

Risk of hand osteoarthritis in new users of hormone replacement therapy:

A nested case-control analysis

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Objective: To estimate the risk of hand osteoarthritis (HOA) associated with hormone replacement therapy (HRT).

Methods: We conducted a nested case-control study using data from the UK-based Clinical Practice Research Datalink (1998-2017). In women entering at age 45 (inception cohort), we matched women with incident HOA during follow-up (cases) 1:4 to osteoarthritis-free controls on age and calendar date (index date, ID). We applied conditional logistic regression to calculate odds ratios (OR) with 95% confidence intervals (CI) of HOA associated with new HRT use compared to non-use overall and in women with recorded menopause, in whom, we calculated separate ORs subdivided by time between menopause and HRT initiation (current users), and by time between HRT cessation and the ID (past users), versus non-users.

Results: Among 3440 cases and 13,760 controls (mean age: 50.9 ± 4.1 years), we observed an adjusted OR (aOR) of HOA of 1.32 (95% CI 1.17-1.48) in HRT users (versus non-users), which attenuated to 0.98 (95% CI 0.85-1.14) in women with recorded menopause. Current users (versus non-users), who initiated HRT within 3 months before/after menopause, had an aOR of 0.72 (95% CI 0.55-0.96), while aORs increased with later HRT initiation. Among past users (versus non-users), we observed an aOR of 1.25 (95% CI 0.86-1.81) when HRT use was stopped ≤ 18 months before the ID, approaching the null with increasing duration between HRT cessation and the ID.

Conclusion: Current HRT use was associated with a decreased risk of HOA if initiated around menopause, but the risk reduction disappeared after HRT cessation.

Keywords: hormone replacement therapy; hand osteoarthritis; menopause; epidemiology

¹HOA: hand osteoarthritis, HRT: hormone replacement therapy, ID: index date, aOR: adjusted odds ratio

1. INTRODUCTION

Hand osteoarthritis is a degenerative disease characterised by joint pain and bony enlargements/ swellings, occurring most frequently in postmenopausal women and the elderly.[1,2] To date, no disease-modifying treatment is available.[3] The exact etiology of osteoarthritis is unknown but was suggested to be mainly mediated by metalloproteinases and aggrecanases.[4] The increase in incidence of hand osteoarthritis in postmenopausal women, the presence of estrogen receptors in cartilage, and estrogen potentially inhibiting factors involved in cartilage degradation suggest that hormone replacement therapy (HRT) may help preventing the development of osteoarthritis.[5]

Preclinical studies mainly assessed the effect of HRT on knee osteoarthritis and yielded contradictory results.[6] Mechanical stress is a major risk factor for osteoarthritis of weight-bearing joints (i.e. knee, hip)[7], which is often not adequately controlled for. Hand joints are perhaps proportionally less affected by mechanical factors than single large joints and are thus likely a more suitable outcome to assess the association between osteoarthritis and systemic drug exposures. However, small cross-sectional studies investigating the association between HRT and hand osteoarthritis or generalized osteoarthritis (≥ 3 joints affected, usually includes hand osteoarthritis) also yielded contradictory results.[8–12] A descriptive study reported that 55% of women who developed hand osteoarthritis after menopause developed it within 4 years after menopause.[13] Thus, timing of HRT use relative to menopause and/or hand osteoarthritis may play an important role in the association between HRT use and hand osteoarthritis, but has not been studied yet.

In this nested case-control analysis we investigated the association of new HRT use on the risk of incident hand osteoarthritis overall and stratified by timing of HRT use. Furthermore, we

assessed the timing of HRT initiation and cessation relative to recorded menopause and diagnoses of hand osteoarthritis, respectively.

2. PATIENTS AND METHODS

2.1 Study design and Data source

We conducted a nested case-control study using data derived from Clinical Practice Research Datalink (CPRD) GOLD which comprises de-identified primary care data of more than 11.3 million patients.[14] General practitioners (GP) act as gatekeepers within the National Health Service (NHS) and electronically record information on diagnoses, prescriptions, medical symptoms, laboratory values, referrals to secondary care, demographics, and lifestyle factors (e.g. body mass index [BMI], smoking status).[15] Prescriptions are (nearly) completely recorded and diagnoses have been repeatedly shown to be of high validity.[16] We further used CPRD-linked patient level data on socio-economic status (index of multiple deprivation, IMD), which is available for patients living in England only.[17,18] The interpretation and conclusions contained in this study are those of the authors alone.

