Parish work	☐	☐	☐	☐	☐
Outdoor activities	☐	☐	☐	☐	☐
Dance	☐	☐	☐	☐	☐
Worked out, sports	☐	☐	☐	☐	☐

Which life philosophy is most like yours? *(One X only)*

- Christian ☐ Atheistic ☐
- Humanistic ☐ Other ☐

When something bad happens in my life, I think that it happened for a purpose.

No ☐ Yes ☐ Don't know ☐

I seek God's help when I need strength and solace.

Never ☐ Sometimes ☐ Often ☐

1

Personality

Describe yourself as you normally are:

	Yes	No
Are you a life of the party type person?	☐	☐
Are you mostly quiet and reserved when you are around other people?	☐	☐
Do you like meeting new people?	☐	☐
Do you like to have a lot of life and excitement around you?	☐	☐
Are you a relatively lively person?	☐	☐
Do you usually take the first step to make new friends?	☐	☐
Are you often worried?	☐	☐
Are your feelings easily hurt?	☐	☐
Do you often feel that you lose interest?	☐	☐
Do you have nervous problems?	☐	☐
Do you often feel tired and indifferent/unmotivated without reason?	☐	☐
Do you worry that terrible things might happen?	☐	☐

Headaches

Have you had headaches in the last year? Yes ☐ No ☐

***If No, skip to* Respiratory Tract**

If Yes, what type of headache?

Migraine ☐ Other headache ☐

Average number of days a month with headaches:

Less than 1 day	1-6 days	7-14 days	More than 14 days
☐	☐	☐	☐

What is the average strength of your headaches?

Mild *(does not affect activity)* ☐

Moderate *(affects activity)* ☐

Strong *(hinders activity)* ☐

How long does the headache usually last?

Less than 4 hours ☐ 1-3 days ☐

4 hours – 1 day ☐ More than 3 days ☐

Are the headaches usually characterized by or accompanied by:

(One X per line)	Yes	No
Throbbing/thumping pain	☐	☐
Pressing pain	☐	☐
Pain on one side of the head (right or left)	☐	☐
Worsening with physical activity	☐	☐
Nausea and/or vomiting	☐	☐
Hypersensitivity to light and/or noise	☐	☐

Before or during the headache, have you had temporary: *(One X per line)*	Yes	No
Visual disturbances *(zigzag lines, flickering/flashing light, fogged vision)*	☐	☐
Numbness in half of your face or hand	☐	☐

Write the number of days you have been absent from work or school in the last month because of headaches ☐ days

Respiratory Tract

	Yes	No
Do you cough daily in periods of the year?	☐	☐
If Yes: **Do you usually bring up phlegm when coughing?**	☐	☐
Have you had a cough with phlegm for periods of at least 3 months during each of the last two years?	☐	☐
Do you have or have you had hayfever or nasal allergies?	☐	☐
If Yes: **Have you had hayfever/allergy symptoms in the last 12 months?**	☐	☐
In the last 12 months have you woken during the night because you were short of breath?	☐	☐

Muscles and Joints

In the last year, have you had pain or stiffness in muscles or joints that has lasted at least 3 consecutive months? Yes ☐ No ☐

If No, skip to question 30

If Yes,

Where have you had this pain or stiffness (One or more Xs)

FIGURE

Neck	☐
Shoulders	☐
Upper back	☐
Elbows	☐
Lower back	☐
Wrists/hands	☐
Hips	☐
Knees	☐

Ankles/feet ☐

Have you had this pain/stiffness on both the right and left side of your body? Yes ☐ No ☐

Does this pain/stiffness hinder your daily activities?

	Yes	No
Work	☐	☐
Leisure	☐	☐

Have you had back surgery? Yes ☐ No ☐

If Yes,
Type of back surgery

- Prolapse/sciatica surgery ☐
- Fixation ☐
- Other ☐

Metabolism

Has it ever been verified that you have/have had:	Yes	No	If Yes, write age first time *Ex:* (45 yrs old)
Hypothyroidism (too low metabolism)	☐	☐	☐ yrs old
Hyperthyroidism (too high metabolism)	☐	☐	☐ yrs old
If Yes: Did you take Neo-Mercazole?	☐	☐	☐ yrs old
Have you had radioiodine treatment?	☐	☐	☐ yrs old

Abdomen

Have you had stomach pain or discomfort <u>in the last 12 months</u>?

Yes, much ☐ Yes, a little ☐ No, never ☐

If No, skip to question 34

If Yes:

	Yes	No
Is it localized in the upper stomach?	☐	☐
<u>In the last 3 months</u>, have you had this as often as 1 day a week for at least 3 weeks?	☐	☐
Is the pain/discomfort relieved by having a bowel movement?	☐	☐
Is the pain/discomfort related to more frequent or less frequent bowel movements than normal?	☐	☐
Is the pain/discomfort related to the stool being softer or harder than normal?	☐	☐
Do you have this pain/discomfort after eating?	☐	☐

To what degree have you had the following <u>in the last 12 months</u>:

	Never	A little	Much
Nausea	☐	☐	☐
Heartburn/acid regurgitation	☐	☐	☐
Diarrhoea	☐	☐	☐
Constipation	☐	☐	☐
Alternating constipation and diarrhoea	☐	☐	☐
Bloating	☐	☐	☐

How You Feel

Read each item below and place an X next to the reply that comes closest to how you have been feeling **in the past week** (only one X per item). Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, thought-out response.

I feel tense or 'wound up'

Not at all ☐ From time to time, occasionally ☐ A lot of the time ☐ Most of the time ☐

I still enjoy the things I used to enjoy

Definitely as much ☐ Only a little ☐
Not quite so much ☐ Hardly at all ☐

I get a sort of frightened feeling as if something awful is about to happen

Very definitely and quite badly ☐ A little, but it doesn't worry me ☐
Yes, but not too badly ☐ Not at all ☐

I can laugh and see the funny side of things

As much as I always could ☐ Definitely not so much now ☐
Not quite so much now ☐ Not at all ☐

Worrying thoughts go through my mind

A great deal of the time ☐ Not too often ☐
A lot of the time ☐ Very little ☐

I feel cheerful

Never ☐ Sometimes ☐
Not often ☐ Most of the time ☐

I can sit at ease and feel relaxed

Definitely ☐ Not often ☐
Usually ☐ Not at all ☐

I feel as if I'm slowed down

Nearly all the time ☐ Sometimes ☐
very often ☐ Not at all ☐

I get a sort of frightened feeling like 'butterflies' in the stomach

Not at all	☐	Quite often	☐
Occasionally	☐	Very often	☐

I have lost interest in my appearance

Definitely	☐	I may not take quite as much care	☐
I don't take as much care as I should	☐	I take just as much care as ever	☐

I feel restless as if I have to be on the move

Very much indeed	☐	Not very much	☐
Quite a lot	☐	Not at all	☐

I look forward with enjoyment to things

As much as I ever did	☐	Definitely less than I used to	☐
Rather less than I used to	☐	Hardly at all	☐

I get sudden feelings of panic

Very often indeed	☐	Not very often	☐
Quite often	☐	Not at all	☐

I can enjoy a good book or radio or TV programme

Often	☐	Not often	☐
Sometimes	☐	Very seldom	☐

Sleep

How often in the last 3 months have you:

	Seldom /never	Some-times	Several x a week
Snored loudly (bothersome)	☐	☐	☐
Stopped breathing when you were sleeping (**Sleep apnoea**)	☐	☐	☐
Had difficulty falling asleep at night	☐	☐	☐
Woken up repeatedly during the night	☐	☐	☐
Woken too early and couldn't get back to sleep	☐	☐	☐
Felt sleepy during the day	☐	☐	☐
Sweat while sleeping (night-time)	☐	☐	☐
Woken with a headache	☐	☐	☐
Felt an uncomfortable or pins and needles feeling in your legs	☐	☐	☐

Alcohol

If you do not drink alcohol, skip to question 54.

	Yes	No
Have you ever felt that you should reduce your alcohol intake?	☐	☐
Have other people ever criticised your use of alcohol?	☐	☐
Have you ever felt bad or guilty because of your use of alcohol?	☐	☐
Have you ever had a drink first thing in the morning as a pick-me-up or to calm your nerves or to cure a hangover?	☐	☐

Diet

How many pieces of bread do you usually eat?
Put an X for each type of bread

	0-4 pr week	*5-7 pr week*	*2-3 pr day*	*4-5 pr day*	*6 or more pr day*
White bread	☐	☐	☐	☐	☐
Wholemeal/ medium ground	☐	☐	☐	☐	☐
Multigrain wholemeal/ coarsely ground	☐	☐	☐	☐	☐

How often do you normally eat these meals?
(One X for each meal)

	Seldom/ never	**1-2 x a week**	**3-4 x a week**	**5-6 x a week**	**Every-day**
Breakfast	☐	☐	☐	☐	☐
Lunch	☐	☐	☐	☐	☐
Warm dinner	☐	☐	☐	☐	☐
Supper/ evening snack	☐	☐	☐	☐	☐
Other meal	☐	☐	☐	☐	☐
Midnight snack (24.00-06.00)	☐	☐	☐	☐	☐

What type of fat do you most often use? *(One X for each line)*

	Butter	Hard marg.	Soft/light margarine	Oils	Don't use
On bread	☐	☐	☐	☐	☐
For cooking	☐	☐	☐	☐	☐

Dental Health

Have you been to the dentist in the last 12 months? Yes ☐ No ☐

How would you say your dental health is?

Very bad	☐	Good	☐
Bad	☐	Very good	☐
OK	☐		

Is good dental health important to you?

Very much	☐	A little	☐
Much	☐	Svært lite	☐
Somewhat	☐		

Use of Non-Prescription Medicine

How often have you taken non-prescription medicine for the following problems in the last month:

	Seldom/ never	*1-3 x a week*	*4-6 x a week*	*Daily*
Heartburn/ acid regurgitation	☐	☐	☐	☐
Constipation	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Pain in muscles/joints	☐	☐	☐	☐

Have you taken any of these non-prescription medicines at least once a week in the last month?

	Yes	No
Paracetamol, Paracet, Panodil, Pamol, Pinex, Perfalgan	☐	☐
Albyl E (500 mg), Aspirin, Globoid, Dispril	☐	☐
Ibuprofen, Ibux, Ibuprox, Ibumetin, Brufen	☐	☐
Naproxen, Naprosyn, Ledox	☐	☐
Other	☐	☐

How You Feel Now

Do you feel, for the most part, strong and fit or tired and worn out?

Very strong and fit	☐
Strong and fit	☐
Somewhat strong and fit	☐
Somewhat in between	☐
Somewhat tired and worn out	☐
Tired and worn out	☐
Very tired and worn out	☐

Additional Section Men 20-29

Employment

Is your work so physically demanding that you are often physically worn out after a day's work? *(Only one X)*

Yes, nearly always	☐	Seldom	☐
Quite often	☐	Never, or almost never	☐

Does your work require so much concentration and attention that you often feel worn out after a day's work? *(Only one X)*

Yes, nearly always	☐	Seldom	☐
Quite often	☐	Never, or almost never	☐

All things considered, how much do you enjoy your work? *(Only one X)*

A great deal	☐	Not much	☐
A fair amount	☐	Not at all	☐

Your Feelings in the Last 14 Days

In the last two weeks, have you: *(One X for each line)*

	No	A little	A good amount	Very much
Been continuously afraid and anxious	☐	☐	☐	☐
Felt tense and restless	☐	☐	☐	☐
Felt hopelessness when you think about the future	☐	☐	☐	☐
Felt down and sad	☐	☐	☐	☐
Worried too much about various things	☐	☐	☐	☐

Life Events

Have you experienced any of the following in the last 10 years? *(Put an X for each question)*

	No	Yes	
		Last 12 mos.	Earlier
Had problems at work or school?	☐	☐	☐
Had financial problems?	☐	☐	☐
Had problems or conflicts with family or friends?	☐	☐	☐
Had big problems in your love life?	☐	☐	☐
Been seriously ill or injured?	☐	☐	☐
Have those nearest you been seriously ill or injured?	☐	☐	☐

Eating Habits

Below are listed things that concern your eating habits. Put an X in the boxes according to how they apply to you. *(Put an X for each line)*

	Never	Seldom	Often	Always
When I first begin eating, it is difficult to stop.	☐	☐	☐	☐
I spend too much time thinking about food.	☐	☐	☐	☐
I feel that food controls my life.	☐	☐	☐	☐
I cut my food into small pieces.	☐	☐	☐	☐
I take longer than others to eat my meals.	☐	☐	☐	☐
Older people think I'm too thin.	☐	☐	☐	☐
I feel that others pressure me to eat.	☐	☐	☐	☐
I vomit after I have eaten.	☐	☐	☐	☐

Gambling

	Yes	No
Have you ever felt the need to gamble with continuously increasing amounts of money?	☐	☐
Have you ever had to lie to people who are important to you about how much you lost gambling?	☐	☐

Additional Section Women 20-29

Pregnancy and Birth Control

Not including pregnancies or post-natal periods, have you ever not menstruated for at least 6 months? Yes ☐ No ☐

If Yes,
How many times? ☐ times

Including all pregnancies, how many times have you been pregnant? ☐ times

Have you ever tried for more than one year to become pregnant? Yes ☐ No ☐

If Yes,
How old were you the first time you had problems becoming pregnant? ☐ yrs old

Do you use/take or have you used/taken:

	Now	Before, but not now	Never
Birth control pills	☐	☐	☐
Birth control patch	☐	☐	☐
Other hormone birth control *(Injection, vaginal ring, implant, IUD/coil)*	☐	☐	☐

If you have taken birth control pills: How old were you when you first began taking them? ☐ yrs old

How many years in total have you taken birth control pills?
Less than 1 yr ☐ 1-3 yrs ☐ 4-10 yrs ☐ over 10 yrs ☐

Urinary Tract

Do you unintentionally leak urine? Yes ☐ No ☐

If No, skip to question 72

If Yes:
How often do you leak urine?
Less than once a month ☐ One or more times a week ☐
One or more times a month ☐ Every day/night ☐

How much urine usually leaks each time?
Drops ☐ Small amount ☐ Quite a lot ☐

	Yes	No
Do you leak urine when you cough, sneeze, laugh or lift something heavy?	☐	☐
When you leak urine is it accompanied by a sudden and strong urge to urinate?	☐	☐

How do you feel about having urinary incontinence?
Not a problem ☐ A great problem ☐
A slight problem ☐ A very great problem ☐
A moderate problem ☐

Employment

Is your work so physically demanding that you are often physically worn out after a day's work? *(Only one X)*
Yes, nearly always ☐ Seldom ☐
Quite often ☐ Never, or almost never ☐

Does your work require so much concentration and attention that you often feel worn out after a day's work? *(Only one X)*
Yes, nearly always ☐ Seldom ☐
Quite often ☐ Never, or almost never ☐

All things considered, how much do you enjoy your work? *(Only one X)*
A great deal ☐ Not much ☐
A fair amount ☐ Not at all ☐

Your Feelings in the Last 14 Days

In the last two weeks, have you: *(One X for each line)*

	No	A little	A good amount	Very much
Been continuously afraid and anxious	☐	☐	☐	☐
Felt tense and restless	☐	☐	☐	☐
Felt hopelessness when you think about the future	☐	☐	☐	☐
Felt down and sad	☐	☐	☐	☐
Worried too much about various things	☐	☐	☐	☐

Life Events

Have you experienced any of the following in the last 10 years? *(Put an X for each question)*

	No	Yes	
		Last 12 mos.	Earlier
Had problems at work or school?	☐	☐	☐
Had financial problems?	☐	☐	☐
Had problems or conflicts with family or friends?	☐	☐	☐
Had big problems in your love life?	☐	☐	☐
Been seriously ill or injured?	☐	☐	☐
Have those nearest you been seriously ill or injured?	☐	☐	☐

Eating Habits

Below are listed things that concern your eating habits. Put an X in the boxes according to how they apply to you. *(Put an X for each line)*

	Never	Seldom	Often	Always
When I first begin eating, it is difficult to stop.	☐	☐	☐	☐
I spend too much time thinking about food.	☐	☐	☐	☐
I feel that food controls my life.	☐	☐	☐	☐
I cut my food into small pieces.	☐	☐	☐	☐
I take longer than others to eat my meals.	☐	☐	☐	☐
Older people think I'm too thin.	☐	☐	☐	☐
I feel that others pressure me to eat.	☐	☐	☐	☐
I vomit after I have eaten.	☐	☐	☐	☐

Gambling

	Yes	No
Have you ever felt the need to gamble with continuously increasing amounts of money?	☐	☐
Have you ever had to lie to people who are important to you about how much you lost gambling?	☐	☐

Additional Section Men 30-69

Evaluating Your Job

Answer if you are or have been employed.

Respond to the following statements/questions about where you work.

There is a good collegiality at work.
Strongly agree ☐ Agree ☐
Disagree ☐ Strongly disagree ☐

My co-workers are there for me (support me).
Strongly agree ☐ Agree ☐
Disagree ☐ Strongly disagree ☐

I get along well with my co-workers.
Strongly agree ☐ Agree ☐
Disagree ☐ Strongly disagree ☐

Are you bullied/ harassed at work?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Does your job require you to work very fast?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Does your job require you to work very hard?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Does your job require too great a work effort?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Does your job require creativity?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Do you have the possibility to decide for yourself how to carry out your work?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Do you have the possibility to decide for yourself what should be done in your work?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Is your work so physically demanding that you are often physically worn out after a long day's work?
Yes, nearly always ☐ Seldom ☐
Quite often ☐ Never, or almost never ☐

Leg Pain

	Yes	No
Do you have ulcer(s) on your toes, foot ankle that will not heal?	☐	☐
Do you have pain in one or both legs when you walk?	☐	☐

If Yes,
Where does it hurt the most?
Foot ☐ Leg ☐ Thigh ☐ Hip ☐

	Yes	No
Does the pain go away if you stand still a while?	☐	☐
Do you have pain in your legs when you are resting?	☐	☐
If Yes: **Is the pain worse when you lay in bed?**	☐	☐
Do you have less pain if you have your legs lower, such as over the edge of the bed?	☐	☐
Have you had pain in your legs continuously for more than 14 days?	☐	☐
Have you taken pain relievers because of pain in your legs?	☐	☐

Vision

Do you have any of the following eye conditions?	Yes	No
Cataract	☐	☐
Glaucoma (raised eye pressure)	☐	☐
Age-Related Macular Degeneration (retinal calcification)	☐	☐

Memory

Do you have problems with your memory?
No, none ☐ Yes, some ☐ Yes, a lot ☐

Has your memory changed since you were younger?
No ☐ Yes, some ☐ Yes, a lot ☐

Do you have trouble remembering:	Never	Sometimes	Often
Things that happened a few minutes ago?	☐	☐	☐
Other peoples' names?	☐	☐	☐
Dates?	☐	☐	☐
To do something you have planned to do?	☐	☐	☐
Things that happened a few days ago?	☐	☐	☐
Things that happened years ago?	☐	☐	☐
Enough to be able to follow along in a conversation?	☐	☐	☐

Urinary Tract

How often do you usually urinate during the day?
1-4 times ☐ 8-11 times ☐
5-7 times ☐ More than 11 times ☐

How many times do you get up during the night to urinate?
None ☐ 1 ☐ 2 ☐ 3 ☐ 4 or more ☐ 5 or more

If you get up during the night to urinate, is this a problem for you?
Not a problem ☐ It's a problem ☐
Somewhat of a problem ☐ It's a very big problem ☐

Do you feel a sudden, compelling urge to urinate that is difficult to suppress?
Never ☐ Several times a week ☐
Monthly ☐ Daily ☐

<u>Over the past month</u>, how often have you had a sensation of not emptying your bladder completely after you finish urinating?
Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐
1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

<u>Over the past month</u>, how often have you had to urinate again less than 2 hours after you finished urinating?
Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐
1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

<u>Over the past month</u>, how often have you found you stopped and started again several times when you urinated?
Never ☐ 1 out of 3 times ☐ 2 av 3 ganger ☐
1 out of 5 times ☐ 1 av 2 ganger ☐ Nesten alltid ☐

<u>Over the last month</u>, how difficult have you found it to postpone urination?
Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐
1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

<u>Over the past month</u>, how often have you had a weak urinary stream?
Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐
1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

<u>Over the past month</u>, how often have you had to push or strain to begin urination?
Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐
1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

Do you unintentionally leak urine? Yes ☐ No ☐
(If No, skip to question about 93)
If Yes:

How often do you leak urine?
Less than once a month ☐ One or more times a week ☐
Several times a month ☐ Every day/night ☐

How much urine usually leaks each time?
Drops ☐ A small amount ☐ Quite a lot ☐

In which situations might you leak urine?
(You may X several answers)
When you cough, sneeze, lift something heavy ☐
When having a sudden urge to urinate ☐
Drops at end of or after urinating ☐
Drops all the time, independent of urinating ☐

How do you feel about having urinary incontinence?
Not a problem ☐ A great problem ☐
A slight problem ☐ A very great problem ☐
A moderate problem ☐

How old were you when you became incontinent? ☐ yrs old
Have you consulted a doctor Yes ☐ No ☐

because of urinary incontinence?

Additional Section Women 30-69

Menstruation, Birth Control and Pregnancy

Not including during pregnancy or post-natal period, have you ever not gotten a period for at least 6 months (premenopause)?
Yes ☐ No ☐

If Yes,
How many times? ☐ times

In total, how many times have you been pregnant? ☐ times

Have you ever tried for more than one year to become pregnant? Yes ☐ No ☐

If Yes,
How old were you the first time you tried to become pregnant? ☐ yrs old

	Yes	No
Have you ever received hormone treatment to become pregnant?	☐	☐
If Yes, **Have you received this treatment in the last 3 months?**	☐	☐

Do you use/take or have you used/taken:

	Now	Before, but not now	Never
Birth control pills	☐	☐	☐
Birth control patch	☐	☐	☐
Other hormone birth control *(injection, vaginal ring, implant, IUD/coil)*	☐	☐	☐

If you have taken birth control pills:
How old were you when you first began taking them? ☐ yrs old

How many years in total have you taken birth control pills?
Less than 1 yr ☐ 1-3 yrs ☐ 4-10 yrs ☐ Over 10 yrs ☐

Menopause

(If you are premenopausal, skip to 75)
Do you have/have you had hot flashes due to menopause?
During the day ☐ **During night** ☐ **Day and night** ☐ **Haven't had any** ☐

If you have had hot flashes, how would you describe them?
Very intense ☐ Moderately intense ☐ Hardly noticable ☐

Have you been to a doctor because of this? No ☐ Yes ☐

Have you ever taken/used medicine that contains oestrogen?	*Now*	*Previously*	*Never*
Tablets or patches *(prescribed by a doctor)*	☐	☐	☐
Creams or suppositories	☐	☐	☐

If you have taken/used prescription oestrogen:
How old were you when you began? ☐ yrs old

How old are/were you the last time you took/used it? ☐ yrs old

If you take/use or have taken/used oestrogen tablets or patches, why did you begin?
Alleviate menapausal symptoms ☐
Prevent osteoporosis ☐
Other ☐

If you have previously taken/used oestrogen tablets or patches, why did you stop?
No longer have/had symptoms ☐ Afraid of side effects ☐
Experienced bothersome side effects ☐ Other ☐

Operations/Radiation Therapy in the Lower Abdomen

Have you had both ovaries surgically removed?
No ☐ Yes ☐ Don't know ☐

If Yes,
How old were you then? ☐ yrs old

Have you had your womb surgically removed (hysterectomy)?
No ☐ Yes ☐ Don't know ☐

If Yes,
How old were you then? ☐ yrs old

Have you ever had radiation therapy in your pelvic region?
No ☐ Yes ☐ Don't know ☐

If Yes,
How old were you then? ☐ yrs old

Urinary Tract

How often do you usually urinate during the day?

1-4 times ☐ 8-11 times ☐

5-7 times ☐ over 11 times ☐

How many times do you get up during the night to urinate?

None ☐ 1 ☐ 2 ☐ 3 ☐ 4 or more ☐

If you get up during the night to urinate, is this a problem for you?

Not a problem ☐ It's a problem ☐

Somewhat of a problem ☐ It's a very big problem ☐

Do you feel a sudden, compelling urge to urinate that is difficult to suppress?

Never ☐ Several times a week ☐

Monthly ☐ Daily ☐

Do you unintentionally leak urine? Yes ☐ No ☐

If No, skip to question 84

If Yes:

How often do you leak urine?

Less than once a month ☐ One or more times a week ☐

One or more times a month ☐ Every day/night ☐

How much urine usually leaks each time?

Drops ☐ Small amount ☐ Quite a lot ☐

	Yes	No
Do you leak urine when you cough, sneeze, laugh or lift something heavy?	☐	☐
When you leak urine is it accompanied by a sudden and strong urge to urinate?	☐	☐

How do you feel about having urinary incontinence?

Not a problem ☐ A great problem ☐

A slight problem ☐ A very great problem ☐

A moderate problem ☐

How old were you when you became incontinent? ☐ yrs old

Have you consulted a doctor because of urinary incontinence? Yes ☐ No ☐

Have you ever been treated for urinary incontinence? *(Several Xs possible here)*

No, I have never had urinary incontinence ☐

No, I had urinary incontinence, but became better on its own ☐

Yes ☐

If Yes, what type of treatment?

Operation ☐ Medicine ☐

Pelvic floor exercises ☐ Other ☐

Bowel Movements

Have you had uncontrollable flatulence in the last month?

Never/seldom ☐ Weekly ☐ Daily ☐

Have you leaked stool (faecal incontinence) in the last month?

Never/seldom ☐ Weekly ☐ Daily ☐

If you answered Yes to one of the above questions, does faecal incontinence affect your daily life?

Never/seldom ☐ Weekly ☐ Daily ☐

Are you able to hold back the stool for 15 minutes after you first feel the urge to evacuate your bowels? Yes ☐ No ☐

Evaluating Your Job

Answer if you are or have been employed.

Respond to the following statements/questions about where you work.

There is a good collegiality at work.

Strongly agree ☐ Agree ☐

Disagree ☐ Strongly disagree ☐

My co-workers are there for me (support me).

Strongly agree ☐ Agree ☐

Disagree ☐ Strongly disagree ☐

I get along well with my co-workers.

Strongly agree ☐ Agree ☐

Disagree ☐ Strongly disagree ☐

Are you bullied/ harassed at work?

Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Does your job require you to work very fast?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Does your job require you to work very hard?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Does your job require too great a work effort?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Does your job require creativity?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Do you have the possibility to decide for yourself how to carry out your work?
Yes, often ☐ Yes, sometimes ☐
No, seldom ☐ No, could say never ☐

Do you have the possibility to decide for yourself what should be done in your work?
Yes, often ☐ Yes, sometimes ☐

Leg Pain

	Yes	No
Do you have ulcer(s) on your toes, foot ankle that will not heal?	☐	☐
Do you have pain in one or both legs when you walk?	☐	☐

If Yes,
Where does it hurt the most?
Foot ☐ Leg ☐ Thigh ☐ Hip ☐

	Yes	No
Does the pain go away if you stand still a while?	☐	☐
Do you have pain in your legs when you are resting?	☐	☐
If Yes: **Is the pain worse when you lay in bed?**	☐	☐
Do you have less pain if you have your legs lower, such as over the edge of the bed?	☐	☐
Have you had pain in your legs continuously for more than 14 days?	☐	☐
Have you taken pain relievers because of pain in your legs?	☐	☐

Vision

Do you have any of the following eye conditions?	Yes	No
Cataract	☐	☐
Glaucoma (raised eye pressure)	☐	☐
Age-Related Macular Degeneration (retinal calcification)	☐	☐

Memory

Do you have problems with your memory?
No, none ☐ Yes, some ☐ Yes, a lot ☐

Has your memory changed since you were younger?
No ☐ Yes, some ☐ Yes, a lot ☐

Do you have trouble remembering:	Never	Sometimes	Often
Things that happened a few minutes ago?	☐	☐	☐
Other peoples' names?	☐	☐	☐
Dates?	☐	☐	☐
To do something you have planned to do?	☐	☐	☐
Things that happened a few days ago?	☐	☐	☐
Things that happened years ago?	☐	☐	☐
Enough to be able to follow along in a conversation?	☐	☐	☐

Eating Disorders

Place a circle around the number that best describes your eating habits during the last month.

