AARHUS UNIVERSITY

Social inequalities in incidence and consequences of fragility fractures

PhD dissertation

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Health
Aarhus University
2021

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Financial support

DEFACTUM, Central Denmark Region
Aarhus University
Osteoporoseforeningen (The Danish Osteoporosis Society)
Aase and Ejnar Danielsens foundation

Acknowledgements

The work presented in this PhD dissertation was carried out between April 2018 and June 2021 at DEFACTUM, Central Denmark Region and the Department of Clinical Medicine, Aarhus University.

I am grateful for the help and support of many people. My thanks go firstly to my main supervisor Professor Bente L. Langdahl and my co-supervisors Associate Professor and Research Director Camilla Palmhøj Nielsen and Senior Researcher Karina Friis, who have given me every opportunity to learn and develop. Thanks for your great support throughout my work with this dissertation. It has been a great privilege to work with you.

Bente L. Langdahl: Through the years, you have always welcomed me with open arms when I have come to you with an idea for a research project. For this, I am truly grateful. Thanks for believing in me and for your dedicated and professional supervision. You always knew which way to go and you have never let me down. You have challenged me and sometimes pushed me outside my comfort zone. I treasure our discussions and your generosity in sharing your knowledge and expertise in the field of osteoporosis and fractures. It has been a privilege to have you as my supervisor, and I hope that we can continue to collaborate in the future. There is still so much work to be done!

Camilla Palmhøj Nielsen: I am truly grateful to have you as my supervisor and research director. Thanks for believing in me and in this project, and thanks for all your effort to support me while planning this dissertation. Without you, this project would not have been possible. I am deeply grateful for all your support and professional advice and for our valuable discussions throughout the project.

Karina Friis: It has been such a pleasure working with you. Thank you for the all the effort and time you have spent introducing me to the Danish National Health Survey. I also wish to express my profound appreciation for your empathic support and your valuable and insightful inputs throughout the project.

A huge shout-out to my amazing colleagues at Public Health and Health Services Research, DEFACTUM for creating an informal, inspirational and fun research environment. Even when times were harsh and forced us to stay at home due to the Covid-19 pandemic, I always felt that you were close. Thanks for always being there for me when I needed a good laugh or a shoulder to cry on. You rock!

I would also like to thank the co-authors of my PhD papers who all provided me with great advice. A special thanks to Sofie Emilie Pedersen, Emma Kejser Jensen and Maiken Bay Ravn for their great effort during the literature search, study selection, risk of bias assessments and data collection for Study I and Study II. These studies would not have been possible without your contribution. Also, thanks to Anne Marie Schack Jensen for data management support for Study III and to Professor Robin Christensen and Associate Professor Carsten Bogh Juhl for data management support and statistical advice on the meta-analyses for Study I and II, as well as for many interesting and challenging discussions. I am very grateful to the individuals who participated in the Danish National Health Survey in 2017 and to the employees in the five Danish regions and the National Institute of Public Health who have put enormous time and effort into carrying out this nationwide health survey.

During my PhD project, I have had excellent collaboration with researchers at the Musculoskeletal Research Unit (MRU) at the University of Bristol. I would like to thank you all at the MRU for your overwhelming hospitality and kindness during my stay in Bristol. Thanks for inviting me for dinner, out for drinks, to the cinema and for accompanying me to the big climate march on a rainy day in February in Bristol. Thanks for all the inspiring talks over lunch and for all your valuable help and inputs to my PhD project. You truly made Bristol a home away from home to me.

My very special thanks go to Professor Celia Gregson at the MRU. You have been a huge inspiration for me since we first met and it has been such an honour to collaborate with you. With your in-depth knowledge and skills in clinical epidemiology and social inequalities combined with your expertise in osteoporosis and fractures, you have provided valuable and constructive feedback to all three PhD papers. I am deeply grateful for all your support – during and after my stay in Bristol. I hope our roads will cross again someday soon.

Finally, lots of hugs and kisses to my family and friends for their support, patience and practical help in the busy periods. A huge appreciation to my husband Mads and our children Liva, Thure and Viggo for all your love and support. Much love to you, Mads, for always believing that I can do everything I put my mind to and for gently pushing me toward a career in academia. You mean the world to me.

List of scientific papers

The PhD dissertation is based on the following papers:

I: Socio-economic inequalities in fragility fracture incidence: a systematic review and meta-analysis of 61 observational studies.

Gitte Valentin, Maiken Bay Ravn, Emma Kejser Jensen, Karina Friis, Arti Bhimjiyani, Yoav Ben-Shlomo, April Hartley, Camilla Palmhøj Nielsen, Bente Langdahl, Celia L. Gregson

Published online in Osteoporosis International 25 June 2021.

DOI: 10.1007/s00198-021-06038-7

II: Socio-economic inequalities in fragility fracture outcomes: a systematic review and meta-analysis of prognostic observational studies.

Valentin G, Pedersen SE, Christensen R, Friis K, Nielsen CP, Bhimjiyani A, et al.

Published in Osteoporos International. 2020;31(1):31-42.

III: Fragility fractures and health-related quality of life: does socio-economic status widen the gap? A population-based study.

Valentin G, Friis K, Nielsen CP, Larsen FB, Langdahl BL.

Published in Osteoporos International. 2021 Jan;32(1):63-73.

Abbreviations

BMI: Body Mass Index
BMD: bone mass density
CI: Confidence interval
CCI: Charlson Comorbidity Index
DCRS: Danish Civil Registration System
DNPR: Danish National Patient Registry
DXA: Dual-energy x-ray absorptiometry
EQ-5D: EuroQol five-dimensional
EUR: Euros
FLS: Fracture Liaison Service
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
HR: Hazard ratio
HRQoL: Health-related quality of life
HTA: Health technology assessment
HUI: Health Utilities Index
HSUV: Health state utility value
ICD: International Classification of Diseases
IMD: Index of Multiple Deprivation
MCS: Mental component score (SF-12)
MeSH: Medical Subject Headings
MID: Minimal importance difference
OLS: Ordinary least square
OR: Odds ratio
PCS: Physical component score (SF-12)
PER: Population's Education Register
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-analysis
PROSPERO: Prospective Register of Systematic reviews
QUIPS: Quality in Prognosis Studies
QoL: Quality of life
QUAL: Quality-adjusted life years
RR: Risk ratio
SD: Standard deviation
SEM: Standard error of the mean
SERM: Selective oestrogen receptor modulators
SES: Socio-economic status
SF-12: Short Form Health Survey

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1 English summary

Background and aim: Fragility fractures, especially of the hip and vertebra, constitute a major and growing public health problem across the world. Mortality rates among older people with hip fracture is approximately 25% within the first year of the injury, and the risk of dying is increased up to eight-fold within the first three months after fracture. Survivors of fragility fractures suffer temporary or permanent disabilities such as pain, decreased mobility and increased dependency on others, potentially imposing important limitations on their health related quality of life (HRQoL). The association between a higher burden of chronic disease and lower socio-economic status (SES) is well established. Studies conducted throughout the world have consistently shown that lower SES is associated with increased morbidity from most diseases, lower HRQoL, shorter life expectancy and increased overall mortality across the lifespan. Despite this well-established social gradient in morbidity and mortality from most diseases, the impact of SES on incidence and consequences of fragility fractures among elderly remains unclear. Studies investigating these associations have generated diverging results. These inconsistencies may be due to the use of different measures of SES across studies (e.g. education, income, occupation or Index of Multiple Deprivation) and differences in study size, duration of follow-up or methodological quality. Thus, the aim of this PhD was to establish the impact of SES on fragility fracture incidence and outcome. Knowledge of the impact of SES on the incidence and consequences of fractures among elderly is important to inform future health policy aiming to reduce cost and suffering associated with fractures.

Methods: The PhD comprises three studies. Study I and Study II are systematic reviews and meta-analyses. The reviews were conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement and are based on predefined protocols registered at the International Prospective Register of Systematic reviews (PROSPERO). Risk ratios are meta-analysed using random effects models. Studies using individual-based SES measures (e.g. education, income and occupation) and area-based SES measures (e.g. Index of Multiple Deprivation and area income) were analysed separately.

Study III is a population-based study based on data from a national representative survey combined with data from health and social registers. In this study including 12,839 individuals with fracture and 91,426 with no history of fracture, HRQoL was measured using the Short Form Health Survey (SF-12). Information about fractures, age, sex, ethnicity, comorbidity and SES was obtained from national registers. Multiple regression analysis was conducted to determine the mean HRQoL difference, termed deficit, between individuals with and without a history of fracture (all fractures combined and fractures at six different skeletal sites).

Results: The impact of SES on fragility fracture incidence was explored in Study I. This systematic review comprises 61 studies from 26 different countries involving more than 19 million individuals. Individual-based low SES was associated with a 27% increased risk of fragility fracture (risk ratio (RR) 1.27 [95% confidence interval (CI): 1.12, 1.44]), whilst no clear association was seen when area-based measures were used (RR 1.08 [95% CI: 0.91, 1.30]). The strength of associations was influenced by the type and number of covariates included in statistical models; RR 2.69 [95% CI: 1.60, 4.53] for individual-based studies adjusting for age, sex and Body Mass Index (BMI), compared with RR 1.06 [95% CI: 0.92, 1.22] when also adjusted for health behaviours (smoking, alcohol and physical activity). Overall, the quality of the evidence was moderate. The impact of SES on post-fracture mortality and HRQoL was explored in Study II and Study III. In Study II (a systematic review), a total of 24 studies from 15 different countries involving more than one million hip fracture cases were included. The overall mortality within one year after fracture in individuals with low SES was 24% higher than in individuals with high SES (RR 1.24, [95% CI: 1.19, 1.29]) for individual-based SES measures, and 14% (RR 1.14, [95% CI: 1.09, 1.19]) for area-based SES measures. The quality of the evidence for the outcome mortality was moderate. Using individual SES measures, we estimated the excess HRQoL loss to be 5% [95% CI: − 1%, 10%] among hip fracture patients with low SES compared with high SES. This finding was based on limited and very low quality evidence. In Study III (a population-based study), we found that both the Physical Component Score (PCS) and the Mental Component Score (MCS) of the SF-12 were significantly lower among individuals with a history of fragility fracture than among individuals with no history of fracture. Statistically and clinically important PCS deficits (≥ 5 points) were observed among individuals with fractures of the spine and hip up to 5 years after the fracture and among individuals with upper arm fractures up to 1 year after the fracture. Greater deficits were observed for MCS but not for PCS in post-fracture HRQoL in the low than in the high SES group. However, due to low pre-fracture PCS and MCS, individuals with low SES were more likely to report very low post-fracture HRQoL in both domains.

Conclusions: We found that individuals with low SES have a 27% increased risk of fragility fractures and a 24% increased risk of dying after a hip fracture comparted with individuals with high SES. Furthermore, we found that post-fracture physical as well as mental HRQoL were lower among individuals with low SES than among individuals with high SES. BMI and health behaviour were important mediators on the pathway between SES and fragility fracture risk. These findings call for increased awareness of individuals with low SES in an

effort to prevent future fractures and improve HRQoL and longevity for those who have suffered a fragility fracture. The effort should include population-based measures aiming to facilitate healthier life style choices throughout the life (e.g. reduce smoking, alcohol intake, poor nutrition and physical inactivity) as well as specific initiatives targeted at individuals at high risk of fragility fractures. The latter should include nationwide implementation of a coordinated multi-disciplinary fracture prevention program and increased awareness of special care and rehabilitation needs in individuals with low SES following a fracture.

2 Dansk resumé

Baggrund og formål: Knoglebrud blandt ældre har betydelige sundheds- og samfundsmæssige konsekvenser. Dødeligheden inden for det første år efter et hoftebrud er ca. 25 %. Blandt dem, som overlever, oplever mange midlertidige eller permanente konsekvenser i form af smerter, nedsat mobilitet samt øget behov for hjælp til at klare daglige gøremål. Sammenhængen mellem en øget forekomst af kroniske sygdomme og lav socioøkonomisk status ("Socio-economic status" (SES)) er veletableret. Studier fra forskellige dele af verden har samstemmende vist, at lav SES er forbundet med øget morbiditet, lavere helbredsrelateret livskvalitet og lavere levealder. Til trods for denne velkendte sociale gradient i morbiditet og mortalitet for de fleste sygdomme er betydningen af lav SES for forekomst og konsekvenser af knoglebrud stadig uklar. Studier, som har undersøgt betydningen af lav SES, har fundet modsatrettede resultater. Disse forskelle kan skyldes anvendelsen af forskellige mål for SES (fx uddannelse, indkomst, beskæftigelse eller områdebaserede mål) eller forskelle i studiernes størrelse, opfølgningstid eller metodologiske kvalitet. Formålet med denne ph.d.-afhandling er således at undersøge betydningen af lav SES for forekomst og konsekvenser af knoglebrud blandt ældre. Viden om konsekvenser af forskellige typer af knoglebrud på fysisk og mentalt helbred er vigtig for at kunne styrke forebyggende og rehabiliterende indsatser målrettet sårbare ældre.

Metoder: Denne afhandling består af tre studier. Studie I og studie II er systematiske reviews med metaanalyser. De to reviews er udarbejdet i overensstemmelse med the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement og er baseret på prædefinerede protokoller registreret i the International prospective register of systematic reviews (PROSPERO). Meta-analyserne blev udført ved hjælp af random effect-modeller. Analyserne blev udført separat for studier, som anvender individuelle mål (fx uddannelse, indkomst og beskæftigelse), og studier, som anvendte områdebaserede mål (fx Index of Multiple Deprivation og områdeindkomst) for SES. Studie III er et populationsbaseret studie baseret på data fra Den Nationale Sundhedsprofil "Hvordan har du det? 2017". I alt er 12.839 personer med et knoglebrud og 91.426 personer uden tidligere knoglebrud inkluderet i studiet. Helbredsrelateret livskvalitet er målt ved hjælp af måleredskabet "12-Item Short-Form Health Survey" (SF-12), som er en integreret del af "Hvordan har du det?"-spørgeskemaet. Information om tidligere knoglebrud opstået efter 50-årsalderen, køn, alder, komorbiditet og etnicitet blev indhentet via nationale registre. Multipel regression blev udført med henblik på at vurdere forskelle i oplevet helbredsrelateret livskvalitet mellem personer med og uden knoglebrud (samlet for alle typer af brud og separat for knoglebrud på seks forskellige anatomiske lokalisationer).

Resultater: Betydningen af SES for risikoen for at få et knoglebrud blev undersøgt i studie I (et systematisk review). Dette studie bestod af en gennemgang af 61 studier fra 26 forskellige lande og med mere end 19 millioner deltagere. Lav SES målt på individniveau var associeret med
27 % højere risiko for knoglebrud (RR 1,27 [95 % CI: 1,12; 1,44]) sammenholdt med høj SES. Der blev ikke fundet nogen klar association mellem SES og knoglebrud i de studier, som anvendte områdebaserede mål for SES (RR 1,08 [95 % CI: 0,91; 1,30]). I de individbaserede SES-studier var styrken af sammenhængen påvirket af, hvilke variable (confoundere) der var inkluderet i de statistiske modeller: RR 2,69 [95 % CI: 1,60, 4,53] for studier, som justerede for alder, køn og BMI sammenholdt med en RR på 1,06 [95 % CI: 0,92; 1,22], når der også blev justeret for sundhedsvaner (rygning, alkohol og fysisk aktivitet). Kvaliteten af evidensen blev i dette review vurderet til at være moderat.

Betydningen af SES for dødelighed og helbredsrelateret livskvalitet efter et knoglebrud blev belyst i studie II og studie III. Studie II (et systematisk review) bestod af en gennemgang af 24 studier fra 15 forskellige lande og med data fra mere end én million personer med knoglebrud. I studier, som anvendte individbaserede SES-mål, var dødeligheden inden for et år efter et hoftebrud 24% højere blandt personer med lav SES sammenholdt med personer med høj SES (RR 1,24, [95 % CI: 1,19; 1,29]). I studier, som anvendte områdebaserede mål, var risikoen 14 % højere (RR 1,14, [95 % CI: 1,09; 1,19]) blandt personer med lav SES sammenholdt med personer med høj SES. Kvaliteten af evidensen for udfaldet "mortalitet" blev vurderet til at være moderat. Der blev der ikke fundet nogen klar sammenhæng mellem reduktion af helbredsrelateret livskvalitet og lav SES (5% [95 % CI: − 1%; 10 %]). Dette fund var baseret på få studier af meget lav kvalitet. I studie III (et populationsbaseret studie) fandt vi, at fysisk såvel som mental livskvalitet var signifikant lavere blandt personer, som havde haft et knoglebrud, sammenholdt med personer uden brud uafhængig af tid siden bruddet. Statistisk og klinisk relevante (≥ 5 points) forskelle i fysisk livskvalitet blev observeret hos personer med brud på hofte eller rygsøjle op til fem år efter bruddet. Forskellene i mental livskvalitet mellem personer med og uden brud var størst blandt personer med kort uddannelse. Derudover havde personer med kort uddannelse større risiko for at få meget lav fysisk og mental livskvalitet efter et knoglebrud sammenholdt med personer med lang uddannelse.

Konklusion: I denne afhandling fandt vi, at lav SES er forbundet med en 27 % øget risiko for knoglebrud samt en 24 % øget risiko for at dø efter et hoftebrud sammenholdt med personer med høj SES. Derudover fandt vi, at fysisk såvel som mental livskvalitet var lavere blandt individer med lav SES sammenholdt med individer med høj SES. BMI og sundhedsvaner er vigtige mediatorer for sammenhængen mellem SES og frakturrisiko.

Disse fund kalder på øget opmærksomhed på personer med lav SES i indsatsen for at forebygge knoglebrud samt øge levetiden og livskvaliteten blandt ældre efter et knoglebrud. Initiativerne bør omfatte populationsbaserede indsatser rettet mod at facilitere en sundere livsstil gennem hele livet (fx reducere rygning og alkoholindtag samt at sikre bedre kost og øget fysisk aktivitet). Derudover bør der iværksættes specifikke indsatser rettet mod risikogrupper. Disse initiativer bør indeholde national implementering af et frakturforebyggelsesprogram samt øget fokus på særlige behov for pleje og rehabilitering efter et knoglebrud hos personer med lav SES.

3 Motivation for this PhD dissertation

"Health inequalities are not inevitable and can be significantly reduced. Avoidable health inequalities are unfair and putting them right is a matter of social justice."

Professor Sir Michael Marmot, Fair society, Healthy Lives: The Marmot Review. London; 2010

The quotation above fits well with the idea of this dissertation, although my motivation for conducting this thesis began long before I learned about this quotation. My interest in osteoporosis and osteoporosis-related fractures goes back a long time. It first awoke in 2008 when I worked as a physiotherapist at the Department of Endocrinology at Aarhus University Hospital, Denmark. Here, I witnessed the devastating acute and long-term consequences of vertebral fractures caused by osteoporosis. At the same time, I learned that osteoporosis is a highly overlooked condition with regard to diagnosis and treatment as well as in research. After finishing my master in Health Sciences in 2013, my work tasks changed from clinical work at the hospital to academic work at the Department of Public Health and Health Services Research at DEFACTUM, Aarhus, Denmark. However, my passion for osteoporosis remained. Thus, when the possibility of doing a PhD emerged, I knew straightaway that I wanted to do my dissertation in the field of osteoporosis and fractures. Through my work in Public Health and Health Services Research, I had become aware of the substantial disparities in health and mortality that exist between groups of individuals according to their socio-economic status (SES). Thus, I was puzzled to read the conclusions from a report published by the Danish National Board of Health in 2014 [1]. The report aimed to explore social inequality in the prevalence of eight chronic diseases including osteoporosis in Denmark. The authors reported social inequality in disease prevalence for all the chosen chronic diseases **except** osteoporosis [1]. Surprisingly, no systematic differences in osteoporosis prevalence between social groups were detected. On the contrary, the results demonstrated a tendency towards reversed social inequality in the oldest age group, where the proportion of elderly registered with osteoporosis increased with rising SES. On this basis, the Board concluded that there was no social inequality in disease prevalence among individuals with osteoporosis. In the Board's report, the outcome, "osteoporosis", was defined based on diagnosis codes or relevant disease-specific drugs rather than "fractures", which is the clinical manifestation of osteoporosis. Research suggests that, although health services are free of charge in Denmark, the use of these services varies by SES [2-5]. Therefore, the association between higher SES and a higher prevalence of osteoporosis could potentially be biased by a higher referral of individuals with higher SES to screening and, consequently, a higher use of anti-osteoporotic drugs by individuals with higher SES than among individuals with lower SES.

Thus, to overcome this potential source to bias, I decided to search the literature for evidence of an association between SES and fractures related to osteoporosis. Here, I was surprised to find that there were no clear conclusions as to whether socio-economic disadvantage was associated with higher fragility fracture risk as studies investigating this association reported diverging and conflicting results [6-9]. Likewise, no clear conclusions on impact of socio-economic position on post-fracture quality of life (QoL) and mortality could be drawn from the existing literature due to sparse and conflicting results.

Thus, my motivation for conducting this thesis was to clarify the role of SES for fracture risk and the consequences of fragility fractures. It is my hope and ambition that this work will inform health policy makers and health professionals and help reduce cost and suffering among men and women with osteoporosis by allowing treatment and rehabilitation to be targeted at the most vulnerable elderly.

4 Introduction

4.1 Osteoporosis and fragility fractures

4.1.1 Osteoporosis

Osteoporosis is a systematic skeletal condition characterized by reduced bone mass and disruption of bone architecture, resulting in increased bone fragility and increased fracture risk [10]. The diagnostic criterion for osteoporosis is based on measurement of bone mass density (BMD). The gold standard for measuring BMD is dual-energy x-ray absorptiometry (DXA). BMD is reported at an absolute value (g/cm2), a T-score or Z-score, reflecting units of standard deviations (SD) below those of gender-matched young adults or individuals of the same age. The cut-off values for osteoporosis are based on the T-score. The operational definition of osteoporosis is a T-score ≤ -2.5 SD (BMD value of 2.5 SD or more below the peak bone mass) [11]. For both men and women, peak bone mass is achieved in the mid-twenties [12]. After the mid-twenties, a gradual decline of BMD continues into old age in both men and women. Among women, an estrogenic-dependent decline of 9%-10% occurs in the years following menopause [13]. The maximum BMD achieved as well as the following menopause- and age-related decline in BMD depend on both genetic and environmental factors [12]. Due to the age-related loss in BMD, the prevalence of osteoporosis increases with increasing age. The prevalence is 3-4 times higher among women than among men due to the accelerated post-menopausal BMD loss combined with a lower peak BMD in women [14]. In the Danish population, it is estimated that 40.8% of women and 17.7% of men above the age of 50 have osteoporosis according to their T-scores [15]. This corresponds to approximately 650,000 Danes. However, only one forth (172,000) is diagnosed and only one in seven (90,000) is receiving anti-osteoporotic medical treatment [16]. A report based on data from six European countries (EU6) estimated the treatment gap (the percentage of eligible individuals not receiving anti-osteoporotic treatment) to be 73% for women and 63% for men in 2017 [4].

4.1.2 Osteoporosis-related fracture

The clinical manifestations of osteoporosis are fractures. However, the definition of an osteoporosis-related fracture is not straightforward. Due to massive underdiagnosing of osteoporosis, restricting osteoporosis-related fractures to fractures that occur in individuals with a diagnosis of "osteoporosis" would not give a true picture of the burden of osteoporosis-related fractures. Thus, an alternative approach is needed. One approach is to consider all "low trauma" fractures to be osteoporotic [14]. Low trauma fractures are fractures that occur due to a fall from standing height or less [17]. The advantages of using "low trauma" to define osteoporosis-related fractures are that this definition acknowledges the multifactorial causation of fracture. One limitation of this approach is that there is no strong concordance between low trauma fractures at any site and low BMD [18]. Another issue that hampers the use of "low trauma" as a definition of a fracture associated with low BMD is the lack of information on the cause of fracture in national patient registers. Thus, in this thesis we used a commonly used approach where a fracture is characterised as osteoporotic if 1) the type of fracture is associated with low BMD and 2) if the incidence increases after the age of 50. Applying these criteria, the following fractures were considered as osteoporosis related: fracture of the hip (and other femoral fractures), spine, forearm, humerus, ribs, sternum, tibia and pelvis. Fractures of the fingers, toes and head or skull were not considered osteoporosis-related fractures [14]. In the following, an osteoporosis-related fracture will be termed a "fragility fracture."

4.1.3 Incidence and burden of fragility fractures

The incidence of fragility fractures varies worldwide. Fracture rates are highest in the western world with the highest rates observed in Scandinavia. The reason for the differences in fracture risk across countries is not entirely clear, but genetic factors and differences in lifestyle and environment are likely responsible – at least in part – for the differences observed [14]. In Western Europe, about 1 in 3 women and 1 in 5 men over the age of 50 will suffer a fracture in their lifetime. More than 3.5 million fragility fractures are observed each year in Europe alone, accounting for an estimated annual cost of Euro (EUR) 37 million [14]. Due to the increase in longevity worldwide, the number of individuals aged 50 years or more at high risk of fragility fracture is estimated to double from 2010 to 2040 posing a significantly increased disease burden in the future [19].

The most common fracture sites comprise fractures of the vertebra, forearm, hip and proximal humerus. Of all fragility fractures, hip fractures are associated with the most serious consequences with nearly all patients requiring hospitalisation [20]. Approximately, one-fourth of individuals die within one year of hip fracture [21]. Survivors of hip fractures suffer from disabilities such as pain, decreased mobility and increased dependency on others [22-24]. Where hip fractures are the most serious and costly, fractures of the vertebra are the most common fracture type with an estimated population prevalence of 28% in post-menopausal women over the age of 50 [25]. Vertebral fractures often occur earlier in disease progression than hip fractures and are associated with an increased risk of additional vertebral and non-vertebral fractures. Having had one or more vertebral fractures is also associated with chronic back pain, limitations in daily activities as well as reduced HRQoL and increased mortality [26-28].

4.1.4 Risk factors for fragility fractures

Risk factors for fragility fractures can be divided into bone-associated risk factors and fall-associated risk factors. Some of these risk factors are the same. Besides female gender, the former include increasing age, early menopause, low Body Mass Index (BMI), previous fragility fracture, parental history of hip fracture, glucocorticoid treatment, current smoking, alcohol intake of ≥3 units pr. day, physical inactivity and comorbidities such as rheumatoid arthritis, type 1 diabetes and chronic obstructive pulmonary disease [29]. Furthermore, given that most fractures occur due to a fall, risk factors for falls (e.g. decreased muscle strength in the lower extremities, poor balance, vision impairments, polypharmacy, dizziness and cognitive decline [30]) also act as important risk factors for fragility fractures. Some of these risk factors affect both; glucocorticoid treatment is an example as it reduces bone mass and strength by reducing osteoblast activity and causing muscle weakness. In addition, it can cause sex hormone deficiency, which again will affect both bone and muscle negatively [31].

4.1.5 Management of individuals at risk of fragility fractures

The aim of pharmacological and non-pharmacological treatment is to reduce the risk of fracture. Several treatment regimens work in whole or in part by increasing BMD. Although BMD is a predictor of fracture risk, other factors also play an important role. BMD is therefore a surrogate measure, and changing BMD is *per se* not an aim of treatment. Both pharmacological and non-pharmacological treatment can reduce fracture risk [32]. Non-pharmacological treatment builds on lifestyle interventions in the form of appropriate diet, calcium and vitamin D supplements, increased physical activity, fall prevention, smoking cessation and reduced alcohol consumption (i.e. an alcohol intake of less than 3 units a day). Non-pharmacological treatment can to a large extent be applied at population level as primary prevention [32].

The aim of pharmacological treatment is to prevent fractures in individuals at high risk of fracture (secondary prevention) and prevent subsequent fractures in individuals who have already sustained a fracture (tertiary prevention). Pharmacological treatment can be divided into two categories [33]:

1. Anti-resorptive agents, which reduce bone resorption, thereby preserving BMD. These agents include oestrogen, selective oestrogen receptor modulators (SERM), bisphosphonates and RANKL antibody [33].
2. Anabolic agents, which stimulate bone formation, thereby increasing BMD. These agents include teriparatide (PTH1-34), abaloparatide (PTHrP) and romosozumab (sclerostin antibody) [33].

Pharmacological treatments have been shown to reduce the risk of hip fracture by up to 40%, vertebral fractures by 30%-70% and non-vertebral fractures by up to 30%-40% [34].

The indication for initiating anti-osteoporotic pharmacological treatment varies across countries. According to the Danish guidelines, the indication for initiating treatment is: 1) a low-energy fracture at the vertebra or hip or 2) a T-score below -2.5 and at least one risk factor [32]

4.2 Social inequalities in health

This section briefly outlines the theory behind the concept of social inequalities in health including policies and measurements to assess SES in epidemiological studies. I describe and justify the socio-economic measures used in this dissertation, namely education, income, occupation, cohabiting, Index of Multiple Deprivation (IMD) and area income.

4.2.1 Definitions

Individual disparities in health arising due to differences in age, genes or history of life exist in every society. Social inequalities in health are systematic differences in health between groups in a society due to differences in SES or position [35]. Social inequalities arise when individuals with lower SES, e.g. measured by education or income, have a different, often higher risk of morbidity than individuals with higher SES. Social inequalities also cover social disparities in consequences of illness, e.g. HRQoL and mortality [36].

4.2.2 Policies

Societal interest in the social gradient in health goes back a long way. The first systematic research programs studying social inequalities in health were initiated in the 1950s. These years saw a dramatical increase in cardiovascular mortality. This increase was almost exclusively found among skilled and unskilled workers [37]. To understand this phenomenon, the first Whitehall study was initiated in 1967 examining more than 17,500 British male civil servants. These studies, led by Michael Marmot, found the mortality rate among the lowest grade (messengers, doorkeepers, etc.) to be three times higher than that of men in the highest grade (administrators). The following decades saw extensive research into the determinants of inequalities in health, morbidity and mortality [38]. In the beginning of the new millennium, reports from the UK, Sweden and Norway on social inequality sparked a range of national policy initiatives. Inequality came on the global agenda in 2005, when the WHO appointed a global Commission on the Social Determinants of Health. The Commission, with Michael Marmot as its chair, suggested a broad range of policy options aimed at reducing social inequality in health in poor as well as in rich countries. These options covered social policies, labour policies, environmental policies and health policies [39]. The Commission’s work was followed by a resolution in the World Health Assembly requesting the member countries to produce national reports on the specific causes of inequality and to suggest measures to reduce it. On this background, several national analyses were conducted. One of them was the British report "Fair society, Healthy Lives - Strategic Review of Health Inequalities in England post-2010", also referred to as the Marmot review [40]. The Danish National Board of Health followed in 2011 with a national review on social inequality in Denmark [41].

Despite effort to reduce inequalities in health, substantial inequalities remain today and are increasing in some countries [42,43]. In Europe, these inequalities lead to a 5-10 years' difference in average life expectancy as well as a 10-20 years' difference in disability-free life expectancy [44]. The degree of inequality in mortality and morbidity varies across countries, and it is not confined to low-income countries. Health and illness follow a social gradient, in countries of all levels of income: the lower the SES, the poorer the health [39]. Research suggests that countries where income inequalities are low have longer mean longevity. However, the persistence of substantial heath inequalities shows that these policies have been insufficient to eliminate the health consequences of social and economic inequality. This is especially evident for Denmark and other Scandinavian countries, which despite their egalitarian policies and generous welfare arrangements still suffer from substantial inequalities in mortality. This puzzling large inequality in mortality in the Nordic countries is known as the Nordic paradox [44]. According to Mackenbach et al., this paradox is likely explained by a combination of three interrelated factors [44]. The first is basically, that although the Nordic countries see a lower prevalence of poverty and smaller income inequalities than most other countries, considerable inequalities in living conditions and income remain. Thus, the welfare state has not eliminated inequalities in material resources [44]. The second explanation concern changes in tendencies in social stratification and social mobility. Due to the rise of the service economy and the expansion of higher education the number of individuals occupied in routine or manual labour has decreased substantially. This smaller group is, compared to previous generations, more likely to be disadvantaged socially. Furthermore, highly educated individuals tend to cohabit with each other and so accumulate advantage within families. These tendencies are especially seen in the Nordic countries [44]. The third explanation concerns the thought that prevention and treatment generally have higher uptake and greater effectiveness among individuals with high SES due to, for example, easier access and higher utilization of health care and better compliance to treatment. In addition, individuals with high SES also find it more easy to change their health behaviours than individuals with lower SES do. Thus, unhealthy behaviour (i.e. smoking, physical inactivity) and obesity are far more common among low than among high SES individuals. Health improvements in the Nordic countries have outpaced those of other countries. This leads to faster improvements. However, it also leaves more scope for inequalities in health improvements [44].

4.2.3 Measures of socio-economic status

The conceptualisation of SES or socio-economic position in epidemiological research rests on the work of Karl Marx and Max Weber [45] Marx classified individuals according to their social class solely in terms of his or her relation to the "means of production" (e.g. factories or land). In contrast, Weber considered society as hierarchically stratified along several dimensions that form groups who share a common position with similar possibilities in life [46]. Weber's ideas on social stratification underpin the use of multiple SES measures such as education, income and occupation [46]. Today, SES is measured by a plethora of variables. Theoretically, there is not one measure that best defines SES. Each measure reflects a specific part of social stratification that may be more or less suitable to different situations at different stages in life. On the other hand, most SES measures are related given that they embody different sides of the underlying social stratification. SES measures can overall be divided into area-based measures and individual-based measures [46]. An overview of SES measures is provided in Table 1. Area-based measures are measures that aim to capture the SES of a geographical area as opposed to individual-based measures that aim to capture SES at an individual level (i.e. education, income, occupation). A brief explanation of each SES indicator is presented below.

4.2.4 Individual-based measures

Education is frequently used as an indicator of SES in epidemiological studies [46]. Education is crucial for future occupation. However, education is also an independent resource that reflects human capital and non-material resources. Education is the most stable indicator because it is not reduced by illness – unless, of course, illness occurs in the youth before maximum educational attainment has been achieved [47]. However, the value of education has changed over time, especially for women. Thus, the number of women with high educational attainment is much higher among younger than among older women. [48].

Income is related directly to material circumstances. Income influences health by having a direct impact on material resources that affect factors in the causal chain such as health behaviours and easier and faster access to health services and leisure activities. Income also has an indirect effect through better education, higher social standing and self-esteem facilitating participation in society, for example. A limitation in using income as a proxy for SES is that the association between income and health outcome can be caused by reversed causality where poor health lead to loss of income [46]. Furthermore, given that fractures occur late in life, most individuals have retired at the time they sustain a fracture, which hampers the validity of income as a marker of SES.

Occupation is closely linked to power and prestige. However, one of the challenges of using occupation as a SES indicator is that it is difficult to form homogeneous occupation groups that reflect both power and prestige and the physical and mental working conditions that influence health [48]. In addition, like income, using occupation as a proxy for SES is limited by the fact that the study population of interest in this dissertation is elderly who may have retired.

Cohabiting was included as a measure of SES. Conway et al argue that, marital status reflects SES given that marriage/cohabiting can provide social support, economic advantage and secure access to healthcare (USA) [45]. In addition, being married has been found to be associated with better health behaviours than being divorced, widowed or never married [49]. Furthermore, all non-married conditions (widowed, divorced, separated and never married) have been shown to be associated with significantly poorer health and increased mortality than married individuals regardless of gender [50].

4.2.5 Area-based measures

Area-based measures can be obtained by aggregating a single individual-level SES measure such as average income or proportion of unemployed individuals or by combining several individual measures into a composite measure. The latter, also known as "deprivation indexes", are frequently used in the United States and in the UK to assign areas on a scale from deprived to affluent. Two frequently used indexes of deprivation are the Townsend Deprivation Index and the Multiple Deprivation Index. The former covers four domains (proportions of unemployed, households with no car, households that are not owner occupied, and households with more than one person per room). The Multiple Deprivation Index includes six domains (income, employment, health and disability, educational skills and training, housing and access to health services within the area) [46]. Area-based SES can be can be used to provide valuable information to health policy makers in the evaluation and provision of health services that are solely implemented and distributed through geographical locations. It can also be applied to determine the effect that living in a given SES area has on health beyond individual SES [46]. In this dissertation, area-based SES measures are used as a proxy for individual-based measures when individual-based measures are not available. The use of area-based SES as a proxy for individual SES is associated with risk of misclassification bias toward the null given the inadequate ability to distinguish between individuals. However, in many countries, nation-wide individual-based data are unavailable or incomplete. Hence, area-based SES indicators are the only possibility for gaining knowledge on the impact of socio-economic inequality.

Table 1: Indicators of socio-economic status

Socio-economic indicator	Measure summary	Advantages	Limitations	Measure used in study
Individual-based indicators				
Education	Educational attainment: highest level attained, qualifications, years completed, ISCED.	Reflects human capital and non-material resources, usually stable across the life-course, strong determinant for income and occupation, easy to measure.	Gender and age differences can be present.	I, II, III
Income	Access to material resources and services: absolute value or categories of gross or disposable income. Measured at individual or household level.	Good indicator of social standing or prestige.	Sensitive to change: health affects level of income (Reversed causality).	I and II
Occupation	Employment or job history: longest, first, last, manual or non-manual, blue or white collar.	Reflects social standing, working relations, and working conditions.	Excludes some groups (e.g. retired people or unemployed people); classification and international comparison can be difficult. Sensitive to change: health affects (un)employment (reversed causality).	I and II
Cohabiting	Living with someone/married vs. living alone/never married/divorced/widowed.	Reflects social support and economic or material advantages and access to health care (USA).	Context-specific: country, culture, age cohort effects.	I and II
Area-based indicators				
Index of deprivation	Deprivation indexes (postal code or zip code) using single or multiple census or administrative data. Characterises areas from deprived to affluent.	Proxy when individual-level SES measures are unavailable. Measures community-level factors that can affect health.	Ecological fallacy (large geographic areas have greater misclassification than small areas). Underestimates the impact of SES on health outcome.	I and II
Area income	Mean individual or household income in a given area (e.g., postal code or zip code).	Proxy when individual-level SES measures are unavailable. Measures community-level factors that can affect health.	Ecological fallacy (large geographic areas have greater misclassification than small areas). Underestimates the impact of SES on health outcome.	I and II

The information in Table 1 is based on the following literature: Conway et al. [45] and Galobardes et al. [46].

4.2.6 Application of SES measures in this dissertation

In this dissertation, all the above-mentioned measures of SES were included in Study I and Study II (the two reviews). However, results from individual-based studies were considered the primary results of interest due to the inherent risk of ecological fallacy in area-based SES studies. Of the individual-based measures, education was chosen as the main SES measure of interest for two reasons: 1) it is the measure with the lowest risk of reversed causation (e.g., length of education is not reduced by future illness) and 2) education is an independent resource that reflects human capital and non-material resources. In Study II, education was selected as the (only) SES measure of interest due to the reasons mentioned above.

4.3 Potential pathways between socio-economic status and fragility fracture

The pathway between SES and fracture incidence or SES and fragility fracture outcome is complex and many factors may confound or mediate the association. In this section, I will define the terms confounder and mediator and present a simplified example of a suggestion of a causal diagram of the association between SES and fracture incidence.

4.3.1 Confounders

Confounding refers to the mixing of the effect of a given factor with the effect of the exposure and outcome of interest. A variable is considered to be a confounder if it is [51]:

I: associated with the exposure of interest

II: an independent cause of the outcome

III: not on the causal pathway from exposure to outcome

A factor that fulfils these criteria can confound (fool) researchers to believe that the exposure of interest has a causal effect on the outcome when is has none (i.e., the confounder is an alternative explanation for the observed association) or masks the true effect (i.e., there is no effect when in truth there is). In most cases, confounding is not absolute, but rather the association is strengthened or weakened compared with the true causal effect [51]. When we are interested in providing the best estimate of the causal effect of an exposure on an outcome, we want to remove the effect of any confounders, for example by controlling for them using multivariable regression [52].

4.3.2 Mediators

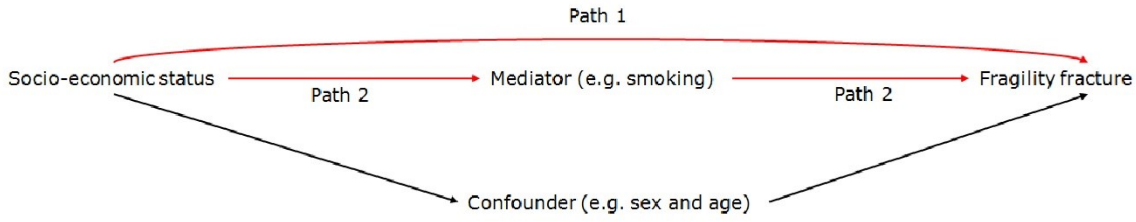
A variable is considered to be a mediator if it is a consequence of the exposure and a cause of the outcome and hence on the path from the exposure of interest to the outcome. If we are trying to get the best estimate of the causal effect of an exposure on the outcome, we do not want to control for mediators, as they are part of the process through which exposures cause the outcome. Controlling for mediators will likely lead to underestimation of the causal effect between an exposure and an outcome. However, if the research question is concerned with how much of the causal effect is mediated through a specific mediator, then one way of examining this is to determine [52]:

I: The total effect of the exposure by, e.g., regressing the outcome on the exposure controlling for confounders.

II: The direct effect that is not achieved via the mediator, e.g., regressing the outcome on the exposure controlling for confounders and the mediator.

Figure 1 illustrate a simplified diagram of the potential causal pathway between SES and fragility fracture incidence. The association of interest (i.e., the association between SES and risk of fragility fracture) is shown in red. The association of interest includes two paths. Path 1 is the direct (unmediated) effect and path 2 is the indirect (mediated association) effect. An example of mediators for SES is health behaviours such as smoking, alcohol consumption and physical inactivity. Hence, we should not adjust for health behaviours when we want to study the association between SES and fragility fracture - unless we are interested in quantifying the direct effect that is not mediated via unhealthy behaviours. Factors like age and gender are associated with both SES and risk of fragility fracture, and they are not on the causal pathway. Hence, these factors can potentially confound the association and should thus be adjusted for in the multivariate analysis.

Figure 1: Simplified diagram of the potential causal pathways between socio-economic status and fragility fracture incidence



A more detailed description of the specific confounders or mediators for each of the studies is presented in the Method section.

5 Objectives

The aim of this dissertation was to improve our understanding of social inequalities in the incidence and consequences of fragility fracture in individuals aged 50 years and above.

This was achieved through three studies with the following specific objectives:

Aim of Study I:

- To establish the association between SES and the risk of fragility fracture.
- To explore the underlying mechanisms for the inconsistencies in previously published associations by examining the impact of different SES measures, participant gender, methodological quality, fracture site (hip or non-hip) and/or factors adjusted for in multivariate analyses.

Hypotheses of Study I:

- The risk of fragility fractures is higher among individuals with low SES than among individuals with high SES, irrespective of the SES measure used.
- Differences in SES measures, participant gender, methodological quality, fracture site (hip or non-hip) and/or factors adjusted for in multivariate analyses explain a substantial part of the between-study variance.

Aims of Study II

- To establish the association between SES and post-fracture mortality.
- To establish the association between SES and post-fracture deficits in HRQoL.

Hypotheses of Study II

- The relative post-fracture mortality is higher among individuals with low SES than among individuals with high SES, irrespective of the SES measure used.
- Deficits in HRQoL following a fragility fracture are greater among individuals with low SES than among individuals with high SES, irrespective of the SES measure used.

Aims of Study III

- To explore the short-term and long-term impact on HRQoL of fragility fractures at different anatomical sites.
- To explore the impact of SES on post-fracture HRQoL.

Hypotheses of Study III

- Physical and mental HRQoL is lower in individuals with fragility fractures than in controls with no history of fragility fractures.
- Deficits in physical and mental HRQoL between controls and fracture cases are greater among those with low educational attainment than among those with high educational attainment.

6 Methods

In this chapter, I describe the design, data sources and methods applied for the three studies in the thesis. Table 2 summarises the design, study population, exposure, outcome and analysis.

Table 2: Overview of the three studies in this dissertation

Study number	Title	Design	Study population	Exposure	Outcome	Analysis
I	Socio-economic inequalities in fragility fracture incidence: a systematic review and meta-analysis of 61 observational studies	Systematic review and meta-analysis	Individuals aged 50 years or above	Low socio-economic status	Fragility fractures	Weighted random effects models and meta-regressions
II	Socio-economic inequalities in fragility fracture outcomes: a systematic review and meta-analysis of prognostic observational studies	Systematic review and meta-analysis	Individuals who had suffered a fragility fracture at the age of 50 years or above	Low socio-economic status	1) All-cause mortality within one year after fracture and 2) health-related quality of life	Weighted random effects models
III	Fragility fractures and health-related quality of life: does socio-economic status widen the gap?	Retrospective cohort study	Respondents aged 50 years or above from the Danish National Health Survey "How are you?" from 2017.	Fragility fracture	Health-related quality of life (SF-12)	Multivariable ordinary least square regression models

Study I and Study II are systematic reviews. Therefore, the methodological approach is presented collectively in the following sections.

6.1 Study I and Study II – Systematic reviews

The reviews were conducted according to the guidelines from the Cochrane Handbook and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement [53,54]. Both reviews were registered in PROSPERO and were conducted according to predefined protocols.

6.1.1 Literature search

Study I and Study II are based on the same literature search. The search strategy was developed in collaboration with Camilla Meyer who is an information specialist at Aarhus University Library, Denmark. The search strategy was validated to make sure that it retrieved a large proportion of relevant studies. This was done by checking if key studies found through any means were captured within the given search strategy. The Medline, Embase and CINAHL databases were initially searched from inception of the study to the first week of July 2018. The search was updated at the end of November 2018 for Study II and at the end of April 2021 for Study I to ensure that more recently published studies were included. The search strategy developed for Medline is presented below:

("Bone fractures" OR "Minimal trauma fracture" OR "Minimal trauma fractures" OR "Osteoporotic fracture" OR "Fragility fracture" OR "Osteoporotic fractures") AND ("Socioeconomic factors" OR "Socioeconomic status" OR "social class" OR "inequality" OR "education" OR "income" OR "marital status" OR "residence" OR "occupations").

The search was structured around the main concept of the reviews (i.e. fractures and SES). A broad set of search terms was used for each concept combined with the OR Boolean operator to increase sensitivity within the concepts [54]. The results for each concept were then combined using the AND Boolean operator to ensure that each concept was represented in the final search result. All three databases were searched using a combination of text words and standardized subject terms (e.g. Medical Subject Headings (MeSH)). We deliberately aimed for a broad search strategy because we wanted the search to capture eligible studies for both reviews. The search was not restricted by language or publication format. Reference lists of eligible studies were reviewed to ensure literature saturation.

6.1.2 Study selection

All records obtained from the searches were uploaded to the Covidence Platform. Covidence is a core component of Cochrane's reviews production toolkit that streamlines the production of systematic reviews [55]. It includes support for collaborative screening of abstracts and full-text review, risk of bias assessment as well as data extraction [54]. Initially, all duplicates were removed automatically by Covidence. The remaining records were screened independently by two review authors at title and abstract level against the predefined eligibility criteria. Inclusion criteria are available from Table 3, exclusion criteria from Table 4. Records were excluded if their title and abstract did not fulfil the eligibility criteria. Full text papers were obtained for all remaining records. Inclusion was agreed upon by consensus and, if necessary, through discussion with a third co-author. Reasons for exclusion of all full text studies were documented and are available from Supplementary Table S2 Appendix 1B (Study I) and Supplementary Table S2 Appendix 2B (Study II).

Table 3: Inclusion criteria, Study I and Study II

Criteria	Study I and II
Population	Men and women aged 50 years or older
Study design	Cohort Case-control Cross-sectional
Fractures	Fragility fracture occurring after the age of 50 years

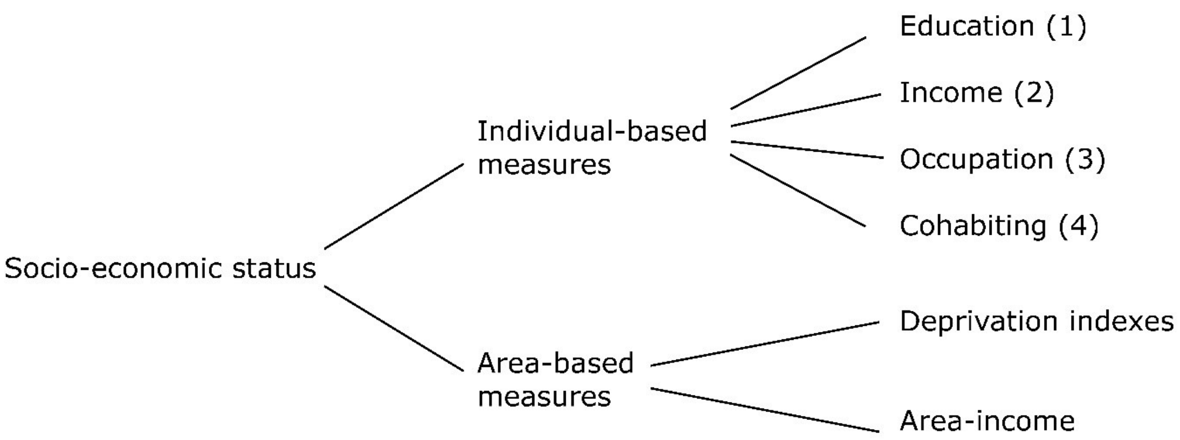
Table 4: Exclusion criteria, Study I and Study II

Criteria	**Study I and II**
Study design	Ecological Case series with less than 50 participants Conference abstracts and unpublished studies
Fractures	Fractures sustained due to traffic accidents or violence Pathological fractures Fractures of the finger phalanges or thumb, toe phalanges, head and skull
Data overlap	If results based on the same cohorts were available from different records (e.g. studies), the oldest study (i.e. with the shortest follow-up) was excluded

6.1.3 Data extraction and management

Data on baseline characteristics (i.e. country, population size, gender, age, fracture site and SES measure) and results were extracted using a standardized data extraction sheet. Data were extracted independently by two authors. In some of the included studies, SES was reported in more than one format (e.g. educational attainment and cohabiting status). Thus, in order to obtain a global risk estimate across different measures of SES without including the same population more than once in the meta-analysis, we *a priori* used the following hierarchy of SES measures developed by Lunquist et al. [56]: Education, income, occupation and cohabiting (see Figure 2).

