Hereditary hemochromatosis and risk of joint replacement surgery: a systematic review and meta-analysis

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Background/Objectives: Arthritis is a known manifestation of hereditary hemochromatosis. However, whether patients with hereditary hemochromatosis have an increased risk of having joint replacement surgery compared to the general population is still unknown. This meta-analysis was conducted to better characterize this risk.
Methods: A comprehensive literature review was conducted utilizing the MEDLINE and EMBASE databases through September 2019 to identify all cohort studies that compared prevalence or incidence of joint replacement surgery (hip, ankle, or knee) between patients with hereditary hemochromatosis and individuals without hereditary hemochromatosis. Effect estimates from each study were extracted and combined together using the random-effect, generic inverse variance method of DerSimonian and Laird.
Results: A total of five studies with 1 293 407 participants fulfilled the eligibility criteria and were included in the meta-analysis. Overall, the risk of having joint replacement surgery was significantly increased in patients with hereditary hemochromatosis compared to individuals without hereditary hemochromatosis with the pooled relative risk (RR) of 3.32 [95% confidence interval (CI), 1.60–6.86; I^2 88%]. Analysis by joint found a significantly increased risk of having hip and ankle replacement surgery among patients with hereditary hemochromatosis compared with the pooled RR of 2.62 (95% CI, 2.09–3.30; I^2 47%) and 8.94 (95% CI, 3.85–20.78; I^2 14%), respectively. The risk of having knee replacement surgery was also increased but was not statistically significant (pooled RR 1.57, 95% CI, 0.83–2.98; I^2 66%).
Conclusions: A significantly increased risk of needed joint replacement surgery among patients with hereditary hemochromatosis compared to patients without hereditary hemochromatosis was demonstrated in this study. Further studies are required to determine whether this association is causal. Eur J Gastroenterol Hepatol XXX: 00–00

Introduction

Hereditary hemochromatosis is an inherited autosomal recessive disorder of iron metabolism in which progressive iron overload leads to damage of multiple organs [1]. The most common cause of hereditary hemochromatosis is the C282Y homozygous mutation in the *homeostatic iron regulator (HFE)* gene on chromosome 6 [2]. For individuals of northern European descent, the prevalence of C282Y homozygosity is estimated to be 1 in 200 [3].

Joints are commonly affected by hereditary hemochromatosis; over two-third of patients with hereditary hemochromatosis report symptoms of arthralgia [4]. Quality of life is significantly impaired in a considerable number of patients with arthralgias related to hereditary hemochromatosis [5]. Arthritis could be the presenting symptom that leads to the diagnosis of hereditary hemochromatosis or could occur after the diagnosis is already established. Arthritis usually starts in the second and third metacarpophalangeal joints and may later progress to involve larger joints, particularly the wrists, knees, hips, and shoulders [6,7].

Interestingly, recent studies have suggested that patients with hereditary hemochromatosis may need joint replacement surgery more often than the general population although the results are inconsistent [7–11]. To better characterize this risk, the current systematic review and meta-analysis was conducted to comprehensively identify all studies that compared the risk of having joint replacement surgery between patients with hereditary hemochromatosis and individuals without hereditary hemochromatosis and summarize their results together.

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Methods

Information sources and search strategy

A systematic literature search of the MEDLINE and EMBASE databases was carried out from inception to September 2019 to identify all original studies that

compared the prevalence or incidence of joint replacement (hip, ankle, or knee) between patients with hereditary hemochromatosis and individuals without hereditary hemochromatosis. The systematic literature review was independently conducted by three investigators (K.W., P.P., and P.U.) using the search strategy that included the terms for 'hemochromatosis', 'joint replacement', 'replacement arthroplasty', 'ankle replacement', 'knee replacement', and 'hip replacement' as described in online supplementary data 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A513*. No language limitation was applied. This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement, which is provided as online supplementary data 2, Supplemental digital content 2, *http://links.lww.com/EJGH/A514*.

Selection criteria

To be eligible for this meta-analysis, the studies must consist of two groups of patients, one with hereditary hemochromatosis and one without hereditary hemochromatosis. Eligible studies must compare prevalence or incidence of hip, ankle, or knee replacement surgery between the groups. This comparison must be reported in the form of relative risk (RR), hazard ratio, or odds ratio. Diagnosis of hereditary hemochromatosis could be established clinically by medical providers or by genetic testing showing C282Y homozygosity. When more than one study utilizing the same database/cohort was available, only the study with the most comprehensive data/analyses was included.

