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

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Conflicts of interest

Gitte Valentin, Sofie Emilie Pedersen, Robin Christensen, Karina Friis, Camilla Palmhøj Nielsen, Arti Bhimjiyani, Celia L Gregson, Bente L Langdahl declare that they have no conflicts of interest.

Abstract

Purpose: 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-analysed using a standard inverse-variance-weighted random effects model. Studies using individual-level and area-based SES measures were analysed 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 one 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, Socio-economic status, inequality, mortality, Health Related Quality of Life.

Mini abstract

Individuals with low socio-economic status (SES) have a higher risk of dying following hip fracture compared to 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.

Background

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 14-36% within one year of the injury, and the risk of dying is increased up to eight-fold within the first three 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 program 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 tumors, 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 standardised 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 recalculated 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 days 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; i.e. 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 Certainty 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: (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 certainty of the evidence was assessed using the 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 **Figure 1**, the database searches yielded 7,086 potential references. Seven additional references were identified through other sources. After removing duplicates, 5,235 references remained. These references were screened for eligibility and 5,160 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 one 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 (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 **Figure 2**. Figure 2A 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 Figure 2B. 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 to 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-3 L 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 **Figure 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 was 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 summarised 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 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 minimise 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 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 to 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 co-morbidity. 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 > 1,000 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 marginalisation. 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 years 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 are 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 US, 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 co-morbidity 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.

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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.

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Supplementary material

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