2.2 Study population

We included all women on July 1st (cohort entry) of the year in which they turned 45 years old (based on their year of birth) between January 1998 and December 2017 in an inception cohort (a cohort only comprising patients who have an incident common characteristic, here, age 45). We excluded all women with ≤ 1 year of active history and/or < 1 GP visit on the database prior to cohort entry. We further excluded women with a history of hand osteoarthritis and with diseases potentially linked to secondary osteoarthritis or differential diagnoses of hand osteoarthritis prior to cohort entry, namely hemarthrosis of the hand, malformation or misalignments of the fingers, hypermobility syndrome,

hyperparathyroidism, acromegaly, previous finger injury (e.g. fracture, dislocation, tear of ligament), Stickler syndrome, Paget's disease, disorder of iron metabolism (hemochromatosis), inflammatory polyarthropathies (i.e. gout, rheumatoid arthritis, and psoriatic arthritis), and Wilson disease.[19,20] Women were not eligible if they had a recorded Read code[14] for any cancer (except non-melanoma skin cancer), alcoholism, alcohol/ other substance abuse, or HIV/ AIDS at any time prior to cohort entry. Furthermore, women were excluded if they used systemic HRT prior to cohort entry. In a post-hoc sensitivity analysis, we additionally excluded women with fibromyalgia or carpal tunnel syndrome/surgery, which may also cause hand pain and could be misdiagnosed as hand osteoarthritis given a subsequent osteoarthritis record.

2.3 Follow-up and case definition/ validity

We followed all women from cohort entry until they developed incident symptomatic hand osteoarthritis (cases) defined as 1) a first-time Read code of hand osteoarthritis or 2) a Read code of hand pain if followed by an incident Read code of hand osteoarthritis, osteoarthritis, or generalized osteoarthritis (Read codes in Supplemental File 1) within 365 days thereafter. The case index date was defined as the first record of either first-time hand osteoarthritis or hand pain. Follow-up was censored at the first of the following: recorded exclusion criterion described above (except for first-time systemic HRT use), disenrollment from the CPRD, age 65, or the end of the study period (December 2017).

As hand osteoarthritis is a diagnosis mainly made in primary care, we could not validate diagnoses using secondary care data. Nonetheless, in a sensitivity analysis, we restricted cases to women with a diagnosis of incident hand osteoarthritis that was preceded or followed by a specialist referral/ discharge (rheumatologist/ orthopaedist/ radiologist), or diagnostic work up (MRI, X-ray, ultrasonography) within 90 days before or after the

diagnosis (19.1% of cases). In a further sensitivity analysis, to account for the slowly developing character of hand osteoarthritis potentially leading to a delayed diagnosis, we reanalysed the data with the index date shifted to 180 days before the hand osteoarthritis diagnosis date or matched date in controls. Women with ≤ 180 days of follow-up were excluded from this analysis.

2.4 Definition of controls

Each hand osteoarthritis case was matched to four controls from the study population who did not have a record of hand osteoarthritis up to 180 days prior to the case index date (risk-set sampling with a lag period to account for gradual disease onset) on age, calendar date (case index date), GP practice, and years of history in the CPRD before the index date.

2.5 Exposure

We defined new HRT use as a first ever recorded prescription for any systemic opposed or unopposed HRT. We included systemic formulations (i.e. oral, transdermal, topical, nasally administered, implanted, or injected formulations), but not vaginal formulations due to their relatively low, variable systemic bioavailability.

A woman was considered exposed from the day after the first HRT prescription, and was considered “currently exposed” for as long as each prescription was followed by a subsequent prescription within a grace period of 180 days after the alleged end of supply (Figure 1). Supply length was determined based on the number of prescribed products and dose instructions. In case of missing or improbable information on supply length, we used previously assessed default values of product quantities and dosing (Supplemental File 2). A person was classified as having past exposure from day 181 after a current prescription

supply ended (Figure 1). Past users were censored whenever a new systemic HRT prescription was recorded (i.e. past users could not become current users again).