Retrieved articles were reviewed for their eligibility independently by the same three investigators (K.W., P.P., and P.U.) with disagreements resolved by consensus. The Newcastle–Ottawa quality assessment scale for cohort study was used to appraise the quality of the studies in three domains, including the selection of participants, the comparability of the groups, and the ascertainment of the outcome of interest [12].

Data abstraction

The investigators used a structured information collection form to extract the following data from each study: title of the study, name of the first author, publication year, year or years of the study, country where the study was conducted, number of participants, demographics of participants, median follow-up time, methods used to diagnose hereditary hemochromatosis, type of measured outcomes (i.e. locations of the joint replacement surgery), adjusted effect estimates with 95% confidence interval (CI), and covariates that were adjusted in the multivariable analysis.

To ensure the accuracy, this data extraction process was independently performed by two investigators (K.W. and P.P.) and was reviewed by the senior investigator (P.U.).

Statistical analysis

Data analysis was performed using the Cochrane Collaboration's Review Manager 5.3 software (London, UK). Adjusted point estimates from each study were consolidated by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study for the pooled analysis in reverse to its variance [13]. In light of the high probability of high between-study variance because of the different background populations, random-effects model was chosen rather than fix-effects model. Analyses were conducted for overall risk and for each location. Cochran's Q test and I^2 statistic were used to quantify the between-study heterogeneity. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and more than 75% represents high heterogeneity [14]. Funnel plot was used for the assessment for the presence of publication bias.

Results

A total of 71 potentially eligible articles were identified using the described search strategy (30 from MEDLINE and 41 from EMBASE). After exclusion of 24 duplicated articles, titles, and abstracts, 47 unique articles were reviewed. Twenty-five articles were excluded at this stage because they were case reports, case series, correspondence, review articles, editorials, in-vitro studies or animal studies; this left 22 articles for full-text review. Seventeen of them were excluded after full-length review because they did not report the outcome of interest. Finally, five studies [7–11] with 1 293 407 participants were included in this meta-analysis. The literature retrieval, review, and selection process are shown in Fig. 1. The characteristics and quality appraisal of the included studies are presented in Table 1.

Hereditary hemochromatosis and overall risk of joint replacement surgery

The risk of having joint replacement surgery was significantly increased in patients with hereditary hemochromatosis compared to individuals without hereditary hemochromatosis with the pooled RR of 3.32 (95% CI, 1.60–6.86). The between-study heterogeneity was high with an I^2 of 88%. The forest plot of this meta-analysis is shown in Fig. 2.

Hereditary hemochromatosis and risk of knee, hip, and ankle replacement surgery

Subgroup analysis demonstrated that the risks of having hip and ankle replacement surgery were significantly increased in patients with hereditary hemochromatosis compared to individuals without hereditary hemochromatosis with the pooled RR of 2.62 (95% CI, 2.09–3.30; I^2 47%) and 8.94 (95% CI, 3.85–20.78; I^2 14%), respectively. The risk of having knee replacement surgery was also increased although was not statistically significant with the pooled RR of 1.57 (95% CI, 0.83–2.98; I^2 66%). The forest plots of the analyses of hip, ankle, and knee replacement surgery are shown in Figs 3–5, respectively.

Evaluation for publication bias

A funnel plot was constructed based on effect estimate and accuracy of each study to assess for the presence of publication bias (Fig. 6). The funnel plot was symmetric and was not suggestive of publication bias.

