EXTENDED REPORT

Hormone replacement therapy and mid-term implant survival following knee or hip arthroplasty for osteoarthritis: a population-based cohort study

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ABSTRACT

Objectives Osteolysis and subsequent prosthesis loosening is the most common cause for revision following total knee arthroplasty (TKA) or total hip arthroplasty (THA). Hormone replacement therapy (HRT) could reduce osteolysis through its antiresorptive effects. We studied whether HRT use is associated with reduced revision rates in a community-based cohort of women undergoing TKA or THA for osteoarthritis.

Methods Female participants in the General Practice Research Database undergoing a primary TKA or THA from 1986 to 2006 were included. We excluded patients aged <40 years at the date of primary, and those with a history of previous hip fracture or rheumatoid arthritis. Women with at least 6 months of HRT were identified as HRT users. We further explored the associations among HRT use of ≥12 months, adherence (medication possession ratio) and cumulative use and revision risk. Cox models were fitted to model implant survival in years. Propensity score matching was used to control for confounding.

Results We matched 2700 HRT users to 8100 non-users, observed for a median (IQR) of 3.3 (1.5–6.1) years after TKA/THA. HR for HRT ≥6 months was 0.62 (95% CI 0.41 to 0.94), whereas HR for ≥12 months was 0.48 (0.29 to 0.78). Higher adherence and therapy duration were associated with further reductions in revision rates. Preoperative HRT appeared unrelated to implant survival.

Conclusions HRT use is associated with an almost 40% reduction in revision rates after a TKA/THA. These findings require replication in external cohorts and experimental studies.

BACKGROUND

Lower limb osteoarthritis (OA) is increasingly common worldwide, and accounted for more than 90% of the 153 000 total knee arthroplasty (TKA) and total hip arthroplasty (THA) procedures carried out in the UK in 2010.1 There is no cure for OA and TKA and THA are the most effective treatments for severe knee and hip OA.2,3 The rates of primary arthroplasties are increasing4–6 due to an increasingly elderly population in addition to an increasing prevalence of obesity.

Together with patient reported outcomes,3 implant survival constitutes the most important element in the evaluation of TKA/THA surgery; revision surgery offers poorer clinical results7,8 and is more costly than primary arthroplasty.6 According to the 8th annual report of the National Joint Registry for England and Wales, revision rates were estimated at 2.3% for THA and 2.2% for TKA after 3 years of follow-up.1 The main causes for failure after the first year are osteolysis and subsequent aseptic loosening, which account for approximately 75% and 40% of revision surgeries after THA and TKA respectively in this same report.1 These occur as a consequence of osteolysis around the prosthesis leading to its migration and, eventually, to function impairment and symptomatic failure.9

Strategies aimed at reducing periprosthetic osteolysis and the consequent bone loss and migration would seem a logical way to reduce arthroplasty failure and hence the need for revision. Antiresorptive agents, due to their antiosteoclastic activity, have been tested for this purpose: several randomised controlled trials10–13 but not all14 have suggested that bisphosphonates could be effective in improving surrogate outcomes. Further, a recent observational study carried out by our group has demonstrated that bisphosphonate use significantly improves implant survival.15

Hormone replacement therapy (HRT) has antiresorptive effects, and was widely used in the 1980s and 1990s, offering an excellent opportunity for research on the potential effects of this kind of drug on long-term implant survival wherever follow-up data for more than 5 years are available.

We took advantage of the existence of a validated source of such data in the UK within the General Practice Research Database (GPRD),14 and aimed to test whether HRT is associated with reduced rates of revision surgery following lower limb total joint replacement.

METHODS

Study design

This is a population-based retrospective cohort study.

