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Summary boxes

What is already known on this subject

Laboratory studies and small trials have suggested a beneficial link between use of hormone replacement therapy (HRT) and age-related brain decline. The Womens' Health Initiative Memory Study, however, found an increased risk of developing dementia among users of oestrogen-progestogen treatments. A recent large observational study, based on the Finnish national registries, has flagged an increased risk of developing Alzheimer's disease both among users of oestrogen-only and oestrogen-progestogen treatments, but this study had a number of methodological weaknesses, which call into question the reliability of their estimates.

What this study adds

This study shows, for all commonly prescribed HRT treatments within the UK, no increased risk associations for the development of dementia globally. Specifically for Alzheimer's disease, it does show a small increased risk but associated only with more than 5 years of use of oestrogen-progestogen treatments. A large observational study, it also provides the most detailed estimates of risk for individual treatments.

Abstract

Objective

To assess risks of developing dementia associated with different types and durations of HRT treatments

Design

Two nested case-control studies

Setting

UK general practices contributing to QResearch or the Clinical Practice Research Datalink (CPRD), using all links to hospital, mortality and social deprivation data.

Participants

118,501 women aged 55 and older with a primary diagnosis of dementia between 1998 and 2020, matched by age, general practice and index date to 497,416 female controls.

Main outcome measures

Dementia diagnoses from general practice, mortality and hospital records. Odds ratios for HRT treatment types adjusted for: demographics; smoking status; alcohol consumption; comorbidities; family history; other prescribed drugs.

Results

Overall, 16,291 (14%) women diagnosed with dementia and 68,726 (14%) controls had used hormone replacement therapy prior to three years before the index date. Overall, we found no increased risks of developing dementia associated with HRT use. A decreased global dementia risk

was found among cases and controls younger than 80 years who had been on oestrogen-only therapy for 10 years or more (adjusted odds ratio 0.85, 95% confidence interval 0.76 to 0.94). Increased risks of developing specifically Alzheimer's disease were found among women who had used oestrogen-progestogen therapy for between 5 and 9 years (1.11, 1.04 to 1.20) and for 10 years or more (1.19, 1.06 to 1.33). This was equivalent to, respectively, 5 and 7 extra cases per 10,000 women-years. Detailed risk associations for the specific progestogens studied are also provided.

Conclusion

This study gives estimates for risks of developing dementia and Alzheimer's disease in women exposed to different types of HRT for different durations, and has demonstrated no increased risks of developing dementia associated with HRT use overall and an only slightly increased risk of developing Alzheimer's disease among long-term users of oestrogen-progestogen therapies.

Introduction

Menopause often manifests itself in a variety of both mental and physical symptoms, such as hot flushes, sleep disturbance, depression or cognitive dysfunction and about 80% of menopausal women are affected by such symptoms. Of these women, about 70% have symptoms that may also be associated with warnings of future neurological decline.[1] Sex hormones, and particularly oestrogen, have been shown to have a neuroprotective effect, so declining levels of these may in fact contribute to development of neurogenerative diseases.[2] While the severity of menopausal symptoms differs widely across the female population, the prescribing of oestrogen for at least some patients has been described as " appropriate and required".[1]

Although hormone replacement therapy (HRT) clearly eases menopausal symptoms, epidemiological evidence has been inconsistent regarding the effects of such treatments with respect to risks of developing dementia. Small studies using various cognitive and radiological measures have demonstrated beneficial effects from HRT.[3 4] However, the largest randomised controlled trial of HRT, the Womens' Health Initiative Memory Study (WHIMS), which allocated post-menopausal women either to placebo or to conjugated equine estrogen with or without medroxyprogesterone, showed an increased risk of dementia in both treated arms (although results were not statistically significant for oestrogen-only users).[5 6] A smaller trial, ELITE-Cog, reported no evidence of harm or of benefit on brain functions from HRT use.[7] Two Finnish observational studies, based on national registries, have also provided conflicting results for risk of Alzheimer's disease in HRT users.[8 9] The first showed decreased risks for long-term oestrogen use and no associations for long-term oestrogen-progestogen use,[8] while the second suggested increased risks for oestrogen treatments, with and without progestogen.[9] Both studies suffered from a relative lack of historical data on HRT prescriptions, with even the more recent study including only cases diagnosed up to 2013. HRT is also associated with other adverse effects like venous thromboembolism or breast cancer, so the benefit *vs* risk of prescribing is finely balanced. The current National Institute for Health and Care

Excellence (NICE) guideline stresses the need for more detailed information on side-effects and adverse outcomes of HRT.[10] Our previous studies on venous thromboembolism and breast cancer risks have shown a range of risk associations with different HRT preparations, highlighting dydrogesterone as a potentially low risk progestogen.[11 12]

This study uses a large data sample from primary care records to investigate the risks of developing dementia following HRT use. It was designed with sufficient power to assess not only overall risk for women exposed to different types of long-term HRT, but also to explore the differences between component hormones. The richness of the data available from two of the largest UK primary care databases (CPRD and QResearch), together with linked hospital data, has allowed us to adjust for many more possible confounding factors, so offering new, more reliable estimates for doctors and their patients.

Methods

Study design

The published protocol contains full details of this study.[13] In summary, we used two large UK primary care databases, QResearch and Clinical Practice Research Datalink (CPRD) GOLD, to conduct two nested case-control studies. The data sources used were all general practices, which had contributed to a database for more than 10 years. Each database provided an open cohort of all women aged over 55 and registered between 1st January 1998 and 31st July 2020. Women were excluded if, prior to their study entry, they had records either for dementia or dementia related prescriptions.

Selection of cases and controls

For both databases, all cases between 1st Jan 1998 and 31st July 2020 were identified using codes for dementia from patient clinical records or records of prescriptions for drugs used to treat dementia – donepezil, rivastigmine, memantine and galantamine. For QResearch, general practice records, hospital episode statistics and mortality data were all used. For CPRD, only a proportion of practices (45%) were linked to hospital and mortality data, so cases from unlinked practices were defined using only general practice records. Using incidence density sampling,[14] cases were matched by year of birth to up to 5 controls – women from the same practice but without a dementia diagnosis at the time of diagnosis of their case (index date). Only those cases and controls with at least 10 years of medical records before the index date were included. There was no overlap between the two sets of cases and controls, because a patient can be registered with only one practice, and QResearch and CPRD GOLD receive data from practices using different computer systems.

Exposure to hormone replacement therapy

We extracted all prescriptions indicated for menopausal treatment for systemic oestrogen and progestogen (oral, subcutaneous or transdermal). The prevalence rate of HRT prescribing by general practitioners was assessed from the CPRD study population. For each study year the number of women with at least one HRT prescription was divided by the total number of women, all being registered for the whole year of interest.

Early symptoms of dementia prior to diagnosis, such as sleep problems or depression, may be taken for menopause symptoms and cognitive decline may also be associated with a cessation of hormone replacement therapy. So, to minimise possible protopathic bias, we excluded HRT prescriptions issued in the last three years before the index date from our main analysis.[15] However, we also ran a sensitivity analysis using all records up to one year before the index date, to check whether any under-reporting bias had been introduced by this exclusion of prescriptions.

A first prescription for systemic oestrogen was taken as initiation of HRT exposure. Patients with no prescriptions containing a progestogen after this date were classified as users of an oestrogen-only therapy. Patients with any subsequent prescription containing a progestogen were classified as a combined therapy users. Prescriptions for tibolone, clonidine and topical hormonal preparations (vaginal pessaries or cream) were included, because these are commonly prescribed to menopausal women.

To address switching between hormonal therapies, we analysed exposures to different preparations separately. For oestrogen only users, we considered two types of oestrogen (conjugated equine oestrogen and estradiol), two routes of application (oral or transdermal/ injection) and two dosage levels – low (defined as ≤0.625 mg/day for oral conjugated equine oestrogen, ≤1 mg/day for oral estradiol, and ≤50 mg for transdermal estradiol) and high (all other doses). For oestrogen-progestogen users, we focused on progestogen types (norethisterone acetate, levonorgestrel,

medroxyprogesterone and dydrogesterone) and did not distinguish between oestrogen types. Norethisterone and dydrogesterone, however, were prescribed only with estradiol and medroxyprogesterone and levonorgestrel were prescribed mostly with conjugated equine oestrogen.[12] Some oestrogen-progestogen users still had periods when they were prescribed oestrogen-only therapy, and these exposures were included.

Durations of exposure were calculated by summing prescription periods (including inter-prescription gaps of fewer than 90 days) and categorising as: never; <1 year; 1 to <3 years; 3 to <5 years; 5 to <10 years; 10 years or more. The time interval between the index date and the last prescription (prior to 3 years before the index date) was categorised as: between 3 and <5 years; 5 to <10 years; 10 years or more. To assess whether associations between HRT and dementia risk depend on age at initiation of HRT, we also analysed separately exposures to HRT initiated before the age of 60 from those initiated at or after 60. For all treatments, no exposure prior to 3 years before the index date was the reference category.

Confounders

We adjusted the analyses for indications for HRT use and factors associated with dementia risk, which may influence a doctor's prescribing decisions.[16] These were extracted if recorded at least 10 years before the index date to make them closer to the likely time of HRT use. A sensitivity analysis using confounders recorded up to 3 years before the index date was also conducted.

The confounders are listed in Table 1 and include: lifestyle factors; self-assigned ethnicity; family history of dementia; records of early menopause; oophorectomy/hysterectomy; menopausal symptoms; co-morbidities, including chronic conditions; use of other relevant medications (if prescribed at any time prior to 10 years before the index date).

Statistical analysis

Data extraction, processing and analysis were run separately for QResearch and CPRD. The analyses were as similar as the data sets permitted. Dementia risks associated with HRT exposures were assessed using conditional logistic regression and presented as odds ratios with 95% confidence intervals. A small proportion of data for body mass index, smoking and alcohol consumption were missing. We compared the patterns of missingness and assumed missingness at random, and then imputed the values using chained equations over ten imputed datasets. The imputation model included all listed confounders, exposures and case-control indicators, and the odds ratios obtained from the imputed datasets were combined using Rubin's rule.[17]

The odds ratios obtained from the analyses of QResearch and CPRD were combined using a meta-analysis technique.[18] Because the data were collected in the same setting and processed and analysed as similarly as possible, we used a fixed effect model with inverse variance weights to combine the results, checking for any heterogeneity with a sensitivity analysis using a random effect model. Only combined results appear in the main figures or text – the separate QResearch and CPRD results can be found in the supplementary data.

