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Hyperlipidaemia and incident osteoarthritis of the hand: a population-based case-control study

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SUMMARY

Objective: Preclinical evidence suggests that increased cholesterol levels might be involved in the pathophysiology of osteoarthritis of the hand (HOA), but evidence from observational studies remains scarce. We aimed to analyse the association between hyperlipidaemia and incident HOA.
Design: We conducted a matched (1:1) case-control study using the UK-based Clinical Practice Research Datalink (CPRD). Cases were patients aged 30–89 years with an incident diagnosis of HOA between 1995 and 2014. In multivariable conditional logistic regression analyses, we calculated odds ratios (OR) for incident HOA in patients with hyperlipidaemia, categorized by gender, age, previous duration of hyperlipidaemia, and recent statin treatment.
Results: Among 19,590 cases and 19,590 controls, we observed an increased risk of HOA in patients with hyperlipidaemia (OR 1.37, 95% confidence intervals (CI) 1.28–1.47), when compared to patients without hyperlipidaemia. Thus, of all HOA cases in our study population, 3.6% may have been attributable to the presence of hyperlipidaemia (population attributable risk). Most patients with HOA were elderly, but the strength of the association between HOA and hyperlipidaemia inversely correlated with increasing age, with the highest OR of 1.72 (95% CI 1.24–2.38) in patients aged 29–49 years. Categorization by previous hyperlipidaemia duration, as well as sub-classification of patients with hyperlipidaemia into those with and without recent statin use did not meaningfully change the effect estimate.
Conclusions: Our results suggest that hyperlipidaemia may be an independent risk factor for new onset HOA.

Introduction

The role of metabolic diseases in the aetiology of osteoarthritis (OA) remains incompletely understood. A large observational cross-sectional study using data from a prospective cohort reported an increased risk of HOA in patients with metabolic syndrome after adjusting for body weight, but no such association in patients who developed knee OA[1]. Among the most common types of OA (hip, knee, hand), OA of the hand (HOA) is least affected by obesity-related mechanical stress, and is thus the outcome of choice to analyse metabolic risk factors in association with OA[2]. Previous studies focusing on HOA in association with diabetes mellitus did not observe an association between the two diseases[3–5]. Preclinical evidence suggests that elevated serum cholesterol levels may be a risk factor for OA[6], but evidence with regard to whether hyperlipidaemia is the driving force behind the observed increased risk of HOA in patients with metabolic syndrome or associated diseases remains scarce. Three hospital/clinic-based observational studies ($n < 500$) reported a positive association between hyperlipidaemia and HOA[2] or generalized OA[7,8], after controlling for body mass index (BMI). However, the cross-sectional design of these studies precluded inference on the temporality of disease manifestation, and hyperlipidaemia may also be a risk factor for the progression of HOA[1,9]. We conducted a large population-based case-control study using data from the UK-based Clinical Practice Research Datalink

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(CPRD), to evaluate whether hyperlipidaemia is an independent risk factor for incident HOA. Statins have been hypothesised to have a protective effect on the development of OA[10], and we therefore categorized hyperlipidaemia patients by statin use.

Method

Study design and data source

We conducted a matched case-control study using data from the UK-based CPRD (described elsewhere[11]). The CPRD is a large anonymised primary care database that is largely representative of the UK population, and contains information on patient characteristics, symptoms, diagnoses, laboratory test results, drug prescriptions, and referrals. The data in the CPRD has been demonstrated to be of high quality, and has been used extensively[11]. This study was approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC protocol 15_137).

Study population

We identified patients aged 30–89 years with a first-time recorded (incident) READ-code for HOA (according to ICD-10 M19.04 wherever congruent with the Read code system) between January 1995 and December 2014, and with ≥3 years of HOA-free history in the CPRD prior to the first recorded HOA diagnosis ('index date'). We excluded cases with a Read-code for a differential diagnosis of HOA (chondrocalcinosis, gout, haemochromatosis, hyperparathyroidism, psoriatic arthritis, rheumatoid arthritis, or spondyloarthrosis) at any time, as well as patients with unknown BMI. We further excluded patients with recorded cancer (except non-melanoma skin cancer), HIV or substance abuse (including alcoholism) prior to the index date, due to an increased risk of unmeasured confounding and bias among these patients (Fig. 1, flow chart of composition of study population).

For each case we randomly identified one control patient with no READ-code for any OA at any time, and matched them on exact BMI (potential risk factor for HOA, and associated with hyperlipidaemia[12]), age (±2 years), sex, general practice and years of history in the CPRD (±2 years). The index date for each control was the index date of the matched case, and we applied the same exclusion criteria to controls as to cases.