2.6 Covariates for adjustment

We captured the following potential confounders of the association between HRT initiation and hand osteoarthritis (selected *a priori* based on clinical knowledge) recorded at any time before the index date (if not specified otherwise): BMI ≥ 30 kg/m² (Read code or measure for BMI),[5,8,9,11,21] current smoking,[9,11,12] heavy alcohol consumption >14 units/week,[11] osteoporosis (Read code or prescription for bone-modifying drug),[5,8] diabetes (Read code or antidiabetic drug), thiazide prescriptions,[9] dyslipidemia (Read code or laboratory value), a vaccination record (proxy for health care seeking behavior), and >5 GP contacts[21] within the year prior to cohort entry (proxy for health care seeking behavior; we assessed GP contacts prior to cohort entry because assessing GP contacts prior to the index date would lie on the causal pathway between HRT initiation and hand osteoarthritis). With dichotomization of lifestyle covariates, we assumed that women with a missing record of BMI (9.0%), smoking status (2.8%), or alcohol consumption (8.3%) were non-obese, non-smokers, or non-heavy drinkers.

2.7 Statistical analysis

We conducted multivariable conditional logistic regression analyses to estimate crude and adjusted odds ratios (OR, adjusted for all covariates listed under 2.6 Covariates for adjustment) with 95% confidence intervals (CI) of the association between new HRT use compared to non-use and hand osteoarthritis overall, and stratified by timing of HRT use (currently exposed, past exposed). In additional analyses, we further adjusted for anytime

vaginal HRT use (yes/no), and separately for socio-economic status in 60.2% of women with available information on IMD (in quintiles).

To assess confounding by whether or not a woman had menopause (i.e. natural or surgically induced menopause such as hysterectomy/ oophorectomy) recorded in the database, we calculated crude and adjusted ORs of hand osteoarthritis in women with recorded menopause compared to women who had no menopause record (menopause records were assessed between cohort entry and the index date only, women with a menopause record before cohort entry were excluded). Because we observed an association between the presence of recorded menopause and a diagnosis for hand osteoarthritis, we restricted the remainder of analyses to women with recorded menopause. We additionally adjusted for age (continuous variable) in all analyses restricted to women with recorded menopause because this restriction may have violated age-matching of cases and controls. In these women, we estimated ORs of the association between hand osteoarthritis and new HRT use, compared to non-use overall and stratified by timing of HRT use (currently exposed, past exposed). We further estimated ORs stratified by timing of HRT initiation relative to recorded menopause in current users compared to non-users (>3 months before menopause [range: 140-2811 days], ≤3 months before/after menopause, 3-36 months after menopause, and >36 months after menopause [range: 1126-4474 days]). Furthermore, we estimated ORs stratified by timing of HRT cessation before the index date among past users, compared to non-users (≤18 months before the index date, >18-54 months before the index date, and >54 months before the index date). Furthermore, among women with recorded menopause, we estimated ORs of hand osteoarthritis in association with current HRT use, compared to non-use, stratified by HRT type (unopposed, opposed), administration route (oral, topical, transdermal, switcher),

and average daily estrogen dose used within 12 months prior to the index date (Supplemental File 3).

Moreover, to describe the temporal trend of hand osteoarthritis onset after menopause, we described the proportion of hand osteoarthritis cases in women with recorded menopause after cohort entry in 1-year intervals after recorded menopause. Proportions were estimated by dividing the number of hand osteoarthritis cases in each interval by the number of total hand osteoarthritis cases at any time between cohort entry and index date. We performed all analyses using SAS statistical software version 9.4 (NC, USA).

3. RESULTS

We identified 623,671 women who turned 45 years old during the study period. After application of exclusion criteria, we included 438,674 women in the inception cohort (Figure 2). Among this cohort, we identified 3440 hand osteoarthritis cases and 13,760 matched controls. Characteristics of cases and controls are displayed in Table 1. The mean age of cases and controls at the index date was 50.9 years (standard deviation [SD]: 4.1 years). Cases had more recorded diagnoses of osteoporosis, diabetes, dyslipidemia, and obesity before the index date, and also saw their GP more often in the year prior to cohort entry, than controls.