To estimate absolute magnitudes of dementia risk for women in different exposure categories, we calculated rates and numbers of extra cases, determining incidence rate in the unexposed female population from CPRD data and using combined odds ratios from the reported analyses.[19]

All analyses were performed using Stata 16. A 1% level of statistical significance was chosen to allow for multiple comparisons, but 95% confidence intervals have been presented to facilitate comparison with other studies.

Additional analyses

HRT was not widely prescribed until the late 1980s,[20] so older women in the cohort might have experienced lesser exposure. To address this possible inconsistency, we analysed women younger than 80 years at their date of diagnosis of dementia or index date and their controls separately from those women aged 80 or older and their controls.

We also analysed separately two subgroups of cases and their controls – the first restricted to cases diagnosed with Alzheimer's disease and the second to cases diagnosed with vascular dementia. This provided estimations of the specific risks associated with HRT use of developing these dementia types and facilitated comparison with other studies.

The results from the subgroup analysis restricted to cases with Alzheimer's disease suggested a possible relationship between continuous durations of HRT exposure and risk of developing the disease. So we used fractional polynomials [21] to model the associations, selected the linear relationship suggested, and ran these analyses using continuous exposure – separately for each database and combining the coefficients using the meta-analysis technique described earlier.

All available records were used for the main analysis. As only about 45% of CPRD practices had links to HES, ONS mortality data and patient-level Townsend deprivation index, we repeated the CPRD analysis on the subgroup of patients with fully linked data. We also ran sensitivity analyses on both databases omitting cases identified only by prescription for a dementia drug. It is possible that some women might have been exposed to HRT before registering with their practice or before the practice installed software to digitise paper records. To address this possibility, we repeated these analyses using subgroups of women with data available from before or at their 50th birthday to investigate the possible effects of some women having unrecorded earlier exposures. Finally, we repeated the analysis using only cases and controls with no missing data for body mass index, smoking or alcohol consumption.

Patient and Public Involvement

This study was initiated because the National Institute for Clinical Excellence (NICE) has noted a need for more detailed information related to HRT use and dementia, recommending further research.[10] Because dementia is a relatively rare condition, we used routinely collected data and employed well-established statistical techniques. Patients were, therefore, not involved in setting the research question or outcome measures and did not help to develop the study design. While working on previous projects on safety of HRT with respect to risks of breast cancer and venous thromboembolism,[11 12] however, we had formal and informal conversations with menopausal and post-menopausal women. In general, the women stressed the importance for them of access to HRT, and all users demonstrated high adherence to their medications. The first author is also a regular attendee at a Menopause Café event at Nottingham University, which both facilitates the acquisition of useful information about women's experience of menopause and dissemination of our research findings.

Results

Sample description

Overall, there were 118,501 cases across the two databases (68,738 from QResearch and 49,763 from CPRD) matched to 497,416 controls.[Supplementary eFig 1] Of these, 4,819 (4%) cases did not have any clinical records of dementia but had prescriptions for anti-dementia drugs. The proportion of cases with dementia data only in their hospital or mortality records were different in the databases – 7,091(10%) for QResearch cases and 7,942 (30%) for the 26,421 linked CPRD cases.

Table 1 shows the descriptive statistics for cases and controls separately for QResearch and CPRD, demonstrating the general similarity between the databases. Across the databases, the mean age of cases was 83.5 (standard deviation 7.0) years, and the mean number of years of recorded clinical and prescription data prior to the index date were, for cases, 16.0 years (SD 4.3) and, for controls, 15.8 (SD 4.2). Cases had records for mental health conditions (anxiety, depression) slightly but consistently more often than controls, and had more records for other general health conditions (coronary heart disease, diabetes, hearing loss, hypertension, and Parkinson's disease). Cases were also more likely than controls to be prescribed anticholinergics, antihypertensives, benzodiazepines and statins.[Table 1]

Exposure to HRT

Fig 1 shows the prevalence rate for HRT prescribing from the earliest available records in CPRD to three years before the end of the study period. The data shows a prevalence rate for HRT use of 1% in 1988, rising consistently to reach a peak by 2000 (30% for women between 50 and 59 years of age) and then falling back after 2003, the lowest subsequent rate being 10% in 2013 for women aged between 50 and 59 years.

Overall, up to three years before the index date 16,291 (13.7%) cases and 68,726 (13.8%) controls had been exposed to HRT. Women prescribed HRT were, in general, younger and more likely to live in an affluent area. They were more often diagnosed with anxiety or depression – 38% of HRT users vs 23% of never users in cases, and 32% of users vs 19% of never users in controls. Oestrogen-progestogen users had better general health than never-users or oestrogen-only users, and had lower prevalence of coronary heart disease, stroke, diabetes and hypertension. HRT users were also more likely to be prescribed anticholinergics (consistent across most types), and benzodiazepines. [Supplementary eTable 1]

Main analysis

The "unadjusted" analysis (accounting only for matching of age and general practice) showed small increased risks of developing dementia associated with HRT use.[Supplementary eTable 2] After adjusting for the full range of available confounders, however, we found no statistically significant overall associations between HRT use and dementia risk, neither for oestrogen-only treatments (adjusted odds ratio 0.99, 95% confidence interval 0.96 to 1.02) nor for oestrogen-progestogen treatments (1.00, 0.97 to 1.03). This finding was independent of the length of exposure to HRT and of the length of time after discontinuation of treatment. The finding was also consistent for all different hormone types used in HRT preparations, with slightly lower risks for oestrogen-dydrogesterone taken between 1 and 11 years (0.88, 0.75 to 1.02).[Supplementary eTables 3-6, Fig 2,3] Analysis of risks associated with the age at which HRT had been initiated (at or after 60 years, or before) also revealed no statistically significant associations.[Supplementary eFig 2]

Additional analyses

By age at diagnosis (younger than 80 and 80 or older)

For patients with a diagnosis of dementia, 27% of women had received their diagnosis before the age of 80. The patterns of confounders relating to life style (social deprivation, smoking and alcohol consumption) were similar in both the younger and older subgroups. Younger women had fewer records for most co-morbidities related to general health, but more records related to diabetes and mental health issues (anxiety or depression).

Within the younger group, 30% of cases and 29% of controls had prescriptions for HRT, but only 8% of the older group had ever used HRT. In general, the analyses for risk of dementia in both subgroups gave results similar to the main analysis, but in the younger group exposure to oestrogen-only treatment for more than 10 years was associated with a significantly decreased risk (adjusted odds ratio 0.85, 95% confidence interval 0.76 to 0.94).[Fig 4, Supplementary eTable 7]

By type of dementia (Alzheimer's disease or vascular dementia)

Overall, 39,876 of patients with dementia (34%) had a diagnosis for Alzheimer's disease alone and 24,867 (21%) had a diagnosis for vascular dementia alone, with 3,626 (3%) having diagnoses for both (cases with both diagnoses were added to both subgroups before analysis). Cases with a diagnosis of Alzheimer's disease were slightly younger than cases with vascular dementia, having respectively a mean age of 82.2 (standard deviation 6.9) and 83.4 (6.6). Cases with Alzheimer's disease had lower use of other drugs and slightly better physical and mental health than cases with vascular dementia.

An increased risk of developing Alzheimer's disease was, for oestrogen-only users, shown only in the shortest exposure category of less than 1 year (adjusted odds ratio 1.11, 95% confidence interval

1.02 to 1.22), with no risks associated for longer-term exposures. For oestrogen-progestogen users, however, we found statistically significantly increased risks for the longer exposures (5-9 years 1.11, 1.04 to 1.20; 10 years or more 1.19, 1.06 to 1.33).[Fig 2, Supplementary eTable 8] A linear relationship found between duration of exposure to oestrogen combined with any-progestogen and risk of Alzheimer's disease suggested that risk of developing the disease may increase by 1.2% per year of HRT use.[Supplementary eFig 3]

Analysis of the different HRT hormones showed similar relationships with Alzheimer's disease risk for conjugated equine oestrogen and estradiol and between most types of progestogen, but no findings reached statistical significance. Although based on small numbers and without the same long-term exposure categories for direct comparison (102 user-cases with exposure and durations between 1 and 10 years), the finding for oestrogen-dydrogesterone (adjusted odds ratio 0.92, 95% confidence interval 0.74 to 1.16) appears, however, to suggest a comparatively lower or no increased risk association, in line with main analysis findings.[Fig 3, Supplementary eTable 8]

Within the subgroup of women based on diagnoses for Alzheimer's, the differences in risk between the component subgroup based on women diagnosed when younger than 80 years and the component subgroup based on those diagnosed at 80 or older are presented in Fig 4. The patterns are similar to those for the complete subgroup, but the confidence intervals are wider for the older group. Risks after discontinuation stayed increased for those oestrogen-progestogen users with a final prescription between 3 and 10 years before the index date.[Supplementary eTable 8] Analysis for component subgroups based on HRT initiation at different ages (before 60 years, or at or after) showed no differences in associated risks.[Supplementary eFig 2]

Analyses of cases with vascular dementia and their controls showed no increase in risks.[Supplementary eTable 8]

Sensitivity analyses

The subgroups of cases and controls registered before their 50th birthday represented about 2% of the main sample (942 cases from QResearch and 1689 cases from CPRD). In contrast with the full samples used in the main and other analyses, these subsamples exhibited some differences in makeup between the databases – on average cases from QResearch were older than those from CPRD, respectively 71.1 years (standard deviation 4.4) and 65.4 (6.0), while the proportion of women exposed to HRT was higher in QResearch (53% in cases and controls vs. 49% cases and 46% controls in CPRD). Associated risks also appeared to differ between the databases. Within the QResearch subgroup, there were no statistically significant associations between HRT exposure and dementia risk. Within the CPRD subgroup, however, while the association for oestrogen-only therapy (adjusted odds ratio 1.18, 95% confidence interval 0.91 to 1.53) did not reach a statistically significant level because of the small numbers involved, the risk for oestrogen-progestogen users of developing dementia appeared increased regardless of exposure duration (1.40, 1.22 to 1.61).[Supplementary eTable 9]

All the results from other sensitivity analyses designed to investigate the effects of different limitations (described in the protocol[13] and referred to in Methods above) were similar to the main findings.

Extra cases in exposed women

Per 10,000 women-years, the overall rate of Alzheimer's for women older than 55 who had no records of HRT prescriptions was 39.4. By the same measure, the estimated rate of Alzheimer's in women who took combined oestrogen-progestogen HRT for between 5 and 9 years was 43.9 (95% confidence interval 40.9 to 47.2), an extra 4.5 cases (1.5 to 7.7), while for women who used combined therapy for 10 or more years, the estimated rate was 46.9 (42.0 to 52.3), an extra 7.4 cases (2.5 to 12.9). For women aged between 55 and 79, the rate of Alzheimer's was 14.3 per

10,000 women years, while the estimated rate for women with combined therapy prescriptions for 10 or more years was 17.9 (15.6 to 20.5), an extra 3.6 cases (1.3 to 6.2).