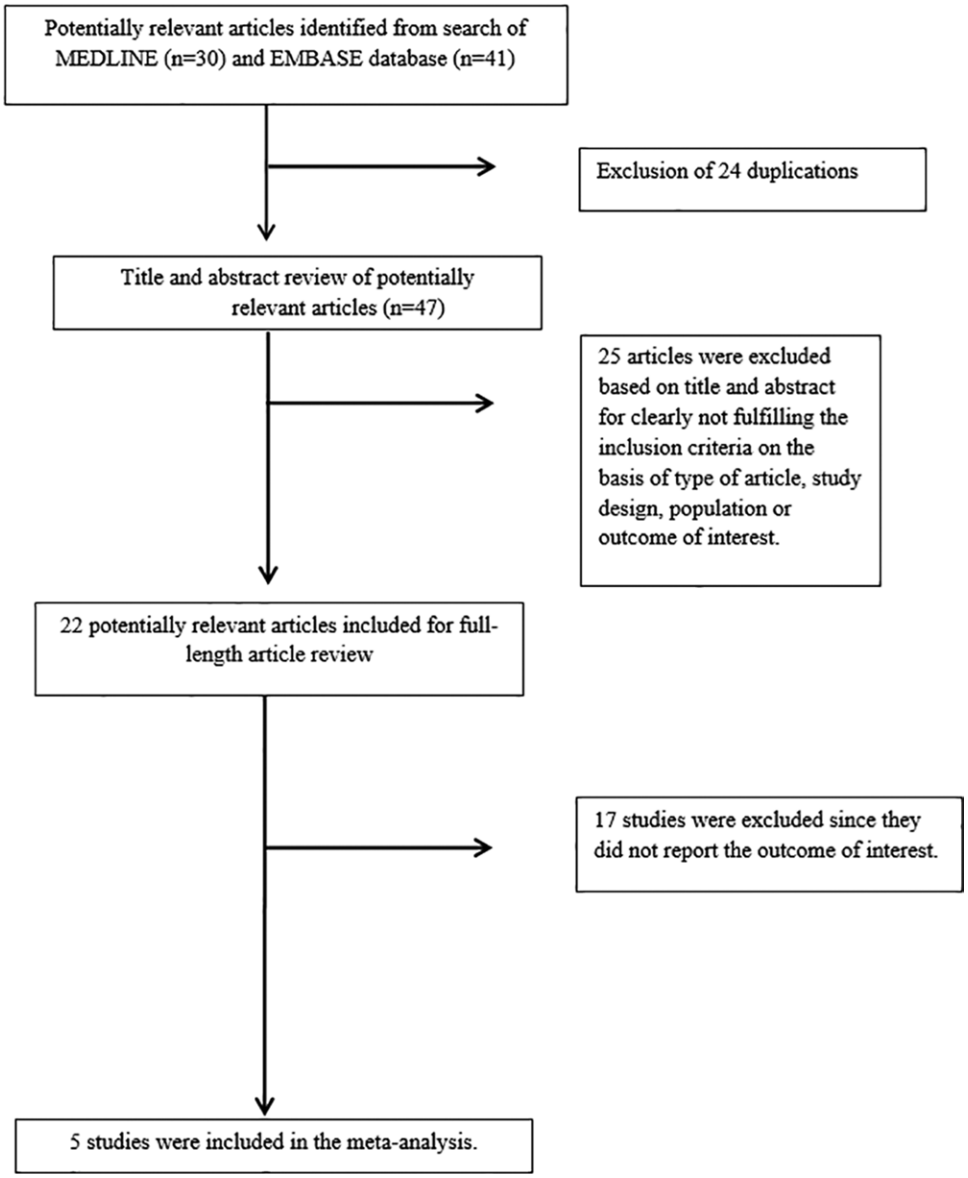

Fig. 1. Literature review process.

Discussion

The current systematic review and meta-analysis found a significant association between hereditary hemochromatosis and risk of having joint replacement surgery. Subgroup analysis found the increased risk in all three analyzed joint locations although the pooled result did not reach statistical significance for the knee. The mechanisms behind the increased risk of joint replacement surgery are probably the same pathogenesis that leads to arthritis in hereditary hemochromatosis.

Excessive iron deposition in joints can stimulate the production of reactive oxygen species, which in turn can lead to inflammation, cartilage degeneration, and damage [15,16]. The presence of ferric salts within the joints can also predispose patients to calcium pyrophosphate deposition disease by promoting crystal formation and inhibiting removal of crystals [17,18], adding further insult to the joints. These factors could eventually lead to chronic inflammation/injury of the joints, resulting in premature secondary osteoarthritis that requires joint replacement surgery.

Nonetheless, the singularity of this explanation has been argued against by the fact that the development of arthritis in patients with hereditary hemochromatosis cannot be predicted by the level of serum iron and not all patients with high serum iron level necessarily have chronic arthritis that requires surgery [19]. In addition, iron depletion therapy through phlebotomy has not been shown to provide symptomatic relief in the majority of patients [20–22]. It is possible that other pathological processes of hereditary hemochromatosis independent of iron overload may also play a role in the pathogenesis of joint disease. Proposed mechanisms include cartilage matrix defect because of noniron metabolic abnormality of hereditary hemochromatosis [23] and abnormalities in immune cell function [24].

