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Anaemia Is Associated with an Increased Risk of Fractures, a Systematic Review, and Meta-Analysis

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Keywords
Older adults · Fracture risk · Bone · Anaemia

Abstract
Background: Anaemia and osteoporotic fractures are both major health problems among older adults worldwide. ***Objectives:*** Previous studies suggest that anaemia may be associated with elevated fracture risk among older adults; however, the exact relationship between them is unknown. We aimed to investigate the association between anaemia and fracture risk. ***Methods:*** A comprehensive literature search was performed in four medical databases. We included articles that were published from inception to February 18, 2021. Odds ratios (ORs), hazard ratios (HRs) with 95% confidence intervals (CIs), and original raw incidences from studies comparing fracture rates in anaemic versus non-anaemic patients were extracted and pooled with the random-effects model. I^2 test was used to assess heterogeneity. Risk of bias assessment was performed using the Quality of Prognostic Studies tool. PROSPERO: CRD42021241109. ***Results:*** A total of 13 studies were identified; 8 of them were included in the quantitative synthesis. Anaemia was found to be a risk factor for fracture compared to non-anaemia. Anaemia increased hip fracture risk in both older men (HR = 1.71; CI: 1.46–2.00, $p < 0.001$, $I^2 = 83.2\%$) and women (HR = 1.31; CI: 1.13–1.52, $p < 0.001$), but the fracture risk was more increased among men. There was also an increased chance of hip fracture in the presence of anaemia in populations, including both older men and women (OR = 1.64; CI: 1.35–2.01, $p < 0.001$, $I^2 = 61.1\%$). Anaemia was also associated with increased vertebral (HR = 1.21; CI: 1.04–1.40, $p = 0.012$) and all-type (HR = 1.49; CI: 1.19–1.86, $p < 0.001$) fracture risk in older men. ***Conclusion:*** Our results suggest that there is a significant relationship between anaemia and fracture risk in older adults. This association is stronger among older men than women and differs in the different types of fractures.

Introduction

In the 21st century, life expectancy has been increasing in developed countries [1], and as a result, the number of older adults is growing rapidly. Anaemia has an estimated prevalence of approximately 25% amongst them [2], resulting in increased mortality and morbidity [3], making it a global health problem.

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Osteoporotic fractures are a significant health burden in older adults [4]. They have several negative consequences, such as impaired quality of life and decreased mental and physical health, and ultimately are associated with high mortality rates [5]. A large retrospective cohort study by Guzon-Illescas et al. [6] revealed that octogenarian patients admitted to hospital with osteoporotic fracture have 10% and 30% mortality rates in 1 month and 1 year, respectively.

Based on previous research, anaemia is associated with different comorbidities, leading to increased fracture risks in older adults, such as impaired physical performance, muscle strength [7], and cognitive functions [8]. In addition, it is also hypothesized that anaemia can lead to decreased bone mineral density (BMD) [9]. These results suggest that anaemia may also be associated with elevated fracture risk in older adults.

Many previous studies investigated the relationship between anaemia and fracture risk, but their results were non-cohesive and heterogeneous. For example, some studies suggested no significant relationship between anaemia and fracture risk in certain circumstances; others reported increased fracture risk without exception [10, 11].

A meta-analysis was published by Teng et al. [12], which drew many conclusions on the association between anaemia and fracture risk. However, their methods did not follow the Cochrane Handbook's recommendations, and their search did not fulfil the criteria of a systematic review. Thus, there remains a question of whether anaemia is associated with an increased risk of fractures and the magnitude of the risk. Based on the abovementioned contradicting studies in the literature, this systematic review and meta-analysis aimed to provide more detailed, comprehensive, and up-to-date information on the association between anaemia and the risk of fractures to improve fracture risk stratification in clinical practice.

Methods

Protocol

A systematic review and meta-analysis were reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement [13]. The PRISMA checklist is shown in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000522591). The review was registered in advance on PROSPERO with the registration number CRD42021241109.

Data Sources and Searches

We systematically searched MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from inception to February 18, 2021. We did not apply any filters (e.g., language, human) or restrictions. Search key was (anemia OR anaemia OR haemoglobin OR hemoglobin) AND (fracture).

Study Selection

Records were managed by EndNote X7.4 (v.7) software (Clarivate Analytics, Philadelphia, PA, USA). After excluding duplicates, two independent authors (E.T. and N.V.) screened the remaining studies by title, abstract, and finally full text. Disagreements were resolved by consensus and the involvement of the senior review author (B.E.). We manually searched the primarily eligible studies' or relevant reviews' reference lists to identify all relevant articles.

Eligibility Criteria

We included studies with the following criteria: (1) the study was conducted in the adult population, (2) the exposure of interest was anaemia, (3) non-anaemic subjects served as control, (4) and sufficient data on the risk or the number of hip, vertebral, non-vertebral, or all-type fractures (outcome) in both the anaemic and non-anaemic groups were provided. Full-text articles and conference abstract with sufficient data were considered eligible.

Data Extraction

Data were extracted independently by two investigators (E.T. and N.V.) and manually populated into a purpose-designed Excel 2016 sheet (Office 365, Microsoft, Redmond, WA, USA). Data were collected on the first author, year of publication, study location, study design, period of enrolment, follow-up period, study population, number of enrolled patients, mean age of the enrolled patients, and most importantly on the number of anaemic and non-anaemic patients. Odds ratios (ORs) or hazard ratios (HRs) and their respective 95% confidence intervals (CIs) from individual studies were extracted. In the case of studies without the OR or HR of fractures, original raw incidences were collected and then ORs with corresponding 95% CIs were calculated. In the case of the studies in which there were multiple HR values with different adjustments, we chose the HRs with the most adjustments, considering the adjustments in other studies with the same outcome. Disagreements were resolved by consensus and the involvement of the senior review author (B.E.).

Risk of Bias and Applicability

We used the Quality of Prognostic Studies tool to assess the quality of the cohort studies [14], and the result of the assessment was graphically demonstrated. The risk of bias was assessed independently by two investigators (E.T. and N.V.). Disagreements were resolved by consensus and the involvement of the senior review author (B.E.). We planned to assess the publication bias by Begg's test and Egger's test, but it could not be performed due to the limited number of eligible studies for the different outcomes.