Figure 2: Hierarchy of individual-based socio-economic status measures



6.1.4 Data synthesis

Data from the included studies in Study I and Study II were synthesized using meta-analysis. A meta-analysis is a statistical combination of results from two or more separate studies. The advantages of applying meta-analysis include an improvement of precision in the ability to answer a given research question and the opportunity to settle controversies in case of conflicting results from individual studies. However, meta-analyses also have the potential to mislead if not performed and interpreted in accordance with the given guidelines [54]. In this section, principles and methods for conducting the meta-analysis in Study I and Study II are briefly presented. More information is provided in the Method sections in Appendix 1 and 2. The meta-analysis were conducted in a two-stage process:

Stage 1: Summary statistics were calculated for each study:

- In studies where no risk ratios (RRs) were reported, the RR was calculated manually as the ratio between proportions.
- If necessary, RRs were re-calculated so that the rate of the lowest RR was divided by the rate of the highest SES category (i.e. to ensure that all RRs had high SES as reference category).
- Risk estimates in the included studies were reported in different formats (e.g. relative RR, hazard ratio (HR) and odds ratio (OR)). ORs in cohort studies derived from logistic regression are often interpreted as if they were relative risks. Subsequently, the term RR often refers to either the relative RR or the OR. However, the OR only approximates the relative RR in cohort studies under certain conditions. When the incidence of an outcome of interest is low (<10%) in the study population, the ORs is close to the relative RR. However, the more frequent the outcome is, the more the OR overestimates the relative RR when it is more than 1 or underestimates the relative RR when it is below 1 [57]. In Study II, the outcome of interest was mortality. Mortality following hip fracture among older people is common (>10%) and, thus, to reduce the risk of overestimating the impact of low SES on post fracture mortality, we converted all risk estimates in the form of ORs using the formula suggested by Zhang and Yu ($RR = \frac{OR}{(1-P0) + (P0 \text{ x OR})}$) [57]. In contrast, we did not convert the ORs in Study I given that the outcome of interest in this study (i.e. fractures) could be considered a rare event (less than 10% in the study population).
- Finally, all RRs from the included studies as well as their corresponding standard errors were transformed into their natural logarithms.

Stage 2: Summary RR including 95% CI across studies were calculated:

- The meta-analyses were performed using STATA, version 16.1 (Study I) and Review Manager provided by the Cochrane collaboration (Study II).
- Summary estimates were calculated using random-effects models as opposed to fixed effects models. Basically, the difference between the random- and the fixed-effects model is that the former incorporates an assumption that the studies do not estimate the same effect, but estimate effects that follow a distribution across studies, whereas the latter assumes that each study estimates the exact same quantity [54]. The two models will give identical results when there is no between-study variance. When between-study heterogeneity is present, the confidence

interval for the summary effect estimate is wider for the random-effect model than for the fixed-effects model [54]. In prognosis studies, unexplained heterogeneity is likely (e.g. due to differences in study population, setting, length of follow-up or treatments) and thus a random-effects approach is recommended [58] .

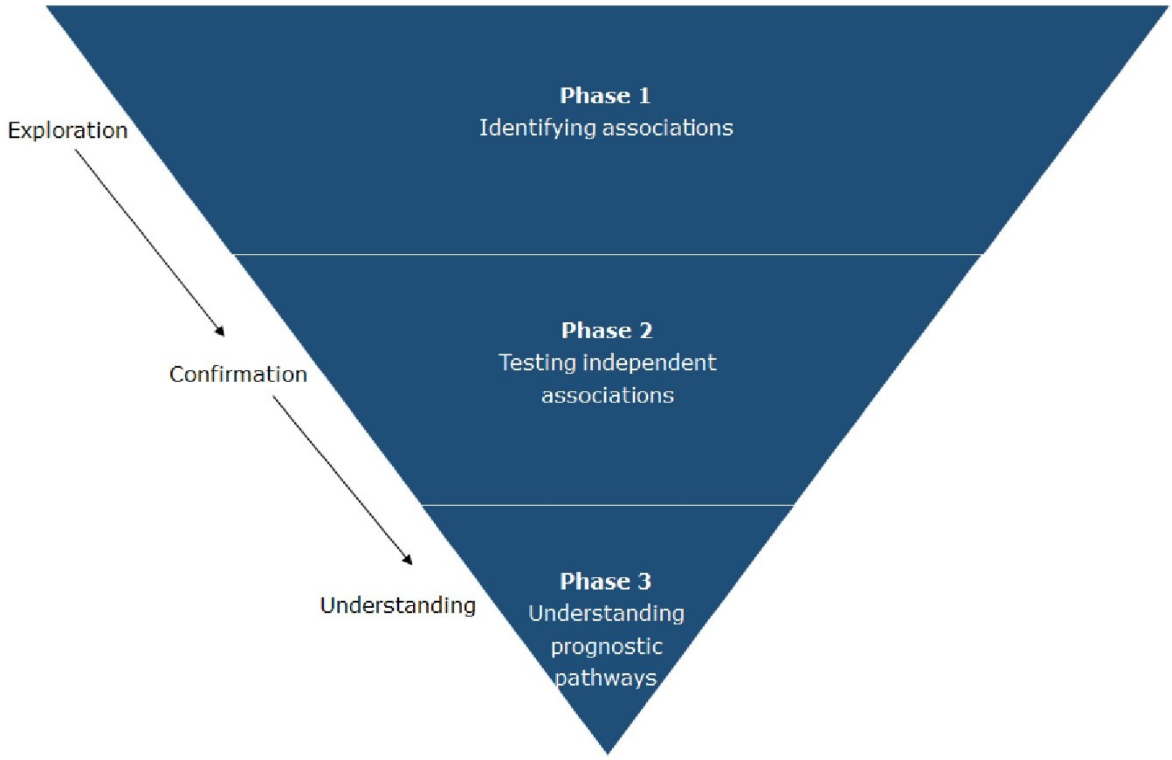
- Results from the meta-analyses were presented visually using forest plots.
- Separate forest-plots summarized data from individual-based and area-based SES studies.
- Results in each forest-plot were stratified according to type of SES measure (e.g. education, income, occupation and cohabiting).
- Heterogeneity across studies was assessed using the Q test and the I^2 index. A low p-value in the Q test provides evidence of heterogeneity (beyond chance) in the results from the included studies. The I^2 represents the percentage of total variation across studies attributable to variance rather than statistical chance. There is no strict cut off, but an I^2 of 50% or higher may represent substantial heterogeneity [54].
- Potential explanations for between-study variance were explored by *a priory* defined sub-group analyses. In addition, in Study I meta-regression analyses were performed. Meta-regression is an extension to subgroup analyses that allows quantification of the impact of selected variables of between-study variance [54]. In meta-regression, the outcome variable is the effect estimate (e.g. RR). The explanatory variables are characteristics of the included studies that might impact the size and/or the direction of the effect (e.g. gender or study quality)[54]. In the present dissertation, these variables are referred to as covariates.

6.1.5 Quality of evidence

The quality of evidence was assessed using an adapted version of the Grading of Recommendations Assessment, Development, and Evaluation' (GRADE) approach proposed for systematic reviews of prognostic factor research [59]. GRADE is a system developed to provide a transparent and structured process for developing and presenting summary of evidence including its quality. GRADE is widely used throughout the world by researchers working with systematic reviews, health technology assessments and clinical practice guidelines [60]. The adapted version of the GRADE approach for prognosis studies is similar to the original GRADE approach in most areas. However, some elements differ. The most important difference is that the starting point for rating the quality of evidence for prognosis studies is not based on study design, given that the vast majority of prognosis research stems from observational studies and not randomized trials. Instead, the starting point in the adapted GRADE approach for prognosis studies is the "phase of investigation". The "phase of investigation" is divided into three phases: Phase 1, identifying associations;

phase 2, testing independent associations; and phase 3, understanding prognostic pathways. The aim of studies in each phase can be described as exploration (phase 1), confirmation (phase 2) and development of understanding (phase 3) (Figure 3).

Figure 3: Phases of investigation in the framework of an explanatory approach to studying prognosis



The figure is based on the work of Hayden et al. [61]

High quality of evidence is derived from studies that seek to understand prognostic pathways (phase 3) or test-independent associations (phase 2), whereas moderate quality is derived from hypothesis-generating studies aimed to identify associations (phase 1) [61,59]. Table 5 illustrates the factors that may lead to rating down or up the quality of evidence from prognosis research.

Table 5: Quality assessment criteria

Phase of investigation	**Initial quality of evidence**	**Lower if**	**Higher if**	**Final quality of evidence***
Explanatory research aimed to understand prognosis pathways (phase 3 study) and explanatory research aimed to confirm independent associations between a potential prognostic factor and the outcome (phase 2 study)	High ++++	Study limitations: - 1. Serious - 2. Very serious Inconsistency - 1. Serious - 2. Very serious Indirectness - 1. Serious - 2. Very serious Imprecision - 1. Serious - 2. Very serious Publication bias - 1. Likely - 2. Very likely	Large effect + 1. Large + 2. Very large Exposure-response gradient + 1. Evidence of a gradient.	High ++++ Moderate +++ Low ++ Very low +
Outcome prediction research or explanatory research aimed at identifying associations between potential prognostic factors and the outcome (phase 1 study)	Moderate +++			

The table is inspired by the work of Guyatt et al. 2011 [60] and Huguet et al. 2013 [59]
*The final quality is evidence is dependent on the downgrading or upgrading of the initial quality of evidence.

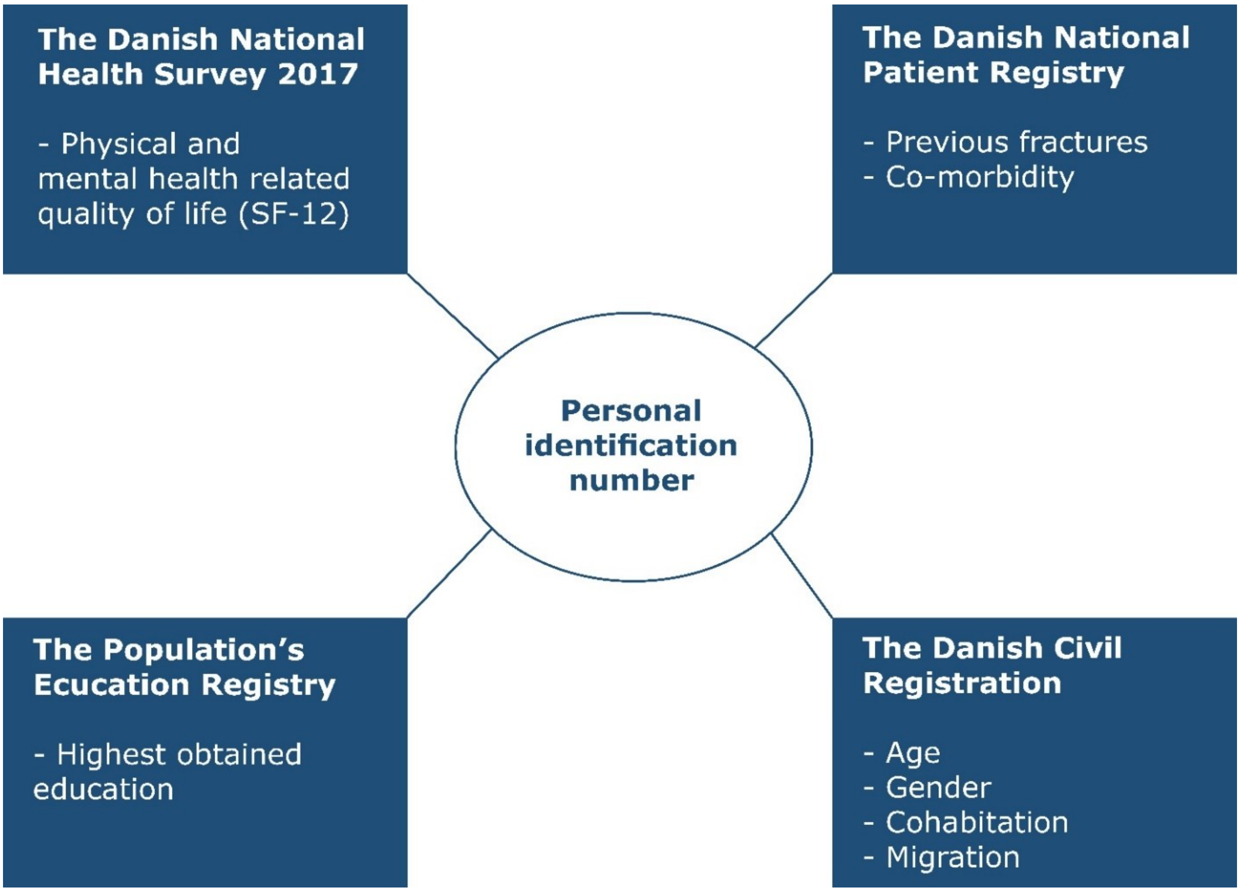
There are no cut-offs for downgrading due to phase of investigation; hence, we decided that the starting point for the quality of evidence was high if more than 50% of the evidence originated from phase 2 or 3 studies and moderate if more than 50% of the studies originated from phase 1 research.

Study limitations (i.e. risk of bias) were assessed independently by two review authors using the Quality in Prognosis Studies (QUIPS) tool [62]. Disagreement between the two assessors was resolved by reaching consensus or by involvement of a third co-author. The quality of evidence was downgraded by one point if more than 50% of the studies were judged as having unclear risk of bias and by two point if more than 50% of the studies were judged as having high risk of bias. Inconsistency was assessed using the Q-test and the inconsistency (I^2) index. In cases where inconsistency across studies appeared to be a potential caveat (I^2 > 50%), the robustness of results from the random effects model was checked against a fixed effects model; the 95% CI from the random effects model was considered robust if the point estimate from the fixed effects model was within the confidence interval of that of the random effects estimate. The risk of "small study" bias was considered likely if the fixed effects point estimate was outside the random effects 95% CI, with the level of evidence rated down for inconsistency as a consequence [54].

6.2 Study III - Retrospective cohort study

Study III is a retrospective cohort study based on data from the 2017 Danish National Health Survey "How are you?" Survey data on self-reported HRQoL were linked to national registers using the personal identification number assigned to all Danish residents. The registers contained individual-level information on previous fractures including information on anatomical site and the date of fracture as well as information on relevant confounders such as age, gender and co-morbidity. By linking survey data with register data, we were able to compare HRQoL in individuals with fractures after the age of 50 years with HRQoL in a representative population-based sample with no history of fractures (Figure 4).

Figure 4: Illustration of the use of the personal identification number as key to link survey data with nationwide health and social registers



6.2.1 Study population

The target population was the general Danish population (men and women) over the age of 50. The study population consisted of respondents from the Danish National Health Survey "How are you?" from 2017. The study population was restricted to individuals aged

50 years or above at the time of survey completion in order to minimize inclusion of non-osteoporosis-related fractures. The exclusion criteria are presented in Table 6.

Table 6: Exclusion criteria, Study III

Exclusion criteria
Individuals who sustained a fracture within the survey completion period (Feb 1 to May 31 2017)
Individuals who had sustained multiple fractures on the same date

6.2.2 Data sources

The data sources for Study III are specified below:

6.2.2.1 Survey data

- **The Danish National Health Survey**: The Danish National Health Survey, also known as the "How are you?" survey is a national, representative, cross-sectional survey of the Danish population aged 16 years and over. The survey is conducted by the five Danish administrative regions and the National Institute of Public Health at the University of Southern Denmark. The survey has been conducted in 2010, 2013 and 2017 and is based on a random sample of individuals with residence in Denmark. The overall aim of the survey is to monitor the status and trends in physical and mental health, health behaviour and morbidity in the Danish adult population [63]. The survey is based on six mutually exclusive random subsamples; one in each of the five Danish administrative regions and one national sample [63]. The study samples was drawn from the Danish Civil Registration System. Data were collected using a mixed mode approach where each invited individual could either fill out an enclosed questionnaire or use a unique web-access [64,63]. The questionnaire includes a broad range of questions on socio-demographic characteristics, HRQoL, health behaviours, chronic diseases, consequences of illness and social relations (See Appendix 4). The specific questions used to explore the hypotheses in Study III are described in the section "outcome".

6.2.2.2 Register data

- **Danish National Patient Registry (DNPR):** The DNPR has registered data on all somatic hospital admissions since 1977 and on all outpatient and emergency visits since 1995, recorded according to the International Classification of Diseases (ICD). The DNPR serves as a basis for reimbursement in the Danish healthcare system and includes administrative data including dates and times of any hospital contact, procedures performed and any secondary and primary diagnoses [65]. In this study, the DNPR was used to obtain information on all fractures that had occurred among the respondents at 50 years or above. The DNPR was further used to identify all in-patient admissions and outpatient visits during the past 10 years. The 10-year hospitalization history for each respondent was used to compute the Charlson Comorbidity Index (CCI). The CCI is described below in the section "Covariates."

- **Danish Civil Registration System (DCRS):** The DCRS has maintained electronic records of changes in vital status and migration for the entire Danish population since 1968 and provides daily updated information on vital status [66]. Through the DCRS, data on age, sex, migration and cohabiting status were obtained.

- **Population's Education Register (PER):** The PER from Statistics Denmark covers several parts of the educational system. PER monitors individuals' education history defined by completed or ongoing levels of education and defines the highest completed level of education. Among the Danish population born between 1945 and 1990, 97% has non-missing education information, indicating excellent coverage [67]. We used PER to gain information on the highest obtained education for each respondent.

6.2.3 Data management

All data (survey and register) were stored at Statistic Denmark and data management and statistical analysis were conducted through the "research machine" controlled by Statistic Denmark. The raw data files were formatted to STATA and data files from different years were appended. The different datasets were merged using the syntax: Merge *type keyvars using dataset*. Data control was performed prior to the analysis. The aim of the data control was to ensure that any later statistical analysis could be performed efficiently and to minimize the risk of incorrect or misleading results.

6.2.4 Exposure

The exposure of interest in Study III was fragility fractures. Fractures were identified from the DNPR using the ICD-9 or ICD-10 fracture codes. Fractures were divided into six categories grouped according to anatomical sites (Table 7).

Table 7: Classification of fractures, Study III

Variable name	Anatomical site of fracture
Vertebra	Thoracic (T1-T12) and lumbar (L1-L5)
Hip	Hip (and femur)*
Lower leg	Tibia and fibula
Upper arm	Shoulder and humerus
Lower arm	Ulna and radius
Other	Ribs, clavicle, scapula and pelvis

*A total of 87% of the fractures were located at the hip

The DNPR does not contain information on the mechanism of injury and, thus, it was not possible to distinguish fragility fractures from other fracture types. However, in order to minimize the risk of classifying non-fragility fractures as fragility fractures, fractures with high-impact trauma codes were not included in the classification; nor were pathological fractures and fractures of the finger phalanges or thumb, toe phalanges and head or scull.

6.2.5 Outcome

The outcome of interest in Study III was self-reported HRQoL. HRQoL was evaluated using the 12-item Short-Form Health Survey (SF-12), which is an integrated part of the Danish National Health Survey. The SF-12 is a generic questionnaire on overall health status covering physical, mental and social functioning [68] It consists of eight subscales and two summary scores, *Physical Component Summary* (PCS) and *Mental Component Summary* (MCS). PCS and MCS were used to measure physical and mental functioning. PCS and MCS are both calculated as weighted sum scores of all eight subscales [69]. The two summary measures were calculated according to the standard procedure based on the SF-12 manual. This procedure followed three steps:

Step one: The eight subscales were calculated by computing a raw score for each subscale and transforming the scores to 0-100 scale scores; zero implying poor health and 100 implying excellent health. The raw score was calculated by adding the sum of responses for the given items included in the given subscale (e.g. response value of item 2a plus response value of item 2b for the subscale Physical Functioning). The raw scale was transformed using the formula below:

$$\text{Transformed scale} = \frac{(\text{Actual raw score} - \text{lowest posible raw score})}{\text{Posible raw score range}} * 100$$

This formula transforms the lowest and highest possible scores to 0 and 100, respectively.

Example: a mental health (MH) raw score of 4 would be transformed as follows:

$$\text{Transformed scale} = \frac{(4-2)}{8} * 100 = 25$$

Step 2: The subscales were standardized using means and SDs for the 1998 general U.S. population using formulas for z-score transformation given in the SF-12 manual.

Step 3: The standardized subscale values were aggregated to PCS and MCS. For PCS, this was done by multiplying the z-score of each subscale by its respective physical factor score coefficient and summing the eight values. Similarly, the MCS was calculated by multiplying the respective mental factor coefficient and summing the values. Finally, the aggregated

PCS and MCS scores were transformed into norm-based scores by multiplying each aggregated summary score by 10 and adding 50 points to the resulting sum.

The standard method described above for scoring the SF-12 is based on weights calculated from a US population-based study from 1998. Thus, the U.S. population is used as the reference population. The advantages of using the U.S. norm-based scores are that the PCS and MCS found in our study can be directly compared with the summary scores found in other studies. Furthermore, it is an advantage that the scores can be interpreted directly given that all scores above 50 are above the mean and all scores below 50 are below the mean of the 1998 U.S. general population [69]. The disadvantages of using the US-derived scores are, firstly, that the data used to calculate the US norm-based scores are quite old; and, secondly, that data from a range of countries have shown that the US-derived weights differ substantially from the country-specific weights [70]. However, to date no Danish-specific weights have been published in a peer-reviewed journal and thus it was not feasible to use Danish norm scores in this dissertation.

The minimally important difference (MID) was applied to quantify the smallest differences in physical and mental HRQoL scores that patients would perceive as important. According to Norman et al., the threshold of MID in HRQoL for individuals with chronic diseases is approximately half a SD [71]. With reference to the norm-based U.S. values where the mean score is 50 and the SD is 10 in the general population, the MID threshold was set to 5 points in PCS or MCS (10/2=5) in this dissertation.

6.2.6 Covariates

- **Educational attainment:** The highest obtained educational attainment was used as proxy for SES in Study III. Educational level was classified according to DISCED-15 which is a dimension that ensures consistency between the Danish and the International Standard Classification of Education (ISCED) [72]. Educational attainment was divided into three categories: low (lower secondary or less), medium (upper secondary or short cycle tertiary) or high (bachelor or equivalent or higher).

- **Comorbidity:** Comorbidity was assessed using the CCI. The CCI is a weighted index that takes into account the number and the seriousness of comorbid diseases [73]. The index, developed by Mary E. Charlson and colleagues in 1987, was initially developed to predict one-year and ten-year mortality. Later, multiple adaptions have been created including modifications from 19 to 17 disease categories and a translation to ICD-9 and later ICD-10 codes [74]. We used the DNPR to identify all in-patient admissions or outpatient visits from 1 February 2017 (survey completion date). Using hospitalization history, we computed the CCI for each respondent. Comorbidity was classified as: "no" (0 points), "low" (1-2 points), "moderate" (3-4 points) and "high" (5-6 points) [73].

- **Other covariates:** Other covariates included in the multivariate models were: age (50-59, 60-69-, 70-79 or 80+), sex (female or male), ethnic background (non-immigrants or immigrants/descendants of immigrants) and co-habiting (living alone or married/co-habiting irrespective of gender).

6.2.7 Handling of missing data and risk of bias

Two approaches were applied in Study III to reduce bias and increase the statistical power of our results. The two approaches consisted of:

1) Use of weighted data
2) Imputation of missing values in SF-12

In this section, I will describe the two approaches and present data with and without the use of weights and/or imputation of missing values in the SF-12 in order to increase the transparency of the methodological approach.

Weighted data: In survey studies, it is important that the respondents are representative of the general population. The representativeness of the sample can be hampered by different sampling probabilities and differences in response rates across sub-groups. To account for these differences, making data representative to the general population, calibrated weights provided by Statistics Denmark were applied. These weights were based on information from the Danish Civil Registration System on both responders and non-responders. The information used to compute the weights included age, gender, municipality of residence, educational attainment, ethnic background, hospitalization and occupational status [63]. As visualized in Table 8, the use of weighted data reduced the mean PCS score by 0.5 point for individuals with no history of fracture and by 1.0 point for individuals with a history of fracture. The higher reduction in the fracture group than in the non-fracture group is not surprising and is most likely explained by a lower response rate among the oldest (especially women) and among the most fragile of those invited to participate.

Imputation: Missing data are not uncommon in surveys [75]. In Study III, the PCS and MCS of the SF-12 were the outcomes of interest. As described earlier, the standard SF-12 algorithm is the weighted sum of all SF-12 items; thus, answers from all 12 items are required in order to calculate the PCS and MCS summary scores [69]. This means that one missing item from the SF-12 from a respondent lead to missing data on both the PCS and MCS. In Study III, the percentage of missing datapoints for PCS and MCS was 11.5% for non-fracture individuals and 17.7% for fracture cases (Table 8). The loss of observations due to missing items can reduce statistical power, increase variation in parameter estimates and potentially lead to bias, especially when the SF-12 is the primary outcome of interest [75]. Thus, in order to reduce the number of missing PCS and MCS scores, we decided to use imputation. At least two different imputation algorithm have been suggested for imputation of missing scores in the SF-12; a simple algorithm where any missing item is replaced by the mean score of the study population and an advanced algorithm based on regression models [75,76]. In the latter model, imputation regression models are fitted using SF-12 items with or without patient demographics (age, gender, ethnicity, education and income), current smoking status and comorbidity [75]. The simple model can provide satisfactory results when three of six key items were replaced with the mean score, whereas the advanced model has no limit on missing values and can thus (in theory) be applied when all 12 items are missing [76]. Initially, before conducting the final analysis, we explored how the different imputation algorithms affected the mean PCS score and the number of missing datapoints. As presented in Table 8, the different imputation methods yielded similar PCS scores. Thus, given that the advanced model could be applied in cases where more than six item were missing, we chose the advanced algorithm. However, although this model could be used with 12 out 12 missing items on the SF-12, we did not find it reasonable to include respondents who had not answered any of the SF-12 items. Thus, we applied the enriched regression-based model with up to 11 missing items corresponding to 0.2% missing data for both fracture and non-fracture respondents.

Table 8: The impact of different methodological approaches on the Physical Component Score of the SF-12, Study III

Methods	**Individuals with no history of fracture N: 91,426 (SD or %)**	**Individuals with fracture N: 12,839 (SD or %)**
No imputation (non-weighted data)	47.5 (10.6)	43.5 (11.9)
No imputation (weighted data)	47.0 (11.0)	42.5 (12.1)
Number of missing entries	10,566 (11.5%)	2,272 (17.7%)
Simple imputation* (non-weighted data)	47.2 (10.6)	43.2 (11.8)
Simple imputation* (weighted data)	46.6 (11.0)	42.2 (12.1)
Missings	1,602 (1.75)	383 (2.98)
Advanced imputation^ (1-12 missing items!) (Non-weighted data)	47.1(10.6)	42.9 (11.8)
Advanced imputation^ (1-12 missing items!) (Weighted data)	46.5 (11.0)	41.9 (12.1)
Missing	0	0
Advanced imputation^ (1-11 missing items) (Non-weighted data)	47.1 (10.7)	42.9 (11.9)
Advanced imputation^ (1-11 missing items) (Weighted data)	46,5 (11,0)	41,9 (12,1)
Missing	143 (0.2%)	31 (0.2%)

*Perneger et Burndand 2005 [76]: A simple algorithm reduced missing data in SF-12 health surveys
^Liu et al. 2005 [75]: Imputation of SF-12 Health Scores for Respondents with Partially Missing Data

6.2.8 Ethical standards

The survey was approved by the Danish Data protection Agency and the respondents were informed in writing about the purpose of the survey and their voluntary completion. Return of the survey constituted implied consent.

6.2.9 Statistical analysis

All analyses were performed in STATA version 16.1. Descriptive statistics were applied on clinical characteristics of the fracture cases and controls. Estimates were presented as numbers and proportions or mean and SD. The hypotheses were investigated using bivariate and multivariable ordinary least square (OLS) regression models with PCS and MCS as dependent variables and history of fracture as the primary independent variable of interest. The results regarding PCS and MCS were stratified according to fracture site (hip, vertebra, upper arm, lower arm, lower leg and other) and time since fracture. Time since fracture was divided into short-term (< 1 year) and long-term (1-5 years and >5 years). The cuff-off of >1 year for "short-term" was based on bone healing times for hip fracture (up to one year). The decision to divide "long-term" into 1-5 and >5 years was pragmatic and not rooted in the literature. However, we were interested in exploring if fragility fractures were associated with permanent deficits. We argue that improvements due to treatment and rehabilitation are much more likely to occur within the first five years after fracture than later than five years after fracture. Thus, we believe that the choice of a cut-off value of 5 years is meaningful and provides useful information on the long-lasting consequences of fragility fractures. The co-variables were included as categorical variables in the multivariate models. Adjusted PCS and MCS with 95% CIs were calculated as average marginal effects using the method of marginal prediction. Finally, data were stratified by educational attainment to explore if SES modified the association between fracture and HRQoL

7 Results

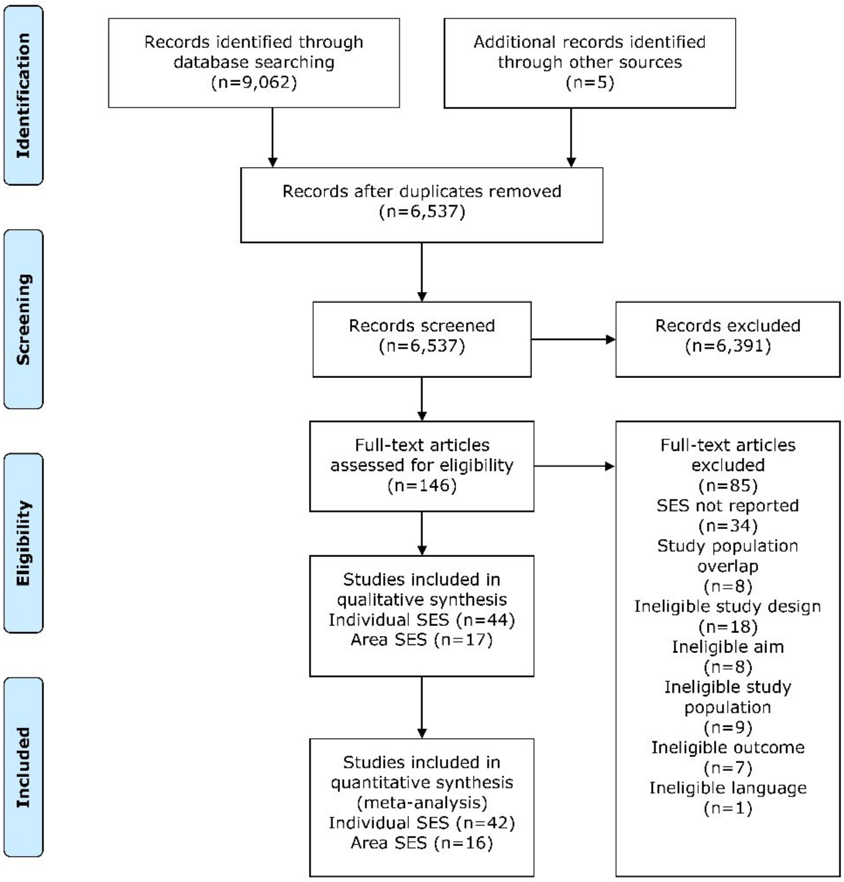
A summary of the main results of the three studies is presented separately. A more detailed presentation of the results is presented in Appendix 1-3.

7.1 Results study I –Socio-economic inequalities in fragility fracture incidence: a systematic review and meta-analysis of 61 observational studies

7.1.1 Searches

The search yielded 6,537 articles when duplicates had been removed and 61 articles fulfilled the inclusion criteria. The most frequent reasons for exclusion were studies not reporting SES and ineligible study design. A list of excluded studies with reasons for exclusion is shown in Supplementary Table 2 in Appendix 1B. Three studies were not eligible for quantitative analysis due to insufficient data [77-79]. Thus, 58 studies were included in the meta-analysis. An overview of inclusion and exclusion of studies is available in Figure 5.

Figure 5: Flow chart of inclusion and exclusion of studies, Study I [80]



7.1.2 Study characteristics

The characteristics of the included studies are presented in Table 9 (individual-based SES) and Table 10 (area-based SES). The year of publication ranged between 1993 and 2021. Twenty-six countries were represented in the review. In total, they included approximately 19.5 million individuals; 1.7 million of those had suffered a fracture. All studies except three [81-83] were carried out in high-income countries. Thirty-three of the included studies focused solely on hip fractures. Four studies examined vertebral fractures. The residual 28 studies included several fracture types. Of the individual-based studies, 59% were categorised as phase 1. For the area-based studies, two out of 17 (12%) studies were phase 1 studies. For the individual-based studies, 14 (32%) were judged as high risk of bias, 21 (48%) as unclear risk, and nine studies (20%) as low risk. For the area-based studies, two (12%) studies were judged as high risk of bias, 12 (70%) as unclear, and three studies (18%) as low. An overview of the risk of bias assessments are presented in Supplementary Figures S2A and S2B in Appendix 1B.

Table 9: Study characteristics of the included studies using individual-based SES indicators, Study I [80]

First author (year)	Study period	Country	N fracture cases/N baseline population	% of women	Mean age at baseline, years (SD)	Fracture type(s)	SES indicator (number of levels)	Phase (Risk of bias)
Al-algawy [83] (2019)	2018-2019	Iraq	75/250	68%	NR (>60)	Hip	Education (5)	1 (-)
Allali [82] (2010)	NR	Morocco	43/356	100%	58.9 (7.7)	Peripheral	Education (4)	2 (?)
Benetou [84] (2015)	NR	Germany Greece Norway Sweden USA	4,185/64,337	0-100%[A]	60.3(1.1) - 69.7(6.9)[B]	Hip	Education (3)	2 (?)
Cano [81] (1993)	1988-1989	Spain Turkey	519/1327	100%	NR (50+)	Hip	Education (4)	1 (-)
Cauley [85] (2007)	1993-2005	USA	23,270/159,579	100%	60.2 (6.8) - 63.6 (7.2)[C]	All	Education (3)	1 (?)
Chen [86] (2018)	2014-2016	Taiwan	100 /200	100%	77.9 (7.6)	Hip	Education (3)	1 (?)
Colon-Emeric [87] (2003)	1999-?	USA	NR/3619	0%	NR (>65)	Hip	Education (2)	1 (-)
Crandall [88] (2014)	NR	USA	94/2,167	100%	45.8 (2.7)	All	Education (4)	2 (?)
Espino [89] (2000)	1993/1994-1995/1996	USA	120/2895	57%	72.9 (SEM 0.22)	Hip	Education (2)	1 (?)
Farahmand [90] (2000)	1993-1995	Sweden	1327 cases/4589	100%	72.5 (6.8)	Hip	Education (3)	2 (+)
Fernandez-Ruiz [91] (2014)	1994-1995	Spain	166/5,278	58%	74.3 (6.9)	Hip	Education (4)	1 (-)
Holmberg [5] (2018)	2010-2016	Denmark	1719/17,155	100%	Range: 65-81	Hip, MOF	Education (3)	2 (+)
Johansson [92] (2018)	1987-2002	Sweden	97,136/3,500,000	36%	55 (12.2)	Hip	Education (3)	2 (?)
Kauppi [93] (2011)	1978-1994	Finland	133/2,028	100%	63.2(9.2)	Hip	Education (3)	2 (?)
Langeard [79] (2019)	NR	France	38/80	70%	69,5 (9.08)	UE	Education (NR)	1 (-)
Ma [94] (2011)	1965-1999	Japan	Hip:33, spine:43/2,737[D]	0%	53.2 (4.8)	Hip, vertebral	Education (Con)	1 (-)
Meyer [95] (1995)	1992-1993	Norway	246/492	78%	77.5	Hip	Education (3)	1 (?)
Pluskiewicz [96] (2014)	2010	Poland	176/625	100%	66.4 (7.8)	All	Education (4)	2 (?)
Ren [97] (2019)	2015	China	431/20,110	53%	62 (10.4)	Hip	Education (4)	1 (?)
Rodrigues [98] (2018)	2011-2013	Portugal	189/884	100%	NR (65+)	All	Education (4)	1 (-)
Sanfélix-Gimeno [99] (2012)	2006-2007	Spain	126/824	100%	64.0	Vertebral	Education (3)	1 (?)
Shin [100] (2012)	2001-2007	South Korea	364/2,684	57%	59.2 (8.7)	Vertebral	Education (3)	1 (+)
Syddall [101] (2012)	1911-2007	UK	159/3,225	48%	66.1	All	Education (2)	2 (?)
Tsutsumimoto [102] (2018)	NR	Japan	NR[E]	NR[E]	NR[E]	All	Education (Con)	1 (-)
Van Lenthe [103] (2010)	1991-2003	Netherlands	192/16 578	NR	NR (25+)	Hip	Education (4)	3 (+)

Table 9 continued

Vestergaard [7] (2006)	2000	Denmark	NR[F]	NR[F]	NR[F]	All	Education(5)	2 (+)
Wang [104] (2019)	2012-2018	China	27/298	81.5%	66	All	Education (2)	1 (-)
Wändell [105] (2021)	1998-2015	Sweden	114,505/1,377,035	49.8%	NR (50+)	All	Education (3)	2 (+)
Wolinsky [77] (2009)	1993-2005	USA	495/5,511	62%	77	Hip	Education (3)	1 (-)
Xavier [106] (2019)	2017	Brazil	108/194	75.3%	70.7 (11.3)	All	Education (2)	1 (-)
Zacharopoulou [107] (2019)	2019	Greece	202/404	62.1%	78.7 (6.4)	Hip	Education (2)	1 (?)
Zhang [108] (2019)	2014	China	184/154,099	NR	NR	UE	Education (4)	1 (?)
Hansen [109] (2018)	1995-2011	Denmark	189,838/379676	68.8-79,5%[G]	65.3-73.9[H]	Hip, humerus, wrist	Income (5)	2 (+)
Kim [110] (2019)	2004-2013	Korea	3943/90,012	60.6%	NR (65+)	Hip	Income (3)	2 (?)
Lin [111] (2018)	2000-2010	Taiwan	5084/20,336	NR	NR	Hip	Income (2)	1 (-)
Navarro [112] (2008)	2005-2007	Spain	203/1,139	100%	58.1 (10,0)	All, Vertebral	Income (2)	2 (+)
Navarro [113] (2013)	2007-2009	Spain	324/1,250	100%	55.1 (11.7)	All, Vertebral	Income (2)	3 (+)
Park [114] (2015)	2011-2012[I]	Korea	2012/117,346	NR	NR	Vertebral	Insurance (2)	2 (?)
Peel [115] (2007)	2003-2004	Australia	126/387	82%	82.6	Hip	Income (2)	1 (-)
Suen [116] (1998)	1990-1991	Australia	200 cases/416	75%	80	Hip	Ocupation (3)	2 (-)
Trimpou [117] (2010)	1970-2003	Sweden	451/7,495	0%	46+	Hip	Ocupation (5)	1 (?)
Korpelainen [118] (2006)	1997	Finland	124/407	100%	72.2 (1.2)	All	Co-habiting (2)	1 (?)
Lee [119] (2014)	2000-2010	Korea	233/2,546	70%	79.2 (10.2)	Hip	Co-habiting (2)	1 (?)
Reimers [120] (2007)	1993-1995	Sweden	7748/235,605	NR	NR (65+)	Hip	Co-habiting (2)	2 (+)

A) Benetou et al. (2015): EPIC-elderly Greece: 59.8%, EPIC-Elderly Umea: 52.8%, ESTHER: 54.4%, Tromsø: 54.7%, COSM: 0% SMC: 100%
B) Benetou et al. (2015): EPIC-elderly Greece: Mean:67.2 (SD:4.5) EPIC-Elderly Umea: Mean:60.3 (SD:1.1) ESTHER: Mean:66.0 (SD:4.1) Tromsø: Mean:69.7(SD:6.9) COSM: Mean:68.8(SD:5.5) SMC: Mean:69.3(SD:6.1)
C) Cauley (2007): White: Mean: 63.6 (SD: 7.2) Black: Mean: 61.6 (SD: 7.1) Hispanic: Mean: 60.2 (SD: 6.8), Asian: Mean: 63.0 (SD: 7.5), American Indian: Mean: 61.6 (SD: 7.5)
D) Ma et al. (2011): Follow-up 1994-1999
E) Tsutsumimoto et al. (2018): Subgroup of fallers with fracture vs. non-fallers
F) Vestergaard et al. (2006): Subgroup aged 60+
G) Hansen et al. (2018): Hip:68.8%, Humerus:73.8%, Wrist:79.5%
H) Hansen et al. (2018): Hip: Mean:73.9 (SD:9.5), Humerus: Mean: 67.5 (SD:10.1), Wrist: Mean: 65.3 (SD:9.3)
I) Park et al. Only data from 2012 included
NR: Not reported
Phase: Phase of investigation divided into studies that aim to identify associations (phase 1), test independent associations (phase 2) or understand prognostic pathways (phase 3)
Risk of bias: A + indicates low risk, ? indicates unclear risk, – indicates high risk
SEM: Standard error of the mean
Con: Continuous[8]

Table 10: Study characteristics of the included studies using area-based SES indicators, Study I [80]

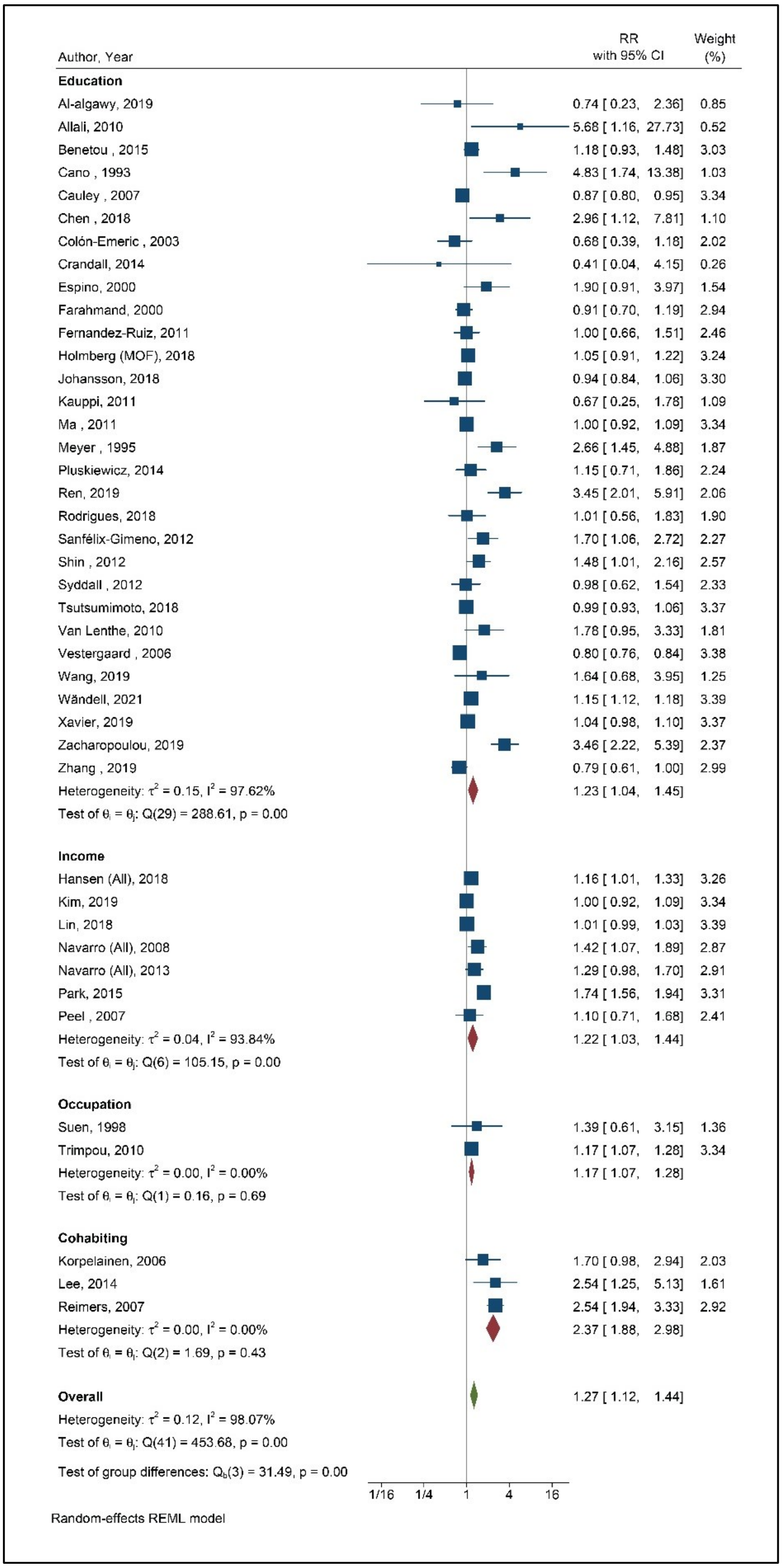
First author (year)	Study period	Country	N fracture cases/ N baseline population	% of women	Mean age at baseline (SD)	Fracture type(s)	SES indicator (number of levels)	Phase of investigation (Risk of bias)
Bhimjiyani [9] (2018)	2001/2002–2014/2015	UK	747,369/national population	74.2%	83 (77-88) [A]	Hip	Index of Multiple Deprivation (5)	2 (+)
Brennan [121] (2012)	2002-2004	Australia	427/1,074	51%	62.3	Vertebral	Indexes for areas (2)	2 (?)
Brennan [122] (2015)	2006-2007	Australia	3,943 / national population	53%	NR (50+)	All, MOF	Index of Relative Socio-economic Disadvantage (5)	2 (+)
Cassell [123](2013)	1998/1999 to 2008/2009	Australia	NR	57.4%	NR (65+)	Hip	Index of Relative Socio-economic Disadvantage (5)	2 (?)
Curtis [124] (2016)	1988-2012	UK	87,174/ national population	74%	NR (18+)	All, hip, radius/ulna, vertebral	Index of Multiple Deprivation (5)	2 (?)
Goldman [78] (2018)	2008-2011	Israel	NR[B]	NR	NR (65+)	Hip	Socioeconomic Index (20)	2 (-)
Jones [125] (2004)	1999-2000	Wales, UK	NR[C]	NR	NR (85+)	All	Towsend Score (3)	2 (?)
Maharlouei [126] (2014)	2008-2010	Iran	1,879/ national population	NR	74.7(10.6)	Hip	Area of residence (3)	1 (-)
Oliveira [127] (2015)	2000-2010[D]	Portugal	10.203/3,789,091	77.3%	79.7 (9.3)	Hip	Area of residence (3)	2 (?)
Petit [6] (2017)	2008	France	59,143/ national population	75%	NR (30+)	Hip	European Deprivation Index (5)	2 (?)
Quah [128] (2011)	1999-2009	UK	6300/ national population	77.7%	83	Hip	Index of Multiple Deprivation (5)	2 (?)
Bacon [129] (2000)	1989-1991	USA	5,161/ national population	72%	NR (50+)	Hip	Area income (6)	2 (?)
Brennan [130] (2013)	1996-2011	Canada	3723/51,327	100%	65.9 (9.8)	Hip, MOF	Mean household income (5)	2 (?)
Brennan [8] (2014)	2000-2007	Canada	15,094/ national population	60%	NR (50+)	All, hip, humerus spine, forearm,	Mean household income (4)	2 (?)
Guilley [131] (2011)	1991-2000	Switzerland	2,454/ national population	74%	79.5 (10.4)	Hip	Median household income (3)	2 (?)
Taylor [132] (2010)	2000-2005	USA	168.316/1,694,051	58%	72	Hip, vertebral, radius/ulna, tibia/fibula, humerus, ankle	Insurance status as proxy for income (5)	1 (?)
Zingmond [133] (2006)	1996-2000	USA	116,919/8,144,469	54%	NR (50+)	Hip	Median income (10)	2 (+)

A: Bhimjiyani et al. (2018)): Median and IQR
B: Goldman et al. (2018)): Not reported for the subgroup aged >65 years
C: Jones et al. (2004)): Not reported for the subgroup aged ≥85 years
D: Only data from 2010 are included
NR: Not reported
Phase: Phase of investigation divided into studies that aim to identify associations (phase 1), test independent associations (phase 2) or understand prognostic pathways (Phase 3.

7.1.3 Individual-based socio-economic status and fragility fracture incidence

A total of 44 studies explored the association between individual-based SES and fragility fracture. Of these, 42 were eligible for inclusion in the meta-analysis. The pooled RR across different individual-based SES measures indicated higher fracture risk with lower SES (1.27 [95% CI 1.12, 1.44; I^2=98%]). The RRs stratified by type of SES measure all pointed toward an increased fragility fracture risk with lower SES. Albeit, the RR for cohabiting status was significantly higher than the RR for the other measures of SES (education: 1.23 [95% CI 1.04, 1.45], income: 1.22 [95% CI 1.03, 1.44], employment: 1.17 [95% CI 1.07, 1.28] and cohabiting 2.37 [95% CI 1.88, 2.98]) (Figure 6). The two studies not included in the meta-analysis both reported a higher risk of fracture with lower educational attainment and were thus in line with the results from the meta-analysis [77,79].