Studies have suggested that iron overload may inhibit osteoblast metabolism, leading to decreased bone formation and, eventually, reduced bone mineral density [19,25–28]. The mechanisms by which iron overload may decrease osteoblast formation may include increased oxidative stress and downregulation of mRNA responsible

Table 1. Main characteristics of the studies included in this meta-analysis

	Richette *et al*. [10]	Sahinbegovic *et al*. [7]	Wang *et al*. [11]	Elmberg *et al*. [8]	Kroner *et al*. [9]
Country	France	Germany	Australia	Sweden	USA
Study design	Cohort study	Cohort study	Cohort study	Cohort study	Cohort study
Year of publication	2010	2010	2012	2013	2018
Number of subjects	610 (306 patients with hereditary hemochromatosis and 304 individuals with nonhereditary hemochromatosis)	1023 (199 patients with hereditary hemochromatosis and 824 individuals with nonhereditary hemochromatosis)	23977 (184 patients with hereditary hemochromatosis and 23793 individuals with nonhereditary hemochromatosis)	40900 (3531 patients with hereditary hemochromatosis and 37369 individuals with nonhereditary hemochromatosis)	1226897 (18250 patients with hereditary hemochromatosis and individuals with nonhereditary hemochromatosis 1208647)
Recruitment of subjects	Patients with hereditary hemochromatosis were identified from the members of Association Hemochromatose France. The survey was conducted in 2006. Comparators without hereditary hemochromatosis were recruited from blood donor centers and local community. Comparators were age and sex-matched to cases.	Patients with hereditary hemochromatosis were recruited from seven centers in Germany from 2005 to 2008. Comparators without hereditary hemochromatosis were identified from the previously identified cohort of Bruneck Study, which was a cohort of random sample of inhabitants of Bruneck.	Patients with hereditary hemochromatosis were identified from database of the Melbourne Collaborative Cohort study, which recruited and collected blood sample of participants born in Australia, New Zealand, the UK, and Ireland from 1990 to 1994. The rest of the participants of the Melbourne Collaborative Cohort Study who did not have hereditary hemochromatosis served as comparators.	Patients with hereditary hemochromatosis were identified from database of the Swedish National Patient Registers, which contained information on inpatient care and nonprimary outpatient care of all citizens from 1 January 1997 to 30 November 2005. Comparators without hereditary hemochromatosis were identified from the same database. Comparators were age, sex, county of residence, and marital status-matched to cases.	Patients with hereditary hemochromatosis were identified from the National Inpatient Sample of the year 2014, which contained information of approximately 20% of admission in the USA. The rest of the patients of in the same database who did not have hereditary hemochromatosis served as comparators.
Diagnosis of hereditary hemochromatosis	Not available	Presence of homozygous mutation of C282Y in the *HFE* gene from DNA extraction from Guthrie cards	Presence of homozygous mutation of C282Y in the *HFE* gene in the stored blood sample drawn at inception of cohort	Presence of ICD codes for hereditary hemochromatosis in the database	Presence of ICD-9 code for hereditary hemochromatosis in the database
Measured outcomes	Prevalent hip, knee, and ankle joint replacement surgery. This history was obtained from self-administered questionnaires.	Prevalent hip, knee, and ankle joint replacement surgery. This history was obtained from self-administered questionnaires.	Incident hip and knee joint replacement surgery from 2001 to 2009. This history was obtained from the Australian Orthopaedic Association National Joint Replacement Registry database.	Incident hip, knee, and ankle joint replacement surgery, defined as presence of ICD codes for those surgeries in the database. Follow-up was until 30 November 2005.	Prevalent hip, knee, and ankle joint replacement surgery, defined as presence of ICD codes for those surgeries in the database.
Average age of participants	Cases: 60.1 ± 11.3 Comparators: 59.6 ± 11.6	Cases: 55.9 ± 12.2 Comparators: not available	Cases: 62.6 ± 8.9 Comparators: 62.1 ± 9.0	Cases: not available Comparators: not available	Cases: 65.5 ± 18.0 Comparators: 66.7 ± 17.0
Percentage of female	Cases: 47.4% Comparators: 42.2%	Cases: 32.7% Comparators: not available	Cases: 55.0% Comparators: 61.0%	Cases: 35.0% Comparators: 35.1%	Cases: 41.0% Comparators: 60.3%
Confounder adjusted in multivariate analysis	Age, sex, and BMI	Age, sex, menopausal status, diabetes mellitus, CRP, and BMI	Age, sex, BMI, and educational level	Sex, age, marital status, and country of residency	Age, sex, ethnicity, Charlson Comorbidity Index, median household income in the patient's zip code, hospital region, urban location, number of hospital beds, and teaching status
Quality assessment (Newcastle–Ottawa scale)	Selection 3 Comparability 1 Outcome 2	Selection 4 Comparability 2 Outcome 2	Selection 4 Comparability 2 Outcome 3	Selection 4 Comparability 2 Outcome 3	Selection 4 Comparability 2 Outcome 3