Statistical Analysis

We calculated Cohen's kappa [15] coefficient to measure the agreement between two raters (E.T. and N.V.) at three levels (title, abstract, and full text) of the selection process. For data synthesis, we used the methods recommended by the working group of the

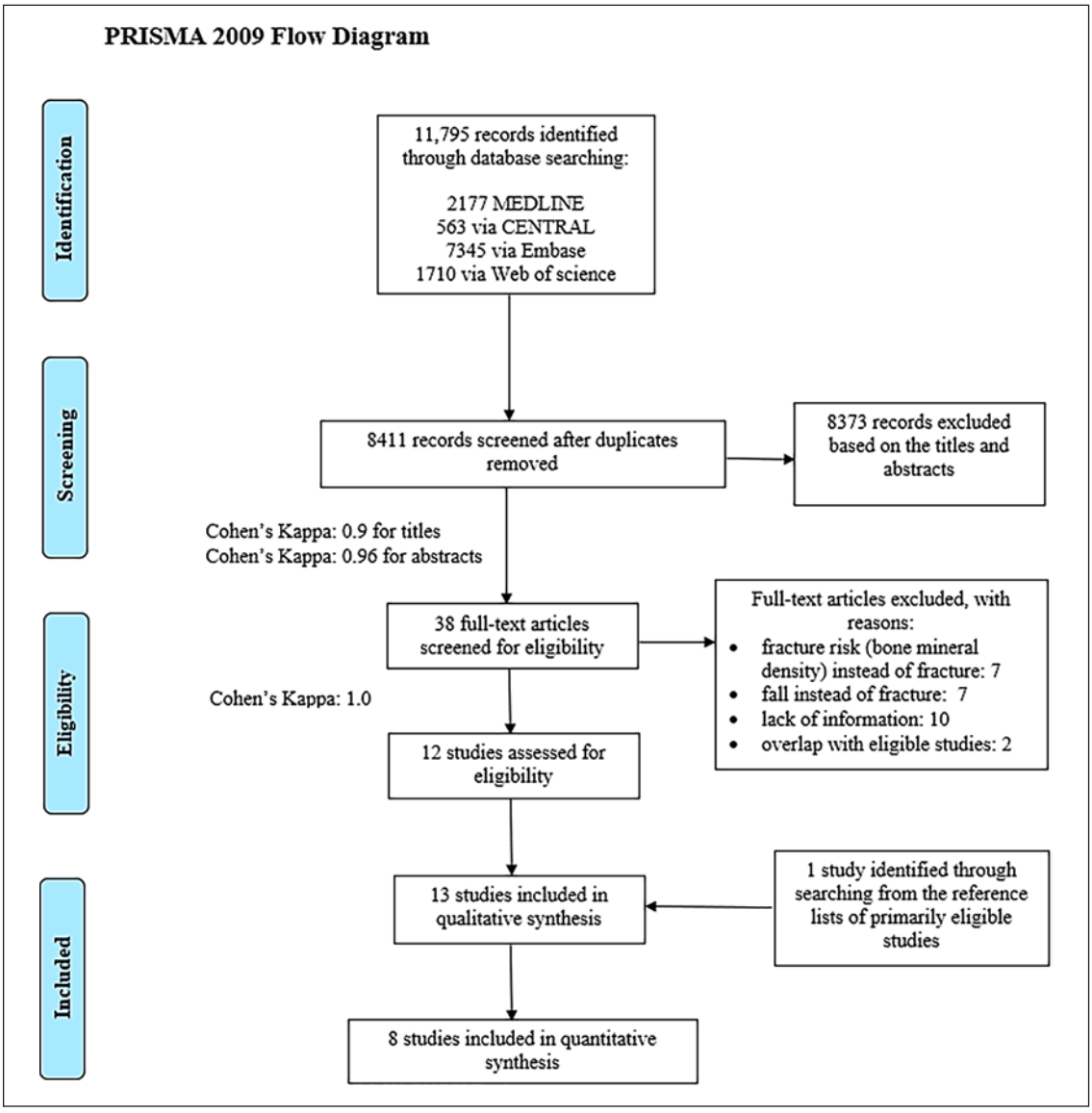

Fig. 1. PRISMA flow diagram of the screening and selection process.

Cochrane collaboration [16]. The natural logarithm of ORs and HRs and their 95% CIs were used to estimate the overall effect. To graphically display the result in forest plots, the original ORs and HRs were used. We used the random-effect model by DerSimonian and Laird [17] in all analyses. We used the I^2 statistics to assess heterogeneity amongst the included studies. I^2 statistic represents the percentage of the total variability across studies: 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity. We considered the Q test significant if $p<0.1$. All analyses were performed in Stata (v16; StataCorp, College Station, TX, USA).

Results

Study Selection of the Included Studies

A total of 11,795 studies were identified through database searching. After removing the duplicates, a total of 8,411 studies remained. Based on the screening process for the title, abstract, and full-text eligibility, and 8,399 studies were excluded. One additional study was identified from the reference lists of primarily eligible studies. Finally, our qualitative synthesis consisted of 13 studies [10, 11, 18–28], and eight of them [11, 18, 19, 21, 23, 26–

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Table 1. Characteristics of the included studies