Study population and setting

We screened the GPRD to identify all women with a medical diagnosis code for primary THA or TKA from 1986 to the end of 2006. The GPRD comprises of computerised records of all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, medication prescription data, clinical events, specialist referrals, hospital admissions and their major outcomes in a sample of 6.5 million patients from 433 contributing practices, chosen to
Clinical and epidemiological research

be representative of the wider UK population. The GPRD is administered by the Medicines and Healthcare products Regulatory Agency. Only practices that pass quality control are used as part of the GPRD database. Deletion or encoding of personal and clinic identifiers ensures the confidentiality of information in the GPRD. Data are stored using OXMIS and Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9) and we used these to identify primary TKA and THA. The used list of codes is available online as supplementary table 1, and shown to be valid to identify patients undergoing TKA/THA in GPRD data for the study period.4

Women were included in this study if they were aged at least 40 years at the time of primary surgery, and those with a medical diagnosis code for rheumatoid arthritis were excluded. We also excluded those with a history of hip fracture prior to primary hip arthroplasty as we could not accurately ascertain whether participants were undergoing THA for OA or for the hip fracture or its late complications. Using these criteria, we identified 24 733 patients.

Ascertainment of outcome
The main outcome of this study was time from primary THA/TKA to implant failure. Subjects with a revision surgery procedure were identified using ‘Read/OXMIS codes’. Participants were followed up until revision date (outcome), loss to follow-up (death or transfer out of the primary care practice), end of year 10 following THA/TKA or end of study (31/12/2006), whichever came first.

Main exposure: HRT use
Participants who had been prescribed HRT by their general practitioner either for at least 6 months before implant revision with a high adherence (medication possession ratio (MPR) >80%, calculated as the number of daily doses received divided by the number of days of follow-up) or if at least six prescriptions had been filled in the first 6 months after treatment initiation were identified as HRT users. Conversely, HRT non-users were defined as those who did not fulfill any of these two criteria, as well as those who had their first prescription of HRT after implant revision.

Covariates
The following potential confounders were considered in the analyses: age, gender, body mass index (BMI), joint replaced (hip/knee), year of joint replacement operation, recorded diagnosis of OA (yes/no), fracture presurgery (yes/no), calcium and vitamin D supplements, use of bisphosphonates, use of selective oestrogen receptor modulators, oral glucocorticosteroid therapy, smoking status and alcohol intake recorded closest to the date of the primary surgery, General Practitioner (GP) practice deprivation score (as defined by the Index of Multiple Deprivation), region of UK, comorbid conditions registered by the physician from the following list (asthma, malabsorptive syndromes, inflammatory bowel disease, hypertension, hyperlipidaemia, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, chronic kidney failure, neoplasms, diabetes), and use of drugs which can affect fracture risk (proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, anti-Parkinson drugs, statins, thiazide diuretics, anxiolytics).

Statistical analyses
To address the issue of confounding by indication, we used propensity score matching methods.16 The propensity score represents the probability that a patient is an HRT user, and was estimated for the whole study population using multivariate logistic regression models.17 In such models, HRT use was a binary outcome, and all the covariates as listed above were introduced as potential confounders. We used multiple imputation (ICE procedure in Stata18) for important missing covariates (BMI, smoking and alcohol intake) for the propensity score models. We imputed the values of these three variables in 10 different datasets using the following covariates as potentially explanatory variables: fracture history, socio-economic status, year of TKA/THA, age at surgery, use of concomitant medications, cardiovascular disease, OA, type 2 diabetes, malignancies, chronic kidney disease, joint replace (knee/hip), number of comorbid conditions and region.

Propensity scores were used to match each HRT user to three comparable non-users using a 0.02 SD calliper.19 This is a standard method for minimising confounding by indication which provides participants with balanced baseline characteristics in both treatment arms and eliminates drug users with no comparable controls as well as unexposed participants with measurable contraindications.20 HRT users and matched non-users were included in Cox regression survival models to estimate the effect of HRT use on implant survival. Proportional hazards assumptions were checked using the formal Schoenfeld's residuals test.