Are you satisfied with your eating habits?
Very satisfied 1 2 3 4 5 6 7 Very dissatisfied

Have you eaten to comfort yourself or because you were unhappy?
Not at all 1 2 3 4 5 6 7 Every-day

Have you felt guilty about eating?

Not at all 1 2 3 4 5 6 7 Every-day

Have you felt that it was necessary for you to use a strict diet or other eating rituals to control your eating?

Not at all 1 2 3 4 5 6 7 Every-day

Have you felt that you are too fat?

Not at all 1 2 3 4 5 6 7 Every-day

Additional Section Men 70+

Leg Pain

	Yes	No
Do you have ulcer(s) on your toes, foot ankle that will not heal?	☐	☐
Do you have pain in one or both legs when you walk?	☐	☐

If Yes,
Where does it hurt the most?
Foot ☐ Leg ☐ Thigh ☐ Hip ☐

	Yes	No
Does the pain go away if you stand still a while?	☐	☐
Do you have pain in your legs when you are resting?	☐	☐
If Yes: **Is the pain worse when you lay in bed?**	☐	☐
Do you have less pain if you have your legs lower, such as over the edge of the bed?	☐	☐
Have you had pain in your legs continuously for more than 14 days?	☐	☐
Have you taken pain relievers because of pain in your legs?	☐	☐

Activities of Daily Life

Can you do the following daily tasks without the help of others?

	Yes	No
Walk around indoors on the same floor	☐	☐
Go to the toilet	☐	☐
Wash yourself	☐	☐
Take a bath or shower	☐	☐
Dress and undress yourself	☐	☐
Go to bed and get up	☐	☐
Eat	☐	☐

Other Daily Tasks

Do you have a driver's licence? Yes ☐ No ☐
If Yes,
Do you still drive a car? Yes ☐ No ☐

Can you do the following daily tasks without the help of others?

	Yes	No
Prepare warm meals	☐	☐
Do light housework (ex: wash dishes)	☐	☐
Do heavier housework (ex: wash floors)	☐	☐
Wash clothes	☐	☐
Do the shopping	☐	☐
Pay bills	☐	☐
Take medicines	☐	☐
Go out	☐	☐
Take the bus	☐	☐

Memory

Do you have problems with your memory?
No, none ☐ Yes, some ☐ Yes, a lot ☐

Has your memory changed since you were younger?
No ☐ Yes, some ☐ Yes, a lot ☐

Do you have trouble remembering:	Never	Sometimes	Often
Things that happened a few minutes ago?	☐	☐	☐
Other peoples' names?	☐	☐	☐
Dates?	☐	☐	☐
To do something you have planned to do?	☐	☐	☐
Things that happened a few days ago?	☐	☐	☐
Things that happened years ago?	☐	☐	☐
Enough to be able to follow along in a conversation?	☐	☐	☐

Falls

Have you fallen and hurt yourself in the last year? No ☐ Yes ☐

If Yes,
Where did it happen? Indoors ☐ Outdoors ☐

	Yes	No
Have you been to a doctor in the last year because of an injury caused by a fall?	☐	☐
Have you been admitted to hospital in the last year because of an injury	☐	☐

caused by a fall?

Have you fallen in the last 3 months? ☐ ☐

Do you have problems with your balance? ☐ ☐

Use of Health Services

	Yes	No
Have you had home care help in the last 12 months?	☐	☐
If Yes, Do you have enough home care help?	☐	☐
Have you received home nursing care in the last 12 months?	☐	☐
If Yes, Do you receive enough home nursing care?	☐	☐
Have you been admitted to a nursing home in the last 12 months?		

Vision

Do you have any of the following eye conditions?	Yes	No
Cataract	☐	☐
Glaucoma (raised eye pressure)	☐	☐
Age-Related Macular Degeneration (retinal calcification)	☐	☐

Urinary Tract

How often do you usually urinate during the day?

1-4 times ☐ 8-11 times ☐

5-7 times ☐ More than 11 times ☐

How many times do you get up during the night to urinate?

None ☐ 1 ☐ 2 ☐ 3 ☐ 4 or more ☐

If you get up during the night to urinate, is this a problem for you?

Not a problem ☐ It's a problem ☐

Somewhat of a problem ☐ It's a very big problem ☐

Do you feel a sudden, compelling urge to urinate that is difficult to suppress?

Never ☐ Several times a week ☐

Monthly ☐ Daily ☐

Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?

Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐

1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?

Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐

1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

Over the past month, how often have you found you stopped and started again several times when you urinated?

Never ☐ 1 out of 3 times ☐ 2 av 3 ganger ☐

1 out of 5 times ☐ 1 av 2 ganger ☐ Nesten alltid ☐

Over the last month, how difficult have you found it to postpone urination?

Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐

1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

Over the past month, how often have you had a weak urinary stream?

Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐

1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

Over the past month, how often have you had to push or strain to begin urination?

Never ☐ 1 out of 3 times ☐ 2 out of 3 times ☐

1 out of 5 times ☐ 1 out of 2 times ☐ Almost always ☐

Do you unintentionally leak urine? Yes ☐ No ☐

If No, skip to question about 89

If Yes:

How often do you leak urine?

Less than once a month ☐ One or more times a week ☐

Several times a month ☐ Every day/night ☐

How much urine usually leaks each time?

Drops ☐ Small amounts ☐ Quite a lot ☐

In which situations might you leak urine?

(You may X several answers)

When you cough, sneeze, lift something heavy ☐

When having a sudden urge to urinate ☐

Drops at end of or after urinating ☐

Drops all the time, independent of urinating ☐

How do you feel about having urinary incontinence?

Not a problem ☐ A great problem ☐

A slight problem ☐ A very great problem ☐

A moderate problem ☐

How old were you when you became incontinent? ☐ yrs old

Have you consulted a doctor because of urinary incontinence? Yes ☐ No ☐

Additional Section Women 70+

Pregnancy, Children and Hormone Therapy

In total, how many times have you been pregnant? ☐ times

Have you ever tried for more than one year to become pregnant? Yes ☐ No ☐

If Yes,
How old were you the first time you had problems becoming pregnant? ☐ yrs old

Do you have/have you had hot flashes due to menopause?
During the day ☐ During night ☐ Day and night ☐ Haven't had any ☐

If you have had hot flashes, how would you describe them?
Very intense ☐ Moderately intense ☐ Hardly noticable ☐

Have you been to a doctor because of this? No ☐ Yes ☐

Have you ever taken/used medicine that contains oestrogen?	*Now*	*Previously*	*Never*
Tablets or patches *(prescribed by a doctor)*	☐	☐	☐
Cream or suppositories	☐	☐	☐

If you have taken/used prescription oestrogen:
How old were you when you began? ☐ yrs old

How old are/were you the last time you took/used it? ☐ yrs old

If you take/use or have taken/used oestrogen tablets or patches, why did you begin?
Alleviate menapausal symptoms ☐
Prevent osteoporosis ☐
Other ☐

If you have previously taken/used oestrogen tablets or patches, why did you stop?
No longer have/had symptoms ☐ Afraid of side effects ☐
Experienced bothersome side effects ☐ Other ☐

Operations/Radiation Therapy in the Lower Abdomen

Have you had both ovaries surgically removed?
No ☐ Yes ☐ Don't know ☐

If Yes,
How old were you then? ☐ yrs old

Have you had your womb surgically removed (hysterectomy)?
No ☐ Yes ☐ Don't know ☐

If Yes,
How old were you then? ☐ yrs old

Have you ever had radiation therapy in your pelvic region?
No ☐ Yes ☐ Don't know ☐

If Yes,
How old were you then? ☐ yrs old

Urinary Tract

How often do you usually urinate during the day?
1-4 times ☐ 8-11 times ☐
5-7 times ☐ over 11 times ☐

How many times do you get up during the night to urinate?
None ☐ 1 ☐ 2 ☐ 3 ☐ 4 or more ☐

If you get up during the night to urinate, is this a problem for you?
Not a problem ☐ It's a problem ☐
Somewhat of a problem ☐ It's a very big problem ☐

Do you feel a sudden, compelling urge to urinate that is difficult to suppress?
Never ☐ Several times a week ☐
Monthly ☐ Daily ☐

Do you unintentionally leak urine? Yes ☐ No ☐

If No, skip to question 79
If Yes:
How often do you leak urine?
Less than once a month ☐ One or more times a week ☐

One or more times a month ☐ Every day/night ☐

How much urine usually leaks each time?
Drops ☐ Small amount ☐ Quite a lot ☐

	Yes	No
Do you leak urine when you cough, sneeze, laugh or lift something heavy?	☐	☐
When you leak urine is it accompanied by a sudden and strong urge to urinate?	☐	☐

How do you feel about having urinary incontinence?
Not a problem ☐ A great problem ☐
A slight problem ☐ A very great problem ☐
A moderate problem ☐

How old were you when you became incontinent? ☐ yrs old
Have you consulted a doctor because of urinary incontinence? Yes ☐ No ☐

Have you ever been treated for urinary incontinence? *(Several Xs possible here)*
No, I have never had urinary incontinence ☐
No, I had urinary incontinence, but became better on its own ☐
Yes ☐

If Yes, what type of treatment?
Operation ☐ Medicine ☐
Pelvic floor exercises ☐ Other ☐

Bowel Movements

Have you had uncontrollable flatulence in the last month?
Never/seldom ☐ Weekly ☐ Daily ☐

Have you leaked stool (faecal incontinence) in the last month?
Never/seldom ☐ Weekly ☐ Daily ☐

If you answered Yes to one of the above questions, does faecal incontinence affect your daily life?
Never/seldom ☐ Weekly ☐ Daily ☐

Are you able to hold back the stool for 15 minutes after you first feel the urge to evacuate your bowels? Yes ☐ No ☐

Leg Pain

	Yes	No
Do you have ulcer(s) on your toes, foot ankle that will not heal?	☐	☐
Do you have pain in one or both legs when you walk?	☐	☐

If Yes,
Where does it hurt the most?
Foot ☐ Leg ☐ Thigh ☐ Hip ☐

	Yes	No
Does the pain go away if you stand still a while?	☐	☐
Do you have pain in your legs when you are resting?	☐	☐
If Yes: **Is the pain worse when you lay in bed?**	☐	☐
Do you have less pain if you have your legs lower, such as over the edge of the bed?	☐	☐
Have you had pain in your legs continuously for more than 14 days?	☐	☐
Have you taken pain relievers because of pain in your legs?	☐	☐

Activities of Daily Life

Can you do the following daily tasks without the help of others?

	Yes	No
Walk around indoors on the same floor	☐	☐
Go to the toilet	☐	☐
Wash yourself	☐	☐
Take a bath or shower	☐	☐
Dress and undress yourself	☐	☐
Go to bed and get up	☐	☐
Eat	☐	☐

Other Daily Tasks

Do you have a driver's licence? Yes ☐ No ☐
If Yes,
Do you still drive? Yes ☐ No ☐

Can you do the following daily tasks without the help of others?
Yes No

Prepare warm meals	☐	☐
Do light housework (ex: wash dishes)	☐	☐
Do heavier housework (ex: wash floors)	☐	☐
Wash clothes	☐	☐
Do the shopping	☐	☐
Pay bills	☐	☐
Take medicines	☐	☐
Go out	☐	☐
Take the bus	☐	☐

Memory

Do you have problems with your memory?
No, none ☐ Yes, some ☐ Yes, a lot ☐

Has your memory changed since you were younger?
No ☐ Yes, some ☐ Yes, a lot ☐

Do you have trouble remembering:	Never	Sometimes	Often
Things that happened a few minutes ago?	☐	☐	☐
Other peoples' names?	☐	☐	☐
Dates?	☐	☐	☐
To do something you have planned to do?	☐	☐	☐
Things that happened a few days ago?	☐	☐	☐
Things that happened years ago?	☐	☐	☐
Enough to be able to follow along in a conversation?	☐	☐	☐

Falls

Have you fallen and hurt yourself in the last year? No ☐ Yes ☐

If Yes, Where did it happen? Indoors ☐ Outdoors ☐

	Yes	No
Have you been to a doctor <u>in the last year</u> because of an injury caused by a fall?	☐	☐
Have you been admitted to hospital <u>in the last year</u> because of an injury caused by a fall?	☐	☐
Have you fallen <u>in the last 3 months</u>?	☐	☐
Do you have problems with your balance?	☐	☐

Use of Health Services

	Yes	No
Have you had home care help <u>in the last 12 months</u>?	☐	☐
***If Yes,* Do you have enough home care help?**	☐	☐
Have you received home nursing care <u>in the last 12 months</u>?	☐	☐
***If Yes,* Do you receive enough home nursing care?**	☐	☐
Have you been admitted to a nursing home <u>in the last 12 months</u>?		

Vision

Do you have any of the following eye conditions?	Yes	No
Cataract	☐	☐
Glaucoma (raised eye pressure)	☐	☐
Age-Related Macular Degeneration (retinal calcification)	☐	☐

8.3 Construction of 51 chronic, single-entities conditions from data in HUNT3, by questionnaires and measurements.

GENERAL COMMENTS

Chronicity of conditions was defined as long-lasting (at least 3 months) or with severe effects or requirements of health care management.[18, 34, 35, 40] The raw data varies in specifying these factors. In absence of direct information, chronicity was determined by lead author K.H. Vinjerui, MD, and co-author S. Krokstad, MD, professor.

Information on missing data was collected from the HUNT Databank. Some topics are covered by 1 question, whereas others include 1 index question and further questions in a block, see section 8.1.. In cases were data was missing in any of the questions in a block, this was corrected based on reply to index question and if any other alternatives were crossed off, missing data was regarded as "no".

References hold information on construction or accuracy of self-reports or comparison of the prevalence of the conditions to primary care and/or nonparticipant data. In general, self-reports give reliable estimates of multimorbidity in studies of large samples.[35]

MAIN QUESTIONNAIRE

Hearing impairment[157]

Index question: "Do you suffer from longstanding (at least 1 year) illness or injury of a physical or psychological nature that impairs your functioning in your daily life?" The possible answers were yes or no.

Options on follow-up questions combined condition type (motor, vision, hearing, somatic, and psychiatric) and severity (slight, moderate, and severe).

Included with hearing impairment were those who reported chronic disease and moderate to severe hearing impairment.

"20 Diseases": Myocardial infarction, angina pectoris, heart failure, other heart disease, stroke or brain hemorrhage, kidney disease, asthma, chronic bronchitis, emphysema or chronic obstructive pulmonary disease, diabetes, psoriasis, eczema on hands, cancer, epilepsy, rheumatoid arthritis, ankylosing spondylitis, sarcoidosis, osteoporosis, fibromyalgia and osteoarthritis

Cluster text: "Have you had or do you have any of the following: myocardial infarction,[105, 131] angina pectoris,[105, 158] heart failure,[131] other heart disease, stroke[105, 131] or brain hemorrhage, kidney disease,[105, 159] asthma,[105] chronic bronchitis, emphysema, or chronic obstructive pulmonary disease, diabetes,[105, 131] psoriasis,[129] eczema on the hands,[160, 161] cancer,[105, 162] epilepsy,[163] rheumatoid arthritis,[105, 127] ankylosing spondylitis,[105, 127] sarcoidosis, osteoporosis,[105, 164] fibromyalgia,[105] and osteoarthritis[105]?"

Separate tick boxes for each diagnosis: Yes, no.

For each diagnosis, included were those who affirmed to have or have had the diagnosis.

Chronicity is assumed based on medical knowledge and clinical experience.

SEX-DIFFERENTIATED AND AGE-DIFFERENTIATED QUESTIONNAIRE

Headache[105]

Seven questions in 1 block. Question 1: "Have you had headaches in the last year?" Yes/no.

i. Migraine without aura[126]

Of those who affirmed headache last year, migraine without aura was constructed from 3 of 7 questions:

"What is the average strength of your headaches?" 1=Mild, 2=Moderate, 3=Strong.

Recoded to dichotomous variable, where 1=Moderate/Strong.

"How long does the headache usually last?" 1=Less than 4 hours, 2=4 hours- to 1 day, 3=1 to 3 days, 4= More than 3 days.

Recoded to dichotomous variable, where 1= Less than 4 hours to 3 days.

Cluster text: "Are the headaches usually characterized or accompanied by

Throbbing/thumping pain?" Yes, no.

Pain on one side of the head?" Yes, no.

Worsening with physical activity?" Yes, no.

Nausea and/or vomiting?" Yes, no.

Hypersensitivity to light and/or noise?" Yes, no.

Included with migraine were those who affirmed to headache lasting 0 to 72 hours and at least 2 of 4 characteristics (pulsating quality, unilateral location, moderate/severe pain intensity, or aggravation by physical activity) and during headache having at least 1 of 2 accompanying symptoms (nausea and/or vomiting or increased sensitivity to light and/or noise).[126]

Chronicity is assumed based on medical knowledge and clinical experience.

ii. Chronic headache[126]

Of those who affirmed headache last year, chronic headache was constructed from 2 of 7 questions:

"If yes (headache in the last year): What type of headache? Migraine, other."

The HUNT Databank created 2 variables with range 1: (1) migraine and (2) other headache.

"Average number of days a month with headaches:"
1=Less than 1 day, 2=1 to 6 days, 3=7 to 14 days, 4=More than 14 days.

Recoded to dichotomous variable, where 1=More than 14 days.

Included as a case with chronic headache were those reporting an "other" type of headache and an average frequency of more than 14 days per month.

Chronicity is assumed based on medical knowledge and clinical experience.

Pain[105]

Index question: "In the last year, have you had pain or stiffness in muscles or joints that has lasted at least 3 consecutive months?" Yes, no.

The follow-up question "If yes: Where have you had this pain or stiffness?" was combined with a figure with arrows and tick boxes at 9 locations (neck, upper back, lower back, shoulder, elbow, hand, hip, knee and ankle/foot).

i. Chronic widespread pain[165]

Dichotomous variables were made for each major body area: (1) Trunk (neck, upper back, and lower back), (2) upper limb (shoulder, elbow, hand), and (3) lower limb (hip, knee, foot/ancle), where 1=at least one painful location. A sum (row total) score variable was made for the major body areas and dichotomized, where 1=3, that is 1 pain in each major body area.

Of those who affirmed to pain or stiffness that had lasted more than 3 consecutive months, chronic widespread pain was defined as pain at more than 3 sites in all major body areas (trunk, upper limbs, and lower limbs) for more than 3 months in the last year.

ii. Chronic local pain

Of those who affirmed to pain or stiffness that has lasted more than 3 consecutive months, chronic local pain was defined as pain in the neck, upper back, lower back, shoulder, elbow, hand, hip, knee, or ankle/foot, excluding the presence of chronic widespread pain, generating 9 dichotomous variables.

Thyroidal disease[105, 166]

Cluster text: “Has it ever been verified that you have/have had hypothyroidism or hyperthyroidism?” Separate tick boxes for each condition (yes, no), generating two dichotomous variables, 1=Yes.

For each diagnosis, included were those who affirmed to have or have had the diagnosis.

Chronicity is assumed based on medical knowledge and clinical experience.

Irritable bowel syndrome[167, 168]

Index question: “Have you had stomach pain or discomfort in the last 12 months?” Answers: Yes, much; yes, a little; no. Irritable bowel syndrome was further constructed from 4 of 6 follow-up questions: “If yes:

“In the last 3 months, have you had this as often as 1 day a week for at least 3 weeks?” Yes, no.

“Is the pain/discomfort relieved by having a bowel movement?” Yes, no.

“Is the pain/discomfort related to more frequent or less frequent bowel movements than normal?” Yes, no.

“Is the pain/discomfort related to the stool being softer or harder than usual?” Yes, no.

Included with irritable bowel syndrome were those who affirmed little or much stomach pain or discomfort in the last year, who for as often as 1 day a week for at least 3 weeks in the last 3 months have had at least 2 of the following: pain or discomfort relieved by having a bowel movement, associated with altered frequency of bowel movements, or associated with altered stool appearance; this resembled a modified version of the Rome criteria.[167, 168]

Gastroesophageal reflux disease[105, 128]

Cluster text: “To what degree have you had the following problems in the last 12 months?” Options combined type (nausea, heartburn/acid regurgitation, diarrhea, constipation, alternating constipation and diarrhea, and bloating) and frequency (never, a little, or much).

Generated 1 dichotomous variable, heartburn, where 1=Much.

Gastroesophageal reflux disease is defined as much heartburn or acid regurgitation in the last 12 months.[128]

Anxiety[105, 169]

Instrument variable: Hospital Anxiety and Depression Scale (HADS).[169] Every other statement of 14 statements covers symptoms on anxiety and depression and is scored 0 to 3.

The HUNT Databank constructed a total score for anxiety (HADS-Anxiety), if all 7 anxiety items were answered.

Anxiety was defined as HADS-Anxiety score of 8 or more of 21, indicating mild or possible anxiety.[170-172]

Chronicity is assumed based on medical knowledge and clinical experience.

Depression[105, 169]

Instrument variable: Hospital Anxiety and Depression Scale (HADS).[169] Every other statement of 14 statements covers symptoms on anxiety and depression and is scored 0-3.

The HUNT Databank constructed total score depression (HADS-Depression), if all 7 depression items were answered.

Depression was defined as HADS-Depression score of 8 or more of 21, indicating mild or possible depression.[170-172]

Chronicity is assumed based on medical knowledge and clinical experience.

Chronic insomnia[105, 173]

There were 9 questions on sleeping pattern in 1 cluster, including 3 concerning insomnia. Initial text: "How often in the last 3 months have you

"Had difficulty falling asleep at night?" Never/seldom, sometimes, several times a week.

"Woken up repeatedly during the night?" Never/seldom, sometimes, several times a week.

"Woken too early and couldn't get back to sleep?" Never/seldom, sometimes, several times a week.

Chronic insomnia was defined as in the last 3 months, several times a week, having difficulty falling asleep at night and waking up repeatedly during the night, and waking up too early. This was a modified version of the diagnostic criteria for insomnia in the International Classification of Sleep Disorders.[26]

Alcohol use disorder[174]

Instrument variable: the CAGE questionnaire for problematic alcohol use, an acronym for 4 questions focused on cutting down on alcohol use, annoyance by criticism, guilt feelings associated with drinking, and eye-openers (drinks taken immediately on waking).[174] The CAGE questionnaire is a 4-item scale with scores of 0 to 1 .

A summary variable was created and dichotomized in which a score of 1 indicates 2 or more positive answers.

Alcohol use disorder was defined as CAGE score greater than 2.[175]

Chronicity is assumed based on medical knowledge and clinical experience.

Dental health problem

"How would you say your dental health is?" Very, bad, OK, good, very good.

Dental health problems were defined as self-reported bad or very bad dental health.[8]

Chronicity is assumed based on medical knowledge and clinical experience.

Menopausal hot flashes

Included: Women older than 30 years only.

Two questions were used to define menopausal illness:

"Do you have/have you had hot flashes due to menopause?" During the day, during the night, day and night, haven't had any.

"If you have had hot flashes, how would you describe them?" Very intense, moderately intense, hardly noticeable.

Included with menopausal hot flashes were those who reported hot flashes occurring daily and/or nightly and of at least moderate severity.

Chronicity is assumed based on medical knowledge[176] and clinical experience.

Nocturia[177]

Excluded: Women and men, 20 to 29 years.

One question on nocturia, identical to that of the International Prostate Symptom Scale, was asked to men and women older than 30 years.

"How many times do you get up during the night to urinate?" None, 1 time, 2 times, 3 times,

4 times, 5 times or more.

Nocturia was defined as 2 or more voids per night.[177]

Chronicity is assumed based on medical knowledge and clinical experience.

Urine incontinence[105, 178]

Excluded: men, 20 to 29 years.

Instrument variable: The Epidemiology of Incontinence in the County of Nord-Trøndelag questionnaire.[178]

Index question: Do you have involuntary loss of urine? Yes, no.

Urine incontinence was constructed from 2 of 6 follow-up questions. "If yes":

"How often do you have involuntary loss of urine?" Less than once a month, once or more per month, once or more per week, every day and/or night

"How much urine do you leak each time?" Drops or little, small amount, large amounts.

Self-reported frequency and volume of leakage were multiplied to obtain the validated 4-level Sandvik Severity Index, categorizing incontinence as slight, moderate, severe, and very severe.[178]

Urine incontinence were included if severe to very severe.

Chronicity is assumed based on medical knowledge and clinical experience.

Prostate symptoms[179, 180]

Included: men older than 30 years only.

Instrument variable: The International Prostate Symptom Scale[179] was slightly modified in HUNT3,[180] becoming a 7-item scale with scores of 0 to 5 per question.

Included were prostate symptoms of at least moderate severity (sum score ≥8 points).[179]

Chronicity is assumed based on medical knowledge and clinical experience.

Eye diseases[181]

Excluded: men and women, 20 to 29 years.

Cluster text: "Do you have any of the following eye conditions?" Cataract, glaucoma, and macular degeneration. Separate tick boxes: yes, no.

For each diagnosis, included were those who affirmed to have or have had the diagnosis.

Chronicity is assumed based on medical knowledge and clinical experience.

MEASUREMENTS

Obesity[182, 183]

HUNT Databank constructed the body mass index (BMI) variable, defined as (weight in kg)/(height in m^2). Obesity was defined as either a BMI of 35 or more or a BMI of 25 to 34.9 and an increased waist circumference (≥88 cm for females; ≥102 cm for males).[182, 183]

Waist circumference had large interobserver variation.[184] The data were checked for outliers.

Chronicity is assumed based on medical knowledge and clinical experience.

Hypertension[105]

Blood pressure (BP) in HUNT3 is measured 3 times at 1 consultation. The mean of measurements 2 and 3 is calculated by the HUNT Databank. If measurements 2 or 3 were missing, the other measurement was used as estimate for the mean.[185]

Hypertension was defined as measured mean systolic BP of 180 mm Hg or more or diastolic BP of 110 mm Hg or more or reporting use of antihypertensive medications, excluding self-reported cardiovascular disease, diabetes, or kidney disease and excluding extreme measures.[8]

Chronicity is assumed based on medical knowledge and clinical experience.

Hypercholesterolemia[186]

Hypercholesterolemia was defined as a total cholesterol level of 8 mmol/L or more.[186]

Chronicity is assumed based on medical knowledge and clinical experience.

8.4 Operationalizing socioeconomic position using occupation

In the HUNT3 Survey interview, all participants were asked: "What is/was the title of your main occupation?" Free-text answers were manually classified according to the *Standard Classifications of Occupations* by Statistics Norway,[80] which is based on the European Union's version of the *International Standard Classification of Occupations-88.*[107]

The standard categorized occupations according to skill level and specialization, degree of independence, and manual labor but not social position.[80] Occupations are coded with up to 4 digits, with increasing detail. One digit indicates major groups; 2 digits, submajor groups; 3 digits, minor groups; and 4 digits, unit groups. The minor occupational group was the highest level of detail available in the HUNT3 Survey.

Occupational socioeconomic positions were operationalized using the European Socio-economic Classification scheme.[79] The full version of the scheme requires employment status and the size of organization in addition to the occupation to assign a class position. We used the simplified class scheme, based on minor occupational group only,[79] because the HUNT3 Survey did not have data corresponding to the employment status and size of organization. It is shown that the agreement between 3-digit full and simplified version of this scheme is 79.7% for the total workforce.[79] The syntax is available from https://www.iser.essex.ac.uk/archives/esec/matrices-and-syntax. It was performed using SPSS version 25.0 (SPSS Inc).

Table 8.4.1 gives details of transformation of data, discrepancies between the Norwegian and European Union standards, and the allocated position in the full classification scheme. A total of 2179 of 38027 individuals had alterations to their occupational data to fit the syntax, 5.7% of the total sample. In the HUNT3 Survey data, the minor occupational group was a string variable. To perform the syntax, it had to be altered to a numeric variable. The string 011 was changed to numeric value 11, which was manually corrected in the syntax. In the 3-digit variable, some participants were classified with 1 digit and 2 digits only. These were transformed to the corresponding 3-digit minor group, at the lowest level of detail, by manually adding suffix digits 0 or 00. This is in line with operationalizing of European Socio-

economic Classification (Table 1).[79] Norwegian minor groups, which were not found in the European Union standard, were altered to the level of detail in which corresponding groups could be identified. These were *Standard Classifications of Occupations* by Statistics Norway codes: 112 (corresponding to 2 digits), 25 (corresponding to 1 digit), 251-6 (corresponding to 1 digit), 349 (corresponding to 2 digits), 631 (corresponding to 1 digit), 641 (corresponding to 1 digit), 735 (corresponding to 2 digits), and 745 (corresponding to 2 digits).