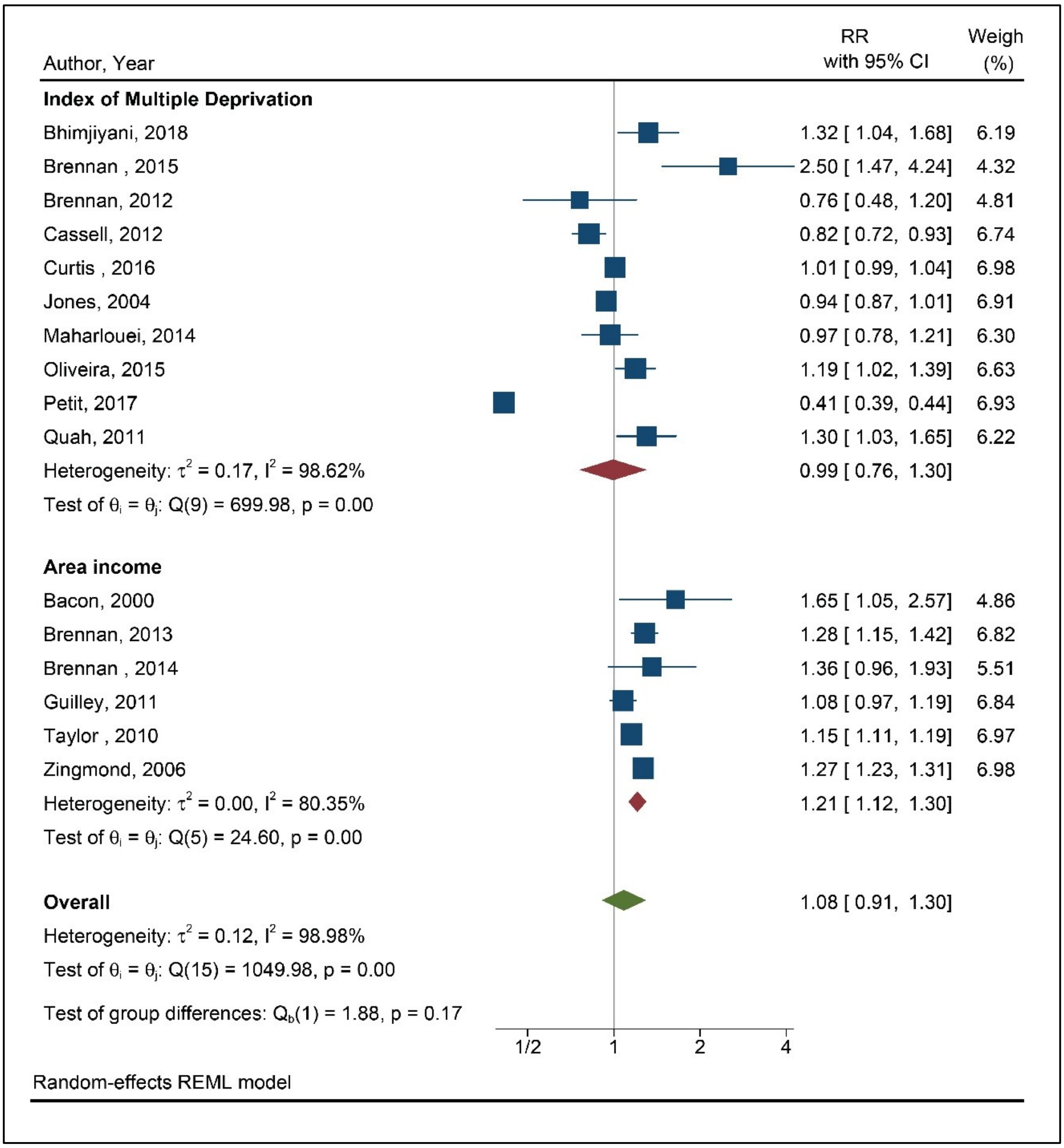
Figure 6: Forest plot of pooled risk estimates for the association between individual-based socio-economic status and fragility fracture, Study I [80]



7.1.4 Area-based socio-economic status and fragility fracture incidence

A total of 17 studies explored the association between area-based SES and fragility fracture incidence. Sixteen of these were eligible for inclusion in the meta-analysis (Figure 7). For the combined area-based SES measures, no evidence was detected to support an association with overall fragility fracture risk RR 1.08 [95% CI: 0.91, 1.30]. We found no association between the IMD and fragility fracture risk (RR: 1.00 [95% CI: 0.74, 1.35]), but low area income was associated with a higher risk of fracture (RR 1.23 [95% CI: 1.12; 1.36]). Goldman et al., the study not included in the meta-analysis, reported that living in cluster 1 (the lowest SES area) was associated with an increased fracture risk (OR 1.6) compared with living in cluster 20 (the highest SES area) [78].

Figure 7: Forest plot of pooled risk estimates for the association between area-based socio-economic status and fragility fracture, Study I [80]



7.1.5 Subgroup analysis

As expected, the overall analysis indicated a substantial between-study heterogeneity. Results from the subgroup analysis of *a priory* defined potential sources of between-study heterogeneity are presented in Table 11. For the individual-based SES studies, the most important explanation for the between-study variance was differences in model adjustments. Hence, the combined estimate for studies adjusting for age, gender and BMI returned a RR of 2.69 [95% CI:1.60, 4.53], which was substantially higher than the RR for studies adjusting for age, gender, BMI and health behaviours such as smoking and alcohol consumption. As presented in Table 12, model adjustment accounted for 39% of the between study variance for the SES measure education ($p<0.05$).

Table 11: Results of the stratified meta-analyses, Study I [80]

Factor	Subgroup	Studies	Risk ratio [95% CI]	Heterogeneity (I^2)
Individual-based SES (All SES combined)				
Quality	High[A]	18	1.19 [1.02, 1.38]	96%
	Low[B]	24	1.37 [1.12, 1.67]	98%
Gender	Women only	23	1.20 [1.01, 1.41]	98%
	Men only	12	1.07 [0.82, 1.40]	99%
Fracture site	Hip	24	1.39 [1.14; 1.70]	97%
	Non-hip	7	1.36 [1.13; 1.64]	89%
Factors adjusted for	Crude	10	1.16 [0.88; 1.53]	83%
	Sex and age	15	1.30 [1.07; 1.57]	95%
	Sex, age and BMI	5	2.69 [1.60; 4.53]	67%
	Sex, age, BMI and Health behaviours[C]	11	1.06 [0.92, 1.22]	92%
Area-based SES (All SES combined)				
Quality	High[A]	14	1.09 [0.89, 1.34]	99%
	Low[B]	2	1.10 [0.94, 1.27]	54%
Gender	Women only	8	1.20 [1.06, 1.37]	98%
	Men only	6	1.41 [0.97, 2,04]	99%
Fracture site	Hip	13	1.08 [0.89; 1.31]	99%
	Non-hip	11	1.10 [1.03; 1.17]	84%

A: Phase 2 or phase 3 studies with low or unclear risk of bias
B: Phase 1 studies or studies with high risk of bias regardless of phase of investigation
C: Smoking, alcohol consumption and/or physical inactivity

Table 12: Results from the meta-regression analysis for the socio-economic status measures education and Index of Multiple Deprivation, Study I [80]

Variable	Studies (n)	Risk ratio [95% CI]	Tau^2 % [A]	p value
All studies (Education)	30	1.23 [1.04, 1.45]		
Quality			4%	0.13
High[B]	12	1.02 [0.90, 1.15]		
Low[C]	18	1.40 [1.08, 1.82]		
Gender			0%	0.18
Women only	18	1.00 [0.91, 1.10]		
Men only	9	0.88 [0.72, 1.09]		
Fracture site			0%	0.85
Hip	16	1.43 [1.07, 1.92]		
Non-hip	3	1.29 [0.92, 1.80]		
Factors adjusted for			39%	0.001
Crude	9	1.17 [0.85, 1.60]		
Gender and age	11	1.10 [0.98, 1.24]		
Gender, age and BMI	3	3.85 [2.44, 6.07]		
Gender, age, BMI and health behaviours [D]	7	1.02 [0.78, 1.32]		
All studies (Index of Multiple Deprivation)	10	0.99 [0.76, 1.30]		
Quality			0%	0.95
High[B]	9	1.00 [0.74, 1.35]		
Low[C]	1	0.97 [0.78, 1.21]		
Gender			0%	0.67
Women only	5	1.20 [0.99, 1.45]		
Men only	5	1.38 [0.89, 2.15]		
Fracture site			0%	0.70
Hip	6	0.93 [0.65, 1.33]		
Non-hip	1	0.76 [0.48, 1.20]		

A: Percentage reduction in Tau^2

B: Phase 2 or phase 3 studies with low or unclear risk of bias

C: Phase 1 studies or studies with high risk of bias regardless of phase of investigation

D: Smoking, alcohol consumption and/or physical inactivity

7.1.6 Quality of evidence (GRADE)

For the individual-based studies, the starting point for the quality of evidence was moderate, given that more than 50% (59%) of the studies were categorised as phase 1. We did not downgrade for inconsistency, given that a large part of the between-study variation could be explained by model adjustment (Table 13). The starting point for the quality of evidence for the area-based studies was high, given that 88% of the included studies were phase 2 studies. The evidence was downgraded due to study limitations, given that more than 50% of the studies had unclear risk of bias. Consequently, the quality of evidence was judged as moderate (Table 13).

Table 13: Summary of findings for the association between socio-economic status and fragility fracture incidence, Study I [80]

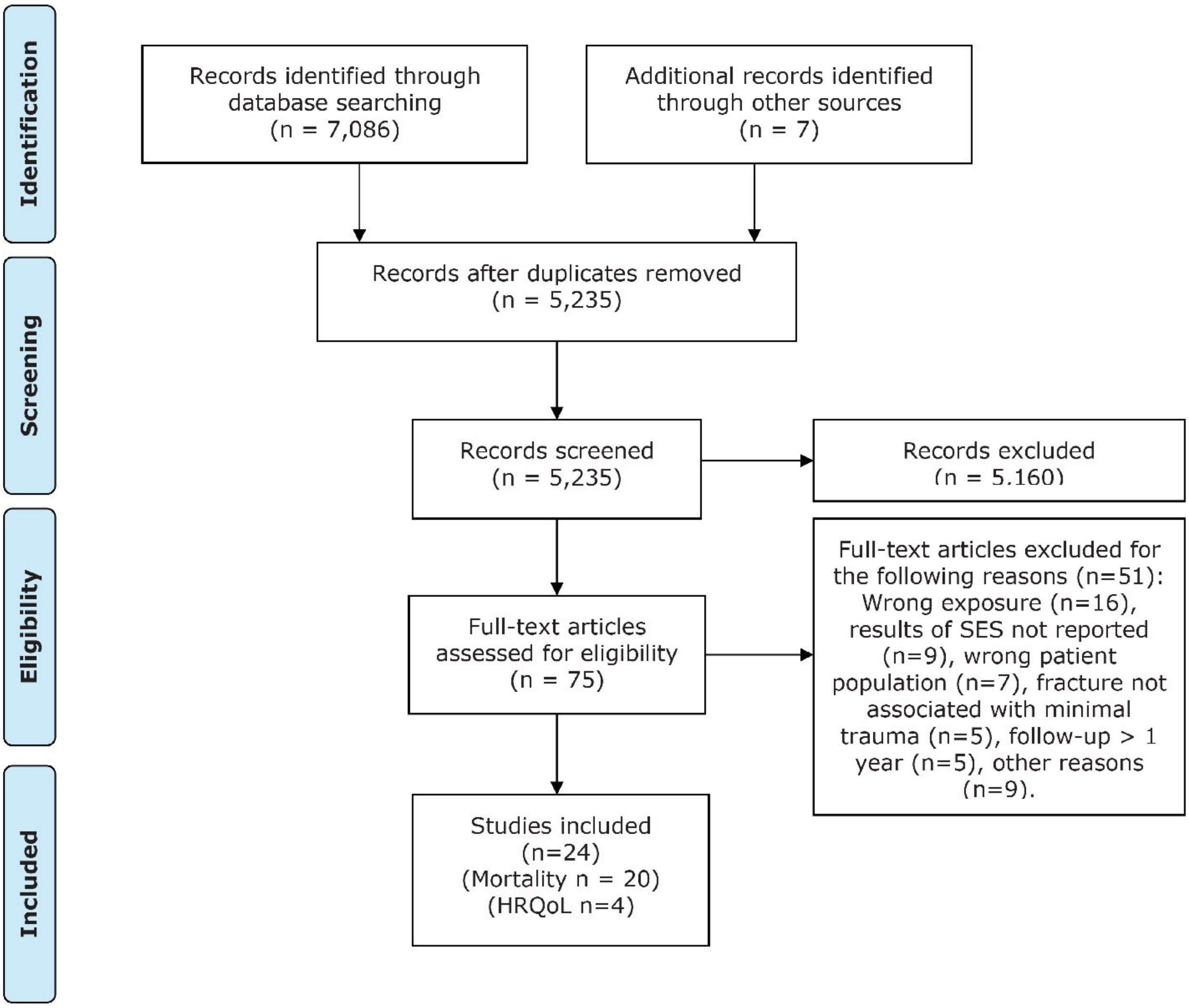
SES measure	Studies (n)	Estimated risk ratio [95% CI]	I^2	Phases	Overall quality	Comments
Individual-based SES						
Education	30	1.23 [1.04, 1.45]	98%	1,2,3	moderate (+++)	Downgraded due low phase of investigation
Income	7	1.22 [1.03, 1.44]	94%			
Occupation	2	1.17 [1.07, 1.28]	0%			
Cohabiting	3	2.37 [1.88, 2.98]	0%			
All SES Combined	42	1.27 [1.12, 1.44]	98%			
Area-based SES						
Index of Multiple Deprivation	10	0.99 [0.76, 1.30]	99%	1,2	Moderate (+++)	Downgraded due to serious limitations.
Area Income	6	1.21 [1.12, 1.30]	80%			
All SES combined	16	1.08 [0.91, 1.30]	99%			

7.2 Results Study II - Systematic review of socio-economic inequalities in mortality and health-related quality of life after fragility fractures

7.2.1 Searches

The in- and exclusion of studies for Study II is illustrated in Figure 8. The database searches for Study II yielded 5,235 potential records of which 75 were read in full text. Of these, 46 were excluded, leaving 24 studies for inclusion. A full list of excluded studies and exclusion criteria is available in Supplementary Table S2 in Appendix 2B. As mentioned in the Method section, Study I and Study II are based on the same search; however, for practical reasons, analysis for Study II was performed prior to analysis for Study I. Hence, the searches from Study I were updated at a later time which explains why the number of records identified through database screening is smaller for Study II than for Study I.

Figure 8: Flow chart of in- and exclusion of studies, Study II [21]



7.2.2 Study characteristics

Twenty studies reported post-fracture mortality as an outcome. The remaining four studies reported post-fracture HRQoL. All of the included studies - except one - were restricted to patients with hip fractures. The publication year ranged from 1994 to 2018. Fifteen different countries were represented, and more than one million fracture patients were included in the analysis. All studies were conducted in high- or middle-income countries. The mean overall 1-year mortality was 20%. The characteristics of the included studies are available from Table 14. A total of eight of the 14 individual-based mortality studies were phase 1 studies. Out of these 14 studies, five had low risk, five had unclear risk and four had high risk of bias. Of the six area-based mortality studies, one was phase one. Of these six, two had low risk, three had unclear risk and one had high risk of bias. The four HRQoL studies were all phase 1 studies; of these, two studies had unclear risk of bias and two studies had high risk of bias (Supplementary Figure S1 in Appendix 2B.

Table 14: Study characteristics of the included studies, Study II [21]

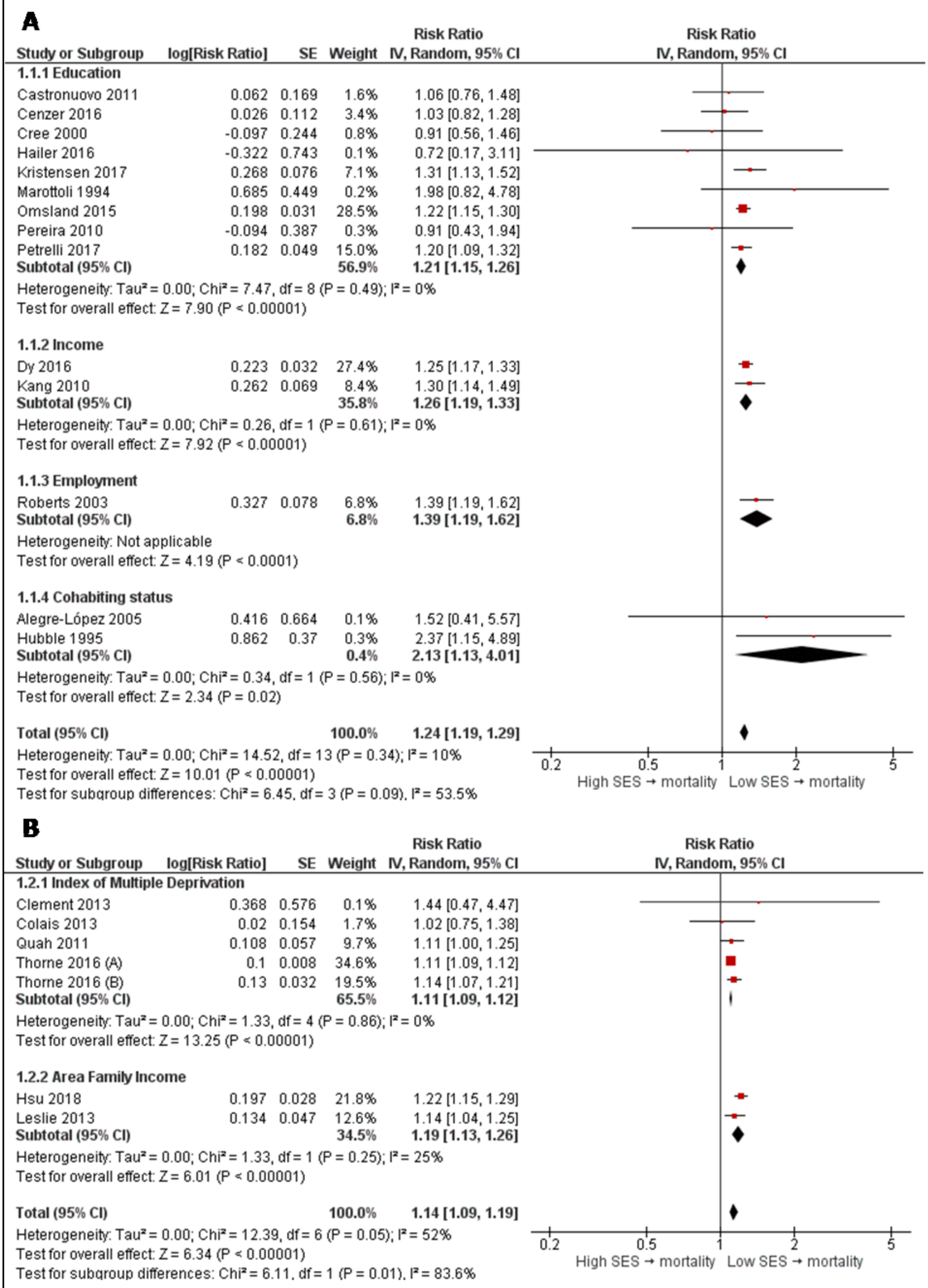
Author (year)	Country of origin	Number of participants at baseline	Women (%)	Mean age in years (SD)	Fracture type	SES indicator (number of levels)	Outcome measure (follow-up in months) Overall mortality	Phase (risk of bias)
Abimanyi-Ochom [134] (2015)	Australia	915	75.7	69.8 (11.5)	All fractures	Education (2*)	HRQoL (12)	1 (?)
Alegre-López [135] (2005)	Spain	218	76.1	81.8 (8.8)	Hip	Cohabiting status (2)	Mortality (12) 22.5%	1 (?)
Castronuovo [136] (2011)	Italy	6,896	78	83 (76-88)*	Hip	Education (2)	Mortality (1) 7%	1 (+)
Cenzer [137] (2016)	USA	857	76.0	83.8 (7.7)	Hip	Education (2)	Mortality (12) 27%	1 (-)
Clement [138] (2013)	Scotland	162	79	81.8 (range 65-98)	Hip	IDM (5)	Mortality (12) 19%	1 (-)
Colais [139] (2012)	Italy	5,701[+]	77.7	83.1 (7.1)	Hip	IDM (3)	Mortality (1) 7.7%	3 (+)
Cree [140] (2000)	Canada	558	74	81	Hip	Education (2)	Mortality (3) 8%	1 (?)
Dy [141] (2016)	USA	197,290	73.2	79.1 (14.5)	Hip	Income^ (2)	Mortality (12) 7.1%[!]	3 (?)
Guirant [142] (2018)	Mexico	193	80.3	77.2 (9.9)	Hip	Education (4)	HRQoL (12)	1 (?)
Hailer [143] (2016)	Sweden	5,928[#]	75	Not reported	Hip	Education (4)	Mortality (3) 3.7%	2 (?)
Hsu [144] (2018)	Taiwan	193,158	61.3	Nor reported	Hip	Mean area-family income (3)	Mortality (12) 10.5%	3 (?)
Hubble [145] (1995)	England	338	Not reported	Not reported	Hip	Cohabiting status (2)	Mortality (12) 28.5%	1 (-)
Kang [146] (2010)	South Korea	9,817	70.2	74.92 (9.13)	Hip	Income^ (2)	Mortality (12) 16.6%	1 (+)
Kristensen [147] (2017)	Denmark	25,354	71	Not reported	Hip	Education (3)	Mortality (1) 8.9%	3 (+)
Leslie [148] (2013)	Canada	10,367[-]	71	Not reported	Hip	Mean area family income (5)	Mortality (12) 17.7%	2 (?)
Marottoli [149] (1994)	USA	120	72	Not reported	Hip	Education (2)	Mortality (6) 18%	1 (-)
Marques [150] (2015)	Portugal	186	78.5	80.5	Hip	Education (3)	HRQoL (1 and 12)	1 (-)
Moerman [151] (2016)	The Netherlands	335	68	79.4 (10.7)	Hip	Cohabiting status (2)	HRQoL (12)	1 (-)
Omsland [152] (2015)	Norway	56,269	70.6	Not reported	Hip	Education (3)	Mortality (12) NA	3 (+)
Pereira [153] (2010)	Brazil	246	71	80	Hip	Education (3)	Mortality (12) 35%	1 (-)
Petrelli [154] (2018)	Italy	21,432	77.7	Not reported	Hip	Education (3)	Mortality (1 and 12) 21.9%	3 (+)
Quah [128] (2011)	England	6,300	77.7	82.8 (range 65-105)	Hip	(5)	Mortality (1 and 12) 34.7%	2 (?)
Roberts [155] (2003)	England	32,590	81.9	81.5 (7.4)	Hip	Employment (3)	Mortality (1 and 12) ≈35%	2 (?)
Thorne (A) [156] (2016)	England	455,862	73.8,	80.7 (11.6),	Hip	IMD (5)	Mortality (1 and 12) 29.0%	3 (+)
Thorne (B) [156] (2016)	Wales	29,733	74	80.4 (11.1)	Hip	IMD (5)	Mortality (1 and 12) 27.9%	3 (+)

+ Only results from population no. 2 (2009-2010) were eligible for inclusion because pop 1 (2006-2007) was included in the study by Castronuovo et al.
! Only in-hospital mortality assessed
Only fracture patients with available American Society of Anesthesiologists Classification (ASA) grade were eligible for inclusion
- Only hip fracture cases from population no. 2 were eligible for inclusion
* Primary vs. secondary or post-secondary university vs. secondary
^Insurance status as proxy for income

7.2.3 Socio-economic status and post-hip fracture mortality

For the individual-based studies, combining effect estimates from studies of education, income, occupation and cohabiting status produced a RR for post-hip fracture mortality of 1.24 [95% CI: 1.19, 1.29] in individuals with the lowest versus the highest SES. The RR for each of the SES measures was as follows: Education: RR 1.21 [95% CI: 1.15, 1.26], income: RR 1.26 [95% CI: 1.19, 1.33], occupation RR: 1.39 [95% CI: 1.19, 1.62] and cohabiting RR: 2.13 [95% CI: 1.13 to 4.01] (Figure 9A). For the area-based studies, combining the RRs from the IMD and area income returned a RR of 1.14 [95% CI: 1.09, 1.19], indicating higher risk of post-hip fracture mortality with lower SES. The RRs for studies using the IMD and area income yielded very similar RR (i.e. 1.11 [95% CI: 1.09, 1.12] for IMD and 1.19 [95% CI: 1.13, 1.26] for area income (Figure 9B).

Figure 9: Forest plot of pooled risk estimates for the association between socio-economic status and post-hip fracture mortality, Study II [21]

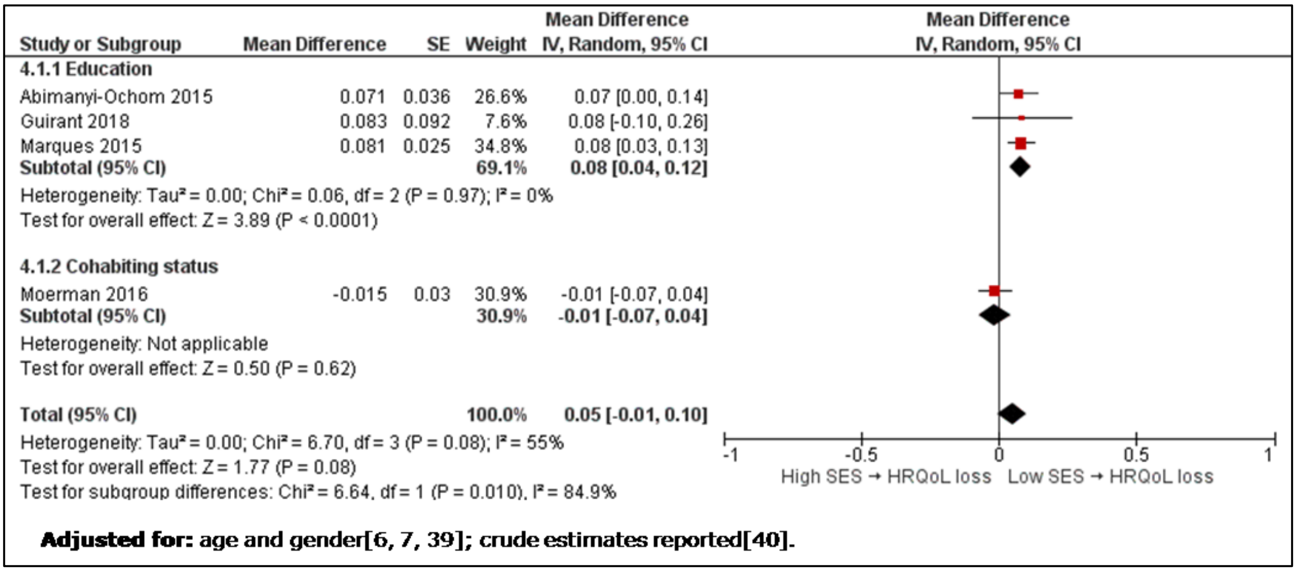


Adjusted for: age, sex and comorbidity [11, 13, 14, 16, 19, 27-32]; age and sex [15, 33]; crude estimates reported [12, 20, 34-38]

7.2.4 Socio-economic status and post-fracture HRQoL

The association between individual-based SES and post-fracture HRQoL was investigated in four studies. [134,142,150,151]. Combining results from the SES measures education and cohabiting we found that low SES was associated with a non-significant additional loss of HRQoL of 5% [95% CI: -1%, 10%]. (Figure 10)

Figure 10: Forest plot of pooled risk estimates for the association between individual-based socio-economic status and changes in health-related quality of life, Study II [21]



7.2.5 Quality of the evidence (GRADE)

For the outcome mortality, the quality of evidence for the individual SES measures was moderate, given that eight of 14 (57%) studies were phase 1 studies. The quality of evidence was not down-graded for the individual-based studies. The quality of evidence for the area-based outcome, was high as a starting point given that only one of seven (14%) were phase 1 studies. The quality of evidence was however, down-graded due to very serious risk of bias. Hence, the final quality of the evidence for the area-based outcome was moderate. The initial quality of evidence for the outcome post-fracture HRQoL was moderate given that all the studies were phase 1 studies. The quality of evidence was rated down due to risk of bias and due to risk of publication bias. Consequently, the final quality of evidence for post-fracture HRQoL was very low. (Figure 15).

Table 15: Summary of findings for the association between SES and post-fracture mortality and loss of health-related quality of life, Study II [21]

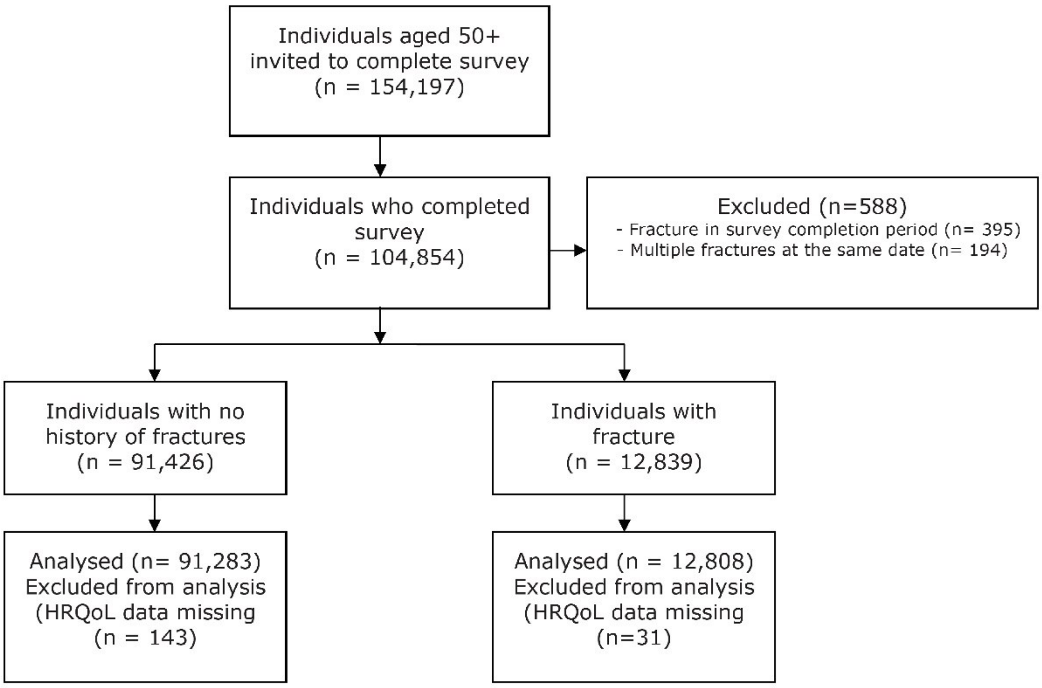
Outcome: Mortality				
Prognostic factor	**No of participants (cohorts)**	**Estimated risk ratio [95% confidence interval]**	**Certainty of the evidence (GRADE)**	**Comments**
Individual-based SES	345,315 (14)	1.24 [1.19 to 1.28]	Moderate (+++)	Downgraded due to phase of investigation
Area-based SES	701,283 (7)	1.14 [1.09 to 1.19]	Moderate (+++)	Downgraded due to serious risk of bias
Outcome: Health-related quality of life				
Prognostic factor	**No of participants (cohorts)**	**Estimated relative mean difference (95% confidence interval)**	**Certainty of the evidence (GRADE)**	**Comments**
Individual-based SES	1,629 (4)	0.05 [-0.01 to 0.10]	Very low (+)	Downgraded due to phase of investigation, serious risk of bias and high risk of publication bias

7.3 Results Study III – Fragility fractures and health-related quality of life: Does socio-economic status widen the gap?

7.3.1 Study population

The study population in Study III consisted of respondents from the national health questionnaire aged 50 years or above. The flow of inclusion and exclusion of participants is presented in Figure 11. A total of 104,854 individuals in the eligible age group completed the survey (68% of those invited) of whom 588 were excluded; 395 because they had sustained a fracture within the survey distribution period and 195 because they had sustained multiple fractures at the same date indicating high trauma fracture. Thus, 91,283 non-fracture individuals and 12,808 fracture cases were included in the analysis.

Figure 11: Flow chart of inclusion and exclusion of participants, Study III



7.3.2 Clinical characteristics

An overview of the clinical characteristics of the study population is available from Table 16. Fracture cases were more likely to be 70+ of age, women, living alone and to have moderate or high level of co-morbidity and a low level of education. Half of the fracture cases had suffered a previous fracture. The most common fracture sites were lower arm (40%) and lower leg (23%). The least common fracture site was spine with 4%.

Table 16: Characteristics of individuals with a history of a fragility fracture and individuals with no history of fracture, Study III [22]

Clinical characteristics	Fracture Number, (%[A]) or mean [A], [sd [A]]	Non-fracture Number, (%[A]) or mean [a], [sd [A]]	Percentage of fracture cases (%[A])	Chi-squared or two-sample t-test for difference
Total number by group	12,839	91,426	13.0%	
Sex				P < 0.01
Female	8,846 (70.0%)	45,793 (49.2)	17.1%	
Male	3,993 (30.0%)	45,633 (50.8)	7.9%	
Missing	0	0	-	
Age				P < 0.01
50-59	1,295 (10.1%)	33,395 (38.7%)	3.6%	
60-69	4,139 (29.6%)	29,822 (30.4%)	12.4%	
70-79	4,831 (35.2%)	21,109 (21.7%)	19.1%	
80+	2,574 (25.1%)	7,100 (9.2%)	28.4%	P < 0.01
Mean	72.8 [9.8]	64.8 [10.2]	-	
Missing	0	0	0%	
Educational level				P < 0.01
Low	4,409 (41.2%)	23,622 (30.6%)	16.4%	
Medium	5,448 (39.3%)	44,686 (46.9%)	10.9%	
High	2,935 (18.7%)	22,869 (22.0%)	11.0%	
Missing	47 (0.7%)	249 (0.6%)	15.9%	
Co-habiting status				P < 0.01
Live with a partner	7,767 (51.4%)	66,658 (66.1%)	10.2%	
Live alone	5,072 (48.6%)	24,768 (33.9%)	17.2%	
Missing	0	0	0%	
Ethnic background				P < 0.01
Danish	12,393 (94.9%)	86,893 (92.0%)	13.0%	
Non-Danish	446 (5.1%)	4,533 (8.0%)	8.6%	
Missing	0 (0%)	0 (0%)	0%	
Type of fragility fracture				-
Upper leg	1,279 (10.9%)		-	
Vertebra	557 (4.4%)		-	
Upper arm	1,503 (12.1%)		-	
Lower arm	5,190 (39.9%)		-	
Lower leg	3,091 (23.4%)		-	
Other	1,219 (9.4%)		-	
Missing	0(0%)		-	-
Previous fractures[B]	6,846 (53.7%)		-	-
Charlson Comorbidity Index score				
No (score 0)	7,821 (58.8%)	65,764 (71.6%)	10.7%	P < 0.01
Low (score 1-2)	3,801 (31.1%)	20,640 (22.7%)	16.6%	
Moderate (3-4)	862 (7.2%)	3,586 (4.1%)	20.5%	
High (score≥5)	355 (3.0%)	1,436 (1.7%)	20.5%	
Missing	0	0	0%	
HRQoL				
PCS[C]	41.9 [12.1]	46.5 [11.0]	-	P < 0.01
MCS[C]	49.3 [11.1]	50.5 [10.3]	-	P < 0.01
Missing	31 (0.2%)	143 (0.2%)	-	-

A: Weighted percentage or mean [sd]
B: Previous fractures after the age of 50 years
C: Multi-pattern regression-based imputation

7.3.3 Effects of fracture

Regardless of time since fracture, fractures at all sites except the lower arm were associated with significant deficits in crude as well as adjusted PCS and MCS (Table 17). In the adjusted model, the MID threshold deficits were exceeded among individuals with fractures of the spine (-6.0 [95% CI: -7.0, -5.0]) and hip (-5.5 [95% CI: -6.2; -4.8]).

Table 17: Crude and adjusted Physical Component Score and Mental Component Score for non-fracture individuals and individuals with a history of fractures regardless of time since fracture, Study III [22]

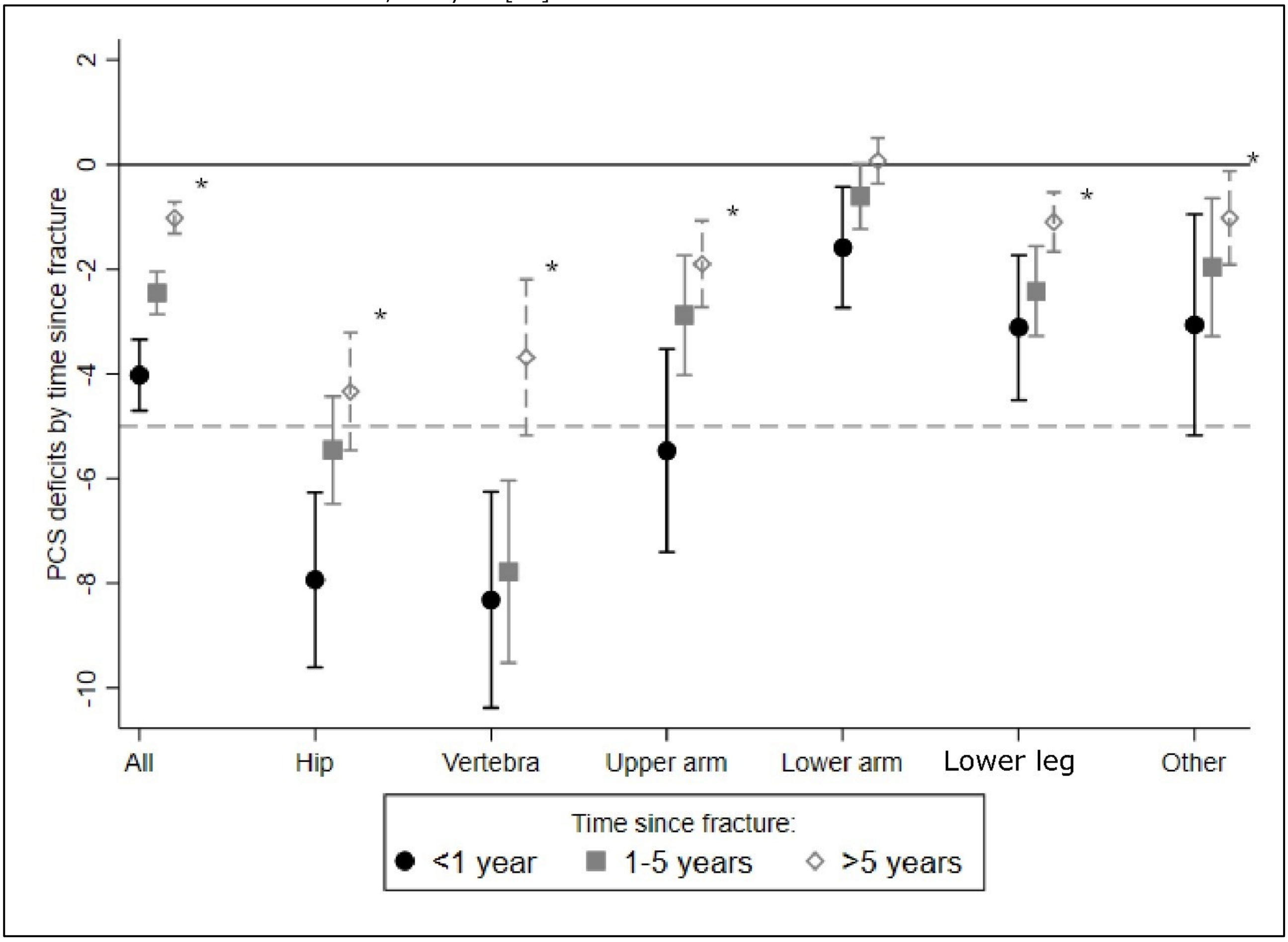
Physical Component Summary score	**Crude**		**Adjusted**[A]	
Fracture site	**Mean score** [95% CI]	**Mean deficit** [95% CI]	**Mean score** [95% CI]	**Mean deficit** [95% CI]
No fractures	46.5 [46.4; 46.6]	**-**	46.2 [46.1; 46.3]	**-**
All fractures	41.9 [41.7; 42.2]	-4.6* [-4.9; -4.4]	44.4 [44.1; 44.6]	-1.8* [-2.1; -1.6]
Upper leg	35.1 [34.4; 35.9]	**-11.4*** [-12.1; -10.7]	40.7 [40.0; 41.4]	**-5.5*** [-6.2; -4.8]
Vertebrae	37.5 [36.4; 38.6]	**-9.0*** [-10.1; -7.9]	40.2 [39.2; 41.3]	**-6.0*** [-7.0; -5.0]
Upper arm	40.3 [39.6; 41.0]	**-6.2*** [-6.9; -5.5]	43.5 [42.9; 44.2]	-2.7* [-3.3; -2.1]
Lower arm	43.7 [43.3; 44.1]	-2.8* [-3.2; -2.5]	45.9 [45.5; 46.2]	-0.3 [-0.7; 0.0]
Lower leg	42.9 [42.4; 43.4]	-3.6* [-4.1; -3.1]	44.5 [44.1; 45.0]	-1.7* [-2.2; -1.2]
Other	43.7 [43.0; 44.5]	-2.8* [-3.6; -2.0]	44.7 [43.9; 45.4]	-1.6* [-2.3; -0.9]
Mental Component Summary score	**Crude**		**Adjusted**[A]	
Fracture site	**Mean score** [95% CI]	**Mean deficit** [95% CI]	**Mean score** [95% CI]	**Mean deficit** [95% CI]
No fractures	50.5 [50.5; 50.6]	-	50.5 [50.5; 50.6]	**-**
All fractures	49.3 [49.1; 49.5]	-1.2* [-1.5; -1.0]	49.5 [49.3; 49.7]	-1.0* [-1.2; -0.7]
Upper leg	46.6 [45.9; 47.4]	-3.9* [-4.7; -3.2]	47.9 [47.2; 48.7]	-2.6* [-3.3; -1.9]
Vertebrae	47.3 [46.2; 48.4]	-3.2* [-4.3; -2.1]	47.4 [46.4; 48.5]	-3.1* [-4.2; -2.0]
Upper arm	48.2 [47.5; 48.9]	-2.3* [-3.0; -1.6]	48.8 [48.1; 49.5]	-1.7* [-2.4; -1.0]
Lower arm	50.1 [49.7; 50.4]	-0.5* [-0.8; -0.1]	50.2 [49.9; 50.5]	-0.3 [-0.7; 0.0]
Lower leg	50.0 [49.5; 50.4]	-0.5* [-1.0; -0.1]	49.9 [49.5; 50.4]	-0.6* [-1.1; -0.2]
Other	49.9 [49.2; 50.6]	-0.6 [-1.4; 0.1]	49.5 [48.9; 50.2]	-1.0* [-1.7; -0.3]

All estimates are based on weighted data. Bold numbers: Clinically significant and minimal important difference ≥ 5 points
Abbreviations: CI, confidence interval
A: Estimates are adjusted for sex, age, ethnicity, educational attainment, co-habiting status and comorbidity
*: Wald test of equality of means between individuals with no history of fracture and individuals with fracture, $p < 0.05$

7.3.4 Effects of time since fracture

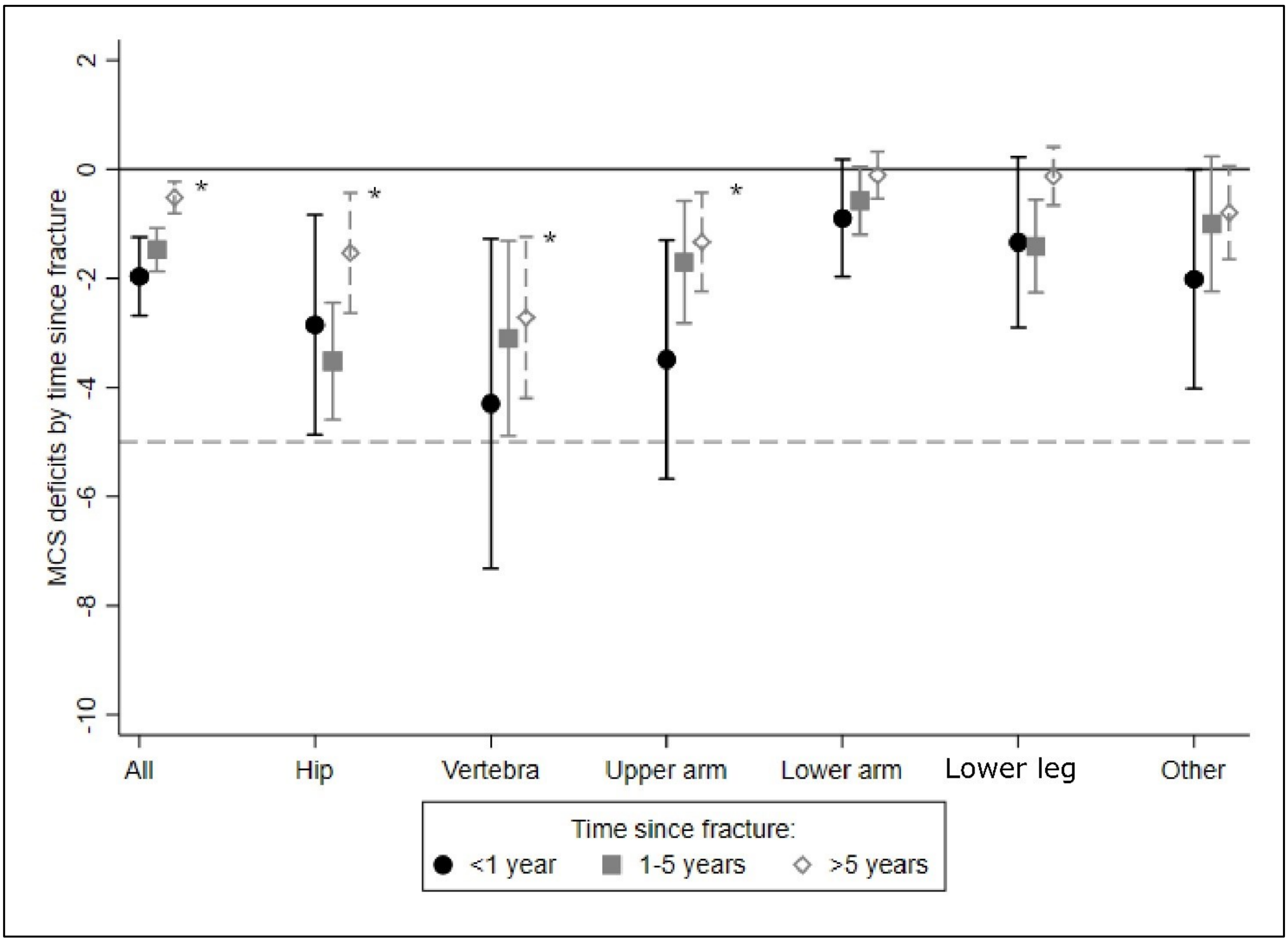
The adjusted deficits in HRQoL between individuals with no history of fracture and fracture cases according to time since fracture are presented in Figure 12 (PCS) and Figure 13 (MCS). The deficits diminished with time since fracture for both PCS and MCS. Significant deficits in PCS were, however, observed more than 5 years after fracture for all fracture sites but the lower arm. The PCS thresholds for MID were exceeded in spine and hip fractures up to five years after fracture and in upper arm fractures up to one year after fracture. Significant deficits in MCS were present for hip, spine and upper arm fractures more than five years after fracture. The MCS thresholds for MID were not exceeded. The results on the deficits in HRQoL are presented in the Supplementary Table 2 in Appendix 3B.

Figure 12: Deficits in the Physical Component Score (PCS) between non-fracture controls and fracture cases by fracture site and time since fracture, Study III [22].



The black y-line (0-line) illustrates PCS in the controls. The grey dashed y-line illustrates the minimal important difference (MID) in PCS. *: Wald test of equality of means between individuals with no history of fracture and individuals with fracture >5 years ago, $p < 0.05$

Figure 13: Deficits in the Mental Component Score (MCS) between non-fracture controls and fracture-cases by fracture site and time since fracture, Study III [22].



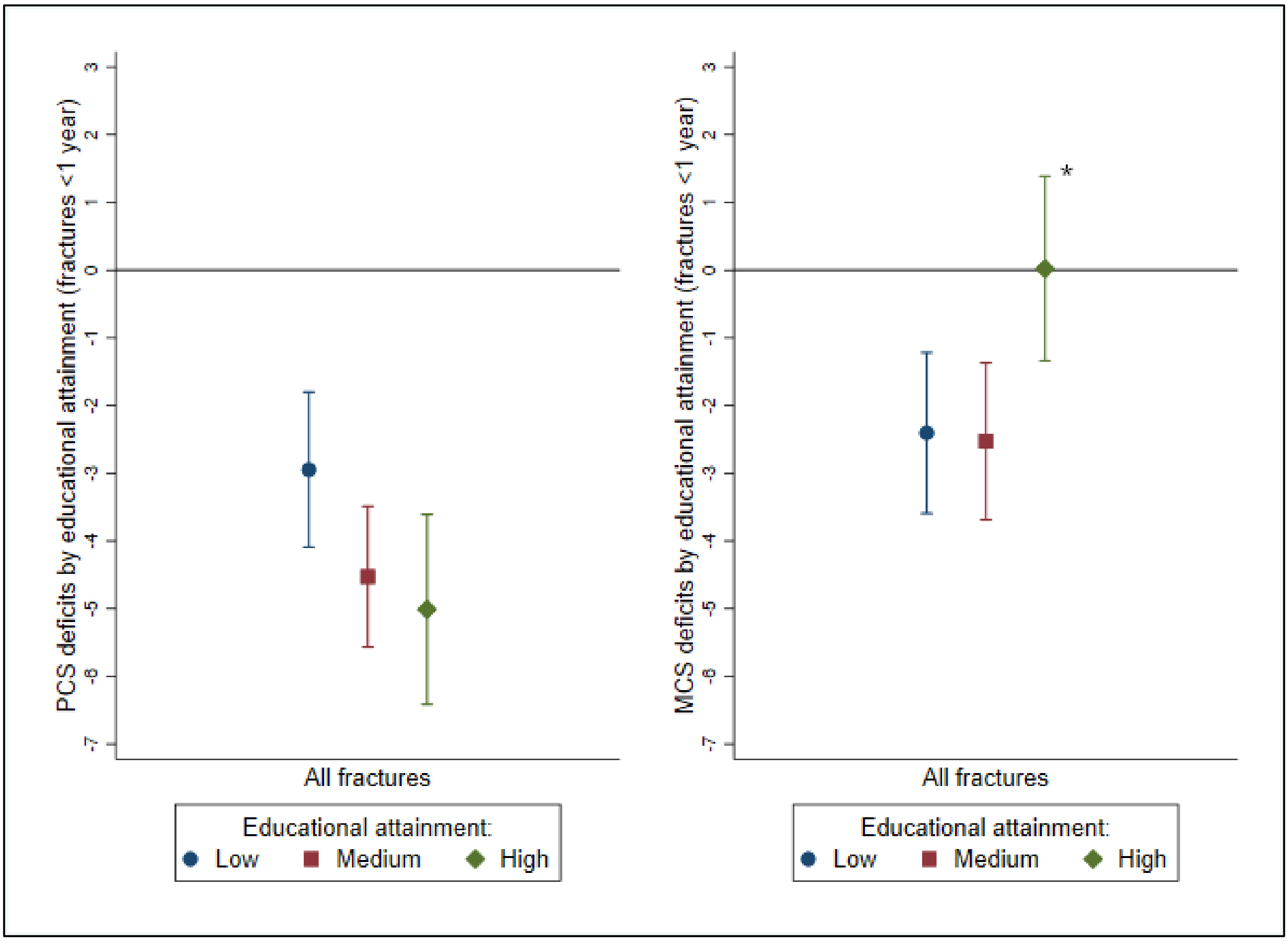
The black y-line (0-line) illustrates MCS in the non-fracture controls. The grey dashed y-line illustrates the minimal important difference (MID) in MCS. *: Wald test of equality of means between individuals with no history of fracture and individuals with fracture >5 years ago, $p < 0.05$.