Discussion

Statement of principal findings

This large observational study found no overall association between use of HRT and risk of developing dementia. This finding was consistent across different types of hormones, doses, applications and time of HRT initiation. A decreased dementia risk was found for cases and controls younger than 80 years at diagnosis who had been on oestrogen-only therapy for 10 years or more. However, a subgroup analysis of cases diagnosed with Alzheimer's disease demonstrated a small increase in risk associated with oestrogen-progestogen therapy. This rose with each year of exposure, reaching 11% after 5 years of use and 19% after 10 years of use, and was equivalent to, respectively, 5 and 7 extra cases per 10,000 women-years.

Strengths and weaknesses of the study

The main strengths of this study were a very large sample representative of the general population, and a study design that captured all known cases and utilised the richness of the data and precision of recording for prescribed medications. The size of the sample allowed us to investigate the risks for specific treatment types and the effects of exposure durations. We were also able to explore risks for specific subgroups of women and the effects of age at initiation of the therapy. The similarity of the results obtained from two databases containing data collected using different software, and the results from our various sensitivity analyses have also demonstrated the robustness of our findings.

The main weakness of our study was a possible lack of available data before the index date for some older women, whose menopause started before their registration or before collection of this data by their practice. We consider, however, that it is unlikely that this group of women were greatly

exposed to HRT because the rate of HRT prescribing was very low 10 years prior to the study start, and our prescribing rate estimation taken from the CPRD database is similar to a rate based on Government prescription data covering the period between 1988 and 1994.[20] We also explored the possible effects of such under-calculations of exposure by analysing separately cases based on women diagnosed before their 80th birthday from those diagnosed after. Younger women were more likely to have fully recorded data preceding their menopause, and the results obtained from both of these subgroup analyses were consistent with those from our main analysis, which suggests that the possible lack of data for some older women has had little effect.

Our main analysis includes all cases of dementia, irrespective of type of dementia, since more than half the sample had no dementia type specified in their GP records. When the subsamples of patients with a recorded diagnosis of Alzheimer's disease or of vascular dementia were considered, about 10% of Alzheimer's cases (15% for vascular dementia cases) also had a recorded diagnosis for the other type, showing that mixed forms of dementia are not uncommon. Our analyses found that there was no association between HRT and dementia risk for the group with dementia as a whole, or for patients who developed vascular dementia. However, we found some increased risk within the subgroup based on patients diagnosed with Alzheimer's disease. It is one of the strengths of this paper that the sample size was large enough to demonstrate these different patterns of risk. It should be borne in mind, however, that many of the patients with a non-specific diagnosis of dementia will in fact have had Alzheimer's disease or mixed Alzheimer's-vascular dementia, so we can presume that the risks of developing Alzheimer's disease are very unlikely to be higher than our estimates – and could be somewhat lower.

Although levels of completeness within the databases are quite high for diagnoses, onset and symptoms of menopause are not consistently recorded. Even in the groups of women with oestrogen-progestogen prescriptions, there were only 48% of women with records of menopausal symptoms against an expected 80%.[1] Because some symptoms of menopause are similar to

symptoms of developing dementia, it is possible that women without menopausal symptoms may have different underlying risk associations with development of dementia. In our sample, most of them fall within the category of non-users (in our unexposed groups the level of recording of menopausal symptoms was only 10%). Comparing symptomatic women with asymptomatic women may, therefore, shift odds ratios away from unity, but our adjusting for records of menopausal symptoms will have reduced that shift.

Because psychological and mental health related symptoms of menopause can be early signs of developing dementia, using prescriptions and confounders from close to the time of diagnosis may introduce confounding by indication bias. Our design reduced this possibility by excluding HRT prescriptions issued within the three years before the index date and records of confounders within the last 10.

As with any study based on routinely collected data, our study had a small proportion of women with missing data for body mass index, smoking and deprivation. This limitation was overcome by using multiple imputations for missing values. Not all known risk factors for dementia were available, so we could not adjust for level of education, for physical or mental inactivity or for social isolation.[16] It is not clear how the lack of data for these confounders may have influenced our estimates of the associations between HRT and dementia risk, so there may be some residual confounding bias.

Strengths and weaknesses in relation to other studies

Associations between increased risk of developing types of dementia and oestrogen replacement therapies have been widely studied but, despite broad agreement in many areas, all studies to date exhibit various weaknesses in terms of coverage, data completeness or methodological consistency. Risk of Alzheimer's disease associated with oestrogen replacement therapy has, for example, has been reported as decreased in a recent meta-analysis of 21 studies (odds ratio 0.63, 95% confidence

interval 0.58 to 0.80) but the included studies were small and heterogeneous in design, and none reported on use of progestogens.[22] The largest trial, WHIMS, based on 40 dementia cases, showed an increased risk of developing dementia for oestrogen-progestogen treatments (hazard ratio 2.05, 95% confidence interval 1.21 to 3.48) but not for oestrogen-only treatments.[5 6] While broadly in line with our results, their trial follow up periods were significantly shorter (only 5.2 years for oestrogen-only arm and 4 years for oestrogen-progestogen arm) than we have achieved with the data available to our study, and the only hormonal types included were conjugated equine oestrogen and medroxyprogesterone. The WHIMS trial also investigated the effect of HRT from the age of 65, but some of the included women had used hormonal therapy prior to entering (45% for oestrogen-only arm and 22% for oestrogen-progestogen arm). Although this information was used in their analysis, there is a lack of clarity about how this was done.

Two large observational studies, both focusing only on cases with Alzheimer's disease, have been based on data from the Finnish national registries.[8 9] The more recent of these highlighted increased risks associations both for oestrogen only and oestrogen-progestogen therapies.[9] The number of cases included in their study was twice as large as ours (84,739 *v* 43,502) but the period for which patient data were available was much shorter (1994 to 2013 *v* 1988 to 2020). The study also had some possibly important methodological weaknesses – the calculation of exposure periods appear in some cases to have been based on assumptions about when treatment was initiated, and all exposure up to the point of diagnosis was included, with no exclusion of any exposure records within a period immediately prior to diagnosis to avoid protopathic bias. Each case was matched to only one control, which is not adequate given the low prevalence of some exposures. Finally, menopausal symptoms and other important confounders relating to HRT use, such as mental health problems and use of other medications, were not used to adjust their study results. As confirmed by the estimates from our unadjusted analysis, this is likely to have produced higher odds ratios.

The earlier study, from a different Finnish team but based on the same data source, appears to have had a methodologically more sound study design. It included four controls per case, it used linkages to hospital data for extracting information for confounding factors, and it excluded data in the last five years before the index date.[8] However, this study had access to data over an even shorter time period – ending in 2011, two years earlier than the later study[9]. Their results for exposure for 10 years or more showed no associations with Alzheimer's disease (for oestrogen only odds ratio 0.91, 95% confidence interval 0.84 to 0.99; for oestrogen-progestogen 1.05, 0.90 to 1.22). The study, however, showed increased risks for shorter term exposures for oestrogen with or without progestogen. Our view is that the estimates of both this and the previous study may have been affected by the relative lack of longer-term historical data (prior to 1994), making their numbers for long-term exposure quite small. In the first study this probably led to some under-ascertainment of exposure in their model, while in the second study, we suspect that methodological weaknesses may have affected their detailed results in unpredictable ways.

Meaning of the study: explanations and implications

Biological studies have suggested possible neuro-protective effects of oestrogen on the brain.[1 2] For long-term exposure (10 years or more) in women younger than 80 at the time of diagnosis (adjusted odds ratio 0.85, 95% confidence interval 0.76-0.94), and to a lesser extent in the subgroup analysis relating to Alzheimer's disease (0.87, 0.74 to 1.02), the results from our main analysis also supported possible protective effects for oestrogen-only therapies. For women 80 years or older at the time of diagnosis, we found no such associations, probably because of the prevailing low rates of prescription at the time of their menopause or, perhaps, because of a decrease in the number of oestrogen receptors with age. Also according to biological studies, progestogen administered with oestrogen may result in the opposite of a protective effect because it can counteract the effects of the oestrogen.[1 2] This would be consistent with our findings which show an increase in risk of

developing Alzheimer's disease risk for long-term oestrogen-progestogen usage, even more expressed among younger women (1.25, 1.09 to 1.43).

This study has shown that women on oestrogen-only therapies are not at greater risk of developing Alzheimer's disease and dementia overall, but that there are increased risks of developing Alzheimer's disease among women with long term exposure of more than five years to oestrogen-progestogen therapies. These associations do not prove any causal link, but breast cancer risks are also associated with longer term HRT use, so the results are in line with existing concerns in guidelines about long term exposures to combined HRT treatments.[23]

Conclusion

This large study of the general female population has used most recently collected clinical and prescribing data and reports no overall risks of developing dementia associated with use of HRT, consistent across types of treatment and durations, age categories and times of HRT initiation. The study, however, did find associations with increased risk of developing Alzheimer's disease among long-term users of oestrogen-progestogen therapies. The findings will be helpful to policy makers, doctors and patients when making choices about HRT treatment.

Statements

Contributors: YV led the work of the study team, contributed to development of the study protocol, reviewed the literature, designed the study, organised the extraction of CPRD data, did the analysis on both datasets and wrote all drafts of the manuscript. JHC initiated the study, undertook the original literature review, drafted the original study protocol, and organised the extraction of the QResearch data. TD provided expertise on dementia and Alzheimer's disease. MM, JHC and LT advised on clinical aspects related to primary care and interpretation of the results. CC contributed to the development of the idea and the study design and to the analysis. All co-authors critically reviewed the paper and approved the submitted version. YV is the guarantor of the study.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work. JHC reports grants from National Institute for Health Research Biomedical Research Centre, Oxford, grants from John Fell Oxford University Press Research Fund, grants from Cancer Research UK (CR-UK) grant number C5255/A18085, through the Cancer Research UK Oxford Centre, grants from the Oxford Wellcome Institutional Strategic Support Fund (204826/Z/16/Z), during the conduct of the study. JHC is an unpaid director of QResearch, a not-for-profit organisation which is a partnership between the University of Oxford and EMIS Health who supply the QResearch database used for this work. JHC is a founder and shareholder of ClinRisk ltd and was its medical director until 31st May 2019. ClinRisk Ltd produces open and closed source software to implement clinical risk algorithms (outside this work) into clinical computer systems. The other authors have no conflicts of interest to declare.