Author	Year	Country	Study design	Follow-up, years	Definition of anaemia	Population	Anaemic patients, *n*	Non-anaemic patients, *n*	Type of fractures			
									hip	vertebral	non-vertebral	all-type
Chen et al. [18]	2010	USA	Prospective cohort	Average 7.8	Haemoglobin level <12 g/dL	Postmenopausal women mean age: 63.2	8,739	151,341	x	x	–	x
Dharmarajan et al. [19]	2004	USA	Retrospective cohort	min 3	Haemoglobin level <13 g/dL in men; <12 g/dL in women	≥65 older adults	2,729	7,648	x	–	–	–
Goerss et al. [20]	1992	USA	Retrospective cohort	Average 11.8	+ Schilling test and low B12 level	Patients with newly diagnosed PA Mean age: 68.7	131	No data	x	x	–	–
Jorgensen et al. [10]	2009	Norway	Prospective cohort	Mean 8.3	Haemoglobin level <13 g/dL in men; <12 g/dL in women	Older adults between 55 and 74	182	5,104	–	–	x	–
Kristjansdottir et al. [21]	2019	Sweden	Prospective cohort	16	Haemoglobin level <13 g/dL	Older men between 70 and 81	66	939	x	x	x	x
Lee et al. [11]	2019	Korea	Retrospective cohort	Mean 8	Haemoglobin level <13 g/dL in men; <12 g/dL in women	≥65 older adults	10,568	61,568	x	x	–	x
Looker et al. [22]	2014	USA	Prospective cohort	No data	Haemoglobin values in decile	≥65 older adults	No data	No data	x	–	–	–
Merriman et al. [23]	2010	UK	Retrospective cohort	Mean 11.4	Diagnosis code	Patients with a diagnosis of PA mean age: 72	9,506	38,024	x	–	–	–
Poór et al. [24]	1995	USA	Retrospective case-control	No data	No data	Older men mean age: 78.5	96	368	x	–	–	–
Shin et al. [25]	2019	Korea	Retrospective cohort	Mean 4.5	Haemoglobin level <12 g/dL	Postgastrectomy gastric cancer survivors, mean age: 58.4	No data	No data	–	–	–	x
Valderrabano et al. [26]	2017	USA	Prospective cohort	Median 7.2	Haemoglobin level <12 g/dL	≥65 older men	249	3,382	–	x	x	x
Valderrabano et al. [27]	2021	USA	Prospective cohort	Median 11.8	Haemoglobin level <13 g/dL in men; <12 g/dL in women	>65 older adults	625	4,045	x	–	–	–
Zapatero et al. [28]	2013	Spain	Prospective cohort	No data	No data	Hospitalized medical patients' mean age: 81.52	306,112	1,828,251	x	–	–	–

USA, United States of America; UK, United Kingdom; PA, pernicious anaemia.

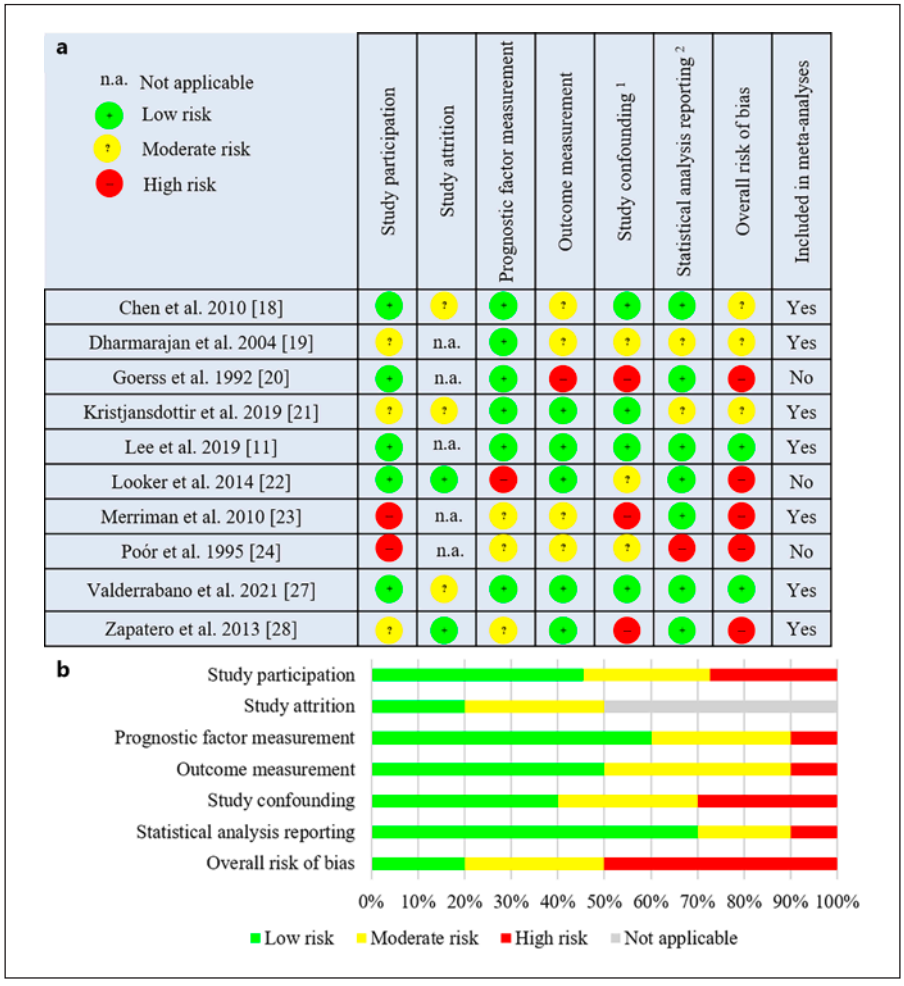

Fig. 2. Risk of bias assessment – hip fracture: risk of bias assessment on study level (**a**) and across studies (**b**).

28] were included in the quantitative synthesis. The study selection process with Cohen's kappa values summarized in a PRISMA flow chart is shown in Figure 1.

Study Characteristics

Characteristics of the studies included in our analysis are shown in Table 1. Eligible studies were reported between 1992 and 2021. The number of study participants ranged between 131 and 2,134,363. From the included 13 studies, seven were prospective [10, 18, 21, 22, 26–28], and six were retrospective [11, 19, 20, 23–25]. Across all the studies, seven were reported from the USA [18–20, 22, 24, 26, 27], two from Korea [11, 25], one from the UK [23], one from Spain [28], one from Norway [10], and one from Sweden [21]. Eleven of the studies were full-text articles [10, 11, 18, 20, 22–28], and two of them were conference abstracts [19, 21].

In eight of the 13 studies, the participants were community-dwelling older adults [10, 11, 18, 19, 21, 22, 26, 27], in two, patients diagnosed with pernicious anaemia [20, 23], in two, patients hospitalized with hip fracture [24, 28], and in one, postgastrectomy gastric cancer survivors [25]. Regarding the outcomes, ten studies detailed hip fracture [11, 18–24, 27, 28], five studies analysed vertebral fractures [11, 18, 20, 21, 26], three studies had non-vertebral fractures [10, 21, 26], and five studies had all type of fractures as an outcome [11, 18, 21, 25, 26].