7.3.5 Effects of educational attainment

Adjusted deficits in PCS and MCS between fracture cases (< 1 year after fracture) and individuals with no history of fracture stratified by educational attainment are presented in Figure 14. Defying our hypothesis, the PCS deficits between fracture cases and individuals without fracture were lower in the low (-2.9 points [95% CI: -4.1, -1.8]) than in the high (-5.0 scoring [95% CI: -6.4, -3.6]) educational attainment group (p = 0.03). However, for MCS, the deficits were higher in the low (-2.4 points [95% CI: -3.6, -1.2]) than in the high (0.0 points [95% CI: -1.3, 1.4]) educational attainment group (p = 0.01).

Detailed information on the educational differences in PCS and MCS by site and time since fracture are presented in Supplementary Table 3 and Supplementary Table 4 in Appendix 3B.

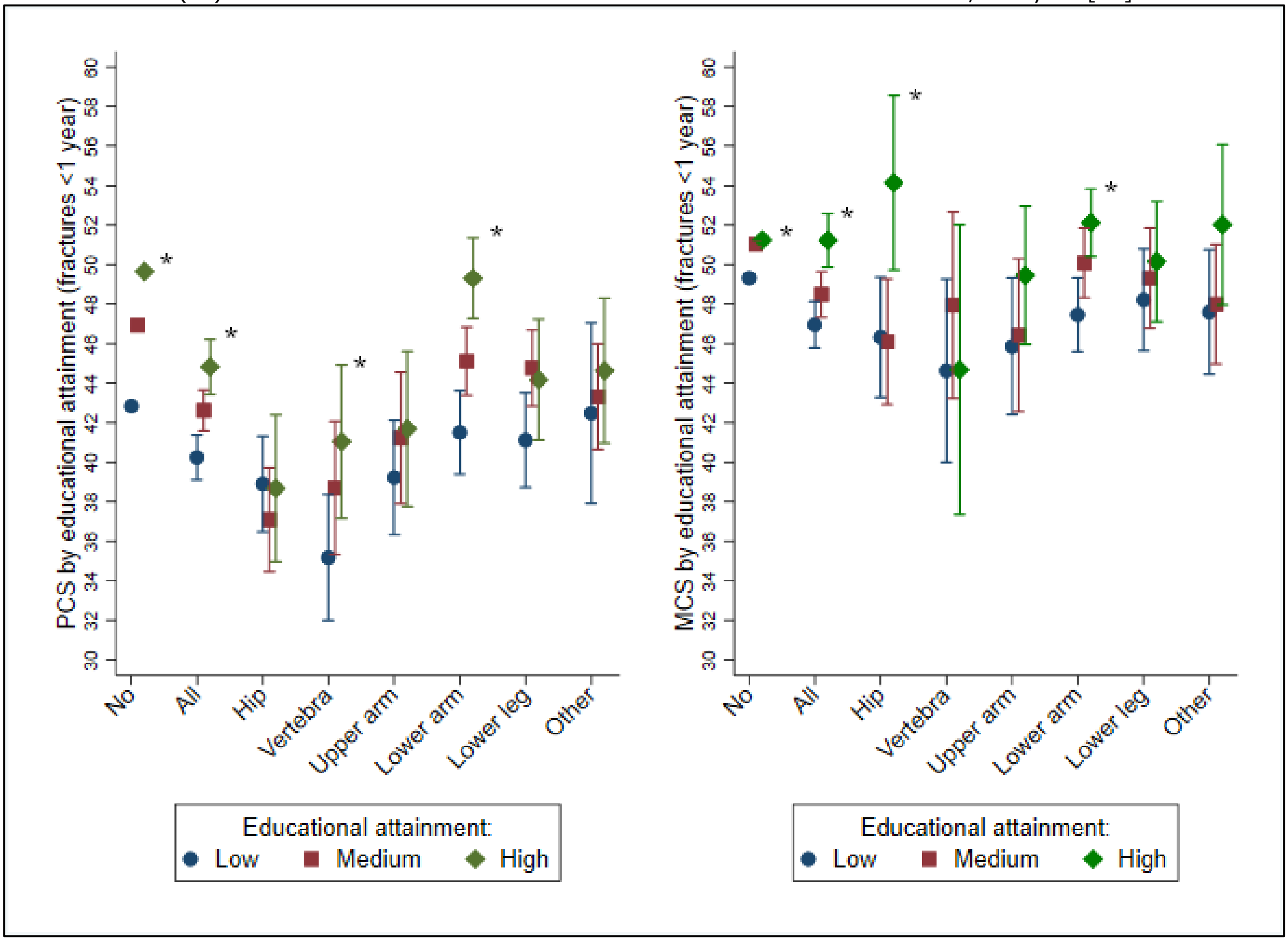
Figure 14: Health-related quality of life deficits by educational attainment between non-fracture controls and fracture-cases (< 1 year after fracture), Study III [22].



Estimates for the Physical Component Score (PCS) are presented in the left side and estimates for the Mental Component Score (MCS) are presented in the right side of the figure. *: HRQoL deficits significantly lower (<0.05) in the low than the high educational attainment group.

Figure 15 illustrates the adjusted PCS and MCS stratified by educational attainment for individuals who had sustained a fracture less than one year prior to survey completion and individuals with no history of fracture. A socio-economic gradient in HRQoL (lower PCS and MCS values with lower educational attainment) appeared to be present for individuals without a prior fracture and individuals with a recent fracture. For PCS, the score was 44.8 points [95% CI: 43.4, 46.2] for individuals with high educational attainment versus 40.2 points [95% CI: 39.1, 41.4] for individuals with low educational attainment ($p < 0.01$). For individuals with no history of fracture, the PCS scores were 49.7 points [95% CI: 49.5, 49.8] for individuals with high educational attainment versus 42.8 points [95% CI: 42.7, 43.0] for individuals with low educational attainment ($p < 0.01$). The impression of a socio-economic gradient in PCS was persistent across fracture sites except for hip fractures, where the mean PCS score in the high educational group was at the same level as in the low educational attainment group. MCS was 51.2 points [95% CI: 49.9, 52.6] for individuals with high educational attainment versus 47.0 points [95% CI 45.8; 48.1] in the low educational attainment group ($p < 0.01$). For individuals with no history of fractures, the corresponding MCS was 51.2 points [95% CI: 51.1, 51.4] versus 49.3 points [95% CI: 49.2, 49.5] ($p < 0.01$). The trend towards slightly lower post-fracture MCS among the low (and medium) educational attainment group than among the high educational attainment group was consistent across fracture regions except for spine fractures, where the high educational attainment group was at the same level as the low educational attainment group.

Figure 15: Health-related quality of life (HRQoL) by educational attainment for non-fracture cases, all fracture cases combined (All) and fracture cases divided into fractures at different anatomical sites, Study III [22].



HRQoL scores for fracture cases are presented as scores <1 year after fracture. Estimates for the Physical Component Score (PCS) are presented in the left side and estimates for the Mental Component Score (MCS) are presented in the right side of the figure. *: Wald test of equality of means between individuals with high and individuals with low educational attainment group, $p < 0.05$

8 Discussion

8.1 The main findings in the context of existing evidence

The overarching aim of this PhD dissertation was to clarify the role of SES in relation to fragility fractures. Study I and Study II were systematic reviews and meta-analyses, which aimed to synthesize existing evidence on social inequalities in fragility fracture incidence (Study I) and outcome (Study II). Study III was a population-based study combining survey data and register data from more than 100,000 Danish men and women of whom 12,839 had suffered a fragility fracture after the age of 50. The aims of Study III were two-fold. The first aim was to explore the short-term and long-term impact of fractures at different anatomical sites on physical and mental HRQoL. The second aim was to explore the effect of SES (using educational attainment as a proxy) on post-fracture HRQoL.

Study I: This review included 61 studies from 26 countries and covered data from more than 19 million men and women. Individual-based low SES was associated with a 27% (RR: 1.27 [95% CI: 1.12, 1.44]) increased risk of fragility fracture compared with individuals with high SES. No clear evidence of an association was seen when area-based SES was applied. BMI and unhealthy behaviours mediated the effect of SES on fracture risk. Thus, studies adjusting for age, sex and BMI yielded an RR of 2.69 [95% CI: 1.60, 4.53], whereas studies adjusting for age, sex, BMI and health behaviours returned an RR of 1.06 [95% CI: 0.92, 1.22]. The quality of evidence was found to be moderate.

The role of SES on fragility fracture incidence has previously been explored in a systematic review by Brennan et al., which included 12 studies published between 1994 and 2007 [157]. Consistent with our findings, the findings of Brennan et al. showed that living alone was associated with an increased risk of fragility fractures. For the other effect measures (education, income, type of residence and occupation), no conclusions could be drawn by Brennan et al. due to sparse and conflicting evidence. Since 2007, interest in the role of social disadvantage has grown, which is reflected in a large number of studies published within the past decade. Furthermore, in addition to the individual-based SES studies, we included studies that used area-based SES measures. Thus, we were able to provide a comprehensive and novel overview of the association between SES and fragility fractures on the basis of 61 observational studies.

Study II: This review included 24 studies from 15 countries involving more than one million individuals with hip fractures. The outcome reported in the vast majority (20/24) of the studies was post-fracture mortality. The remaining four studies concerned inequalities in post-fracture HRQoL. We found that compared with high SES, low SES was associated with a 24% (RR: 1.24 [95% CI: 1.19, 1.28] increase in mortality when SES was measured using individual-based measures and a 14% (RR: 1.14 [95% CI: 1.09, 1.19] increase when area-based SES measures were used. These findings were based on evidence of moderate quality. For the outcome HRQoL, no clear evidence of socio-economic inequality was detected (excess loss of HRQoL was non-significant; 5% [95% CI -1, 10%] among individuals with low SES).

To our knowledge, evidence on social inequalities in the consequences of fragility fractures has not previously been synthesized. Thus, our review is the first to synthesize and quantitatively present data on social inequalities in fragility fracture outcomes. Since the publication of our review, a couple of new studies have emerged. Hence, a Swedish register based study from 2020 including almost one million individuals found that low educational attainment was associated with a 40% increased risk of post-hip fracture mortality and a 20% increased risk of post non-hip fracture mortality compared with high educational attainment (RR: 1.4 [95% CI: 1.2, 1.5] and 1.2 [95% CI: 1.0, 1.4], respectively) [158]. Another study published in 2020 based on 200,000 hospital admissions in the UK found that individuals living in the most deprived areas had an increased risk of post-fracture mortality of 24% compared with individuals living in the least deprived areas (OR: 1.24 [95% CI: 1.20, 1.28]). Furthermore, in those who did survive, deprivation was associated with longer hospital stays and greater risk of subsequent emergency readmission [159]. In addition, hospital costs in the year following hip fracture were £1,120 higher in those living in deprived areas than among those living in more affluent areas [160]. Thus, the results of studies presenting the most recent evidence on social inequalities in the consequences of fragility fracture confirm the social gradient in post-hip fracture mortality reported in the present thesis.

Study III: Using self-reported data on HRQoL from the SF-12 survey, we found that physical and mental HRQoL was significantly lower among individuals who had suffered a fragility fracture after the age of 50 than among individuals who had suffered no fractures after the age of 50. The physical component was more negatively affected than the mental component. The fracture sites with the largest and clinically relevant negative impact on physical HRQoL were fractures of the hip and spine. Low educational attainment was associated with increased deficits in the mental but not in the physical component of the SF-12. However, individuals with a low educational attainment level had lower physical and mental post-fracture scores than individuals with a high educational attainment level due to low pre-facture scores.

The impact of fractures on HRQoL: The impact of fractures on HRQoL has previously been explored in a range of studies. However, the vast majority of these studies were restricted to fractures of the hip, spine and wrist and to HRQoL within one year following fracture. Furthermore, direct comparison with previous studies is hampered by disparities in the questionnaires used to measure HRQoL, as well as disparities in the reporting of the results. A systematic review from 2014 on utility-based QoL, concluded that although fractures of the hip was associated with large deficits in QoL, the progresses during the first year after the fracture were higher than what was seen after a spine fracture [161]. These observations are in line with ours and may reflect the lack of effective treatment and rehabilitation for individuals with fractures of the spine. Another review by Al-sari et al. focusing solely on the impact of spine fractures on HRQoL reported a pooled standardized mean difference of 0.53 [95% CI: 0.38, 0.67] for the physical component and 0.04 [95% CI: -0.32, 0.41] for the mental component [162]. These results are also in line with our results given that the estimates for physical and mental HRQoL from our study lay within the 95% CI of the results reported in the review. Al-sari et al. pointed out the need for studies reporting adjusted HRQoL as well as the need for studies reporting HRQoL stratified by time since fracture [162]. Our study report both and thus adds valuable new knowledge on HRQoL following fractures of the spine as well as fractures at other sites. The impact of fractures of the spine and hip found in our study is comparable to the impact of cancer and rheumatoid arthritis, indicating considerable negative impact of these fracture types on HRQoL [69].

The impact of SES on post-fracture HRQoL: Social differential consequences of illness are regarded important in preventive health policies but have yet to become the object of extensive investigation [163]. A differential impact on HRQoL according to SES has been observed for diseases such as diabetes, obesity and hypertension (i.e. lower SES is associated with greater HRQoL deficits) [164]. On the contrary, the results from our study found little support for the theories of Diderichsen and Hallquist. For MCS, only small but significant differential effects were observed. For PCS, we found an opposite trend toward reversed socio-economic inequality with the greatest deficits in HRQoL observed in the high educational attainment group. We would like to address three possible explanations why the theory of Diderichsen and Hallquist finds little support in our study:

- Fracture is an acute, serious event with a considerable negative impact on physical health regardless of SES.
- Mortality after a fracture may generally be higher for individuals with low than for individual with high SES as demonstrated for patients suffering a hip fracture [21]. The higher mortality among individuals with low SES may mask real SES disparities in HRQoL between individuals with and without fractures.
- Cross sectional data could be less suitable than longitudinal data for observing deficits in HRQoL. However, the few longitudinal studies included in our review (study II) exploring differential effects of fractures on HRQoL also failed to demonstrate a clear differential impact of fractures by SES [21].

For the mental component, our results suggest that low and medium SES was associated with higher deficits in HRQoL than high SES. These results could imply a larger mental vulnerability among these subgroups. To our knowledge, this has not been explored in previous studies and should therefore be further investigated. Despite the fact that the hypothesis of greater PCS deficits among individuals with low SES could not be confirmed, it is important to acknowledge that individuals with low SES are still more prone to end up with very low post-fracture physical and mental HRQoL due to the low pre-fracture scores observed in this subgroup. Post-fracture PCS for individuals with low SES and hip or spine fractures is comparable to norm values for individuals with kidney disease and heart disease, respectively [69].

8.2 Strengths and limitations

Before drawing conclusions of this dissertation, it is important to consider its strengths and limitations.

8.2.1 Strengths

Overall, this dissertation has several strengths owing to its methodological approach. The methods used to explore the impact of SES were considered appropriate for the following reasons:

Study I and Study II (reviews)

- The two reviews were based on a rigorous protocol registered in PROSPERO. Protocol adherence strengthens the credibility of the results.
- The results were reported according to the PRISMA guidelines.
- The quality of the evidence was thoroughly assessed using the adapted GRADE approach for prognostic factor research, which ensures transparency in reporting.
- The robustness of the results was explored by sensitivity analyses.

Study III

- Study III was based on data from a large population-based survey linked with individual-level data from national health and population registers. By linking survey data with register data, we were able to compare HRQoL in a large sample of individuals who had suffered a fracture after the age of 50 with HRQoL in a population-based sample of individuals with no history of fracture.
- Due to the population-based design and the large study sample, we were able to study different fracture sites (combined and separately).
- Furthermore, we were able to stratify the data by time since fracture and by educational attainment and thereby gain important insights into HRQoL after fracture.

8.2.2 Limitations

Bias is a systematic error in a study that leads to a distortion of the results [51]. Bias can broadly be divided into the following three categories: selection bias, information bias and confounding.

8.2.2.1 Selection bias

Selection bias is a distortion in a measure of association due to a sample selection that does not accurately reflect the target population. In cohort studies, selection bias will occur if participation or loss to follow-up differs by exposure and outcome status. Survival bias is one type of selection bias. Survival bias occurs when the selection process in a study favours individuals who made it past a certain obstacle or point in time and ignores individuals who did not [51]. Given that the study population of interest in this dissertation are elderly, some individuals will have died before reaching old age. Individuals with low SES have a lower life expectancy than individuals with high SES. Thus, individuals with low SES who survive into old age may not be representative to the general population of individuals with low SES regarding health status. This healthy survivor effect could have led to bias toward the null in all three studies (e.g. underestimating the effect of low SES). Another type of selection bias, sometimes referred to as "volunteer bias", is bias that occurs when subjects who choose to participate in a research project differ from the general population [165]. This type of bias must be considered in Study III, given that the study population was based on survey responders. In surveys, the health profile of non-responders is most often poorer than the health profile of responders. In Study III, selection bias may have been introduced if participation depends on fractures, HRQoL and SES. However, given that we had information on both responders and non-responders, we were able to weigh the data to represent the Danish population and thereby reduce the risk of "volunteer bias." "Volunteer bias" could also play a role in Study I, given that exposure (SES) and outcome (fractures) were based on self-reported survey data in some of the included studies. In Study II, volunteer bias is not an issue, given that information about the outcome (mortality) for obvious reasons was collected through register data.

8.2.2.2 Information bias

Information bias is bias that occurs during data collection [166]. The most relevant types of information bias to discuss in the context of this dissertation are misclassification bias and ecological fallacy. Misclassification refers to the classification of exposed individuals as unexposed/non-diseased (or vice versa) [166]. In this dissertation, misclassification could be related to the classification of individuals with low SES as high SES (or vice versa) or the classification of a fracture case as a non-fracture case (or vice versa). Misclassification can be categorized as differential or non-differential. Non-differential classification arises when the misclassification is the same across the groups to be compared, whereas differential misclassification refers to systematic differences in misclassification between groups. Non-differential misclassification will (almost) always lead to bias toward the null (no association), whereas differential misclassification can lead to bias in both directions [166].

Misclassification bias: In the studies included in the two reviews (Study I and Study II), data on exposure (SES) and outcome (fracture or mortality) were collected using either register data or survey data or both. Hence, the quality of the data relies on the quality of the registers used or the quality of the survey data. Misclassification of the outcome could, occur, for example, due to missing data on fractures in the registers or due to missing information on a previous fracture in survey data due to recall bias. This underreporting of fractures is more likely for some fracture type than for others. I.e. underreporting of fractures of the spine is expected to be substantially larger than underreporting of hip fractures given that only approximately 30% of spine fractures are clinically recognised [167]; and even if they are recognised, symptomatic spine fractures are often managed outside the hospitals. However, there is no reason to suspect that the underreporting of fractures would differ according to SES group and thus, it is most likely that the potential misclassification of outcome would lead to bias toward the null.

In Study III, information on exposure (educational attainment and fractures) was obtained from Danish national registers. The highest obtained educational attainment was assessed using the population educational register and was available for 99.3% of fracture cases and 99.4% of the controls, indicating excellent coverage. Information on fractures was obtained from the Danish National Patient Register. In Denmark, nearly all individuals with fractures are managed in the hospital system with the exception of spine fractures as mentioned above. The capture of fractures except spine fractures is thus very high, minimizing the risk of misclassification bias. Information on the outcome (HRQoL) was obtained through self-reported information from the national health survey. Health-related QoL was obtained using the SF-12 questionnaire, which is a standardized and validated tool. The percentage of missing data was very low and similar in the fracture group and the non-fracture group (0.2%). Thus, overall there is no indication of misclassification bias in Study III.

Ecological fallacy: Ecological fallacy emerges when data obtained at group level are used to make inference at the individual level. In this dissertation, ecological fallacy is observed in the two reviews when data from studies using area-based SES measures are used as a proxy for individual SES. Using area-based measures, we assume that individuals living in the same geographical area have similar SES even though we know that this is not true. Hence, area-based SES is a less precise measure than individual-based SES and can thus lead to bias toward the null. In both reviews, the pooled association between SES and fracture/mortality was weaker for the area-based studies than for the individual-based studies, confirming that ecological fallacy is inherent in area-based studies.

8.2.2.3 Confounding

As described in the Background section, confounding refers to the mixing of the effect of a given factor with the effect of the exposure and outcome of interest. The risk of confounding can be minimized by applying a randomized controlled design where individuals are randomly assigned to an intervention group or a control group. In this dissertation, a randomized controlled trial is for obvious reasons not feasible, as this would entail random assignment of SES to individuals. Thus, an observational design is the only design with which we can study the effect of SES on fracture incidence and outcome. Thus, given that exposures are not equally distributed between groups in observational studies, it is important to identify and account for possible confounders. To address this issue, we have identified important confounders and mediators for the association between SES and fragility fractures (Study I), SES and post-fracture mortality (Study II) and fractures and HRQoL (Study III).

In Study I, it became apparent how the choice of confounders in the statistical model affected the results. We found that a substantial part of the across-study heterogeneity detected could be explained by the type and number of model covariates. Studies that adjusted for gender, age, and BMI found substantial stronger associations between SES and fragility fracture than studies that solely adjusted for age and gender. In comparison, studies that in addition adjusted for health behaviours such as smoking, alcohol and physical activity found weaker associations between SES fracture risk. These findings highlight the importance of appropriate model adjustment in future studies of SES [80]. Overall, although some of the studies included in Study I adjusted for variables that may be on the mediating pathway between SES and fragility fracture, the combined estimate 1.27 is very close to the estimate for studies that adjusted only for age and gender (RR: 1.28 [95% CI: 1.08, 1.53]. Thus, it is unlikely that the conclusions are biased by inappropriate confounder control.

8.2.2.4 Internal validity

Internal validity is the extent to which the results of an investigation reflect the true situation of the study population. The internal validity can be hampered by information bias, selection bias and confounding [51]. The internal validity of the results of Study I and Study II is presumably high. The conclusions are based on a large amount of data and the robustness of the results has been assessed carefully. If the potential limitations mentioned above regarding selection bias, information bias and confounding have affected the effect estimates, this will most likely have resulted in bias toward the null. Thus, removing all bias could potentially reveal a slightly stronger association between SES and fragility fracture/mortality than found in our reviews. The internal validity of Study III is also assumed to be high. The conclusions are based on a large population-based sample. Overall, the risk of bias is considered low, although we acknowledge that survival bias is inherent in this study given that those most affected by their fracture may have died before they could participate. However, since the study aimed to explore the long-term HRQoL among fracture survivors, it is considered to be acceptable and in line with the scope of the study.

8.2.2.5 External validity

External validity is the extent to which the results of a study are applicable to other populations [51]. Two of the studies in this dissertation (Study I and Study II) are systematic reviews covering data from different countries with different welfare arrangements and healthcare systems. As described in the Background section, health and illness follow a social gradient in countries at all levels of income. Thus, social health inequalities exit in both high-, medium- and low-income counties. However, differences in living standards and social and health policies affect the degree or even the direction of the association regarding SES and fragility fracture incidence and outcome. Thus, given that 98% of the data included in the two reviews originated from high-income countries, the results are generalizable only within this context. Even within high-income countries, the social gradient in health varies. In Study II, we found that the study from Denmark (RR: 1.31 [95% CI: 1.13, 1.52] revealed substantial educational inequalities in post-fracture mortality. This was not surprising and fits well with the "Nordic paradox" phenomenon. As described in the introduction, this paradox can be partly explained by autonomous trends in social stratification and social mobility and in health behaviour that have partly reduced the effect of the egalitarian policies and generous welfare arrangements in these countries [44].

Surprisingly, a different picture emerges when considering the results of the three Danish studies of inequalities in fragility fracture incidence. The two studies by Holmberg et al. (2018) and Vestergaard et al. (2006), included in Study I, found no association between low educational attainment and increased risk of fragility fracture [5,7]. The third Danish study by Hansen et al. (2018) found that low income was associated with a 16% (RR: 1.16 [95% CI: 1.01; 1.33]) increased fracture risk. These three Danish studies should be interpreted with caution given that the results could be influenced by many factors (e.g., in the study by Vestergaard et al., the RR was adjusted for multiple variables including alcohol consumption and other SES measured). However, the finding of small or no inequalities in fragility fracture in Denmark is surprising because it negates the "Nordic paradox" phenomenon. Furthermore, it is puzzling that the high fragility fracture risk seen in Denmark does not seem follow a social gradient. If the results of the Danish studies do in fact reflect "the true" association in the Danish society, some possible explanations should be considered. One is that factors other than health behaviour, e.g. genetics or sun exposure and thus vitamin D, contribute to the high fracture risk independently of SES at northern latitudes. However, the vitamin D hypothesis is hardly plausible given that vitamin D levels in the southern parts of Europe are lower than those in the Nordic countries [168]. In addition, the hypothesis that genetics may partly explain the high fracture incidence in the Nordic countries was recently challenged by Wändell et al., who found that Swedish second-generation immigrants had similar (high) fragility fracture risk as Swedish natives [105]. Thus, a better understanding of the contribution and impact of different risk factors in the Nordic countries and the underlying pathways is an ongoing challenge for future research.

Another factor that should be considered when assessing the external validity of the results is fracture type. The results in Study II stem solely from data from individuals with hip fractures, and the results on post-fracture mortality are therefore applicable only to this group of individuals.

In Study III, the sample was based on a large sample randomly drawn from the Danish Civil Registration System. Furthermore, data were weighted to increase their generalizability to the entire Danish population. Fractures were not restricted to hip fractures but included all fragility fractures (combined and divided into six categories). Thus, the results of Study III regarding post-fracture HRQoL are most likely applicable to the Danish adult population aged 50 years and above.

In summary, the internal validity of the results of this dissertation is high, and the results are generalizable to the general population of individuals above 50 in high-income countries. However, disparities in political structures and social and health infrastructure lead to disparities in the degree of inequality across high-income countries. Thus, data from studies conducted in a Danish setting suggest that the inequality in post-hip fracture mortality may be slightly higher than the combined risk derived in our meta-analysis (Study II). Furthermore, regarding the impact of SES on fracture risk (Study I), the data from Denmark suggest that inequalities are small or perhaps even non-existing.

9 Conclusions

The overall aim of this dissertation was to improve our understanding of the importance of social inequalities for the incidence and consequences of fragility fracture in individuals aged 50 years and above. Conducting a systematic review and meta-analysis of 61 studies, we found that individually assessed low SES was associated with a 27% increased risk of fragility fractures compared with high SES. Further analyses revealed that adjusting for BMI yielded much stronger associations between SES and fracture risk, whilst studies adjusting for health behaviours attenuated the associations. The implications of this finding are two. First, in future research on social inequalities, special attention should be given to model adjustment with careful considerations of confounders versus mediators that lie on the causal pathway (and/or that act as proxies for the exposure). Second, the attenuated associations between low SES and fragility fracture risk in studies adjusting for health behaviour emphasize the potential gain in fracture prevention effect by reducing unhealthy behaviour among individuals with low SES.

The second systematic review and meta-analysis including 24 studies demonstrated that that low compared with high SES was associated with a 24% increase in mortality after hip fracture. This inequality in post-fracture mortality was consistent across countries with different health and social care systems and different political structures. The impact of SES on HRQoL after a fracture could not be determined due to limited evidence.

Combining questionnaire and register-based data, we showed that physical and mental HRQoL was significantly lower among individuals who had sustained a fragility fracture than among individuals with no history of fracture, regardless of time since fracture. Fractures of the spine and hip were associated with statistically significant and clinically relevant deficits in physical HRQoL up to five years after fracture. Low educational attainment widened the gap in mental but not in physical post-fracture HRQoL. However, due to their low pre-fracture HRQoL scores, individuals with low SES are more prone to low post-fracture HRQoL.

In conclusion, this dissertation has demonstrated a consistently increased risk of fragility fractures and increased risk of poor outcome (i.e. mortality or low HRQoL) in individuals with low SES across different SES measures. The higher vulnerability among individuals with low SES calls for increased awareness of special needs for prevention as well as post-fracture care for individuals with low SES.

10 Perspectives

10.1 Implications for policy and practice

This dissertation has revealed clear socioeconomic inequality in fragility fracture incidence as well as in HRQoL and mortality following a fragility fracture. Unhealthy health behaviour may at least partly explain these findings. Higher rates of smoking, alcohol consumption and physical inactivity and the consequences of these unhealthy behaviours may play a role for the higher incidence of fragility fractures and the higher post-fracture mortality observed among individuals with low SES. Thus, initiatives to reduce such unhealthy behaviour are warranted. Effective measures to reduce unhealthy behaviour require attention to the causes of ill health as poverty limits options and makes it more difficult to make healthy choices. Thus, health and social policies must aim to improve the living conditions for the most deprived individuals and facilitate healthier life style choices throughout life. It is beyond the scope of this dissertation to go into details about upstream life course interventions to promote healthy living in the general population. Instead, I will focus on the potentially effective measures that can be initiated in the healthcare sector to reduce inequality in fragility fracture incidence and outcome.

The first measure I would like to address is the potential benefits of successful implementation of post-fracture care coordination programs such as the Fracture Liaison Service (FLS). FLS is a coordinated multi-disciplinary fracture prevention program designed to bridge the wide gap in anti-osteoporotic treatment following fracture [169]; only 10% of those who have suffered a fragility fracture are treated with anti-osteoporotic medication within one year from the fracture [170]. FLS aims to systematically identify all individuals who sustain a fragility fracture, assess their bone mineral density and implement appropriate interventions to prevent subsequent falls and fractures as well as the associated morbidity and mortality (e.g. advice on smoking cessation, alcohol reduction, physical exercises and prescription of anti-osteoporotic medication) [169]. FLS is recognized as the single most important step in improving patient care and reducing fracture-related healthcare costs worldwide [171]. However, FLS is poorly implemented in many countries including Denmark [16]. FLS is not designed to reduce inequality. However, screening for osteoporosis today is often initiated by the patients. Thus, it is plausible that a systematic approach to secondary fracture prevention will benefit the least advantageous given that this subgroup is less likely to take the initiative for getting a DXA themselves compared with individuals with high educational attainment level or high income [5].

Thus, successful implementation of FLS may promote equal access to secondary fracture prevention. However, when implementing FLS, it is important to monitor attendance according to SES (e.g. by educational attainment or co-habiting status) in order to enable socially differentiated fracture prevention if needed.

Post-fracture rehabilitation represents another area harbouring potential to reduce health inequalities. Low SES is strongly associated with inadequate health literacy, implying that individuals with low SES have lower motivation and ability to gain access to, understand and use information in ways that promote and maintain good health [172-174]. Thus, individuals with high SES may have more resources to navigate in the healthcare system after fracture. As post-fracture rehabilitation is not an integrated part of fracture treatment, receiving the help needed may require additional resources from the patient, potentially making the barrier to equal access even higher. Thus in light of this, disparities in the provision and/or the outcome of rehabilitation may contribute to the inequality in post-fracture mortality and post-fracture HRQoL. Research on social inequalities in rehabilitation is sparse and to our knowledge, disparities in post-fracture rehabilitation according to SES have not yet been studied. However, studies on social inequalities in cancer rehabilitation in a Danish setting with equal access to health care found that low SES was associated with significantly higher needs for rehabilitation, lower participation and higher unmet needs [175-177].

10.2 Future research

This dissertation offers insights into the role of SES in relation to incidence and consequences of fragility fractures. However, many areas of research remain to be further explored. Such research should serve to test and challenge the results of this dissertation as well as explore other areas of interest that we have been unable to address within the scope of this dissertation. We propose two overarching research areas in particular: Risk factors, and prevention and rehabilitation.

Future research on risk factors

- As presented in Study I, a large number of studies on social inequalities in fragility fractures from a range of high-income countries have been published. However, the results from the Nordic countries indicate that the impact of SES as well as the pathways and impact of different risk factors in the Nordic countries need further investigations. This research should aim to unravel the impact of different risk factors related to low SES and if these risk factors influence fracture risk in the same way universally. For example, the prevalence of smoking is highly variable among women in the Nordic countries and women in Southern Europe and also dependent on SES. In addition, knowledge on the impact of SES on fragility fracture incidence in middle- and low-income countries is warranted.

- Little is known about social inequalities in relation to the consequences of non-hip fragility fractures. Thus, future studies should aim to clarify the role of SES on post-fracture HRQOL and mortality for fractures other than the hip.

- In Study I and Study II (the systematic reviews), living alone was found to be associated with a more than two-fold higher risk of fragility fracture and a more than two-fold higher risk of post-fracture mortality than cohabiting. This remarkably high risk for this sub-group warrants special attention toward individuals who live alone with regard to fracture prevention and rehabilitation. However, the estimates are based on few (two versus three) studies, and thus further high-quality evidence on the impact of living alone and the pathophysiological mechanisms underlying this effect on fracture incidence and outcome is much needed.

Future research on prevention and rehabilitation

- In this dissertation, we suggested that fracture prevention programs should be implemented in Denmark and other countries. However, in order to inform decision-makers and to ensure that implementation are based the best current evidence, a health technology assessment (HTA) should be conducted prior to the implementation of a nationwide fracture prevention program in Denmark. An HTA is a multidisciplinary process that uses well-defined methods to determine the value of health technology at different points in its lifecycle. In this context, a "health technology" is a broad term that covers any intervention developed to prevent, diagnose or treat health conditions, promote health, provide rehabilitation or organise healthcare delivery. An HTA is a systematic and transparent process that aims to explore the intended and unintended consequences of using a given health technology compared with existing alternatives. The process includes dimensions such as clinical effectiveness and safety, organisational and patient-related issues and health economic implications. The HTA should include an assessment of the expected uptake and effectiveness for the general population of elderly with fractures and for subgroups of individuals with low SES.

- Another important research area is to gain knowledge of the needs, provision, contents and effectiveness of post-fracture rehabilitation in Denmark in the general population of elderly and for specific subgroups such as individuals with low SES. This knowledge is a perquisite for achieving equitable, efficient and high-quality post-fracture rehabilitation and thereby improve HRQoL and longevity for individuals who have sustained a fragility fracture.

11 References

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12 Appendices

Appendix 1A	Study I – Socio-economic inequalities in fragility fracture incidence
Appendix 1B	Study I – Supplementary material
Appendix 2A	Study II – Socio-economic inequalities in fragility fracture outcomes
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Appendix 1A Study I – Socio-economic inequalities in fragility fracture incidence

Osteoporosis International
https://doi.org/10.1007/s00198-021-06038-7

REVIEW

Socio-economic inequalities in fragility fracture incidence: a systematic review and meta-analysis of 61 observational studies

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Received: 18 March 2021 / Accepted: 14 June 2021

Abstract

Summary Individuals with low socio-economic status (SES) have a more than 25% higher risk of fragility fractures than individuals with high SES. Body mass index and lifestyle appear to mediate the effect of SES on fracture risk. Strategies to prevent fractures should aim to reduce unhealthy behaviours through tackling structural inequalities.

Introduction This systematic review and meta-analysis aimed to evaluate the impact of socio-economic status (SES) on fragility fracture risk.

Methods Medline, Embase, and CINAHL databases were searched from inception to 28 April 2021 for studies reporting an association between SES and fragility fracture risk among individuals aged ≥50 years. Risk ratios (RR) were combined in meta-analyses using random restricted maximum likelihood models, for individual-based (education, income, occupation, cohabitation) and area-based (Index of Multiple Deprivation, area income) SES measures.

Results A total of 61 studies from 26 different countries including more than 19 million individuals were included. Individual-based low SES was associated with an increased risk of fragility fracture (RR 1.27 [95% CI 1.12, 1.44]), whilst no clear association was seen when area-based measures were used (RR 1.08 [0.91, 1.30]). The strength of associations was influenced by the type and number of covariates included in statistical models: RR 2.69 [1.60, 4.53] for individual-based studies adjusting for age, sex and BMI, compared with RR 1.06 [0.92, 1.22] when also adjusted for health behaviours (smoking, alcohol, and physical activity). Overall, the quality of the evidence was moderate.

Conclusion Our results show that low SES, measured at the individual level, is a risk factor for fragility fracture. Low BMI and unhealthy behaviours are important mediators of the effect of SES on fracture risk. Strategies to prevent fractures and reduce unhealthy behaviours should aim to tackle structural inequalities in society thereby reducing health inequalities in fragility fracture incidence.

Keywords Deprivation · Fracture · Health inequality · Systematic review · Meta-analysis · Socio-economic status

Introduction

The social gradient in health is a growing health concern throughout the world; reducing social inequalities in health is central to the 17 UN Sustainable Development Goals [1–3]. The association between lower socio-economic status (SES) and greater multi-morbidity is well-established and includes a range of diseases (e.g. cardiovascular disease,

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Published online: 25 June 2021

diabetes, and different cancer types) [4, 5]. A recent systematic review and meta-analysis, exploring the impact of SES on participant outcomes following a fragility fracture, found that low SES was associated with an 24% higher mortality risk following hip fracture compared to individuals with high SES [6]. Whether socio-economic disadvantage is associated with higher fragility fracture risk is less clear as studies investigating this association have generated diverging and conflicting results [7–10].

Reduced bone mass density (BMD) is a major risk factor for fragility fracture [11]. Risk factors for low BMD include old age, female gender, low body mass index (BMI), family history of hip fracture, previous fracture, use of glucocorticoids, rheumatoid arthritis, smoking, and excessive alcohol consumption [12]. The associations between SES and risk factors for fragility fracture are complex. For example, SES has strong links with health behaviours which potentially influence fracture risk via various pathways (both protective and deleterious) (Supplementary Figure S1). Factors like smoking, high alcohol consumption, and physical inactivity potentially increase fracture risk through their negative effect on BMD and/or through an increased risk of falls. Such unhealthy behaviours are more prevalent in lower than higher socio-economic groups [13–15]. Obesity has for many years been considered protective against fractures [16, 17]. The generally accepted explanation for this relationship is that higher BMI induces greater mechanical loading of the skeleton, with a consequent increase in BMD [18]. However, more recent evidence suggests that the association between obesity and fracture may be site-dependent, with obesity protecting against hip and pelvic fractures (through cushioning of impacts when falling) but increasing risk of non-hip fractures [18]. In high- and middle-income countries, obesity is more common among individuals with low rather than high SES [19]. Thus, given these complexities, the relationship between low SES and fragility fracture risk remains unclear, and it may conceivably vary by, for example, fracture type. Understanding the relationship between SES and fragility fracture risk is important to inform effective targeting of public health strategies for prevention and treatment of osteoporosis and fragility fractures.

Studies to date have measured SES using a variety of methods. These methods can be divided into individual-based measures (i.e. education, income, occupation, or cohabiting status) and area-based measures (i.e. Index of Multiple Deprivation [IMD] or area income). Each type of SES measure has strengths and limitations. Area-based measures assume homogeneity between individuals in a given region and minimize distinctions between households or individuals within a household [20], whereas individual-based measures provide SES information at an individual level and are thus considered to carry a lower risk of misclassification bias than area-based measures [21]. However, in most countries, national individual-level data are not available, or are incomplete, leaving area-based measures as the only option for assessing effects of socio-economic inequality.

The aim of this systematic review and meta-analysis was to establish the association between SES and the risk of fragility fracture. Results from individual-based studies were considered the primary results of interest due to the inherent risk of ecological fallacy in area-based SES studies. Furthermore, we aimed to understand the reasons for the inconsistencies in previously published associations, by exploring the influence of different types of SES measure, methodological quality, participant gender, fracture site (hip or non-hip), and/or factors adjusted for in multivariate analyses.

Methods

This review was conducted according to guidelines from the Cochrane handbook and reported in accordance to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement [22]. The study protocol for this review was registered with PROSPERO (registration number: CRD42016032866).

Literature search, study selection, and data extraction

Medline, Embase, and CINAHL databases were searched from inception to 28 April 2021, using the following terms: ("Bone fractures" OR "Minimal trauma fracture" OR "Minimal trauma fractures" OR "Osteoporotic fracture" OR "Osteoporotic fractures") AND ("Socioeconomic factors" OR "Socioeconomic status" OR "social class" OR "inequality" OR "education" OR "income" OR "marital status" OR "residence" OR "occupations"). The search strategy for each database is detailed in Supplementary Table S1. Reference lists of eligible studies were reviewed to identify additional studies eligible for inclusion.

Eligibility criteria

Observational epidemiological studies were eligible for inclusion, specifically cohort, case-control, and cross-sectional studies that estimated the association between SES and a fragility fracture outcome among individuals aged 50 years and older (with a margin of tolerance if <10% of the study population were aged <50 years). A fragility fracture was defined as a fracture that occurred after the age of 50 years following minimal trauma. Ecological studies, case series including fewer than 50 individuals, conference abstracts, and unpublished studies were excluded. Titles and abstracts yielded by the search were independently screened by two assessors against the listed eligibility criteria. Full-text manuscripts were obtained for all records that appeared to fulfil the inclusion criteria.

Inclusion was agreed by consensus and, if necessary, through discussion with a third assessor.

Data extraction

Data from the eligible studies were extracted independently by two assessors using a standardized data extraction form. The exposure of interest was SES measured at individual level (education, income, occupation, or cohabitation) or area level (Index of Multiple Deprivation (IMD) or area income). In this review, cohabitation was considered to reflect SES given that living with someone can provide economic and social support. If the individual papers contained multiple individual-based SES measures, only one measure was included, using the following hierarchy of SES measures, as previously applied by Lundquist et al. and Valentin et al.: education was prioritized over income, income over occupation, and occupation over cohabiting status [6, 23]. This approach was used to enable an overall estimation, across all independent measures of SES, to be calculated, without including the same participants more than once in the meta-analysis. Education was prioritized for several reasons: educational level is important for occupation and income, is a resource that reflects human capital and non-material resources, and is a SES variable relatively stable through adulthood, unaffected by future health conditions. Cohabiting status and marital status were considered the same SES measure and are referred to as cohabiting status in the analysis. Results from the individual-based SES studies were considered the primary results of interest and results from area-based SES studies, secondary results.

Relative measures, in the form of relative risks, hazard ratios, and odds ratios, were treated as equivalent measures of risk ratios (RR) (i.e. having the same clinical interpretation). Odds ratios were used as an equivalent measure to RR because fracture incidence is a rare outcome, e.g. <10 in 100 people per year. When only unadjusted associations in the form of proportions were reported, the RR was calculated manually as the ratio between the proportions. RR estimates from individual studies were transformed to their natural logarithms (as for the standard errors). To enable comparability between the studies, all ratios were re-calculated so that the incidence rate of the lowest was divided by the rate of the highest socio-economic level (i.e. using the highest as the reference category). RRs were combined irrespective of the number of SES categories. In publications where the middle SES category was used as the reference group, indirect comparison methods were applied to estimate the RR for the lowest versus the highest SES group (i.e. lnRR for the lowest SES group minus lnRR for the highest SES group). When data were available after serial adjustments, data from "fully adjusted" analyses were prioritized for inclusion. However, where data were presented both with and without adjustment for another measurement of SES (e.g. educational level adjusted for income), data without adjustment for other SES measures were prioritized to avoid over-adjustment. For the overall analysis, in studies where results were presented only by strata (e.g. stratified by fracture type [hip *vs*. non-hip], race, or gender), results were pooled at study level before being added to the overall model. Thus, each study was only represented by one estimate in each forest plot.

Applying the Grading of Recommendations Assessment, Development, and Evaluation framework for assessing the quality of evidence

The quality of evidence was assessed using an adaption of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach proposed for systematic reviews of prognostic factor research [24]. In this approach, the quality of evidence is downgraded based on early phase of investigation, study limitations, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence may be upgraded based on moderate or large effect size and an exposure-response gradient. Phase of investigation is, within this framework, divided into studies that aim to identify associations (phase 1), test independent associations (phase 2), or understand prognostic pathways (phase 3) [24, 25]. There are no fixed cut-offs for downgrading due to phase of investigation; hence, we decided to downgrade if more than 50% of the evidence originated from early phase of investigation (phase 1) studies. Study limitations (i.e. risk of bias) were assessed independently by two assessors using the Quality in Prognosis Studies (QUIPS) [26]. Disagreement between the two assessors was resolved by reaching consensus. The overall risk of bias for each of the studies was judged as (1) low if there was a low risk of bias in all domains in individual-based studies and low risk of bias in all domains except "prognostic factor measurement" for area-based studies (area-based studies could at best be rated "unclear risk of bias" in the prognostic factor measurement domain, due to the inherent risk of misclassification in these studies), (2) unclear risk of bias if there was an unclear risk of bias for one or more domain(s), and (3) high risk of bias if there was a high risk of bias for one or more domain(s). The quality of evidence was downgraded due to study limitations if more than 50% of studies were judged as having unclear risk of bias (–1 point) or high risk of bias (– 2 points), respectively. Inconsistency was assessed using the Q-test and the inconsistency (I^2) index.

Statistical analysis

Meta-analyses were performed using Stata, version 16.1 (StataCorp, College Station, TX, USA). Random restricted maximum likelihood (REML) models were used to estimate the summary RR along with 95% CIs. Separate analyses were performed for individual-based and area-based measures of

SES. Results in each analysis were stratified by type of SES measure (e.g. education, income, occupation, or cohabitation). Heterogeneity was investigated using Cochrane's Q-test and I^2. I^2 expresses the percentage of total variation across studies due to heterogeneity [27]. In analyses where inconsistency across studies appeared to be a potential caveat ($I^2 > 50\%$), the robustness of results from the random effects model was checked against a fixed effects model; the 95% confidence interval (CI) from the random effects model was considered robust if the point estimate from the fixed effects model was within the confidence interval of that of the random effects estimate. The risk of "small study" bias was considered likely if the fixed effects point estimate was outside the random effects 95% CI, with the level of evidence rated down due to inconsistency [27]. To further evaluate the robustness of results, a leave-one-out analysis was performed by iteratively removing one study at a time to confirm that the combined RRs were not driven by one single study. Potential publication bias was assessed using funnel plots and Egger's test. We anticipated severe heterogeneity and, hence, chose to use a random effects model for our primary analysis, with pre-specified subgroup and meta-regression analyses. A priori, we selected the following factors as potential contributors of heterogeneity: study quality (low quality [e.g. phase 1 studies and/or studies with high risk of bias] versus high quality [phase 2 or 3 studies with unclear or low risk of bias]), type of fracture (hip versus non-hip), gender (women versus men), and type of covariates in the analysis (divided into four categories: crude; adjusted for age and sex; adjusted for age, sex, and BMI; and adjusted for age, sex, BMI, and health behaviours [i.e. smoking, alcohol consumption, and physical activity]). For the subgroup analysis, a factor was considered to potentially impact the association between SES and fracture risk if the subgroup 95% CIs did not overlap.

Meta-regression analysis was only performed if the given SES measure (e.g. education) was included in at least 10 studies, as recommended by Higgins et al. [27]. For the meta-regression analysis, a factor was considered a potential source (i.e. covariate) of heterogeneity if between-study variance (measured as tau squared [T^2]) was reduced in the meta-regression analysis.

Results

Searches

In total, 6537 studies were screened for eligibility after which 6391 were excluded, the most frequent reason being studies not addressing SES. The remaining 146 studies were scrutinized by full manuscript review for possible inclusion; of these, 85 studies were excluded because they either did not fulfil the inclusion criteria (n=77) or the data presented were included in another subsequent study (n=8) (Figure 1). A list of excluded studies with reasons for exclusion is shown in Supplementary Table S2. A total of 61 studies were included in the qualitative review, of which 58 were included in the meta-analysis. Three studies could not be included in the meta-analysis because it was not possible to extract standard errors [28–30].

Study characteristics

The 61 included studies were published between 1993 and 2021, the majority (72%) within the last decade. Data from a total of 26 countries were represented including approximately 19.5 million individuals of whom 1.7 million had experienced a fracture. Most studies were conducted in high-income countries except for three studies from Turkey, Morocco, and Iraq [31–33]. More than half of the studies (n=33) examined hip fractures alone, whilst four studies focused solely on vertebral fractures. The remaining studies reported outcomes for more than one fracture type (separately or all fractures combined). A total of 44 studies reported individual-based SES measures (education, income, occupation, and/or cohabitation), and 17 studies reported area-based SES (IMD and/or area income). More than half (59%) of the individual-based studies were categorized as phase 1, whilst only two of the 17 area-based studies (12%) were phase 1 studies. The characteristics of the included studies are presented in Tables 1, (individual-based SES) and 2 (area-based SES).

Risk of bias

The study limitations assessed using the QUIPS methodological checklist tool are presented in Supplementary Figures S2A and S2B. For the individual-based studies, 9 (20%) were judged as low risk, 21 (48%) as unclear risk, and 14 (32%) as high risk of bias. For the area-based studies, 3 (18%) were judged as low, 12 (70%) as unclear, and 2 (12%) as high risk of bias. Overall, the domain "prognostic factor measurement" carried the highest risk of bias with 8 (13%) studies having high risk in this domain. This high risk was attributed primarily to lack of information on how SES data were collected and lack on information on whether or not SES was classified based on predefined categories (i.e. quintiles).