CRP; C-reactive protein; HFE, homeostatic iron regulator; ICD; International Classification of Diseases.

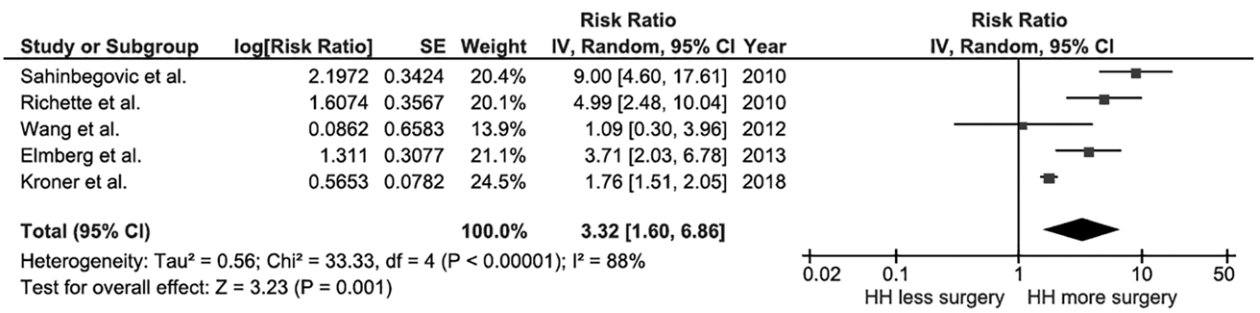

Fig. 2. Forest plot of association between hereditary hemochromatosis and overall risk of joint replacement surgery.

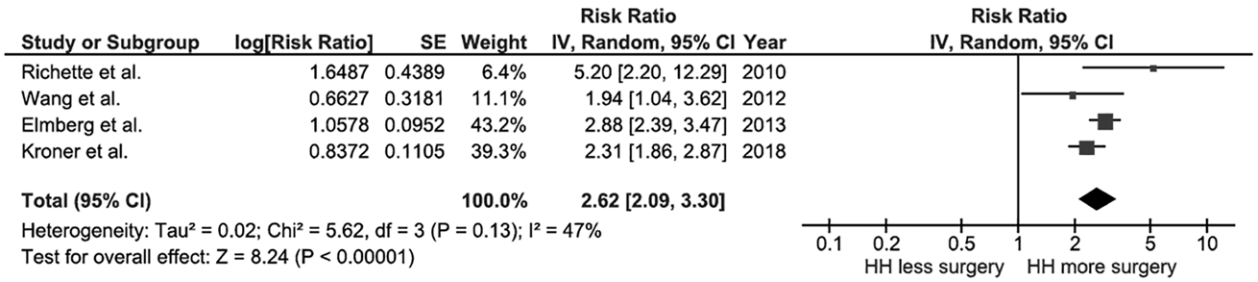

Fig. 3. Forest plot of association between hereditary hemochromatosis and risk of hip replacement surgery.

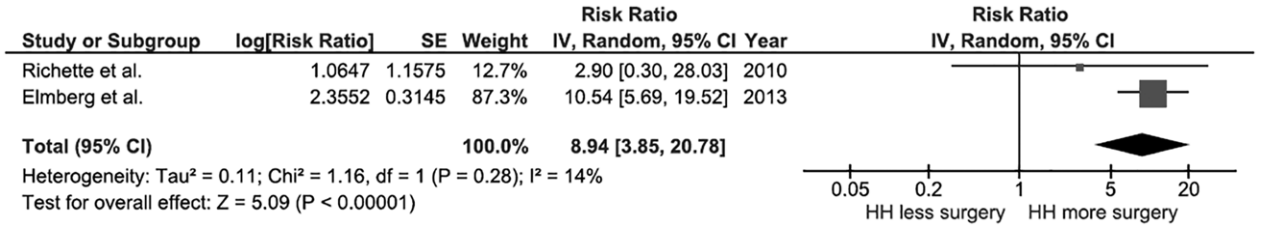

Fig. 4. Forest plot of association between hereditary hemochromatosis and risk of ankle replacement surgery.