In total, 9 classes were created. To increase power and simplify interpretation, the full scheme was collapsed into a 3-class version, with high combining class 1 and 2, middle combining 3 to 6, and low combining 7 to 9.[79] The high occupational class represents large employers, higher-grade and lower-grade professionals, administrative and managerial occupations, higher-grade technician occupations, and supervisory occupations. The middle occupational class consist of small employers, self-employed individuals, lower supervisory occupations, and lower technician occupations. The low occupational class contain lower services, sales and clerical occupations, lower technical occupations, and routine occupations.

Table 8.4.1 The distribution of transformed occupational data and discrepancies between the Norwegian and International Standard Classifications of Occupations and allocation in the European Socio-economic Classification scheme.

Standard Classifications of Occupations		European Socio-economic		
Norwegian	**International**	**Classification scheme**	***n***	**%**
1	100	1	262	(0.69)
011 (=num 11)	011=11	3	134	(0.35)
112*	→ 11=110	1	31	(0.08)
12	120	1	73	(0.19)
13	130	4	20	(0.05)
2	200	1	10	(0.03)
21	210	1	10	(0.03)
22	220	1	1	(0.00)
23	230	2	27	(0.07)
24	240	1	9	(0.02)
25	→ 2=200	1	4	(0.01)
251*	→ 2=200	1	296	(0.78)
252*	→ 2=200	1	48	(0.13)
253*	→ 2=200	1	20	(0.05)
254*	→ 2=200	1	138	(0.36)
255*	→ 2=200	1	64	(0.17)
256*	→ 2=200	1	46	(0.12)
3	300	3	39	(0.10)
31	310	2	37	(0.10)
33	330	3	241	(0.63)
34	340	3	45	(0.12)
349*	→34=340	3	160	(0.42)
4	400	3	1	(0.00)
41	410	3	1	(0.00)
42	420	3	1	(0.00)
5	500	7	1	(0.00)
51	510	7	8	(0.02)
61	610	5	4	(0.01)
631*	→6=600	5	93	(0.24)
641*	→6=600	5	99	(0.26)
7	700	8	20	(0.05)
71	710	8	1	(0.00)
72	720	8	6	(0.02)
73	730	6	1	(0.00)
735*	→73=730	6	38	(0.10)
74	740	8	1	(0.00)
745*	→74=740	8	46	(0.12)
8	800	9	62	(0.16)
81	810	9	38	(0.10)
82	820	9	35	(0.09)
83	830	9	6	(0.02)
9	900	9	1	(0.00)
93	930	9	1	(0.00)
Sum			2179	(5.73)

Bold*, divergence Norwegian and international standard; →, change made to fit the standards.

9 References

1. Wyller TB and Hem E. Kommentar: De skrøpelige. *Tidsskrift for omsorgsforskning* 2020; 6: 1-3. DOI: 10.18261/issn.2387-5984-2020-01-04 ER.
2. Wyller TB. [Frail--vulnerable or fragile?]. *Tidsskr Nor Laegeforen* 2014; 134: 2300. 2014/12/11. DOI: 10.4045/tidsskr.14.0970.
3. Commission on Social Determinants of Health. *Closing the gap in a generation: health equity through action on the social determinants of health: final report of the commission on social determinants of health*. Geneva 2008, p.256.
4. Nicholson K, Makovski TT, Griffith LE, et al. Multimorbidity and comorbidity revisited: refining the concepts for international health research. *J Clin Epidemiol* 2019; 105: 142-146. 2018/09/27. DOI: 10.1016/j.jclinepi.2018.09.008.
5. Valderas JM, Starfield B, Sibbald B, et al. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med* 2009; 7: 357-363. 2009/07/15. DOI: 10.1370/afm.983.
6. Wallace E, Salisbury C, Guthrie B, et al. Managing patients with multimorbidity in primary care. *BMJ* 2015; 350: h176. Journal Article 2015/02/04. DOI: 10.1136/bmj.h176.
7. Nguyen H, Manolova G, Daskalopoulou C, et al. Prevalence of multimorbidity in community settings: A systematic review and meta-analysis of observational studies. *Journal of comorbidity* 2019; 9: 2235042X19870934. 2019/09/07. DOI: 10.1177/2235042X19870934.
8. Tomasdottir MO, Getz L, Sigurdsson JA, et al. Co-and multimorbidity patterns in an unselected Norwegian population: Cross-sectional analysis based on the HUNT Study and theoretical reflections concerning basic medical models. *European Journal for Person Centered Healthcare* 2014; 2: 335-345. DOI: 10.5750/ejpch.v2i3.
9. Nunes BP, Flores TR, Mielke GI, et al. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. *Arch Gerontol Geriatr* 2016; 67: 130-138. 2016/08/09. DOI: 10.1016/j.archger.2016.07.008.
10. Tomasdottir MO. *Multimorbidity in the Norwegian HUNT population: An epidemiological study with reference to the concept allostatic load*. Doctoral thesis, Norwegian University of Science and Technology (NTNU), NTNU, 2017.
11. Wendt C. Mapping European healthcare systems: a comparative analysis of financing, service provision and access to healthcare. *Journal of European Social Policy* 2009; 19: 432-445. DOI: 10.1177/0958928709344247.
12. Vikum E, Bjorngaard JH, Westin S, et al. Socio-economic inequalities in Norwegian health care utilization over 3 decades: the HUNT Study. *Eur J Public Health* 2013; 23: 1003-1010. 2013/06/05. DOI: 10.1093/eurpub/ckt053.
13. Bergqvist K, Yngwe MA and Lundberg O. Understanding the role of welfare state characteristics for health and inequalities - an analytical review. *BMC Public Health* 2013; 13: 1234. 2013/12/29. DOI: 10.1186/1471-2458-13-1234.
14. Esping-Andersen G. *The Three Worlds of Welfare Capitalism*. Princeton, New Jersey: Princeton University Press, 1990.
15. Lovdata. Lov om folketrygd (folketrygdloven), https://lovdata.no/dokument/NL/lov/1997-02-28-19 (1997, accessed 10-04 2020).

16. Mackenbach JP. The persistence of health inequalities in modern welfare states: the explanation of a paradox. *Soc Sci Med* 2012; 75: 761-769. 2012/04/06. DOI: 10.1016/j.socscimed.2012.02.031.
17. Bentzen N, Bjerre B, Peterson C, et al. *Wonca Dictionary of General/Family Practice.* Copenhagen, . Wonca International Classification

Committee:, 2003, p.147.
18. World Health Organisation. *Innovative care for chronic conditions: building blocks for actions: global report*. Geneva, Switzerland 2002.
19. Uijen AA and van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008; 14 Suppl 1: 28-32. 2008/10/31. DOI: 10.1080/13814780802436093.
20. van Oostrom SH, Gijsen R, Stirbu I, et al. Time Trends in Prevalence of Chronic Diseases and Multimorbidity Not Only due to Aging: Data from General Practices and Health Surveys. *PLoS One* 2016; 11: e0160264. 2016/08/03. DOI: 10.1371/journal.pone.0160264.
21. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; 380: 37-43. 2012/05/15. DOI: 10.1016/S0140-6736(12)60240-2.
22. World Health Organization. Multimorbidity: Technical Series on Safer Primary Care. Geneva.: World Health Organization, 2016.
23. van Weel C and Schellevis FG. Comorbidity and guidelines: conflicting interests. *Lancet* 2006; 367: 550-551. 2006/02/21. DOI: 10.1016/S0140-6736(06)68198-1.
24. Guthrie B, Payne K, Alderson P, et al. Adapting clinical guidelines to take account of multimorbidity. *BMJ* 2012; 345: e6341. Journal Article 2012/10/06. DOI: 10.1136/bmj.e6341.
25. Hughes LD, McMurdo MET and Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age Ageing* 2012; 42: 62-69. 2012/08/23. DOI: 10.1093/ageing/afs100.
26. Sondergaard E, Willadsen TG, Guassora AD, et al. Problems and challenges in relation to the treatment of patients with multimorbidity: General practitioners' views and attitudes. *Scand J Prim Health Care* 2015; 33: 121-126. 2015/07/15. DOI: 10.3109/02813432.2015.1041828.
27. Almirall J and Fortin M. The coexistence of terms to describe the presence of multiple concurrent diseases. *Journal of comorbidity* 2013; 3: 4-9. 2013/10/08. DOI: 10.15256/joc.2013.3.22.
28. van den Akker M, Buntinx F and Knottnerus JA. Comorbidity or multimorbidity. *European Journal of General Practice* 1996; 2: 65-70. 11 Jul 2009. DOI: 10.3109/13814789609162146.
29. Willadsen TG, Bebe A, Koster-Rasmussen R, et al. The role of diseases, risk factors and symptoms in the definition of multimorbidity - a systematic review. *Scand J Prim Health Care* 2016; 34: 112-121. 2016/03/10. DOI: 10.3109/02813432.2016.1153242.
30. van den Akker M, Buntinx F, Roos S, et al. Problems in determining occurrence rates of multimorbidity. *J Clin Epidemiol* 2001; 54: 675-679. 2001/07/05. DOI: 10.1016/s0895-4356(00)00358-9.

31. Feinstein AR. The Pre-Therapeutic Classification of Co-Morbidity in Chronic Disease. *J Chronic Dis* 1970; 23: 455-468. 1970/12/01. DOI: 10.1016/0021-9681(70)90054-8.
32. Le Reste JY, Nabbe P, Manceau B, et al. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. *J Am Med Dir Assoc* 2013; 14: 319-325. 2013/02/16. DOI: 10.1016/j.jamda.2013.01.001.
33. World Health Organization. *The World Health Report 2008. Primary Health Care - Now more than ever*. Geneva: World Health Organization, 2008.
34. Diederichs C, Berger K and Bartels DB. The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci* 2011; 66: 301-311. 2010/11/30. DOI: 10.1093/gerona/glq208.
35. Fortin M, Stewart M, Poitras ME, et al. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012; 10: 142-151. 2012/03/14. DOI: 10.1370/afm.1337.
36. Huntley AL, Johnson R, Purdy S, et al. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. *The Annals of Family Medicine* 2012; 10: 134-141.
37. Violan C, Foguet-Boreu Q, Flores-Mateo G, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One* 2014; 9: e102149. 2014/07/23. DOI: 10.1371/journal.pone.0102149.
38. Harrison C, Britt H, Miller G, et al. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open* 2014; 4: e004694. 2014/07/13. DOI: 10.1136/bmjopen-2013-004694.
39. Goodman RA, Posner SF, Huang ES, et al. Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Prev Chronic Dis* 2013; 10: E66. 2013/04/27. DOI: 10.5888/pcd10.120239.
40. National Institute for Health and Care Excellence. *Multimorbidity: clinical assessment and management*. London: National Institute for Health and Care Excellence (UK). 2016.
41. Valderas JM. Multimorbidity, not a health condition or complexity by another name. *Eur J Gen Pract* 2015; 21: 213-214. 2015/12/19. DOI: 10.3109/13814788.2015.1108404.
42. Starfield B. Threads and yarns: weaving the tapestry of comorbidity. *Ann Fam Med* 2006; 4: 101-103. 2006/03/30. DOI: 10.1370/afm.524.
43. Safford MM, Allison JJ and Kiefe CI. Patient complexity: more than comorbidity. the vector model of complexity. *J Gen Intern Med* 2007; 22 Suppl 3: 382-390. 2007/12/06. DOI: 10.1007/s11606-007-0307-0.
44. Schaink AK, Kuluski K, Lyons RF, et al. A scoping review and thematic classification of patient complexity: offering a unifying framework. *Journal of comorbidity* 2012; 2: 1-9. 2012/10/10. DOI: 10.15256/joc.2012.2.15.
45. Dahlgren G and Whitehead M. *Policies and strategies to promote social equity in health. Background document to WHO - Strategy paper for Europe. Arbetsrapport 2007:14*. Stockholm: Institute for Futures Studies, 1991/2007, p.1-69.
46. Piette JD and Kerr EA. The impact of comorbid chronic conditions on diabetes care. *Diabetes Care* 2006; 29: 725-731. 2006/03/01. DOI: 10.2337/diacare.29.03.06.dc05-2078.

47. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, et al. In search of an integral conceptual definition of frailty: opinions of experts. *J Am Med Dir Assoc* 2010; 11: 338-343. 2010/06/01. DOI: 10.1016/j.jamda.2009.09.015.
48. Villacampa-Fernandez P, Navarro-Pardo E, Tarin JJ, et al. Frailty and multimorbidity: Two related yet different concepts. *Maturitas* 2017; 95: 31-35. 2016/11/28. DOI: 10.1016/j.maturitas.2016.10.008.
49. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; 59: 255-263. 2004/03/20. DOI: 10.1093/gerona/59.3.m255.
50. Vetrano DL, Palmer K, Marengoni A, et al. Frailty and Multimorbidity: A Systematic Review and Meta-analysis. *J Gerontol A Biol Sci Med Sci* 2019; 74: 659-666. 2018/05/05. DOI: 10.1093/gerona/gly110.
51. Cesari M, Perez-Zepeda MU and Marzetti E. Frailty and Multimorbidity: Different Ways of Thinking About Geriatrics. *J Am Med Dir Assoc* 2017; 18: 361-364. 2017/03/11. DOI: 10.1016/j.jamda.2016.12.086.
52. Vetrano DL, Calderon-Larranaga A, Marengoni A, et al. An International Perspective on Chronic Multimorbidity: Approaching the Elephant in the Room. *J Gerontol A Biol Sci Med Sci* 2018; 73: 1350-1356. 2017/09/29. DOI: 10.1093/gerona/glx178.
53. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013; 381: 752-762. 2013/02/12. DOI: 10.1016/S0140-6736(12)62167-9.
54. Mitnitski AB, Mogilner AJ and Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001; 1: 323-336. 2003/06/14. DOI: 10.1100/tsw.2001.58.
55. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146-156. 2001/03/17. DOI: 10.1093/gerona/56.3.m146.
56. Rockwood K and Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* 2007; 62: 722-727. 2007/07/20. DOI: 10.1093/gerona/62.7.722.
57. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. *BMC Geriatr* 2008; 8: 24. DOI: 10.1186/1471-2318-8-24.
58. Jones DM, Song X and Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *J Am Geriatr Soc* 2004; 52: 1929-1933. 2004/10/28. DOI: 10.1111/j.1532-5415.2004.52521.x.
59. Theou O, Brothers TD, Pena FG, et al. Identifying common characteristics of frailty across seven scales. *J Am Geriatr Soc* 2014; 62: 901-906. 2014/04/05. DOI: 10.1111/jgs.12773.
60. Aguayo GA, Donneau AF, Vaillant MT, et al. Agreement Between 35 Published Frailty Scores in the General Population. *Am J Epidemiol* 2017; 186: 420-434. 2017/06/22. DOI: 10.1093/aje/kwx061.
61. Vermeiren S, Vella-Azzopardi R, Beckwee D, et al. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. *J Am Med Dir Assoc* 2016; 17: 1163 e1161-1163 e1117. 2016/11/26. DOI: 10.1016/j.jamda.2016.09.010.

62. Theou O, Brothers TD, Mitnitski A, et al. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *J Am Geriatr Soc* 2013; 61: 1537-1551. 2013/09/14. DOI: 10.1111/jgs.12420.
63. O'Caoimh R, Galluzzo L, Rodriguez-Laso A, et al. Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: a systematic review and meta-analysis. *Ann Ist Super Sanita* 2018; 54: 226-238. 2018/10/05. DOI: 10.4415/ANN_18_03_10.
64. Franse CB, van Grieken A, Qin L, et al. Socioeconomic inequalities in frailty and frailty components among community-dwelling older citizens. *PLoS One* 2017; 12: e0187946. 2017/11/10. DOI: 10.1371/journal.pone.0187946.
65. Szanton SL, Seplaki CL, Thorpe RJ, Jr., et al. Socioeconomic status is associated with frailty: the Women's Health and Aging Studies. *J Epidemiol Community Health* 2010; 64: 63-67. 2009/08/21. DOI: 10.1136/jech.2008.078428.
66. Hanlon P, Nicholl BI, Jani BD, et al. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *The Lancet Public health* 2018; 3: e323-e332. 2018/06/18. DOI: 10.1016/S2468-2667(18)30091-4.
67. Elstad JI. *Social inequalities in health and their explanations*. Oslo Metropolitan University-OsloMet: NOVA, 2000.
68. Whitehead M. The concepts and principles of equity and health. *Int J Health Serv* 1992; 22: 429-445. 1992/01/01. DOI: 10.2190/986L-LHQ6-2VTE-YRRN.
69. Krieger N. A glossary for social epidemiology. *J Epidemiol Community Health* 2001; 55: 693-700. 2001/09/13. DOI: 10.1136/jech.55.10.693.
70. McCartney G, Collins C and Mackenzie M. What (or who) causes health inequalities: theories, evidence and implications? *Health Policy* 2013; 113: 221-227. 2013/07/03. DOI: 10.1016/j.healthpol.2013.05.021.
71. Arcaya MC, Arcaya AL and Subramanian SV. Inequalities in health: definitions, concepts, and theories. *Glob Health Action* 2015; 8: 27106. 2015/06/27. DOI: 10.3402/gha.v8.27106.
72. Krieger N. Theories for social epidemiology in the 21st century: an ecosocial perspective. *Int J Epidemiol* 2001; 30: 668-677. 2001/08/21. DOI: 10.1093/ije/30.4.668.
73. McEwen BS and Wingfield JC. What is in a name? Integrating homeostasis, allostasis and stress. *Horm Behav* 2010; 57: 105-111. 2009/09/26. DOI: 10.1016/j.yhbeh.2009.09.011.
74. Mæland JG, Elstad JI, Næss Ø, et al. *Sosial epidemiologi: sosiale årsaker til sykdom og helsesvikt*. Gyldendal Akademisk, 2009.
75. Marmot M. Society and the slow burn of inequality. *Lancet* 2020; 395: 1413-1414. 2020/05/04. DOI: 10.1016/S0140-6736(20)30940-5.
76. Bambra C, Riordan R, Ford J, et al. The COVID-19 pandemic and health inequalities. *J Epidemiol Community Health* 2020: jech-2020-214401. DOI: 10.1136/jech-2020-214401.
77. Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health* 2006; 60: 7-12. 2005/12/20. DOI: 10.1136/jech.2004.023531.
78. Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 2). *J Epidemiol Community Health* 2006; 60: 95-101. 2006/01/18. DOI: 10.1136/jech.2004.028092.

79. Rose D and Harrison E. The European Socio-Economic Classification: A New Social Class Schema for Comparative European Research. *Eur Soc* 2007; 9: 459-490. DOI: 10.1080/14616690701336518.
80. Statistics Norway. *Standard Classification of Occupations*. Oslo/Kongsvinger: Statistics Norway, 1998.
81. Galobardes B, Lynch J and Smith GD. Measuring socioeconomic position in health research. *Br Med Bull* 2007; 81-82: 21-37. 2007/02/08. DOI: 10.1093/bmb/ldm001.
82. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic status in health research: one size does not fit all. *JAMA* 2005; 294: 2879-2888.
83. Greenland S, Rothman KJ and Lash TL. Chapter 4 Measures of Effect and Measures of Association. In: Rothman KJ, Greenland S and Lash TL (eds) *Modern epidemiology*. 3rd edition ed. Philadelphia: Lippincott, Williams and Wilkins, 2012, pp.758.
84. Mackenbach JP and Kunst AE. Measuring the magnitude of socio-economic inequalities in health: an overview of available measures illustrated with two examples from Europe. *Soc Sci Med* 1997; 44: 757-771. 1997/03/01. DOI: 10.1016/s0277-9536(96)00073-1.
85. Harrison C, Henderson J, Miller G, et al. The prevalence of complex multimorbidity in Australia. *Aust N Z J Public Health* 2016; 40: 239-244. 2016/03/31. DOI: 10.1111/1753-6405.12509.
86. Diaz E, Poblador-Pou B, Gimeno-Feliu LA, et al. Multimorbidity and Its Patterns according to Immigrant Origin. A Nationwide Register-Based Study in Norway. *PLoS One* 2015; 10: e0145233. 2015/12/20. DOI: 10.1371/journal.pone.0145233.
87. Storeng SH, Vinjerui KH, Sund ER, et al. Associations between complex multimorbidity, activities of daily living and mortality among older Norwegians. A prospective cohort study: the HUNT Study, Norway. *BMC Geriatr* 2020; 20: 21. 2020/01/23. DOI: 10.1186/s12877-020-1425-3.
88. Kersten H, Hvidsten LT, Gloersen G, et al. Clinical impact of potentially inappropriate medications during hospitalization of acutely ill older patients with multimorbidity. *Scand J Prim Health Care* 2015; 33: 243-251. 2015/11/11. DOI: 10.3109/02813432.2015.1084766.
89. Naess G, Kirkevold M, Hammer W, et al. Nursing care needs and services utilised by home-dwelling elderly with complex health problems: observational study. *BMC Health Serv Res* 2017; 17: 645. 2017/09/14. DOI: 10.1186/s12913-017-2600-x.
90. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing research reviews* 2011; 10: 430-439. 2011/03/16. DOI: 10.1016/j.arr.2011.03.003.
91. van den Akker M, Buntinx F, Metsemakers JF, et al. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol* 1998; 51: 367-375. 1998/06/10. DOI: 10.1016/s0895-4356(97)00306-5.
92. Schafer I, Hansen H, Schon G, et al. The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. First results from the multicare cohort study. *BMC Health Serv Res* 2012; 12: 89. 2012/04/05. DOI: 10.1186/1472-6963-12-89.
93. Schiotz ML, Stockmarr A, Host D, et al. Social disparities in the prevalence of multimorbidity - A register-based population study. *BMC Public Health* 2017; 17: 422. 2017/05/11. DOI: 10.1186/s12889-017-4314-8.

94. McLean G, Gunn J, Wyke S, et al. The influence of socioeconomic deprivation on multimorbidity at different ages: a cross-sectional study. *Br J Gen Pract* 2014; 64: e440-447. 2014/07/02. DOI: 10.3399/bjgp14X680545.
95. Balaj M, Huijts T, McNamara CL, et al. Non-communicable diseases and the social determinants of health in the Nordic countries: Findings from the European Social Survey (2014) special module on the social determinants of health. *Scand J Public Health* 2017; 45: 90-102. 2017/01/28. DOI: 10.1177/1403494816686026.
96. Chan MS, van den Hout A, Pujades-Rodriguez M, et al. Socio-economic inequalities in life expectancy of older adults with and without multimorbidity: a record linkage study of 1.1 million people in England. *Int J Epidemiol* 2019. DOI: 10.1093/ije/dyz052 %J International Journal of Epidemiology.
97. Lund Jensen N, Pedersen HS, Vestergaard M, et al. The impact of socioeconomic status and multimorbidity on mortality: a population-based cohort study. *Clin Epidemiol* 2017; 9: 279-289. 2017/05/27. DOI: 10.2147/CLEP.S129415.
98. Jani BD, Hanlon P, Nicholl BI, et al. Relationship between multimorbidity, demographic factors and mortality: findings from the UK Biobank cohort. *BMC Med* 2019; 17: 74. 2019/04/11. DOI: 10.1186/s12916-019-1305-x.
99. Dugravot A, Fayosse A, Dumurgier J, et al. Social inequalities in multimorbidity, frailty, disability, and transitions to mortality: a 24-year follow-up of the Whitehall II cohort study. *The Lancet Public health* 2020; 5: e42-e50. 2019/12/16. DOI: 10.1016/S2468-2667(19)30226-9.
100. Palmer K, Marengoni A, Forjaz MJ, et al. Multimorbidity care model: Recommendations from the consensus meeting of the Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS). *Health Policy* 2018; 122: 4-11. 2017/10/03. DOI: 10.1016/j.healthpol.2017.09.006.
101. Getz L. *Sustainable and responsible preventive medicine: Conceptualising ethical dilemmas arising from clinical implementation of advancing medical technology*. Det medisinske fakultet, 2006.
102. Holmen J, Midthjell K, Forsen L, et al. [A health survey in Nord-Trondelag 1984-86. Participation and comparison of attendants and non-attendants]. *Tidsskr Nor Laegeforen* 1990; 110: 1973-1977. 1990/06/10.
103. Holmen J, Midthjell K, Krüger Ø, et al. The Nord-Trøndelag Health Study 1995–97 (HUNT 2): objectives, contents, methods and participation. *Norsk epidemiologi* 2003; 13: 19-32.
104. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. *Int J Epidemiol* 2013; 42: 968-977. 2012/08/11. DOI: 10.1093/ije/dys095.
105. Langhammer A, Krokstad S, Romundstad P, et al. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med Res Methodol* 2012; 12: 143. 2012/09/18. DOI: 10.1186/1471-2288-12-143.
106. Direktoratet for e-helse. FinnKode - Helsedirektoratet medisinske kodeverk, https://finnkode.ehelse.no/#icd10/0/0/0/-1 (2017, accessed 1 Feb 2017).
107. International Labour Organization (ILO). The International Standard Classification of Occupations, ISCO-88,

https://www.ilo.org/public/english/bureau/stat/isco/isco88/index.htm (1988, accessed 24.05. 2019).
108. Harrell FE. Chapter 10 Binary Logistic Regression. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. Second ed. Cham: Springer, 2015, pp.582.
109. Harrell FE. Chapter 20 Cox Proportional Hazards Regression Model. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. Second ed. Cham: Springer, 2015, pp.582.
110. Greenland S, Lash TL and Rothman KJ. Chapter 5 Concepts of Interaction In: Rothman KJ, Greenland S and Lash TL (eds) *Modern epidemiology*. 3rd edition ed. Philadelphia: Lippincott, Williams and Wilkins, 2012, pp.758.
111. Norton EC, Miller MM and Kleinman LC. Computing Adjusted Risk Ratios and Risk Differences in Stata. *The Stata Journal: Promoting communications on statistics and Stata* 2018; 13: 492-509. DOI: 10.1177/1536867x1301300304.
112. Harrell FE. Chapter 2 General Aspects of Fitting Regression Models. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. Second ed. Cham: Springer, 2015, pp.582.
113. Rothman KJ, Greenland S and Lash TL. *Modern epidemiology*. 3rd edition ed. Philadelphia: Lippincott, Williams and Wilkins, 2012, p.758.
114. VanderWeele TJ. The Interaction Continuum. *Epidemiology* 2019; 30: 648-658. 2019/06/18. DOI: 10.1097/EDE.0000000000001054.
115. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999; 8: 3-15. 1999/05/29. DOI: 10.1177/096228029900800102.
116. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; 338: b2393. 2009/07/01. DOI: 10.1136/bmj.b2393.
117. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007; 18: 805-835. 2007/12/01. DOI: 10.1097/EDE.0b013e3181577511.
118. Rothman KJ, Greenland S and Lash TL. Chapter 6 Types of Epidemiologic Studies. In: Rothman KJ, Greenland S and Lash TL (eds) *Modern epidemiology*. 3rd edition ed. Philadelphia: Lippincott, Williams and Wilkins, 2012, pp.758.
119. Rothman KJ, Greenland S and Lash TL. Chapter 10 Precision and Statistics in Epidemiologic Studies. In: Rothman KJ, Greenland S and Lash TL (eds) *Modern epidemiology*. 3rd edition ed. Philadelphia: Lippincott, Williams and Wilkins, 2012, pp.758.
120. Rothman KJ, Greenland S and Lash TL. Chapter 9 Validity in Epidemiologic Studies. In: Rothman KJ, Greenland S and Lash TL (eds) *Modern epidemiology*. 3rd edition ed. Philadelphia: Lippincott, Williams and Wilkins, 2012, pp.758.
121. Rothman KJ. Chapter 7 Dealing with Biases. *Epidemiology: an introduction*. 2012.
122. Ahrens W and Pigeot I. *Handbook of Epidemiology*. 2nd ed.: Springer New York, 2014.
123. Martikainen P and Valkonen T. Bias related to the exclusion of the economically inactive in studies on social class differences in mortality. *Int J Epidemiol* 1999; 28: 899-904. 1999/12/22. DOI: 10.1093/ije/28.5.899.