Risk of Bias and Applicability Assessment

Among the ten studies with hip fracture as an outcome, 5 (50%) were considered high [20, 22–24, 28], 3 (30%) moderate [18, 19, 21], and 2 (20%) low risk [11, 27]. In the case of vertebral fracture from the five studies, 1 (20%) study was considered high [20], 2 (40%) moderate [18, 21], and 2 (40%) low risk [11, 26]. From the three studies with non-vertebral fracture as an outcome, 1 (33%) was considered moderate [21], and 2 (67%) were considered high risk [10, 26]. Finally, among the five

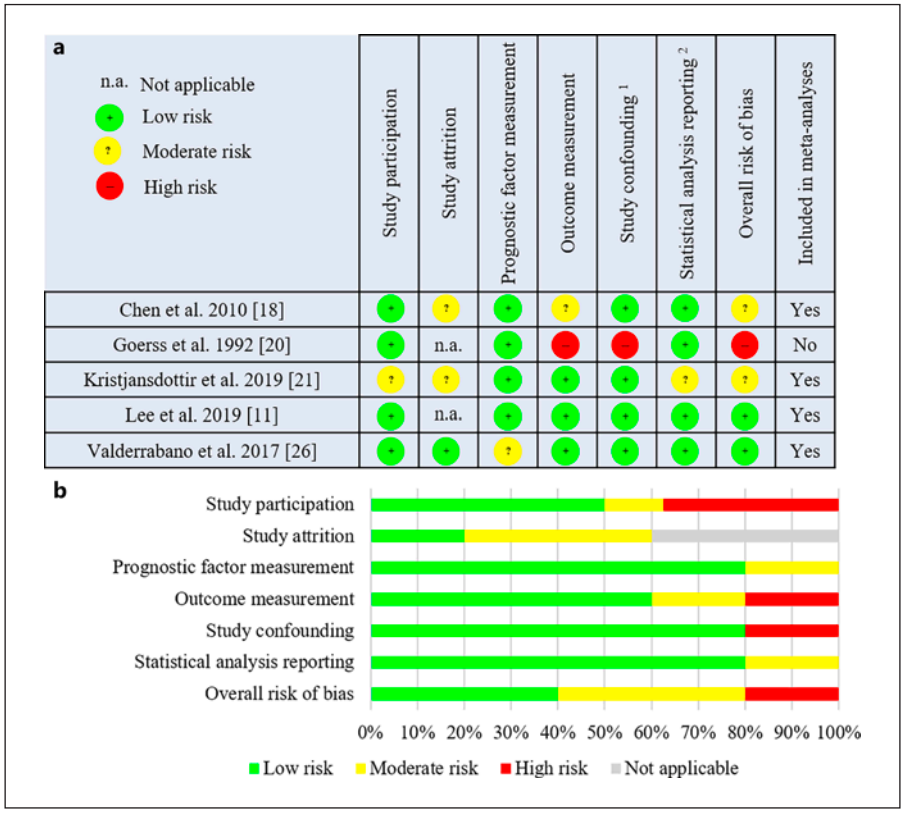

Fig. 3. Risk of bias assessment – vertebral fracture: risk of bias assessment on study level (**a**) and across studies (**b**).

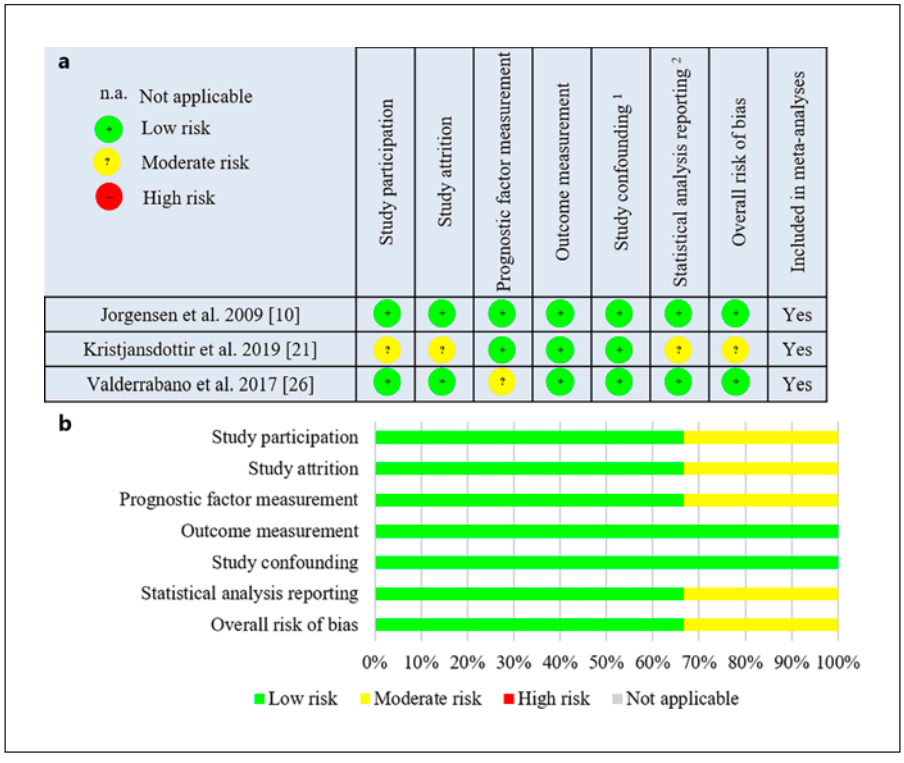

Fig. 4. Risk of bias assessment – non-vertebral fracture: risk of bias assessment on study level (**a**) and across studies (**b**).