Ethical approval: The project has been reviewed in accordance with the QResearch® agreement with NRES Committee East Midlands – Derby [reference 18/EM/0400]. The protocol for CPRD has been approved by The Independent Scientific Advisory Committee for MHRA Database Research (N 20_139R).

Data sharing: To guarantee the confidentiality of personal and health information only the authors have had access to the data during the study in accordance with the relevant licence agreements. Access to the QResearch data is according to the information on the QResearch website (www.qresearch.org). CPRD linked data were provided under a licence that does not permit sharing.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Dissemination: We used anonymised data, therefore, did not have direct contact information for individual study participants for dissemination of the results.

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Tables

Table 1 Characteristics in cases with dementia and matched controls, 10 years before the index date by database (QResearch and CPRD)

	QResearch		CPRD	
	Cases; % (N)	Controls; % (N)	Cases; % (N)	Controls; % (N)
Total	68738	267490	49763	229926
Age in years				
age (mean, SD)	83.8 (6.6)	83.5 (6.3)	83.0 (7.5)	82.6 (7.3)
55 to 64	0.2 (138)	0.2 (552)	1.9 (958)	2.0 (4500)
65 to 74	8.7 (5995)	8.8 (23518)	10.9 (5417)	11.3 (25890)
75 to 84	42.6 (29255)	44.6 (119413)	41.4 (20616)	43.2 (99347)
85 to 110	48.5 (33350)	46.4 (124007)	45.8 (22772)	43.6 (100189)
Years of records (mean, SD)	16.5 (4.4)	16.5 (4.4)	14.9 (4.1)	15.4 (4.3)
Ethnicity				
White	70.6 (48521)	72.7 (194586)	64.9 (32296)	63.4 (145691)
Not recorded	26.0 (17893)	24.3 (64983)	34.0 (16941)	35.7 (82078)
Bangladeshi	0.2 (110)	0.1 (335)	<0.1 (15)	<0.1 (11)
Black African	0.2 (150)	0.2 (523)	<0.1 (16)	<0.1 (88)
Caribbean	1.2 (852)	0.9 (2387)	0.2 (113)	0.2 (392)
Chinese	0.1 (51)	0.1 (305)	<0.1 (21)	0.1 (141)
Indian	0.7 (470)	0.7 (1988)	0.2 (110)	0.2 (492)
Other	0.5 (347)	0.4 (1141)	0.4 (176)	0.3 (677)
Other Asian	0.2 (154)	0.2 (605)	0.1 (29)	0.1 (211)
Pakistani	0.3 (190)	0.2 (637)	0.1 (46)	0.1 (145)
Townsend quintile*				
Most affluent	28.1 (19293)	30.1 (80449)	22.3 (5878)	23.7 (28557)
2	25.2 (17322)	25.7 (68878)	23.9 (6301)	24.4 (29378)
3	21.5 (14781)	20.8 (55771)	21.7 (5723)	21.7 (26051)
4	15.7 (10772)	14.7 (39251)	19.9 (5259)	18.9 (22773)
Most deprived	9.6 (6570)	8.7 (23141)	12.2 (3226)	11.3 (13556)
Body mass index				
recorded	73.2 (50302)	72.5 (194020)	77.0 (38311)	76.6 (176054)
mean (SD)	26.7 (4.9)	26.9 (4.8)	27.2 (4.9)	27.3 (4.8)
Smoking				
recorded	79.8 (54853)	79.0 (211450)	85.9 (42726)	85.0 (195355)
Non-smoker	52.7 (36235)	53.7 (143671)	59.7 (29724)	61.2 (140763)
Ex-smoker	17.7 (12163)	17.0 (45365)	17.0 (8458)	15.7 (36120)
light (1-9 cigarettes/day)	7.2 (4947)	6.4 (17205)	3.9 (1953)	3.5 (8060)
moderate (10-19)	1.5 (1046)	1.4 (3640)	3.3 (1660)	3.0 (6907)
heavy (≥20)	0.7 (462)	0.6 (1569)	1.9 (931)	1.5 (3505)
Alcohol				
recorded	73.2 (50327)	72.5 (194027)	77.0 (38313)	75.9 (174560)

none	50.5 (34721)	49.2 (131524)	37.5 (18638)	35.5 (81517)
trivial (<1units/day)	15.8 (10887)	16.3 (43483)	23.5 (11683)	23.8 (54700)
light (1-2)	4.5 (3065)	4.7 (12610)	9.8 (4856)	10.3 (23744)
moderate (3-6)	2.3 (1599)	2.3 (6225)	5.8 (2865)	5.9 (13461)
heavy (7-9)	0.1 (41)	0.1 (149)	0.4 (208)	0.4 (894)
very heavy (≥10)	<0.1 (14)	<0.1 (36)	0.1 (63)	0.1 (244)
Chronic conditions				
anxiety	8.1 (5550)	7.0 (18639)	13.0 (6481)	11.3 (25989)
cancer	6.2 (4281)	6.2 (16584)	5.8 (2909)	6.0 (13784)
coronary heart disease	11.1 (7663)	9.6 (25780)	12.6 (6251)	10.8 (24722)
depression	17.9 (12319)	14.8 (39570)	21.6 (10725)	18.0 (41500)
diabetes	8.7 (5948)	6.5 (17378)	8.2 (4074)	6.0 (13753)
hearing loss	5.4 (3696)	4.9 (13091)	9.9 (4935)	8.8 (20170)
hypertension	41.4 (28484)	40.2 (107524)	41.1 (20454)	40.0 (91877)
Parkinson's disease	0.5 (351)	0.2 (571)	0.6 (313)	0.2 (560)
stroke	5.2 (3557)	3.9 (10441)	5.6 (2779)	4.2 (9733)
Other characteristics				
early menopause	9.0 (6182)	8.7 (23152)	7.8 (3871)	7.4 (17023)
hysterectomy/ oophorectomy	21.9 (15020)	21.7 (58079)	20.2 (10071)	19.8 (45446)
menopausal symptoms	13.3 (9158)	13.2 (35197)	15.3 (7637)	15.8 (36309)
family history of dementia	0.2 (121)	0.1 (192)	0.1 (54)	0.0 (111)
Any use of other medications before the index date				
anticholinergics	45.8 (31499)	41.6 (111367)	48.8 (24282)	44.8 (103089)
antiarrhythmic	0.1 (88)	0.1 (337)	0.1 (67)	0.1 (334)
antidepressants	23.3 (15998)	19.8 (52858)	23.5 (11685)	20.0 (46059)
antiepileptics	2.2 (1538)	1.9 (5058)	2.7 (1319)	2.2 (5135)
antihistamines	9.6 (6618)	8.7 (23277)	11.1 (5530)	10.4 (23945)
antimuscarinics	5.1 (3496)	4.0 (10653)	5.6 (2791)	4.3 (9962)
antiparkinsonian drugs	0.6 (409)	0.3 (881)	0.7 (360)	0.3 (750)
antipsychotics	2.8 (1946)	2.0 (5339)	3.0 (1481)	2.1 (4933)
antispasmodics	6.8 (4650)	6.3 (16754)	7.9 (3923)	7.7 (17734)
antivertigo	18.8 (12897)	17.3 (46224)	21.1 (10514)	19.9 (45673)
bronchodilators	3.6 (2443)	3.1 (8192)	3.8 (1890)	3.2 (7375)
muscle relaxants	0.6 (431)	0.6 (1517)	1.1 (566)	1.1 (2537)
antihypertensives	55.7 (38315)	53.0 (141821)	57.2 (28452)	54.4 (125180)
benzodiazepines	12.6 (8694)	10.9 (29288)	15.5 (7716)	13.8 (31821)
statins	22.2 (15292)	19.2 (51379)	22.2 (11061)	19.4 (44561)

* based on linked practices

Figures

Figure 1 Proportion of women exposed to HRT by age over the study period in CPRD

Figure 2 Use of oestrogen only, oestrogen-progestogen, and tibolone and adjusted odds ratios for dementia overall and for Alzheimer's disease.

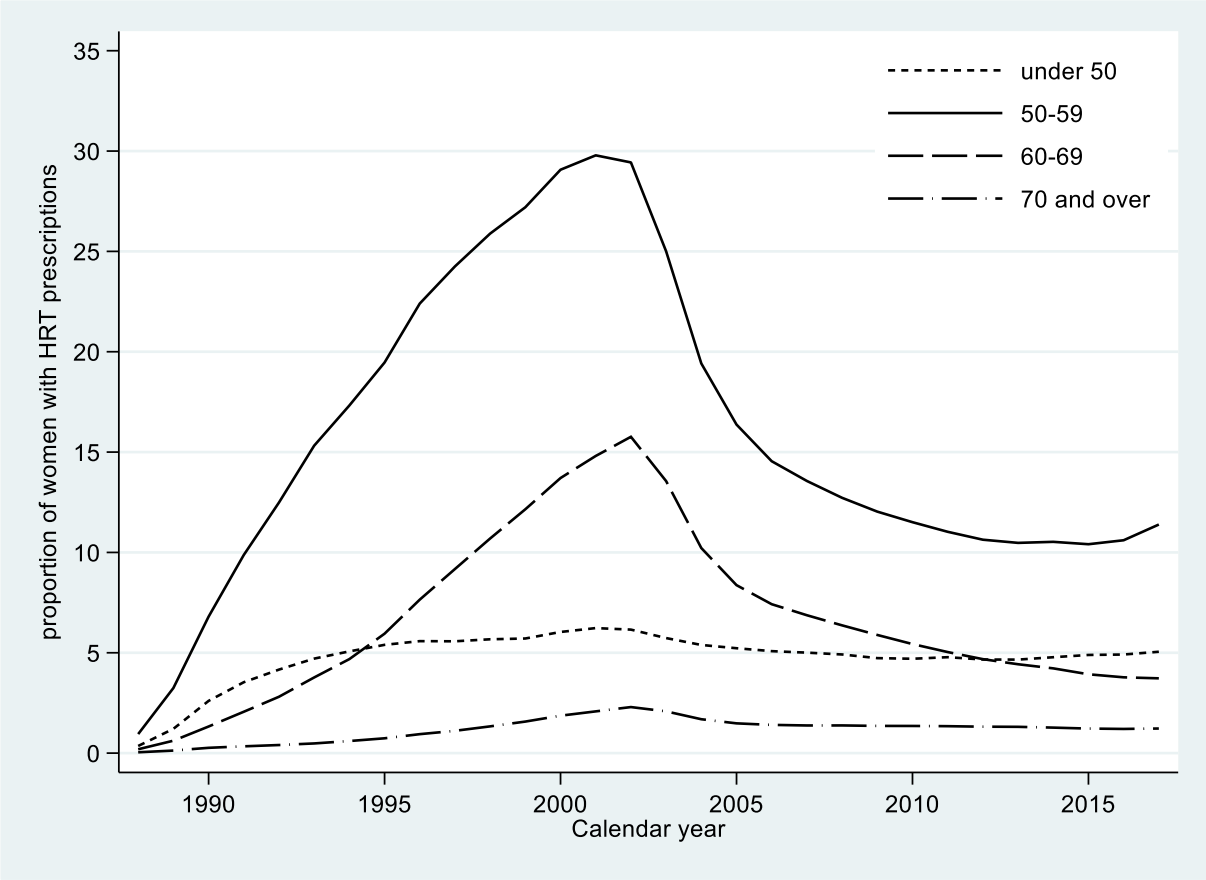
Odds ratios are adjusted for smoking, alcohol consumption, Townsend quintile (QResearch only), body mass index, ethnicity, family history of dementia, oophorectomy/hysterectomy, records of menopause, comorbidities, other medications, years of data. Cases are matched to controls by age, general practice and index date.