124. Johnston MC, Crilly M, Black C, et al. Defining and measuring multimorbidity: a systematic review of systematic reviews. *Eur J Public Health* 2019; 29: 182-189. 2018/06/08. DOI: 10.1093/eurpub/cky098.
125. Nicholson K, Almirall J and Fortin M. The measurement of multimorbidity. *Health Psychol* 2019; 38: 783-790. 2019/04/26. DOI: 10.1037/hea0000739.
126. Hagen K, Zwart JA, Aamodt AH, et al. The validity of questionnaire-based diagnoses: the third Nord-Trondelag Health Study 2006-2008. *J Headache Pain* 2010; 11: 67-73. 2009/12/01. DOI: 10.1007/s10194-009-0174-7.
127. Videm V, Thomas R, Brown MA, et al. Self-reported Diagnosis of Rheumatoid Arthritis or Ankylosing Spondylitis Has Low Accuracy: Data from the Nord-Trondelag Health Study. *J Rheumatol* 2017; 44: 1134-1141. 2017/04/17. DOI: 10.3899/jrheum.161396.
128. Ness-Jensen E, Lindam A, Lagergren J, et al. Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: a prospective population-based cohort study, the HUNT study. *Gut* 2012; 61: 1390-1397. 2011/12/23. DOI: 10.1136/gutjnl-2011-300715.
129. Modalsli EH, Snekvik I, Asvold BO, et al. Validity of Self-Reported Psoriasis in a General Population: The HUNT Study, Norway. *J Invest Dermatol* 2016; 136: 323-325. 2016/01/15. DOI: 10.1038/JID.2015.386.
130. Mackenbach JP, Looman CW and van der Meer JB. Differences in the misreporting of chronic conditions, by level of education: the effect on inequalities in prevalence rates. *Am J Public Health* 1996; 86: 706-711. 1996/05/01. DOI: 10.2105/ajph.86.5.706.
131. Okura Y, Urban LH, Mahoney DW, et al. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004; 57: 1096-1103.
132. Holzer BM, Siebenhuener K, Bopp M, et al. Evidence-based design recommendations for prevalence studies on multimorbidity: improving comparability of estimates. *Popul Health Metr* 2017; 15: 9. 2017/03/09. DOI: 10.1186/s12963-017-0126-4.
133. Theou O, O'Connell MD, King-Kallimanis BL, et al. Measuring frailty using self-report and test-based health measures. *Age Ageing* 2015; 44: 471-477. 2015/02/18. DOI: 10.1093/ageing/afv010.
134. HUNT Databank. Country Age 01 Edited, https://hunt-db.medisin.ntnu.no/hunt-db/#/variable/17848 (2008, accessed 12.04. 2020).
135. Statistics Norway. Immigrants and Norwegian-born to immigrant parents, https://www.ssb.no/en/statbank/table/12548/ (2020, accessed 17/03 2020).
136. Statistics Norway. Educational attainment of the population, https://www.ssb.no/en/statbank/table/08921 (2020, accessed 17/03 2020).
137. Statistics Norway. Income and wealth statistics for households, https://www.ssb.no/en/statbank/table/06946/ (2020, accessed 17/03 2020).
138. Skaftun EK, Verguet S, Norheim OF, et al. Geographic health inequalities in Norway: a Gini analysis of cross-county differences in mortality from 1980 to 2014. *Int J Equity Health* 2018; 17: 64. 2018/05/26. DOI: 10.1186/s12939-018-0771-7.

139. Collaboration NCDRF. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389: 37-55. 2016/11/20. DOI: 10.1016/S0140-6736(16)31919-5.
140. Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 2017; 390: 2627-2642. 2017/10/17. DOI: 10.1016/S0140-6736(17)32129-3.
141. Krokstad S, Kunst AE and Westin S. Trends in health inequalities by educational level in a Norwegian total population study. *J Epidemiol Community Health* 2002; 56: 375-380. 2002/04/20. DOI: 10.1136/jech.56.5.375.
142. Woo J and Leung J. Multi-morbidity, dependency, and frailty singly or in combination have different impact on health outcomes. *Age (Dordr)* 2014; 36: 923-931. 2013/10/05. DOI: 10.1007/s11357-013-9590-3.
143. Singer L, Green M, Rowe F, et al. Trends in multimorbidity, complex multimorbidity and multiple functional limitations in the ageing population of England, 2002-2015. *Journal of comorbidity* 2019; 9: 2235042X19872030. 2019/09/17. DOI: 10.1177/2235042X19872030.
144. Petarli GB, Cattafesta M, Sant'Anna MM, et al. Multimorbidity and complex multimorbidity in Brazilian rural workers. *PLoS One* 2019; 14: e0225416. 2019/11/20. DOI: 10.1371/journal.pone.0225416.
145. Ravesteijn B, van Kippersluis H and van Doorslaer E. The contribution of occupation to health inequality. *Res Econ Inequal* 2013; 21: 311-332. 2013/01/01. DOI: 10.1108/S1049-2585(2013)0000021014.
146. MacMahon S. *Multimorbidity: A priority for global health research*. London, UK: The Academy of Medical Sciences, 2018, p.127.
147. Singer L. *Understanding health inequalities in multimorbidity and functional limitation of the ageing population in England*. University of Liverpool, 2019.
148. Altman DG and Royston P. The cost of dichotomising continuous variables. *BMJ* 2006; 332: 1080. 2006/05/06. DOI: 10.1136/bmj.332.7549.1080.
149. Onder G, Palmer K, Navickas R, et al. Time to face the challenge of multimorbidity. A European perspective from the joint action on chronic diseases and promoting healthy ageing across the life cycle (JA-CHRODIS). *Eur J Intern Med* 2015; 26: 157-159. 2015/03/24. DOI: 10.1016/j.ejim.2015.02.020.
150. Muth C, van den Akker M, Blom JW, et al. The Ariadne principles: how to handle multimorbidity in primary care consultations. *BMC Med* 2014; 12: 223. 2014/12/09. DOI: 10.1186/s12916-014-0223-1.
151. Marmot M, Goldblatt P, Allen J, et al. *Fair Society, Healthy Lives.*: The Marmot Review, 2010, p.242.
152. Fortin M, Soubhi H, Hudon C, et al. The International Research Community on Multimorbidity (IRCMo) - A Welcome Post, http://crmcspl-blog.recherche.usherbrooke.ca/?page_id=248 (accessed 2015-03-30 2015).
153. Getz L, Kirkengen AL and Ulvestad E. Kapittel 10 Kroppsliggjøring av erfaring og mening - belastende erfaringers innvirkning på menneskets biologi. In: Mæland JG (ed) *Sykdommers sosiale røtter*. 2020, pp.205-230.

154. Tomasdottir MO, Sigurdsson JA, Petursson H, et al. Self Reported Childhood Difficulties, Adult Multimorbidity and Allostatic Load. A Cross-Sectional Analysis of the Norwegian HUNT Study. *PLoS One* 2015; 10: e0130591. 2015/06/19. DOI: 10.1371/journal.pone.0130591.
155. Tomasdottir MO, Sigurdsson JA, Petursson H, et al. Does 'existential unease' predict adult multimorbidity? Analytical cohort study on embodiment based on the Norwegian HUNT population. *BMJ Open* 2016; 6: e012602. 2016/11/18. DOI: 10.1136/bmjopen-2016-012602.
156. Skalicka V, van Lenthe F, Bambra C, et al. Material, psychosocial, behavioural and biomedical factors in the explanation of relative socio-economic inequalities in mortality: evidence from the HUNT study. *Int J Epidemiol* 2009; 38: 1272-1284. 2009/08/08. DOI: 10.1093/ije/dyp262.
157. Valete-Rosalino CM and Rozenfeld S. Auditory screening in the elderly: comparison between self-report and audiometry. *Braz J Otorhinolaryngol* 2005; 71: 193-200. 2006/02/01. DOI: 10.1016/s1808-8694(15)31310-0.
158. Heckbert SR, Kooperberg C, Safford MM, et al. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. *Am J Epidemiol* 2004; 160: 1152-1158. 2004/12/08. DOI: 10.1093/aje/kwh314.
159. Corser W, Sikorskii A, Olomu A, et al. Concordance between comorbidity data from patient self-report interviews and medical record documentation. *BMC Health Serv Res* 2008; 8: 85.
160. Svensson Å, Lindberg M, Meding B, et al. Self-reported hand eczema: symptom-based reports do not increase the validity of diagnosis. *Br J Dermatol* 2002; 147: 281-284.
161. Meding B and Barregard L. Validity of self-reports of hand eczema. *Contact Dermatitis* 2001; 45: 99-103. 2001/09/13. DOI: 10.1034/j.1600-0536.2001.045002099.x.
162. Navarro C. Validity of self reported diagnoses of cancer in a major Spanish prospective cohort study. *J Epidemiol Community Health* 2006; 60: 593-599. 2006/06/23. DOI: 10.1136/jech.2005.039131.
163. Keezer MR, Bouma HK and Wolfson C. The diagnostic accuracy of screening questionnaires for the identification of adults with epilepsy: a systematic review. *Epilepsia* 2014; 55: 1772-1780. Article 2014/11/08. DOI: 10.1111/epi.12811.
164. Cunningham TD and DeShields SC. Factors associated with the accuracy of self-reported osteoporosis in the community. *Rheumatol Int* 2016; 36: 1633-1640. 2016/10/08. DOI: 10.1007/s00296-016-3573-5.
165. Mundal I, Grawe RW, Bjorngaard JH, et al. Prevalence and long-term predictors of persistent chronic widespread pain in the general population in an 11-year prospective study: the HUNT study. *BMC Musculoskelet Disord* 2014; 15: 213. 2014/06/22. DOI: 10.1186/1471-2474-15-213.
166. Brix TH, Kyvik KO and Hegedus L. Validity of self-reported hyperthyroidism and hypothyroidism: comparison of self-reported questionnaire data with medical record review. *Thyroid* 2001; 11: 769-773. 2001/08/30. DOI: 10.1089/10507250152484619.
167. Hammer J and Talley NJ. Diagnostic criteria for the irritable bowel syndrome. *Am J Med* 1999; 107: 5S-11S. 1999/12/10. DOI: 10.1016/s0002-9343(99)00276-4.

168. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006; 130: 1480-1491. 2006/05/09. DOI: 10.1053/j.gastro.2005.11.061.
169. Zigmond AS and Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-370. 1983/06/01. DOI: 10.1111/j.1600-0447.1983.tb09716.x.
170. Mykletun A, Stordal E and Dahl AA. Hospital Anxiety and Depression (HAD) scale: Factor structure, item analyses and internal consistency in a large population. *Br J Psychiatry* 2018; 179: 540-544. 2001/12/04. DOI: 10.1192/bjp.179.6.540.
171. Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; 52: 69-77. 2002/02/08. DOI: 10.1016/s0022-3999(01)00296-3.
172. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res* 1997; 42: 17-41. 1997/01/01. DOI: 10.1016/s0022-3999(96)00216-4.
173. Medicine AAoS. *The international classification of sleep disorders: diagnostic and coding manual*. American Acad. of Sleep Medicine, 2005.
174. Ewing JA. Detecting alcoholism. The CAGE questionnaire. *JAMA* 1984; 252: 1905-1907. 1984/10/12. DOI: 10.1001/jama.252.14.1905.
175. Skogen JC, Overland S, Knudsen AK, et al. Concurrent validity of the CAGE questionnaire. The Nord-Trondelag Health Study. *Addict Behav* 2011; 36: 302-307. 2010/12/21. DOI: 10.1016/j.addbeh.2010.11.010.
176. Avis NE, Crawford SL, Greendale G, et al. Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition. *JAMA Internal Medicine* 2015; 175: 531-539. 2015/02/17. DOI: 10.1001/jamainternmed.2014.8063.
177. Tikkinen KA, Johnson TM, 2nd, Tammela TL, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. *Eur Urol* 2010; 57: 488-496. 2009/04/14. DOI: 10.1016/j.eururo.2009.03.080.
178. Sandvik H, Seim A, Vanvik A, et al. A severity index for epidemiological surveys of female urinary incontinence: comparison with 48-hour pad-weighing tests. *Neurourol Urodyn* 2000; 19: 137-145. 2000/02/19. DOI: 10.1002/(sici)1520-6777(2000)19:2<137::aid-nau4>3.0.co;2-g.
179. Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association Symptom Index for Benign Prostatic Hyperplasia. *J Urol* 1992; 148: 1549-1557. 1992/11/11. DOI: 10.1016/s0022-5347(17)36966-5.
180. HUNT Databank. International Prostate Symptom Scale in HUNT3 Questionnaire 2, https://hunt-db.medisin.ntnu.no/hunt-db/#/instrumentpart/45_11 (2008, accessed 2016-10-04 2016).
181. MacLennan PA, McGwin G, Jr., Searcey K, et al. Medical record validation of self-reported eye diseases and eye care utilization among older adults. *Curr Eye Res* 2013; 38: 1-8. 2012/10/20. DOI: 10.3109/02713683.2012.733054.
182. Janssen I, Katzmarzyk PT and Ross R. Waist circumference and not body mass index explains obesity-related health risk. *The American Journal of Clinical Nutrition* 2004; 79: 379-384. 2004/02/27. DOI: 10.1093/ajcn/79.3.379.
183. Perreault L. *Obesity in adults: Prevalence, screening, and evaluation*. Waltham, MA: UpToDate, 2018.

184. HUNT Databank. Waist Circumference, https://hunt-db.medisin.ntnu.no/hunt-db/#/variable/28 (2008, accessed 2016-10-04).
185. HUNT Databank. Blood Pressure Systolic Mean 23, https://hunt-db.medisin.ntnu.no/hunt-db/#/variable/144 (2008, accessed 2016-10-04 2016).
186. Helsedirektoratet. Nasjonal faglig retningslinje for individuell primærforebygging av hjerte-og karsykdommer, kortversjon, IS-1675. 2009.

Articles I-III

Paper I

BMJ Open

Prevalence of multimorbidity with frailty and associations with socioeconomic position in an adult population: findings from the cross-sectional HUNT Study in Norway

Kristin Hestmann Vinjerui ,[1,2] Pauline Boeckxstaens,[3] Kirsty A Douglas,[4] Erik R Sund[1,5,6]

To cite: Vinjerui KH, Boeckxstaens P, Douglas KA, *et al*. Prevalence of multimorbidity with frailty and associations with socioeconomic position in an adult population: findings from the cross-sectional HUNT Study in Norway. *BMJ Open* 2020;**10**:e035070. doi:10.1136/bmjopen-2019-035070

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-035070).

Received 17 October 2019
Revised 11 March 2020
Accepted 09 April 2020

For numbered affiliations see end of article.

Correspondence to
Dr Kristin Hestmann Vinjerui; kristin.vinjerui@ntnu.no

ABSTRACT

Objectives To explore prevalences and occupational group inequalities of two measures of multimorbidity with frailty.

Design Cross-sectional study.

Setting The Nord-Trøndelag Health Study (HUNT), Norway, a total county population health survey, 2006–2008.

Participants Participants older than 25 years, with complete questionnaires, measurements and occupation data were included.

Outcomes ≥2 of 51 multimorbid conditions with ≥1 of 4 frailty measures (poor health, mental illness, physical impairment or social impairment) and ≥3 of 51 multimorbid conditions with ≥2 of 4 frailty measures.

Analysis Logistic regression models with age and occupational group were specified for each sex separately.

Results Of 41 193 adults, 38 027 (55% female; 25–100 years old) were included. Of them, 39% had ≥2 multimorbid conditions with ≥1 frailty measure, and 17% had ≥3 multimorbid conditions with ≥2 frailty measures. Prevalence differences in percentage points (pp) with 95% confidence intervals of those in high versus low occupational group with ≥2 multimorbid conditions and ≥1 frailty measure were largest in women age 30 years, 17 (14 to 20) pp and 55 years, 15 (13 to 17) pp and in men age 55 years, 15 (13 to 17) pp and 80 years, 14 (9 to 18) pp. In those with ≥3 multimorbid conditions and ≥2 frailty measures, prevalence differences were largest in women age 30 years, 8 (6 to 10) pp and 55 years, 10 (8 to 11) ppand in men age 55 years, 9 (8 to 11) pp and 80 years, 6 (95% CI 1 to 10) pp.

Conclusion Multimorbidity with frailty is common, and social inequalities persist until age 80 years in women and throughout the lifespan in men. To manage complex multimorbidity, strategies for proportionate universalism in medical education, healthcare, public health prevention and promotion seem necessary.

Strengths and limitations of this study

- The HUNT Study is a large total county population general health survey with a multitude of variables, suitable to estimate prevalences of multimorbidity and frailty by self-reports and clinical measurements.
- Occupation is used as a marker for socioeconomic position, enabling international comparison.
- Sex-specific occupational group differences in multimorbidity with frailty are reported as both absolute and relative measures of inequality.
- As a secondary analysis, the measures in this study need to be adjusted to fit previously collected data.
- In particular, the original data lacked information of chronicity of conditions, which may lead to overestimation of multimorbidity.

INTRODUCTION

Multimorbidity, the co-occurrence of multiple, chronic conditions, where none is more central,[1] is increasingly prevalent and is becoming the norm.[2–4] Multimorbidity is associated with high healthcare utilisation[5] and challenges clinicians in a fragmented healthcare system, aided by single disease guidelines.[6] The treatment burden to patients is often substantial including lowered ability to self-care.[6] Ways to harmonise guidelines to fit multimorbidity[7 8] and manage patients with multimorbidity in clinical practice[6] have been explored, and specific multimorbidity care guidelines are emerging.[9 10]

Multimorbidity alone may not imply a need for complex, multidisciplinary care.[1] Sociodemographic characteristics, individual health and social experiences, and mental and somatic health characteristics[11] increase patient complexity. The British National Institute for Health and Care Excellence (NICE) guideline[10] defines multimorbidity as two or more long-term, single-count health conditions and recommends a multimorbid approach to care in various contexts,

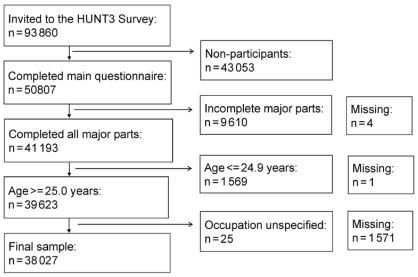


Figure 1 Flowchart for sample selection: inclusion and exclusion criteria and missing data.

including mixed mental and somatic multimorbidity and multimorbidity with frailty.

Frailty increases the vulnerability for adverse outcomes. It has been understood as characterised by loss of biophysical reserves in elderly,[12] operationalised as the frailty phenotype.[12] Another approach is the frailty index,[13] which calculates a ratio of accumulation of numerous deficits in several domains. An opinion of experts further emphasises the latter multidimensional view and defines frailty as a dynamic state of multicausality, involving loss of function in spheres such as physical, psychological and social domains.[14] This can be regarded as a biopsychosocial frailty model.[15] The NICE guideline proposes identification of frailty through observation of a low gait speed or poor self-rated health or by scoring a frailty scale combining demographic characteristics and multidimensional impairments.[10]

Social health inequalities are established; low socioeconomic position is associated with poorer health outcomes in Nordic countries[16] and globally.[17] Multimorbidity and frailty are no exception. Common determinants are socioeconomic deprivation,[18 19] female sex[18 20] and higher age.[18 20] In descriptive studies, any indicator of socioeconomic position will detect occurring differences.[21] Socioeconomic gradients in prevalence of multimorbidity and frailty have been explored by education,[18 19 22 23] income,[22 23] occupation[3] and deprivation indexes.[18 19] Occupation is associated with education and income and may have an impact on health outcomes through biopsychosocial work exposures.[21] Although proportions with multimorbidity and frailty increase with higher age, more multimorbid are young and middle aged than old,[4 24] and frailty is associated with multimorbidity and mortality from middle age.[25] The NICE guideline emphasises assessment of a multimorbid approach to care for adults of all ages but does not take into account social position.

There are numerous operational definitions of both multimorbidity and frailty and prevalence vary by setting, definitions and methods.[18 26–28] The literature suggests that multimorbidity, defined as three or more single health conditions, increases specificity especially in older age groups.[26 29] Common frailty scales require multidimensional loss of function to identify frail individuals[20] and share ability to show associations to age, sex and mortality.[20]

The overall purpose of this study is to identify how many in a general adult population is likely to need complex, multidisciplinary care as given by one of the contexts suggested by the NICE guideline; multimorbidity with frailty. Two measures will be assessed, one in line with the guideline (two conditions of multimorbidity plus one dimension of frailty) and the other with expected increased specificity (three conditions of multimorbidity plus two dimensions of frailty). The second aim is to examine associations of these measures according to age, sex and socioeconomic position.

MATERIALS AND METHODS

Reporting statement

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) cross-sectional reporting guidelines[30] were used for reporting this observational study.

Study design and population

This cross-sectional study use data from the third wave in the Norwegian HUNT Study (the HUNT3 Survey, 2006–2008). Details on data collection and the cohort profile of this total county population health survey were published previously.[31] In brief, 93 860 residents older than 20 years were invited. Of these. 54% (n=50 807 of 93 860) completed the main questionnaire, meeting the minimum requirement for HUNT3 Survey attendance.[31] Figure 1 presents the sample selection for this analysis.

Eighty-one per cent (41 193 of 50 807) of eligible participants completed all major parts of the HUNT3 Survey; the main, age-specific and sex-specific questionnaires, interviews and measurements. Incomplete participation excluded 9610 individuals, while four missed complete information on participation. Of the responders, 1569 were younger than 25 years and were excluded on the assumption that the highest level of occupational group may not yet be obtained by those in this age category. One missed information on age. A total of 1571 individuals missed information on occupation, while 25 people had 'unspecified occupation' and was excluded. Of 41 193 (92%) participants, 38 027 were included in the final sample.

Overall, lower socioeconomic position was associated with lower participation rate in the HUNT3 Survey.[32] In this study, the distribution of occupational groups was 24% (high), 27% (middle) and 49% (low) in the sample and 17% (high), 20% (middle), 52% (low) and 11% (missing) among non-eligible. One hundred per cent of the missing were due to missing classifiable occupational data. Women constituted 55%, 51% and 81% of the sample, non-eligible and missing, respectively. The mean (SD) age was 55 (14) years in the sample, 44 (18) years among non-eligible and 66 (18) years among those missing data.

Box 1 Conditions grouped by ICD-10 chapter

ICD-10 chapter	Conditions
II Neoplasms	Cancer
III Blood/blood-forming organs/immune mechanism	Sarcoidosis
IV Endocrine/nutritional/metabolic	Obesity Hypercholesterolemia Diabetes Hypothyroidism Hyperthyroidism
V Mental/behavioural	Alcohol problem Depression Anxiety Insomnia
Nervous system	Epilepsy Migraine Chronic headache, other
VII Eye/adnexa	Cataract Macula degeneration Glaucoma
VIII Ear/mastoid	Hearing impairment
IX Circulatory system	Hypertension Angina pectoris Myocardial infarction Heart failure Other heart disease* Stroke or brain haemorrhage*
X Respiratory system	Chronic bronchitis, emphysema or COPD* Asthma
XI Digestive system	Dental health status Gastro-oesophageal reflux disease Irritable bowel syndrome
XII Skin/subcutaneous tissue	Hand eczema Psoriasis
XIII Musculoskeletal/connective tissue	Rheumatoid arthritis Osteoarthritis Ankylosing spondylitis Fibromyalgia Osteoporosis Local musculoskeletal pain/stiffness in: Neck or upper back or lower back or shoulder or elbow or Hand or hip or knee or foot/ankle
XIV Genitourinary system	Kidney disease Urine incontinence Prostate symptoms Menopausal hot flashes
XVIII Symptoms/signs/abnormal clinical/laboratory findings	Nocturia. Chronic widespread pain.

*Exception to single entity.
COPD, Chronic Obstructive Pulmonary Disease.

Continued

Box 1 Continued

Demographic and socioeconomic characteristics

Sex and age at participation in the HUNT3 Survey was constructed by the HUNT Databank. Occupational group was used as indicator of socioeconomic position.[21] In the HUNT3 Survey interview, all participants were asked, "What is/was the title of your main occupation?" Free-text answers were manually categorised corresponding to Standard Classifications of Occupations by Statistics Norway,[33] which is based on the International Standard Classification of Occupations–88.[34] Occupational socioeconomic position was operationalised using occupation only, corresponding to a simplified version of the European Socio-economic Classification scheme.[35] The scheme aims to differentiate occupational groups on employment relationships and is not hierarchical per se. Still, the higher occupational groups are likely to have higher and more secure income.[35] Collapsed to a three-class version, the high level represents large employers, higher grade and lower grade professionals, administrative and managerial occupations, and higher grade technician and supervisory occupations. The middle group consists of small employers, self-employed individuals, and lower-grade supervisory and technician occupations. The low level contains lower-grade service positions, sales and clerical occupations, and lower-grade technical and routine occupations. Details are provided in online supplementary appendix A.

Outcomes

Multimorbidity

The construction of 51 single, chronic conditions from the HUNT3 Survey data is described in online supplementary appendix B. Box 1 lists the 51 conditions by 14 International Classification of Diseases 10th Revision (ICD-10) chapters, a disease classification system in major organised by organ systems. In this study, a simple, non-weighted summary score was generated and two multimorbidity variables created, with cut-off values of at least 2 of 51 and 3 of 51 conditions.

Frailty

Original data did not match any exact frailty scale. A qualitative judgement of available data was undertaken and general, mental, physical and social dimensions[10 14 20] of frailty were operationalised from six original variables:

1. General health status, defined as those reporting the answers 'poor' or 'not so good' (vs 'good' and 'very good') to the single question, "How is your health at the moment?"

2. Mental health status, included those reporting symptoms of anxiety and/or depression, on the Hospital Anxiety and Depression Scale. The HUNT Databank calculated a total score for subscales of anxiety and depression, if all items for anxiety and depression, respectively, were answered. In this study, cut-off was set at 8/21 points for both conditions[36] and a combined variable was created.
3. Physical impairment was identified by combining those reporting 'yes' (vs 'no') in response to the question, "Do you suffer from any long-term (at least 1 year) illness or injury of a physical or psychological nature that impairs your functioning in your daily life?" and reporting either motor ability, vision or hearing impairment to a moderate or severe degree.
4. Social impairment was derived from answers to the single question, "To what extent has your physical health or emotional problems limited you in your usual socializing with family or friends during the last 4 weeks?" Included were those reporting 'much' and 'not able to socialise' (vs 'not at all,' 'very little,' or 'somewhat').

A summary score was generated and two frailty variables created, with cut-off values of at least one of four and two of four frailty measures with impairment.

Multimorbidity with frailty

The two final outcome variables were created by combining self-reported multimorbidity and frailty as at least 2 of 51 chronic health conditions plus impairment in 1 of 4 dimensions of frailty and 3 of 51 chronic health conditions plus impairments in 2 of 4 dimensions of frailty.

Statistical analysis

We used cross-tables to identify sociodemographic characteristics by occupational group (table 1) and by multimorbidity with frailty, stratified by sex (table 2).

Associations between occupational group and the two measures of multimorbidity with frailty were analysed using logistic regression, adjusted for age and sex. All models were stratified by sex and included occupational group, continuous age, age squared and an interaction term between occupational group and age. Likelihood ratio tests were used to compare models.

Given the high prevalence of multimorbidity with frailty and the knowledge that odds ratios will deviate from relative risks,[37] we used postestimation commands to obtain prevalence differences and prevalence ratios[38] between the occupational groups with high occupational group as the reference category. The prevalence difference is the difference in mean predicted probability, and prevalence ratio is the ratio between the mean predicted probabilities while holding other covariates constant.[38] Prevalence difference and prevalence ratio between occupational groups were calculated at age 25–100 years in 5-year intervals (online supplementary appendix C). Calculations (with 95% confidence intervals) are presented at the ages 30, 55 and 80 years to reflect young adults, middle aged and elderly (table 3).

We performed complete case analysis and used Stata V.15.1 (StataCorp., College Station, Texas, USA) to analyse the data.

Patient and public involvement

During the preparation of the HUNT3 Survey, there was a wide citizen and stakeholder participation. This study is a secondary analysis of data collected in 2006–2008. Multimorbidity is a universal topic, not represented by any particular patient group, thus no patient or public representatives were involved in designing the study.

RESULTS

A total of 38 027 individuals, older than 25 years, who had completed all major parts of the HUNT3 Survey and had data on occupation, comprised the final sample for this study (figure 1). Further sociodemographic characteristics are presented in table 1.