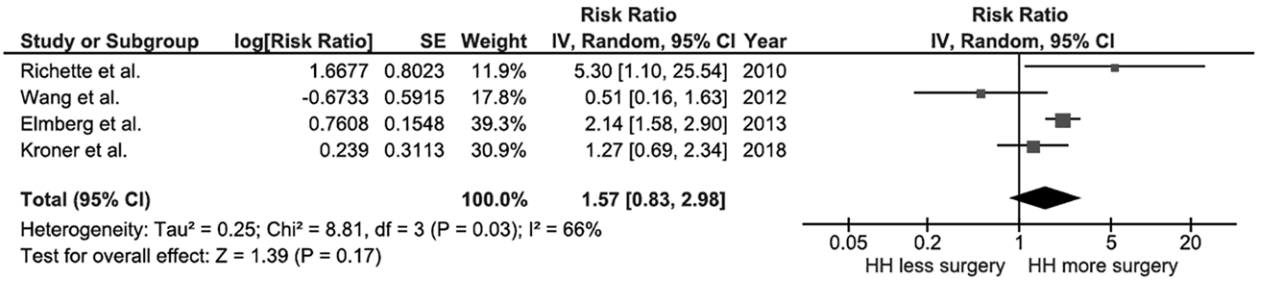

Fig. 5. Forest plot of association between hereditary hemochromatosis and risk of knee replacement surgery.

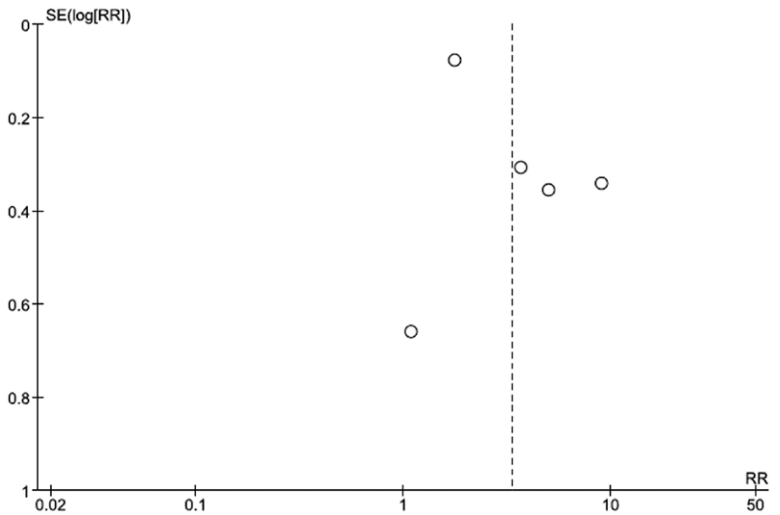

Fig. 6. Funnel plot of association between hereditary hemochromatosis and overall risk of joint replacement surgery.

for osteoblastogenesis [29–32]. This can predispose affected individuals to osteoporotic fractures, including hip fracture, which may necessitate hip replacement surgery. However, further studies are still required to prove this theory.

Although the quality of included studies was high and the literature identification process was comprehensive, this meta-analysis has some limitations and, therefore, the results should be interpreted with caution. First, statistical heterogeneity was not low. We believe that the differences in study populations and methodologies were the main sources of the between-study variation. Second, almost all of the included studies were conducted in Western countries. Thus, we may not be able to apply the results to non-Western populations. Third, most of the included studies only minimally adjusted their results for potential confounders. Thus, the observed association could be a function of confounding effect rather than true causation.

In conclusion, the current study found that patients with hereditary hemochromatosis had an increased risk of having joint replacement surgery. However, some limitations are noted and further studies are required to investigate whether iron is the main cause of arthritis in patients with hereditary hemochromatosis.

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All authors had access to the data and a role in writing the manuscript.

Conflicts of interest

There are no conflicts of interest.

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