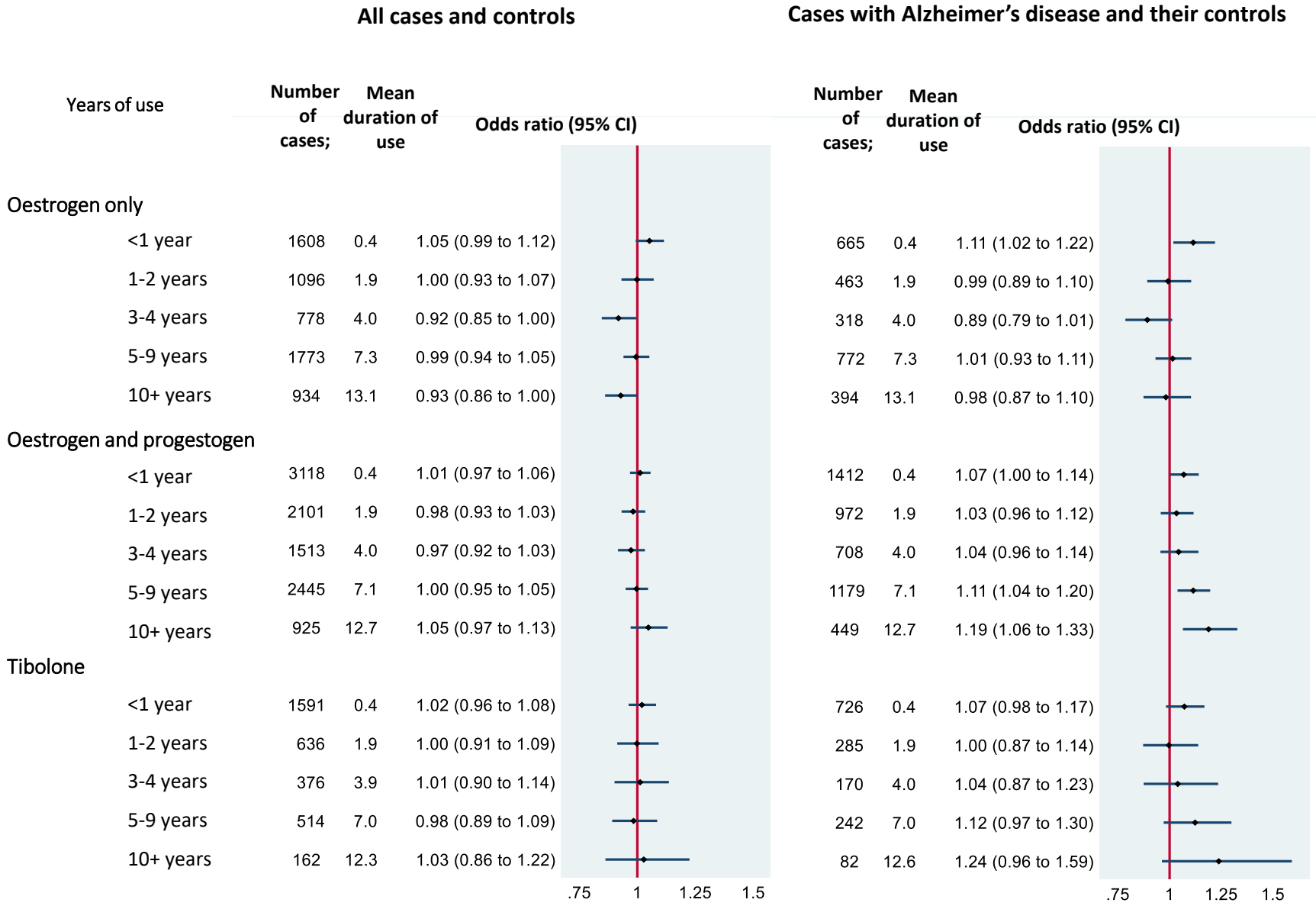
Figure 3 Use of different hormones and adjusted odds ratios for dementia overall and for Alzheimer's disease

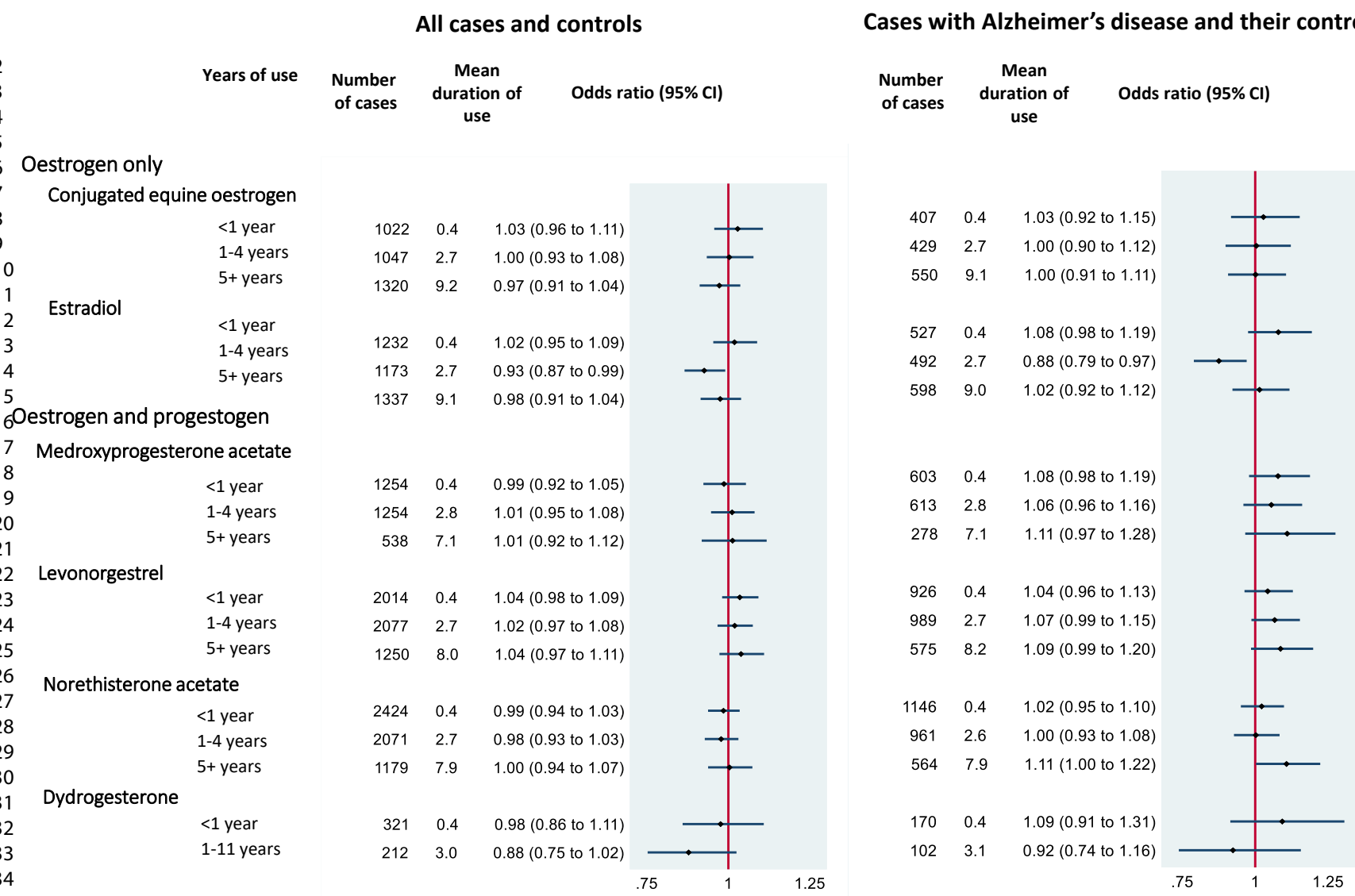
Odds ratios are adjusted for smoking, alcohol consumption, Townsend quintile (QResearch only), body mass index, ethnicity, family history of dementia, oophorectomy/hysterectomy, records of menopause, comorbidities, other medications, years of data. Cases are matched to controls by age, general practice and index date