The adjusted OR of hand osteoarthritis in HRT users compared to non-users was 1.32 (95% CI 1.17-1.48) [Table 2]. A record of menopause (irrespective of HRT use) was associated with an increased adjusted OR of hand osteoarthritis of 1.42 (95% CI 1.29-1.57) when compared to women without recorded menopause (Figure 3, crude ORs in Supplemental File 4). In women with recorded menopause (860 of 3440 cases [25%] and 2610 of 13,760 controls [19%]), there was no association between HRT use and risk of hand osteoarthritis: adjusted

OR 0.98 (95% CI 0.85-1.14) when compared to non-use (Figure 3, crude ORs in Supplemental File 4). Current HRT users, versus non-users, had a decreased adjusted OR of hand osteoarthritis of 0.72 (95% CI 0.55-0.96), when HRT was initiated within 3 months before/after menopause with ORs increasing with later HRT initiation. Women with past HRT use had a statistically non-significantly adjusted OR of hand osteoarthritis of 1.25 (95% CI 0.86-1.81) if HRT was stopped ≤ 18 months before the index date, which decreased towards the null with increasing duration between HRT cessation and the index date (Figure 3, crude ORs in Supplemental File 4).

When stratifying current HRT users by HRT type, administration route, and average daily estrogen dose used within 12 months prior to the index date, opposed HRT users and oral HRT users yielded the lowest adjusted ORs with 0.81 (95% CI 0.62-1.03) and 0.74 (95% CI 0.56-0.98), respectively (Supplemental File 5), when compared to non-users. There was no difference in effect estimates between low dose and other doses (Supplemental File 5).

The proportion of women with hand osteoarthritis diagnoses decreased with increasing number of 1-year intervals after recorded menopause. A maximum proportion of 18.4% of women had hand osteoarthritis recorded (158 of 860 cases) within 1 year after recorded menopause. Cumulatively, 54.9% and 79.9% of women had hand osteoarthritis recorded within 4 years and 7 years, respectively (Figure 4, Supplemental File 6).

In all analyses, adjusted ORs of hand osteoarthritis were lower in current and higher in past HRT users than when HRT was assessed overall (Table 2, Figure 3). When we further adjusted the overall analysis for vaginal HRT use and socioeconomic status, results remained unchanged (Table 2). In sensitivity analyses related to outcome validity, results remained largely unchanged as well (Table 2).

4. DISCUSSION

In this nested case-control study embedded in an inception cohort of women aged 45 at entry, we assessed the risk of hand osteoarthritis in HRT users compared to non-users overall, stratified by timing of HRT, and in women with recorded menopause only. In women with recorded menopause only, we further investigated separate ORs subdivided by time between menopause and HRT initiation (current users), and by time between HRT cessation and the index date (past users), compared to non-users.

Previous small observational studies investigating the association between HRT and hand osteoarthritis, or generalized osteoarthritis, yielded contradictory results.[8–12] Though authors had access to hospital-based information on diagnosis, the cross-sectional study design prevented them from assessing temporality of HRT use in relation to hand osteoarthritis or menopausal status.[8–12] We observed a 32% increased risk of hand osteoarthritis in all HRT users when compared to non-users which attenuated to a null result after restriction to women with recorded menopause. We assumed that HRT use is a proxy for menopause onset in women without recorded menopause and therefore abstained from analyses in women without recorded menopause. Our results suggest that menopause is a risk factor for incident hand osteoarthritis (42% increased risk in our study). Other observational studies assessing the association between menopause with or without HRT use and hand osteoarthritis did not yield precise results mainly due to small sample sizes.[22] Watt et al. performed a small study (n=82) describing the association between menopause or HRT cessation and onset of hand osteoarthritis symptoms in women in a UK secondary care clinic.[13] The authors reported a median duration between HRT cessation and onset of hand osteoarthritis of 6 months. We observed that, among women with

recorded menopause who developed hand osteoarthritis, 55% of women did so within 4 years after menopause, the same proportion was reported by Watt et al..

Women who initiated HRT shortly before/after menopause were at a reduced risk of hand osteoarthritis (around 28% lower risk for women with current HRT use at the index date).

We hypothesize that women who use systemic HRT to alleviate vasomotor symptoms may profit from a delayed onset or progression of hand osteoarthritis, when HRT is initiated around menopause and used continuously. Thus, our results support position statements of the North American Menopause Society[23] and International Menopause Society[24], which postulate a potential benefit of HRT on joint/ muscle pain and joint stiffness based on evidence from the well-known Women's Health Initiative reporting reduced arthroplasty and joint pain among unopposed oral HRT users[25,26], and reduced joint pain and stiffness among opposed oral HRT users[27], compared to non-users. To date, there is no information on the effect of progesterone alone or in conjunction with estrogen on articular cartilage. We observed a trend of decreasing risk of hand osteoarthritis with increasing time after HRT cessation (25% risk increase ≤ 18 months after HRT cessation, null result thereafter). However, as the CPRD contains no information on how HRT was stopped (e.g. abrupt cessation or slow weaning) and as these results were based on small sample sizes, the observed risk increase after HRT cessation needs to be interpreted with caution. Nonetheless, it may suggest that women are more likely to experience hand symptoms shortly after stopping HRT when compared to later on. Postmenopausal symptoms exacerbations (including joint pain) after HRT cessation are a known phenomenon.[23]