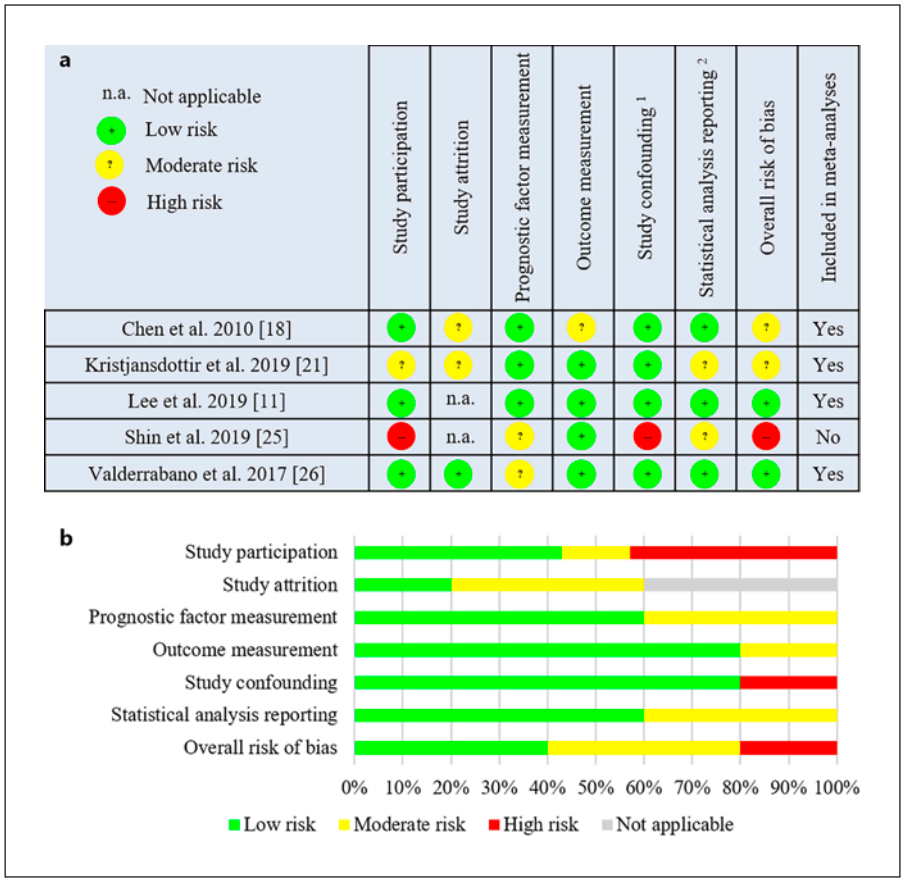

Fig. 5. Risk of bias assessment – all-type fracture: risk of bias assessment on study level (**a**) and across studies (**b**).

studies in which all-type fracture was the outcome, 1 (20%) was considered high [25], 2 (20%) moderate [18, 21], and 2 (20%) low risk [11, 26]. The results of the risk of bias assessment for each outcome are shown in Figures 2–5.

Results of the Systematic Review and Meta-Analysis

Hip Fracture

In our analysis, anaemia was associated with increased hip fracture risk in both older men (HR = 1.71; CI: 1.46–2.00; $p< 0.001$) (shown in Fig. 6) and women (HR = 1.31; CI: 1.13–1.52; $p< 0.001$) (shown in Fig. 6), but the association was stronger among men. There was also a significant relationship between anaemia and hip fracture in populations, including both older men and women (OR = 1.64; CI: 1.35–2.01; $p< 0.001$) (shown in Fig. 7). Moderate heterogeneity ($I^2 = 61.1\%$; $p< 0.08$) was observed for hip fractures in the case of populations, including both older men and women. There was no significant heterogeneity in the case of hip fractures in men or women.

The study by Looker [22] found that there is a non-linear, U-shaped relationship between hip fracture risk and haemoglobin values. In the presence of anaemia, there was an increased hip fracture risk (HR = 2.24; CI: 1.09–4.63), and higher haemoglobin values were also associated with elevated hip fracture risk (HR= 2.37; CI: 1.35–4.16).

We found three studies that investigated the relationship between pernicious anaemia and hip fracture risk. In all three studies, there was an elevated fracture risk in the presence of pernicious anaemia. In the study by Merriman et al. [23], the risk for hip fracture in older patients with pernicious anaemia was HR = 1.74 (CI: 1.45–2.08). In the study by Poór et al. [24], the risk was OR = 3.8 (CI: 1.2–11), and in the study by Goerss et al. [20], it was standardized morbidity ratio = 1.9 (CI: 1.2–3.0).

Vertebral Fracture

In older men, anaemia was associated with increased vertebral fracture risk (HR = 1.21; CI: 1.04–1.40; p = 0.012) (shown in Fig. 8). No significant heterogeneity was observed.

We could not perform a statistical analysis in the case of women because of the limited number of eligible stud-

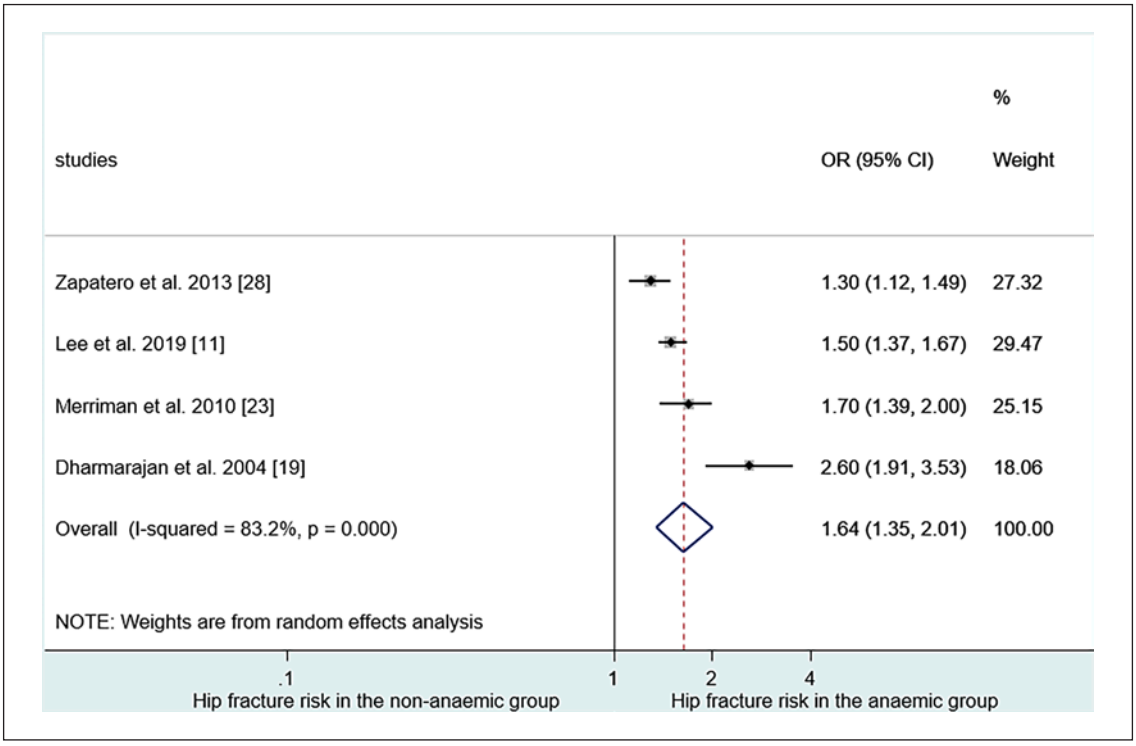

Fig. 6. Forest plot of anaemia associated with hip fractures in older men and women.