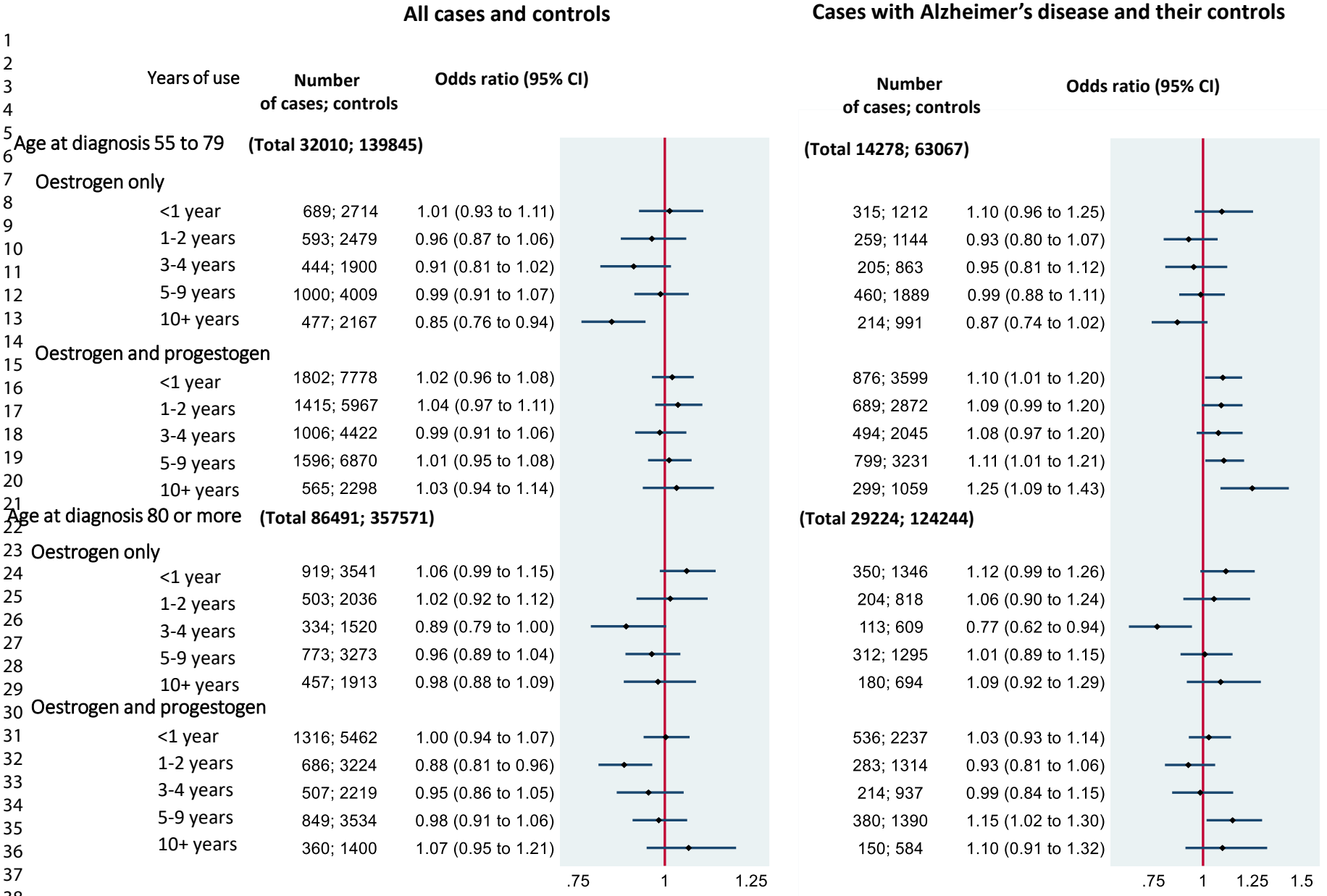
Figure 4 Use of oestrogen only, oestrogen-progestogen, and tibolone in women of different ages and adjusted odds ratios for dementia overall and for Alzheimer's disease.

Odds ratios are adjusted for smoking, alcohol consumption, Townsend quintile (QResearch only), body mass index, ethnicity, family history of dementia, oophorectomy/hysterectomy, records of menopause, comorbidities, other medications, years of data. Cases are matched to controls by age, general practice and index date


under 50
50-59
60-69
70 and over
proportion of women with HRT prescriptions
0
5
10
15
20
25
30
35
1990
1995
2000
2005
2010
2015
Calendar year


All cases and controls
Cases with Alzheimer's disease and their controls
Years of use
Number of cases;
Mean duration of use
Odds ratio (95% CI)
Number of cases;
Mean duration of use
Odds ratio (95% CI)
Oestrogen only
<1 year 1608 0.4 1.05 (0.99 to 1.12) 665 0.4 1.11 (1.02 to 1.22)
1-2 years 1096 1.9 1.00 (0.93 to 1.07) 463 1.9 0.99 (0.89 to 1.10)
3-4 years 778 4.0 0.92 (0.85 to 1.00) 318 4.0 0.89 (0.79 to 1.01)
5-9 years 1773 7.3 0.99 (0.94 to 1.05) 772 7.3 1.01 (0.93 to 1.11)
10+ years 934 13.1 0.93 (0.86 to 1.00) 394 13.1 0.98 (0.87 to 1.10)
Oestrogen and progestogen
<1 year 3118 0.4 1.01 (0.97 to 1.06) 1412 0.4 1.07 (1.00 to 1.14)
1-2 years 2101 1.9 0.98 (0.93 to 1.03) 972 1.9 1.03 (0.96 to 1.12)
3-4 years 1513 4.0 0.97 (0.92 to 1.03) 708 4.0 1.04 (0.96 to 1.14)
5-9 years 2445 7.1 1.00 (0.95 to 1.05) 1179 7.1 1.11 (1.04 to 1.20)
10+ years 925 12.7 1.05 (0.97 to 1.13) 449 12.7 1.19 (1.06 to 1.33)
Tibolone
<1 year 1591 0.4 1.02 (0.96 to 1.08) 726 0.4 1.07 (0.98 to 1.17)
1-2 years 636 1.9 1.00 (0.91 to 1.09) 285 1.9 1.00 (0.87 to 1.14)
3-4 years 376 3.9 1.01 (0.90 to 1.14) 170 4.0 1.04 (0.87 to 1.23)
5-9 years 514 7.0 0.98 (0.89 to 1.09) 242 7.0 1.12 (0.97 to 1.30)
10+ years 162 12.3 1.03 (0.86 to 1.22) 82 12.6 1.24 (0.96 to 1.59)
.75
1
1.25
1.5
.75
1
1.25
1.5


All cases and controls
Cases with Alzheimer's disease and their controls
Years of use
Number of cases
Mean duration of use
Odds ratio (95% CI)
Number of cases
Mean duration of use
Odds ratio (95% CI)
Oestrogen only
Conjugated equine oestrogen
<1 year 1022 0.4 1.03 (0.96 to 1.11) 407 0.4 1.03 (0.92 to 1.15)
1-4 years 1047 2.7 1.00 (0.93 to 1.08) 429 2.7 1.00 (0.90 to 1.12)
5+ years 1320 9.2 0.97 (0.91 to 1.04) 550 9.1 1.00 (0.91 to 1.11)
Estradiol
<1 year 1232 0.4 1.02 (0.95 to 1.09) 527 0.4 1.08 (0.98 to 1.19)
1-4 years 1173 2.7 0.93 (0.87 to 0.99) 492 2.7 0.88 (0.79 to 0.97)
5+ years 1337 9.1 0.98 (0.91 to 1.04) 598 9.0 1.02 (0.92 to 1.12)
Oestrogen and progestogen
Medroxyprogesterone acetate
<1 year 1254 0.4 0.99 (0.92 to 1.05) 603 0.4 1.08 (0.98 to 1.19)
1-4 years 1254 2.8 1.01 (0.95 to 1.08) 613 2.8 1.06 (0.96 to 1.16)
5+ years 538 7.1 1.01 (0.92 to 1.12) 278 7.1 1.11 (0.97 to 1.28)
Levonorgestrel
<1 year 2014 0.4 1.04 (0.98 to 1.09) 926 0.4 1.04 (0.96 to 1.13)
1-4 years 2077 2.7 1.02 (0.97 to 1.08) 989 2.7 1.07 (0.99 to 1.15)
5+ years 1250 8.0 1.04 (0.97 to 1.11) 575 8.2 1.09 (0.99 to 1.20)
Norethisterone acetate
<1 year 2424 0.4 0.99 (0.94 to 1.03) 1146 0.4 1.02 (0.95 to 1.10)
1-4 years 2071 2.7 0.98 (0.93 to 1.03) 961 2.6 1.00 (0.93 to 1.08)
5+ years 1179 7.9 1.00 (0.94 to 1.07) 564 7.9 1.11 (1.00 to 1.22)
Dydrogesterone
<1 year 321 0.4 0.98 (0.86 to 1.11) 170 0.4 1.09 (0.91 to 1.31)
1-11 years 212 3.0 0.88 (0.75 to 1.02) 102 3.1 0.92 (0.74 to 1.16)
.75
1
1.25
.75
1
1.25



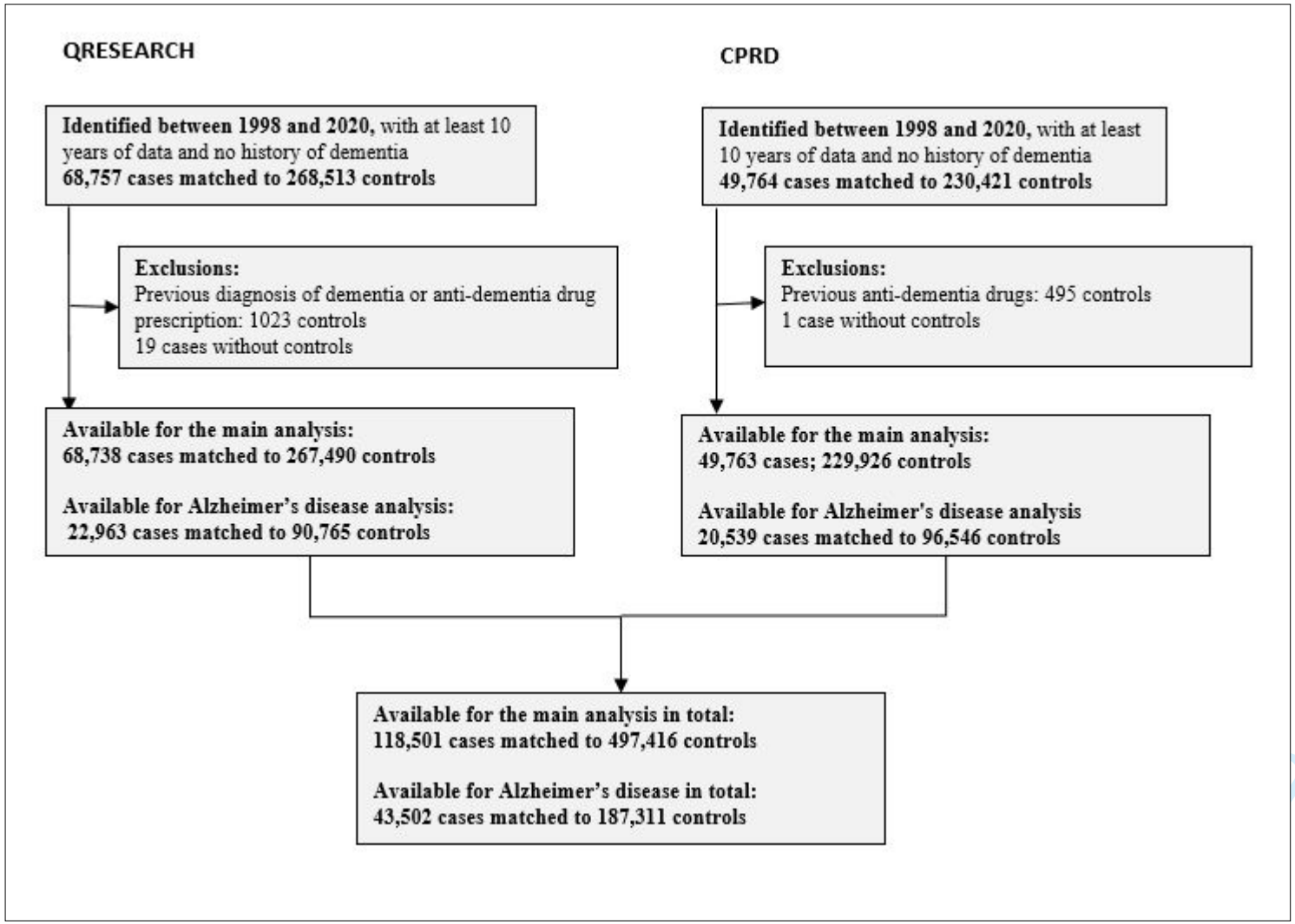
Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs

Use of hormone replacement therapy and risk of dementia: two nested case-control studies in primary care

Supplementary tables

Supplementary figures

eFigure 1 Flow-chat for included cases and controls by database



eTable 1 Characteristics in cases and controls at least 1 years before the index date across the databases by exposure to HRT

	No exposure		Oestrogen only		Oestrogen-progestogen	
	Cases; % (N)	Controls; % (N)	Cases; % (N)	Controls; % (N)	Cases; % (N)	Controls; % (N)
Total	102210	428690	6189	25552	10102	43174
Age in years						
age (mean, SD)	84.4 (6.6)	83.9 (6.4)	79.1 (6.7)	79.0 (6.7)	77.2 (6.6)	77.2 (6.5)
Townsend quintile*	*) based on linked cases and controls					
Most affluent	25.9 (21349)	27.3 (91689)	29.1 (1410)	32.4 (6372)	31.3 (2412)	34.2 (10945)
2	24.7 (20362)	25.2 (84681)	26.1 (1266)	26.1 (5132)	25.9 (1995)	26.4 (8443)
3	21.8 (18000)	21.4 (71884)	20.2 (979)	19.6 (3864)	19.8 (1525)	19.0 (6074)
4	17.1 (14120)	16.4 (55214)	15.9 (772)	13.9 (2743)	14.8 (1139)	12.7 (4067)
Most deprived	10.6 (8734)	9.7 (32631)	8.8 (426)	8.0 (1566)	8.3 (636)	7.8 (2500)
Body mass index mean (SD)	26.9 (4.9)	27.1 (4.8)	27.1 (4.9)	27.2 (4.7)	26.5 (4.8)	26.6 (4.7)
Chronic conditions						
Anxiety	9.2 (9391)	8.2 (35052)	15.3 (947)	13.4 (3420)	16.8 (1693)	14.3 (6156)
Cancer	6.1 (6243)	6.2 (26489)	6.0 (372)	5.7 (1468)	5.7 (575)	5.6 (2411)
Coronary heart disease	11.9 (12171)	10.4 (44494)	13.2 (820)	11.3 (2879)	9.1 (923)	7.2 (3129)
Depression	17.4 (17835)	14.7 (62825)	32.0 (1981)	26.9 (6863)	32.0 (3228)	26.4 (11382)
Diabetes	8.5 (8714)	6.4 (27398)	9.5 (591)	6.3 (1606)	7.1 (717)	4.9 (2127)
Hearing loss	7.3 (7445)	6.7 (28555)	7.6 (472)	7.0 (1795)	7.1 (714)	6.7 (2911)
Hypertension	41.6 (42558)	40.6 (173877)	44.1 (2728)	41.4 (10571)	36.2 (3652)	34.6 (14953)
Parkinson's disease	0.5 (542)	0.2 (985)	0.6 (40)	0.2 (53)	0.8 (82)	0.2 (93)
Stroke	5.4 (5546)	4.2 (17865)	5.5 (339)	4.1 (1054)	4.5 (451)	2.9 (1255)
Other characteristics						
early menopause	6.7 (6856)	6.4 (27468)	40.9 (2531)	40.1 (10258)	6.6 (666)	5.7 (2449)
hysterectomy/oophorectomy	17.9 (18252)	17.5 (75175)	88.2 (5461)	89.4 (22854)	13.6 (1378)	12.7 (5496)
menopausal symptoms	9.5 (9668)	9.6 (40981)	36.0 (2225)	37.7 (9621)	48.5 (4902)	48.4 (20904)

Any use of other medications before the index date						
anticholinergics	44.2 (45216)	40.5 (173719)	67.4 (4169)	61.8 (15797)	63.3 (6396)	57.8 (24940)
anti-hypertensive drugs	55.8 (57066)	53.4 (228759)	65.1 (4026)	60.4 (15434)	56.2 (5675)	52.8 (22808)
benzodiazepines	12.4 (12691)	11.0 (47230)	23.3 (1444)	20.9 (5343)	22.5 (2275)	19.8 (8536)
statins	21.4 (21885)	18.7 (80235)	31.4 (1946)	25.9 (6628)	25.0 (2522)	21.0 (9077)

eTable 2 ***All cases and controls:*** *Duration of use for different types of HRT: number of cases and controls and* ***unadjusted odds ratios*** *by database and combined results.*

	QResearch		CPRD		Combined	
	N of cases; controls	Unadjusted odds ratio[#] (95% confidence interval)	N of cases; controls	Unadjusted odds ratio[#] (95% confidence interval)	N of cases; controls	unadjusted odds ratio[#] (95% confidence interval)
OVERALL USE						
HRT	9296; 35843	1.04 (1.01 to 1.07)[α]	6995; 32883	1.04 (1.01 to 1.07)	16291; 68726	1.04 (1.02 to 1.06)[β]
Oestrogen only	3569; 13650	1.05 (1.01 to 1.09)	2620; 11902	1.06 (1.01 to 1.11)	6189; 25552	1.05 (1.02 to 1.08)[β]
Combined therapy	5727; 22193	1.04 (1.00 to 1.08)	4375; 20981	1.01 (0.97 to 1.05)	10102; 43174	1.03 (1.00 to 1.05)
DURATION OF EXPOSURE						
HRT						
<1 year	2250; 8296	1.08 (1.03 to 1.14)[α]	2090; 9553	1.05 (1.00 to 1.11)	4340; 17849	1.07 (1.03 to 1.11)[β]
1 to <3 years	1624; 6402	1.02 (0.96 to 1.08)	1471; 6804	1.05 (0.98 to 1.11)	3095; 13206	1.03 (0.99 to 1.07)
3 to <5 years	1286; 5177	0.99 (0.93 to 1.05)	1001; 4910	0.99 (0.92 to 1.06)	2287; 10087	0.99 (0.94 to 1.04)
5 to <10 years	2754; 10725	1.04 (0.99 to 1.08)	1691; 7927	1.04 (0.98 to 1.10)	4445; 18652	1.04 (1.00 to 1.07)
10+ years	1382; 5243	1.07 (1.00 to 1.14)	742; 3689	0.99 (0.91 to 1.07)	2124; 8932	1.04 (0.99 to 1.09)
OESTROGEN ONLY						
<1 year	846; 2948	1.13 (1.05 to 1.23)[α]	762; 3307	1.10 (1.01 to 1.19)	1608; 6255	1.12 (1.06 to 1.18)[β]
1 to <3 years	578; 2247	1.03 (0.94 to 1.13)	518; 2268	1.10 (1.00 to 1.21)	1096; 4515	1.06 (0.99 to 1.14)
3 to <5 years	430; 1833	0.93 (0.83 to 1.03)	348; 1587	1.06 (0.94 to 1.19)	778; 3420	0.99 (0.91 to 1.07)
5 to <10 years	1110; 4222	1.06 (0.99 to 1.13)	663; 3060	1.05 (0.96 to 1.14)	1773; 7282	1.06 (1.00 to 1.11)
10+ years	605; 2400	1.02 (0.93 to 1.11)	329; 1680	0.96 (0.85 to 1.08)	934; 4080	0.99 (0.92 to 1.07)
***OESTROGEN COMBINED with* any progestogen**						
<1 year	1604; 6154	1.04 (0.98 to 1.10)	1514; 7086	1.03 (0.97 to 1.10)	3118; 13240	1.04 (0.99 to 1.08)
1 to <3 years	1125; 4408	1.02 (0.95 to 1.09)	976; 4783	0.99 (0.92 to 1.06)	2101; 9191	1.00 (0.95 to 1.06)
3 to <5 years	879; 3387	1.04 (0.96 to 1.12)	634; 3254	0.94 (0.86 to 1.03)	1513; 6641	1.00 (0.94 to 1.06)
5 to <10 years	1510; 6014	1.02 (0.96 to 1.08)	935; 4390	1.04 (0.96 to 1.12)	2445; 10404	1.02 (0.98 to 1.07)
10+ years	609; 2230	1.11 (1.01 to 1.22)	316; 1468	1.06 (0.93 to 1.20)	925; 3698	1.09 (1.01 to 1.18)
GAP AFTER THE LAST EXPOSURE						
OESTROGEN ONLY						

3 to <5 years	523; 2112	0.97 (0.88 to 1.07)	350; 1693	0.98 (0.87 to 1.10)	873; 3805	0.97 (0.90 to 1.05)
5 to <10 years	884; 3133	1.13 (1.05 to 1.22)[α]	616; 2624	1.12 (1.02 to 1.22)	1500; 5757	1.13 (1.06 to 1.19)[β]
10 years or more	2162; 8405	1.03 (0.98 to 1.09)	1654; 7585	1.06 (1.00 to 1.12)	3816; 15990	1.04 (1.01 to 1.08)
***OESTROGEN COMBINED with* any progestogen**						
3 to <5 years	498; 1950	1.02 (0.92 to 1.13)	405; 1609	1.17 (1.04 to 1.31)[α]	903; 3559	1.09 (1.01 to 1.17)
5 to <10 years	1080; 3993	1.10 (1.02 to 1.18)	825; 3489	1.12 (1.04 to 1.22) [α]	1905; 7482	1.11 (1.05 to 1.17)[β]
10 years or more	4149; 16250	1.02 (0.98 to 1.07)	3145; 15883	0.97 (0.92 to 1.01)	7294; 32133	1.00 (0.97 to 1.03)

[#]Odds ratios are based on cases and controls matched by age and practice.