Individual-based socio-economic status and fragility fracture risk

The association between individual-based SES and fragility fracture incidence was investigated in 44 studies of which 42 were included in the meta-analysis. The overall combined RR across different individual-based SES measures was 1.27 (95% CI 1.12, 1.44; I^2=98%) indicating higher fracture risk with lower SES. The RRs for each SES measure were

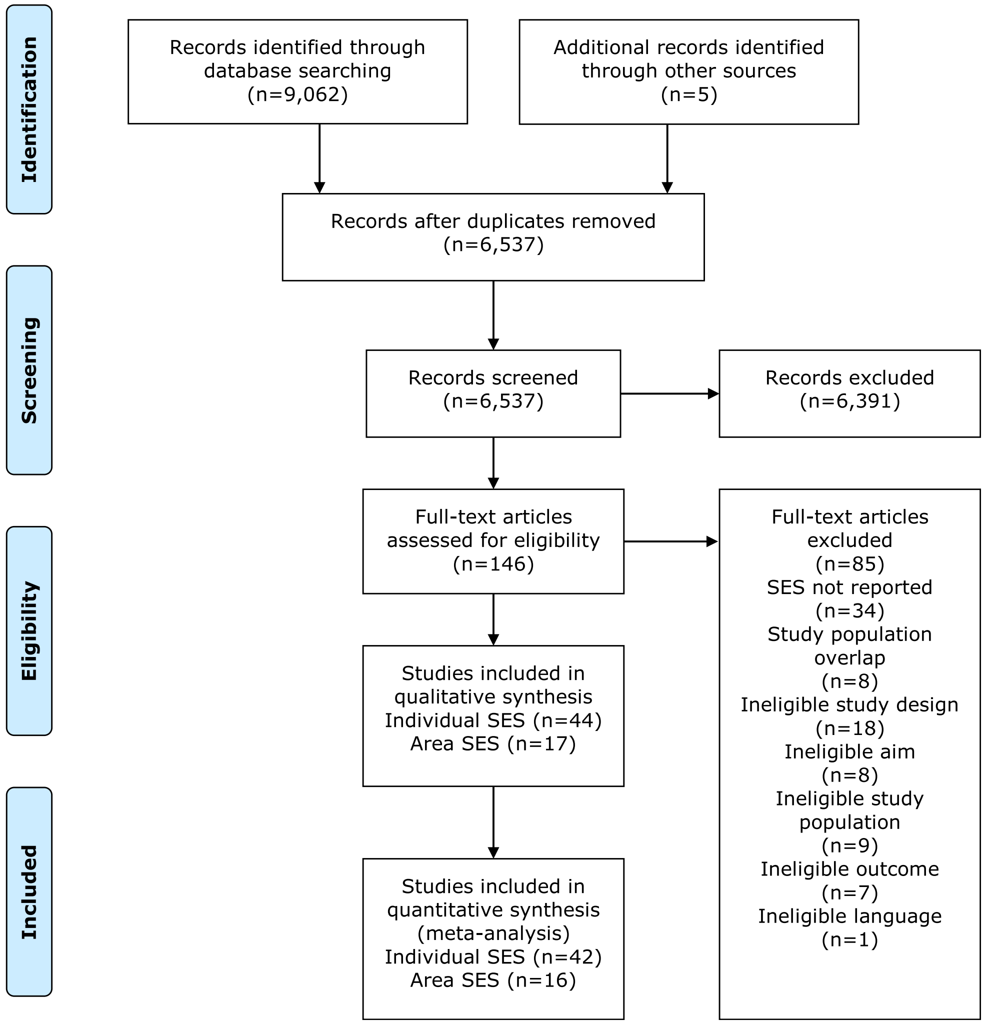

Fig. 1 Flow diagram for study selection and exclusion. *Individual SES, studies that measured socio-economic status at an individual level (i.e. education, income, occupation, or cohabiting); area SES, studies that measured socio-economic status at an area level (i.e. Index of Multiple Deprivation or area income)*

consistent, indicating a higher risk of fragility fracture with lower SES, although the RR associated with living alone was substantially higher than the RR associated with other SES measures (education, 1.23 [95% CI 1.04, 1.45]; income, 1.22 [95% CI 1.03, 1.44]; occupation, 1.17 [95% CI 1.07, 1.28]; and living alone, 2.37 [95% CI 1.88, 2.98]) (Figure 2 and Table 3). The RR remained stable in the leave-one-out sensitivity analysis. The two studies by Wolinsky et al. and Langeard et al., which were not included in the meta-analysis, supported a similar inverse association between SES and fragility fracture risk, as they both reported a greater risk of fracture with lower educational attainment [28, 30].

The overall analysis indicated, as expected, substantial between-study heterogeneity. Meta-regression analysis revealed that 17% of the between-study variance could be explained by the different SES measures included in the model (i.e. education, income, occupation, and cohabitation). Results from the stratified analysis of the pre-specified potential sources for between-study heterogeneity are presented in Table 4. There were no marked differences in the RR when stratified by study quality, participant gender, or fracture type. However, marked differences were detected when the analysis was stratified according to model adjustment.

The combined RR for studies adjusting for age and sex was 1.28 (95%CI 1.08, 1.53); however, across those studies that also adjusted for BMI, the RR was 2.69 (95% CI 1.60, 4.53) which was substantially higher than for studies adjusting for age, sex, BMI, and health behaviours such as smoking, alcohol consumption, and/or physical activity (RR 1.06 [95% CI 0.92, 1.22]). Furthermore, given the possible site-dependent effect of BMI on fracture risk, the effect of BMI adjustment was explored separately for hip and non-hip fractures. The combined RR for the effect of SES on hip fracture risk in studies adjusting for age and sex was 1.23 (95% CI: 0.96, 1.58) and for age, sex, and BMI, 3.29 (95% CI: 2.22, 4.89), and in those adjusting for age, sex, BMI, and health behaviours, it was 1.18 (95% CI: 0.03, 1.36). The corresponding RRs for non-hip fracture studies were 1.69 (95% CI: 1.53, 1.86) when adjusted for age and sex; 1.40 (0.71, 2.74) adjusted for age, sex, and BMI; and 1.08 (0.96, 1.22) when adjusted for age, sex, BMI, and health behaviours. These results suggest that the effect of BMI adjustment differs according to

Table 1 Characteristics of the included studies with individual-based SES measures

First author (year)	Study period	Country	N fracture cases/N baseline population	% of women	Mean age at baseline, years (SD)	Fracture type(s)	SES indicator (number of levels)	Phase (Risk of bias)
Al-algawy [33] (2019)	2018–2019	Iraq	75/250	68%	NR (>60)	Hip	Education (5)	1 (–)
Allali [32] (2010)	NR	Morocco	43/356	100%	58.9 (7.7)	Peripheral	Education (4)	2 (?)
Benetou [34] (2015)	NR	Germany Greece Norway Sweden USA	4185/64,337	0–100%[A]	60.3 (1.1)–69.7 (6.9)[B]	Hip	Education (3)	2 (?)
Cano [31] (1993)	1988–1989	Spain Turkey	519/1327	100%	NR (50+)	Hip	Education (4)	1 (–)
Cauley [35] (2007)	1993–2005	USA	23,270/159,579	100%	60.2 (6.8)–63.6 (7.2)[C]	All	Education (3)	1 (?)
Chen [36] (2018)	2014–2016	Taiwan	100/200	100%	77.9 (7.6)	Hip	Education (3)	1 (?)
Colon-Emeric [37] (2003)	1999–?	USA	NR/3619	0%	NR (>65)	Hip	Education (2)	1 (–)
Crandall [38] (2014)	NR	USA	94/2167	100%	45.8 (2.7)	All	Education (4)	2 (?)
Espino [39] (2000)	1993/1994–1995/1996	USA	120/2895	57%	72.9 (SEM 0.22)	Hip	Education (2)	1 (?)
Farahmand [40] (2000)	1993–1995	Sweden	1327 cases/4589	100%	72.5 (6.8)	Hip	Education (3)	2 (+)
Fernandez-Ruiz [41] (2014)	1994–1995	Spain	166/5278	58%	74.3 (6.9)	Hip	Education (4)	1 (–)
Holmberg [42] (2018)	2010–2016	Denmark	1719/17,155	100%	Range: 65–81	Hip, MOF	Education (3)	2 (+)
Johansson [43] (2018)	1987–2002	Sweden	97,136/3,500,000	36%	55 (12.2)	Hip	Education (3)	2 (?)
Kauppi [44] (2011)	1978–1994	Finland	133/2028	100%	63.2 (9.2)	Hip	Education (3)	2 (?)
Langeard [30] (2019)	NR	France	38/80	70%	69.5 (9.08)	UE	Education (NR)	1 (–)
Ma [45] (2011)	1965–1999	Japan	Hip:33, spine:43/2737[D]	0%	53.2 (4.8)	Hip, vertebral	Education (Con)	1 (–)
Meyer [46] (1995)	1992–1993	Norway	246/492	78%	77.5	Hip	Education (3)	1 (?)
Pluskiewicz [47] (2014)	2010	Poland	176/625	100%	66.4 (7.8)	All	Education (4)	2 (?)
Ren [48] (2019)	2015	China	431/20,110	53%	62 (10.4)	Hip	Education (4)	1 (?)
Rodrigues [49] (2018)	2011–2013	Portugal	189/884	100%	NR (65+)	All	Education (4)	1 (–)
Sanfélix-Gimeno [50] (2012)	2006–2007	Spain	126/824	100%	64.0	Vertebral	Education (3)	1 (?)
Shin [51] (2012)	2001–2007	South Korea	364/2684	57 %	59.2 (8.7)	Vertebral	Education (3)	1 (+)
Syddall [52] (2012)	1911–2007	UK	159/3225	48%	66.1	All	Education (2)	2 (?)
Tsutsumimoto [53] (2018)	NR	Japan	NR[E]	NR[E]	NR[E]	All	Education (Con)	1 (–)
Van Lenthe [54] (2010)	1991–2003	Netherlands	192/16,578	NR	NR (25+)	Hip	Education (4)	3 (+)
Vestergaard [8] (2006)	2000	Denmark	NR[F]	NR[F]	NR[F]	All	Education(5)	2 (+)
Wang [55] (2019)	2012–2018	China	27/298	81.5%	66	All	Education (2)	1 (–)
Wändell [56] (2021)	1998–2015	Sweden	114,505/1,377,035	49.8%	NR (50+)	All	Education (3)	2 (+)
Wolinsky [28] (2009)	1993–2005	USA	495/5511	62%	77	Hip	Education (3)	1 (–)
Xavier [57] (2019)	2017	Brazil	108/194	75.3%	70.7 (11.3)	All	Education (2)	1 (–)
Zacharopoulou [58] (2019)	2019	Greece	202/404	62.1%	78.7 (6.4)	Hip	Education (2)	1 (?)
Zhang [59] (2019)	2014	China	184/154,099	NR	NR	UE	Education (4)	1 (?)
Hansen [60] (2018)	1995–2011	Denmark	189,838/379,676	68.8–79.5%[G]	65.3–73.9[H]	Hip, humerus, wrist	Income (5)	2 (+)
Kim [61] (2019)	2004–2013	Korea	3943/90,012	60.6%	NR (65+)	Hip	Income (3)	2 (?)
Lin [62] (2018)	2000–2010	Taiwan	5084/20,336	NR	NR	Hip	Income (2)	1 (–)
Navarro [63] (2008)	2005–2007	Spain	203/1139	100%	58.1 (10.0)	All, vertebral	Income (2)	2 (+)
Navarro [64] (2013)	2007–2009	Spain	324/1250	100%	55.1 (11.7)	All, vertebral	Income (2)	3 (+)
Park [65] (2015)	2011–2012[I]	Korea	2012/117,346	NR	NR	Vertebral	Insurance status as proxy for income (2)	2 (?)
Peel [66] (2007)	2003–2004	Australia	126/387	82%	82.6	Hip	Income (2)	1 (–)

Table 1 (continued)

First author (year)	Study period	Country	N fracture cases/N baseline population	% of women	Mean age at baseline, years (SD)	Fracture type(s)	SES indicator (number of levels)	Phase (Risk of bias)
Suen [67] (1998)	1990–1991	Australia	200 cases/416	75%	80	Hip	Occupation (3)	2 (–)
Trimpou [68] (2010)	1970–2003	Sweden	451/7495	0%	46+	Hip	Occupation (5)	1 (?)
Korpelainen [69] (2006)	1997	Finland	124/407	100%	72.2 (1.2)	All	Cohabiting (2)	1 (?)
Lee [70] (2014)	2000–2010	Korea	233/2546	70%	79.2 (10.2)	Hip	Cohabiting (2)	1 (?)
Reimers [71] (2007)	1993–1995	Sweden	7748/235,605	NR	NR (65+)	Hip	Cohabiting (2)	2 (+)

[A] Benetou et al. (2015): EPIC-elderly Greece, 59.8%; EPIC-elderly Umea, 52.8%; ESTHER, 54.4%; Tromsø, 54.7%; COSM, 0%; SMC, 100%. [B] Benetou et al. (2015): EPIC-elderly Greece: mean: 67.2 (SD: 4.5), EPIC-elderly Umea: mean: 60.3 (SD: 1.1), ESTHER: mean: 66.0 (SD: 4.1), Tromsø: mean: 69.7 (SD: 6.9), COSM: mean: 68.8 (SD: 5.5), SMC: mean: 69.3 (SD: 6.1). [C] Cauley (2007): White: mean: 63.6 (SD: 7.2), Black: mean: 61.6 (SD: 7.1), Hispanic: mean: 60.2 (SD: 6.8), Asian: mean: 63.0 (SD: 7.5), American Indian: mean: 61.6 (SD: 7.5). [D] Ma et al. (2011): follow-up 1994–1999. [E] Tsutsumimoto et al. (2018): subgroup of fallers with fracture vs. non-fallers. [F] Vestergaard et al. (2006): subgroup aged 60+. [G] Hansen et al. (2018): hip: 68.8%, humerus: 73.8%, wrist: 79.5%. [H] Hansen et al. (2018): hip: mean: 73.9 (SD: 9.5), humerus: mean: 67.5 (SD: 10.1), wrist: mean: 65.3 (SD: 9.3). [I] Park et al. Only data from 2012 included. NR, not reported. Phase, phase of investigation, divided into studies that aim to identify associations (phase 1), test independent associations (phase 2), or understand prognostic pathways (phase 3). Risk of bias: A + indicates low risk, a ? indicates unclear risk, and a – indicates high risk. SEM, standard error of the mean. Con, continuous

fracture site. However, the number of studies in each stratum was low for non-hip fractures, and thus, these estimates should be interpreted with caution.

To further explore the impact of different model adjustments on the association between SES and fragility fracture risk, meta-regression analysis was performed for the SES measure education (it was not possible to perform meta-regression for the other individual-based SES exposures due to insufficient number of studies). Results showed that different models of adjustment could be important contributors to the inconsistency seen across individual-based SES studies (Supplementary Table S3). The summary RR of fragility fracture in those with lower educational level varied from 3.85 (95% CI 2.44, 6.07) for studies adjusting for age, sex, and BMI to 1.02 (95% CI 0.78, 1.32) in studies adjusting for age, sex, BMI, and health behaviours; the difference in model adjustment accounted for 39% between-study variance. By comparison, study quality, participant gender, and fracture type explained 3%, 0%, and 0%, respectively, of this variance.

The overall quality of evidence was rated as moderate as more than 50% (59%) of the evidence originated from phase 1 studies. We did not downgrade for inconsistencies as a substantial part of between-study variance was explained by model adjustment. Initial inspection of funnel plots and Egger's tests ($p<0.05$) indicated publication bias (Supplementary Figure S3). However, this finding was primarily driven by the large number of phase 1 studies (Egger's test excluding phase 1 studies $p=0.50$). Thus, given that the quality of evidence had already been downgraded due to the large number of phase 1 studies, no further downgrading was applied [24].

Area-based socio-economic status and fragility fracture risk

The association between area-based SES and fragility fracture incidence was investigated in 17 studies, of which all but one was included in the meta-analysis (Figure 3 and Table 3). When stratified by area-based measure, whilst IMD was not associated with fragility fracture risk (RR 0.99 [95% CI 0.76, 1.30]), low area income was associated with increased fracture risk (RR 1.21 [95% CI 1.12; 1.30]). For the overall combined area-based SES measures, no association with overall fragility fracture risk, RR 1.08 (95% CI 0.91, 1.30), was seen. Within this meta-analysis, the large study by Petit et al. showed a strong inverse association between area-based SES and fracture risk [7]. When repeating the meta-analysis using the leave-one-out approach, the RR was 1.13 (95% CI: 1.03, 1.22) indicating evidence of an association between area-based SES measures and fragility fracture risk. The study by Goldman et al., which could not be included in the meta-analysis, found that living in the lowest socio-economic level area (cluster 1) was associated with odds of fracture of 1.6

Table 2 Characteristics of the included studies with area-based SES measures

First author (year)	Study period	Country	N fracture cases/N baseline population	% of women	Mean age at baseline (SD)	Fracture type(s)	SES indicator (number of levels)	Phase of investigation (risk of bias)
Bhimjiyani [10] (2018)	2001/2002–2014/2015	UK	747,369/national population	74.2%	83 (77–88)[A]	Hip	Index of Multiple Deprivation (5)	2 (+)
Brennan [72] (2012)	2002–2004	Australia	427/1074	51%	62.3	Vertebral	Indexes for areas (2)	2 (?)
Brennan [9] (2015)	2006–2007	Australia	3943/national population	53%	NR (50+)	All, MOF	Index of relative socio-economic disadvantage (5)	2 (+)
Cassell [73] (2013)	1998/1999 to 2008/2009	Australia	NR	57.4%	NR (65+)	Hip	Index of relative socio-economic disadvantage (5)	2 (?)
Curtis [74] (2016)	1988–2012	UK	87,174/national population	74%	NR (18+)	All, hip, radius/ulna, vertebral	Index of Multiple Deprivation (5)	2 (?)
Goldman [29] (2018)	2008–2011	Israel	NR[B]	NR	NR (65+)	Hip	Socio-economic index (20)	2 (–)
Jones [75] (2004)	1999–2000	Wales, UK	NR[C]	NR	NR (85+)	All	Townsend score (3)	2 (?)
Maharlouei [76] (2014)	2008–2010	Iran	1879/national population	NR	74.7(10.6)	Hip	Area of residence (3)	1 (–)
Oliveira [77] (2015)	2000–2010[D]	Portugal	10,203/3,789,091	77.3%	79.7 (9.3)	Hip	Area of residence (3)	2 (?)
Petit [7] (2017)	2008	France	59,143/national population	75%	NR (30+)	Hip	European deprivation index (5)	2 (?)
Quah [78] (2011)	1999–2009	UK	6300/national population	77.7%	83	Hip	Index of Multiple Deprivation (5)	2 (?)
Bacon [79] (2000)	1989–1991	USA	5161/national population	72%	NR (50+)	Hip	Area income (6)	2 (?)
Brennan [80] (2013)	1996–2011	Canada	3723/51,327	100%	65.9 (9.8)	Hip, MOF	Mean household income (5)	2 (?)
Brennan [9] (2014)	2000–2007	Canada	15,094/national population	60%	NR (50+)	All, hip, humerus, spine, forearm,	Mean household income (4)	2 (?)
Guilley [81] (2011)	1991–2000	Switzerland	2454/national population	74%	79.5 (10.4)	Hip	Median household income (3)	2 (?)
Taylor [82] (2010)	2000–2005	USA	168,316/1,694,051	58%	72	Hip, vertebral, radius/ulna, tibia/fibula, humerus, ankle	Insurance status as proxy for income (5)	1 (?)
Zingmond [83] (2006)	1996–2000	USA	116,919/8,144,469	54%	NR (50+)	Hip	Median income (10)	2 (+)

[A] Bhimjiyani et al. (2018): median and IQR. [B] Goldman et al. (2018): not reported for the subgroup aged >65 years. [C] Jones et al. (2004): not reported for the subgroup aged ≥85 years. [D] Only data from 2010 are included. NR, not reported. Phase, phase of investigation, divided into studies that aim to identify associations (phase 1), test independent associations (phase 2), or understand prognostic pathways (phase 3). Risk of bias: A + indicates low risk, a ? indicates unclear risk, and a – indicates high risk

Table 3 Summary of findings for the association between socio-economic status and fragility fracture incidence

SES measure	Studies (n)	Estimated risk ratio (95% CI)	I^2	Phases	Overall quality	Comments
Individual-based SES						
Education	30	1.23 (1.04,1.45)	98%	1,2,3	Moderate	Downgraded due low phase of
Income	7	1.22 (1.03, 1.44)	94%		(+++)	investigation (59% phase 1)
Occupation	2	1.17 (1.07, 1.28)	0%			
Cohabiting	3	2.37 (1.88, 2.98)	0%			
All SES Combined	42	1.27 (1.12, 1.44)	98%			
Area-based SES						
Index of Multiple Deprivation	10	0.99 (0.76, 1.30)	99%	1,2	Moderate	Downgraded due to imprecision
Area income	6	1.21 (1.12, 1.30)	80%		(+++)	
All SES combined	16	1.08 (0.91, 1.30)	99%			

compared to living in the highest socio-economic level area (cluster 20) (95% CIs were not reported) [29].

Stratified analyses for the area-based SES measures were restricted to study quality, participant gender, and fracture type. It was not possible to investigate the effect of model adjustment on associations between SES and fracture risk, given the inherent lack of individual-level covariates in area-based studies. There were no marked differences in risk estimates according to study quality, participant gender, or fracture type (Table 4). This finding was supported by the meta-regression analysis performed for the exposure measure IMD. Study quality, participant gender, and fracture type did not contribute to the heterogeneity across area-based studies (Supplementary Table S3). An insufficient number of studies precluded meta-regression analysis for the exposure measure of area income on fracture risk.

The quality of evidence in studies of area-based SES on fracture risk was high as a starting point given that the majority (88%) of evidence originated from phase 2 studies. The evidence was downgraded due to study limitations given that more than 50% of the studies had unclear risk of bias. Consequently, the quality of evidence was judged as moderate. Although the between-study heterogeneity was substantial (>50%), evidence quality was not downgraded for inconsistency because the point estimate from the overall fixed effects model (RR 1.04 [95% CI 1.03, 1.06]) was within the 95% CI of the random effects model (RR 1.08 [95% CI 0.91, 1.30]). No clear evidence of publication bias was detected (Egger's test p=0.06) (Funnel plot shown in Supplementary Figure S4).

Discussion

Main results

Of the 61 studies reviewed, more than 2/3 used an individual-based measure to define SES. These studies identified a significant relationship between lower SES and a more than 25% increased risk of fragility fracture. This relationship was consistent across all individual-based SES measures, although the magnitude of effect differed, with the highest fracture risk, a 2-fold increase, being seen in those living alone compared to those cohabiting. Between-study variance was substantial. Meta-regression analysis revealed that individual study differences in covariate (e.g. BMI, smoking, alcohol consumption, and physical inactivity) adjustment accounted for much of the inconsistency in study findings, explaining 39% of the between-study variance. Results derived from studies of area-based SES similarly detected an association between low SES and fracture risk, when SES was defined by area income but not by Index of Multiple Deprivation.

Comparisons with other studies

The association between different individual-based indicators of SES (education, income, occupation, type of residence, and cohabitation) and fracture incidence was explored more than a decade ago in a systematic review by Brennan et al. [20]. The review by Brennan et al. included 12 studies published between 1994 and 2007 of which only five were considered high quality. Consistent with our results, Brennan et al. found strong evidence for an association between living alone and increased fracture risk. For the other effect measures (including education, income, and employment), no conclusions could be drawn as evidence was limited and conflicting, and authors highlighted the need for further high-quality research [20]. We were able to include a large number of studies, reflecting the growing interest in the role of social disadvantage on fragility fracture risk. Furthermore, in addition to the individual-level SES studies, we have added assessment of the effect of area-based deprivation on fracture risk, data which have not previously been synthesized. Thus, our review provides a comprehensive and novel overview of the evidence supporting an association between SES and fragility fracture risk.

Fig. 2 Forest plot of pooled risk estimates for the association between individual-based SES and fragility fracture

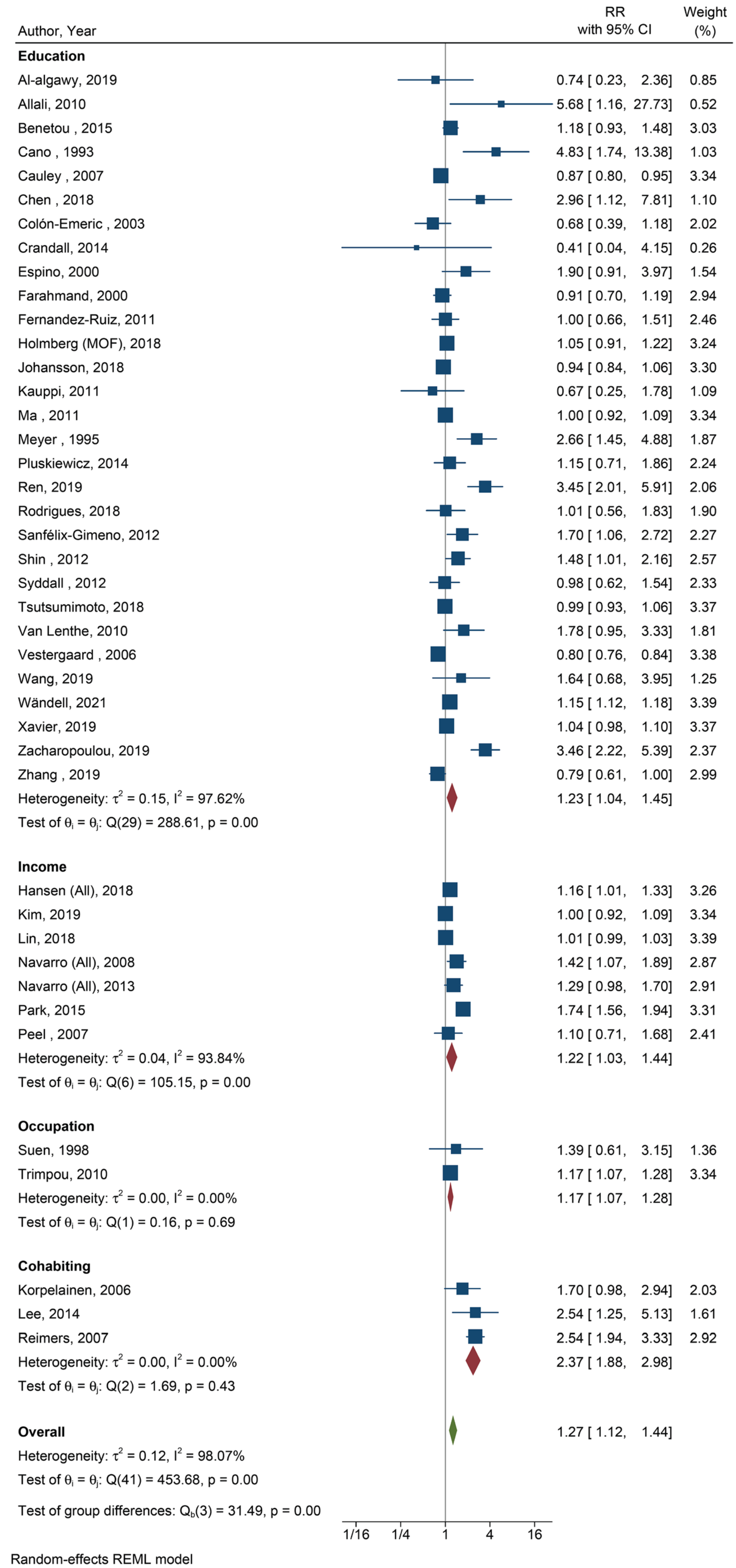

Table 4 Results of the stratified meta-analyses

Factor	Subgroup	Studies	RR (95% CI)	Heterogeneity (I^2)
Individual-based SES (All SES combined)				
Quality	High[A]	18	1.19 (1.02, 1.38)	96%
	Low[B]	24	1.37 (1.12, 1.67)	98%
Gender	Women only	24	1.18 (1.01, 1.39)	99%
	Men only	13	1.07 (0.84, 1.37)	99%
Fracture site	Hip	24	1.39 (1.14; 1.70)	97%
	Non-hip	7	1.36 (1.13; 1.64)	89%
Factors adjusted for	Crude	10	1.16 (0.88; 1.53)	83%
	Sex and age	16	1.28 (1.08; 1.53)	98%
	Sex, age, and BMI	5	2.69 (1.60; 4.53)	67%
	Sex, age, health behaviours[C] (and BMI[D])	11	1.06 (0.92, 1.22)	92%
Area-based SES (All SES combined)				
Quality	High[A]	14	1.09 (0.89, 1.34)	99%
	Low[B]	2	1.10 (0.94, 1.27)	54%
Gender	Women only	8	1.20 (1.06, 1.37)	98%
	Men only	6	1.41 (0.97, 2,04)	99%
Fracture site	Hip	13	1.08 (0.89; 1.31)	99%
	Non-hip	11	1.10 (1.03; 1.17)	84%

A, phase 2 or phase 3 studies with low or unclear risk of bias; B, phase 1 studies or studies with high risk of bias regardless of phase of investigation; C, smoking and/or alcohol consumption and/or physical inactivity and/or physical disability as proxy for physical inactivity; D, in addition to health behaviours. BMI was adjusted for in 8/11 studies, 1/11 studies adjusted for triceps skinfold thickness, and 2/11 studies did not adjust for BMI

Interpretation of results and implication for policy and practice

This evidence synthesis highlights a clear increase in fragility fracture risk associated with lower SES. This finding was more evident from studies using individual-based than area-based measures. The weaker associations in area-based research imply that census data likely underestimate the socioeconomic gradient in health though this may differ dependent on the outcome [6]. For the individual-based SES studies, the strength of the association was influenced by the type and number of covariates included in the statistical model. Studies that adjusted for age, sex, and BMI, rather than simply age and sex, reported much stronger associations between SES and fracture risk, whilst studies that adjusted for age, sex, BMI, and other health behaviours (smoking, alcohol consumption, and physical inactivity) reported attenuated associations between SES and fracture risk. This suggests, firstly, that failing to account for low BMI in studies of fracture incidence risks underestimating the true risk of fracture and, secondly, that adverse health behaviours such as smoking and alcohol consumption, which are associated with low SES [14, 15], may attenuate the association between SES and fracture risk conditional on BMI (Supplementary Figure S1). The impact of BMI adjustment was further highlighted by results from studies stratified by the type of fracture outcome (hip *vs.* non-hip). In hip fracture only analyses, whilst no clear association was seen between SES and hip fracture risk in studies accounting for age and sex, in those in which additional adjustment was made for BMI, a more than 3-fold increased risk of fracture was seen in those with low SES. In contrast, in non-hip fracture studies, those models that took account of BMI overall found no association between SES and non-hip fracture risk, whilst in age and sex only adjusted models, an association was evident. Our findings highlight the need for special attention to be paid to model adjustment in future studies of SES on fracture risk, with careful consideration of confounders versus mediating variables that lie on the causal pathway (and/or which act as proxies for the exposure).

The important public health implications of our findings are two-fold. Firstly, our results imply that individuals with low SES, who also have a low BMI, are at particular risk of hip fracture, and thus, targeted fracture prevention strategies, for example, through timely fall and fracture risk assessments, may be warranted. Secondly, the attenuated association between low SES and fracture risk in studies adjusting for health behaviours emphasizes the conclusions from the 2010 Marmot review that "health inequalities are not inevitable and can be significantly reduced" [77]. Reducing unhealthy behaviours such as smoking, excessive alcohol consumption, and physical inactivity among people with low SES may potentially reduce fracture incidence. However, effective

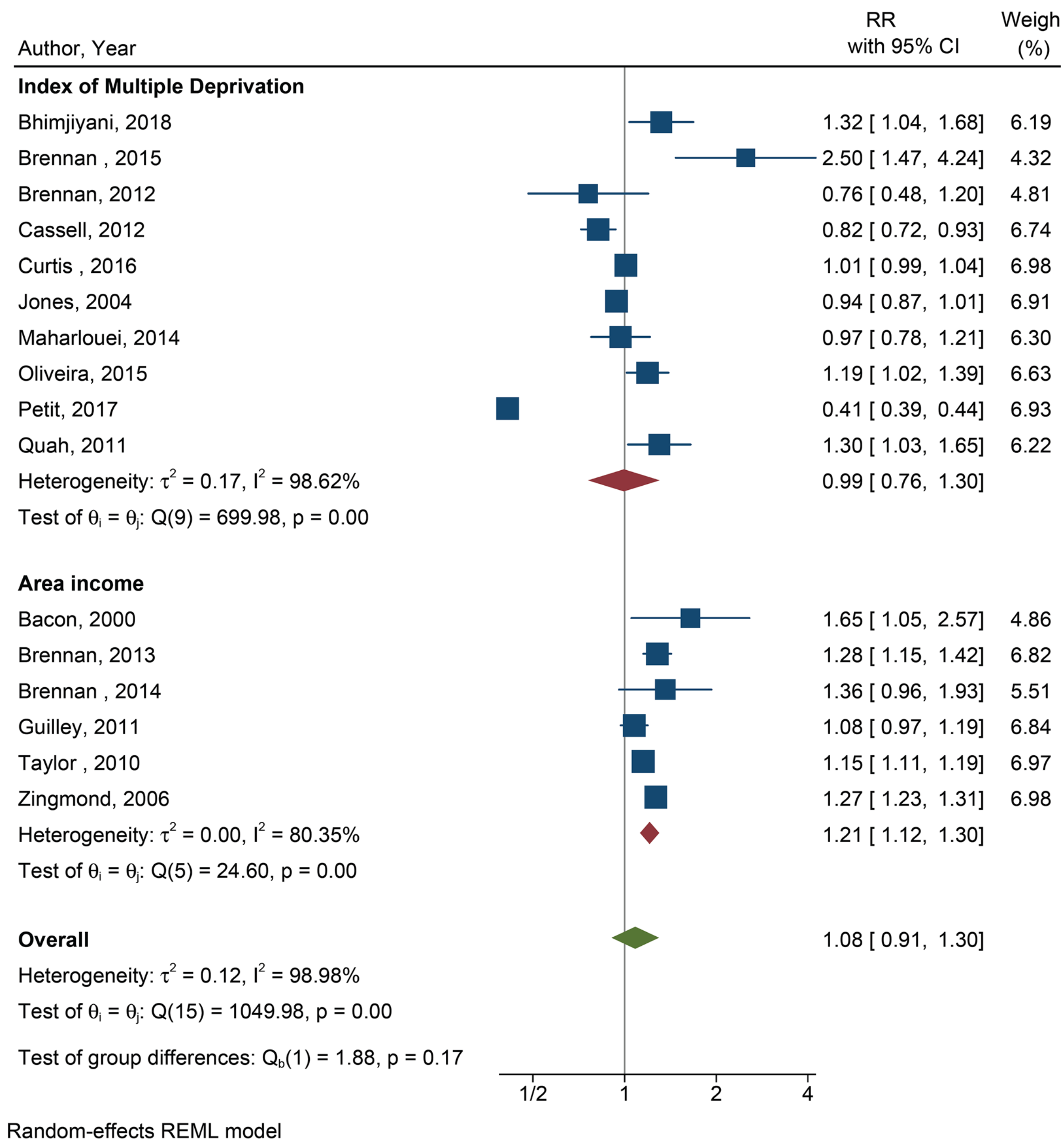

Fig. 3 Forest plot of pooled risk estimates for the association between area-based SES and fragility fracture

measures, Marmot argued, require action on the causes of the causes of ill health; for example, it is difficult to change unhealthy behaviours when faced with challenges of debt and/or poor housing conditions. Poverty limits options and makes it more difficult to make healthy choices [2]. Thus, health and social care policy must aim to both improve the living conditions for older adults and facilitate healthier life choices towards improved health behaviours [2].

Methodological strengths and limitations

To our knowledge, this is the first review to synthesize and quantitatively assess the effect of social inequalities on fragility fracture risk. Our review was registered in PROSPERO, and the findings are reported in accordance with PRISMA [22]. The quality of evidence was thoroughly assessed using the adapted GRADE approach for prognostic factor research which ensures transparency in reporting [24]. The broad scope of this review potentially introduced heterogeneity reducing confidence in summary estimates. However, the large study size enabled stratified analysis, providing valuable information on potential factors that impact or explain diverging results. Of the SES measures included in this review, cohabitation is the least well recognized (compared with education, income, and occupation). However, according to Conway et al., wider sociodemographic factors such as marital status and living arrangements are increasingly considered to be important in epidemiological research to capture SES [84].

According to Conway et al., marital status relates to SES given that marriage can infer social support and provide economic or material advantage and access to healthcare (USA) [84]. Furthermore, being married has been found to be associated with better health behaviours compared to being never married/divorced/widowed [85]. Thus, inclusion of cohabitation as an indicator of SES is acceptable and in line with the scope of this review. Furthermore, omitting the three studies based on cohabitation did not alter the conclusions drawn by our study (combined RR excluding "cohabiting": 1.21 (95% CI 1.08, 1.36). Our analysis was unable to take account of potential survival bias: i.e. the association between low SES and fracture risk may be underestimated as low SES is associated with early death, occurring before an incident fracture. As hip fractures occur later in life than non-hip fractures, the analysis stratified by fracture type offers some insight. The RR adjusted for age and sex was higher for non-hip (RR 1.69 [95% CI: 1.53, 1.86]) than for hip (RR 1.23 [95% CI: 0.96, 1.58]) fractures suggesting larger impact of socio-economic inequality among the youngest age groups. We were unable to account for the number of SES levels in the meta-analysis; for example, the RR will be weaker if the SES exposure is dichotomized on the median, than if the first and fifth quintiles were compared. Ignoring this could have contributed to heterogeneity due to differences in the coding of SES rather than true heterogeneity of effect. Although the quality of evidence was judged as moderate implying moderate confidence in the results, restricting the analysis to studies with high-quality evidence did not change our conclusions. As most studies were conducted in high-income countries, our findings are not likely to be generalizable to populations living in low- and middle-income countries with differing socio-economic structures and healthcare systems. In addition, most studies focused on hip fractures; thus, the association between SES and fractures at non-hip sites requires further confirmation.

In conclusion, our results highlight the importance of low SES, measured at the individual level, as a risk factor for incident fragility fracture. Furthermore, our analyses demonstrate the importance of BMI and unhealthy behaviours in mediating the effect of SES on fracture risk. Public health and social care strategies aimed at preventing fragility fractures should tackle structural inequalities thus reducing unhealthy behaviours, such as smoking, alcohol consumption, and physical inactivity. This upstream approach is most likely to reduce socio-economic inequalities in fragility fracture incidence.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-021-06038-7.

Funding AB was supported by a Linda Edwards Memorial PhD Studentship funded by the Royal (formerly National) Osteoporosis Society.

Declarations

Conflict of interest GV, MBR, EKJ, KF, AB, YBS, AH, CPN, and CLG declare that they have no conflicts of interest. BL has received research funding for her institution from Amgen and Novo Nordisk and honoraria for advisory boards and lectures from UCB, Eli Lilly, Amgen, Gedeon Richter, and Gilead.

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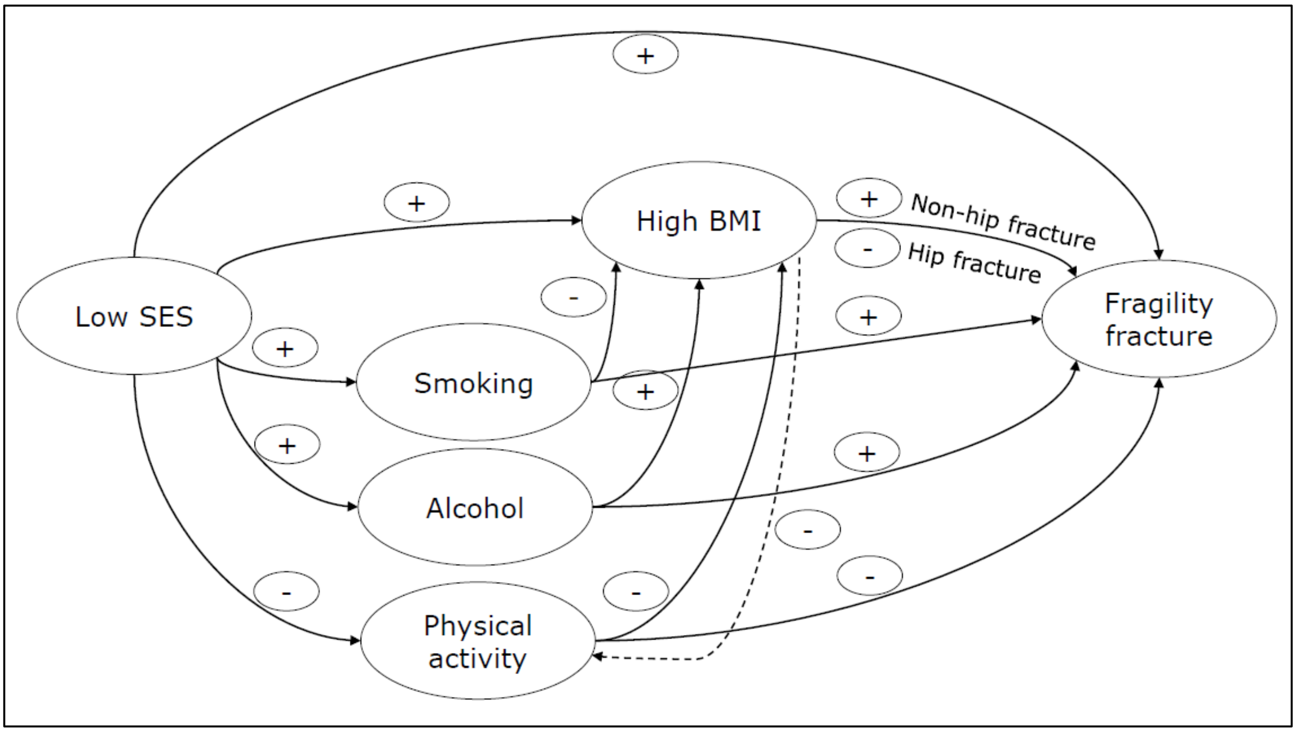
85. Osler M, McGue M, Lund R, Christensen K (2008) Marital status and twins' health and behavior: an analysis of middle-aged Danish twins. Psychosom Med 70(4):482–487

Appendix 1B Study I – Supplementary material

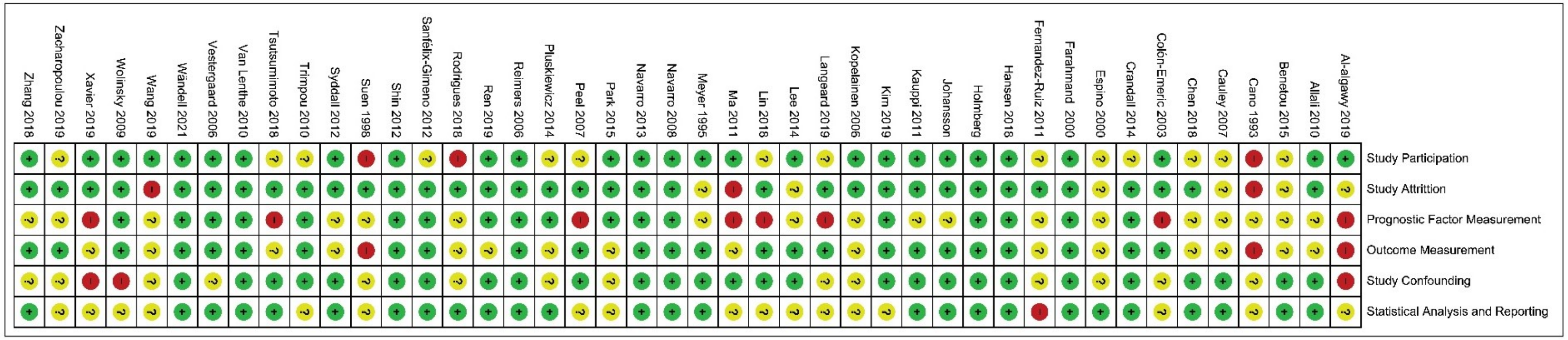
Supplementary material

Supplementary Figure S1: Hypothesized causal diagram illustrating the association between socio-economic status (SES) and fragility fracture.



A + indicates a positive association between the exposure and the mediator or the outcome (e.g. lower SES is associated with higher smoking)
A - indicates a negative association between the exposure and the mediator or the outcome (e.g. lower SES is associated with lower physical activity)

Supplementary figure S2A: Risk of bias summary for the individual-based SES studies: Review authors' judgements about each risk of bias item for each included study.



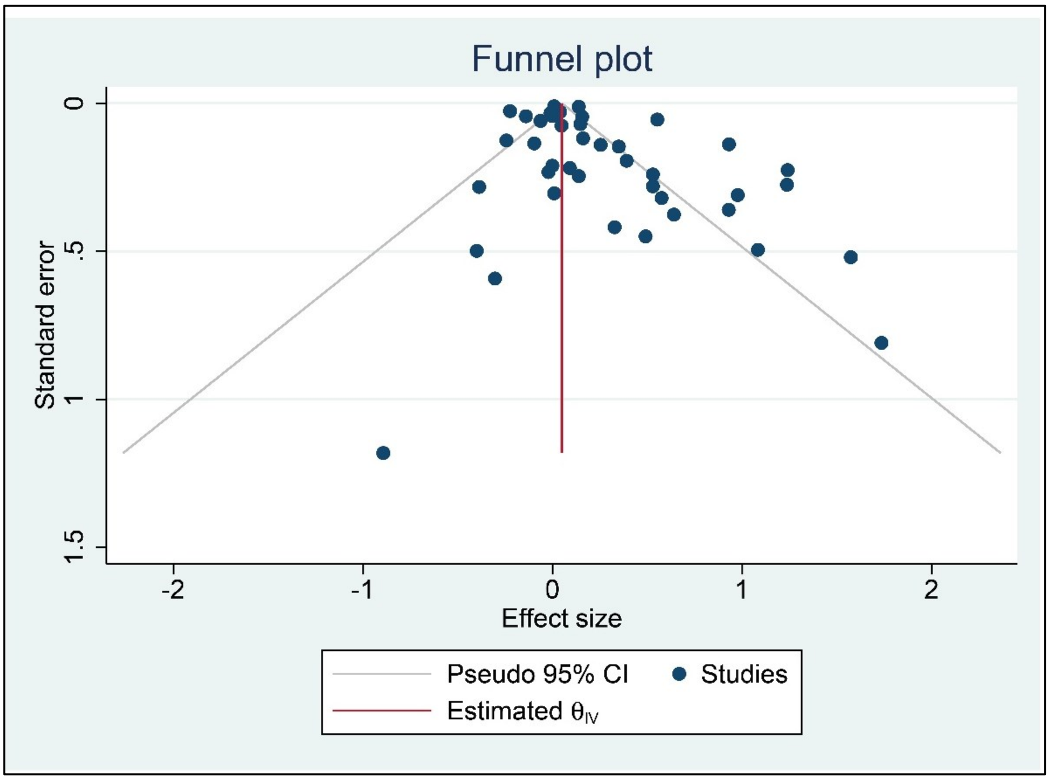
Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool, which rates individual studies according to the potential risk of bias associated with six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) confounding measurement and account, and (6) analysis (Hayden, van der Windt et al. 2013). The overall risk of bias for each of the studies was judged as: (1) low if there was a low risk of bias in all domains in individual-based studies and low risk of bias in all domains except "prognostic factor measurement" for area-based studies (area-based studies could at best be rated "unclear risk of bias" in the prognostic factor measurement domain due to the inherent risk of misclassification in these studies), (2) unclear risk of bias if there was an unclear risk of bias for one or more domains, and (3) high risk of bias if there was a high risk of bias for one or more domains

Supplementary Material S2B: Risk of bias summary for the area-based SES studies: Review authors' judgements about each risk of bias item for each included study.

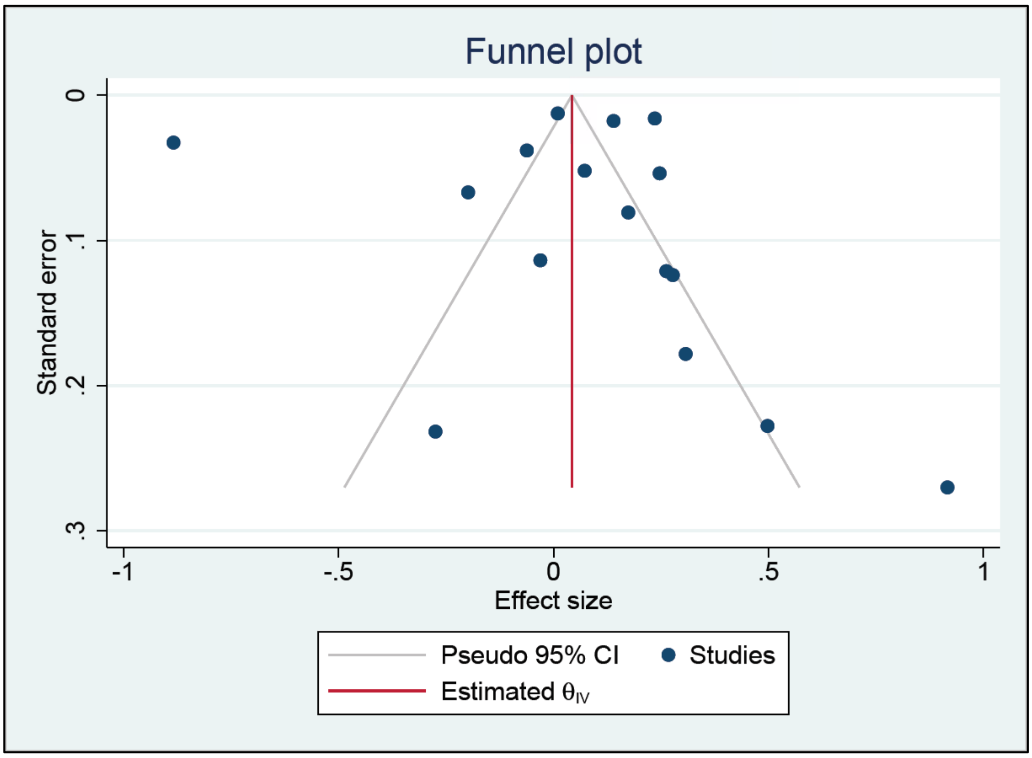
	Zigmond 2006	Taylor 2010	Quah 2011	Petit 2017	Oliveira 2015	Maharlouei 2014	Jones 2004	Guilley	Goldman 2018	Curtis 2016	Cassell 2013	Brennan 2015	Brennan 2014	Brennan 2013	Brennan 2012	Bhimjiyani 2018	Bacon 2000
Study Participation	+	+	+	?	+	+	+	+	?	+	+	+	+	+	+	+	+
Study Attrition	+	?	+	+	+	+	+	+	+	?	+	+	?	?	?	+	+
Prognostic Factor Measurement	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Outcome Measurement	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+
Study Confounding	+	+	?	?	+	-	+	?	?	?	?	+	+	+	+	+	+
Statistical Analysis and Reporting	+	+	+	+	?	+	?	+	-	?	+	+	+	+	+	+	?

Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool, which rates individual studies according to the potential risk of bias associated with six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) confounding measurement and account, and (6) analysis (Hayden, van der Windt et al. 2013). The overall risk of bias for each of the studies was judged as: (1) low if there was a low risk of bias in all domains in individual-based studies and low risk of bias in all domains except "prognostic factor measurement" for area-based studies (area-based studies could at best be rated "unclear risk of bias" in the prognostic factor measurement domain due to the inherent risk of misclassification in these studies), (2) unclear risk of bias if there was an unclear risk of bias for one or more domains, and (3) high risk of bias if there was a high risk of bias for one or more domains

Supplementary figure S3: Funnel plot for the individual-based studies.



Supplementary figure S4: Funnel plot for the area-based studies.