A strength of this study is its large population of more than 3'000 hand osteoarthritis cases among women observed longitudinally from age 45. Furthermore, we applied a new user design, allowing us to assess temporality of HRT use and hand osteoarthritis. Moreover, we

likely captured near complete HRT prescription information, as CPRD prescriptions are issued electronically by the GP. We do not know if women took all prescriptions. However, of women who had HRT prescribed during follow-up, 77.4% had >1 HRT prescription recorded, suggesting that most women filled their prescriptions repeatedly, and thus likely took the medication.

A major limitation of this study is the inconsistent recording of menopause in the CPRD. However, according to the inception cohort, database wise, every women had the same chance of a menopause record after age 45. Yet, women have a different threshold of discomfort until they see a GP or menopause may have been recorded by chance when the women was there for a different reason. Therefore, we hypothesize that the range of symptom severity among women with a menopause record likely varied. HRT use, however, among women with recorded menopause in our study (mean age 53 years [SD: 3.7 years], before 2003 around 45%, as of 2003 around 30%) was higher than HRT use among the general UK female population aged 50-59 from 1998 to 2005 (around 30-35% from 1998 to 2003, around 15% in 2004/2005)[28]. This may imply that, among women with recorded menopause, HRT users had more severe menopause symptoms or were rather health care seekers. However, more severe menopause symptoms or health care seeking behavior as a potential risk factor of hand osteoarthritis would increase hand osteoarthritis risks and therefore introduce a null bias to our observed protective associations with HRT use. In our cohort, we suspect under-recording of hand osteoarthritis (prevalence of 0.8%) because GPs may frequently lack to specify joint localization of osteoarthritis. However, by only including specific records of hand osteoarthritis we achieve a high specificity which is relevant for reliable risk estimation in comparative analyses. Moreover, potential outcome misclassification given potential under recording of hand osteoarthritis may have

introduced a null bias and the observed ORs may thus be underestimated. However, despite rigorous control for confounding, residual confounding by physical impact on finger joints, occupations, genetic predisposition, and other hormonal factors, cannot be ruled out, as these factors are not recorded in the CPRD.[2] Sample sizes for the pre-planned stratified analyses by HRT type, administration route, and dose used within 12 months prior to the index date ~~because we~~ were small and therefore the results of these analyses were imprecise. However, they suggest that the main drivers of the observed decreased risk of hand osteoarthritis in current HRT users were likely oral opposed HRT users. Yet, results have to be confirmed before drawing causal conclusions for clinical practice.

5. CONCLUSION

This nested case-control study yielded an increased risk of hand osteoarthritis in HRT users compared to non-users. However, this result was likely confounded by menopausal status, as the risk was attenuated after restriction to women with recorded menopause. Moreover, we observed a decreased risk of hand osteoarthritis in current HRT users who initiated HRT around the time of the first menopause record, but the risk reduction disappeared after therapy cessation. Replication of these findings are warranted

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ETHICAL APPROVAL

This study is based on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The data is provided by patients and collected by the National Health Service as part of their care

and support. The study protocol was approved by the Independent Scientific Advisory Committee for MHRA database research (protocol 18_089R, made available to journal editors).

CONTRIBUTORSHIP

Theresa Burkard: 'I declare that I participated in the design of the work, analysis and interpretation of data, drafting the manuscript, and that I have seen and approved the final version. I have no conflicts of interest.'

Marlene Rauch: 'I declare that I participated in the design of the work, interpretation of data, critical revision for important intellectual content, and that I have seen and approved the final version. I have no conflicts of interest.'

Julia Spoendlin: 'I declare that I participated in the design of the work, interpretation of data, critical revision for important intellectual content, and that I have seen and approved the final version. I have no conflicts of interest.'

Daniel Prieto-Alhambra: 'I declare that I participated in the conception of the work, interpretation of data, critical revision for important intellectual content, and that I have seen and approved the final version. I have the following conflicts of interest: my research group has received research grants, speaker, and advisory board fees from AMGEN, research grants from Servier Laboratoires and UCB Pharma, and speaker and consultancy fees from UCB.'