Most participants, 49% (n=18 814 of 38 027), are categorised as low occupational group, which is comprised of

Table 1 Sex and age distribution by occupational group

	Occupational group							
	High		Middle		Low		Total	
	Frequency	(%)	Frequency	(%)	Frequency	(%)	Frequency	(%)
Total	8970	(100)	10243	(100)	18814	(100)	38027	(100)
Sex								
Female	4505	(50)	5386	(53)	10922	(58)	20813	(55)
Male	4465	(50)	4857	(47)	7892	(42)	17214	(45)
Age, years								
25–44	2837	(32)	2600	(25)	4487	(24)	9924	(26)
45–64	4468	(50)	4787	(47)	8951	(48)	18206	(48)
65–74	1118	(12)	1846	(18)	3297	(18)	6261	(16)
75–100	547	(6)	1010	(10)	2079	(11)	3636	(10)

Table 2 Frequency distribution of two definitions of multimorbidity with frailty across occupational groups and age categories, stratified by sex

	Women						Men					
	Two conditions of multimorbidityand one dimension of frailty*						Two conditions of multimorbidity and one dimension of frailty*					
	No, freq.	(%)	Yes, freq.	(%)	Total, freq.	(%)	No, freq.	(%)	Yes, freq.	(%)	Total, freq.	(%)
Total	12304	(59)	8482	(41)	20813	(100)	10826	(63)	6378	(37)	17214	(100)
Occupational group												
High	3222	(72)	1282	(28)	4505	(100)	3220	(72)	1242	(28)	4465	(100)
Middle	3370	(63)	2009	(37)	5386	(100)	2995	(62)	1860	(38)	4857	(100)
Low	5712	(52)	5191	(48)	10922	(100)	4611	(58)	3276	(42)	7892	(100)
Age, years												
25–44	4298	(72)	1680	(28)	5 981	(100)	3 075	(78)	867	(22)	3 943	(100)
45–64	5712	(58)	4122	(42)	9 840	(100)	5 398	(65)	2 967	(35)	8 366	(100)
65–74	1615	(51)	1 548	(49)	3 168	(100)	1 681	(54)	1 409	(46)	3 093	(100)
75–100	679	(37)	1 132	(62)	1 824	(100)	672	(37)	1 135	(63)	1 812	(100)
Mean (SD)	52	(14)	58	(14)	54	(14)	54	(14)	61	(14)	56	(14)
	Three conditions of multimorbidity and two dimensions of frailty*						Three conditions of multimorbidity and two dimensions of frailty*					
	No, freq.	(%)	Yes, freq.	(%)	Total, freq.	(%)	No, freq.	(%)	Yes, freq.	(%)	Total, freq.	(%)
Total	16983	(82)	3803	(18)	20813	(100)	14367	(83)	2837	(16)	17214	(100)
Occupational group												
High	4029	(89)	475	(11)	4505	(100)	3977	(89)	485	(11)	4465	(100)
Middle	4491	(83)	888	(16)	5386	(100)	3995	(82)	860	(18)	4857	(100)
Low	8463	(77)	2440	(22)	10922	(100)	6395	(81)	1492	(19)	7892	(100)
Age, years												
25–44	5378	(90)	600	(10)	5981	(100)	3651	(93)	291	(7)	3943	(100)
45–64	7920	(80)	1914	(19)	9840	(100)	7024	(84)	1341	(16)	8366	(100)
65–74	2449	(77)	714	(23)	3168	(100)	2472	(80)	618	(20)	3093	(100)
75–100	1236	(68)	575	(32)	1824	(100)	1220	(67)	587	(32)	1812	(100)
Mean (SD)	53	(14)	60	(14)	54	(14)	55	(14)	63	(13)	56	(14)

*In total, 27 women and 10 men miss data on both measures of multimorbidity with frailty.
freq., frequency.

58% (n=10922 of 18 814) women, while women constitute 55% (n=20813 of 38027) of the total sample.

In total, 77% reported more than two and 62% more than three conditions of multimorbidity. Frailty with one impairment was identified in 41% and with two impairments in 18%. Table 2 shows the distribution of the combined measures across occupational groups and stratified by sex.

Overall, 39% met the criteria of having at least two conditions of multimorbidity with one dimension of frailty (41% (n=8482 of 20813) of women, 37% (n=6378 of 17214) of men) and 17% met the criteria of three-condition multimorbidity with two dimensions of frailty (18% (n=3803 of 20813) of women, 16% (n=2837 of 17 214) of men).

Proportions of multimorbidity with frailty increased with lower occupational rank and increasing age, in both sexes, regardless of definition. Most individuals with any definition of multimorbidity with frailty were younger than 64 years.

Table 3 shows prevalence differences and prevalence ratios with 95% CI for each definition of multimorbidity with frailty between occupational groups for women and men at the ages 30, 55 and 80 years.

Prevalence differences in percentage points (pp) for two-condition multimorbidity with one dimension of frailty between high and low occupational groups were largest in women at 30 years, 17 (14 to 20) pp and 55 years, 15 (13 to 17) pp, and for men at 55 years, 15 (13 to 17) pp and 80 years, 14 (9 to 18) pp. The prevalence ratio

Table 3 Prevalence ratios (PR) and prevalence differences (PD) with 95% CI between occupational groups and multimorbidity with frailty, stratified by sex

Age, years	Occupational group	Women				Men			
		Two conditions of multimorbidity and one dimension of frailty							
		PR	(95% CI)	PD	(95% CI)	PR	(95% CI)	PD	(95% CI)
30	High	1.00	(Ref.)	0.00	(Ref.)	1.00	(Ref.)	0.00	(Ref.)
	Middle	1.36	(1.11 to 1.65)	0.06	(0.02 to 0.09)	0.93	(0.70 to 1.23)	−0.01	(−0.06 to 0.03)
	Low	2.09	(1.76 to 2.47)	0.17	(0.14 to 0.20)	1.32	(1.04 to 1.67)	0.05	(0.01 to 0.09)
55	High	1.00	(Ref.)	0.00	(Ref.)	1.00	(Ref.)	0.00	(Ref.)
	Middle	1.22	(1.13 to 1.31)	0.07	(0.04 to 0.09)	1.34	(1.23 to 1.45)	0.08	(0.06 to 0.11)
	Low	1.48	(1.38 to 1.58)	0.15	(0.13 to 0.17)	1.60	(1.48 to 1.72)	0.15	(0.13 to 0.17)
80	High	1.00	(Ref.)	0.00	(Ref.)	1.00	(Ref.)	0.00	(Ref.)
	Middle	0.96	(0.86 to 1.08)	−0.02	(−0.09 to 0.05)	1.23	(1.12 to 1.35)	0.12	(0.06 to 0.17)
	Low	1.05	(0.95 to 1.16)	0.03	(−0.03 to 0.09)	1.27	(1.15 to 1.39)	0.14	(0.09 to 0.18)
Age, years	Occupational group	Three conditions of multimorbidity and two dimensions of frailty							
		PR	(95% CI)	PD	(95% CI)	PR	(95% CI)	PD	(95% CI)
30	High	1.00	(Ref.)	0.00	(Ref.)	1.00	(Ref.)	0.00	(Ref.)
	Middle	2.31	(1.56 to 3.40)	0.04	(0.02 to 0.06)	1.29	(0.77 to 2.17)	0.01	(−0.01 to 0.03)
	Low	3.59	(2.53 to 5.08)	0.08	(0.06 to 0.10)	1.60	(1.02 to 2.51)	0.02	(0.00 to 0.04)
55	High	1.00		0.00		1.00		0.00	
	Middle	1.31	(1.14 to 1.50)	0.04	(0.02 to 0.06)	1.62	(1.40 to 1.87)	0.06	(0.04 to 0.07)
	Low	1.78	(1.59 to 2.00)	0.10	(0.08 to 0.11)	2.05	(1.80 to 2.33)	0.09	(0.08 to 0.11)
80	High	1.00	(Ref.)	0.00	(Ref.)	1.00	(Ref.)	0.00	(Ref.)
	Middle	1.17	(0.94 to 1.47)	0.05	(−0.02 to 0.11)	1.26	(1.06 to 1.50)	0.07	(0.02 to 0.11)
	Low	1.16	(0.94 to 1.42)	0.04	(−0.01 to 0.10)	1.22	(1.04 to 1.44)	0.06	(0.01 to 0.10)

for the low occupational group compared with the high occupational group, for two-condition multimorbidity with one dimension of frailty, was greatest in women at 30 years, 2.09 (1.76 to 2.47) and in men at 55 years, 1.60 (1.48 to 1.72). The prevalence ratio decreased in both sexes in high age and was at 80 years 1.05 (0.95 to 1.16) for women and 1.27 (1.15 to 1.39) for men.

Correspondingly, prevalence differences between high and low occupational groups for three-condition multimorbidity with two dimensions of frailty were largest in women at 30 years, 8 (6 to 10) pp and 55 years, 10 (8 to 11) pp and in men at 55 years, 9 (8 to 11) pp and 80 years, 6 (1 to 10) pp. Prevalence ratio, comparing the low occupational group with the highest occupational group for three-conditions multimorbidity with two conditions of frailty, was greatest in women at 30 years, 3.59 (1.43 to 5.08) and in men at 55 years, 2.05 (1.80 to 2.33). The prevalence ratio decreased in both sexes in high age and was at 80 years 1.16 (0.94 to 1.42) for women and 1.22 (1.04 to 1.44) for men.

DISCUSSION

Main results

In this adult population health study, multimorbidity with frailty was common as 39% met the criteria of two-condition multimorbidity plus one dimension of frailty and 17% met the criteria of three-condition multimorbidity plus two dimensions of frailty. Proportions increased with lower occupational group, higher age and female sex from 25 to 74 years, but was common across age groups in both sexes. Occupational inequalities were consistent in both sexes until high age, diminishing in women, while still present in men at age 80 years.

Comparison with existing literature

Investigating two measures of multimorbidity with frailty in one sample offers a unique direct comparison of occurrences and socioeconomic gradients. Lower overall prevalence for the stricter measure three-condition multimorbidity with two dimensions of frailty is expected. Defining multimorbidity by three or more conditions differentiates into older age.[26 29] The joint measure multimorbidity and frailty show the same tendency, as 62% of 75–100 year olds met the criteria of at least two-condition multimorbidity with one dimension of frailty, while 32% reported three-condition multimorbidity with two dimensions of frailty. In line with individual studies on multimorbidity[4 24] and frailty,[25] most individuals with co-present multimorbidity and frailty are younger than 64 years.

A recent commentary[1] emphasised exploring multimorbidity guidelines and frailty as part of multimorbidity's

complexity, and overlap of multimorbidity and frailty has newly been reviewed.[28] A pooled prevalence of 16% (95% CI 12% to 21%) was reported for two conditions multimorbidity with the frailty phenotype among elderly,[28] while 39% in our study reported at least two conditions of multimorbidity with one dimension of frailty. The prevalence differences are likely explained by differences in methods. The articles included in the review studied age 60 years and older. Still, the prevalence of multimorbidity is low. All but one defined multimorbidity from lists of less than 12 conditions and prevalences are probably underestimated.[26 29] Frailty too was only operationalised with the biophysical model, while more people are expected to be detected using a multidimensional measure.

We have not identified studies on prevalence and social determinants of multimorbidity with frailty. Low social position,[18 19] older age[18 20] and female sex[18 20] are known common determinants of multimorbidity and frailty. We therefore argue that the direction of the sociodemographic determinants in this study is as expected. The magnitudes of these gradients, however, have not been comparable with other studies.

Mechanisms to explain findings

The aggregation of ill health, multimorbidity and frailty included in lower socioeconomic positions is explained by numerous theories. Overall, unequal distribution of power, income and resources result in fundamental different conditions of daily life yielding inequalities in health.[17] With regard to occupation, several mechanisms can explain associations to health outcomes. The higher occupational group is expected to have higher, more stable income,[35 39] more beneficial social networks[39] and more autonomy and control[35 39] at work. Adverse working conditions such as exposure to toxic work environments[21] or demanding physical requirements[39] tend to cluster in lower occupational groups.[17] Persisting health inequalities in assumed egalitarian Nordic countries is partly understood as mortality selection, where, given the well-developed healthcare and welfare systems, frail individuals survive, but likely end up in a low social position.[16] Further, smoking, overall morbidity and mortality decrease at a higher rate among higher than lower social groups.[16] In this study, the demographic age distribution explain the high number of 45 to 64 years old with co-present multimorbidity and frailty. Additionally, incidence of new conditions is associated with count of conditions at baseline,[4] as well as age,[4] thus individuals in lower occupational groups may aggregate conditions faster. The bidirectional association of health and occupation may explain higher occupational group prevalence ratios in younger individuals,[21] while lower ratios by increasing age are expected, since multimorbidity with frailty is more common[40] with advancing age. Finally, survival bias justifies diminishing occupational differences at age 80 years.

Strengths and limitations

Materials and methods meet the standards of studies on multimorbidity, frailty and social health inequalities, strengthening this study. In multimorbidity studies, population-based health surveys are the most frequent study design,[41] and prevalence estimates from self-reports are justified when studying large samples.[26] Deriving the condition count multimorbidity measures from a complete list of single-entity conditions is shown to yield proper prevalence estimates.[29] A multidimensional frailty measure agrees with a holistic, unrestricted on age, conceptual definition of frailty[14] and with common frailty scales, which share ability to show associations to age, sex and mortality.[20] In descriptive studies, any measure of socioeconomic position will reveal health inequalities, if such exists.[21] Occupation is an established marker for socioeconomic position,[21] in which this study had individual data classified to facilitate international comparison. Finally, socioeconomic differences are explored as both absolute and relative measures[16] and presented by sex.[18]

There are always limitations in secondary analysis of data collected a priori and not for the purpose of the current study. Measures of multimorbidity and frailty are also manifold, and operationalisations were adjusted to fit the available data. This challenges the external validity, and comparability between studies, however, is sought reduced through transparency of morbidities included and construction of variables. A majority of included multimorbidity conditions do not contain information regarding duration. Thus, reported prevalence of multimorbidity may be overestimated and not represent true chronicity. It is recognised that frailty scales may differ in accuracy of detecting frailty in younger age groups[10 20]; however, frailty symptoms are of great clinical value regardless of age.[10 42] The accuracy of the frailty variables were not explored and frailty was measured solely as self-report, an approach that may underestimate overall prevalence[43] and overestimate proportion among women compared with men.[43]

Lastly, in the HUNT3 Survey, participants were asked for their 'main' occupation, which is not necessarily the current or longest lasting occupation, more commonly studied.[39] Younger than middle aged may to some extent be misclassified in the lower occupational group, which will underestimate social differences in health among younger subjects. Occupational data may obscure current social context[39] and underestimate socioeconomic inequalities. Thus, the study would have benefitted from exploring socioeconomic position with several indicators,[44] such as individual education and income or a household measure.

Attendance in the HUNT3 Survey varied by age, sex and social position[32]; still, the HUNT Study is considered representative for Norway as a whole[45] and the cohort follows trends in health development in western high-income countries.[46–48] Depression hindered participation,[32] which may yield underestimation of both

multimorbidity and frailty. An overall bias towards healthy elders is probable, since eligibility depended on attendance at a screening station.

Implications for clinical practice and policy makers

This study aimed to quantify the total prevalence of adults in the general population who might need complex, multidisciplinary care assessed as the joint measure multimorbidity with frailty. In a clinical context, the definition of at least three-condition multimorbidity with two dimensions of frailty to detect individuals for whom to initiate a multimorbid approach to care seems more feasible. Despite acknowledgement of the association of multimorbidity and frailty with age, sex and socioeconomic position, guidelines and interventions have yet to take this into account in assessment and management for multimorbidity.[49] Based on literature and reproduction of social gradients in our study, we suggest that clinicians consider evaluation of multimorbidity and frailty in younger age groups with social context in mind. Further research on implementation of the multimorbid approach to care model and mortality is needed before recommending changing inclusion criteria in a guideline. Since multimorbidity is becoming the norm, the organisation of healthcare should reform to fit person-centred, coordinated, multidisciplinary care.[6 10 50] To prevent cases of multimorbidity and frailty and minimise social discrepancies, both universal and targeted life cycle approaches seem necessary.[51]

Frailty is independently associated with mortality, adjusted for multimorbidity,[25] and is reversible.[52] Thus, detection of frailty is relevant for both public health and clinical purposes.

Future research

Some forms of biases are possible for both multimorbidity, frailty and social position, and a careful interpretation of findings is warranted. However, multimorbidity with frailty is common in this general population and with occupational inequalities throughout adulthood, even with stricter definitions. This adds knowledge to the public health literature about the sociodemographic distribution of multimorbidity with frailty in younger age groups, as well as very old individuals. On this background, we recommend exploring the sociodemographic distribution of alternative measures on multimorbidity, including patterns, aiming to detect individuals suspected in high need of complex, multidisciplinary healthcare. Furthermore, such measurements can be compared as prognostic factors for healthcare utilisation and mortality.

CONCLUSION

Multimorbidity with frailty is common from young adulthood onward, with consistent socioeconomic inequalities until 80 years old. Prevention will require a proportionate universal approach on social determinants of health throughout the entire life span. The crucial need for person-centred multimorbid approach to care that acknowledges social context, demands reforms in healthcare organisational structure, medical education and treatment. Further research on competing measures of high-need multimorbidity and the association of these factors with healthcare utilisation and mortality should be explored by socioeconomic position, age and sex.

Author affiliations
[1]Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, HUNT Research Centre, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
[2]Psychiatric Department, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway
[3]Department of Public Health and Primary Care, Ghent University, Ghent, Belgium
[4]Australian National University Medical School, Australian National University, Canberra, Australian Capital Territory, Australia
[5]Faculty of Nursing and Health Sciences, Nord University, Levanger, Norway
[6]Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway

Twitter Kristin Hestmann Vinjerui @KHVinjerui

Acknowledgements L Getz, J Sigurdsson and C Harrison for thorough discussions on measures of multimorbidity. E Solheim for guidance in the use of the European Socio-economic Classification scheme. MS Newman for writing assistance. The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU)), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Contributors KHV, ERS and KAD conceptualised the study and all authors contributed to its design. KHV has analysed the data under the supervision of ERS and all authors have contributed to interpreting the data. KHV wrote the original draft, which has been revised critically by ERS, KAD and PB. All authors have read and approved the final version of the manuscript to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study was funded by the Faculty of Medicine and Health Science at the Norwegian University of Science and Technology (NTNU) through the PhD programme in Behaviour and Health (KHV). NTNU has partly funded the HUNT3 Survey and have funded open access for this article. The Liaison Committee for Education, Research and Innovation in Central Norway (17/38297) supported a research stay for KHV at the Australian National University, Canberra. The funding sources have had no role in conceptualization this study, its design and methods, analysis and interpretation of data, writing of the article or the decision to submit the article for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The Regional Committee for Medical and Health Research Ethics in Norway approved the current study (Project No. 2014/2265).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. To protect participants' privacy, HUNT Research Centre aims to limit storage of data outside HUNT databank and cannot deposit data in open repositories. HUNT databank has precise information on all data exported to different projects and are able to reproduce these on request. There are no restrictions regarding data export given approval of applications to HUNT Research Centre. For more information, see http://www.ntnu.edu/hunt/data.

ORCID iD
Kristin Hestmann Vinjerui http://orcid.org/0000-0003-1828-6943

REFERENCES

1 Nicholson K, Makovski TT, Griffith LE, *et al*. Multimorbidity and comorbidity revisited: Refining the concepts for international health research. *J Clin Epidemiol* 2019;105:142–6.
2 van Oostrom SH, Gijsen R, Stirbu I, *et al*. Time trends in prevalence of chronic diseases and multimorbidity not only due to aging: data from general practices and health surveys. *PLoS One* 2016;11:e0160264.
3 Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008;14:28–32.
4 van den Akker M, Buntinx F, Metsemakers JF, *et al*. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol* 1998;51:367–75.
5 Glynn LG, Valderas JM, Healy P, *et al*. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Fam Pract* 2011;28:516–23.
6 Wallace E, Salisbury C, Guthrie B, *et al*. Managing patients with multimorbidity in primary care. *BMJ* 2015;350:h176.
7 Guthrie B, Payne K, Alderson P, *et al*. Adapting clinical guidelines to take account of multimorbidity. *BMJ* 2012;345:e6341.
8 Muth C, Kirchner H, van den Akker M, *et al*. Current guidelines poorly address multimorbidity: pilot of the interaction matrix method. *J Clin Epidemiol* 2014;67:1242–50.
9 Palmer K, Marengoni A, Forjaz MJ, *et al*. Multimorbidity care model: recommendations from the consensus meeting of the joint action on chronic diseases and promoting healthy ageing across the life cycle (JA-CHRODIS). *Health Policy* 2018;122:4–11.
10 National Institute for Health and Care Excellence. *Multimorbidity: clinical assessment and management*. London: National Institute for Health and Care Excellence (UK), 2016.
11 Schaink AK, Kuluski K, Lyons RF, *et al*. A scoping review and thematic classification of patient complexity: offering a unifying framework. *J Comorb* 2012;2:1–9.
12 Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–57.
13 Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001;1:323–36.
14 Gobbens RJJ, Luijkx KG, Wijnen-Sponselee MT, *et al*. In search of an integral conceptual definition of frailty: opinions of experts. *J Am Med Dir Assoc* 2010;11:338–43.
15 Solfrizzi V, Scafato E, Lozupone M, *et al*. Biopsychosocial frailty and the risk of incident dementia: the Italian longitudinal study on aging. *Alzheimers Dement* 2019;15:1019–28.
16 Huijts T, Eikemo TA, Causality ETA. Causality, social selectivity or artefacts? why socioeconomic inequalities in health are not smallest in the Nordic countries. *Eur J Public Health* 2009;19:452–3.
17 Commission on Social Determinants of Health. *Closing the gap in a generation: health equity through action on the social determinants of health: final report of the Commission on social determinants of health*. Geneva, 2008.
18 Violan C, Foguet-Boreu Q, Flores-Mateo G, *et al*. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One* 2014;9:e102149.
19 Franse CB, van Grieken A, Qin L, *et al*. Socioeconomic inequalities in frailty and frailty components among community-dwelling older citizens. *PLoS One* 2017;12:e0187946.
20 Theou O, Brothers TD, Peña FG, *et al*. Identifying common characteristics of frailty across seven scales. *J Am Geriatr Soc* 2014;62:901–6.
21 Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull* 2007;81-82:21–37.
22 Agborsangaya CB, Lau D, Lahtinen M, *et al*. Multimorbidity prevalence and patterns across socioeconomic determinants: a cross-sectional survey. *BMC Public Health* 2012;12:201.
23 Szanton SL, Seplaki CL, Thorpe RJ, *et al*. Socioeconomic status is associated with frailty: the women's health and aging studies. *J Epidemiol Community Health* 2010;64:63–7.
24 Barnett K, Mercer SW, Norbury M, *et al*. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380:37–43.
25 Hanlon P, Nicholl BI, Jani BD, *et al*. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health* 2018;3:e323–32.
26 Fortin M, Stewart M, Poitras M-E, *et al*. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012;10:142–51.
27 O'Caoimh R, Galluzzo L, Rodríguez-Laso Ángel, *et al*. Prevalence of frailty at population level in European advantage joint action member states: a systematic review and meta-analysis. *Ann Ist Super Sanita* 2018;54:226–38.
28 Vetrano DL, Palmer K, Marengoni A, *et al*. Frailty and multimorbidity: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci* 2019;74:659–66.
29 Harrison C, Britt H, Miller G, *et al*. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open* 2014;4:e004694.
30 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg* 2014;12:1495–9.
31 Krokstad S, Langhammer A, Hveem K, *et al*. Cohort profile: the HUNT study, Norway. *Int J Epidemiol* 2013;42:968–77.
32 Langhammer A, Krokstad S, Romundstad P, *et al*. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med Res Methodol* 2012;12:143.
33 Norway S. *Standard classification of occupations*. Statistics Norway: Oslo/Kongsvinger, 1998.
34 International Labour Organization (ILO). The International Standard Classification of Occupations, ISCO-88 [Webpage], 1988. Available: https://www.ilo.org/public/english/bureau/stat/isco/isco88/index.htm
35 Rose D, Harrison E. The European socio-economic classification: a new social class schema for comparative European research. *European Societies* 2007;9:459–90.
36 Bjelland I, Dahl AA, Haug TT, *et al*. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res* 2002;52:69–77.
37 Sedgwick P. Relative risks versus odds ratios. *BMJ* 2014;348:g1407–g07.
38 Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in Stata. *Stata J* 2013;13:492–509.
39 Galobardes B, Shaw M, Lawlor DA, *et al*. Indicators of socioeconomic position (Part 1). *J Epidemiol Community Health* 2006;60:7–12.
40 Scanlan JP, Editorial G. Guest editorial. *CHANCE* 2006;19:47–51.
41 Willadsen TG, Bebe A, Køster-Rasmussen R, *et al*. The role of diseases, risk factors and symptoms in the definition of multimorbidity - a systematic review. *Scand J Prim Health Care* 2016;34:112–21.
42 Schuurmans H, Steverink N, Lindenberg S, *et al*. Old or frail: what tells us more? *J Gerontol A Biol Sci Med Sci* 2004;59:M962–5.
43 Theou O, O'Connell MDL, King-Kallimanis BL, *et al*. Measuring frailty using self-report and test-based health measures. *Age Ageing* 2015;44:471–7.
44 Braveman PA, Cubbin C, Egerter S, *et al*. Socioeconomic status in health research: one size does not fit all. *JAMA* 2005;294:2879–88.
45 Holmen J, Midthjell K, Ø K, *et al*. The Nord-Trøndelag health study 1995–97 (Hunt 2): objectives, contents, methods and participation. *Norsk epidemiologi* 2003;13:19–32.
46 Ncd risk factor collaboration (NCD-RisC). rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature* 2019;569:260–4.
47 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet* 2017;389:37–55.
48 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* 2017;390:2627–42.
49 Smith SM, Soubhi H, Fortin M, *et al*. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. *BMJ* 2012;345:e5205.
50 World Health Organization. Multimorbidity: Technical Series on Safer Primary Care. In: *Organization WH*. Geneva: World Health Organization, 2016: 4–5.
51 Marmot M, Goldblatt P, Allen J, *et al*. *Fair Society*. Healthy Lives: The Marmot Review, 2010.
52 Gill TM, Gahbauer EA, Allore HG, *et al*. Transitions between frailty states among community-living older persons. *Arch Intern Med* 2006;166:418–23.

Paper II

BMJ Open

Socioeconomic inequalities in the prevalence of complex multimorbidity in a Norwegian population: findings from the cross-sectional HUNT Study

Kristin Hestmann Vinjerui ,[1,2] Ottar Bjerkeset,[3,4] Johan H Bjorngaard,[3,5] Steinar Krokstad,[1,2] Kirsty A Douglas,[6] Erik R Sund[1,3,7]

To cite: Vinjerui KH, Bjerkeset O, Bjorngaard JH, *et al*. Socioeconomic inequalities in the prevalence of complex multimorbidity in a Norwegian population: findings from the cross-sectional HUNT Study. *BMJ Open* 2020;**10**:e036851. doi:10.1136/bmjopen-2020-036851

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-036851).

Received 07 January 2020
Revised 31 March 2020
Accepted 12 May 2020

For numbered affiliations see end of article.

Correspondence to
Dr Kristin Hestmann Vinjerui; kristin.vinjerui@ntnu.no

ABSTRACT

Objectives Multimorbidity, the co-occurrence of multiple long-term conditions, is common and increasing. Definitions and assessment methods vary, yielding differences in estimates of prevalence and multimorbidity severity. Sociodemographic characteristics are associated with complicating factors of multimorbidity. We aimed to investigate the prevalence of complex multimorbidity by sex and occupational groups throughout adulthood.

Design Cross-sectional study.

Setting The third total county survey of The Nord-Trøndelag Health Study (HUNT), 2006–2008, Norway.

Participants Individuals aged 25–100 years with classifiable occupational data and complete questionnaires and measurements.

Outcome measure Complex multimorbidity defined as ‘the co-occurrence of three or more chronic conditions affecting three or more different body (organ) systems within one person without defining an index chronic condition’.

Analysis Logistic regression models with age and occupational group were specified for each sex separately.

Results 38 027 of 41 193 adults (55% women) were included in our analyses. 54% of the participants were identified as having complex multimorbidity. Prevalence differences in percentage points (pp) of those in the low occupational group (vs the high occupational group (reference)) were 19 (95% CI, 16 to 21) pp in women and 10 (8 to 13) pp in men at 30 years; 12 (10 to 14) pp in women and 13 (11 to 15) pp in men at 55 years; and 2 (–1 to 4) pp in women and 7 (4 to 10) pp in men at 75 years.