In these models, HRT users who started therapy postoperatively were imputed the date when they were defined as drug users (6 or 12 months after first prescription) as index date, and corresponding matched non-users were assigned the same index date. HRT users who started HRT treatment before surgery and their matched non-users had joint replacement date defined as their index date. This method has been proposed as a solution to overcome immortal time bias in pharmaco-epidemiological studies.21

In order to investigate whether the timing of therapy initiation has an impact on implant survival, we differentiated HRT users with a first prescription before primary arthroplasty from those who started HRT after surgery. We then compared these with HRT non-users using similar Cox regression models.

Sensitivity analyses
A series of sensitivity analyses were carried out in order to test whether the existing association between HRT use and time to revision could be causal. First, HRT use was redefined: only patients with at least 12 prescriptions were here considered HRT users with controls rematched to the new index date (date of first prescription of HRT plus 12 months). Second, we categorized HRT users into low adherence (MPR <0.4), intermediate adherence (MPR 0.4 to <0.8) and high adherence (MPR ≥0.8), and estimated HRs for each of these categories when compared with HRT non-users after adjusting for propensity scores. Finally, in order to study whether a higher cumulative use of HRT provided better protection, we classified HRT users into: <365 daily defined doses (DDD), 365–1065 DDDs and >1065 DDDs. Propensity-adjusted HRs were calculated for each of these using the methods described above.

One final sensitivity analysis was run to measure the potential impact that possible unobserved confounders could have on our findings: the Rosenbaum boundaries sensitivity analysis22 23 measures the required imbalance of a confounder to explain the observed associations (if any) in propensity-matched cohort analyses.

All statistical analyses were carried out in Stata IC (V12).
RESULTS
Out of the eligible 24,733 women identified, 3,644 were defined as HRT users, and the remaining 21,089 were non-users. Out of these, propensity-matching methods were used to select 2,700 HRT users and three comparable controls (8,100 women). These were followed up for a median (inter-quartile range) of 3.3 (1.5–6.1) years after primary arthroplasty (figure 1), making a total of 43,481 person-years (32,845 HRT non-users and 10,636 HRT users) of observation. Baseline characteristics for both arms are shown in table 1. Matched HRT users and non-users only differed significantly in the use of medications with a potential deleterious effect on fracture risk (see Covariates section above), which was higher in HRT users. The final propensity score logistic equation yielded a c statistic of 0.81 (95% CI 0.80 to 0.81), indicating a good ability to predict HRT use.

Out of the 10,800 study participants, 10,632 (98.4%) were censored before revision (8,609 subjects at end of study, 803 at the end of year 10 postsurgery and 1,220 lost to follow-up) and 168 (1.6%) were revised. Overall cumulative revision rate at 3 years were 0.97% (0.74% to 1.25%) for THA and 0.76% (0.53% to 1.05%) for TKA. HRT use for at least 6 months was associated with a significant reduction in risk of failure: failure incidence was 2.61/1000 person-years-at-risk (pyar) (1.79 to 3.61) in HRT users, and 4.25 (3.81 to 5.02) pyar among HRT non-users, with corresponding HR of 0.62 (0.41 to 0.94; p=0.023) (figure 2). Adjustment for use of drugs with a potential deleterious effect on bone metabolism did not change these results: HR 0.61 (0.40 to 0.92; p=0.019). Similarly, use of HRT for a year or more was related to a further reduction in failure risk: HRT 0.48 (0.29 to 0.78; p=0.003). When HRT users were stratified into those starting therapy before or after primary arthroplasty, no significant protection was observed for those starting preoperatively (HR 1.06 (0.66 to 1.70; p=0.80)), but a strong protective effect was present for those with a first prescription after surgery (HR 0.24 (0.10 to 0.55); p=0.001) (table 2).