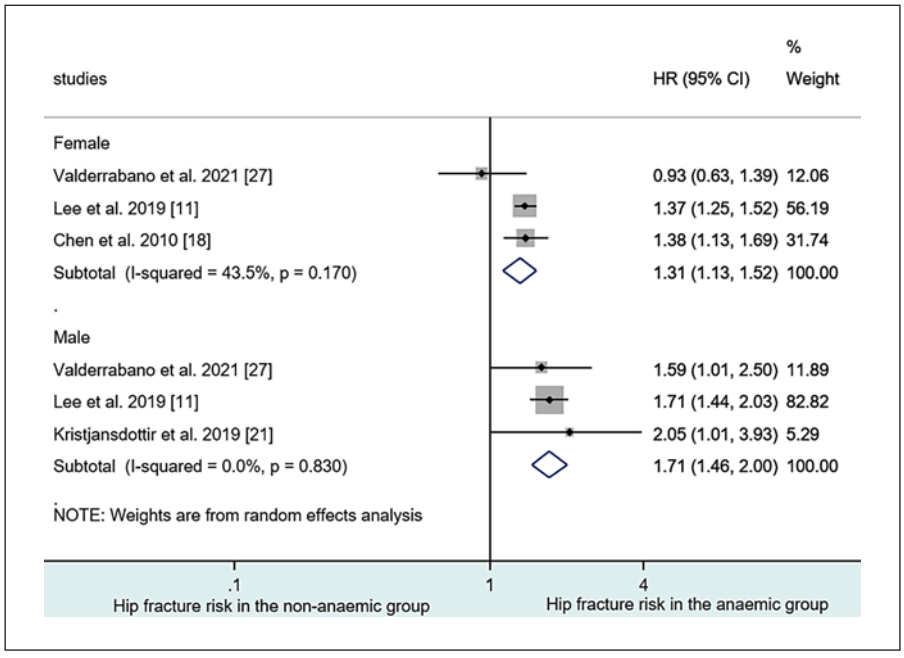

Fig. 7. Forest plot of anaemia associated with hip fractures in populations including both older female and male patients.

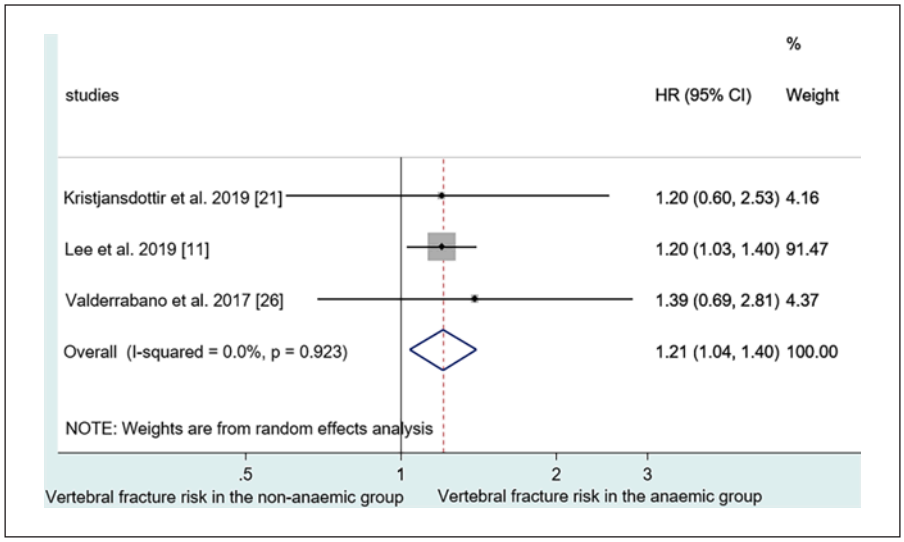

Fig. 8. Forest plot of anaemia associated with vertebral fractures in older men.

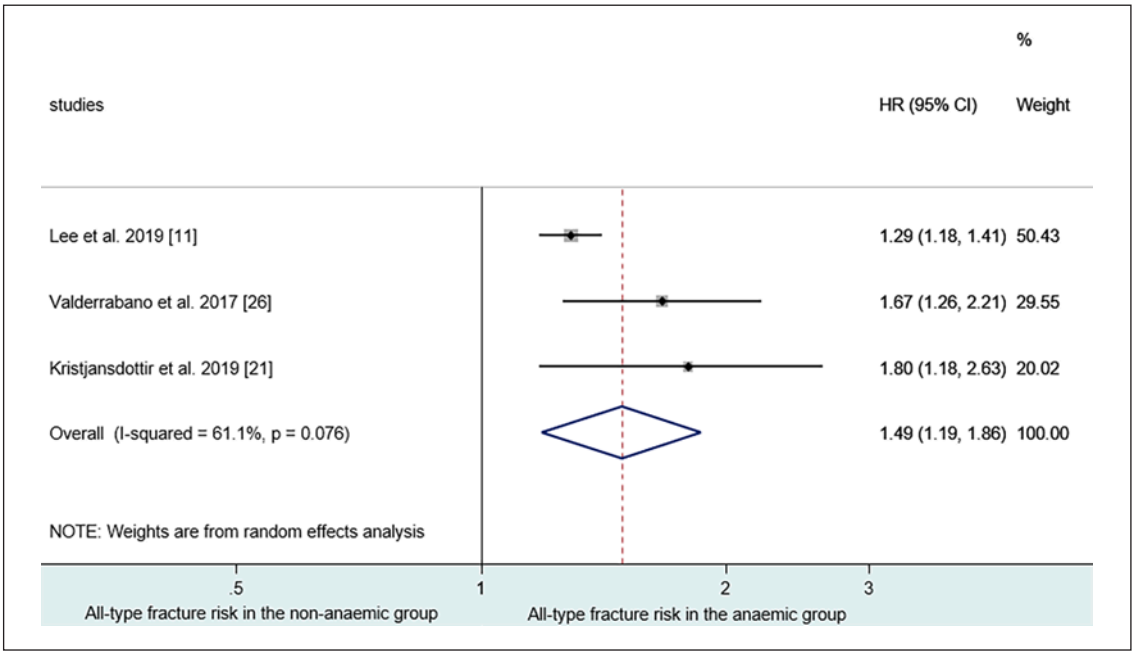

Fig. 9. Forest plot of anaemia associated with all-type fractures in older men.