Conclusion Complex multimorbidity is common from early adulthood, and social inequalities persist until 75 years in women and 90 years in men in the general population. These findings have policy implications for public health as well as healthcare, organisation, treatment, education and research, as complex multimorbidity breaks with the specialised, fragmented paradigm dominating medicine today.

Strengths and limitations of this study

- As a large, entire-county, general population health survey with a vast number of variables, the HUNT Study is ideal to estimate the prevalence of multimorbidity by self-reports and clinical measurements.
- Complex multimorbidity operationalised as three or more organ systems affected is relevant in both clinic and research, with high specificity into old age, implicating the need for coordinated multidisciplinary care and increasing comparability between studies.
- Socioeconomic position operationalised as occupations allocated in the European Socio-economic Classification scheme makes international comparison of gradients possible.
- Non-participants have lower socioeconomic position and higher mortality, thus the social gradients in prevalence of complex multimorbidity detected are likely conservative.
- The original data lacked information of chronicity of a majority of the conditions, which may lead to overestimation of complex multimorbidity.

INTRODUCTION

Multimorbidity, the co-occurrence of multiple long-term conditions in which none holds priority,[1] is common and increasing.[2 3] It challenges the individual s ability to self-manage[4 5] as well as clinical decision-making[5 7] due to complexity that conflicts with subspecialised medicine and clinical guidelines. Multimorbidity is associated with high healthcare utilisation in both primary and specialist care,[8] including emergency department visits.[9]

Multimorbidity is heterogeneous, and a mere count of conditions may not imply complexity,[1 5] requiring coordinated multidisciplinary care. In attempts to detect individuals with high needs, guidelines by and large are focused on combinations of conditions, such as concurrent mental and somatic conditions[5 10 11] or three or more conditions in separate organ systems,[5 12] and consequences thereof, such as polypharmacy[5 10 11] and requirements for assistance in daily living.[5 10 11] Individual factors that increase patient complexity include

sociodemographic characteristics,[13] social resources,[13] and health and social experiences.[13] Recent recommendations on multimorbidity care have taken into account social networks,[11] socioeconomic positions[11] and patient experiences, such as treatment burden.[10 11]

Research results from cross-sectional studies on multimorbidity prevalence have been difficult to compare because of differences in definitions, methods, and the number and types of conditions included.[14 15] Still, associations with lower socioeconomic position,[3 14 16] female sex[3 14 16] and increasing age[3 14 16] persist across studies. Further, defining multimorbidity as simultaneously having three or more conditions increases the specificity of the multimorbidity measure into older age groups,[12 15] and comparability between studies increases when multimorbidity is operationalised as multiple organ systems affected.[12]

Inequalities in health according to socioeconomic position are persistent,[17] even in comparatively egalitarian Nordic societies.[18] The association of socioeconomic differences with the occurrence of multimorbidity has been explored using multiple measures, such as education,[14 19] income,[19] occupation[3] and deprivation indexes.[14 16] In fact, any measure of socioeconomic position will detect health differences in descriptive studies, if differences exist.[20] Using an occupational classification may reflect specific work-related exposures in addition to general associations to income, material resources and social status.[20]

In sum, multimorbidity represents a challenge both for the individual and clinician, as well as for the coordination of healthcare. Previous multimorbidity prevalence research suggests that demographic and socioeconomic gradients operate. In Norway, multimorbidity prevalence and patterns have been partly explored.[21] Studies on complex multimorbidity is lacking, and no studies have investigated sociodemographic differences. Such data can strengthen healthcare planning and clinical management of multimorbidity, as well as guide public health interventions.

Our aim is to add to former knowledge by assessing the prevalence of complex multimorbidity, defined as three or more conditions in separate organ systems, by age, sex and occupational groups, in a general population health survey.

METHODS

Reporting statement

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cross-sectional reporting guidelines[22] were used for reporting this observational study.

Study population

The HUNT Study is a population-based health study for all adults 20 years and older living in Nord-Tr ndelag County, Norway. Four surveys have been completed since the 1980s, and cohort profiles and data collection procedures have been described in detail elsewhere.[23 24] This study is a secondary analysis of data from the HUNT3 Survey (2006 2008), where 93 860 citizens were invited to participate. In short, the survey consisted of a main questionnaire received with the invitation by email and handed in when attending a screening station, where participants were interviewed and clinical measurements and biological samples were taken. A second sex-specific and age-specific questionnaire was handed out at the screening station and returned by email.

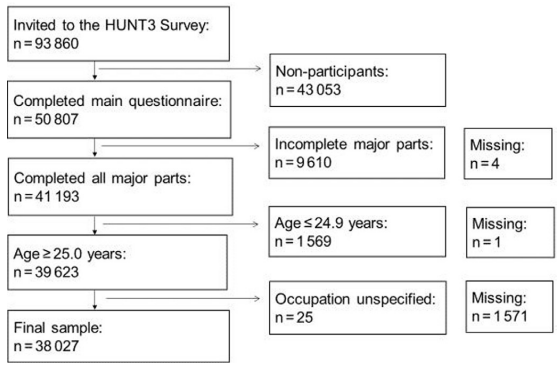


Figure 1 Flowchart for sample selection; inclusion and exclusion criteria and missing data.

A total of 50 807 individuals (54% of 93 860 invited) completed the main questionnaire, required to be considered an attendant of the HUNT3 Survey.[23] Sampling is described in figure 1. In this study, 41 193 of 50 807 participants (81%) had data on all major parts of the survey (both questionnaires, interview, measurements and samples) and were designated as respondents. Thus, 9610 were excluded due to incomplete participation, while 4 people missed complete participation data. Under the assumption that young adults may not have obtained their highest level of occupational class at the time of participation, 1569 participants younger than 25 years were excluded, as well as 1 person with missing age data. Occupation data were missing for 1571 respondents, and 25 people were excluded due to unspecified occupation data. Finally, 38 027 of 41 193 (92%) respondents were eligible for data analysis, 11 204 were non-eligible and 1576 had missing data.

Participation in the HUNT3 Survey varies with socioeconomic position, age and sex.[25] The distribution of occupational groups among the sample was 24% (high), 27% (middle) and 49% (low) and in non-eligible: 17% (high), 20% (middle), 52% (low) and 11% (missing). The average (SD) age in the sample was 55 (14) years, in the non-eligible group 44 (18) years and among missing 66 (18) years. Women constituted 55% (n=20 813 of 38 027) of the sample, 51% (n=5662 of 11 203) of the non-eligible and 81% of the missing (n=1281 of 1576).

Box 1 Conditions grouped by ICD-10 chapter

ICD-10 chapter / Conditions
II Neoplasms
Cancer
III Blood/blood-forming organs/immune mechanism
Sarcoidosis
IV Endocrine/nutritional/metabolic
Obesity
Hypercholesterolemia
Diabetes
Hypothyroidism
Hyperthyroidism
V Mental/behavioural
Alcohol problem
Depression
Anxiety
Insomnia
Nervous system
Epilepsy
Migraine
Chronic headache, other
VII Eye/adnexa
Cataract
Macula degeneration
Glaucoma
VIII Ear/mastoid
Hearing impairment
IX Circulatory system
Hypertension
Angina pectoris
Myocardial infarction
Heart failure
Other heart disease*
Stroke or brain haemorrhage*
X Respiratory system
Chronic bronchitis, emphysema or COPD*
Asthma
XI Digestive system
Dental health status
Gastro-oesophageal reflux disease
Irritable bowel syndrome
XII Skin/subcutaneous tissue
Hand eczema
Psoriasis
XIII Musculoskeletal/connective tissue
Rheumatoid arthritis
Osteoarthritis
Ankylosing spondylitis
Fibromyalgia
Osteoporosis
Local musculoskeletal pain/stiffness in:
Neck or upper back or lower back or
shoulder or elbow or hand or
hip or kne or foot/ankle
XIV Genitourinary system
Kidney disease
Urine incontinence
Prostate symptoms
Menopausal hot flashes
XVIII Symptoms/signs/abnormal clinical/laboratory findings
Nocturia
Chronic widespread pain.

*Exception to single entity
COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases,Tenth Revision.

Outcome variable

Complex multimorbidity was defined as the co-occurrence of three or more chronic conditions affecting three or more different body (organ) systems within one person without defining an index chronic condition , as suggested by previous research.[5 12]

All conditions possible to generate from the HUNT3 Survey data were included to meet recommendations on deriving the best estimate of prevalence of multimorbidity.[12] In total, 51 chronic conditions, defined singly as far as original data permitted, were constructed, and details are described in online supplementary appendix A. This list of 51 conditions is more comprehensive and homogeneous than previous operationalisations of multimorbidity in the HUNT3 Survey.[21]

Further, the conditions were grouped according to the International Classification of Diseases,Tenth Revision (ICD-10), in 13 organ-specific chapters and one chapter on symptoms, signs and abnormal clinical and laboratory findings (box 1), using general terms of the conditions in the Norwegian Directorate of eHealth online search engine[26] on 1 February 2017.

Chapters were counted once if affected by at least one chronic condition, and a summary score of the chapter variables was generated. In this study, complex multimorbidity was defined as having conditions in at least 3 of 14 chapters.

Sociodemographic characteristics

Occupation data from the HUNT3 Survey were free-text answers to the interview question, What is/was the title of your main occupation? Answers were manually categorised corresponding to Standard Classifications of Occupations by Statistics Norway,[27] which is based on the International Standard Classification of Occupations-88 (ISCO-88).[28] Socioeconomic position was allocated according to the simplified, 3-class version European Socio-economic Classification (ESeC) scheme.[29] The simplified scheme is based solely on occupational data, classified according to ISCO-88.[28] Details are provided in online supplementary appendix B. The intention of the full ESeC scheme is to measure qualitative distinctions between employment relationships and does not reflect a clear hierarchy.[29] However, income is considered more stable in the salariat class.[29] In the 3-class version, the salariat class consists of large employers, higher-grade and lower-grade professionals, administrative and managerial occupations, and higher-grade technician and

Table 1 Sex and age distribution by occupational group

	Occupational group			
	High	Middle	Low	Total
	Freq. (%)	Freq. (%)	Freq. (%)	Freq. (%)
Total	8.970 (100)	10.243 (100)	18.814 (100)	38.027 (100)
Sex				
Women	4.505 (50)	5.386 (53)	10.922 (58)	20.813 (55)
Men	4.465 (50)	4.857 (47)	7.892 (42)	17.214 (45)
Age, years				
25–44	2.837 (32)	2.600 (25)	4.487 (24)	9.924 (26)
45–64	4.468 (50)	4.787 (47)	8.951 (48)	18.206 (48)
65–74	1.118 (12)	1.846 (18)	3.297 (18)	6.261 (16)
75–100	547 (6)	1.010 (10)	2.079 (11)	3.636 (10)

Freq., Frequency.

supervisory occupations. The intermediate class contains small employers, self-employed individuals, and lower-grade supervisory and technician occupations. The working class represents lower-grade service positions, sales and clerical occupations, and lower-grade technical and routine occupations. For practical reasons in this study, the terms high, middle and low occupational group replaced the terms salariat, intermediate and working class, respectively.

In addition, continuous age and categorical sex data, provided by the HUNT Databank, were used in the analyses.

Statistical analysis

Cross-tables were used to present sociodemographic characteristics of the sample by occupational group (table 1) and by complex multimorbidity, stratified by sex (table 2).

Associations between occupational group and complex multimorbidity were analysed using logistic regression. The final models were stratified by sex, included occupational group, continuous age and an interaction term between occupational group and age. Choice of models was guided by likelihood ratio tests.

Since complex multimorbidity was highly prevalent, ORs would deviate from relative risks[30] and be challenging to interpret. Thus, we used the estimates from the logistic regression models to derive prevalence differences, the difference in mean predicted probability,[31] and prevalence ratios, the ratio between the mean predicted probabilities,[31] between occupational groups, while holding other covariates constant. The high occupational group

Table 2 Sociodemographic distribution of complex multimorbidity

	Complex multimorbidity					
	Women			Men		
	No, n (%)	Yes, n (%)	Total, n (%)	No, n (%)	Yes, n (%)	Total, n (%)
Total	8.505 (41)	12.308 (59)	20.813 (100)	9.137 (53)	8.077 (47)	17.214 (100)
Occupational group						
High	2.460 (55)	2.045 (45)	4.505 (100)	2.712 (61)	1.753 (39)	4.465 (100)
Middle	2.384 (44)	3.002 (56)	5.386 (100)	2.525 (52)	2.332 (48)	4.857 (100)
Low	3.661 (34)	7.261 (66)	10.922 (100)	3.900 (49)	3.992 (51)	7.892 (100)
Age, years						
25–44	3.859 (65)	2.122 (35)	5.981 (100)	2.958 (75)	985 (25)	3.943 (100)
45–64	3.668 (37)	6.172 (63)	9.840 (100)	4.621 (55)	3.745 (45)	8.366 (100)
65–74	721 (23)	2.447 (77)	3.168 (100)	1.155 (37)	1.938 (63)	3.093 (100)
75–100	257 (14)	1.567 (86)	1.824 (100)	403 (22)	1.409 (78)	1.812 (100)
Mean (SD)	48 (13)	59.(14)	54 (14)	52 (13)	62 (13)	56 (14)

Table 3 Prevalence ratios (PRs) and prevalence differences (PDs) with 95% CIs in complex multimorbidity between occupational groups, stratified by sex

Age, years	Occupational group	Women		Men	
		PR (95% CI)	PD (95% CI)	PR (95% CI)	PD (95% CI)
30	High	1.00 (ref.)	0.00 (ref.)	1.00 (ref.)	0.00 (ref.)
	Middle	1.47 (1.28 to 1.68)	0.08 (0.05 to 0.11)	1.28 (1.05 to 1.55)	0.03 (0.01 to 0.06)
	Low	2.06 (1.84 to 2.32)	0.19 (0.16 to 0.21)	1.92 (1.63 to 2.26)	0.10 (0.08 to 0.13)
55	High	1.00 (ref.)	0.00 (ref.)	1.00 (ref.)	0.00 (ref.)
	Middle	1.08 (1.03 to 1.12)	0.04 (0.02 to 0.06)	1.16 (1.10 to 1.23)	0.06 (0.04 to 0.08)
	Low	1.22 (1.18 to 1.26)	0.12 (0.10 to 0.14)	1.35 (1.28 to 1.41)	0.13 (0.11 to 0.15)
75	High	1.00 (ref.)	0.00 (ref.)	1.00 (ref.)	0.00 (ref.)
	Middle	0.98 (0.95 to 1.02)	−0.01 (−0.04 to 0.02)	1.07 (1.02 to 1.12)	0.05 (0.02 to 0.08)
	Low	1.02 (0.99 to 1.05)	0.02 (−0.01 to 0.04)	1.10 (1.06 to 1.15)	0.07 (0.04 to 0.10)
90	High	1.00 (ref.)	0.00 (ref.)	1.00 (ref.)	0.00 (ref.)
	Middle	0.98 (0.96 to 1.00)	−0.02 (−0.04 to 0.00)	1.03 (0.99 to 1.07)	0.03 (−0.01 to 0.06)
	Low	0.99 (0.97 to 1.01)	−0.01 (−0.03 to 0.01)	1.03 (0.99 to 1.07)	0.02 (−0.01 to 0.05)

was chosen as the reference group. Prevalence differences and prevalence ratios were calculated in 5-year intervals from 25 to 100 years, with 95% CIs (online supplementary appendix C). Results for the ages 30, 55, 75 and 90 years are presented in table 3 to represent adult, middle aged, aged and oldest old in the sample.

To visualise the differential association between age and complex multimorbidity in each occupational group, we specified separate models using restricted cubic splines and graphed the findings from each model into a common plot for each sex.

Sensitivity analysis was performed to investigate if the number and types of conditions showed a similar pattern with respect to the overall prevalence as well as differences between occupational groups (online supplementary appendix D). The alternative complex multimorbidity measure was derived from data in the main questionnaire only (22 conditions, grouped in 12 ICD-10 chapters).

Complete case analysis was performed, and StataIC 15.1 was used to analyse the data (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Patient and public involvement

There was a broad participant, patient and stakeholder involvement during the planning of the HUNT3 Survey. Data collection was performed in 2006 2008. Complex multimorbidity is a universal subject, not represented by any particular patient group, and thus no patient or public representative was involved in the design of this secondary analysis study.

RESULTS

Thirty-eight thousand twenty-seven individuals, aged 25 100 years, 55% women (n=20 813), who had completed all major parts of the HUNT3 Survey and had a classifiable occupation comprised the eligible sample, as figure 1 depicts. table 1 presents further sociodemographic characteristics.

Nearly half the sample (49%; n=18 814 of 38 027; of which 58% were women, n=10 922) was allocated in the low occupational group. In absolute numbers, the low occupational group was the largest socioeconomic category in both sexes and all age groups. The proportion of individuals aged 25 44 years decreased from 32% in the high occupational group (n=2837) to 24% in the low occupational group (n=4487), while the proportion of individuals aged 75 to 100 years increased from 6% (n=547) to 11% (n=2079). Participants aged 45 to 64 years were the largest age group in total and in all occupational groups (high, n=4468; middle, n=4787; low, n=8951).

Overall, a majority (54%; n=20 385 of 38 027) of the sample met the criteria for having complex multimorbidity, including 59% of women (n=12 308) and 47% of men (n=8077; table 2). The percentages increased from high to low occupational group in women from 45% (n=2045) to 66% (n=7261) and in men from 39% (n=1753) to 51% (n=3992). The proportions further increased by age, from 35% (n=2122) of women aged 25 to 44 years to 86% (n=1567) of women aged 75 to 100 years. In men, the increase was from 25% (n=985) to 78% (n=1409) in the same age groups. In absolute numbers, most people classified as having complex multimorbidity were aged 45 to 64 years (women, n=6172; men, n=3745).

Table 3 shows prevalence ratios and prevalence differences between the occupational groups after adjusting for age and occupation age interaction and thus presented at ages 30, 55, 75 and 90 years. Prevalence differences for complex multimorbidity between high and low occupational groups varied; at 30 years, 19 (16 to 21) percentage points (pp) in women and 10 (8 to 13) pp in men; at 55 years, 12 (10 to 14) pp in women and 13 (11 to 15) pp in

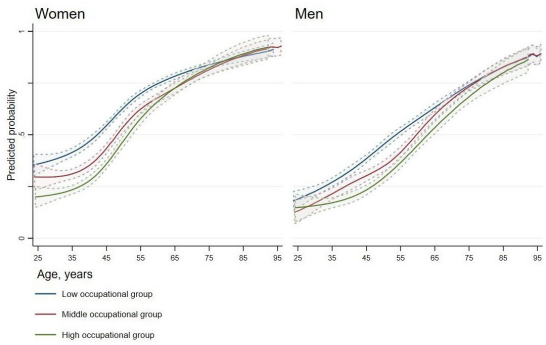


Figure 2 Estimated prevalence of complex multimorbidity with 95% CIs by age and occupational group for women and men.

men; at 75 years, 2 (−1 to 4) pp in women and 7 (4 to 10) pp in men; and at 90 years, −1 (−3 to 1) pp in women and 2 (−1 to 5) in men. Compared with the high occupational group, the prevalence ratios for the low occupational group for complex multimorbidity were at 30 years, 2.06 (1.84 to 2.32) in women and 1.92 (1.63 to 2.26) in men; at 55 years, 1.22 (1.18 to 1.26) in women and 1.35 (1.28 to 1.41) in men; at 75 years, 1.02 (0.99 to 1.05) in women and 1.10 (1.06 to 1.15) in men; and at 90 years, 0.99 (0.97 to 1.01) in women and 1.03 (0.99 to 1.07) in men.

In the sensitivity analyses where the complex multimorbidity measure was derived from fewer conditions (22 vs 51) and ICD-10 chapters (12 vs 14), the total prevalence was 15% (n=5836 of 38 027, online supplementary appendix D). Proportions were greater in women, higher age and the low occupational group. Compared with the results from the main analysis, prevalence differences between high and low occupational groups were smaller in women at all ages and in men at age 30 years and 55 years, while prevalence ratios were greater in men at all ages and in women aged 30 and 55 years.

Figure 2 depicts estimated prevalence of complex multimorbidity by occupational group and sex in individuals aged 25 to 100 years. In all occupational groups in both sexes, the predicted prevalence increased with age throughout the age span. Further, estimated prevalence differed between the occupational groups in women until age 75 years and in men until age 90 years. Women had a consistently higher prevalence for complex multimorbidity than men.

DISCUSSION

Main results

More than half (54%) of this total county adult population sample were identified with complex multimorbidity, measured as occurrence of chronic conditions in minimum three separate organ systems. Prevalence of complex multimorbidity was common from early adulthood, increased with age and was higher in women and in the low occupational group. Occupational group prevalence differences and ratios in complex multimorbidity were diminishing in women, while still present in men, at age 75 years.

Comparison with existing literature

Few, if any, studies (to our knowledge) have investigated the prevalence and determinants of complex multimorbidity in a general population. The findings are in keeping with known determinants of lower social position, female sex and higher age for multimorbidity in both general population[19] and primary care studies.[3 14 16] An Australian study using a comparable operationalisation of complex multimorbidity identified nearly 25% of patients in general practice with complex multimorbidity and estimated a national prevalence of 17%.[32] However, higher prevalence findings from our predominantly self-reported data are compatible with studies comparing prevalence estimates from self-reports and health record data.[33 34] In absolute numbers, the incidence of individuals identified with the stricter measure of complex multimorbidity is still highest among the group younger than 64 years, as has been shown for multimorbidity.[16 19 35] The sensitivity analysis confirms how number and types of conditions influence prevalence[12 15] and effect estimates of age, sex and socioeconomic position.[36]

Mechanisms to explain findings

The association between lower socioeconomic position and poor health is well established. In general, unequal distribution of income, power and wealth is understood to be socially determined fundamental causes that impact conditions of everyday life and result in social health inequalities.[17] In Nordic countries assumed to be egalitarian and offering universal healthcare, social health inequalities still exist.[18] Theories put forward are the survival of individuals with greater frailty, who are more likely to obtain a lower social position.[37] The gap in health is also explained by overall morbidity and mortality decreasing faster among the higher than the lower socioeconomic groups.[37]

In this study, occupational group serves as the proxy variable for socioeconomic position. Occupation may affect health outcomes through universal and specific mechanisms. In general, the higher occupational groups will have more secure and higher income,[29 38] as well as advantageous social networks.[38] In particular, jobs vary in psychosocial factors, such as stress, control and autonomy and biological factors, such as physical demands or harmful and hazardous work environments.[38] Overall, the higher occupational groups have greater autonomy and control,[29] while lower occupational groups are more exposed to malign work factors.[17] Generations may have different associations between a profession and health outcomes,[38] as occupations, tasks and exposures shift over time.

The bidirectional relationship between health and occupation[20] may partly explain the larger prevalence differences and ratios between low and high occupational

groups in the younger age categories. Higher rates of multimorbidity in young individuals in lower socioeconomic positions may also be explained by detection bias[35] in which the initiation of therapy and healthcare follow-up increase the likelihood of diagnosing more conditions. Diminishing occupational ratios and differences among the oldest may be explained by the higher overall prevalence of complex multimorbidity[39] and also survival bias, whereby the individuals with greatest fragility have already died. While probability of complex multimorbidity increases with age, the age distribution results in a higher number of cases occurring in those younger than 64 years.

Strengths and limitations

Strength of this study is the estimation of prevalence of complex multimorbidity from a general population survey, the most common study design in multimorbidity studies.[40] A vast number of self-reported conditions are included, almost exclusively diagnoses and symptoms.[40] Self-report is considered a valid approach when studying large samples.[15] Furthermore, using all available data will produce the most proper prevalence estimates,[12] which in this study is demonstrated by the sensitivity analysis and which seems necessary to detect occupational differences in younger age groups. The sensitivity analyses confirm that the spectrum of conditions included may affect associations with socioeconomic position, age and sex.[36]

Our operationalisation of complex multimorbidity makes the prevalence estimates comparable with other studies categorising conditions by any organ-based system.[12] The occurrence of conditions in separate organ, and number of organ systems, could have been explored as a continuous measure with assumed increasing severity; however, this was beyond the scope of this study.

The allocation of occupations in the ESeC also makes international comparison of social gradients possible.[29] We presented absolute and relative differences in compliance with recommendations on measurements of socioeconomic inequalities in health.[41] Results are further stratified by age and sex, which are stated as minimum requirements for proper reporting of multimorbidity.[14]

A number of limitations should be noted. Our study is based on data collected for a general health survey, and this limits data on conditions included in the complex multimorbidity measure. In particular, we did not have explicit information on chronicity for a majority of the conditions. Thus, the prevalence of complex multimorbidity may be overestimated.

Socioeconomic position was explored using only occupation, and while social health inequalities will be detected,[20] socioeconomic measures are not interchangeable.[20 42] Different measures of socioeconomic position will act through varying mechanisms and may associate distinctively with health outcomes.[20 42] Participants in the HUNT3 Survey reported their main occupation, while current or longest lasting occupation is more often studied.[38] Younger subjects may be misclassified in lower socioeconomic position, which may underestimate the occupational differences in health in this age group, whereas reverse causation, whereby prior health status determines job opportunities, is unavoidable and will increase detected differences. This study excludes those never having worked, which will underestimate social gradients in complex comorbidity.[43] Further, individuals with data missing due to unclassifiable occupation, a circumstance more common in elderly women than other participants, were excluded. Occupational data may misrepresent present social context[38] and thereby underestimate social inequalities. It would have been favourable if the study had included education, income or household indicators for socioeconomic position.

Participation in the HUNT3 Survey varied by age, sex, socioeconomic position and pattern of morbidity.[25] This may weaken the effect estimates of the determinants to complex multimorbidity. A healthy elders bias is likely, since participation required attendance at a screening station.[23] Overall, prevalence of individual conditions has shown only slight differences between participants and non-participants.[25] The HUNT Study is considered fairly representative for Norway,[24] and the health development in the material follows western high-income country trends closely.[44 46]

Implications for clinical practice and policy makers

Our study confirms that complex multimorbidity, a suggested measure to identify multimorbid individuals with high need for coordinated multidisciplinary care,[12] is highly prevalent in the general population, where social differences are evident from young to old adulthood. This is in line with international studies, and at policy level, an emphasis on public health intervention to prevent complex multimorbidity and social differences seems necessary. As proposed elsewhere, this will likely require a proportionate universalism life-cycle approach.[47] To improve and secure healthcare for this large patient group, clinical guidelines and the organisation of healthcare are suggested to adapt to a person-centred, generalist approach.[5 10 48]

Future research

Complex multimorbidity is common in this general population sample, with a clear social gradient throughout adulthood. Careful interpretation is necessary, since there are possible biases in measures of multimorbidity and occupation. However, the HUNT3 Survey data cover a broad spectrum of conditions and give a unique opportunity to create several measures of multimorbidity in the same sample, with directly comparable prevalence estimates and gradients. On this background, we recommend exploring alternative measures suggested to detect individuals with high needs and multimorbidity and investigate differences in patterns and consequences of such measures by social health determinants. Since multimorbidity is the norm and represents a large challenge to healthcare across levels, research on overall healthcare

utilisation and organisation should be a priority, as well as studying competing measures as prognostic factors for mortality. Studies on social differences in the use of healthcare may identify vulnerable subgroups, where any specific organisation of treatment later on could be evaluated.

CONCLUSION

Complex multimorbidity, defined as occurrence of chronic conditions in three separate organ systems, is common, and occupational differences exist throughout adulthood in both sexes. The magnitude of complex multimorbidity in all age groups implies the need for public health management to universally improve, targeted proportionate to need and disadvantage in subpopulations, social health determinants throughout the lifespan. Complex multimorbidity, indicating the accumulation of conditions of different aetiology requiring coordinated multidisciplinary care, should inspire health caregivers, healthcare organisations, educational institutions and researchers to take on a generalist and person-centred focus. Studying alternative multimorbidity measures, including healthcare utilisation and mortality according to social background, as well as multimorbidity management, should be prioritised in future research.