In addition, there was a significant association between HRT adherence and implant survival (p for trend 0.007): HR 0.70 (0.44 to 1.14; p=0.15) for HRT users with an MPR of <0.4; HR 0.66 (0.29 to 1.50; p=0.33) for those with an MPR of 0.4 to <0.8; and HR 0.22 (0.05 to 0.89; p=0.033) for users with an MPR ≥0.8 (table 3, figure 3A).

Similarly, cumulative use of HRT was also directly related to prosthesis survivorship (p for trend 0.008): HR 1.23 (0.63 to 2.42; p=0.54) for users of <365 DDDs; HR 0.40 (0.19 to 0.86; p=0.019) for users of 365 to 1065 DDDs; and HR 0.53 (0.29 to 0.99; p=0.046) for HRT users with >1065 DDDs (table 3, figure 3B).

Finally, a Rosenbaum boundaries sensitivity analysis suggested a γ of 1.50 for the observed association between 6-month HRT use and implant survival. This means that for any unmeasured confounder to explain the observed association, that confounder would need to produce a 30% increase in the odds of receiving HRT. This same analysis, when applied to the 12-month HRT analysis, suggested a γ of 1.65, suggesting that a confounder related to a 65% imbalance in the probability of receiving HRT would explain the observed association.

DISCUSSION
Key findings
We have shown that HRT use for at least 6 months after primary arthroplasty is associated with a significant reduction in prosthesis failure of up to almost 40% after lower limb total joint arthroplasty. Hormone therapy for at least 1 year appeared related to further reduction in failure rates to about 50% of that in HRT non-users. In addition, higher adherence to HRT, as well as higher duration of the treatment, appeared directly related to improved effects on implant survival.

Preoperative HRT use did not appear related to implant survival in these data.

Interpretation
Aseptic loosening, leading to symptomatic failure, is the most common indication of late revision surgery after a THA/TKA.24 The mechanisms underlying loosening are still obscure, but it is widely accepted that periprosthetic bone loss secondary to chronic inflammation and osteoclastic activity is the main pathway. Osteolysis within this process can be at least partially prevented with antiresorptive agents,25 and bisphosphonates seem to be currently the group of drugs with a wider body of evidence to support them: most of the clinical trials carried out up to date10 11 pointed towards a beneficial effect on surrogates for loosening, such as periprosthetic bone loss or implant migration. In addition, a recent cohort study has suggested that bisphosphonate therapy could also extend implant survival and almost halve the risk of failure.15

Regarding HRT, animal studies have suggested that oestrogen deficiency exerts a negative influence on bone tissue around knee implants, while HRT minimises periprosthetic bone loss26 and improves bone ingrowth around the implant,27 comparable with alendronate therapy28 and more effectively than calcitonin.29 Some studies have shown that both in animals30 and in
humans, treatment with HRT improves osseointegration after dental implantation surgery. These are the first data, to our knowledge, that have been published describing the effect of HRT on prothesis survival in women undergoing a TKA/THA.

The observed lack of association between preoperative HRT use and implant survival can be due to several reasons. We speculate that reducing bone resorption before surgery might have deleterious effects on the integration of the prosthesis immediately after surgery. In contrast, postoperative initiation of HRT appeared strongly associated with an improved implant survival in our data. These findings are novel and require validation in future studies.

As the rate of revision at 7 years is under 5% (NJR), it is likely that any antiresorptive drugs would be used in a targeted manner to patients identified as being at high risk of failure. Given the risk of venous thromboembolic events with HRT, HRT should be stopped 6 weeks before and after surgery. This is supported by our observation that the protective effect of HRT was only evident when started after and not before the primary arthroplasty. These findings are encouraging for the research of antiresorptive agents that might improve outcomes following total joint replacement surgery in the future.