Supplementary table S1: Literature search

Literature search

Medline April 28 2021

(((((("Fractures, Bone"[Mesh] OR "Minimal trauma fracture"[tiab]) OR "Minimal trauma fractures"[tiab]) OR "Osteoporotic fracture"[tiab]) OR "Osteoporotic fractures"[tiab]) OR "fragility fractures"[tiab]) OR "fragility fracture"[tiab]) AND (((((((((("Socioeconomic Factors"[Mesh] OR "Socioeconomic Factors"[tiab]) OR "Socio economic Factors"[tiab]) OR "Socioeconomic status"[tiab]) OR "Socio economic status"[tiab]) OR "social class"[tiab]) OR ("socioeconomic factors"[MeSH Terms] OR ("socioeconomic"[tiab] AND "factors"[tiab]) OR "socioeconomic factors"[tiab] OR "inequality"[tiab])) OR ("education"[Subheading] OR "education"[tiab] OR "educational status"[MeSH Terms] OR ("educational"[tiab] AND "status"[tiab]) OR "educational status"[tiab] OR "education"[tiab] OR "education"[MeSH Terms])) OR ("income"[MeSH Terms] OR "income"[tiab])) OR ("marital status"[MeSH Terms] OR ("marital"[tiab] AND "status"[tiab]) OR "marital status"[tiab])) OR residence[tiab]) OR ("occupations"[MeSH Terms] OR "occupations"[tiab] OR "occupation"[tiab]))

Embase April 28 2021

('socioeconomics'/exp OR 'socioeconomic factors':ab OR 'socio economic factors':ab OR 'socioeconomic status':ab OR 'socio economic status':ab OR 'social class':ab OR 'inequalities':ab OR 'education':ab OR income:ab OR 'marital status':ab OR residence:ab OR occupation:ab) AND ('fracture'/exp OR 'minimal trauma fracture':ab OR 'minimal trauma fractures':ab OR 'osteoporotic fracture':ab OR 'osteoporotic fractures':ab OR 'fragility fracture':ab OR 'fragility fractures':ab) AND ('article'/it OR 'review'/it) AND [2018-2020]/py

CINAHL April 28 2021

(S39 OR S40 OR S41 OR S42 OR S43 OR S56 OR S57) AND (S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55) View Dependent Searches

Dependent Searches Close

S39(MH "Fractures+")	Search modes - Boolean/Phrase
S40AB "minimal trauma fracture"	Search modes - Boolean/Phrase
S41AB "minimal trauma fractures"	Search modes - Boolean/Phrase
S42AB "osteoporotic fracture"	Search modes - Boolean/Phrase
S43AB "osteoporotic fractures"	Search modes - Boolean/Phrase
S44(MH "Socioeconomic Factors")	Search modes - Boolean/Phrase
S45AB "socioeconomic status"	Search modes - Boolean/Phrase
S46AB "socio economic status"	Search modes - Boolean/Phrase
S47AB "social class"	Search modes - Boolean/Phrase
S48AB "socioeconomic factors"	Search modes - Boolean/Phrase
S49AB "socio economic factors"	Search modes - Boolean/Phrase
S50AB "inequality"	Search modes - Boolean/Phrase
S51AB "education"	Search modes - Boolean/Phrase
S52AB "income"	Search modes - Boolean/Phrase
S53AB "marital status"	Search modes - Boolean/Phrase
S54AB "residence"	Search modes - Boolean/Phrase
S55AB "occupations"	Search modes - Boolean/Phrase
S56"fragility fracture"	Search modes - Boolean/Phrase
S57"fragility fractures"	Search modes - Boolean/Phrase

Search Options

Supplementary table S2: Full text articles assessed for eligibility which were excluded, with reason for exclusion.

First author (Year)	**Title**	**Reason for exclusion**
Ahmeidat (2021)	Long-term effects of gestational diabetes on bone mineral density and fracture risk: Analysis of the Norfolk cohort of the European Prospective Instigation into Cancer (EPIC-Norfolk) population-based study	1
Aleksic (2018)	Cross-cultural validation of the Modified Falls Efficacy Scale in Serbian community-dwelling women at risk for osteoporotic fracture	2
Al-Rukabi (2020)	Risk factors of osteoporosis in postmenopausal women in karbala governorate–Iraq 2019	6
Aramisova (2018)	Medical and social aspects of low-energy fractures among residents of the Kabardino-Balkar Republic.	1
Arshad (2021)	Clinical characteristics and outcomes of patients presenting with hip fractures at a tertiary care hospital in Pakistan	1
Bäcker (2021)	Epidemiology of proximal femoral fractures	1
Bawab (2014)	Evaluation of hip fracture risk factors in older adults in the Lebanese population	1
Bhimjiyani (2018)	Inequalities in hip fracture incidence are greatest in the North of England: regional analysis of the effects of social deprivation on hip fracture incidence across England.	3
Borensztein (2018)	Analysis of Risk Factors for New Vertebral Fracture After Percutaneous Vertebroplasty	1
Brennan (2011)	Incident hip fracture and social disadvantage in an Australian population aged 50 years or greater	3
Brennan (2015)	Is there an interaction between socioeconomic status and FRAX 10-year fracture probability determined with and without bone density measures? Data from the Geelong Osteoporosis Study of female cohort.	2
Bugeta (2018)	Demographic Study of Hip Fractures in the Maltese Islands	4

Byberg (2018)	Comments on Feskanich et al.: Milk and other dairy foods and risk of hip fracture in men and women...Feskanich D, Meyer HE, Fung TT, et al. Milk and other dairy foods and risk of hip fracture in men and women.	4
Cha (2019)	Establishment of Fracture Liaison Service in Korea: Where Is It Stand and Where Is It Going?	4
Chen (2016)	Risk factor for first-incident hip fracture in Taiwanese postmenopausal women	3
Chen (2018)	Demographic and socioeconomic factors influencing the incidence of clavicle fractures, a national population-based survey of five hundred and twelve thousand, one hundred and eighty-seven individuals.	5
Coulson (2009)	Factors influencing fracture risk, T score, and management of osteoporosis in patients with rheumatoid arthritis in the Consortium of Rheumatology Researchers of North America (CORRONA) registry.	5
Court-Brown (2006)	Social deprivation and adult tibial diaphyseal fractures	2
Court-Brown (2013)	Relationship between social deprivation and the incidence of adult fractures	6
Court-Brown (2010)	The relationship of fall-related fractures to social deprivation	5
DenOuden (2019)	Epidemiology of spinal fractures in a level one trauma center in the Netherlands: A 10 years review	1
DePew (2018)	Ezekiel	4
Domiciano (2021)	Incidence and risk factors for osteoporotic non-vertebral fracture in low-income community-dwelling elderly: a population-based prospective cohort study in Brazil. The São Paulo Ageing and Health (SPAH) study	4
Fujiwara (1997)	Risk factors for Hip Fracture in a Japanese Cohort	5
Gavilánez (2018)	Osteoporotic hip fractures in older adults in Ecuador 2016	1

Gomez-de-Tejada Romero (2013)	Prevalence of osteoporosis, vertebral fractures and hypovitaminosis D in postmenopausal women living in a rural environment	1
Hadji (2020)	Estimated epidemiology of osteoporosis diagnoses and osteoporosis-related high fracture risk in Germany: a German claims data analysis	1
Halim (2018)	Preventative Care in Orthopedics: Treating Injuries Before They Happen	1
Hokby (2003)	Hip fractures among older people: do marital status and type of residence matter	3
Holloway (2018)	The epidemiology of hip fractures across western Victoria, Australia	4
Icks (2009)	Hip fractures and area level socioeconomic conditions: a population-based study.	4
Illanes (2021)	Higher latitude and lower solar radiation influence on hip fracture admissions in Chilean older population	4
Jin (2021)	Epidemiological investigation of hospitalized patients with traumatic fractures: a cross-sectional study	5
Kowski (1998)	Risk factors for Major Injurious Falls among the Home-Dwelling Elderly by Functional Abilities	6
Kristensen (2020)	Fractures after stroke—A Danish register-based study of 106 001 patients	3
Kunutsor (2019)	Serum Albumin and Future Risk of Hip, Humeral, and Wrist Fractures in Caucasian Men: New Findings from a Prospective Cohort Study	1
La Vecchia (1991)	Cigarette Smoking, Body Mass and Other Risk Factors for Fractures of the Hip in Women	1
Laji (2020)	Osteoporosis risk analysis in women residing in selected urban areas	2
Leslie (2005)	Demographic risk factors for fracture in First Nations people	5
Li (2019)	Epidemiological profile of thoracolumbar fracture (TLF) over a period of 10 years in Tianjin, China	1
Litwic (2020)	Self-perceived Fracture Risk in the Global Longitudinal Study of Osteoporosis in Women: Its Correlates and Relationship with Bone Microarchitecture	1
Liu (2018)	Demographic and socioeconomic factors influencing the incidence of ankle fractures, a	5

	national population-based survey of 512187 individuals	
Machado-Duque (2018)	Association between the use of benzodiazepines and opioids with the risk of falls and hip fractures in older adults	1
Maher (2019)	295 Characteristics of Older Hip Fracture Adults Admitted to a Dublin Hospital...67th Annual & Scientific Meeting of the Irish Gerontological Society, Innovation, Advances and Excellence in Ageing, 26-28 September 2019, Cork, Ireland	4
Mathieu (2019)	Fractures ouvertes de jambe de type III en situation sanitaire dégradée. Partie 3 : relance de la consolidation et traitement des pertes de substances osseuses	1
Mattson (2019)	Musculoskeletal Injuries and Outcomes Pre- and Post- Emergency Medicine Training Program	1
Meyer (2021)	The role of having children for the incidence of and survival after hip fracture – A nationwide cohort study	1
Morosano (2004)	Incidence of hip fracture in the six districts of Rosario city, Argentina	1
Nabian (2020)	Epidemiology of traumatic injuries in the elderly patients: A descriptive study from a developing country	1
O'Donnell (2018)	Screening, Prevention and management of osteoporosis among Canadian adults	1
Oliviera (2015)	The interactions between municipal socioeconomic status and age on hip fracture risk	4
Ong (2014)	Are Fractures and a Diagnosis of Osteoporosis in the Elderly Related to Social Deprivation	4
Ong (2015)	The relationship between socioeconomic status and fracture in a fracture clinic setting: data from the Nottingham Fracture Liaison Service	2
Pinheiro (2010)	The burden of osteoporosis in Brazil: regional data from fractures in adult men and women--the Brazilian Osteoporosis Study (BRAZOS)	1
Pouramin (2019)	A multicenter observational study on the distribution of orthopaedic fracture types across 17 low- And middle-income countries	5
Prieto-Alhambra (2019)	Smoking and Alcohol Intake but Not Muscle Strength in Young Men Increase Fracture Risk at	1

	Middle Age: A Cohort Study Linked to the Swedish National Patient Registry	
Qi (2018)	Current status of falls and related injuries among Chinese elderly in 2013	7
Reyes (2015)	Socioeconomic status and its association with the risk of developing hip fractures: a region-wide ecological study.	4
Rodriguez (2019)	At what price decreased mortality risk?	4
Rundgren (2020)	Epidemiology, classification, treatment and mortality of distal radius fractures in adults: an observational study of 23,394 fractures from the national Swedish fracture register	1
Schneider (2019)	Fall Recovery and Prevention	4
Scholes (2013)	Epidemiology of lifetime fracture prevalence in England: a population study of adults aged 55 and over	6
Shu (2018)	Profile of patients with osteoporotic fractures at a tertiary orthopedic trauma center	3
Singh (2020)	Inpatient hip fractures: Understanding and addressing the risk of this common injury	1
Skuladottir (2019)	Hip fractures among older people in Iceland between 2008 and 2012.	2
Skuladottir (2021)	Characteristics of incidence hip fracture cases in older adults participating in the longitudinal AGES-Reykjavik study	1
Smith (2013)	Focus on hip fracture: Trends in emergency admissions for fractured neck of femur, 2001 to 2011	4
Sung (2020)	Association of air pollution with osteoporotic fracture risk among women over 50 years of age	1
Søgaard (2018)	The association between alcohol consumption and risk of hip fracture differs by age and gender in Cohort of Norway: a NOREPOS study	1
Søgaard (2020)	Grip strength in men and women aged 50-79 years is associated with non-vertebral osteoporotic fracture during 15 years follow-up: The Tromsø Study 1994-1995	1
Tirupathi (2020)	Impact of socio-demographic factors on the bone in diabetic osteoporosis postmenopausal women	6

Tomioka (2019)	Equality of Treatment for Hip Fracture Irrespective of Regional Differences in Socioeconomic Status: Analysis of Nationwide Hospital Claims Data in Japan	1
Turner (2009)	Spatial temporal modelling of hospitalizations for fall-related hip fractures in older people.	4
Veronese (2018)	Adherence to a Mediterranean diet is associated with lower incidence of frailty: A longitudinal cohort study.	6
Vieira (2018)	Falls among older adults in the South of Brazil: prevalence and determinants	6
Wang (2018)	Visualisation of the unmet treatment need of osteoporotic fracture in Taiwan: A nationwide cohort study	1
Wang (2019)	Estimation of Prevalence of Osteoporosis Using OSTA and Its Correlation with Sociodemographic Factors, Disability and Comorbidities	6
West (2004)	Do rates of hospital admission for falls and hip fracture in elderly people vary by socio-economic status?	4
Wilson (2006)	Hip Fracture Risk Among Community-Dwelling Elderly People in the United States: A Prospective Study of Physical, Cognitive, and Socioeconomic Indicators.	3
Wolinsky (1994)	The risk of Hip fracture Among Noninstitutionalized Older Adults	3
Yang (2006)	Decreased Bone Mineral Density and Fractures in Low-Income Korean Women	5
Yang (2019)	Geographic Variations in Intertrochanteric Femoral Fractures in China	1
Yoo (2018)	Prevalence and associated risk factors for osteoporosis in Korean men	6
Zeba (2018)	ABC OM Distal radiusfrakturhos vuxna	4
Zhu (2020)	Epidemiology of low-energy wrist, hip, and spine fractures in Chinese populations 50 years or older: A national population-based survey	1

1: SES not reported, 2: Ineligible aim, 3: Study population overlap, 4: Ineligible study design, 5: Ineligible study population, 6: Ineligible outcome, 7: Chinese language.

Supplementary table S3: Results from the meta-regression analysis for the SES measures education and Index of Multiple Deprivation

Variable	**Studies (n)**	**Risk ratio**	**95%CI**	**Tau^2 %** [A]	**p value**
All studies (Education)	30	1.23	1.04, 1.45		
Quality				3 %	0.13
High[B]	12	1.02	0.90, 1.15		
Low[C]	18	1.40	1.08, 1.82		
Gender				0 %	0.18
Women only	18	1.00	0.91, 1.10		
Men only	9	0.88	0.72, 1.09		
Fracture site				0 %	0.85
Hip	16	1.43	1.07, 1.92		
Non-hip	3	1.29	0.92, 1.80		
Factors adjusted for				39 %	0.001
Crude	9	1.17	0.85, 1.60		
Gender and age	11	1.10	0.98, 1.24		
Gender, age and BMI	3	3.85	2.44, 6.07		
Gender, age, health behaviours[D] (and BMI[E])	7	1.02	0.78, 1.32		
All studies (Index of Multiple Deprivation)	10	0.99	0.76, 1.30		
Quality				0 %	0.95
High[B]	9	1.00	0.74, 1.35		
Low[C]	1	0.97	0.78, 1.21		
Gender				0 %	0.67
Women only	5	1.20	0.99, 1.45		
Men only	5	1.38	0.89, 2.15		
Fracture site				0 %	0.70
Hip	6	0.93	0.65, 1.33		
Non-hip	1	0.76	0.48, 1.20		

A: Percentage reduction in Tau^2

B: Phase 2 or phase 3 studies with low or unclear risk of bias.

C: Phase 1 studies or studies with high risk of bias regardless of phase of investigation.

D: Smoking and/or alcohol consumption and/or physical inactivity and/or physical disability as proxy for physical inactivity.

E: 6/7 studies adjusted for BMI/triceps skinfold thickness in addition to heath behaviours.

Appendix 2A Study II – Socio-economic inequalities in fragility fracture outcomes

Osteoporosis International (2020) 31:31–42
https://doi.org/10.1007/s00198-019-05143-y

REVIEW

Socio-economic inequalities in fragility fracture outcomes: a systematic review and meta-analysis of prognostic observational studies

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Received: 27 June 2019 / Accepted: 20 August 2019 / Published online: 30 August 2019

Abstract

Summary Individuals with low socio-economic status (SES) have a higher risk of dying following hip fracture compared with individuals with high SES. Evidence on social inequalities in non-hip fractures is lacking as well as evidence on the impact of SES on health-related quality of life post fracture.

Introduction Fragility fractures, especially of the hip, cause substantial excess mortality and impairment in health-related quality of life (HRQoL). This systematic review and meta-analysis aimed to investigate the association between socio-economic status (SES) and post-fracture mortality and HRQoL.

Methods PubMed, EMBASE and CINAHL databases were searched from inception to the last week of November 2018 for studies reporting an association between SES and post-fracture mortality and/or HRQoL among people aged ≥ 50 years. Risk ratios (RRs) were meta-analyzed using a standard inverse-variance-weighted random effects model. Studies using individual-level and area-based SES measures were analyzed separately.

Results A total of 24 studies from 15 different countries and involving more than one million patients with hip fractures were included. The overall risk of mortality within 1-year post-hip fracture in individuals with low SES was 24% higher than in individuals with high SES (RR 1.24, 95% CI 1.19 to 1.29) for individual-level SES measures, and 14% (RR 1.14, 95% CI 1.09 to 1.19) for area-based SES measures. The quality of the evidence for the outcome mortality was moderate. Using individual SES measures, we estimated the excess HRQoL loss to be 5% (95% CI − 1 to 10%) among hip fracture patients with low SES compared with high SES.

Conclusions We found a consistently increased risk of post-hip fracture mortality with low SES across SES measures and across countries with different political structures and different health and social care infrastructures. The impact of SES on post-fracture HRQoL remains uncertain due to sparse and low-quality evidence.

Keywords Fractures · Health-related quality of life · Inequality · Mortality · Socio-economic status

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-019-05143-y) contains supplementary material, which is available to authorized users.

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Introduction

Fragility fractures, especially of the hip and vertebrae, constitute a major and growing public health problem across the world [1]. Approximately one in three women and one in five men over 50 years of age will suffer an osteoporosis-related fracture in their lifetime [1]. Mortality rates among older people with hip fracture range between 14 and 36% within 1 year of the injury, and the risk of dying is increased up to eight-fold within the first 3 months after fracture [2, 3]. This excess mortality risk wanes over time but never returns to the rate of age-matched controls [3]. Survivors of fragility fractures suffer temporary or permanent disabilities such as pain, decreased mobility and increased dependency on others, potentially imposing important limitations on their health-related quality of life (HRQoL) [4, 5]. In the acute fracture period, the mean decline in HRQoL is estimated to be 51% across skeletal sites of fractures, ranging from 70% post-hip fracture to 36% post wrist fracture [6]. One year post fracture, the decline in HRQoL is estimated to be 22–42% for patients with hip fractures and 20% for patients with vertebral fractures; thus, the burden imposed by fragility fractures is substantial [6–8]. The economic costs caused by fragility fractures are estimated to be EUR 37 billion annually in Europe alone. Due to increasing longevity with an associated increase in the incidence of most fracture types, these costs are expected to have increased by 25% by 2025 [1]. Better understanding of factors leading to excess mortality and loss of HRQoL is important to inform future health policy aimed at reducing the health and social care costs and suffering associated with fragility fractures.

Inequalities in mortality and HRQoL between individuals with lower and higher socio-economic status (SES), as indicated by educational level, occupation, income or cohabiting status, are a persistent challenge for health policy [9, 10]. Studies conducted around the world consistently show that lower SES is associated with increased morbidity from most diseases, lower HRQoL, lower life expectancy and increased all-cause mortality throughout life [9, 10]. Despite this well-established socio-economic gradient on mortality and loss of HRQoL, evidence for an association between SES and outcomes following fragility fractures remains unclear. Studies investigating these associations generate diverging results [11–16]. These inconsistencies may be due to the use of different measures of SES across studies (e.g. education, income, occupation or cohabiting status) and differences in study size, duration of follow-up or methodological quality. Thus, a systematic review and meta-analysis combining data from the available evidence is appropriate for establishing the impact of SES on post-fracture mortality and HRQoL.

This systematic review and meta-analysis aimed to investigate the association between measures of SES and post-fracture outcomes across the world. Specifically, we wanted to test the following hypotheses: (1) relative post-fracture mortality is higher among individuals with low SES than among individuals with high SES (irrespective of the SES measure used) and (2) reductions in HRQoL following a fragility fracture are greater among individuals with low SES than among individuals with high SES (irrespective of the SES measure used).

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) [17] statement. The review was conducted according to a predefined protocol registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD42018118211).

Literature search

The PubMed, EMBASE and CINAHL databases were searched from inception to the first week of July 2018 using the following terms: (“Bone fracture” OR “Minimal trauma fracture” OR “Fragility fracture” OR “Osteoporotic fracture”) AND (“Socioeconomic factors” OR “Socioeconomic status” OR “Social class” OR Inequality OR Education OR Income OR “Marital status” OR Residence OR Occupation). The literature search strategy was developed in collaboration with a research librarian using medical subject headings (MeSH) and text words related to fractures and SES. The search strategy developed for the PubMed database was adapted to the syntax and subject headings of the EMBASE and CINAHL databases.

The search strategy was validated to make sure that the strategy retrieved a high proportion of eligible studies found through any means (see supplementary file S1). The search was updated in the last week of November 2018 to ensure that more recently published studies were included. The reference lists of eligible studies were reviewed to ensure literature saturation.

Study selection

All records retrieved from the literature search were uploaded to the Covidence platform, an Internet-based software programme that streamlines the production of systematic reviews. Titles and abstracts yielded by the search were independently screened by two of the review authors (GV and SP) according to the listed eligibility criteria. Studies that were clearly not relevant were excluded directly. Full manuscripts were obtained for all papers appearing to meet the inclusion criteria. Inclusion of a study was agreed by consensus and, if necessary, through discussion with a third co-author (KF). Reasons for excluding studies (full text) were recorded.

Study eligibility

Studies were eligible for inclusion if they met the following criteria: cohort, case-control or cross-sectional studies investigating the association between SES and mortality or SES and HRQoL following a fragility fracture in men and/or women aged ≥ 50 years. Case series including fewer than 50 individuals were not considered eligible. Abstracts and unpublished studies were not eligible for inclusion. A fragility fracture was defined as a fracture associated with minimal trauma. Minimal trauma includes fractures resulting from unintentional contact with the ground where a person falls from standing height or less, including falls going upstairs or falls onto furniture. Fractures sustained due to traffic accidents or violence were considered high trauma, and such studies were excluded. Studies of pathological fractures (arising from benign and malignant bone tumours, infections, bone cysts or monogenic bone disorders) were also excluded along with studies of fractures of the finger phalanges or thumb, toe phalanges and head or skull since these fracture types are not considered typical fragility fractures.

Socio-economic status

Current literature deploys a plethora of variables to measure SES [14]. These measures can be divided into individual-based measures and area-based measures. The most frequently used individual-based measures are education, income and occupation [18]. Area-based measures, also known as census measures, are designed to assess area-based levels of deprivation to allow socio-economic evaluation of local and national populations [19]. They can consist of one single measure e.g. mean family income in the area, or a composite SES measure where different domains (e.g. income, employment, health, education, housing and crime) are combined into an Index of Multiple Deprivation [20]. In this systematic review and meta-analysis, we aimed to capture and synthesize results from both individual-based and area-based SES studies. The analyses are presented separately according to SES type, allowing identification of differences in risk estimates between the different types of SES measures.

Outcomes

Outcomes of interest were all-cause mortality and HRQoL following a fragility fracture. Both generic and disease-specific HRQoL measurement tools were eligible for inclusion. However, HRQoL had to be measured using a validated instrument such as SF36, SF12, EQ-5D or the Quality of Life Questionnaire of the European Foundation for Osteoporosis. In order to ensure that the outcome (mortality or HRQoL) was related to the fracture, only studies reporting the post-fracture outcome within the first year were included.

Data extraction and management

Data from the eligible studies were extracted independently by two authors (GV and SP) using a standardized data extraction form. Pilot calibration exercises were conducted to ensure consistency across the two assessors. Data describing characteristics of the study population were extracted. Disagreement between data assessors was resolved by consensus and/or by consulting a third author.

Relative measures in the form of relative risk (RR) and hazard ratios (HR) were treated as equivalent measures of risk ratios (i.e. having the same clinical interpretation). Adjusted odds ratios (ORs) derived from logistic regression are, if mistakenly interpreted as a risk, known to over-estimate a risk association, especially when the outcome is common (> 10%). Thus, in order to provide a measure that more accurately reflected the concept of RR, we converted risk estimates in the form of ORs to RRs using the following formula: $RR = \frac{OR}{(1-P0)+(P0 \text{ x } OR)}$ as suggested by Zhang and Yu [21]; P_0 indicates the incidence of the outcome of interest in the non-exposed group. The corresponding standard errors were derived from the CIs reported in each study.

In cases where only unadjusted associations in the form of proportions were presented in a study, the RR was calculated manually as the ratio between the proportions. The RR estimates from individual studies were transformed to their natural logarithms (as for the standard errors). To enhance comparability between the studies, all ratios were re-calculated so that the mortality rate of the lowest was divided by the rate of the highest socio-economic level (i.e. using the highest as reference category). HRQoL data were extracted and re-calculated as the relative difference in HRQoL between the lowest and the highest SES groups. If regression models in the individual papers contained multiple individual SES measures, only one measure was included, using the following hierarchy of SES measures, as previously applied by Lundquist et al. (see Box 1): education was prioritized over income, income over occupation and occupation over cohabiting status [22]. This approach was applied in order to obtain a global estimation across all independent measures of SES without including the same participants more than once in the meta-analysis (i.e. avoid double counting leading to an inflated precision). Cohabiting status and marital status were considered the same SES measure and were referred to as cohabiting status in the analysis. Studies of area-based SES measures were divided into those that used multiple deprivation and those that used area income. When data were available in different formats, data from "fully adjusted" analyses were prioritized for inclusion. However, where data were presented both with and without adjustment for another measurement of SES (e.g. educational level adjusted for income), data without adjustment for other SES measures were prioritized to avoid over-adjustment.

Data synthesis

Study results were combined using a standard inverse-variance random effects model [23]. Separate forest plots summarized data from individual-based and area-based SES studies. Results in each forest plot were stratified by type of SES measure. A pre-planned stratified analysis of follow-up period split studies into those reporting short-term mortality (follow-up ≤ 30-day post fracture) and those reporting longer-term mortality (follow-up = 1 year). Heterogeneity across studies was assessed using the Q test and the inconsistency (I^2) index [24]: I^2 represents the percentage of total variation across studies attributable to heterogeneity rather than (statistical) chance. Publication bias was explored via funnel plots. In cases where inconsistency across studies appeared to be a potential caveat ($I^2 > 50\%$), the robustness of results from the "random effects" model was checked against a "fixed effects" model; for example, the 95% confidence interval (CI) from the random effects model was considered robust if the point estimate for "fixed effects" was within the confidence interval of "random effects". The risk of "small study" bias was considered likely if the fixed effects point estimate was outside the random effects 95%CI, with the level of evidence rated down for inconsistency as a consequence. Meta-analyses were performed using Review Manager developed and provided by the Cochrane Collaboration.

Risk of bias and quality of the evidence

Risk of bias was assessed by two reviewers (GV and SP) using the Quality in Prognosis Studies (QUIPS) tool, which rates studies within six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) confounding measurement and (6) statistical analysis and reporting [25]. The overall risk of bias for each of the studies was judged as the following: (1) low—low risk of bias in all key domains, (2) unclear—unclear risk of bias for one or more key domains and (3) high—high risk of bias for one or more key domains. Disagreement between the two assessors was resolved by consensus. The quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for prognostic factor research [26] which evaluates the certainty of evidence according to six potentially negative factors (phase of investigation, study limitations, inconsistency, indirectness, impression and publication bias) and two potentially positive factors (moderate [clearly RR > 2] or large [clearly RR > 5] effect size or exposure gradient [i.e. consistent dose-response relationship]) [26].

For prognostic factor research evidence, the phase of investigation determines the starting point for the quality of evidence: high-quality evidence is derived from phase 3 and phase 2 studies which are cohort studies seeking to generate understanding of the underlying processes for the prognosis or confirm independent associations between the prognostic factor and the outcome. Phase 1 studies, which are predictive modelling or explanatory studies, generate a hypothesis and provide moderate-quality evidence [26].

Results

Literature search

As illustrated in Fig. 1, the database searches yielded 7086 potential references. Seven additional references were identified through other sources. After removing duplicates, 5235 references remained. These references were screened for eligibility and 5160 records were excluded, the most frequent reason being studies not addressing SES. The remaining 75 studies were read in full text; of these, 46 were excluded because they did not fulfil the inclusion criteria or because of cohort overlap. In addition, five studies were excluded because they did not report outcome within 1 year of fracture. A full list of excluded studies and exclusion criteria is available (see supplementary file S2).

Despite the aim of this review was to include all types of fragility fractures, all of the eligible studies—except one—were restricted to patients with hip fractures. Of the 24 eligible papers included in the quantitative synthesis, 20 reported post-hip fracture mortality as an outcome and four reported post-hip fracture HRQoL. In addition, one of the HRQoL studies reported outcome on individuals with other fractures than hip (e.g. wrist, vertebral, humerus and ankle) [6]. The included studies were published between 1994 and 2018, with most (≈ 80%) being published since 2010. More than one million fracture patients were included in the analysis. Fifteen different countries were represented, the vast majority of which were high-income countries (22/24 [92%]). None of the studies were from low-income countries. The mean overall 1-year mortality was 20%, with reports ranging from 7 to 35%. Table 1 provides details of the included studies.

Risk of bias

The risk of bias within studies was assessed using QUIPS (see supplementary figure S1). Seven studies (29%) were judged "low risk", 12 (50%) were judged "unclear risk" and five

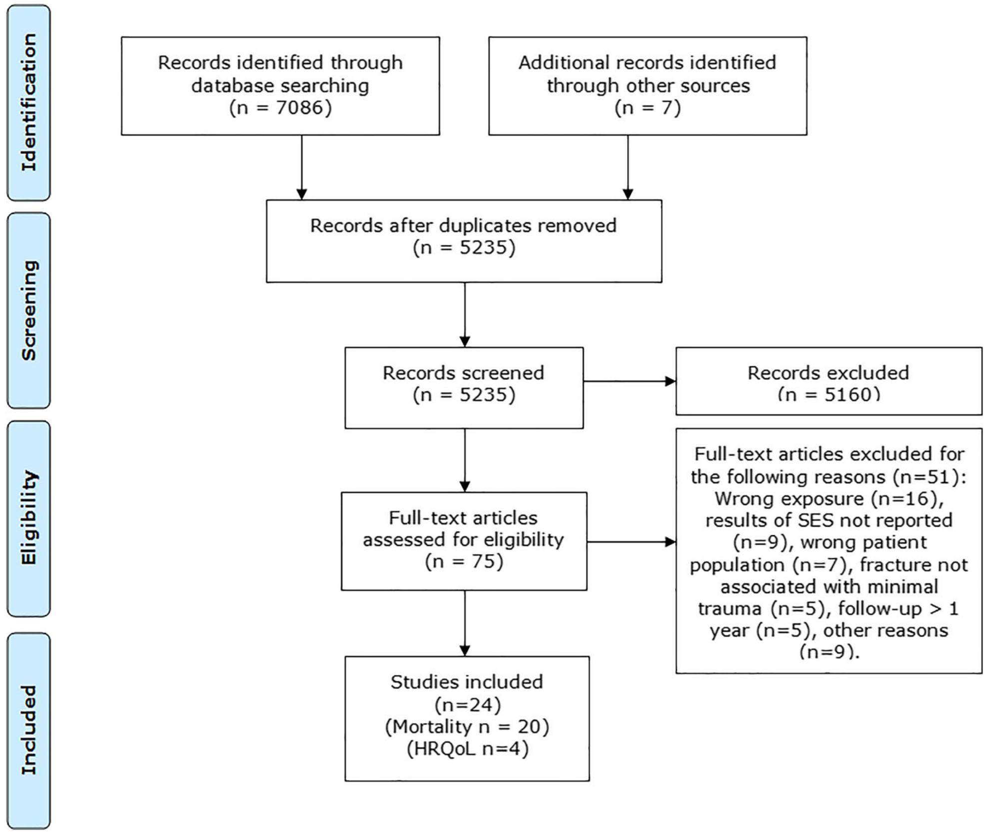


Fig. 1 Flow diagram for study selection and exclusion

(21%) were considered to have a "high risk" of bias. The domains "study confounding" and "statistical analysis and reporting" carried the highest risk of bias with six (25%) of the studies having high risk of bias in both of these domains. This high risk of bias was attributed primarily to lack of information on variables included in the multivariable analysis and the high risk of selective reporting of results.

Socio-economic status and post-hip fracture mortality

The overall results for the association between SES and post-hip fracture mortality are presented in Fig. 2. Figure 2(a) illustrates the pooled risk estimates stratified by individual-based measures of SES. Nine studies assessing education were combined, generating a risk ratio of 1.21 (95% CI 1.15 to 1.26) in individuals with the lowest SES versus the highest SES. The meta-analysis combining the two eligible studies of income generated a risk ratio of 1.26 (95% CI 1.19 to 1.33). For the SES measures of employment, one study was eligible; it had a risk ratio of 1.39 (95% CI 1.19 to 1.62).

Combining two studies of cohabiting status yielded a risk ratio of 2.13 (95% CI 1.13 to 4.01). Combining effect estimates from studies of education, income, employment and cohabiting status produced a risk ratio of 1.24 (95% CI 1.19 to 1.29). Results remained unchanged when analyses were restricted to prognostic level 2 and 3 studies (high-level studies) and to studies with low risk of bias.

Results concerning area-based SES measures are presented in Fig. 2(b). Combining results from five studies reporting on Index of Multiple Deprivation (IMD) generated a risk ratio of 1.11 (95% CI 1.09 to 1.12) for death in individuals living in areas with high levels of deprivation compared with those living in areas with low deprivation. Two studies reported on family area income, giving a combined risk ratio of 1.19 (95% CI 1.13 to 1.26). Combining the risk ratios from IMD and Family Area Income returned a risk ratio of 1.14 (95% CI 1.09 to 1.19). Risk estimates were altered neither by sensitivity analysis restricted to prognostic level 2 or 3 studies nor by analysis restricted to low risk of bias studies.

A stratified analysis exploring socio-economic differences in post-hip fracture mortality depending on follow-up period (≤ 30 days vs. 12 months) found no evidence of differences in associations for short-term vs. longer-term mortality for individual-based SES measures (≤30 days RR 1.30 (95% CI 0.95 to 1.77) vs. 12 months RR 1.24 (95% CI 1.18 to 1.30)) or for area-based measures (≤ 30 days RR 1.16 (95% CI 1.13 to 1.20) vs. 1-year RR 1.14 (1.09 to 1.20)). For further details, see supplementary figure S2A and S2B.

Socio-economic status and post-fracture health-related quality of life

A total of four studies reported post-fracture HRQoL. Three of the studies estimated HRQoL using the EuroQoL EQ-5D-3L

Table 1 Study characteristics of included studies

Author (year)	Country of origin	Number of participants at baseline	Women (%)	Mean age in years (SD)	Fracture type	SES indicator (number of levels)	Outcome measure (follow-up in months) Overall mortality	Phase of investigation
Abimanyi-Ochom [6] (2015)	Australia	915	75.7	69.8 (11.5)	All fractures	Education (2*)	HRQoL (12)	1
Alegre-López [27] (2005)	Spain	218	76.1	81.8 (8.8)	Hip	Cohabiting status (2)	Mortality (12) 22.5%	1
Castronuovo [11] (2011)	Italy	6896	78	83 (76–88)*	Hip	Education (2)	Mortality (1) 7%	1
Cenzer [12] (2016)	USA	857	76.0	83.8 (7.7)	Hip	Education (2)	Mortality (12) 27%	1
Clement [28] (2013)	Scotland	162	79	81.8 (range 65–98)	Hip	Index of Multiple Deprivation (5)	Mortality (12) 19%	1
Colais [29] (2012)	Italy	5701[+]	77.7	83.1 (7.1)	Hip	Index of Multiple Deprivation (3)	Mortality (1) 7.7%	3
Cree [30] (2000)	Canada	558	74	81	Hip	Education (2)	Mortality (3) 8%	1
Dy [31] (2016)	USA	197,290	73.2	79.1 (14.5)	Hip	Income^ (2)	Mortality (12) 7.1%[!]	3
Guirant [7] (2018)	Mexico	193	80.3	77.2 (9.9)	Hip	Education (4)	HRQoL (12)	1
Hailer [13] (2016)	Sweden	5928[#]	75	Not reported	Hip	Education (4)	Mortality (3) 3.7%	2
Hsu [32] (2018)	Taiwan	193,158	61.3	Nor reported	Hip	Mean area-family income (3)	Mortality (12) 10.5%	3
Hubble [33] (1995)	England	338	Not reported	Not reported	Hip	Cohabiting status (2)	Mortality (12) 28.5%	1
Kang [34] (2010)	South Korea	9817	70.2	74.92 (9.13)	Hip	Income^ (2)	Mortality (12) 16.6%	1
Kristensen [14] (2017)	Denmark	25,354	71	Not reported	Hip	Education (3)	Mortality (1) 8.9%	3
Leslie [35] (2013)	Canada	10,367[-]	71	Not reported	Hip	Mean area family income (5)	Mortality (12) 17.7%	2
Marotolli [36] (1994)	USA	120	72	Not reported	Hip	Education (2)	Mortality (6) 18%	1
Marques [37] (2015)	Portugal	186	78.5	80.5	Hip	Education (3)	HRQoL (1 and 12)	1
Moerman [38] (2016)	The Netherlands	335	68	79.4 (10.7)	Hip	Cohabiting status (2)	HRQoL (12)	1
Omsland [15] (2015)	Norway	56,269	70.6	Not reported	Hip	Education (3)	Mortality (12) NA	3
Pereira [39] (2010)	Brazil	246	71	80	Hip	Education (3)	Mortality (12) 35%	1
Petrelli [16] (2018)	Italy	21,432	77.7	Not reported	Hip	Education (3)	Mortality (1 and 12) 21.9%	3
Quah [20] (2011)	England	6300	77.7	82.8 (range 65–105)	Hip	Index of Multiple Deprivation (5)	Mortality (1 and 12) 34.7%	2
Roberts [40] (2003)	England	32,590 (NB. Only 1221 analyzed regarding social class)	81.9	81.5 (7.4)	Hip	Employment (3)	Mortality (1 and 12) ≈35%	2
Thorne [19] (A) (2016)	England	455,862	73.8,	80.7 (11.6),	Hip	Index of Multiple Deprivation (5)	Mortality (1 and 12) 29.0%	3
Thorne [19] (B) (2016)	Wales	29,733	74	80.4 (11.1)	Hip	Index of Multiple Deprivation (5)	Mortality (1 and 12) 27.9%	3

[+] Only results from population no. 2 (2009–2010) were eligible for inclusion because pop 1 (2006–2007) was included in the study by Castronuovo et al.

[!] Only in-hospital mortality assessed

[#] Only fracture patients with available American Society of Anesthesiologists Classification (ASA) grade were eligible for inclusion

[-] Only hip fracture cases from population no. 2 were eligible for inclusion

*Primary vs. secondary or post-secondary university vs. secondary

^ Insurance status as proxy for income

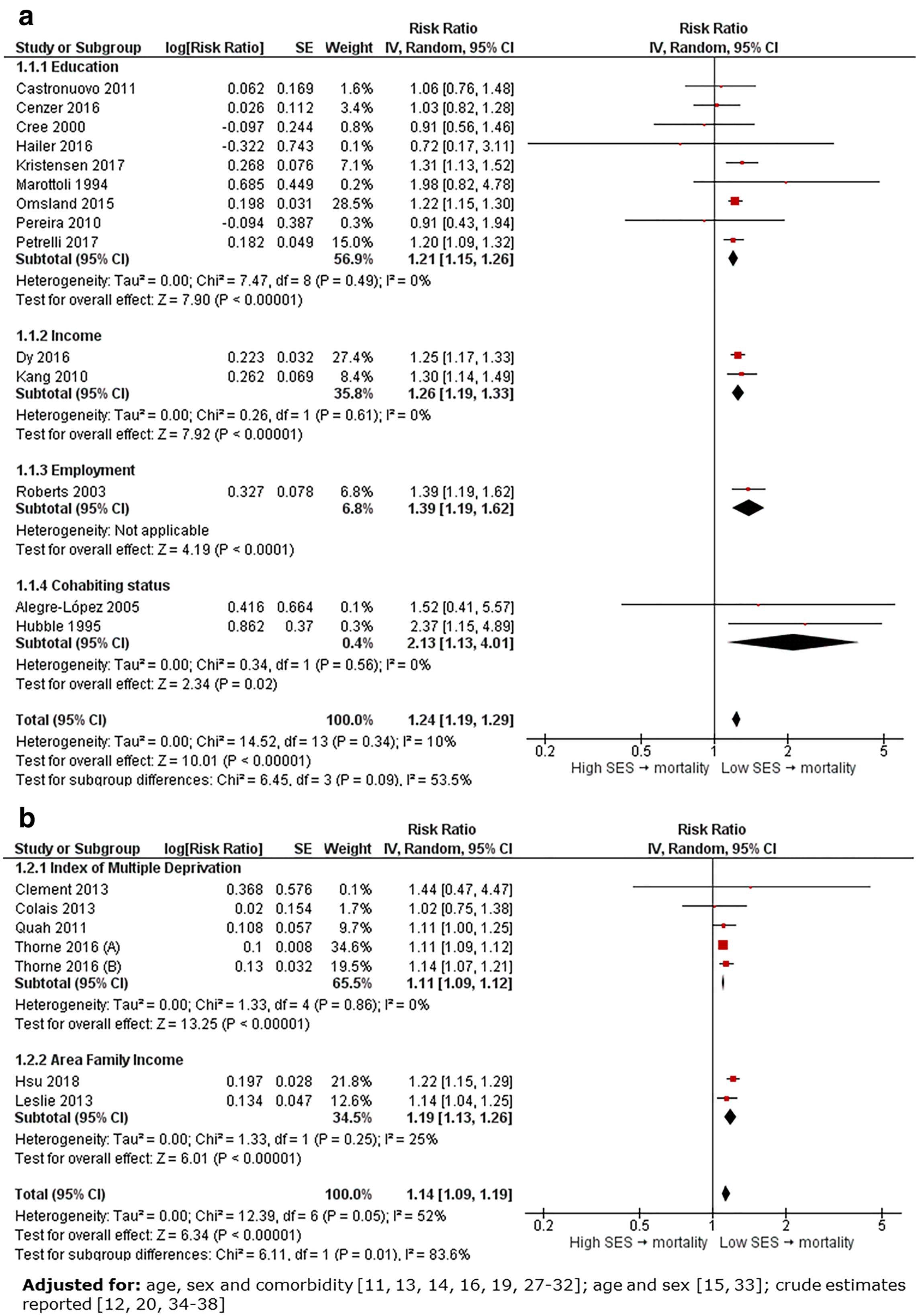
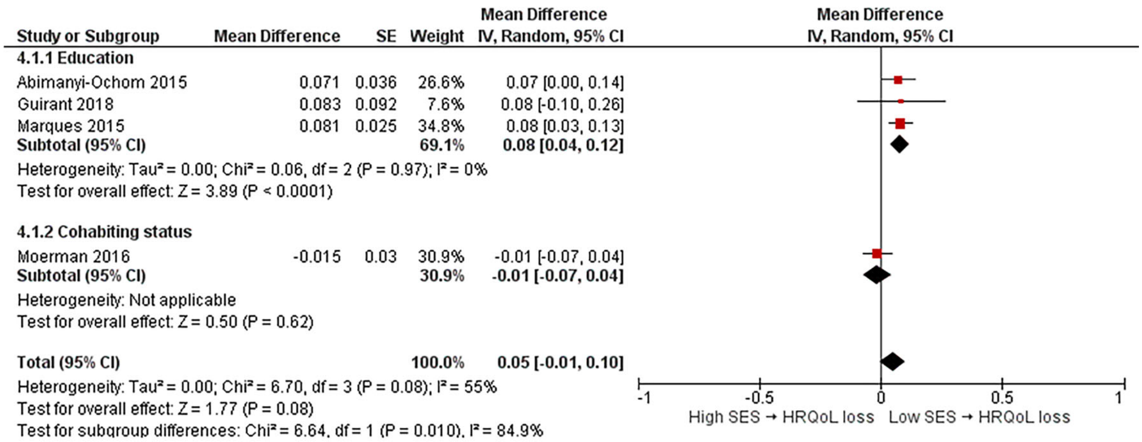


Fig. 2 Forest plot of pooled risk estimates for mortality stratified by measure of SES



Adjusted for: age and gender[6, 7, 39]; crude estimates reported[40].

Fig. 3 Forest plot of pooled risk estimates for changes in HRQoL stratified by individual-based measures of SES

questionnaire [6, 7, 37] and one study used the SF-12 Health Survey [38]. The results of the association between changes in HRQoL post-hip fracture in patients with low compared with patients with high SES are presented in Fig. 3. Based on the three studies reporting the effects of education, the estimated additional loss of HRQoL was 8% (95% CI 4–12%) higher among hip fracture patients with low SES than among patients with high SES. The one study reporting cohabiting status reported a 1% (95% CI − 7 to 4%) lower reduction in HRQoL in patients with low SES compared with patients with high SES. The estimate for the overall additional loss combining results from education and cohabiting status was 5% (95% CI − 1 to 10%). For non-hip fractures, no differences in HRQoL loss were observed when primary education was compared with secondary education [6]. A significant difference in HRQoL loss was reported only in patients with vertebral fractures when post-secondary education was compared with secondary education, implying that more highly educated people with vertebral fractures experienced a lower decline in HRQoL following a vertebral fracture [6] (results not presented).

Quality of the evidence (GRADE)

The quality of the evidence for the association between SES and fragility fracture outcomes was assessed using the GRADE approach [26]. The findings are summarized in Table 2. For mortality, the quality was initially high because a substantial amount of evidence (6/14 [43%]) came from phase 2 or 3 (high level) prognostic studies. This quality was down rated due to serious risk of bias as five of thirteen studies were judged to have unclear risk of bias, and three studies were judged to have high risk of bias. Heterogeneity was very low (I^2 = 10%), implying that between-study inconsistency was not an issue. Publication bias was explored using funnel plots, and no obvious asymmetry was found. The quality of

Table 2 Summary of findings for the association between SES and post-fracture mortality and loss of health-related quality of life

Outcome: mortality				
Prognostic factor	No of participants (cohorts)	Estimated risk ratio (95% confidence interval)	Certainty of the evidence (GRADE)	Comments
Individual-based SES	345,315 (14)	1.24 (1.19 to 1.28)	Moderate (+++)	Downgraded due to serious risk of bias.
Area-based SES	701,283 (7)	1.14 (1.09 to 1.19)	Moderate (+++)	Downgraded due to serious risk of bias.
Outcome: health-related quality of life				
Prognostic factor	No of participants (cohorts)	Estimated relative mean difference (95% confidence interval)	Certainty of the evidence (GRADE)	Comments
Individual-based SES	1629 (4)	0.05 (−0.01 to 0.10)	Very low (+)	Downgraded due to studies coming from low-level prognostic studies, serious risk of bias and high risk of publication bias.

evidence for the individual SES measures was moderate, implying that we are moderately confident in the effect estimate.

For the area-based risk estimates, the quality of evidence was initially high as the majority (6/7 [86%]) came from high-level prognostic studies. The quality of evidence was rated down due to serious risk of bias, as 4/7 (57%) of studies were "unclear risk" studies. Heterogeneity corresponded to an I^2 of 52%; however, the point estimate for "fixed effects" (1.12) was within the confidence interval of "random effects" (95% CI 1.09–1.19); thus, we did not rate down for inconsistency. Publication bias was not detected by funnel plot. Consequently, the quality of the evidence for the area-based risk estimates was moderate.

The quality of the evidence for the association between SES and post-fracture HRQoL was initially moderate as all the evidence came from phase 1 prognostic level studies (low level). These four studies had high or unclear risk of bias, leading to downgrading due to serious risk of bias. The quality level was further rated down due to high risk of publication bias. Consequently, the certainty of the estimates for the association between SES and HRQoL following a fragility fracture was very low.

Discussion

Main findings

This review aimed to explore the effects of socio-economic inequalities on mortality and loss of HRQoL following fragility fractures. All data from the included studies on mortality outcomes concerned patients with hip fractures, so results are generalizable only to this context. Pooling results from SES measured by education, income, occupation and cohabiting status showed that post-hip fracture mortality risk was 24% higher among people with low SES than among those with high SES. Results from the meta-analysis stratified by types of SES measure were consistent across all individual-based SES measures. Pooling results from studies using area-based SES measures, we found that living in the most deprived areas was associated with a 14% higher risk of post-hip fracture mortality than living in the least deprived areas. Overall, the quality of evidence for the mortality outcome was judged to be moderate. Thus, we conclude that post-hip fracture mortality is higher among individuals with low SES than among individuals with high SES. By contrast, given the limited and low-quality evidence base, conclusions regarding post-fracture changes in HRQoL are less certain. However, the few studies reporting education as a risk factor for loss of HRQoL post-fracture do suggest a negative impact of SES on HRQoL, which requires further investigation.

Methodological strengths and limitations

To our knowledge, this study is the first to synthesize and quantitatively present data on social inequalities in association with fragility fracture outcomes across multiple countries and types of SES measure. This review followed a rigorous protocol (registered in PROSPERO) that prespecified outcomes of interest and analyses. Protocol adherence strengthens the credibility of this synthesis. Our findings are reported in accordance with the PRISMA statement [17]; evidence quality was thoroughly assessed using the adapted GRADE approach for prognostic factor research which ensures transparency in reporting [26]. This review synthesized both individual-based and area-based SES measures, which each have strengths and limitations [41]. The former measures assume homogeneity between individuals in a given region and minimize distinctions between households or individuals within the household [41]. On the other hand, individual-based measures provide SES information at an individual level and are considered to carry a lower risk of misclassification bias than area-based measures [14]. However, in most countries, national individual-level data are not available or are incomplete, leaving area-based measures as the only option for providing evidence of the impact of socio-economic inequality.