Author affiliations
[1]HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Science, Norwegian University of Science and Technology, Levanger, Tr□ndelag, Norway
[2]Psychiatric Department, Levanger Hospital, Nord-Tr□ndelag Hospital Trust, Levanger, Tr□ndelag, Norway
[3]Faculty of Nursing and Health Sciences, Nord Universitet - Levanger Campus, Levanger, Norway
[4]Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Tr□ndelag, Norway
[5]Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Tr□ndelag, Norway
[6]Academic Unit of General Practice, Australian National University Medical School, Australian National University, Canberra, Australian Capital Territory, Australia
[7]Levanger Hospital, Nord-Tr□ndelag Hospital Trust, Levanger, Tr□ndelag, Norway

Twitter Kristin Hestmann Vinjerui @KHVinjerui and Steinar Krokstad @steinak

Acknowledgements L Getz, J Sigurdsson and C Harrison for through discussions on measures of multimorbidity. E Solheim for guidance in the use of the European Socio-economic Classification scheme.MS Newman for writing assistance. The Nord-Tr□ndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Nord-Tr□ndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.)

Contributors KHV, ERS, SK and JHB conceptualised the study and KHV, ERS, SK, JHB, OB and KAD contributed to its design. KHV has analysed the data under supervision of ERS, and KHV, ERS, SK, JHB, OB and KAD have contributed to interpreting the data. KHV wrote the original draft, which has been revised critically by ERS, SK, JHB, OB and KAD. KHV, ERS, SK, JHB, OB and KAD have read and approved the final version of the manuscript to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study was funded by the Faculty of Medicine and Health Science at the Norwegian University of Science and Technology (NTNU) through the PhD program in Behavior and Health (KHV). NTNU has partly funded the HUNT3 Survey and have funded open access for this article. The Liaison Committee for Education, Research and Innovation in Central Norway (17/38297) supported a research stay at the Australian National University, Canberra. The funding sources have had no role in conceptualisation this study, its design and methods, analysis and interpretation of data, writing of the article or the decision to submit the article for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The Regional Committee for Medical and Health Research Ethics in Norway approved the current study (project no. 2014/2265).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. To protect participants□privacy, HUNT Research Centre aims to limit storage of data outside HUNT Databank and cannot deposit data in open repositories. HUNT Databank has precise information on all data exported to different projects and are able to reproduce these on request. There are no restrictions regarding data export given approval of applications to HUNT Research Centre. For more information see: http://www.ntnu.edu/hunt/data.

ORCID iD
Kristin Hestmann Vinjerui http://orcid.org/0000-0003-1828-6943

REFERENCES

1 Nicholson K, Makovski TT, Griffith LE, *et al*. Multimorbidity and comorbidity revisited: Refining the concepts for international health research. *J Clin Epidemiol* 2019;105:142□6.
2 van Oostrom SH, Gijsen R, Stirbu I, *et al*. Time trends in prevalence of chronic diseases and multimorbidity not only due to aging: data from general practices and health surveys. *PLoS One* 2016;11:e0160264.
3 Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008;14:28□32.
4 Coventry PA, Fisher L, Kenning C, *et al*. Capacity, responsibility, and motivation: a critical qualitative evaluation of patient and practitioner views about barriers to self-management in people with multimorbidity. *BMC Health Serv Res* 2014;14:536.
5 Wallace E, Salisbury C, Guthrie B, *et al*. Managing patients with multimorbidity in primary care. *BMJ* 2015;350:h176.
6 S□ndergaard E, Willadsen TG, Guassora AD, *et al*. Problems and challenges in relation to the treatment of patients with multimorbidity: general practitioners' views and attitudes. *Scand J Prim Health Care* 2015;33:121□6.
7 Guthrie B, Payne K, Alderson P, *et al*. Adapting clinical guidelines to take account of multimorbidity. *BMJ* 2012;345:e6341.
8 Glynn LG, Valderas JM, Healy P, *et al*. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Fam Pract* 2011;28:516□23.
9 Agborsangaya CB, Lau D, Lahtinen M, *et al*. Health-Related quality of life and healthcare utilization in multimorbidity: results of a cross-sectional survey. *Qual Life Res* 2013;22:791□9.
10 National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management. NICE guideline [NG56]. National Institute for Health and Care Excellence, 2016. Available: https://www.nice.org.uk/guidance/ng56
11 Palmer K, Marengoni A, Forjaz MJ, *et al*. Multimorbidity care model: recommendations from the consensus meeting of the joint action on chronic diseases and promoting healthy ageing across the life cycle (JA-CHRODIS). *Health Policy* 2018;122:4□11.
12 Harrison C, Britt H, Miller G, *et al*. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open* 2014;4:e004694.
13 Schaink AK, Kuluski K, Lyons RF, *et al*. A scoping review and thematic classification of patient complexity: offering a unifying framework. *J Comorb* 2012;2:1□9.

14 Violan C, Foguet-Boreu Q, Flores-Mateo G, *et al*. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One* 2014;9:e102149.
15 Fortin M, Stewart M, Poitras M-E, *et al*. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012;10:142–51.
16 Barnett K, Mercer SW, Norbury M, *et al*. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380:37–43.
17 Commission on Social Determinants of Health, In Marmot M, ed. *Closing the gap in a generation: health equity through action on the social determinants of health: final report of the Commission on social determinants of health*. Geneva, 2008: 256.
18 Mackenbach JP, Stirbu I, Roskam A-JR, *et al*. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 2008;358:2468–81.
19 Agborsangaya CB, Lau D, Lahtinen M, *et al*. Multimorbidity prevalence and patterns across socioeconomic determinants: a cross-sectional survey. *BMC Public Health* 2012;12:201.
20 Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull* 2007;81:21–37.
21 Tomasdottir MO, Getz L, Sigurdsson JA, *et al*. Co- and multimorbidity patterns in an unselected Norwegian population: cross-sectional analysis based on the HUNT study and theoretical reflections concerning basic medical models. *Eur J Pers Cent Healthc* 2014;2:335–45.
22 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg* 2014;12:1495–9.
23 Krokstad S, Langhammer A, Hveem K, *et al*. Cohort profile: the HUNT study, Norway. *Int J Epidemiol* 2013;42:968–77.
24 Holmen J, Midthjell K, Ø K, *et al*. The Nord-Trøndelag health study 1995–97 (Hunt 2): objectives, contents, methods and participation. *Norsk epidemiologi* 2003;13:19–32.
25 Langhammer A, Krokstad S, Romundstad P, *et al*. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med Res Methodol* 2012;12:143.
26 Direktoratet for e-helse. FinnKode - Helsedirektoratet medisinske kodeverk, 2017. Available: https://finnkode.ehelse.no/#icd10/0/0/0/-1
27 Norway S. *Standard classification of occupations*. Statistics Norway: Oslo/Kongsvinger, 1998.
28 International Labour Organization (ILO). The International Standard Classification of Occupations, ISCO-88 [Webpage], 1988. Available: https://www.ilo.org/public/english/bureau/stat/isco/isco88/index.htm [Accessed 18 Sep 2004].
29 Rose D, Harrison E. The European socio-economic classification: a new social class schema for comparative European research. *Eur Soc* 2007;9:459–90.
30 Sedgwick P. Relative risks versus odds ratios. *BMJ* 2014;348:g1407–g.
31 Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in Stata. *Stata J* 2013;13:492–509.
32 Harrison C, Henderson J, Miller G, *et al*. The prevalence of complex multimorbidity in Australia. *Aust N Z J Public Health* 2016;40:239–44.
33 Cricelli C, Mazzaglia G, Samani F, *et al*. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Public Health Med* 2003;25:254–7.
34 Fortin M, Haggerty J, Sanche S, *et al*. Self-Reported versus health administrative data: implications for assessing chronic illness burden in populations. A cross-sectional study. *CMAJ Open* 2017;5:E729–33.
35 van den Akker M, Buntinx F, Metsemakers JF, *et al*. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol* 1998;51:367–75.
36 Schäfer I, Hansen H, Schön G, *et al*. The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. first results from the multicare cohort study. *BMC Health Serv Res* 2012;12:89.
37 Huijts T, Eikemo TA. Causality, social selectivity or artefacts? why socioeconomic inequalities in health are not smallest in the Nordic countries. *Eur J Public Health* 2009;19:452–3.
38 Galobardes B, Shaw M, Lawlor DA, *et al*. Indicators of socioeconomic position (Part 1). *J Epidemiol Community Health* 2006;60:7–12.
39 Scanlan JP, Editorial G. Guest editorial. *CHANCE* 2006;19:47–51.
40 Willadsen TG, Bebe A, Køster-Rasmussen R, *et al*. The role of diseases, risk factors and symptoms in the definition of multimorbidity - a systematic review. *Scand J Prim Health Care* 2016;34:112–21.
41 Mackenbach JP, Kunst AE. Measuring the magnitude of socio-economic inequalities in health: an overview of available measures illustrated with two examples from Europe. *Soc Sci Med* 1997;44:757–71.
42 Braveman PA, Cubbin C, Egerter S, *et al*. Socioeconomic status in health research: one size does not fit all. *JAMA* 2005;294:2879–88.
43 Martikainen P, Valkonen T. Bias related to the exclusion of the economically inactive in studies on social class differences in mortality. *Int J Epidemiol* 1999;28:899–904.
44 NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature* 2019;569:260–4.
45 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet* 2017;389:37–55.
46 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* 2017;390:2627–42.
47 Marmot M, Goldblatt P, Allen J, *et al*. Fair Society, healthy lives: the Marmot review 2010:242.
48 World Health Organization. *Multimorbidity: technical series on safer primary care*. Geneva: World Health Organization, 2016: 4–5.

Paper III

Journal of
Clinical Medicine

MDPI

Article

Socioeconomic Position, Multimorbidity and Mortality in a Population Cohort: The HUNT Study

Kristin Hestmann Vinjerui [1,2,3,*], Johan H. Bjorngaard [4,5], Steinar Krokstad [1,3], Kirsty A. Douglas [2] and Erik R. Sund [1,4,6]

1 HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU–Norwegian University of Science and Technology, 7600 Levanger, Norway; steinar.krokstad@ntnu.no (S.K.); erik.r.sund@ntnu.no (E.R.S.)
2 Academic Unit of General Practice, Australian National University Medical School, the Australian National University, Canberra 2600, Australian Capital Territory, Australia; kirsty.a.douglas@anu.edu.au
3 Psychiatric Department, Levanger Hospital, Nord-Trøndelag Hospital Trust, 7601 Levanger, Norway
4 Faculty of Nursing and Health Sciences, Nord University–Levanger Campus, 7601 Levanger, Norway; johan.h.bjorngaard@ntnu.no
5 Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU–Norwegian University of Science and Technology, 7491 Trondheim, Norway
6 Levanger Hospital, Nord-Trøndelag Hospital Trust, 7601 Levanger, Norway
* Correspondence: Kristin.vinjerui@ntnu.no; Tel.: +47-90173201 or +47-74019240 or +47-74075180

Received: 18 July 2020; Accepted: 20 August 2020; Published: 26 August 2020

Abstract: Multimorbidity and socioeconomic position are independently associated with mortality. We investigated the association of occupational position and several multimorbidity measures with all-cause mortality. A cohort of people aged 35 to 75 years who participated in the Trøndelag Health Study in 2006–2008 and had occupational data was linked to the Norwegian National Population Registry for all-cause mortality from study entry until 1 February 2019. Logistic regression models for each occupational group were used to analyze associations between the number of conditions and 10-year risk of death. Cox regression models were used to examine associations between combinations of multimorbidity, occupational position, and mortality. Analyses were conducted for men and women. Included were 31,132 adults (16,950 women (54.4%)); occupational groups: high, 7501 (24.1%); low, 15,261 (49.0%)). Increased mortality was associated with lower occupational group, more chronic conditions, and all multimorbidity measures. The joint impact of occupational group and multimorbidity on mortality was greater in men than women. All multimorbidity measures are strongly associated with mortality, with varying occupational gradients. Social differences in multimorbidity are a public health challenge and necessitate consideration in health care. Men in lower occupational groups seem to be a particularly vulnerable group.

Keywords: multimorbidity; frailty; socioeconomic status; mortality; occupations; public health; health inequality; The HUNT Study

1. Introduction

The burdens of disease and death are greater for people in lower socioeconomic positions worldwide [1]. Multimorbidity, the concurrence of multiple chronic conditions [2], is highly prevalent [3,4], while health inequalities are most often studied in association with individual diseases.

Multimorbidity may co-occur with frailty [5,6], which is a dynamic, multidimensional symptom complex of accumulated decline in homeostatic reserves that results in increased vulnerability [4]. Both concepts are proxy measures of biological aging [7].

Numerous operational definitions and differences in methods and settings hamper the comparability of research on multimorbidity [8–10] and frailty [6,11]. Still, in cross-sectional studies, acknowledged common determinants associated with multimorbidity and frailty are socioeconomic deprivation [8,12], female sex [8,13], and higher age [8,13]. In Norway, previous studies on complex measures of multimorbidity, including frailty, reproduced increased prevalence in people in lower occupational groups, women, and older adults [14,15]. While the prevalence of multimorbidity and frailty rise with higher age, those younger than 65 years encompass a larger number of individuals with multimorbidity and frailty [15–18].

A review of 26 cohort studies in populations older than 65 years established that, despite heterogeneity, any multimorbidity increases mortality [19]. Only five studies adjusted for sociodemographic variables which reduced the effect estimates of multimorbidity on mortality [19]. It was not possible to pool the existing data with regards to sex differences [19]. Multimorbidity measured as three or more long-term conditions increases specificity in older age [9,20]. Furthermore, requiring these multiple conditions to be present in separate body systems identifies multimorbidity that is likely to require care from several specialists, which has been termed complex multimorbidity [20]. Such complex multimorbidity presented a moderate relationship with mortality, adjusted for sociodemographic characteristics, in a study on individuals aged 60 to 69 years in Norway [21].

While various frailty measures identify distinct subgroups, all are associated with mortality [22]. Frailty consistently increased mortality risk when adjusted for multimorbidity and socioeconomic position in a population cohort aged 37 to 73 years [18]. Joint multimorbidity and frailty increased the mortality risk in older adults, while the separate measures did not [23]. Adjustment by socioeconomic position did not modify this relationship [23].

The relation of socioeconomic position with health outcomes vary by measure because each act through distinct mechanisms [24,25]. Modification of multimorbidity's association with mortality has been explored by education [26,27], occupation [27], and deprivation indices [28,29]. Occupation is a comprehensive measure, reflecting income, material resources, and networks, as well as specific outcomes of biopsychosocial exposure on the job [25].

There are few studies examining the joint outcome of socioeconomic position and multimorbidity on mortality [26–29]. The studies vary in exploring one measure [27,28] or several measures [26,29] of multimorbidity and 1 measure [26,28,29] or several measures [27] of socioeconomic position throughout adulthood [26,28] or in restricted age groups [27,29] with a follow-up time ranging from 4 years [26] to 24 years [27]. Overall, they find multimorbidity is more common in those with social deprivations [26,28,29], while the association with subsequent mortality varies in presence [28,29] or absence [26,27] of sex differences and is reported as stable [29], reduced [26], and nonexistent [27] across socioeconomic strata.

In summary, multimorbidity and frailty share determinants, and like socioeconomic position, they are associated with mortality. There is a research gap in exploring the impact of multimorbidity, and possible pooled effect of multimorbidity and frailty [7] on mortality in various social strata and younger age groups [10].

Our aim was to explore how occupational position may modify the relationship between several measures of multimorbidity, including multimorbidity with frailty, and mortality in the general population. The study is conducted in a Nordic welfare state and results can be contrasted with similar studies conducted in a different welfare regime type model [30]. We report absolute and relative differences in all-cause mortality by occupational groups and sex and compare the prognostic value of different multimorbidity measures. We hypothesize that socioeconomic position will interact with all measures of multimorbidity and individuals in lower occupational groups will have worse prognoses.

2. Materials & Methods

2.1. Study Population and Sample

The Trøndelag Health Study (HUNT) is an ongoing population-based health study that invites all citizens of Trøndelag County, Norway, 20 years and older to participate. The current study used baseline data from the HUNT Study 2006–2008 (HUNT3), which invited a total of 93,860 individuals to participate. We report in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies [31]. Details on cohort profiles and data collection procedures have been published previously [32,33]. In short, participants were defined as responders to the main questionnaire, which was sent with the invitation by mail. Overall, 50,807 of 93,860 individuals (54.1%) participated in HUNT3 [32].

To be eligible for analysis in this cohort study, participants had to complete all major parts of HUNT3 (the main questionnaire, attend a screening station for interview, clinical measurements, and blood samples and return by mail a second questionnaire specific to age group and sex). Finally, classifiable occupational data, in addition to registry data (age, sex, and mortality status), were required. Figure 1 presents a flowchart for the sample selection. Individuals younger than 35 years were excluded upon expected low statistical power and to minimize the risk of misclassification by occupational group. Participants 75 years or older were omitted to minimize the effect of older adults in good health causing underestimation of occupational group differences in the association of multimorbidity with mortality.

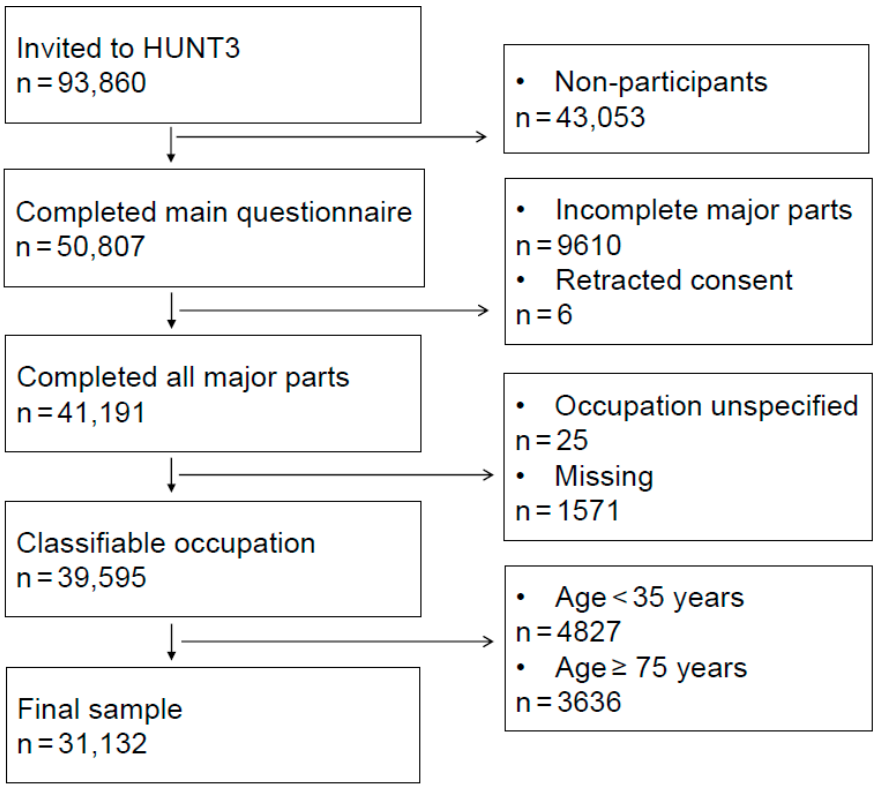


Figure 1. Flowchart for sample selection.

2.2. Outcome Variable

All-Cause Mortality

The Norwegian National Population Registry administers all-cause mortality, from which the HUNT Databank regularly obtains registry status describing individuals in its cohort as being alive, having emigrated out of the country, or being dead. The registry data are linked on an individual level and there is no loss to follow-up. The last update from the National Population Registry and end of follow-up was 1 February 2019.

2.3. Independent Variables

Multimorbidity

We previously generated a set of 51 individual, chronic conditions from HUNT3 data [14,15] and further allocated those to body systems [14] by use of 14 chapters in the International Statistical Classification of Diseases 10th Revision (ICD-10) (supplementary data 1), hereafter called organ-grouped conditions.

From this set and categorization of chronic conditions, we created five multimorbidity measures of which two were continuous and three were categorical measures as follows:

(1) individual disease counts;
(2) organ-grouped disease counts;
(3) a threshold of three or more individual conditions;
(4) a threshold of three or more organ-grouped conditions called complex multimorbidity;
(5) co-occurrence of two or more individual conditions and frailty (measured as one of four dimensions (poor self-rated health, mental illness, physical impairment or social impairment)) called multimorbidity with frailty.

Both the multimorbidity and frailty measure included anxiety and depression. In total, 23 of 11,861 individuals met the criteria of two-condition multimorbidity plus one dimension of frailty, with the presence of anxiety and depression only.

Complex multimorbidity [20] and multimorbidity with frailty [34] are measures suggested to detect individuals in higher need of coordinated care which was previously operationalized in HUNT3 [14,15]. Organ-grouped disease counts were used in sensitivity analyses.

2.4. Sociodemographic Variables

Continuous age and categorical sex variables were provided by the HUNT Databank. Our proxy variable for socioeconomic position was occupation, derived from the interview question "What is/was the title of your main occupation?" Occupation is a comprehensive measure reflecting income, material resources, and networks, as well as specific biopsychosocial exposures on the job [25]. Occupations were categorized according to the simplified, 3-class version of the European Socio-economic Classification scheme (supplementary data 2) [35].

2.5. Statistical Analysis

To show the distribution of follow-up time and events, demographic factors, and baseline health characteristics across occupational groups, cross-tabulations were conducted. Numbers of affected individuals, percentages, and measures of central tendency and variability are presented.

Logistic, linear, and Cox regression models were used. First, logistic regression models were fitted separately for each sex and occupational group to study associations between the number of individual chronic conditions, entered as restricted cubic splines, and death in the following 10-year period. These models were adjusted for continuous age. Results from each model were subsequently combined in a joint graph showing mortality as estimated proportions (with 95% confidence intervals

(CIs)) at age 60 years and presented for 0 to 12 individual chronic conditions. Joint graphs of the complete range of individual chronic conditions, as well as a sensitivity analysis in which the same method was used to study the association between the number of organ-grouped chronic conditions and 10-year risk of death and accompanying descriptive tables of frequencies and number of events by individual and organ-grouped conditions, are in supplementary data 3. The logistic regression model to study the associations of organ-grouped chronic conditions necessitated the inclusion of age squared. Second, to formally test if multimorbidity was modified by occupation, we specified linear regression models to investigate statistical interactions between continuous multimorbidity and occupation on an additive scale. We also fit models with statistical interactions between multimorbidity and sex. The threshold significance level was $p < 0.05$.

Finally, we modeled time to death using sex-stratified Cox proportional hazard models with a composite variable containing different combinations of multimorbidity (yes or no) and occupation (low, middle, or high). We used age measured in years as the time scale to either date of emigration, all-cause mortality, or end of follow-up (1 February 2019), whichever came first. We report hazard ratios with 95% CIs in forest plots. The number of deaths, total frequency, and proportions are listed by joint multimorbidity and occupational group measures, sex, and occupational groups in supplementary data 4.

All statistical analyses were done in Stata IC (StataCorp. 2019. Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX, USA) and all visualizations were created with the user-written Stata coefplot command [36]. Data analysis took place from January to June 2020.

2.6. Patient and Public Involvement

Participants, patients, and stakeholders took part in the preparation of HUNT3. The data collection was completed from October 2006 to June 2008. At the time of designing this secondary analysis study, no patient groups represented the universal topic multimorbidity, and therefore no patient or public representatives were involved.

2.7. Ethics Statement

The Regional Committee for Medical and Health Research Ethics in Norway approved the current study (project no. 2014/2265).

3. Results

Included in the analyses were 31,132 of 50,807 HUNT3 participants (61.3%) with complete data on multimorbidity, work, and registry status (Figure 1), followed for a mean (standard deviation (SD)) of 11.1 (1.5) years (Table 1). Individuals were excluded because of withdrawn consent ($n = 6$), incomplete participation ($n = 9610$), unspecified occupation ($n = 25$), or missing occupational data ($n = 1571$), younger than 35 years ($n = 4827$) or 75 years or older ($n = 3636$). No individuals were excluded due to missing registry data. Sociodemographic characteristics for individuals who were ineligible or had missing data are presented in supplementary data 5.

Nearly half the sample (15,261 of 31,132 (49.0%)) were designated as part of the low occupational groups, and a quarter (7501 of 31,132 (24.1%)) were in the high occupational group. The low occupational group had higher proportions of all measures of multimorbidity and reported a higher number of long-term conditions. A total of 2254 of 31,132 individuals (7.2%) died by the end of the study. By occupational group, this included 373 of 7501 (5.0%) in the high occupational group and 1310 of 15,261 (8.6%) in the low occupational group. Among the groups of multimorbidity, 1795 of 19,409 individuals (9.2%) with three or more individual conditions died, as did 1642 of 16,546 individuals (9.9%) with complex multimorbidity and 1312 of 11,861 individuals (11.1%) with multimorbidity and frailty (supplementary data 4). Risk of death according to occupation and number of individual chronic conditions are depicted for women and men in Figure 2.

Table 1. Sociodemographic characteristics and health profile at baseline and follow-up time and events in occupational strata, the HUNT Study 2006–2008 (HUNT3).

Characteristics and Outcomes	Occupational Group							
	High		Middle		Low		Total	
Cohort, baseline, No. (%)	7501	(100)	8370	(100)	15,261	(100)	31,132	(100)
Women No. (%)	3702	(49.4)	4427	(52.9)	8821	(57.8)	16,950	(54)
Men No. (%)	3799	(50.6)	3943	(47.1)	6440	(42.2)	14,182	(46)
Age, years, mean (SD)	53	(10.2)	55	(10.7)	56	(10.5)	55	(10.5)
Health status, baseline								
Individual LTCs, median (IQR)	3	(1 to 5)	3	(2 to 5)	4	(2 to 6)	3	(2 to 5)
Organ-grouped LTCs, median (IQR)	2	(1 to 3)	3	(1 to 4)	3	(2 to 4)	3	(1 to 4)
≥3 individual LTCs, No. (%)	3919	(52.2)	5088	(60.8)	10,402	(68.2)	19,409	(62.3)
Complex multimorbidity, No. (%) [a]	3191	(42.5)	4298	(51.4)	9057	(59.3)	16,546	(53.1)
Multimorbidity with frailty, No. (%) [b,c]	2070	(27.6)	3081	(36.8)	6710	(44.0)	11,861	(38.1)
End of follow-up								
Follow-up time, years, mean (SD)	11.1	(1.3)	11.1	(1.5)	11.0	(1.6)	11.1	(1.5)
Person-years, thousands (%)	83.5	(24.3)	93.0	(27.0)	167.6	(48.7)	344.2	(100)
Deaths, No. (%)	373	(5.0)	571	(6.8)	1310	(8.6)	2254	(7.2)
Deaths in women, No. (%)	118	(31.6)	210	(36.8)	608	(46.4)	936	(41.5)
Deaths in men, No. (%)	255	(68.4)	361	(63.2)	702	(53.6)	1318	(58.5)
Age at death, years, mean (SD)	71.2	(8.7)	72.9	(8.2)	71.9	(8.6)	72.0	(8.5)

Abbreviations: No., number; SD, standard deviation; IQR, interquartile range; LTC, long-term condition. [a] Three or more organ-grouped LTCs. [b] Two or more individual LTCs and one dimension of frailty (poor health, mental illness, physical or social impairment). [c] In total, 15 people had data missing on frailty.

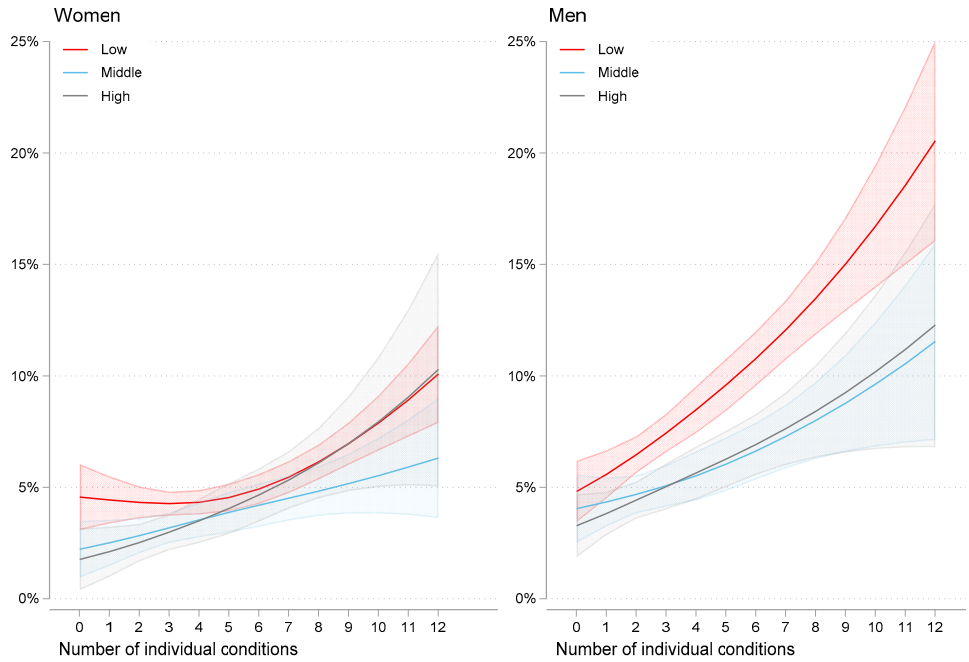


Figure 2. Estimated 10-year all-cause risk of death by number of individual long-term conditions and occupational group for women and men. Shading indicates 95% Cis. Low, middle, and high indicate occupational groups.