Strengths and limitations

Our study has several strengths and limitations. The main limitation of this study is its observational nature. We have used propensity score matching to control for confounding by indication, which has been proposed as the gold standard analytical strategy to reduce such confounding. Unsolved issues are residual confounding (due to unobserved variables, such as bone mineral density, ethnicity or design of implant or type of fixation) and the lack of a placebo drug to which HRT can be

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total population (n=10 800)</th>
<th>HRT users (n=2700 (74.1%))</th>
<th>HRT non-users (n=8100 (1 to 3))</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.7 (8.2)</td>
<td>64.5 (7.7)</td>
<td>64.8 (8.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 (5.4)</td>
<td>28.4 (5.5)</td>
<td>28.5 (5.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Smoking status</td>
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<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Yes</td>
<td>1330 (12.3%)</td>
<td>340 (12.6%)</td>
<td>990 (12.2%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6455 (60.0%)</td>
<td>1624 (60.1%)</td>
<td>4831 (59.6%)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>2934 (27.2%)</td>
<td>710 (26.3%)</td>
<td>2224 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>Current alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Yes</td>
<td>7892 (73.1%)</td>
<td>1958 (73.3%)</td>
<td>5934 (73.3%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1310 (12.1%)</td>
<td>345 (12.8%)</td>
<td>965 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Ex-drinker</td>
<td>847 (7.8%)</td>
<td>205 (7.6%)</td>
<td>642 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>Joint replaced (hip)</td>
<td>6060 (56.1%)</td>
<td>1549 (57.4%)</td>
<td>4511 (55.7%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Knee/hip OA</td>
<td>9118 (84.4%)</td>
<td>2278 (84.4%)</td>
<td>6840 (84.4%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Diabetes</td>
<td>882 (8.2%)</td>
<td>217 (8.0%)</td>
<td>665 (8.2%)</td>
<td>0.78</td>
</tr>
<tr>
<td>CVD</td>
<td>471 (4.4%)</td>
<td>126 (4.7%)</td>
<td>345 (4.3%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Deprivation score (GP practice)</td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>0</td>
<td>2639 (24.4%)</td>
<td>678 (25.3%)</td>
<td>1961 (24.4%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1854 (17.2%)</td>
<td>441 (16.5%)</td>
<td>1413 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2260 (20.9%)</td>
<td>558 (20.8%)</td>
<td>1702 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2117 (19.6%)</td>
<td>538 (20.1%)</td>
<td>1579 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1840 (17.1%)</td>
<td>464 (17.3%)</td>
<td>1376 (17.1%)</td>
<td></td>
</tr>
<tr>
<td>Number of comorbid conditions*</td>
<td></td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>0</td>
<td>4166 (38.6%)</td>
<td>1061 (39.3%)</td>
<td>3105 (38.3%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4071 (37.7%)</td>
<td>1006 (37.3%)</td>
<td>3065 (37.8%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1828 (16.9%)</td>
<td>459 (17.0%)</td>
<td>1369 (16.9%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>554 (5.1%)</td>
<td>134 (5.0%)</td>
<td>420 (5.2%)</td>
<td></td>
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<tr>
<td>≥4</td>
<td>181 (1.7%)</td>
<td>40 (1.5%)</td>
<td>141 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Failures (0–10 years)</td>
<td>168 (1.56%)</td>
<td>27 (1.00%)</td>
<td>141 (1.74%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Follow-up time before failure (years)†</td>
<td>3.29 (1.50–6.09)</td>
<td>3.23 (1.51–5.97)</td>
<td>3.33 (1.50–6.13)</td>
<td>0.18</td>
</tr>
<tr>
<td>Fracture prior to primary surgery</td>
<td>1444 (13.4%)</td>
<td>364 (13.5%)</td>
<td>1080 (13.3%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Bisphosphonate use</td>
<td>685 (6.3%)</td>
<td>178 (6.6%)</td>
<td>507 (6.3%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Calcium–vitamin D supplements use</td>
<td>151 (1.4%)</td>
<td>47 (1.7%)</td>
<td>104 (1.3%)</td>
<td>0.080</td>
</tr>
<tr>
<td>Oral corticosteroid use</td>
<td>38 (0.35%)</td>
<td>10 (0.37%)</td>
<td>28 (0.35%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Other medications‡</td>
<td>2860 (26.5%)</td>
<td>761 (28.2%)</td>
<td>2099 (25.9%)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

*Any of the following: asthma, malabsorption syndromes, inflammatory bowel disease, hypertension, hyperlipidaemia, ischaemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure and cancer.