Some limitations should be mentioned. First, the initial literature search was restricted to studies published in English or Scandinavian languages, which carries a risk that relevant evidence could be missed. We therefore repeated the search without language restrictions to make sure that no studies had been excluded due to language issues. Second, all studies except one is related to hip fractures, so results are generalizable only to this context.

Interpretation of results

This review demonstrates a consistent increase in post-hip fracture mortality with low SES across different measures of SES and across a range of studies from high-income and middle-income countries with different political structures and different health and social care resource infrastructures. Importantly, the pooled results were robust across all measures of SES. However, the association between SES and post-hip fracture mortality was stronger for the individual-based measures (RR 1.24) than for the area-based measures (RR 1.14). Given that area-based SES measures are considered to carry a higher risk of misclassification bias than individual-based measures, this difference in the strength of associations is most likely explained by non-differential misclassification associated with the use of census data, resulting in bias toward the null. This implies that use of census data in general may underestimate the socio-economic gradient in mortality.

Combining data that originate from different countries enables comparison of socio-economic disparities in post-hip fracture mortality across countries. We were not surprised to find that Nordic countries, namely Denmark and Norway, which are well known for their egalitarian policies and generous welfare arrangements, were represented among the studies with substantial inequality. Indeed, in these countries, inequalities are well established which in the inequality research literature is referred to as the Nordic Paradox [9]. According to Mackenbach et al., this paradox may be explained by trends in social stratification and social mobility due to early modernisation in the Nordic countries [9]. Due to the rise in the service economy and the expansion of higher education, the proportion of individuals in routine or manual occupations or with limited education has decreased considerably. Mackenbach argues that compared with previous generations, this smaller group is likely to be more disadvantaged socially and have more unfavourable individual characteristics [9]. Furthermore, in recent generations, individuals with higher education are more advantaged than those in previous generations; they increasingly tend to cohabit with each other and so accumulate advantage within couples and families [9]. It is further thought that prevention and treatment interventions generally have better reach and greater effectiveness among more highly educated individuals, who find it easier to access and utilize care and have better adherence to treatment despite a lower prevalence of comorbidity. In many areas, health improvements in the Nordic countries have been greater than those of other European countries because of their better resourced health care or public healthcare systems or because of autonomous behavioural trends. This not only means faster improvements but also more scope for inequalities in health improvement [9].

In the larger studies included in this review with > 1000 hip fracture cases, only studies from Sweden and from Italy were unable to demonstrate an association between SES and adverse patient outcome. This concurs with Mackenbach et al.'s argument that the Nordic Paradox does not apply in Sweden. The low inequality in mortality in Sweden may be explained by the fact that Sweden has the lowest prevalence of poverty (and smoking) among the Nordic countries. Especially the low prevalence of smoking among men with little or no education may partly explain the smaller inequalities in mortalities in Sweden [9]. Southern European countries are known to have low levels of health inequality in mortality as well [9]. The Italian studies by Petrelli et al., Colais et al. and Catronuevo et al. all found no evidence of association between SES and mortality at 30 days; however, after extending follow-up to 1 year, Petrelli et al. were able to demonstrate inequalities in mortality. The low inequality in Southern Europe is consistent with the Nordic paradox [9] because later modernisation in southern European countries resulted in a birth cohort still represented in current older generations who have relatively limited educational attainment, but are sufficiently numerous to avoid social marginalization. Furthermore, variation in smoking habits and diet is small in these countries, which limits inequalities in associated all-cause mortality [9, 42]. These factors combined with relatively good access to health care for patients with low socio-economic status may explain the limited inequalities in early post-hip fracture mortality in Italian studies.

Implication for policy and practice

Overall, in high-income populations, health inequalities are substantial. These inequalities are usually reflected in a between 4.5 and 10 years average life expectancy difference and a between 10- and 20-year disability-free life expectancy difference between those who are least and those who are most deprived [9, 43]. Thus, we were not surprised to find higher mortality among hip fracture patients with low SES than among patients with high SES. However, the excess post-hip fracture mortality of 24% among patients with low SES was remarkably high. Authors of a large nationwide register study included in the meta-analysis reported 30–50 excess deaths per 10,000 person-years among low compared with high SES hip fracture patients, contrasting with a general population rate of 8 to 12 deaths per 10,000 person-years [15]. This discrepancy highlights the socio-economic gradient in post-fracture mortality.

Preventive strategies aiming to reduce socio-economic inequalities have the potential of impacting overall post-hip fracture mortality. Socio-economic inequalities in post-hip fracture mortality may be explained partly by a healthier pre-fracture lifestyle in those with higher SES (better diet, more exercise and lower tobacco and alcohol consumption), reducing risk of comorbidities [44]. Greater comorbidity leads to vulnerability following a hip fracture. Several of the large registry-based studies included in our analysis adjusted for comorbidity differences between SES groups. One could therefore argue that comorbidity is not likely to explain the differences we identified in mortality. However, since registers very seldom capture all data (e.g. smoking and alcohol intake), residual confounding is likely. A second factor that may explain inequalities in post-hip fracture mortality is SES-driven differences in access to and quality of post-fracture care. Only a few studies have addressed this; in Italy, Petrelli et al. reported that lower SES was associated with higher risk of delayed surgery [16]. Similarly, in the USA, patients on Medicaid have been reported to be at increased risk of delayed hip fracture surgery compared with Medicare-insured patients [31]. By contrast, in Denmark, Kristensen et al. specifically excluded differences in quality of in-hospital care, time to surgery and length of hospital stay as explanations for the socio-economic gradient in mortality [14]. Vestergaard et al. demonstrated that the post-fracture conditions related to the trauma rather than the pre-fracture comorbidity status predict mortality post fracture. Their registry study identified infection and deterioration in chronic lung diseases as the most common causes of death [45]. Bearing in mind that prevention and treatment interventions are generally more effective among individuals with higher SES, these findings may suggest that care differentiated to meet individual need can provide a basis for policy and practice that reduces social inequalities in post-fracture outcomes.

Future research

We found evidence of substantial socio-economic inequalities in post-hip fracture mortality risk. In order to develop and implement preventive strategies aimed at reducing these socio-economic inequalities, an understanding of the underlying determinants of social inequalities is needed. The potential for post-fracture care differentiated to meet individual needs should be carefully explored. This review has highlighted a gap in the literature regarding the impact of social inequality on change in HRQoL following fragility fracture that requires further investigation. Future HRQoL studies should include measures of SES in order to determine the impact of SES on HRQoL. Our review also highlighted an almost complete lack of data on fracture types other than the hip. It is especially striking that only one of the included studies included patients with vertebral fractures, despite this being one of the most common and deleterious osteoporotic fracture types. Furthermore, given that the proportion of the world's population living with fracture burdens in low-income countries is increasing, the complete absence of data from low-income countries should be addressed in the future.

Details of contributors All of the authors were responsible for the design and the search strategy. The literature search was conducted by GV with input from a research librarian with expertise in systematic searches. Selection, risk of bias assessment and data extraction were conducted independently by GV and SP. GV and SP led the meta-analysis with supervision from RC. All authors were involved in grading the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The initial draft of the manuscript was prepared by GV, and then circulated among all authors for critical revision. BL was the guarantor for the scientific integrity of the work. All authors have provided final approval of the version to be published. GV confirms that the material has not been published previously.

Funding The work was supported by the Danish Osteoporosis Society, the Department of Clinical Medicine, Aarhus University, and by DEFACTUM, Central Denmark Region. The Parker Institute, Bispebjerg and Frederiksberg Hospital (Professor Christensen), was supported by a core grant from the Oak Foundation (OCAY-13-309). AB was funded by the UK Royal Osteoporosis Society. CLG was funded by Versus Arthritis (ref 20000). The funding parties had no influence on the design of the review or the interpretation of the results.

Compliance with ethical standards

Conflict of interest None.

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Appendix 2B Study II – Supplementary material

Supplementary Figure S1: risk of bias figure

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk of bias
Abimanyi-Ochom 2015	?	−	?	+	?	?	?
Alegre-López 2005	?	?	?	+	?	?	?
Castronuovo 2011	+	+	+	+	+	+	+
Cenzer 2016	?	+	−	+	−	−	−
Clement 2013	+	+	?	+	−	−	?
Colais 2013	+	+	?	+	+	+	+
Cree 2000	+	?	−	?	?	?	?
Dy 2016	?	+	?	−	?	?	?
Guirant 2018	?	−	?	+	?	?	?
Hailer 2016	+	?	?	+	+	?	?
Hsu 2018	+	+	?	?	+	?	?
Hubble 1995	−	+	−	−	−	−	−
Kang 2010	+	+	?	+	+	?	+
Kristensen 2017	+	+	+	+	+	+	+
Leslie 2013	?	+	?	+	?	?	?
Marottoli 1994	?	−	?	?	−	−	−
Marques 2015	?	+	−	−	−	?	−
Moerman 2016	+	?	+	?	−	−	?
Omsland 2015	+	+	+	+	+	?	+
Pereira 2010	?	+	?	?	−	−	−
Petrelli 2017	+	?	+	+	+	+	+
Quah 2011	?	+	+	?	?	?	?
Roberts 2003	?	+	−	+	?	?	?
Thorne 2016	+	+	?	+	+	+	+

Supplementary material S2A and S2B: Sub-group analysis

Figure S2A: Forest plot of pooled risk estimates for mortality stratified by length of follow-up for the individual-based SES measures.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Follow-up ≤ 30-days				
Castronuovo 2011	0.062	0.169	22.2%	1.06 [0.76, 1.48]
Kristensen 2017	0.268	0.076	27.8%	1.31 [1.13, 1.52]
Petrelli 2017	-0.049	0.115	25.7%	0.95 [0.76, 1.19]
Roberts 2003	0.754	0.138	24.3%	2.13 [1.62, 2.79]
Subtotal (95% CI)			**100.0%**	**1.30 [0.95, 1.77]**
Heterogeneity: Tau² = 0.08; Chi² = 21.39, df = 3 (P < 0.0001); I² = 86%				
Test for overall effect: Z = 1.63 (P = 0.10)				
2.1.2 Follow-up 12 months				
Alegre-López 2005	0.416	0.664	0.1%	1.52 [0.41, 5.57]
Cenzer 2016	0.026	0.112	4.2%	1.03 [0.82, 1.28]
Dy 2016	0.223	0.032	29.3%	1.25 [1.17, 1.33]
Hubble 1995	0.862	0.37	0.4%	2.37 [1.15, 4.89]
Kang 2010	0.262	0.069	10.0%	1.30 [1.14, 1.49]
Omsland 2015	0.198	0.031	30.2%	1.22 [1.15, 1.30]
Pereira 2010	-0.094	0.387	0.4%	0.91 [0.43, 1.94]
Petrelli 2017	0.182	0.049	17.2%	1.20 [1.09, 1.32]
Roberts 2003	0.327	0.078	8.1%	1.39 [1.19, 1.62]
Subtotal (95% CI)			**100.0%**	**1.24 [1.18, 1.30]**
Heterogeneity: Tau² = 0.00; Chi² = 9.96, df = 8 (P = 0.27); I² = 20%				
Test for overall effect: Z = 8.96 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%				

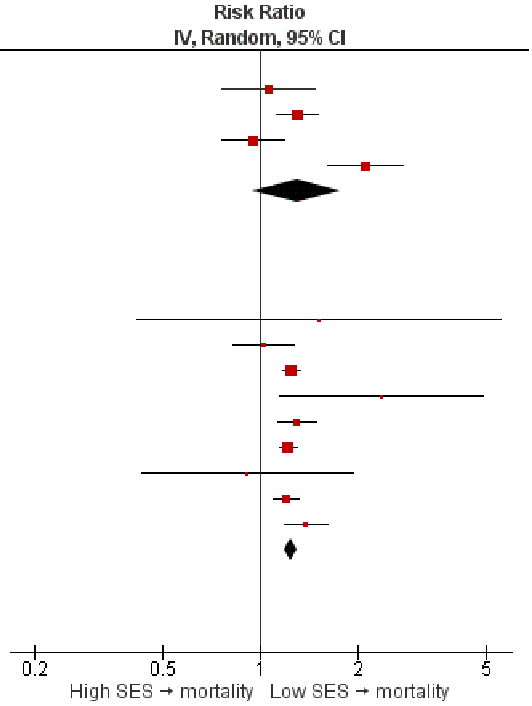
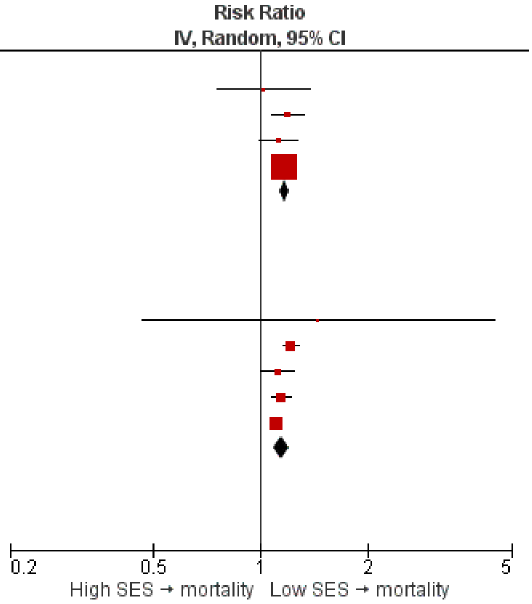


Figure S2B: Forest plot of pooled risk estimates for mortality stratified by length of follow-up for the area-based SES measures.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 Follow-up ≤ 30-days				
Colais 2013	0.02	0.154	0.9%	1.02 [0.75, 1.38]
Quah 2011	0.174	0.051	8.4%	1.19 [1.08, 1.32]
Thorne 2016 (A)	0.116	0.063	5.5%	1.12 [0.99, 1.27]
Thorne 2016 (B)	0.154	0.016	85.2%	1.17 [1.13, 1.20]
Subtotal (95% CI)			**100.0%**	**1.16 [1.13, 1.20]**
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 3 (P = 0.74); I² = 0%				
Test for overall effect: Z = 10.32 (P < 0.00001)				
2.2.2 Follow-up 12 months				
Clement 2013	0.368	0.576	0.2%	1.44 [0.47, 4.47]
Hsu 2018	0.197	0.028	26.1%	1.22 [1.15, 1.29]
Quah 2011	0.108	0.057	13.1%	1.11 [1.00, 1.25]
Thorne 2016 (A)	0.13	0.032	23.8%	1.14 [1.07, 1.21]
Thorne 2016 (B)	0.1	0.008	36.9%	1.11 [1.09, 1.12]
Subtotal (95% CI)			**100.0%**	**1.14 [1.09, 1.20]**
Heterogeneity: Tau² = 0.00; Chi² = 11.77, df = 4 (P = 0.02); I² = 66%				
Test for overall effect: Z = 5.28 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%				



Supplementary material S1: Literature search (Pubmed)

Literature search

(PUBMED July 3 2018)

((((("Fractures, Bone"[Mesh] OR "Minimal trauma fracture"[tiab]) OR "Minimal trauma fractures"[tiab]) OR "Osteoporotic fracture"[tiab]) OR "Osteoporotic fractures"[tiab]) OR "fragility fractures"[tiab]) OR "fragility fracture"[tiab]) AND (((((((((("Socioeconomic Factors"[Mesh] OR "Socioeconomic Factors"[tiab]) OR "Socio economic Factors"[tiab]) OR "Socioeconomic status"[tiab]) OR "Socio economic status"[tiab]) OR "social class"[tiab]) OR ("socioeconomic factors"[MeSH Terms] OR ("socioeconomic"[tiab] AND "factors"[tiab]) OR "socioeconomic factors"[tiab] OR "inequality"[tiab])) OR ("education"[Subheading] OR "education"[tiab] OR "educational status"[MeSH Terms] OR ("educational"[tiab] AND "status"[tiab]) OR "educational status"[tiab] OR "education"[tiab] OR "education"[MeSH Terms])) OR ("income"[MeSH Terms] OR "income"[tiab])) OR ("marital status"[MeSH Terms] OR ("marital"[tiab] AND "status"[tiab]) OR "marital status"[tiab])) OR residence[tiab]) OR ("occupations"[MeSH Terms] OR "occupations"[tiab] OR "occupation"[tiab])) AND ((Danish[lang] OR English[lang] OR Norwegian[lang] OR Swedish[lang]))

Supplementary material S2: list of excluded studies and the reason for exclusion

Table S2: List of excluded studies and the reason for exclusion

Author, year	Title	Reason for exclusion
Androulaki-Charalambaki, 2005	*Prognostic factors for patients operated on hip fractures*	(6)
Ariza-Vega et al., 2015	*Predictors of long-term mortality in older people with hip fracture*	(1)
Baczyk et al., 2013	*Effect of selected socio-demographic, clinical and biochemical factors on self-reported quality of life among post-menopausal women with osteoporosis*	(3)
Barone et al., 2009	*Effects of socioeconomic position on 30-day mortality and wait for surgery after hip fracture*	(9)
Bentler et al., 2009	*The aftermath of hip fracture: discharge placement, functional status change, and mortality*	(5)
Beringer et al., 2006	*Outcome following proximal femoral fracture in Northern Ireland*	(2)
Bhandari et al., 2004	*Health-related quality of life following operative treatment of unstable ankle fractures: a prospective observational study*	(3), OBS: er det ikke (4)? Ikke fragility fractures men ankel frakturer blandt 18+ årige.
Campos et al., 2015	*Time to death in a prospective cohort of 252 patients treated for fracture of the proximal femur in a major hospital in Portugal*	(2)
Clement et al., 2014	*Elderly pelvic fractures: the incidence is increasing and patient demographics can be used to predict the outcome*	(2)
Clement et al., 2017	*Does socioeconomic status influence the epidemiology and outcome of distal radial fractures in adults?*	(7)
Clement et al., 2014	*Social deprivation influences the epidemiology and outcome of proximal humeral fractures in adults for a defined urban population of Scotland*	(7)
Cree, 1998	*Outcome following hip fracture*	(6)
Cutillas-Ybarra et al., 2015	*Prognostic factors of health-related quality of life in patients after tibial plafond fracture. A pilot study*	(4), Tibial plafond fractures, 43 patients, mean age 45.6 years.

De Oliveira Ferreira et al., 2012	*Prevalence of vertebral fractures and quality of life in a sample of postmenopausal Brazilian women with osteoporosis*	(3)
De Oliveira et al., 2011	*Relationship between quality of life and vertebral fractur in older women living in Southern Brazil*	(8)
Elsoe et al., 2018	*Complex tibial fractures are associated with lower social classes and predict early exit from employment and worse patient-reported QOL: a prospective observational study of 46 complex tibial fractures treated with a ring fixator*	(4), patients with a complex tibial fracture treated with a ring external fixator. Mean age: 54.6 years.
Espinosa et al., 2018	*Pre-operative factors associated with increased mortality in elderly patients with a hip fracture: A cohort study in a developing country*	(1)
Evans et al., 1979	*A prospective study of fractured proximal femur: factors predisposing to survival*	(1)
Fitzpatrick et al., 2001	*Predictors of first hip fracture and mortality post fracture in older women*	(3)
González et al., 2014	*Health-related quality of life and functionality in elderly men and women before and after a fall-related wrist fracture*	(1)
Holt et al., 2008	*Gender differences in epidemiology and outcome after hip fracture: evidence from the Scottish Hip Fracture Audit*	(1)
Jiang et al., 2005	*Development and initial validation of a risk score for predicting in-hospital and 1-year mortality in patients with hip fractures*	(1)
Johansen et al., 2010	*Outcome following hip fracture: post-discharge residence and long-term mortality*	(1)
Kessenich, 1996	*Quality of life of elderly women with spinal fractures secondary to osteoporosis*	(6)
Kirke et al., 2002	*Outcome of hip fracture in older Irish women: a 2-year follow-up of subjects in a case-control study*	(1)
Klop et al., 2017	*The epidemiology of mortality after fracture in England: variation by age, sex, time, geographic location, and ethnicity*	(1)
Lin et al., 2011	*Risk factors for hip fracture sites and mortality in older adults*	(2)
Magaziner et al., 1997	*Excess mortality attributable to hip fracture in white women aged 70 years and older*	(1)
Marcinkowska et al., 2013	*Prognostic factors in patients surgically treated after hip fracture*	(2)
Mariconda et al., 2015	*The determinants of mortality and morbidity during the year following fracture of the hip: a prospective study*	(2)
Morris, 1997	*Patterns of recovery during the first three months after a distal radius fracture*	(6)
Morris, 2000	*Distal radius fracture in adults: self-reported physical functioning, role functioning, and meaning of injury*	(4), Distal radius fracture. 48 % of studypopulation are 18-44 år.
Nather et al., 1995	*Morbidity and mortality for elderly patients with fractured neck of femur treated by hemiarthroplasty*	(1)
Paksima et al., 2008	*Predictors of mortality after hip fracture: a 10-year prospective study*	(2)
Pande et al., 2006	*Quality of life, morbidity, and mortality after low trauma hip fracture in men*	(5)
Papaioannou et al., 2006	*Determinants of health-related quality of life in women with vertebral fractures*	(5)
Rohde et al., 2009	*No long-term impact of low-energy distal radius fracture on health-related quality of life and global quality of life: a case-control study*	(3)
Rostom et al., 2012	*The prevalence of vertebral fractures and health-related quality of life in postmenopausal women*	(3)
Ruths et al., 2017	*Municipal resources and patient outcomes through the first year after a hip fracture*	(1)
Rutledge et al., 2003	*Social networks and marital status predict mortality in older women: prospective evidence from the Study of Osteoporotic Fractures (SOF)*	(3)
Salaffi et al., 2007	*The burden of prevalent fractures on health-related quality of life in postmenopausal women with osteoporosis: the IMOF study*	(1)

Sanfélix-Genovés et al., 2011	*Impact of osteoporosis and vertebral fractures on quality-of-life. a population-based study in Valencia, Spain (The FRAVO Study)*	(1)
Sanz-Reig et al., 2017	*Risk factors for in-hospital mortality following hip fracture*	(1)
Schouten et al., 2014	*Health-related quality-of-life outcomes after thoracic (T1-T10) fractures*	(4)
Schurch et al., 1996	*A prospective study on socioeconomic aspects of fracture of the proximal femur*	(2)
Shin et al., 2016	*Relationship between socioeconomic status and mortality after femur fracture in a Korean population aged 65 years and older: Nationwide retrospective cohort study*	(5)
Sugeno et al., 2008	*Quality of life in postoperative Japanese hip fracture patients: A hospital-based prospective study*	(1)
Suriyawongpaisal et al., 2003	*Quality of life and functional status of patients with hip fractures in Thailand*	(5)
Williams et al., 2004	*Factors affecting outcome in tibial plafond fractures*	(4)
Wilson et al, 2014	*Risk factors and predictors of mortality for proximal humeral fractures.*	(2)
Wu et al, 2010	*Admission rates and in-hospital mortality for hip fractures in England 1998 to 2009: time trends study*	(9)

51 studies excluded

(1): Wrong exposure (e.g. urban/rural, ethnicity, geographical comparison, type of residence) *(16 studies)*
(2): Results of SES not reported *(9 studies)*
(3): Wrong patient population *(7 studies)**
(4): Fracture not associated with low BMD, age≥50, or minimal trauma *(5 studies)*
(5): Outcome is not measured within 1 year/follow-up time is more than 1 year *(5 studies)*
(6): Not a scientific paper (e.g. dissertation, conference abstract etc.) *(4 studies)*
(7): Wrong outcomes *(2 studies)*
(8): Published only in Portuguese *(1 study)*
(9): Results from the given cohort are included in another study (*2 studies)*
* Analyses are performed on fracture patients and non-fracture patients together – and not on fracture patients alone.

Appendix 3A Study III – Fragility fractures and health-related quality of life

Osteoporosis International (2021) 32:63–73
https://doi.org/10.1007/s00198-020-05540-8

ORIGINAL ARTICLE

Fragility fractures and health-related quality of life: does socio-economic status widen the gap? A population-based study

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Received: 7 May 2020 / Accepted: 7 July 2020 / Published online: 17 July 2020

Abstract

Summary Studying 12,839 fracture cases and 91,426 controls, we found that fractures of the spine and hip are associated with clinically important HRQoL deficits up to 5 years post-fracture. Fracture cases with a low educational attainment are more likely to report very low HRQoL due to a low pre-fracture HRQoL.

Introduction The aim of this study was to explore the short-term and long-term impact of fractures on health-related quality of life (HRQoL) and to study the effect of educational attainment as a proxy for socio-economic status (SES) on post-fracture HRQoL.

Methods In a population-based survey including 12,839 fracture cases and 91,426 controls, HRQoL was measured using the physical component score (PCS) and the mental component score (MCS) of the 12-Item Short Form Health Survey (SF-12). Information about fractures, age, sex, ethnicity, comorbidity and SES was obtained from national registers. Multiple regression analysis was conducted to measure the mean HRQoL difference, termed deficit, between non-fracture controls and fracture cases (all fractures combined and fractures at six different skeletal sites).

Results PCS and MCS were significantly lower among fracture cases than among controls. Statistically and clinically important PCS deficits (≥ 5 points) were observed among people with fractures of the spine and hip up to 5 years post-fracture and among people with upper arm fractures up to 1 year post-fracture. Greater deficits were observed for MCS but not for PCS in post-fracture HRQoL in the low than in the high SES group.

Conclusion Fractures of the spine and hip are associated with clinically important deficits in physical HRQoL up to 5 years post-fracture. Low educational attainment widened the gap in mental but not in physical post-fracture HRQoL. However, due to low pre-fracture PCS and MCS, people with a low educational attainment and fractures were more likely to report very low HRQoL post-fracture.

Keywords Fractures · Health-related quality of life · Health survey · Inequality · Population-based study · Socio-economic status

Introduction

Fragility fractures constitute a major and growing public health problem due to the increased longevity of the population. In their lifetime, approximately one in three women and one in five men aged over 50 years will suffer a fragility fracture [1]. These fractures carry an increased risk of additional fractures and increased mortality [2]. Survivors of fractures suffer temporary or permanent disabilities such as pain, decreased mobility and increased dependency on others, potentially imposing important limitations on their health-related quality of life (HRQoL) [3, 4]. Several studies, mostly concerning fractures of the hip or spine, have demonstrated that fractures are associated

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-020-05540-8) contains supplementary material, which is available to authorized users.

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with a significantly reduced HRQoL immediately after a fracture [5]. Less is known about the impact of fractures at other skeletal sites and about the long-term impact of fractures on HRQoL.

Theories on socio-economic inequalities in health assume that illness has more severe consequences for individuals with low socio-economic status (SES) than for individuals with high SES due to differences in personal and contextual factors (socially differential effects of illness) [6]. Whether this is true for individuals with fractures has recently been explored in a systematic review and meta-analysis [7]. This review consistently found an increase in post-hip fracture mortality in people with low SES across different SES measures and across countries with different health and social care infrastructures, confirming the hypothesis of socio-economic inequalities in post-fracture mortality. By contrast, no certain conclusions on socio-economic differences in post-fracture HRQoL could be drawn due to very sparse and low-quality evidence [7].

Research on post-fracture HRQoL may improve our knowledge about life after a fracture and our understanding of rehabilitation needs. Thus, HRQoL research may help identify subgroups of individuals with special rehabilitation needs. With this study, we aimed (1) to explore the short-term and long-term impact of fragility fractures at different anatomical sites on HRQoL and (2) to explore the impact of SES on post-fracture HRQoL. We hypothesised that HRQoL would be lower in individuals with fragility fractures than in controls with no history of fragility fractures. We further hypothesised that HRQoL deficits between controls and fracture cases would be greater among those with lower SES. The impact of fragility fractures on HRQoL was explored using HRQoL data from a large national population-based survey combined with individual-level register data.

Methods

Design and study population

This study is a retrospective cohort study. The study population comprised respondents from the Danish National Health Survey "How are you" from 2017. The Danish National Health Survey is a national, representative, cross-sectional survey of the Danish population aged 16 years and older [8]. The survey is conducted every fourth year by the five Danish regions and the National Institute of Public Health at the University of Southern Denmark. The aim of the survey is to monitor the health and well-being of the Danish adult population. Using the Danish Civil Registration System, the study sample for the survey was drawn randomly with a minimum of 2000 individuals in each of the 98 Danish municipalities. Although some participants may have participated in this survey more than once, only data from the 2017 survey was included in this study. HRQoL data from the survey was linked to Danish national health and social registers using the personal identification number assigned to all Danish residents. This procedure allowed comparison of HRQoL among individuals with a history of fracture (cases) and individuals with no history of fracture (controls). In order to minimise inclusion of non-osteoporosis-related fractures, respondents who were below the age of 50 years at the time of survey data collection were excluded from the analyses. A total of 104,854 individuals above the age of 50 years completed the survey (68% of those invited). To minimise the risk of misclassification bias, 395 respondents were excluded because they had sustained a fracture within the survey distribution period (1 Feb–31 May 2017). Furthermore, 194 fracture cases were excluded because they had sustained multiple fractures at the same date. A total of 91,426 controls and 12,839 fracture cases were included in the analysis.

Exposure

The key exposures of interest were *fracture* and *time since fracture*. Information on all fractures having occurred after the age of 50 years was obtained from the Danish National Patient Register (DNPR). The DNPR has recorded information on all patients discharged from Danish somatic hospitals since 1977 and on all outpatient and emergency visits since 1995. For each patient contact, one primary and, optionally, any secondary diagnoses are recorded according to the International Classification of Diseases (ICD-9 until the end of 1993 and the ICD-10 thereafter) [9]. Fracture sites were identified from the DNPR using the ICD-9 or ICD-10 fracture codes and grouped into anatomical sites: (1) Thoracic and lumbar spine T1-T12 and L1-L5 (vertebra), (2) hip (87%) and femur (13%) (hip), (3) tibia and fibula (lower leg), (4) shoulder and humerus (upper arm), (5) ulna and radius (lower arm) and (6) ribs, sternum, clavicle, scapulae and pelvis (other). The ICD codes used to identify low-trauma fractures are provided in Supplementary table 1. A fragility fracture was defined as a fracture associated with minimal trauma. Minimal trauma includes fractures resulting from unintentional contact with the ground, where a person falls from standing height or less, including falls going upstairs or falls onto furniture [10]. In order to minimise inclusion of non-fragility fractures, fractures with high-impact trauma codes were excluded along with pathological fractures (arising from benign and malignant bone tumours, infections, bone cysts or monogenic bone disorders). Furthermore, we excluded fractures of the fingers, toes and head or skull as these fracture types are not considered typical fragility fractures. Time since fracture was defined as years from the fracture date to the date of survey distribution (1 Feb 2017) and divided into the following three categories: < 1 year, 1–5 years and > 5 years since the most recent fracture. Only fractures sustained at or after the age of

50 years were included. If a respondent had sustained more than one fracture since the age of 50 years, the most recent fracture was chosen as the exposure. In order to distinguish between a new fracture and a control visit for the same fracture, a window of 180 days was applied (i.e. the date of fracture was the date of the earliest registered diagnosis code if a respondent had been registered with the same diagnosis code (fracture code) within the past 6 months from the date of the most recent fracture). This procedure was established to avoid underestimating the impact of fracture on HRQoL.

Outcome

The outcome of interest in this study was HRQoL evaluated using the physical component score (PCS) and the mental component score (MCS) of the 12-Item Short Form Health Survey (SF-12). The SF-12 is a generic questionnaire on overall health status and an integrated part of the National Health Survey.

PCS and MCS were standardised with the general US population norms with a US mean of 50 and a US standard deviation (SD) of 10 [11]. In this norm-based scoring, each component in the US general population has an average score of 50, with scores above 50 indicating better than average health and scores below 50 indicating poorer than average health [12]. The threshold of discrimination of clinically minimal important differences (MIDs) in HRQoL for chronic diseases is, according to Norman et al., approximately half a SD [13]. Thus, in this study with an SD of 10, MID was defined as a ≥ 5-point between-group difference in PCS or MCS.

Covariates

Information on all covariates was obtained from national registers. The following variables were a priori identified as potential confounders of the association between fractures and HRQoL and were therefore included as categorical variables in the multivariate models: age (50–59, 60–69, 70–79 or 80+), sex (female or male), ethnic background (non-immigrants or immigrants/descendants of immigrants), co-habiting status (living alone or married/co-habiting irrespective of gender), comorbidity assessed using the Charlson Comorbidity Index (0 points: “No”, 1–2 points: “Low”, 3–4 points: “Moderate” and 5–6 points: “High”) [14, 15] and socio-economic status. In this study, the highest obtained education was used as a proxy for SES. In Denmark and many other countries, educational level is widely accepted as the most important indicator of SES, for two main reasons: (1) Educational level is crucial for future occupation and income; and (2) given that most individuals reach their highest level of educational in their twenties, the SES variable is least affected by future health conditions, and its use will therefore reduce the risk of “reversed causality” [16]. The DISCED-15 was applied for classification of highest obtained educational level. The DISCED-15 is a dimension that ensures consistency between classification in the Danish educational system and the international classification, ISCED2011 [17]. Educational level was categorised as low (lower secondary or less), medium (upper secondary or short cycle tertiary) or high (bachelor or equivalent or higher).

Statistical analysis

Descriptive statistics was applied on socio-demographic factors and comorbidity among fracture cases and controls. Estimates are presented as numbers and percentages or mean and SD. The hypotheses were investigated using bivariate and multivariable ordinary least square (OLS) regression models with PCS and MCS as dependent variables and history of fracture as the primary independent variable of interest. The co-variables were included as categorical variables in the multivariate models. Using these models, we estimated adjusted PCS and MCS with 95% confidence intervals (CI). Adjusted PCS and MCS were calculated as average marginal effects using the method of marginal prediction [18]. To explore if SES modified the association between fracture and HRQoL, data were stratified by educational attainment. All analyses were performed in STATA version 16.

Bias and handling of missing data

In order to reduce bias and to make data representative for the general population, calibrated weights were applied for all analyses to account for differences in selection probabilities and for differences in response rates for different subgroups [19]. These weights were computed by Statistics Denmark and are based on information from both responders and non-responders obtained from various central national registers. Missing items in SF-12 were imputed using an enhanced multi-pattern imputation regression model [20].

Ethical standards

The Danish Data Protection Agency approved the survey and each invited individual was informed in writing about the purpose of the survey, and their voluntary completion and return of the survey questionnaires constituted implied consent.

Results

Study characteristics

The most frequent fracture sites were the lower arm (40%) and lower leg (23%), whereas the least frequent was the spine (4%).

Individuals with fractures were more likely to be women, above 70 years of age, living alone, and to have moderate or high level of comorbidity and a low level of education. Half (53%) of the fracture cases had suffered a previous fracture (Table 1).

Effects of fracture

Crude and adjusted PCS and MCS for fracture cases regardless of time since fracture and controls are presented in Table 2. For both crude and adjusted PCS and MCS, fractures at all regions except the lower arm were associated with significant deficits regardless of time since fracture (Table 2). In the adjusted analysis, the MID threshold deficits were exceeded among individuals with fractures of the spine (− 6.0 (− 7.0; − 5.0)) and hip (− 5.5 (− 6.2; − 4.8)).

Effects of time

The adjusted effects of fractures on HRQoL at each time interval (< 1 year, 1–5 years and > 5 years) are provided in Fig. 1 (PCS) and Fig. 2 (MCS). The deficits in PCS and MCS decreased with time since fracture. However, significant deficits in PCS remained > 5 years post-fracture for all fracture regions except the lower arm. For PCS, the MID threshold deficits were exceeded for fractures of the spine and hip up to 5 years post-fracture and in fractures of the upper arm up to 1 year post-fracture. For MCS, significant deficits were observed for fractures of the hip, spine and upper arm more than 5 years post-fracture. The MCS deficits did not exceed the MID threshold. Deficit HRQoL estimates with 95% CIs are available from Supplementary table 2.

Effects of educational attainment

The adjusted deficits in PCS and MCS between fracture cases (< 1 year post-fracture) and controls by educational attainment are presented in Fig. 3. The PCS deficits between fracture cases and controls were significantly lower in the low (− 2.9 (− 4.1; − 1.8)) than in the high (− 5.0 (− 6.4; − 3.6)) educational attainment group ($p = 0.03$). On the contrary, for MCS, the deficits were significantly higher in the low (− 2.4 (− 3.6; − 1.2)) than in the high (0.0 (− 1.3; 1.4)) educational attainment group ($p = 0.01$). Educational differences in PCS and MCS by fracture region and time since fracture are available from Supplementary tables 3 and 4.

Figure 4 illustrates the adjusted PCS and MCS for fracture cases (< 1 year post-fracture) and controls by educational attainment. In both fracture cases and controls, the PCS was lowest among individuals with low educational attainment (fracture cases: high: 44.8 (43.4; 46.2) versus low 40.2 (39.1; 41.4) $p < 0.01$); controls: high: 49.7 (49.5; 49.8) versus low: 42.8 (42.7; 43.0) $p < 0.01$). The impression of a socio-economic gradient (higher PCS scores with higher educational attainment) was preserved across fracture sites except in hip fractures where the point estimate in the high educational group reached the same low PCS level as in the low SES group. Both controls and fracture cases in the low educational attainment group reported slightly lower mental HRQoL scores than the high educational attainment group (fracture cases: high: 51.2 (49.9; 52.6) versus low: 47.0 (45.8; 48.1) $p < 0.01$; controls high: 51.2 (51.1; 51.4) versus low: 49.3 (49.2; 49.5) $p < 0.01$). The trend towards slightly lower post-fracture MCS among the low (and medium) educational group than among the high group was consistent across fracture regions except for spine fractures.

Discussion

This very large retrospective cohort study reporting post-fracture HRQoL in more than 12,000 men and women above 50 years of age with fractures and more than 90,000 non-fracture controls demonstrated that the physical (PCS) and the mental (MCS) components of the SF-12 were significantly lower among fracture cases than among non-fracture controls. The deficits in PCS and MCS between fracture cases and controls decreased with time since fracture. Generally, for all six fracture regions and at all time points, PCS was more negatively affected than MCS. The fracture regions with the highest and clinically most important impact on PCS were fractures of the spine and hip up to 5 years post-fracture and of the upper arm up to 1 year post-fracture. Interestingly, the deficits in PCS among individuals with a vertebral fracture 1–5 years ago were almost at the same level as deficits < 1 year ago, indicating little improvement in PCS with time since the fracture among individuals with vertebral fractures. The analyses also demonstrated that the deficits between fracture cases and controls were greater among those with lower SES for MCS, but not for PCS.

Comparison with other studies and implications for practice

Associations between fragility fractures and HRQoL

It is difficult to directly compare our findings with results from most previous studies due to differences in the tools used to measure HRQoL (e.g. EQ-5D, HUI, Quality of Well Being), differences in the reporting of results (e.g. HSUVs, Quality Adjusted Life Years (QALYs)) and differences in the length of follow-up. Furthermore, only few studies have explored the effect on HRQoL of fractures at other sites than the hip, spine and wrist, and very few studies have focused on the long-term consequences of fractures (> 5 years). Moreover, the majority of the current evidence focuses solely on statistical

Table 1 Characteristics of fracture cases and non-fracture controls

Clinical characteristics	Fracture cases Number, (%[A]) or mean[A], [sd[A]]	Controls Number, (%[A]) or mean[A], [sd[A]]	Percentage of fracture cases (%[A])	Chi-squared or two-sample *t* test for difference
Total number by group	12,839	91,426	13.0%	
Sex				$p < 0.01$
Female	8846 (70.0%)	45,793 (49.2)	17.1%	
Male	3993 (30.0%)	45,633 (50.8)	7.9%	
Missing	0	0	-	
Age				$p < 0.01$
50–59	1295 (10.1%)	33,395 (38.7%)	3.6%	
60–69	4139 (29.6%)	29,822 (30.4%)	12.4%	
70–79	4831 (35.2%)	21,109 (21.7%)	19.1%	
80+	2574 (25.1%)	7100 (9.2%)	28.4%	$p < 0.01$
Mean	72.8 [9.8]	64.8 [10.2]	-	
Missing	0	0	0%	
Educational level				$p < 0.01$
Low	4409 (41.2%)	23,622 (30.6%)	16.4%	
Medium	5448 (39.3%)	44,686 (46.9%)	10.9%	
High	2935 (18.7%)	22,869 (22.0%)	11.0%	
Missing	47 (0.7%)	249 (0.6%)	15.9%	
Co-habiting status				$p < 0.01$
Live with a partner	7767 (51.4%)	66,658 (66.1%)	10.2%	
Live alone	5072 (48.6%)	24,768 (33.9%)	17.2%	
Missing	0	0	0%	
Ethnic background				$p < 0.01$
Danish	12,393 (94.9%)	86,893 (92.0%)	13.0%	
Non-Danish	446 (5.1%)	4533 (8.0%)	8.6%	
Missing	0 (0%)	0 (0%)	0%	
Type of fragility fracture				-
Hip	1279 (10.9%)		-	
Vertebra	557 (4.4%)		-	
Upper arm	1503 (12.1%)		-	
Lower arm	5190 (39.9%)		-	
Lower leg	3091 (23.4%)		-	
Other	1219 (9.4%)		-	
Missing	0 (0%)		-	-
Previous fractures[B]	6846 (53.7%)		-	-
Charlson Comorbidity Index score				
No (score 0)	7821 (58.8%)	65,764 (71.6%)	10.7%	$p < 0.01$
Low (score 1–2)	3801 (31.1%)	20,640 (22.7%)	16.6%	
Moderate (3–4)	862 (7.2%)	3586 (4.1%)	20.5%	
High (score ≥ 5)	355 (3.0%)	1436 (1.7%)	20.5%	
Missing	0	0	0%	
HRQoL				
PCS[C]	41.9 [12.1]	46.5 [11.0]	-	$p < 0.01$
MCS[C]	49.3 [11.1]	50.5 [10.3]	-	$p < 0.01$
Missing	31 (0.002%)	143 (0.002%)	-	-

[A] Weighted percentage or mean [sd]

[B] Previous fractures after the age of 50 years

[C] Multi-pattern regression-based imputation

Table 2 Crude and adjusted PCS and MCS for controls and fracture cases regardless of time since fracture and crude and adjusted mean deficits between controls and fracture cases

Fracture site	Crude		Adjusted[A]	
	Mean score (95% CI)	Mean deficit (95% CI)	Mean score (95% CI)	Mean deficit (95% CI)
Physical component summary score				
No fractures	46.5 (46.4; 46.6)	-	46.2 (46.1; 46.3)	-
All fractures	41.9 (41.7; 42.2)	− 4.6* (− 4.9; − 4.4)	44.4 (44.1; 44.6)	− 1.8* (− 2.1; − 1.6)
Hip	35.1 (34.4; 35.9)	*− 11.4** (− 12.1; − 10.7)	40.7 (40.0; 41.4)	*− 5.5** (− 6.2; − 4.8)
Vertebrae	37.5 (36.4; 38.6)	*− 9.0** (− 10.1; − 7.9)	40.2 (39.2; 41.3)	*− 6.0** (− 7.0; − 5.0)
Upper arm	40.3 (39.6; 41.0)	*− 6.2** (− 6.9; − 5.5)	43.5 (42.9; 44.2)	− 2.7* (− 3.3; − 2.1)
Lower arm	43.7 (43.3; 44.1)	− 2.8* (− 3.2; − 2.5)	45.9 (45.5; 46.2)	− 0.3 (− 0.7; 0.0)
Lower leg	42.9 (42.4; 43.4)	− 3.6* (− 4.1; − 3.1)	44.5 (44.1; 45.0)	− 1.7* (− 2.2; − 1.2)
Other	43.7 (43.0; 44.5)	− 2.8* (− 3.6; − 2.0)	44.7 (43.9; 45.4)	− 1.6* (− 2.3; − 0.9)
Mental component summary score				
No fractures	50.5 (50.5; 50.6)	-	50.5 (50.5; 50.6)	-
All fractures	49.3 (49.1; 49.5)	− 1.2* (− 1.5; − 1.0)	49.5 (49.3; 49.7)	− 1.0* (− 1.2; − 0.7)
Hip	46.6 (45.9; 47.4)	− 3.9* (− 4.7; − 3.2)	47.9 (47.2; 48.7)	− 2.6* (− 3.3; − 1.9)
Vertebrae	47.3 (46.2; 48.4)	− 3.2* (− 4.3; − 2.1)	47.4 (46.4; 48.5)	− 3.1* (− 4.2; − 2.0)
Upper arm	48.2 (47.5; 48.9)	− 2.3* (− 3.0; − 1.6)	48.8 (48.1; 49.5)	− 1.7* (− 2.4; − 1.0)
Lower arm	50.1 (49.7; 50.4)	− 0.5* (− 0.8; − 0.1)	50.2 (49.9; 50.5)	− 0.3 (− 0.7; 0.0)
Lower leg	50.0 (49.5; 50.4)	− 0.5* (− 1.0; − 0.1)	49.9 (49.5; 50.4)	− 0.6* (− 1.1; − 0.2)
Other	49.9 (49.2; 50.6)	− 0.6 (− 1.4; 0.1)	49.5 (48.9; 50.2)	− 1.0* (− 1.7; − 0.3)

All estimates are based on weighted data. Italic numbers: clinically significant and minimal important difference ≥ 5 points

Abbreviations: *CI*, confidence interval

[A] Estimates are adjusted for sex, age, ethnicity, educational attainment, co-habiting status and comorbidity

*Wald test of equality of means between individuals with no history of fracture and individuals with fracture, $p < 0.05$

significance; thus, reporting of clinical importance of findings is lacking, which further hampers study comparisons. However, a large systematic review and meta-analysis from 2014 on utility-based quality of life for hip, vertebral and wrist fractures concluded that even though hip fractures had a high impact on HRQoL, the improvements in HRQoL after the first

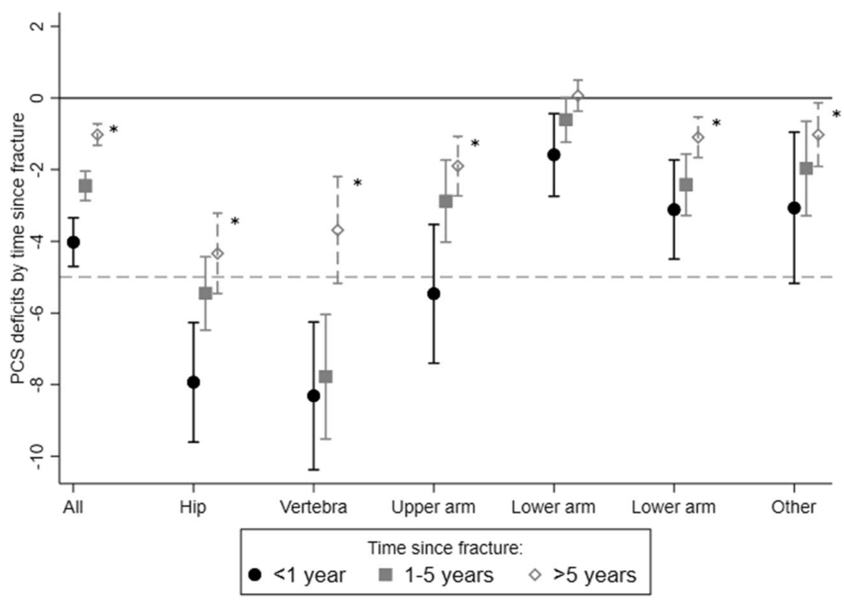

Fig. 1 Deficits in the physical component score (PCS) between non-fracture controls and fracture cases by fracture site and time since fracture. The black y-line (0-line) illustrates PCS in the controls. The grey dashed y-line illustrates the 5-point minimal important difference in PCS. The asterisk indicates Wald's test of equality of means between individuals with no history of fracture and individuals with fracture > 5 years ago, $p < 0.05$

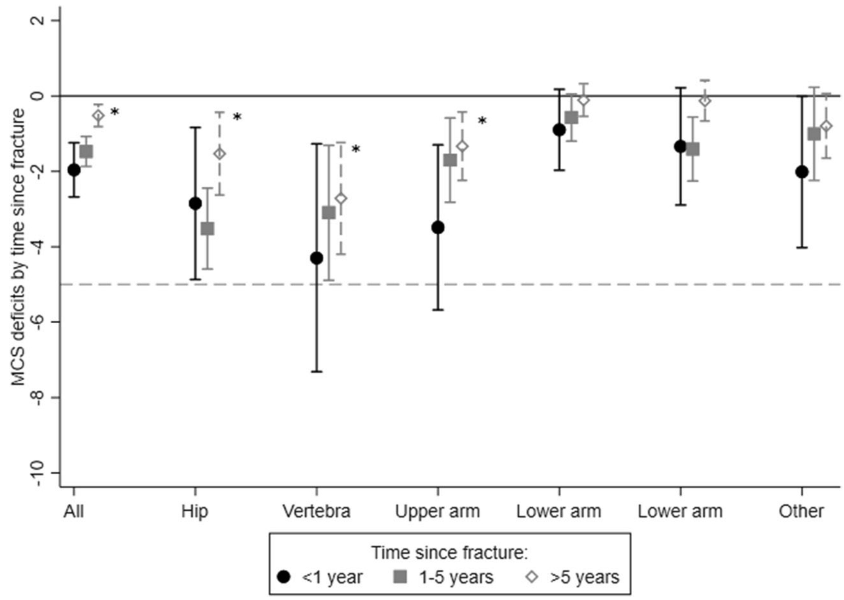

Fig. 2 Deficits in the mental component score (MCS) between non-fracture controls and fracture cases by fracture site and time since fracture. The black y-line (0-line) illustrates MCS in the non-fracture controls. The grey dashed y-line illustrates the 5-point minimal important difference in MCS. The asterisk indicates Wald's test of equality of means between individuals with no history of fracture and individuals with fracture > 5 years ago, $p < 0.05$

year were significant and higher than what was seen after vertebral fractures [5]. These findings are in line with ours and may reflect the differences in both treatment and rehabilitation between hip fractures and vertebral fractures (i.e. lack of effective treatment and rehabilitation for individuals with vertebral fractures). Al-sari et al. performed a systematic review and meta-analysis focusing solely on the impact of vertebral fractures on HRQoL reporting separate pooled standardised mean differences for physical and mental post-fracture HRQoL [21]. The findings in our study regarding PCS and MCS for individuals with vertebral fractures are within the 95% CIs reported in the review by Al-sari et al. (PCS: SMD = 0.53 (95% CI 0.38; 0.67) and MCS: SMD = 0.04 95% CI − 0.32; 0.41)) implying high validity of our results. In addition, Al-sari et al. stated that there was a lack of studies reporting adjusted HRQoL as well as a lack of studies presenting results stratified by time since fracture [21]. Our study provides both, and it thus adds valuable new insights about the impact of vertebral as well as other fractures. The impact of fractures besides those of the hip, vertebra and wrist has previously been explored in a large Canadian cohort study including 5057 individuals receiving home care [22]. In that study, Tarride et al. found that, independently of fracture type, HRQoL did not return to pre-fracture levels for up to 3 years post-fracture [22]. These results are in line with our results with respect to hip and spine fractures. Another study,

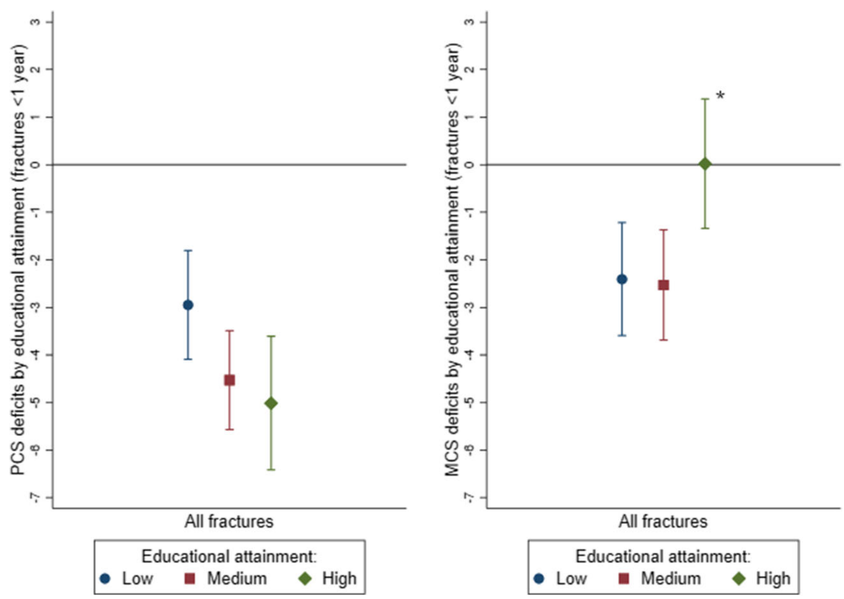

Fig. 3 HRQoL deficits by educational attainment between non-fracture controls and fracture cases (< 1 year post-fracture). Estimates for the physical component score (PCS) are presented at the left side and estimates for the mental component score (MCS) are presented at the right side of the figure. The asterisk indicates HRQoL deficits significantly lower (< 0.05) in the low than the high educational attainment group

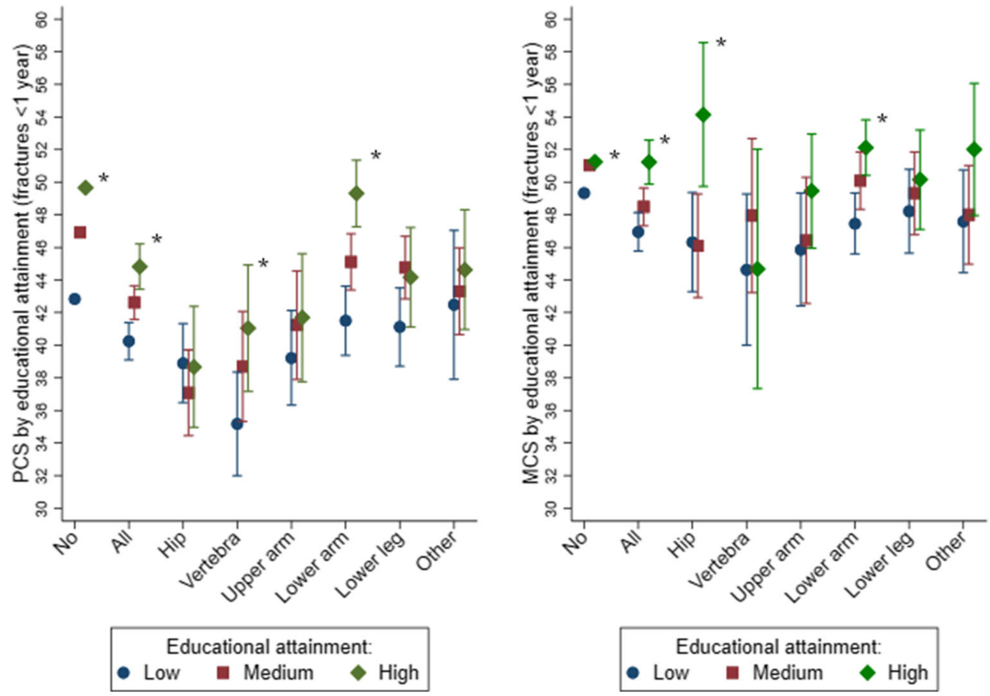

Fig. 4 HRQoL by educational attainment for non-fracture cases, all fracture cases combined (all) and fracture cases divided into fractures at different anatomical sites. HRQoL scores for fracture cases are presented as scores < 1 year post-fracture. Estimates for the physical component score (PCS) are presented at the left side and estimates for the mental component score (MCS) are presented at the right side of the figure. The asterisk indicates Wald's test of equality of means between individuals with high and individuals with low educational attainment group, $p < 0.05$

published in 2019, presented post-fracture HRQoL for different fracture sites (the pelvic, hip, rib, spine, forearm and shoulder) divided into 1–5 years or 6–10 years post-fracture [23]. This study was based on data from the Canadian Multicentre Osteoporosis Study (CaMos); and the design was similar to that of our study comparing post-fracture HRQoL in women (*N*: 770) and men (*N*: 138) with HRQoL in non-fracture controls within the cohort. In concordance with our results, Borhan et al. found clinically important deficits in HRQoL among individuals with fractures at the spine, hip, rib and pelvis up to 5 years post-fracture, but no clinically important deficits 6 years or more post-fracture [23].