ies; however, both studies that examined the relationship between anaemia and vertebral fracture risk among women found elevated fracture risk in the anaemic population. In the study by Lee et al. [11], the risk of vertebral fractures in anaemic women was HR = 1.11 (CI: 1.03–1.20), and in the study by Chen et al. [18], it was HR = 1.30 (CI: 1.09–1.55).

Non-Vertebral Fracture

Three studies examined the relationship between anaemia and non-vertebral fracture risk. In the study by Kristjansdottir et al. [21], the results showed increased non-vertebral fracture risk among men with anaemia (HR = 1.8; CI: 1.05–3.15). In the study by Valderrabano et al. [26], 2017, the results also suggested that there is a significant relationship between anaemia and non-verte-

bral fracture risk in older men (HR = 1.7; CI: 1.25–2.31). Finally, in the study by Jorgensen et al. [10], they found that in the study population, anaemia was associated with increased non-vertebral fracture risk in men (risk ratio [RR] = 2.15; CI: 1.18–3.92), but amongst women (RR = 0.98; CI: 0.57–1.67), there was no significant relationship between anaemia and non-vertebral fracture risk.

All-Type Fracture

In older men, anaemia was also associated with increased all-type fracture risk (HR = 1.49; CI: 1.19–1.86; $p< 0.001$) (shown in Fig. 9). High heterogeneity (I^2 = 83.2%; $p< 0.001$) was observed.

In the case of women, we could not perform statistical analysis; however, both eligible studies found elevated all-type fracture risk in anaemic women. In the study by Lee et al. [11], the risk was HR = 1.10 (CI: 1.04–1.16), and in the study by Chen et al. [18], it was HR = 1.07 (CI: 1.01–1.14).

In the study by Shin et al. [25], they investigated the relationship between anaemia and all-type fracture risk in postgastrectomy gastric cancer survivors. They found that there was also a significant relationship between anaemia and all-type fracture risk (HR = 1.34; CI: 1.13–1.59).

In the study by Lee et al. [11], they investigated the association between anaemia and all-type, vertebral, and hip fracture risk individually, in both older men and women. The association between anaemia and fracture risk was more substantial in all three types of fractures in men than women.

Discussion

Our systematic review and meta-analysis aimed to investigate the association between anaemia and fracture risk in older adults. We found that anaemia was associated with increased hip fracture risk in older men and women, compared to non-anaemic subjects. However, the association was stronger in men. In the studies with male and female participants, we also found an elevated fracture risk in the anaemic population. Furthermore, there was a significant association between anaemia and fracture risk in older men in the case of vertebral and all-type fractures. We could not perform a meta-analytical calculation in the case of older women due to the limited number of eligible studies. Still, the studies included in the qualitative synthesis suggested increased vertebral and all-type fracture risk in this population. In the case of non-vertebral fractures, there was an elevated risk in men in the presence of anaemia. However, there was no significant relationship between anaemia and non-vertebral fracture risk in women.

Anaemia is a public health problem worldwide. After the age of 50, the prevalence of anaemia increases with advancing age and exceeds 20% in those 85 and older [29]. Likewise, the incidence and prevalence of fractures increase with age [4]. Both are major health problems in older adults, but the exact association between them is unknown.

It is hypothesized that anaemia results in consequent BMD loss. Still, there are contradicting individual studies in the literature regarding the fact that this is the reason behind the elevated fracture risk in the presence of anaemia [9, 30]. The study by Valderrabano et al. [26], 2017, found that even after adjusting for BMD loss, there was an increased fracture risk in the anaemic population. Anaemia itself has several other consequences throughout it and could potentially increase fracture risk, for example, reduced muscle strength, impaired physical function [7], fatigue [31], or cognitive impairment [32].

Previous meta-analyses showed that anaemia is also associated with increased frailty in older adults, independent of the presence of other comorbidities [33]. It is also hypothesized that there is an increased risk for fractures in the presence of frailty. In the meta-analysis by Chen et al. [34], the risk of fracture in frail people (HR = 1.67; CI: 1.46–1.91) and prefrail people (HR = 1.28; CI: 1.16–1.40) was significantly higher than those people with a robust physical condition (HR = 1.30; CI: 1.20–1.41). These results could also partially explain the association between anaemia and fracture risk since the incidence of frailty is approximately 40% among older adults [35].

Our findings suggest that the association between anaemia and fracture risk is stronger amongst men than women. Jorgensen et al. [10] considered that sex hormones could be the reason behind it, but in their subgroup analysis after the adjustment for testosterone, the association between anaemia and fracture risk was not statistically significant. However, there are contradicting studies in the literature on whether low testosterone level is associated with BMD loss or not [36, 37]. Current observational studies described a decreased circulating testosterone level in men with advanced age, resulting in impaired bone quality and bone geometry, causing weakened bone strength. In a placebo-controlled, double-blind trial, the Testosterone Trial, 1-year testosterone treatment was associated with increased BMD of trabecular bone in the hip and the spine. Testosterone can also affect

body composition, meaning impaired androgen levels could increase fracture risk throughout a decline in muscle mass, causing impaired balance and increased risk of falls [37]. Moreover, it is known that testosterone increases haemoglobin levels via stimulating erythropoiesis directly. In the Testosterone Trial, testosterone treatment substantially increased the haemoglobin levels in older men with a known cause of anaemia [38]. These results suggest that lower testosterone levels in older men can increase fracture risk and worsen anaemia.