†Median (IQR) is reported.

‡Any of the following: antiarrhythmic drugs, anticonvulsants or tricyclic antidepressants.

BMI, body mass index; CVD, cardiovascular disease; HRT, hormone replacement therapy; OA, osteoarthritis.
compared. The GPRD has been widely used for epidemiological research, and has previously been shown to be valid for prescription data and discrete outcomes such as fracture and surgery. However, we cannot exclude that in a small number of cases, the side of primary or revision surgery may be contralateral to the index primary. This would lead to a misclassification of the outcome, a random bias and therefore would drive any association of HRT with revision towards the null hypothesis.

Although propensity scores are one of the gold standard methods to account for confounding by indication, there is always the risk of unobserved (residual) confounding. Based on our Rosenbaum sensitivity analysis, one such unmeasured confounder would need to be associated with a 30%–65% increase in revision rates to explain the observed association between HRT use (6 and 12 months, respectively) and implant survival. The most likely unobserved predictor of revision in our data is implant type and fixation: there are no data available in GPRD either about the type of prosthesis used or on the use of

Table 2  Cox models on the effect of hormone replacement therapy (HRT) use on implant survival

<table>
<thead>
<tr>
<th>Exposure</th>
<th>N (%)</th>
<th>Failure incidence (/1000 person-years) (95% CI)</th>
<th>HR (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT ≥6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8100 (75.0%)</td>
<td>4.22 (3.57 to 4.98)</td>
<td>REF</td>
</tr>
<tr>
<td>Yes</td>
<td>2700 (25.0%)</td>
<td>2.61 (1.79 to 3.81)</td>
<td>0.62 (0.41 to 0.94); p=0.023</td>
</tr>
<tr>
<td>HRT ≥12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8566 (78.2%)</td>
<td>4.29 (3.65 to 5.04)</td>
<td>REF</td>
</tr>
<tr>
<td>Yes</td>
<td>2388 (21.8%)</td>
<td>2.05 (1.29 to 3.26)</td>
<td>0.48 (0.29 to 0.78); p=0.003</td>
</tr>
<tr>
<td>HRT time of initiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-user</td>
<td>8100 (75.0%)</td>
<td>4.25 (3.60 to 5.02)</td>
<td>REF</td>
</tr>
<tr>
<td>Preoperative</td>
<td>1639 (15.2%)</td>
<td>4.47 (2.89 to 6.93)</td>
<td>1.10 (0.69 to 1.77); p=0.70</td>
</tr>
<tr>
<td>Postoperative</td>
<td>1061 (9.8%)</td>
<td>1.15 (0.52 to 2.56)</td>
<td>0.24 (0.10 to 0.53); p=0.001</td>
</tr>
<tr>
<td>p Value for trend</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Sensitivity analyses: effect of adherence and cumulative use of HRT on implant survival