Susan S. Jick: 'I declare that I participated in the acquisition and interpretation of data, critical revision for important intellectual content, and that I have seen and approved the final version. I have no conflicts of interest.'

Christoph R. Meier: 'I declare that I participated in the acquisition and interpretation of data, critical revision for important intellectual content, and that I have seen and approved the final version. I have no conflicts of interest.'

RESEARCH DATA (DATA SHARING AND COLLABORATION)

The data analyzed in this study is available from the corresponding author upon reasonable request and after having received approval from the license holder (UK Medicines and Healthcare products Regulatory Agency).

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FIGURE CAPTIONS

Fig1. Hormone replacement therapy exposure definition in the case-control analysis

OA: osteoarthritis, HRT: hormone replacement therapy

Fig2. Flowchart of the study composition

CPRD: Clinical Practice Research Datalink, GP: general practitioner, HRT: hormone replacement therapy

Fig3. Odds ratios of hand osteoarthritis in association with recorded menopause after cohort entry, and, in patients with recorded menopause after cohort entry, odds ratios of hand osteoarthritis in association with hormone replacement therapy and stratified by timing of hormone replacement therapy use (current/past use) and by timing of hormone replacement therapy initiation relative to recorded menopause (in current users) and of hormone replacement therapy cessation before the index date (in past users).

HRT: hormone replacement therapy, ID: index date, OR: odds ratio, CI: confidence interval,

^a adjusted for the following categorical variables (yes/no): osteoporosis, smoking, alcohol consumption >14 units/week, diabetes, thiazide prescriptions, dyslipidemia, obesity, vaccine use at any time prior to index date and for >5 GP contacts ≤1 year prior to cohort entry; additionally adjusted for age (continuous variable) at index date because age-matched sets of cases and controls were potentially broken by the stratification by recorded menopause. Crude odds ratios are shown in Supplemental File 3.

Fig4. Proportion of hand osteoarthritis cases in 1-year intervals after recorded menopause

TABLES

Tab1. Patient characteristics of hand osteoarthritis cases and matched controls before the index date

| Variables used for matching | Cases (n=3440) | Controls (n=13,760) |
|---|-------------------|------------------------|
| Mean age at index date (SD) | 50.9 (4.1) | 50.9 (4.1) |
| Mean number of years of history in the database (SD) | 15.9 (5.6) | 15.9 (5.6) |
| Variables used for covariate adjusting in logistic regression | | |
| >5 GP contacts ≤1 year prior to cohort entry ^a (%) | 2573 (74.8%) | 8474 (61.6%) |
| Osteoporosis (%) | 63 (1.8%) | 210 (1.5%) |
| Smokers ^b (%) | 592 (17.2%) | 2435 (17.7%) |
| Heavy alcohol drinker (>14 units/ week) ^c [%] | 100 (2.9%) | 415 (3.0%) |
| Diabetes diagnosis (%) | 148 (4.3%) | 502 (3.7%) |
| Thiazide prescriptions (%) | 454 (13.2%) | 1405 (10.2%) |
| Dyslipidemia diagnosis or according laboratory value (%) | 1174 (34.1%) | 4018 (29.2%) |
| Obesity diagnosis or BMI≥30 kg/m ² ^d (%) | 907 (26.4%) | 3364 (24.5%) |
| Vaccine use (%) | 1619 (47.1%) | 6086 (44.2%) |
| Variables used for covariate adjusting in logistic regression in additional analyses | | |
| Vaginal hormone replacement therapy use | 218 (6.4%) | 670 (4.9%) |
| IMD quintile 1 (least deprived) | 632 (18.4%) | 2424 (17.6%) |
| IMD quintile 2 | 498 (14.5%) | 2024 (14.7%) |
| IMD quintile 3 | 393 (11.4%) | 1567 (11.4%) |
| IMD quintile 4 | 321 (9.3%) | 1348 (9.8%) |
| IMD quintile 5 (most deprived) | 229 (6.7%) | 914 (6.6%) |
| IMD unknown | 1367 (39.7%) | 5483 (39.9%) |

| Variables used for stratification in additional analyses | | |
|---|-------------|--------------|
| Recorded menopause after cohort entry | 860 (25.0%) | 2610 (19.0%) |