One of the other reasons behind the stronger association in men than women could be that osteoporosis is considered mainly the disease of older women, which leads to the fact that it often remains underdiagnosed and undertreated among older men. In the presence of anaemia, which already has several consequences, this untreated osteoporosis could lead to elevated fracture risk in older men.

Furthermore, the difference in physical activity in anaemic men and women could also play a stronger association between anaemia and fracture risk in older men than women. We noted that in the study populations, older anaemic men were more physically active than women. For example, in the study by Jorgensen et al. [10], 41% of the anaemic men were physically inactive, but among anaemic women, this number was almost 54%. In the study by Leet et al. [11], 20% of anaemic men did physical activity regularly, comparing that, among anaemic women, this number was only 12.9%. These results raise the possibility that in the older, vulnerable, multimorbid population, physical activity may be a risk factor for an increased risk of falls and fractures.

In addition to that, we found that in several studies, the average body mass index (BMI) was lower in the anaemic group than in the non-anaemic control group [10, 11, 22, 26]. The meta-analysis by Laet et al. [39], which included 60,000 men and women from 12 prospective population-based cohorts, found that compared with a BMI of 25 kg/m^2, a BMI of 20 kg/m^2 was associated with a nearly two-fold increase in RR (RR = 1.95; CI: 1.71–2.22) for hip fracture. Our results suggest that the same trend could also be observed in the presence of anaemia, and therefore, a higher BMI could potentially lower fracture risk in older adults.

Some of the studies suggest that besides sex, the race may also play an essential role in the relationship between anaemia and hip fracture risk in older adults. For example, Valderrabano et al. [27], 2021, found that the risk of hip fractures in white women was HR = 1.03 (CI: 0.73–1.45). Compared to that, in African American women, this number was HR = 2.74 (CI: 1.36–5.50). Furthermore, in the study by Chen et al. [18], where the study population included older multi-ethnic women in the African American group, anaemia's prevalence was three times higher than in the non-Hispanic white population.

Anaemia is not a well-defined disease itself. It has multiple classifications, aetiologies, and types. We are aware that it would be optimal to investigate the risk of fractures in the different types of anaemia individually (e.g., in iron deficiency anaemia, in pernicious anaemia, or anaemia of chronic diseases), but we had no opportunity for that due to lack of eligible studies.

The only specific type of anaemia which we had eligible studies on is pernicious anaemia. As mentioned above, all of the 3 studies [20, 23, 24], which investigated the association between pernicious anaemia and risk of fractures, reported increased fracture risk in the presence of the disease. Pernicious anaemia is caused by vitamin B12 deficiency, an essential factor in bone remodelling throughout DNA synthesis leading to BMD loss, partially explaining the association behind the elevated fracture risk [40]. Peripheral neuropathy, also caused by B12 deficiency, is characterized by paraesthesia, loss of perception, and reduced vibration sense in the lower extremities, which is a potential risk factor for falling, increasing the risk of fractures [41].

Even though our study focuses on the association between anaemia and fracture risk, we would like to highlight that multiple studies in the literature suggest that there is also an increased risk of falls in the presence of anaemia besides the elevated fracture risk. For example, Duh et al. [42] found that anaemia increased the risk of injurious falls by 1.66 (CI: 1.41–1.95) times in older adults.

Strengths of the Study

To the best of our knowledge, this is the largest and most comprehensive systematic review and meta-analysis which examined the relationship between anaemia and fracture risk. In contrast to the previous meta-analysis by Teng et al. [12] in 2020, instead of two, we searched in four medical databases. In addition, we examined the different types of fractures in the context of the patients' gender individually. Besides that, we found multiple studies that were not included in the meta-analysis mentioned above.

Limitations of the Study

Despite all the advantages, this study also had some limitations. In certain analyses, there was considerable statistical heterogeneity. The reason behind it could be

the clinical heterogeneity across studies. Most of the articles used the WHO definition for anaemia (haemoglobin values below 13 g/dL in men and below 12 g/dL in women, excluding pernicious anaemia); however, some did not define anaemia or used the 12 g/dL cut-off value regardless of sex. Moreover, despite the considerably high mean age in the studies, which was over 65 years in the anaemic group and over 63.7 years in the non-anaemic control groups in the studies included in the meta-analytical calculations, there was heterogeneity in the populations. Most articles included only community-dwelling older adults; however, some studies included hospitalized patients, postgastrectomy gastric cancer survivors, or patients with pernicious anaemia. Besides that, in many of the included articles, the risk of bias assessment was moderate or high, and some of the included studies were retrospective.

Implications for Clinical Practice

Our results help to improve fracture risk stratification and prevention in clinical practices. Based on our findings, physicians should be aware of the elevated fracture risk in anaemic patients, especially older men. We recommend that risk of fall and fracture assessment tools should potentially include anaemia.

Implication for Research

More high-quality research is needed to investigate the exact reasons behind the stronger association between anaemia and fracture risk in men than women, most likely in the context of different types of anaemia individually. Besides that, the role of physical activity in older anaemia adults and higher BMI as a possible preventive factor in this population could be studied further in comprehensive, large sample-size research. Finally, randomized controlled studies are needed to investigate whether increased screening and treatment of anaemia could reduce fracture risk in older adults.

Conclusion

We found that anaemia increases fracture risk in older men and women, but the association between anaemia and fracture risk was more significant among men than women. Thus, in clinical practice, older anaemic adults, especially older men, should be considered a high-risk group, and physicians should start fracture prevention treatment.

Statement of Ethics

No ethical approval was required for this review as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct, or interpretation of our review.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E.T., K.S., S.K., and P.H. conceptualized and designed the study in cooperation with B.E. S.K., H.A., and B.E. constructed the search query. N.V. and E.T. carried out the search process. N.V. and E.T. screened the articles for eligibility. N.V., B.T., and E.T. performed the data extraction. N.V., E.T., and B.E. conducted the risk of bias assessment. E.T., N.V., and B.E. wrote the article. A.V. carried out the statistical analysis. K.S., S.K., H.A., B.T., P.H., and A.V. provided valuable feedback after critically reviewing the first drafts of the manuscript. All authors contributed and approved the final manuscript for publication.

Data Availability Statement

All data generated or analysed during this study are included in this article and/or its online supplementary material files. Further enquiries can be directed to the corresponding author.

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