<table>
<thead>
<tr>
<th>Exposure</th>
<th>N (%)</th>
<th>Failure incidence (/1000 person-years) (95% CI)</th>
<th>HR (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT MPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-user</td>
<td>8100 (75.0%)</td>
<td>4.25 (3.61 to 5.02)</td>
<td>REF</td>
</tr>
<tr>
<td>&lt;0.4</td>
<td>1631 (15.1%)</td>
<td>3.04 (1.94 to 4.76)</td>
<td>0.70 (0.44 to 1.14); p=0.15</td>
</tr>
<tr>
<td>0.4 to &lt;0.8</td>
<td>594 (5.5%)</td>
<td>2.98 (1.34 to 6.63)</td>
<td>0.66 (0.29 to 1.50); p=0.33</td>
</tr>
<tr>
<td>≥0.8</td>
<td>475 (4.4%)</td>
<td>0.97 (0.24 to 3.86)</td>
<td>0.22 (0.05 to 0.89); p=0.033</td>
</tr>
<tr>
<td>p Value for trend</td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>HRT cumulative use (DDD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-user</td>
<td>8100 (75.0%)</td>
<td>4.25 (3.61 to 5.02)</td>
<td>REF</td>
</tr>
<tr>
<td>&lt;365</td>
<td>507 (4.7%)</td>
<td>5.24 (2.73 to 10.07)</td>
<td>1.23 (0.63 to 2.42); p=0.54</td>
</tr>
<tr>
<td>365 to 1065</td>
<td>1180 (10.9%)</td>
<td>5.14 (0.83 to 3.65)</td>
<td>0.04 (0.19 to 0.86); p=0.019</td>
</tr>
<tr>
<td>&gt;1065</td>
<td>1013 (9.4%)</td>
<td>2.39 (1.33 to 4.32)</td>
<td>0.53 (0.29 to 0.99); p=0.046</td>
</tr>
<tr>
<td>p Value for trend</td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
</table>

DDD, daily defined doses; HRT, hormone replacement therapy; MPR, medication possession ratio; REF, reference group.
cement. According to data from the National Joint Registry,16 3-year revision rates can vary from 0.98% to 2.2% for THA and from 1.4% to 2.1% for TKA based on these two elements. Therefore, only an unexpected strong association between HRT use and implant used, for which there is no previous evidence or biological plausibility, would explain our findings.

Finally, the revision rates observed in our data (about 2% for a median 3.3 years of follow-up) are similar to those reported by the National Joint Registry (1.7% for THAs and 1.8% for TKAs for 3 years of follow-up),16 suggesting completeness of the data. However, it must be admitted that the study period (1986–2006) could explain some differences in revision rates in our data compared with the most current National Joint Registry report (clinical activity in 2012). For all these reasons, our findings require replication in external cohorts and, if possible, in randomised controlled trial data, before these results can be implemented in clinical practice.

The main strengths of this study are the number of participants studied and the duration of follow-up. Furthermore, it is a population-based study, which increases the generalisability of the results. Data from GPRD include all population groups, including older and high complexity patients, and are fully representative of clinical practice in the UK, as clinical information is collected through actual primary care practice.

CONCLUSIONS
In our observational cohort study, HRT use after arthroplasty is associated with an almost 40% reduction in implant failure after a TKA/THA for OA. Higher adherence and longer treatment duration further improve implant survival. These findings require replication in experimental studies.

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Collaborators The Coast Study Group—The COAST Study Group consists of the following members: Mark Mullee, James Rafferty, Andrew Carr, Andrew Price, Kassim Javid, David Beard, Douglas Altman and Nicholas Clarke.

Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. DP-A had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: DP-A, NKR, AJ, MKJ and CC. Acquisition of data: DP-A, CC, JM and NKA. Analysis and interpretation of data: DP-A, JM, MKJ, AJ, CC and NKA.

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Competing interests All authors have completed the统一竞争利益声明 form at http://www.icr.org/doi_disclosure.pdf (available on request from the corresponding author) and declare: this article presents independent research commissioned by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research funding scheme (RP-PG-0407-10064) and unrestricted educational grants from Merck, Sharpe and Dohme, Novartis and Southampton Rheumatology Trust; Daniel Prieto-Alhambra received partial funding by the Instituto Catálico de la Salud-IDIAP Jordi Gol; all authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Hormone replacement therapy and mid-term implant survival following knee or hip arthroplasty for osteoarthritis: a population-based cohort study

D Prieto-Alhambra, M K Javaid, A Judge, J Maskell, C Cooper and N K Arden

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