SD: standard deviation, GP: general practitioner, BMI: body mass index, IMD: index of multiple deprivation

^a number of general practitioner contacts prior to the index date would lie on the causal pathway

^b percentage of women with missing data on smoking status: 2.8%

^c percentage of women with missing data on alcohol consumption: 8.3%

^d percentage of women with missing data on body mass index: 9.0%

Tab2. Odds ratios of hand osteoarthritis in association with hormone replacement therapy overall and stratified by timing of HRT use at the index date

| Overall | Cases: 3440 (%) | Controls: 13,760 (%) | OR crude ^a (95% CI) | OR adjusted ^b (95% CI) |
|--|----------------------------|---------------------------------|---|--|
| No HRT use | 2982 (86.7) | 12,415 (90.2) | 1.00 ref | 1.00 ref |
| Overall HRT use | 458 (13.3) | 1345 (9.8) | 1.45 (1.29-1.63) | 1.32 (1.17-1.48) |
| Overall HRT use additionally adjusted for vaginal HRT use | | | | 1.31 (1.16-1.47) |
| Current HRT use | 189 (5.5) | 627 (4.6) | 1.27 (1.07-1.50) | 1.11 (0.93-1.31) |
| Past HRT use | 269 (7.8) | 718 (5.2) | 1.62 (1.39-1.89) | 1.52 (1.31-1.78) |
| Patients with information on IMD | Cases: 2073 (%) | Controls: 8277 (%) | OR crude ^a (95% CI) | OR adjusted ^b (95% CI) |
| No HRT use | 1797 (86.7) | 7480 (90.4) | 1.00 ref | 1.00 ref |
| Overall HRT use additionally adjusted for IMD in quintiles | 276 (13.3) | 797 (9.6) | 1.47 (1.27-1.72) | 1.34 (1.15-1.57) |
| Index date shift to 180 days before the index date ^c | Cases: 3308 (%) | Controls: 13,154 (%) | OR crude ^a (95% CI) | OR adjusted ^b (95% CI) |
| No HRT use | 2850 (86.2) | 11,813 (89.8) | 1.00 ref | 1.00 ref |
| Overall HRT use | 458 (13.9) | 1341 (10.2) | 1.31 (1.19-1.45) | 1.23 (1.11-1.36) |
| Cases with a secondary care entry ^d | Cases: 660 (%) | Controls: 2640 (%) | OR crude ^a (95% CI) | OR adjusted ^b (95% CI) |
| No HRT use | 572 (86.7) | 2403 (91.0) | 1.00 ref | 1.00 ref |
| Overall HRT use | 88 (13.3) | 237 (9.0) | 1.62 (1.23-2.14) | 1.43 (1.08-1.89) |
| Fibromyalgia and carpal tunnel syndrome excluded ^e | Cases: 3033 (%) | Controls: 12,132 (%) | OR crude ^a (95% CI) | OR adjusted ^b (95% CI) |
| No HRT use | 2655 (87.5) | 10,794 (90.5) | 1.00 ref | 1.00 ref |
| Overall HRT use | 378 (12.5) | 1158 (9.6) | 1.38 (1.21-1.56) | 1.25 (1.10-1.42) |

OR: odds ratio, CI: confidence interval, HRT: hormone replacement therapy, IMD: index of multiple deprivation

^a controls were matched to cases on age, calendar date (case index date), GP practice, and years of history in the CPRD before the index date (i.e. the odds ratio is conditional on matching factors)

^b matched OR additionally adjusted for the following categorical variables (yes/no): osteoporosis, smoking, alcohol consumption >14 units/week, diabetes, thiazide prescriptions, dyslipidemia, obesity, vaccine use at any time prior to index date and for >5 GP contacts ≤1 year prior to cohort entry

^c cases with ≤180 days of follow-up and their matched controls as well as any control with ≤180 days of follow-up were excluded

^d hand osteoarthritis preceded or followed by a specialist referral/ discharge (rheumatologist/ orthopedist/ radiologist) or diagnostic work up (MRI, X ray, ultrasonography) within 90 days before or after the diagnosis. Other hand osteoarthritis cases and their matched controls were excluded

^e Women with a history of fibromyalgia or carpal tunnel syndrome/surgery prior to cohort entry were additionally excluded. Follow-up of women with a record of fibromyalgia or carpal tunnel syndrome/surgery was censored upon its occurrence (during follow-up).