Exposure

Exposure was defined as a previous READ-code for hyperlipidaemia (ICD-10 E78.0–78.9). We also captured whether patients had a recorded prescription for a statin (WHO-ATC C10AA) within 365 days prior to the index date.

Statistical analysis

We conducted multivariable conditional logistic regression analyses using SAS 9.4 (SAS Institute, Cary, NC, USA), to calculate odds ratios (OR) with 95% confidence intervals (CI) for the association between hyperlipidaemia and incident HOA. We categorized patients with incident hyperlipidaemia (≥1 year of hyperlipidaemia-free history) according to disease duration (<1, 1 to <5, 5 to <10, and ≥10 years). We further sub-classified patients with and without hyperlipidaemia, into those with and without a statin prescription within 365 days prior to the index date.

Based on clinical knowledge, we a priori adjusted ORs for smoking (non-smokers, current, past, unknown), alcohol consumption (<15, ≥15 units per week, unknown), and for the following potential confounders; a Read-code for hand fracture, osteoporosis (Read-code or new bisphosphonate treatment), diabetes mellitus, hypertension, or COPD (proxy for smoking and physical activity) prior to the index date. We also adjusted for first-time prescription of hormone replacement therapy within </≥2 years prior to the index date (proxy for onset of menopause, which is not captured well in the CPRD), and for statin use within 365 days prior to the index date.[13]

We tested the fully adjusted model for statistical interaction by age (in decades, continuous variable) and sex (significance level Wald *P*-value 0.10). We observed significant interaction by sex (*P*-value 0.034) and age (*P*-value 0.09), and therefore stratified results by sex and decades of age. We further performed a sensitivity analysis, to account for diagnostic bias by increased medical attention, where we additionally included the number of GP visits (number of different dates with recorded diagnoses or prescriptions) within the year prior to the index date into the multivariable model.

To assess the role of BMI in the association between hyperlipidaemia and HOA, we performed an additional analysis where we created a study population (study population 2) with identical cases as in the original study population, and new controls which were not matched to the cases on BMI. All above described analyses were repeated in study population 2 (no multivariable adjustment for BMI).

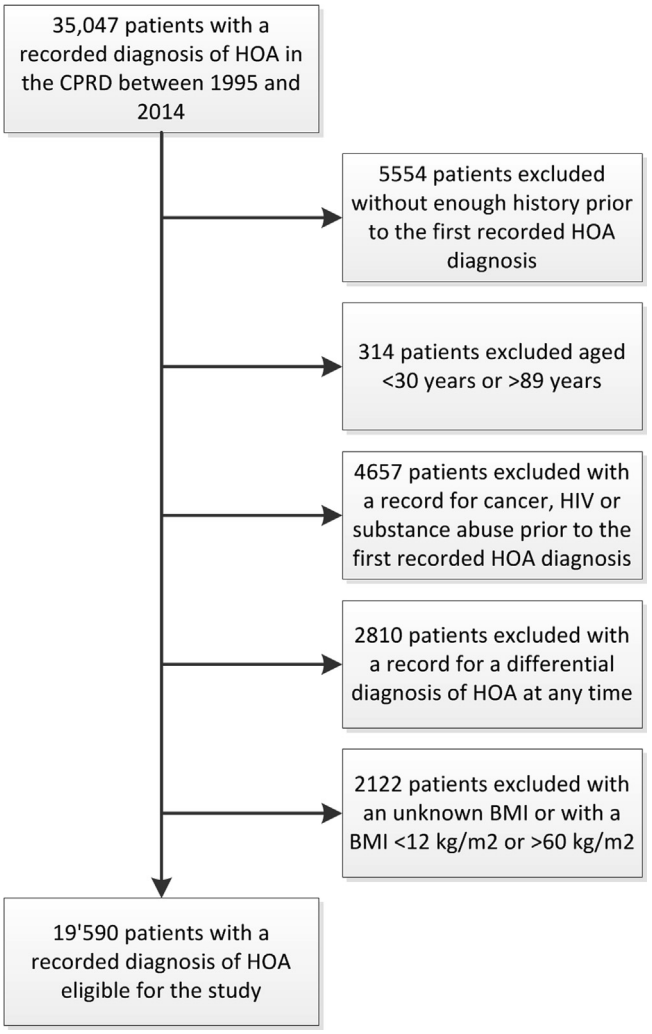

Fig. 1. Selection of eligible HOA cases for the study population.