The impact of HRQoL on fractures of the spine (PCS: 40.2, MCS: 47.4) and hip (PCS: 40.7, MCS: 47.9) found in our study mirrored the HRQoL impact of cancer (PCS: 40.7, MCS: 47.1) and rheumatoid arthritis (PCS: 40.6, MCS: 47.2), indicating a substantial, negative impact of spine and hip fractures [24].

Socio-economic disparities in post-fracture HRQoL

The socially differential effect of illness is considered to be important in preventive health policies, but it has yet to become the object of extensive investigations [25]. Stafford et al. found a differential association between obesity, hypertension, and diabetes and HRQoL by SES; a lower SES was associated with greater reductions in HRQoL [26]. In contrast to the theories of Diderichsen and Hallqvist [6], the results from our study do not support a socially differential effect of fractures for PCS and only small differential effects for MCS. On the contrary, for PCS, a trend was observed towards a reversed socio-economic gradient with the greatest deficits observed in the high educational attainment group. Several possible explanations may explain why Diderichsen and Hallqvist's theory finds little support in relation to PCS in our study. One explanation may be that a fracture is an acute event with a considerable, negative impact on the physical well-being irrespective of educational attainment. Another factor contributing to the lack of differential effects of post-fracture PCS may be that post-fracture mortality may be higher for individuals with a low than for individuals with a high educational attainment [7]. The higher post-fracture mortality rates among individuals with a low educational attainment may mask actual educational differences in HRQoL between fracture and non-fracture individuals (potential mortality bias). A third potential explanation may be that cross-sectional data are less appropriate than longitudinal data for detecting changes over time. However, the sparse longitudinal data on socio-economic inequalities in post-fracture HRQoL also failed to demonstrate a clear socially differential effect in post-fracture HRQoL [7]. Interestingly, we did see a statistically different impact of fractures on MCS by educational attainment; fractures had a negative impact on MCS in individuals with a low or medium but not in individuals with a high educational attainment (Fig. 3). This was especially evident in individuals with hip fractures. In the high educational attainment group, great post-fracture PCS deficits were observed, bringing the high educational attainment group to the same low post-fracture PCS level as the low educational attainment group. On the other hand, for MCS, no deficits were observed in the high educational attainment group (Fig. 4). The results of a socio-economically differentiated impact of mental HRQoL could reflect a larger mental vulnerability among individuals with low and medium educational attainment. To our knowledge, no previous studies have reported post-fracture mental HRQoL data stratified by educational attainment, so this finding requires further investigations.

Despite the fact that our hypothesis of greater PCS deficits among those with a lower SES could not be confirmed, fracture survivors in the lowest educational attainment group were still more prone to end up with a very low post-fracture HRQoL due to low pre-fracture PCS. Hence, PCS for low educational attainment individuals with fractures at the spine (PCS: 37.3) mirrored norm values for individuals with kidney disease (PCS: 37.9). Similarly, PCS for low educational attainment individuals with fractures at the hip (PCS: 38.7) mirrored the norm values for individuals with heart disease (38.8) [24]. The low pre-fracture HRQoL combined with the higher post-(hip)fracture mortality among individuals with low SES warrants increased awareness of special needs for post-fracture care in individuals with a low educational attainment.

Strengths and limitations

The present study has several strengths. We linked HRQoL data from a large national population-based survey with individual-level register data from national health and population registers. The national health and population registers contain valid individual-level information on previous fractures including information on anatomical site and date of fracture as well as information on relevant confounders such as comorbidity, educational attainment, age, sex, ethnicity and co-habiting status. The survey contains information on self-reported HRQoL that is not available from the registers. By linking survey data with register data, we were able to compare HRQoL in individuals with fractures after the age of 50 years with HRQoL in a representative population-based sample with no history of fractures. The population-based design and large sample size allowed for analysis of all types of fractures combined and for six different fracture regions separately. Furthermore, it allowed for stratification of data by time since fracture and educational attainment, providing unique information on post-fracture HRQoL. Furthermore, it is considered a strength that we used an individual-level SES measure (educational attainment) as opposed to area-based SES measures because this reduces the risk of misclassification bias. Data on incident fractures and fracture site were obtained from the DNPR. In Denmark, nearly all patients with fractures are managed in the hospital system. The capture of fractures, with the exception of spine fractures, is thus very high, minimising the risk of misclassification bias.

This study has some potential limitations. First, it is a well-known fact that the overall health profile of non-responders is poorer than that of responders. These differences between responders and non-responders may introduce bias if non-response is related to both the exposure and the outcome. In this study, selection bias may have been introduced if participation in the survey depends on both fractures, SES and HRQoL. However, because we have information on both responders and non-responders, we were able to weight our data to represent the Danish population and thereby reduce the risk of selection bias. Furthermore, the response rate was relatively high, implying that issues regarding selection bias may be limited. Second, the HRQoL data were measured only at one time point; it was thus not possible to follow individuals and analyse HRQoL changes over time. Third, survival bias is inherent to this study because those who were most affected by their fracture may have died before they could participate. However, social inequality in mortality following fractures has been studied previously in other studies; and since this study aimed to study long-term consequences of fractures, the selection of "fracture survivors" is considered to be acceptable and in line with our scope. Finally, while we believe that the vast majority of low-trauma fractures included in our analysis were fragility fractures, the mechanism of injury cannot be reliably ascertained from the use of ICD codes. In a recent publication by Leslie et al., high-trauma and low-trauma fractures showed similar relationships with regard to low BMD and future fracture risk [27]. Thus, the potential inclusion of high-trauma fractures in this study might not impact the validity of the results.

Conclusion

In conclusion, fragility fractures are associated with a short-term and long-term decline in physical and mental HRQoL assessed by the physical (PCS) and the mental (MCS) component of SF-12. Fractures at the spine and hip were associated with clinically important deficits in PCS up to 5 years post-fracture. Post-fracture HRQoL scores in individuals with fractures of the spine or hip mirrored the scores found in individuals with cancer and rheumatoid arthritis indicating a substantial, negative impact of these fracture types on HRQoL. The HRQoL deficits between fracture cases and non-fracture controls were greater for MCS but not for PCS among those with a lower SES. However, given that individuals with low SES have lower pre-fracture PCS and MCS, this sub-group is more likely to report very low post-fracture HRQoL. This finding in combination with the higher post-fracture mortality among low SES individuals warrant increased awareness of special needs for post-fracture care in individuals with a low SES.

Authors' contribution All of the authors were responsible for the design and analysis plan. The analysis was conducted by GV with input from the co-authors. The initial draft of the manuscript was prepared by GV, and then circulated among all authors for critical revision. All authors have provided final approval of the version to be published.

Funding information The Danish National Health Survey was funded by The Capital Region, Region Zealand, The South Denmark Region, The Central Denmark Region, The North Denmark Region, The Ministry of Interior and Health and the National Institute of Public Health, University of Southern Denmark. The conduction of the paper was supported by the Department of Clinical Medicine, Aarhus University and by DEFACTUM, Central Denmark Region.

Data availability There are restrictions prohibiting the provision of data in this manuscript. The data were obtained from a third party upon application to the national steering group (NATSUP). All interested researchers can apply for data from the Danish National Health Survey at the National Institute of Public Health.

Code availability Not applicable.

Compliance with ethical standards

Conflicts of interest Gitte Valentin, Karina Friis, Camilla Palmhøj Nielsen, Finn Breinholt Larsen declare that they have no conflicts of interest. Bente L Langdahl has received research funding from Amgen and Novo Nordisk for her institution. She serves on advisory boards and speaker bureaus for Amgen, UCB, Eli Lilly, Gilead and Gedeon-Richter.

Ethics approval The study was approved by the Danish Data Protection Agency (journal number 2016-051-000001).

Consent to participate Written information about the purpose of the survey was given to each invited participant, and respondents were informed that by completing and submitting the questionnaire they gave their consent to participate in the survey.

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Appendix 3B Study III – Supplementary material

Supplementary table 1: List of diagnosis codes by type of fracture

Fracture type	Diagnosis code
Spine (T1-T12 and L1-L5)	DS220 (A-L); DS320(A-E)
Lower arm (wrist, elbow and radius and ulna)	DS525 (A-C); DS526; DS52; DS520 (A-C); DS520D; DS521 (A+B); DS522; DS523; DS524; DS527; DS422.
Upper arm (shoulder and humerus)	DS422 (A+B); DS422C; DS423 (A); DS42
Hip (hip and femur)	DS720; DS721 (A+B); DS722; S720; S721; S722; DS72; DS723; DS724 (A-C); DS727; DS728 (A); DS729
Lower Leg (tibia and fibula)	DS820; DS82; DS821 (A-D); DS822; DS823 (A+C); DS824; DS829; DS825; DS826; DS827 (A+B); DS828 (B+D); DS32
Other fractures (ribs, sternum, clavicle, scapulae and pelvis)	DS22; DS223; DS420; DS421

Supplementary table 2: Adjusted differences in HRQoL between controls and fracture cases, by time since fracture

Physical Component Summary score	Mean (95% CI)	Fracture cases: Time since latest fracture Difference between fracture cases and controls All	< 1 year	1-5 years	> 5 years
No fractures	46.2 (46.1; 46.3)	-	-	-	-
All fractures combined	44.4 (44.1; 44.6)	-1.8* (-2.1; -1.6)	-4.0* (-4.7; -3.3)	-2.5* (-2.9; -2.0)	-1.0* (-1.3; -0.7)
Upper leg	40.7 (40.0; 41.4	**-5.5*** (-6.2; -4.8)	**-7.9*** (-9.6; -6.3)	**-5.5*** (-6.5; -4.4)	-4.3* (-5.5; -3.2)
Vertebrae	40.2 (39.2; 41.3)	**-6.0*** (-7.0; -5.0)	**-8.3*** (-10.4; -6.2)	**-7.8*** (-9.5; -6.0)	-3.7* (-5.2; -2.2)
Upper arm	43.5 (42.9; 44.2)	-2.7* (-3.3; -2.1)	**-5.5*** (-7.4; -3.5)	-2.9* (-4.0; -1.7)	-1.9* (-2.7: -1.1)
Lower arm	45.9 (45.5; 46.2)	-0.3 (-0.7; 0.0)	-1.6* (-2.7; -0.4)	-0.6 (-1.2; 0.0)	0.1 (-0.4; 0.5)
Lower leg	44.5 (44.1; 45.0)	-1.7* (-2.2; -1.2)	-3.1* (-4.5; -1.7)	-2.4* (-3.3; -1.6)	-1.1* (-1.7; -0.5)
Other	44.7 (43.9; 45.4)	-1.6* (-2.3; -0.9)	-3.1* (-5.2; -1.0)	-2.0* (-3.3; -0.6)	-1.0* (-1.9; -0.1)
Mental Component Summary score	Mean (95% CI)	Fracture cases: Time since latest fracture Difference between fracture cases and controls All	< 1 year	1-5 years	> 5 years
No fractures	50.5 (50.5; 50.6)	-	-	-	-
All fractures combined	49.5 (49.3; 49.7)	-1.0* (-1.2; -0.7)	-2.0* (-2.7; -1.2)	-1.5* (-1.9; -1.1)	-0.5* (-0.8; -0.2)
Upper leg	47.9 (47.2; 48.7)	-2.6* (-3.3; -1.9)	-2.9* (-4.9; -0.8)	-3.5* (-4.6; -2.4)	-1.5* (-2.6; -0.4)
Vertebra	47.4 (46.4; 48.5)	-3.1* (-4.2; -2.0)	-4.3* (-7.3; -1.3)	-3.1* (-4.9; -1.3)	-2.7* (-4.2; -1.2)
Upper arm	48.8 (48.1; 49.5)	-1.7* (-2.4; -1.0)	-3.5* (-5.7; -1.3)	-1.7* (-2.8; -0.6)	-1.3* (-2.2; -0.4)
Lower arm	50.2 (49.9; 50.5)	-0.3 (-0.7; 0.0)	-0.9 (-2.0; 0.2)	-0.6 (-1.2; 0.1)	-0.1 (-0.5; 0.3)
Lower leg	49.9 (49.5; 50.4)	-0.6* (-1.1; -0.2)	-1.3 (-2.9; 0.2)	-1.4* (-2.3; -0.6)	-0.1 (-0.7; 0.4)
Other	49.5 (48.9; 50.2)	-1.0* (-1.7; -0.3)	-2.0* (-4.0; -0.0)	-1.0 (-2.2; 0.2)	-0.8 (-1.7; 0.1)

All estimates are based on weighted data. Bold numbers: Clinically significant and minimal important difference are larger than 2 points.
Abbreviations: CI, confidence interval.
Estimates are adjusted for sex, age, educational attainment, co-habiting status and comorbidity.
*:Wald test of equality of means between individuals with no history of fracture and individuals with fracture, $p < 0.05$.

Supplementary table 3: Adjusted PCS deficits by educational attainment and time since fracture

Physical Component Summary score	Educational level	Mean (95% CI)	Difference between controls and fracture cases according to educational attainment.			
			Fracture cases: time since fracture			
Fracture site			All	<1 year	1-5 years	>5 years
No fracture	Low	42.8 (42.7; 43.0)	-	-	-	-
	Medium	46.9 (46.8; 47.0)	-	-	-	-
	High	49.7 (49.5; 49.8)	-	-	-	-
All fractures combined	Low	41.6 (41.2; 41.9)	-1.3* (-1.7; -0.9)	-2.9* (-4.1; -1.8)	-2.3* (-2.9; -1.6)	-0.4 (-0.9; 0.1)
	Medium	45.0 (44.6; 45.3)	-2.0* (-2.3; -1.6)	-4.5* (-5.6; -3.5)	-2.4* (-3.0; -1.8)	-1.2* (-1.6; -0.7)
	High	46.9 (46.5; 47.4)	-2.7* (-3.2; -2.3)	**-5.0*** (-6.4; -3.6)	-3.0* (-3.8; -2.1)	-2.0* (-2.6; -1.4)
Upper leg	Low	38.7 (37.7; 39.6)	-4.1* (-5.2; -3.2)	-4.3* (-6.7; -1.9)	-4.6* (-6.0; -3.1)	-3.6* (-5.2; -1.9)
	Medium	40.6 (39.4; 41.7)	**-6.3*** (-7.5; -5.2)	**-10.1*** (-12.7; -7.4)	**-5.9*** (-7.7; -4.1)	-4.8* (-6.7; -3.0)
	High	41.8 (40.2; 43.5)	**-7.8*** (-9.5; -6.2)	**-11.2*** (-14.9; -7.4)	**-7.8*** (-10.3; -5.3)	**-5.7*** (-8.3; -3.0)
Vertebra	Low	37.3 (35.6; 39.0)	**-5.5*** (-7.2; -3.8)	**-8.0*** (-11.2; -4.8)	**-7.9*** (-11.2; -4.5)	-3.0* (-5.2; -0.8)
	Medium	40.5 (39.0; 42.0)	**-6.4*** (-8.0;-4.9)	**-8.4*** (-11.8; -5.1)	**-7.8*** (-10.0; -5.6)	-4.6* (-7.0; -2.1)
	High	43.9 (41.7; 46.0)	**-5.8*** (-7.9; -3.6)	**-8.8*** (-12.7; -4.9)	**-7.5*** (-11.1;-4.0)	-3.0 (-6.0; 0.1)
Upper arm	Low	40.9 (39.9; 41.9)	-1.9* (-2.9; -0.9)	-4.0* (-6.9; -1.1)	-2.4* (-4.1; -0.6)	-1.1 (-2.4; 0.2)
	Medium	44.6 (43.6; 45.6)	-2.4* (-3.4; -1.4)	**-5.9*** (-9.2; -2.6)	-2.3* (-4.1; -0.5)	-1.7* (-2.9; -0.5)
	High	44.7 (43.3; 46.2)	-4.9* (-6.3;-3.5)	**-8.1*** (-12.1; -4.2)	**-5.0*** (-7.4;-2.5)	-4.1* (-6.0; -2.1)
Lower arm	Low	42.9 (42.3; 43.5)	0.1 (-0.5; 0.7)	-1.7 (-3.8; 0.4)	-0.6 (-1.6; 0.5)	0.7 (-0.1; 1.4)
	Medium	46.6 (46.1; 47.1)	-0.3 (-0.9; 0.2)	-2.0* (-3.8; -0.3)	-0.3 (-1.3; 0.6)	0.0 (-0.6; 0.7)
	High	48.5 (47.8; 49.2)	-1.1* (-1.8; -0.5)	-0.5 (-2.6; 1.5)	-1.2 (-2.5; 0.1)	-1.2* (-2.0; -0.3)
Lower leg	Low	41.6 (40.9; 42.4)	-1.2* (-2.0; -0.4)	-2.1 (-4.5; 0.3)	-2.3* (-3.9; -0.7)	-0.6 (-1.5; 0.4)
	Medium	45.1 (44.4; 45.8)	-1.9* (-2.6; -1.2)	-2.4* (-4.3; -0.5)	-2.7* (-4.0; -1.4)	-1.3* (-2.2; -0.4)
	High	47.4 (46.6; 48.2)	-2.3* (-3.1; -1.4)	**-5.7*** (-8.7; -2.6)	-2.1* (-3.6; -0.6)	-1.6* (-2.7; -0.6)
Other	Low	42.2 (40.9; 43.5)	-0.6 (-2.0;0.7)	-0.7 (-5.3; 3.9)	-1.1 (-3.6; 1.4)	-0.3 (-2.0; 1.3)
	Medium	45.2 (44.2; 46.2)	-1.7* (-2.7; -0.8)	-3.8* (-6.5; -1.2)	-2.1* (-3.9; -0.4)	-1.0 (-2.3; 0.3)
	High	46.8 (45.4; 48.3)	-2.8* (-4.3; -1.4)	**-5.2*** (-8.9; -1.5)	-3.1* (-6.0; -0.2)	-2.3* (-4.1; -0.6)

All estimates are based on weighted data. Bold numbers: minimal important difference (≥ 5 points).
Abbreviations: CI, confidence interval.
Estimates are adjusted for sex, age, co-habiting, ethnicity and comorbidity.
*Wald test of equality of means between controls and fracture cases, $p < 0.05$.

Supplementary table 4: Adjusted MCS deficits by educational attainment and time since fracture

Mental Component Summary score	Educational level	Mean (95% CI)	Difference between controls and fracture cases by educational attainment			
			Fracture cases: time since fracture			
Fracture site			All	< 1 year	1-5 years	> 5 years
No fracture	Low	49.3 (49.2; 49.5)	-	-	-	-
	Medium	51.0 (50.9; 51.1)	-	-	-	-
	High	51.2 (51.1; 51.4)	-	-	-	-
All fractures combined	Low	48.1 (47.7; 48.4)	-1.3* (-1.7; -0.9)	-2.4* (-3.6; -1.2)	-2.1* (-2.8; -1.4)	-0.6* (-1.1; -0.1
	Medium	49.9 (49.6; 50.3)	-1.1* (-1.4; -0.7)	-2.5* (-3.7; -1.4)	-1.5* (-2.0; -0.9)	-0.6* (-1.0; -0.2)
	High	51.1 (50.7; 51.5)	-0.2 (-0.6; 0.3)	0.0 (-1.3; 1.4)	-0.3 (-1.0; 0.4)	-0.1 (-0.7; 0.4)
Upper leg	Low	46.6 (45.5; 47.6)	-2.7* (-3.8; -1.7)	-3.0* (-6.1; -0.0)	-3.7* (-5.3; -2.2)	-1.5 (-3.1; 0.2)
	Medium	47.8 (46.7; 49.0)	-3.2* (-4.3; -2.0)	-4.9* (-8.1; -1.7)	-4.2* (-5.9; -2.4)	-1.5 (-3.0; 0.1)
	High	50.7 (48.8; 52.6)	-0.6 (-2.5; 1.3)	-2.9 (-1.5; 7.4)	-1.2 (-3.7; 1.4)	-2.0 (-5.4; 1.3)
Vertebra	Low	45.8 (44.1; 47.4)	-3.6* (-5.3; -1.9)	-4.7* (-9.4; -0.1)	-3.6* (-6.6; -0.6)	-3.2* (-5.4; -1.0)
	Medium	48.1 (46.5; 49.8)	-2.9* (-4.5; -1.2)	-3.1 (-7.8; 1.7)	-2.8* (-5.4; -0.1)	-2.9* (-5.2; -0.6)
	High	48.9 (46.3; 51.5)	-2.3 (-4.9; 0.2)	-6.5 (-13.9; 0.8)	-2.9 (-6.7; 0.9)	-0.3 (-3.8; 3.2)
Upper arm	Low	47.4 (46.2; 48.5)	-2.0* (-3.1; -0.8)	-3.5 (-7.0; -0.0)	-1.9 (-3.9; 0.2)	-1.7* (-3.2; -0.1)
	Medium	48.7 (47.7; 49.8)	-2.3* (-3.3; -1.2)	-4.6* (-8.5; -0.7)	-2.5* (-4.2; -0.8)	-1.7* (-3.0; -0.4)
	High	51.1 (50.0; 52.3)	-0.1 (-1.3; 1.0)	-1.8 (-5.2; 1.8)	0.1 (-1.8; 2.0)	0.2 (-1.4; 1.8)
Lower arm	Low	48.7 (48.1; 49.2)	-0.7 (-1.3; -0.1)*	-1.9 (-3.8; -0.0)	-0.8 (-1.9; 0.3)	-0.4 (-1.2; 0.3)
	Medium	50.8 (50.3; 51.3)	-0.3 (-0.8; 0.3)	-0.9 (-2.7; 0.8)	-0.9 (-1.9; 0.1)	0.2 (-0.4; 0.8)
	High	51.5 (50.9; 52.1)	0.2 (-0.4; 0.9)	0.9 (-0.8; 2.6)	0.4 (-0.6; 1.5)	0.0 (-0.8; 0.9)
Lower leg	Low	48.8 (48.0; 49.5)	-0.6 (-1.4; 0.2)	-1.1 (-3.7; 1.4)	-2.2* (-3.9; -0.6)	0.2 (-0.8; 1.2)
	Medium	50.3 (49.6; 50.9)	-0.8* (-1.4; -0.1)	-1.7 (-4.2; 0.8)	-1.1 (-2.3; 0.2)	-0.5 (-1.2; 0.3)
	High	50.8 (50.0; 51.6)	-0.4 (-1.2; 0.4)	-1.1 (-4.1; 2.0)	-0.8 (-2.3; 0.6)	-0.1 (-1.0; 0.9)
Other	Low	47.8 (46.4; 49.1)	-1.6* (-2.9; -0.2)	-1.8 (-4.9; 1.4)	-3.4* (-6.2; -0.6)	-0.5 (-2.0; 1.0)
	Medium	50.2 (49.3; 51.1)	-0.8 (-1.7; 0.1)	-3.0 (-6.0; 0.0)	0.7 (-0.5; 2.0)	-1.3* (-2.6; -0.0)
	High	51.0 (49.7; 52.2)	-0.3 (-1.5; 1.0)	0.8 (-3.2; 4.9)	-0.6 (-2.6; 1.5)	-0.2 (-1.9; 1.4)

All estimates are based on weighted data. Bold numbers: minimal important difference (≥ 5 points).
Abbreviations: CI, confidence interval.
Estimates are adjusted for sex, age, co-habiting status, ethnicity and comorbidity.
*Wald test of equality of means between controls and fracture cases, $p < 0.05$.

Appendix 4 The Danish National Survey "How are you?" 2017

Køn og alder

1. Er du:

Mand	☐
Kvinde	☐

2. Hvornår er du født?

Dag	Måned	År
⎣ ⎸ ⎦	⎣ ⎸ ⎦	⎣ ⎸ ⎸ ⎸ ⎦

Helbred og trivsel

3. Hvordan synes du, dit helbred er alt i alt?

	(Kun ét X)
Fremragende	☐
Vældig godt	☐
Godt	☐
Mindre godt	☐
Dårligt	☐

4. De følgende spørgsmål handler om aktiviteter i dagligdagen. Er du <u>på grund af dit helbred</u> begrænset i disse aktiviteter? I så fald, hvor meget?

(Sæt ét X i hver linje)	Ja, meget begrænset	Ja, lidt begrænset	Nej, slet ikke begrænset
<u>Lettere aktiviteter</u>, såsom at flytte et bord, støvsuge eller cykle	☐	☐	☐
At gå <u>flere</u> etager op ad trapper	☐	☐	☐

5. Hvor stor en del af tiden inden for <u>de sidste 4 uger</u> har du haft følgende problemer med dit arbejde eller andre daglige aktiviteter <u>på grund af dit fysiske helbred</u>?

(Sæt ét X i hver linje)	Hele tiden	Det meste af tiden	Noget af tiden	Lidt af tiden	På intet tidspunkt
Jeg har <u>nået mindre</u>, end jeg gerne ville	☐	☐	☐	☐	☐
Jeg har været begrænset i hvilken <u>slags</u> arbejde eller andre aktiviteter, jeg har kunnet udføre	☐	☐	☐	☐	☐

6. **Hvor stor en del af tiden inden for <u>de sidste 4 uger</u> har du haft følgende problemer med dit arbejde eller andre daglige aktiviteter <u>på grund af følelsesmæssige problemer</u>?**

(Sæt ét X i hver linje)	Hele tiden	Det meste af tiden	Noget af tiden	Lidt af tiden	På intet tidspunkt
Jeg har <u>nået mindre</u>, end jeg gerne ville	☐	☐	☐	☐	☐
Jeg har udført mit arbejde eller andre aktiviteter mindre <u>omhyggeligt</u>, end jeg plejer	☐	☐	☐	☐	☐

7. **Inden for <u>de sidste 4 uger</u>, hvor meget har fysisk smerte vanskeliggjort dit daglige arbejde (både arbejde uden for hjemmet og husarbejde)?**

	(Kun ét X)
Slet ikke	☐
Lidt	☐
Noget	☐
En hel del	☐
Virkelig meget	☐

8. **Disse spørgsmål handler om, hvordan du har haft det i <u>de sidste 4 uger</u>. For hvert spørgsmål, vælg venligst det svar, som bedst beskriver, hvordan du har haft det. Hvor stor en del af tiden i <u>de sidste 4 uger</u> …**

(Sæt ét X i hver linje)	Hele tiden	Det meste af tiden	Noget af tiden	Lidt af tiden	På intet tidspunkt
har du følt dig rolig og afslappet?	☐	☐	☐	☐	☐
har du været fuld af energi?	☐	☐	☐	☐	☐
har du følt dig trist til mode?	☐	☐	☐	☐	☐

9. **Inden for <u>de sidste 4 uger</u>, hvor stor en del af tiden har dit fysiske helbred eller følelsesmæssige problemer gjort det vanskeligt at se andre mennesker (f.eks. besøge venner, slægtninge osv.)?**

	(Kun ét X)
Hele tiden	☐
Det meste af tiden	☐
Noget af tiden	☐
Lidt af tiden	☐
På intet tidspunkt	☐

+

Dagligdagens stress

10. Spørgsmålene drejer sig om dine følelser og tanker inden for de seneste 4 uger. For hvert spørgsmål bedes du markere med et kryds, hvor ofte du følte eller tænkte på den pågældende måde.

Hvor ofte inden for de seneste 4 uger:

(Sæt ét X i hver linje)	Aldrig	Næsten aldrig	En gang imellem	Ofte	Meget ofte
Er du blevet oprevet over noget, der skete uventet?	☐	☐	☐	☐	☐
Har du følt, at du ikke kunne kontrollere de betydningsfulde ting i dit liv?	☐	☐	☐	☐	☐
Har du følt dig nervøs og "stresset"?	☐	☐	☐	☐	☐
Har du følt dig sikker på din evne til at klare dine personlige problemer?	☐	☐	☐	☐	☐
Har du følt, at tingene gik, som du gerne ville have det?	☐	☐	☐	☐	☐
Har du følt, at du ikke kunne overkomme alle de ting, du skulle?	☐	☐	☐	☐	☐
Har du været i stand til at håndtere dagligdags irritations-momenter?	☐	☐	☐	☐	☐
Har du følt, at du havde styr på tingene?	☐	☐	☐	☐	☐
Er du blevet vred over ting, som du ikke havde indflydelse på?	☐	☐	☐	☐	☐
Har du følt, at dine problemer hobede sig så meget op, at du ikke kunne klare dem?	☐	☐	☐	☐	☐

Symptomer og ubehag de seneste 14 dage

11. Har du inden for de seneste 14 dage været generet af nogle af de her nævnte former for smerter og ubehag? Var du meget eller lidt generet af det?

(Sæt ét X i hver linje)	Ja, meget generet	Ja, lidt generet	Nej
Smerter eller ubehag i skulder eller nakke	☐	☐	☐
Smerter eller ubehag i arme, hænder, ben, knæ, hofter eller led	☐	☐	☐
Smerter eller ubehag i ryg eller lænd	☐	☐	☐
Træthed	☐	☐	☐
Hovedpine	☐	☐	☐
Søvnbesvær, søvnproblemer	☐	☐	☐
Nedtrykthed, deprimeret, ulykkelig	☐	☐	☐
Ængstelse, nervøsitet, uro og angst	☐	☐	☐

Langvarige sygdomme og eftervirkninger

12. Har du nogen langvarig sygdom, langvarig eftervirkning af skade, handicap eller anden langvarig lidelse? Med langvarig menes mindst 6 måneder.

Ja	☐
Nej	☐

13. For hver af de følgende sygdomme og helbredsproblemer bedes du angive, om du har den nu eller har haft den tidligere. Hvis du har haft den tidligere, bedes du også angive, om du har eftervirkninger.

(Sæt mindst ét X i hver linje)	Nej, det har jeg **aldrig** haft	Ja, det har jeg **nu**	Ja, det har jeg haft **tidligere**	Hvis du har haft det tidligere: Har du stadig **eftervirkninger?** Ja	Nej
Astma	☐	☐	☐ →	☐	☐
Allergi (ikke astma)	☐	☐	☐ →	☐	☐
Sukkersyge (diabetes)	☐	☐	☐ →	☐	☐
Forhøjet blodtryk	☐	☐	☐ →	☐	☐
Blodprop i hjertet	☐	☐	☐ →	☐	☐
Hjertekrampe (angina pectoris)	☐	☐	☐ →	☐	☐
Hjerneblødning, blodprop i hjernen	☐	☐	☐ →	☐	☐
Kronisk bronkitis, for store lunger, rygerlunger (emfysem, KOL)	☐	☐	☐ →	☐	☐
Slidgigt	☐	☐	☐ →	☐	☐
Leddegigt	☐	☐	☐ →	☐	☐
Knogleskørhed (osteoporose)	☐	☐	☐ →	☐	☐
Kræft	☐	☐	☐ →	☐	☐
Migræne eller hyppig hovedpine	☐	☐	☐ →	☐	☐
Psykisk lidelse, som varede eller indtil nu har varet mindre end 6 måneder	☐	☐	☐ →	☐	☐
Psykisk lidelse af mere end 6 måneders varighed	☐	☐	☐ →	☐	☐
Diskusprolaps eller andre rygsygdomme	☐	☐	☐ →	☐	☐
Grå stær	☐	☐	☐ →	☐	☐
Tinnitus (hyletone, susen for ørerne)	☐	☐	☐ →	☐	☐

Rygning

14. Ryger du? (gælder ikke e-cigaretter)

	(Kun ét X)		
Ja, hver dag	☐		
Ja, mindst én gang om ugen	☐	→	Gå til spørgsmål 16
Ja, sjældnere end hver uge	☐	→	Gå til spørgsmål 16
Nej, jeg er holdt op	☐	→	Gå til spørgsmål 18
Nej, jeg har aldrig røget	☐	→	Gå til spørgsmål 18

15. Hvor meget ryger du i gennemsnit pr. dag?

	(Skriv antal)
Antal cigaretter	☐☐
Antal cerutter	☐☐
Antal cigarer	☐☐
Antal pibestop	☐☐

16. Vil du gerne holde op med at ryge?

	(Kun ét X)		
Nej	☐	→	Gå til spørgsmål 18
Ja, men jeg har ikke planlagt hvornår	☐		
Ja, jeg planlægger rygeophør inden for 6 måneder	☐		
Ja, jeg planlægger rygeophør inden for 1 måned	☐		

17. Hvis du vil holde op med at ryge, vil du så gerne have støtte og hjælp til at gennemføre det (f.eks. rygestopkursus, støtte fra din læge)?

Ja	☐
Nej	☐

18. **Hvor mange timer om dagen opholder du dig i rum, hvor der bliver røget, eller hvor der lugter af tobaksrøg?**

	(Kun ét X)
Over 5 timer om dagen	☐
1 – 5 timer om dagen	☐
½ - 1 time om dagen	☐
Mindre end ½ time om dagen	☐
0 timer	☐

Alkohol

19. **Har du drukket alkohol inden for <u>de seneste 12 måneder</u>?**

Ja	☐	
Nej	☐	→ Gå til spørgsmål 29

20. **Har du inden for <u>de seneste 12 måneder</u> følt, at du burde nedsætte dit alkoholforbrug?**

Ja	☐	Nej	☐

21. **Er der nogen, inden for <u>de seneste 12 måneder</u>, der har "brokket" sig over, at du drikker for meget?**

Ja	☐	Nej	☐

22. **Har du inden for <u>de seneste 12 måneder</u> følt dig skidt tilpas eller skamfuld på grund af dine alkoholvaner?**

Ja	☐	Nej	☐

23. **Har du inden for <u>de seneste 12 måneder</u> jævnligt taget en genstand som det første om morgenen for at "berolige nerverne" eller blive "tømmermændene" kvit?**

Ja	☐	Nej	☐

24. **Hvor mange dage om ugen drikker du alkohol?**

0-1 dag	2 dage	3 dage	4 dage	5 dage	6 dage	7 dage
☐	☐	☐	☐	☐	☐	☐

25. Drikker du alkohol uden for måltiderne på hverdage?

Ja	☐	Nej	☐

26. Hvor mange genstande drikker du typisk på hver af dagene i løbet af ugen?
Start med mandag og tag en dag ad gangen (udfyld alle felter, også selv om svaret er 0).

	Antal genstande		
	Øl eller alkoholcider	Vin eller hedvin	Spiritus eller alkoholsodavand
Mandag	☐☐	☐☐	☐☐
Tirsdag	☐☐	☐☐	☐☐
Onsdag	☐☐	☐☐	☐☐
Torsdag	☐☐	☐☐	☐☐
Fredag	☐☐	☐☐	☐☐
Lørdag	☐☐	☐☐	☐☐
Søndag	☐☐	☐☐	☐☐

1 genstand = 1 almindelig øl
1 glas rød-/hvidvin
1 glas hedvin
1 drink/cocktail
1 snaps/shot
1 alkoholsodavand
1 alkoholcider

1 flaske rød-/hvidvin = 6 genstande
1 flaske hedvin = 10 genstande
1 flaske spiritus = 20 genstande

27. Hvor tit drikker du 5 genstande eller flere ved samme lejlighed?

	(Kun ét X)
Næsten dagligt eller dagligt	☐
Ugentligt	☐
Månedligt	☐
Sjældent	☐
Aldrig	☐

28. Vil du gerne nedsætte dit alkoholforbrug?

(Kun ét X)

Ja	☐	Nej	☐	Ved ikke	☐

Kost

Sæt X ved de svar, som passer bedst til dine kostvaner.

29. Hvor ofte spiser du brød med følgende slags fedtstof på?

(Sæt ét X i hver linje)	Mere end 2 gange om dagen	1-2 gange om dagen	4-6 gange om ugen	1-3 gange om ugen	Sjældnere/ aldrig
Smør, Kærgården eller tilsvarende	☐	☐	☐	☐	☐
Minarine eller plantemargarine	☐	☐	☐	☐	☐
Fedt	☐	☐	☐	☐	☐
Spiser brød uden fedtstof på	☐	☐	☐	☐	☐

30. Hvor ofte spiser du følgende slags pålæg?

(Sæt ét X i hver linje)	Mere end 2 gange om dagen	1-2 gange om dagen	4-6 gange om ugen	1-3 gange om ugen	Sjældnere/ aldrig
Pålæg, kød	☐	☐	☐	☐	☐
Fiskepålæg	☐	☐	☐	☐	☐
Æg	☐	☐	☐	☐	☐
Pålægssalater eller mayonnaisesalater	☐	☐	☐	☐	☐

31. Hvor ofte spiser du følgende slags varm mad?

(Sæt ét X i hver linje)	Mere end 1 gang om dagen	5-7 gange om ugen	3-4 gange om ugen	1-2 gange om ugen	Sjældnere/ aldrig
Kød (okse, kalv, svin eller lam)	☐	☐	☐	☐	☐
Fjerkræ (f.eks. kylling, kalkun, and)	☐	☐	☐	☐	☐
Fisk	☐	☐	☐	☐	☐
Grøntsags- eller vegetarretter	☐	☐	☐	☐	☐

32. Hvor ofte spiser du følgende slags grøntsager?

(Sæt ét X i hver linje)	Mere end 1 gang om dagen	5-7 gange om ugen	3-4 gange om ugen	1-2 gange om ugen	Sjældnere/ aldrig
Blandet salat, råkost	☐	☐	☐	☐	☐
Andre rå grøntsager	☐	☐	☐	☐	☐
Tilberedte grøntsager (kogte, bagte, stegte, sammenkogte eller wokretter)	☐	☐	☐	☐	☐

33. Hvor ofte bruger du eller andre i din husholdning følgende slags fedtstof i madlavningen?

(Sæt ét X i hver linje)	Mere end 1 gang om dagen	5-7 gange om ugen	3-4 gange om ugen	1-2 gange om ugen	Sjældnere/ aldrig
Stegemargarine	☐	☐	☐	☐	☐
Plantemargarine	☐	☐	☐	☐	☐
Smør, Kærgården og lignende	☐	☐	☐	☐	☐
Fedt/palmin	☐	☐	☐	☐	☐
Olivenolie	☐	☐	☐	☐	☐
Majs-, solsikke- eller vindruekerneolie	☐	☐	☐	☐	☐
Rapsolie, madolie, salatolie	☐	☐	☐	☐	☐
Laver mad uden fedtstof	☐	☐	☐	☐	☐

Hvis du ikke ved det, f.eks. fordi du får mad udefra, sæt X her ☐

34. Hvor mange portioner frugt plejer du at spise?

1 portion = 1 stk eller 1 dl – medregn også frugtgrød og frugtmos

(Kun ét X)

Mere end 6 om dagen	5-6 om dagen	3-4 om dagen	1-2 om dagen	5-6 om ugen	3-4 om ugen	1-2 om ugen	Ingen
☐	☐	☐	☐	☐	☐	☐	☐

35. Vil du gerne spise mere sundt?

(Kun ét X)

Ja ☐ Nej ☐ Ved ikke ☐

Bevægelse i dagligdagen

Fysisk aktivitet i fritiden

De følgende spørgsmål handler om, hvor fysisk aktiv du er i din fritid og ved transport (inkl. transport til og fra arbejde/skole/uddannelse).

36. På en typisk uge, hvor meget tid bruger du i alt på moderat og hård fysisk aktivitet, hvor du kan mærke pulsen og vejrtrækningen øges (det kan f.eks. være rask gang, cykling som transport eller motion, tungt havearbejde, løb eller motionsidræt)?
Medtag kun aktiviteter, der varer i mindst 10 minutter ad gangen.

☐☐ timer og ☐☐ minutter pr. uge

37. Hvor meget af den tid, du ovenfor angav at bruge på fysisk aktivitet på en typisk uge, bruger du i alt på hård fysisk aktivitet? Det er aktiviteter, som øger pulsen væsentligt, får dig til at svede og gør dig så forpustet, at det er svært at tale (det kan f.eks. være svømning, løb, cykling i højt tempo, konditionstræning, hård styrketræning eller boldspil).
Medtag kun aktiviteter, der varer i mindst 10 minutter ad gangen.

☐☐ timer og ☐☐ minutter pr. uge

Stillesiddende tid

38. På en typisk hverdag/arbejdsdag, hvor meget tid bruger du på at sidde ned i hver af de følgende situationer?
Du skal tænke på din samlede siddetid og fordele den på de angivne kategorier.

	På en hverdag/arbejdsdag		
(Udfyld alle felter)	Timer	og	minutter
Transport (f.eks. i bil, bus eller tog. Medregn ikke cykling)	☐☐		☐☐
Arbejde/skole/uddannelse (f.eks. siddende ved skrivebord eller til møde)	☐☐		☐☐
Fritid: ved skærm (f.eks. TV, computer, tablet, smartphone)	☐☐		☐☐
Fritid: andet (f.eks. måltider, læsning, socialt samvær)	☐☐		☐☐

39. Vil du gerne være mere fysisk aktiv?

Ja ☐ Nej ☐ Ved ikke ☐

Højde og vægt

40. Hvor høj er du (uden sko)?

Skriv højde ☐☐☐ cm (f.eks. 172 cm)

41. Hvor meget vejer du i <u>hele</u> kg (uden tøj)?

Skriv vægt ☐☐☐ kg	

42. Hvordan vurderer du selv din vægt?

	(Kun ét X)
Alt for lav	☐
Lidt for lav	☐
Tilpas	☐
Lidt for høj	☐
Alt for høj	☐

43. Vil du gerne tabe dig?

	(Kun ét X)
Ja, i høj grad	☐
Ja, i nogen grad	☐
Nej	☐
Ved ikke	☐

Kontakt med sundhedsvæsenet

44. Har du været ved din <u>egen læge</u> i løbet af <u>de seneste 12 måneder</u>?

	(Kun ét X)	
Ja	☐	
Nej	☐	→ Gå til spørgsmål 46

45. Har din <u>egen læge</u> i løbet af <u>de seneste 12 måneder</u> rådet dig til:

(Sæt ét X i hver linje)	Ja	Nej	Kan ikke huske/ ved ikke
At holde op med at ryge	☐	☐	☐
At tabe dig	☐	☐	☐
At tage på i vægt	☐	☐	☐
At dyrke motion	☐	☐	☐
At nedsætte dit alkoholforbrug	☐	☐	☐
At ændre dine kostvaner	☐	☐	☐
At tage den med ro	☐	☐	☐

Kontakt med andre mennesker

46. Hvor ofte er du i kontakt med venner, bekendte og familie, som du ikke bor sammen med?
(Med kontakt menes der, at I er sammen, taler i telefon sammen, skriver til hinanden m.v.)

(Sæt ét X i hver linje)	Dagligt eller næsten dagligt	1 eller 2 gange om ugen	1 eller 2 gange om måneden	Sjældnere end 1 gang om måneden	Aldrig
Familie, som du ikke bor sammen med	☐	☐	☐	☐	☐
Venner	☐	☐	☐	☐	☐
Kolleger eller studiekammerater i fritiden	☐	☐	☐	☐	☐
Naboer eller beboere i dit lokalområde	☐	☐	☐	☐	☐
Personer, du mest kender fra internettet (mail, sociale medier og lignende)	☐	☐	☐	☐	☐

47. Sker det nogensinde, at du er alene, selvom du mest har lyst til at være sammen med andre?

	(Kun ét X)
Ja, ofte	☐
Ja, en gang imellem	☐
Ja, men sjældent	☐
Nej	☐

48. Har du nogen at tale med, hvis du har problemer eller brug for støtte?

	(Kun ét X)
Ja, altid	☐
Ja, for det meste	☐
Ja, nogen gange	☐
Nej, aldrig eller næsten aldrig	☐

Personlige forhold

49. Bor du sammen med andre?

(Sæt ét X i hver linje)	Ja	Nej
Jeg bor sammen med ægtefælle/samlever/kæreste	☐	☐
Jeg bor sammen barn/børn under 16 år	☐	☐
Jeg bor sammen med andre på 16 år eller derover	☐	☐

50. Hvilken skoleuddannelse har du?

	(Kun ét X)
Går stadig i skole	☐
7 eller færre års skolegang	☐
8-9 års skolegang	☐
10-11 års skolegang	☐
Studenter-, HF-eksamen (inkl. HHX, HTX)	☐
Andet (herunder udenlandsk skole)	☐

51. Har du fuldført en uddannelse udover en skole- eller ungdomsuddannelse?

	(Kun ét X)
Nej	☐
Et eller flere kortere kurser *(f.eks. specialarbejderkurser, arbejdsmarkedskurser m.v.)*	☐
Erhvervsfaglig uddannelse/faglært *(f.eks. kontor- eller butiksassistent, frisør, murer, lægesekretær, social- og sundhedshjælper/assistent, landmand)*	☐
Kort videregående uddannelse, 2-3 år *(f.eks. markedsøkonom, politibetjent, laborant, maskintekniker, datamatiker, multimediedesigner, økonoma, tandplejer)*	☐
Mellemlang videregående uddannelse, 3-4 år *(f.eks. folkeskolelærer, socialrådgiver, bygningskonstruktør, sygeplejerske, fysioterapeut, diplomingeniør, pædagog, bachelor)*	☐
Lang videregående uddannelse, mere end 4 år *(f.eks. civilingeniør, cand.mag., læge, psykolog)*	☐
Anden uddannelse	☐

52. Er du under uddannelse?

Ja	☐
Nej	☐

53. Er du i arbejde?

Ja	☐
Nej	☐