Mortality increased by the number of individual chronic conditions in all occupational groups, but to varying degrees. For women, there was no clear tendency that occupation modified the association between the number of single conditions and mortality (additive statistical interaction

$p = 0.41$), whereas for men, the low occupational group had a steeper increase than the middle and high occupational groups (additive statistical interaction $p < 0.001$). We also found evidence of a statistically significant interaction in which the number of conditions was more strongly associated with mortality for men compared with the same association in women (additive statistical interaction $p = 0.03$). A sensitivity analysis with multimorbidity measured as organ-grouped chronic conditions found the same statistical interactions and associations. In contrast to individual disease count, occupational differences in the risk of death in women were detectable for the full range of organ-grouped conditions (supplementary data 3, Figure S2).

Figure 3 shows hazard ratios (HRs) and 95% CI for mortality according to combinations of the categorical multimorbidity measures and occupation levels for women and men.

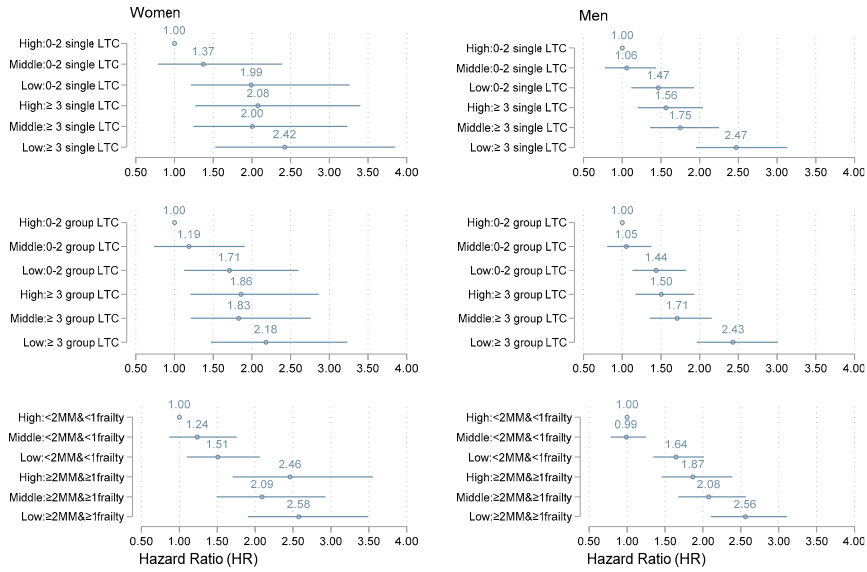


Figure 3. Hazard Ratios and 95% CIs for all-cause mortality between occupational groups with and without multimorbidity, separate for men and women. Abbreviations: LTC = long-term condition; MM, multimorbidity; 2MM & 1frailty = two individual long-term conditions plus one dimension of frailty (poor self-rated health, mental illness, physical impairment, or social impairment). Top panels, multimorbidity with a threshold of at least three individual long-term conditions; middle panels, multimorbidity as a threshold with at least three organ-grouped long-term conditions; bottom panel, multimorbidity with more than two individual long-term conditions and frailty.

Compared with the reference category (individuals in the high occupation group whose health status was below the threshold of multimorbidity), the overall pattern suggests that the relative risk of death increased gradually with decreasing occupation levels and the presence of multimorbidity for both women and men. There was more than a two-fold risk of death in the low occupational group with all measures of multimorbidity compared with the reference category for both women and men.

4. Discussion

4.1. Summary of Findings

In this population cohort study on joint outcomes of socioeconomic position and multimorbidity on mortality, we found that all measures of multimorbidity and all-cause mortality were more common in lower occupational groups. Mortality increased with the number of chronic conditions, and occupational gradients were consistent. There was a tendency toward a stronger association

between multimorbidity and mortality in men in lower occupational groups. Relative risk differences increased with lower occupational groups and the presence of multimorbidity.

4.2. Possible Mechanisms and Explanations

Socioeconomic differences in mortality result from unequal distribution of power, income, and resources [1]. Occupational position entails these general elements and particular outcomes of biopsychosocial exposures in the workplace [25], where negative factors tend to concentrate in lower occupational groups [1]. Multimorbidity may be associated with death through the lethality of each condition, interplay between conditions (including frailty), and conditions and treatments (such as polypharmacy and fragmented health care) [19]. The presence of frailty should initiate comprehensive, integrated care in patients with 2 or more individual conditions [34]. In this study, the relative risks were greatest with the presence of joint multimorbidity and frailty.

Because mortality increases with individual disease counts and any multimorbidity measure, a decrease in absolute and relative socioeconomic differences can be expected [37]. In women, absolute risk differences were diminished in the high occupational group, while the gradient between middle and low occupational groups persisted. This may imply heterogeneity in the multimorbidity measure, particularly in women. The occupational differences in mortality were greater by count of organ-grouped chronic conditions (supplementary data 3), and this may reflect that grouping by body system makes the measure more uniform and enables it to detect social gradients to a greater extent than simple disease counts. It seems that a continuous measure of multimorbidity better captures the impact of socioeconomic position on mortality.

4.3. Comparison with Existing Literature

In a review of 26 articles on the association between multimorbidity and mortality, all measures of multimorbidity increased mortality [19]. Three recent population cohorts, including 240,000 individuals [26] to 1.1 million individuals [28] and one worker cohort of 6425 people [27], have studied the joint outcome of socioeconomic position and multimorbidity on mortality. Two studies also explored the association of socioeconomic position with the transition from healthy to multimorbid [27,28] and frail [27]. Multimorbidity was measured as individual disease counts of 39 chronic conditions [26] or 43 chronic conditions [29] and as a threshold of 2 or more of 9 long-term conditions [27] and 30 long-term conditions [28]. Proxies for socioeconomic position were education [26,27], occupation [27], and area deprivation [28,29].

Similar to our findings, all [26–29] reported higher prevalence of multimorbidity in lower socioeconomic groups and more deaths with increasing multimorbidity and lower social position. With increasing disease count in a range of zero to more than four conditions, the impact of socioeconomic position on mortality were considered to decrease [26] or be stable [29]. The effect of increasing disease counts on mortality risk was larger among men [29], which corresponds to our findings. On the other hand, our study suggests increased mortality with consistent occupational gradients, with increasing disease counts for a greater range of individual conditions.

Socioeconomic position measured as occupation had the strongest association with onset of multimorbidity, physical frailty, and mortality [27]. In the presence of multimorbidity and frailty studied as separate measures, there were no social gradients in mortality [27]. In contrast, our study suggested intact occupational gradients in the presence of all categorical measures of multimorbidity.

Finally, in women with multimorbidity, life expectancy was equal across social strata, while men with multimorbidity had sustained social differences in survival [28]. Our findings also suggest that socioeconomic position can modify the association between multimorbidity and mortality in men but not in women.

We have not identified other studies of the outcome of socioeconomic position and joint multimorbidity and frailty on mortality. One study [23] reported the combination of multimorbidity and frailty to increase mortality risk, and adjustment by socioeconomic position resulted in no modification.

In contrast, our stratified analysis on joint multimorbidity and frailty reveals occupational gradients in association with mortality.

Bias toward healthy older adults [26,28] and healthy workers [27] is likely in several of the studies, which will underestimate socioeconomic differences. Measuring multimorbidity as two individual chronic conditions has lower age specificity and detects smaller socioeconomic gradients than measures of organ-grouped conditions [9,20,38], which may impair the ability of such studies to detect socioeconomic differences in mortality. In sum, differences in setting and measures may explain variation in the impact of socioeconomic position and multimorbidity with mortality.

4.4. Strengths and Limitations

The HUNT Study is illustrative for Norway [33], and trends in the material match those of Western high-income countries [39–41]. To avoid a bias toward healthy older adults and misclassification of socioeconomic positions in younger age groups, we restricted the age range. Job opportunities and exposures in work may differ among birth cohorts; therefore, we adjusted by age and used age as the time scale in the analyses.

Occupation is an established comprehensive measure of socioeconomic position that may show stronger associations with health outcomes than unidimensional measures [27]. Occupational group classification enables international comparison [35].

There are no standard definitions or operationalizations of multimorbidity or frailty; however, self-report is a valid approach to measure multimorbidity in larger samples [9]. HUNT3 covers a broad range of conditions suitable to obtain proper estimates of multimorbidity [20]. We fitted HUNT3 data to a multidimensional frailty measure in agreement with a holistic, conceptual definition of frailty [42]. Registry data ensured no loss to follow-up and the ability to link outcomes on an individual level.

Our cohort study offers a unique opportunity to directly compare the outcome of occupational positioning and several multimorbidity measures on all-cause mortality. We compared mortality with reference groups that may have some morbidities, as recommended by a recent review on multimorbidity and mortality [19]. We reported absolute and relative mortality risk differences stratified by sex and socioeconomic position to clarify characteristics that may be useful to inform future interventions and are compliant with recommendations on reports of socioeconomic inequalities in health [43].

The participants in this study may to some extent have higher socioeconomic position and lower mortality compared with nonparticipants [44]. Further age restriction increased the proportion of individuals categorized in high occupational groups compared with the occupational groups of noneligible individuals. In sum, estimates of the association of multimorbidity and socioeconomic position with mortality will be conservative. Events are relatively few, and imprecision limits the interpretation of the results.

We only explored socioeconomic gradients by use of occupational positions. Various measures of socioeconomic position act through distinct mechanisms and associate differently with health outcomes [24,25]. Reverse causation, whereby prior health determines job opportunities, will increase detected differences. Our measure excludes those who had never worked, and older women are more likely to be missing because of unclassifiable occupations. This will probably underestimate social gradients [45].

To assess prospective health outcomes, there are recommendations to use weighted multimorbidity measures [46]. However, this was not possible with the data available. We lack information on chronicity for most conditions and may overestimate prevalence of multimorbidity. The multimorbidity and frailty measures are based on a count of conditions and dimensions and not types, which may vary among occupational groups. The heterogeneity may bias estimates in either direction. As for recognized frailty scales, our measure may differ in accuracy of detecting frailty across age groups [13,34]. This may underestimate outcome measures.

In this classic cohort study, we have measured multimorbidity at baseline. The duration of exposure prior to HUNT3 will vary by occupational group. A lack of updated measurements of health status may underestimate socioeconomic gradients [19].

4.5. Interpretation/Implication

Cautious of limitations and confounding, there was evidence of effect measure differences in mortality between occupational groups by the number of chronic conditions in this population cohort study, and these were stronger in men than women. Even complex measures of multimorbidity were prevalent. All multimorbidity measures were strongly associated with mortality with varying but consistent gradients between occupational groups and sex. It seems a continuous measure of organ-grouped multimorbidity would better capture the impact of socioeconomic positioning on mortality than categorical multimorbidity measures.

Norway is a high-income country with a well-developed welfare system. Primary and specialist health care are mostly public and financed through taxation with low costs for the individual, as are all levels of education. Job security and standards for health, safety, and environment in the workplace are high. The results can be transferable to similar welfare state models but can also be contrasted across different regime types. As others have noted, political systems and priorities shape population health and the magnitude of health inequities [30]. Observed marked differences in multimorbidity and mortality between occupational groups in our setting might suggest that labor protection legislation is important in all societies.

The results support that social differences in multimorbidity must be a priority in public health and should receive increased attention in health care. Improved management in the health care sector necessitates reforms to fit the complexity of multimorbidity, from research and education to clinicians and organization [34,47,48].

4.6. Future Research

The use of heterogenous multimorbidity measures in this study may obscure the relation to mortality and any socioeconomic modification thereof [10]. It may be advantageous to study clusters of multimorbidity to clarify causes and consequences [10]. Others have argued that clusters undermine that the norm is multiplicity, which is more than the sum of its morbidities [49,50]. Complex multimorbidity seems a relevant measure that captures this multiplicity while remaining sufficiently uniform to detect social differences in mortality.

On this background, we recommend exploration of complex multimorbidity as well as clusters of multimorbidity with repeated recordings and their association with a variety of socioeconomic position measures, health care utilization, and mortality, in an attempt to enhance future prevention and management of multimorbidity.

5. Conclusions

Multimorbidity is common and strongly associated with mortality with varying occupational gradients. Men in lower occupational groups seems to be a particularly vulnerable group. Prevention of multimorbidity is of public health importance in prolonging survival of all people. The health care sector, from workforce to organization, needs to enhance the generalist and person-centered focus sensitive to social context to better care for this large patient group. Continuous research on various measures of multimorbidity and associations to multiple sociodemographic variables, health care use, and mortality will be necessary to guide prevention and management.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/9/2759/s1, Supplementary data 1: Construction of chronic, individual conditions and categorization; Table S1. 51 chronic conditions grouped by 14 ICD-10 chapters. Supplementary data 2: Details on operationalization of socioeconomic position; Table S2. The distribution of transformed occupational data and discrepancies between the Norwegian and International Standard Classifications of Occupations, and allocation in the European Socio-economic

Classification scheme. Supplementary data 3: Estimated 10-year risk of death by all individual and organ-grouped chronic conditions, occupational groups and sex and descriptive data; Figure S1. Estimated 10-year all-cause risk of death by number of individual chronic conditions and cccupational group, women & men; Table S3. 10-year mortality by increasing individual chronic conditions, by sex and occupational strata; Figure S2. Estimated 10-year all-cause risk of death by number of organ-grouped chronic conditions and occupational group, women & men; Table S4. 10-year mortality by increasing organ-grouped chronic conditions, by sex and occupational strata. Supplementary data 4: Descriptive data supplementary to hazard ratios for mortality of combined occupational group and health status; Table S5. Number of deaths by occupational group and health status in women and men. Supplementary data 5: Baseline sociodemographic characteristics of eligible, non-eligible and missing.

Author Contributions: Conceptualization, K.H.V., J.H.B. and E.R.S.; data curation, S.K.; formal analysis, K.H.V. and E.R.S.; funding acquisition, S.K. and E.R.S.; investigation, K.H.V., J.H.B., S.K., K.A.D. and E.R.S.; methodology, K.H.V., J.H.B., S.K., K.A.D. and E.R.S.; project administration, E.R.S.; supervision, K.A.D. and E.R.S.; visualization, K.H.V. and E.R.S.; writing—original draft, K.H.V.; writing—review & editing, J.H.B., S.K., K.A.D. and E.R.S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by the Faculty of Medicine and Health Science at the Norwegian University of Science and Technology through the PhD program in Behavior and Health (Vinjerui). The funding source has partly funded HUNT3 and fully funded open access for this article. The PhD program in Behavior and Health is a joint program with the Australian National University. The Liaison Committee for Education, Research and Innovation in Central Norway (Samarbeidsorganet), awarded a mobility grant (grant 17/38297 (Vinjerui)) for her research stay at Australian National University (July 2018 to February 2019). The funding sources have had no role in conceptualization this study, its design and methods, analysis and interpretation of data, writing of the article, or decision to submit the article for publication.

Acknowledgments: M. Sophia Newman, for writing assistance. The Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU)), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. To protect participants' privacy, HUNT Research Centre aims to limit storage of data outside HUNT Databank and cannot deposit data in open repositories. HUNT Databank has precise information on all data exported to different projects and are able to reproduce these on request. There are no restrictions regarding data export, given approval of applications at the HUNT Research Centre. For more information: http://www.ntnu.edu/hunt/data.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Commission on Social Determinants of Health. *Closing the Gap in a Generation: Health Equity through Action on the Social Determinants of Health: Final Report of the Commission on Social Determinants of Health*; World Health Organisation: Geneva, Switzerland, 2008; p. 256.
2. Nicholson, K.; Makovski, T.T.; Griffith, L.E.; Raina, P.; Stranges, S.; van den Akker, M. Multimorbidity and comorbidity revisited: Refining the concepts for international health research. *J. Clin. Epidemiol.* **2019**, *105*, 142–146. [CrossRef] [PubMed]
3. Van Oostrom, S.H.; Gijsen, R.; Stirbu, I.; Korevaar, J.C.; Schellevis, F.G.; Picavet, H.S.; Hoeymans, N. Time trends in prevalence of chronic diseases and multimorbidity not only due to aging: Data from general practices and health surveys. *PLoS ONE* **2016**, *11*, e0160264. [CrossRef] [PubMed]
4. Uijen, A.A.; van de Lisdonk, E.H. Multimorbidity in primary care: Prevalence and trend over the last 20 years. *Eur. J. Gen. Pract.* **2008**, *14* (Suppl. 1), 28–32. [CrossRef]
5. Fried, L.P.; Ferrucci, L.; Darer, J.; Williamson, J.D.; Anderson, G. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *J. Gerontol. A Biol. Sci. Med. Sci.* **2004**, *59*, 255–263. [CrossRef] [PubMed]
6. Vetrano, D.L.; Palmer, K.; Marengoni, A.; Marzetti, E.; Lattanzio, F.; Roller-Wirnsberger, R.; Lopez Samaniego, L.; Rodriguez-Manas, L.; Bernabei, R.; Onder, G.; et al. Frailty and multimorbidity: A systematic review and meta-analysis. *J. Gerontol. A Biol. Sci. Med. Sci.* **2019**, *74*, 659–666. [CrossRef] [PubMed]
7. Vetrano, D.L.; Calderon-Larranaga, A.; Marengoni, A.; Onder, G.; Bauer, J.M.; Cesari, M.; Ferrucci, L.; Fratiglioni, L. An international perspective on chronic multimorbidity: Approaching the elephant in the room. *J. Gerontol. A Biol. Sci. Med. Sci.* **2018**, *73*, 1350–1356. [CrossRef]
8. Violan, C.; Foguet-Boreu, Q.; Flores-Mateo, G.; Salisbury, C.; Blom, J.; Freitag, M.; Glynn, L.; Muth, C.; Valderas, J.M. Prevalence, determinants and patterns of multimorbidity in primary care: A systematic review of observational studies. *PLoS ONE* **2014**, *9*, e102149. [CrossRef]

9. Fortin, M.; Stewart, M.; Poitras, M.E.; Almirall, J.; Maddocks, H. A systematic review of prevalence studies on multimorbidity: Toward a more uniform methodology. *Ann. Fam. Med.* **2012**, *10*, 142–151. [CrossRef]
10. MacMahon, S. *Multimorbidity: A Priority for Global Health Research*; The Academy of Medical Sciences: London, UK, 2018; p. 127.
11. O'Caoimh, R.; Galluzzo, L.; Rodriguez-Laso, A.; Van der Heyden, J.; Ranhoff, A.H.; Lamprini-Koula, M.; Ciutan, M.; Lopez-Samaniego, L.; Carcaillon-Bentata, L.; Kennelly, S.; et al. Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: A systematic review and meta-analysis. *Ann. Ist. Super. Sanita* **2018**, *54*, 226–238. [CrossRef]
12. Franse, C.B.; van Grieken, A.; Qin, L.; Melis, R.J.F.; Rietjens, J.A.C.; Raat, H. Socioeconomic inequalities in frailty and frailty components among community-dwelling older citizens. *PLoS ONE* **2017**, *12*, e0187946. [CrossRef]
13. Theou, O.; Brothers, T.D.; Pena, F.G.; Mitnitski, A.; Rockwood, K. Identifying common characteristics of frailty across seven scales. *J. Am. Geriatr. Soc.* **2014**, *62*, 901–906. [CrossRef] [PubMed]
14. Vinjerui, K.H.; Bjerkeset, O.; Bjorngaard, J.H.; Krokstad, S.; Douglas, K.A.; Sund, E.R. Socioeconomic inequalities in the prevalence of complex multimorbidity in a Norwegian population: Findings from the cross-sectional HUNT Study. *BMJ Open* **2020**, *10*, e036851. [CrossRef]
15. Vinjerui, K.H.; Boeckxstaens, P.; Douglas, K.A.; Sund, E.R. Prevalence of multimorbidity with frailty and associations with socioeconomic position in an adult population: Findings from the cross-sectional HUNT Study in Norway. *BMJ Open* **2020**, *10*, e035070. [CrossRef]
16. Barnett, K.; Mercer, S.W.; Norbury, M.; Watt, G.; Wyke, S.; Guthrie, B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* **2012**, *380*, 37–43. [CrossRef]
17. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **2015**, *386*, 743–800. [CrossRef]
18. Hanlon, P.; Nicholl, B.I.; Jani, B.D.; Lee, D.; McQueenie, R.; Mair, F.S. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: A prospective analysis of 493 737 UK Biobank participants. *Lancet. Public Health* **2018**, *3*, e323–e332. [CrossRef]
19. Nunes, B.P.; Flores, T.R.; Mielke, G.I.; Thume, E.; Facchini, L.A. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. *Arch. Gerontol. Geriatr.* **2016**, *67*, 130–138. [CrossRef]
20. Harrison, C.; Britt, H.; Miller, G.; Henderson, J. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open* **2014**, *4*, e004694. [CrossRef]
21. Storeng, S.H.; Vinjerui, K.H.; Sund, E.R.; Krokstad, S. Associations between complex multimorbidity, activities of daily living and mortality among older Norwegians. A prospective cohort study: The HUNT Study, Norway. *BMC Geriatr.* **2020**, *20*, 21. [CrossRef]
22. Theou, O.; Brothers, T.D.; Mitnitski, A.; Rockwood, K. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *J. Am. Geriatr. Soc.* **2013**, *61*, 1537–1551. [CrossRef]
23. Woo, J.; Leung, J. Multi-morbidity, dependency, and frailty singly or in combination have different impact on health outcomes. *Age* **2014**, *36*, 923–931. [CrossRef]
24. Braveman, P.A.; Cubbin, C.; Egerter, S.; Chideya, S.; Marchi, K.S.; Metzler, M.; Posner, S. Socioeconomic status in health research: One size does not fit all. *JAMA* **2005**, *294*, 2879–2888. [CrossRef] [PubMed]
25. Galobardes, B.; Lynch, J.; Smith, G.D. Measuring socioeconomic position in health research. *Br. Med. Bull.* **2007**, *81–82*, 21–37. [CrossRef] [PubMed]
26. Lund Jensen, N.; Pedersen, H.S.; Vestergaard, M.; Mercer, S.W.; Glumer, C.; Prior, A. The impact of socioeconomic status and multimorbidity on mortality: A population-based cohort study. *Clin. Epidemiol.* **2017**, *9*, 279–289. [CrossRef] [PubMed]
27. Dugravot, A.; Fayosse, A.; Dumurgier, J.; Bouillon, K.; Rayana, T.B.; Schnitzler, A.; Kivimaki, M.; Sabia, S.; Singh-Manoux, A. Social inequalities in multimorbidity, frailty, disability, and transitions to mortality: A 24-year follow-up of the Whitehall II cohort study. *Lancet. Public Health* **2020**, *5*, e42–e50. [CrossRef]
28. Chan, M.S.; van den Hout, A.; Pujades-Rodriguez, M.; Jones, M.M.; Matthews, F.E.; Jagger, C.; Raine, R.; Bajekal, M. Socio-economic inequalities in life expectancy of older adults with and without multimorbidity: A record linkage study of 1.1 million people in England. *Int. J. Epidemiol.* **2019**, *48*, 1340–1351. [CrossRef]

29. Jani, B.D.; Hanlon, P.; Nicholl, B.I.; McQueenie, R.; Gallacher, K.I.; Lee, D.; Mair, F.S. Relationship between multimorbidity, demographic factors and mortality: Findings from the UK Biobank cohort. *BMC Med.* **2019**, *17*, 74. [CrossRef]
30. Beckfield, J.; Krieger, N. Epi + demos + cracy: Linking political systems and priorities to the magnitude of health inequities—Evidence, gaps, and a research agenda. *Epidemiol. Rev.* **2009**, *31*, 152–177. [CrossRef]
31. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gotzsche, P.C.; Vandenbroucke, J.P.; Initiative, S. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Int. J. Surg.* **2014**, *12*, 1495–1499. [CrossRef]
32. Krokstad, S.; Langhammer, A.; Hveem, K.; Holmen, T.L.; Midthjell, K.; Stene, T.R.; Bratberg, G.; Heggland, J.; Holmen, J. Cohort profile: The HUNT study, norway. *Int. J. Epidemiol.* **2013**, *42*, 968–977. [CrossRef]
33. Holmen, J.; Midthjell, K.; Krüger, Ø.; Langhammer, A.; Holmen, T.L.; Bratberg, G.H.; Vatten, L.; Lund-Larsen, P.G. The nord-trøndelag health study 1995–97 (HUNT 2): Objectives, contents, methods and participation. *Norsk Epidemiologi* **2003**, *13*, 19–32.
34. National Institute for Health and Care Excellence. *Multimorbidity: Clinical Assessment and Management*; National Institute for Health and Care Excellence: London, UK, 2016.
35. Rose, D.; Harrison, E. The european socio-economic classification: A new social class schema for comparative european research. *Eur. Soc.* **2007**, *9*, 459–490. [CrossRef]
36. Jann, B. Plotting regression coefficients and other estimates. *Stata J.* **2018**, *14*, 708–737. [CrossRef]
37. Scanlan, J.P. Guest editorial. *Chance* **2013**, *19*, 47–51. [CrossRef]
38. Singer, L.; Green, M.; Rowe, F.; Ben-Shlomo, Y.; Morrissey, K. Social determinants of multimorbidity and multiple functional limitations among the ageing population of England, 2002–2015. *SSM Popul. Health* **2019**, *8*, 100413. [CrossRef] [PubMed]
39. NCD Risk Factor Collaboration. Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature* **2019**, *569*, 260–264. [CrossRef]
40. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* **2017**, *389*, 37–55. [CrossRef]
41. NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* **2017**, *390*, 2627–2642. [CrossRef]
42. Gobbens, R.J.; Luijkx, K.G.; Wijnen-Sponselee, M.T.; Schols, J.M. In search of an integral conceptual definition of frailty: Opinions of experts. *J. Am. Med. Dir. Assoc.* **2010**, *11*, 338–343. [CrossRef]
43. Mackenbach, J.P.; Kunst, A.E. Measuring the magnitude of socio-economic inequalities in health: An overview of available measures illustrated with two examples from Europe. *Soc. Sci. Med.* **1997**, *44*, 757–771. [CrossRef]
44. Langhammer, A.; Krokstad, S.; Romundstad, P.; Heggland, J.; Holmen, J. The HUNT study: Participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med. Res. Methodol.* **2012**, *12*, 143. [CrossRef]
45. Martikainen, P.; Valkonen, T. Bias related to the exclusion of the economically inactive in studies on social class differences in mortality. *Int. J. Epidemiol.* **1999**, *28*, 899–904. [CrossRef] [PubMed]
46. Nicholson, K.; Almirall, J.; Fortin, M. The measurement of multimorbidity. *Health Psychol.* **2019**, *38*, 783–790. [CrossRef] [PubMed]
47. *Multimorbidity: Technical Series on Safer Primary Care*; World Health Organization: Geneva, Switzerland, 2016; pp. 4–5.
48. Wallace, E.; Salisbury, C.; Guthrie, B.; Lewis, C.; Fahey, T.; Smith, S.M. Managing patients with multimorbidity in primary care. *BMJ* **2015**, *350*, h176. [CrossRef] [PubMed]
49. Valderas, J.M. Multimorbidity, not a health condition or complexity by another name. *Eur. J. Gen. Pract.* **2015**, *21*, 213–214. [CrossRef]
50. Starfield, B. Threads and yarns: Weaving the tapestry of comorbidity. *Ann. Fam. Med.* **2006**, *4*, 101–103. [CrossRef]

ISBN 978-82-326-6616-4 (printed ver.)
ISBN 978-82-326-5844-2 (electronic ver.)
ISSN 1503-8181 (printed ver.)
ISSN 2703-8084 (online ver.)

NTNU

Norwegian University of
Science and Technology