[α] P-value<0.01; [β] P-value<0.001

eTable 3 ***All cases and controls:*** *Duration of use for different types and hormones of HRT, by database*

	QResearch		CPRD		Combined analysis	
	N of cases; controls	Adjusted odds ratio# (95% confidence interval)	N of cases; controls	Adjusted odds ratio# (95% confidence interval)	Combined odds ratio (95% confidence interval)	P-value
OVERALL USE						
HRT	9296; 35843	1.00 (0.97 to 1.03)	6995; 32883	0.99 (0.96 to 1.02)	0.99 (0.97 to 1.01)	0.5
Oestrogen only	3569; 13650	0.99 (0.95 to 1.04)	2620; 11902	0.99 (0.94 to 1.04)	0.99 (0.96 to 1.02)	0.5
Combined therapy	5727; 22193	1.00 (0.96 to 1.04)	4375; 20981	1.00 (0.96 to 1.04)	1.00 (0.97 to 1.03)	1
DURATION OF EXPOSURE						
HRT						
<1 year	2250; 8296	1.04 (0.99 to 1.09)	2090; 9553	1.02 (0.97 to 1.07)	1.03 (0.99 to 1.07)	0.1
1 to <3 years	1624; 6402	0.98 (0.92 to 1.04)	1471; 6804	1.00 (0.94 to 1.07)	0.99 (0.95 to 1.03)	0.6
3 to <5 years	1286; 5177	0.95 (0.89 to 1.01)	1001; 4910	0.95 (0.88 to 1.02)	0.95 (0.90 to 0.99)	0.03
5 to <10 years	2754; 10725	0.98 (0.94 to 1.03)	1691; 7927	1.00 (0.94 to 1.06)	0.99 (0.95 to 1.03)	0.6
10+ years	1382; 5243	1.00 (0.94 to 1.07)	742; 3689	0.95 (0.87 to 1.03)	0.98 (0.93 to 1.03)	0.4
OESTROGEN ONLY						
<1 year	846; 2948	1.08 (1.00 to 1.17)	762; 3307	1.02 (0.94 to 1.11)	1.05 (0.99 to 1.12)	0.08
1 to <3 years	578; 2247	0.99 (0.90 to 1.09)	518; 2268	1.01 (0.91 to 1.11)	1.00 (0.93 to 1.07)	1
3 to <5 years	430; 1833	0.87 (0.78 to 0.97)	348; 1587	0.98 (0.87 to 1.11)	0.92 (0.85 to 1.00)	0.04
5 to <10 years	1110; 4222	1.00 (0.93 to 1.07)	663; 3060	0.99 (0.90 to 1.08)	0.99 (0.94 to 1.05)	0.8
10+ years	605; 2400	0.94 (0.86 to 1.04)	329; 1680	0.90 (0.80 to 1.02)	0.93 (0.86 to 1.00)	0.05
Conjugated equine oestrogen						
<1 year	566; 2080	1.03 (0.94 to 1.14)	456; 1982	1.02 (0.92 to 1.14)	1.03 (0.96 to 1.11)	0.5
1 to <3 years	342; 1375	0.96 (0.85 to 1.09)	284; 1154	1.09 (0.95 to 1.24)	1.02 (0.93 to 1.11)	0.7
3 to <5 years	233; 950	0.92 (0.79 to 1.06)	188; 793	1.07 (0.90 to 1.26)	0.98 (0.88 to 1.09)	0.7
5 to <10 years	557; 2124	0.99 (0.90 to 1.09)	314; 1540	0.94 (0.83 to 1.06)	0.97 (0.90 to 1.05)	0.5
10+ years	291; 1094	0.99 (0.87 to 1.14)	158; 771	0.93 (0.78 to 1.11)	0.97 (0.87 to 1.08)	0.6

Estradiol						
<1 year	610; 2224	1.03 (0.93 to 1.13)	622; 2733	1.01 (0.92 to 1.11)	1.02 (0.95 to 1.09)	0.6
1 to <3 years	375; 1447	0.99 (0.88 to 1.12)	342; 1642	0.92 (0.82 to 1.04)	0.96 (0.88 to 1.04)	0.3
3 to <5 years	264; 1106	0.90 (0.78 to 1.03)	192; 997	0.85 (0.73 to 1.00)	0.88 (0.79 to 0.98)	0.02
5 to <10 years	568; 2151	1.00 (0.91 to 1.11)	352; 1566	1.02 (0.90 to 1.15)	1.01 (0.93 to 1.09)	0.8
10+ years	273; 1150	0.89 (0.78 to 1.02)	144; 723	0.93 (0.77 to 1.12)	0.91 (0.81 to 1.01)	0.08
OESTROGEN COMBINED with any progestogen						
<1 year	1604; 6154	1.00 (0.94 to 1.07)	1514; 7086	1.02 (0.96 to 1.09)	1.01 (0.97 to 1.06)	0.6
1 to <3 years	1125; 4408	0.99 (0.92 to 1.06)	976; 4783	0.98 (0.90 to 1.05)	0.98 (0.93 to 1.03)	0.5
3 to <5 years	879; 3387	1.01 (0.93 to 1.09)	634; 3254	0.92 (0.84 to 1.01)	0.97 (0.92 to 1.03)	0.4
5 to <10 years	1510; 6014	0.98 (0.92 to 1.04)	935; 4390	1.03 (0.95 to 1.11)	1.00 (0.95 to 1.05)	0.9
10+ years	609; 2230	1.05 (0.96 to 1.16)	316; 1468	1.04 (0.91 to 1.18)	1.05 (0.97 to 1.13)	0.2
Medroxyprogesterone						
<1 year	740; 2779	1.02 (0.93 to 1.11)	514; 2562	0.94 (0.85 to 1.05)	0.98 (0.92 to 1.05)	0.6
1 to <3 years	424; 1609	1.03 (0.92 to 1.15)	311; 1522	0.96 (0.85 to 1.09)	1.00 (0.92 to 1.09)	1
3 to <5 years	327; 1180	1.07 (0.94 to 1.22)	192; 973	0.95 (0.81 to 1.11)	1.02 (0.92 to 1.13)	0.7
5 years or more	341; 1333	0.98 (0.87 to 1.12)	197; 890	1.05 (0.90 to 1.23)	1.01 (0.92 to 1.11)	0.8
Levonorgestrel						
<1 year	1052; 4038	1.01 (0.93 to 1.08)	962; 4429	1.07 (0.99 to 1.15)	1.03 (0.98 to 1.09)	0.2
1 to <3 years	733; 2974	0.96 (0.88 to 1.05)	531; 2608	1.01 (0.91 to 1.12)	0.98 (0.92 to 1.05)	0.6
3 to <5 years	513; 1754	1.15 (1.04 to 1.28)[a]	300; 1515	0.99 (0.87 to 1.13)	1.08 (1.00 to 1.18)	0.05
5 to <10 years	604; 2275	1.03 (0.93 to 1.13)	397; 1855	1.06 (0.94 to 1.19)	1.04 (0.97 to 1.12)	0.3
10+ years	158; 605	1.01 (0.85 to 1.21)	91; 424	1.06 (0.84 to 1.34)	1.03 (0.90 to 1.19)	0.7
Norethisterone						
<1 year	1261; 4755	1.00 (0.94 to 1.07)	1163; 5650	0.97 (0.90 to 1.04)	0.99 (0.94 to 1.03)	0.6
1 to <3 years	736; 2838	1.00 (0.92 to 1.09)	551; 2739	0.97 (0.88 to 1.07)	0.99 (0.92 to 1.05)	0.7
3 to <5 years	451; 1827	0.96 (0.86 to 1.07)	333; 1580	0.97 (0.86 to 1.10)	0.97 (0.89 to 1.05)	0.4
5 to <10 years	623; 2405	1.01 (0.92 to 1.11)	354; 1620	1.05 (0.93 to 1.19)	1.03 (0.95 to 1.10)	0.5

10+ years	142; 600	0.89 (0.73 to 1.07)	60; 281	0.98 (0.74 to 1.31)	0.91 (0.78 to 1.07)	0.3
Dydrogesterone						
<1 year	176; 716	0.91 (0.77 to 1.09)	145; 674	1.05 (0.87 to 1.27)	0.97 (0.86 to 1.11)	0.7
1 to <3 years	81; 345	0.91 (0.71 to 1.17)	54; 296	0.86 (0.64 to 1.17)	0.89 (0.73 to 1.08)	0.2
3 years or more	50; 194	0.92 (0.67 to 1.26)	27; 172	0.77 (0.50 to 1.17)	0.86 (0.67 to 1.11)	0.2
TIBOLONE						
<1 year	845; 3007	1.06 (0.98 to 1.15)	746; 3602	0.98 (0.90 to 1.06)	1.02 (0.96 to 1.08)	0.5
1 to <3 years	340; 1330	0.99 (0.87 to 1.12)	296; 1396	1.01 (0.89 to 1.15)	1.00 (0.91 to 1.09)	1
3 to <5 years	208; 808	1.00 (0.86 to 1.17)	168; 772	1.03 (0.86 to 1.22)	1.01 (0.90 to 1.14)	0.8
5 to <10 years	298; 1247	0.94 (0.82 to 1.07)	216; 998	1.05 (0.90 to 1.22)	0.98 (0.89 to 1.09)	0.7
10+ years	84; 354	0.91 (0.71 to 1.16)	78; 319	1.18 (0.91 to 1.52)	1.03 (0.86 to 1.22)	0.8

[#]Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs; [α] P-value<0.01; [β] P-value<0.001

eTable 4 ***All cases and controls:*** *Duration of use for different doses of hormones and types of application by database*

	QResearch		CPRD		Combined analysis	
	N of cases; controls	Adjusted odds ratio[#] (95% confidence interval)	N of cases; controls	Adjusted odds ratio[#] (95% confidence interval)	Combined odds ratio (95% confidence interval)	P-value
OESTROGEN ONLY						
Conjugated equine oestrogen						
≤0.625mg						
<1 year	482; 1771	1.03 (0.93 to 1.15)	351; 1498	1.05 (0.93 to 1.19)	1.04 (0.96 to 1.13)	0.3
1 to <3 years	273; 1127	0.94 (0.82 to 1.08)	210; 890	1.04 (0.89 to 1.21)	0.98 (0.89 to 1.09)	0.8
3 to <5 years	194; 781	0.93 (0.79 to 1.09)	137; 608	1.01 (0.83 to 1.22)	0.96 (0.85 to 1.09)	0.5
5 to <10 years	431; 1726	0.94 (0.84 to 1.05)	230; 1135	0.94 (0.81 to 1.08)	0.94 (0.86 to 1.03)	0.2
10+ years	211; 817	0.96 (0.82 to 1.13)	112; 550	0.96 (0.78 to 1.19)	0.96 (0.85 to 1.09)	0.6
>0.625mg						
<1 year	84; 309	1.02 (0.80 to 1.31)	105; 484	0.92 (0.74 to 1.14)	0.96 (0.82 to 1.13)	0.6
1 to <3 years	69; 248	1.04 (0.79 to 1.37)	74; 264	1.24 (0.95 to 1.62)	1.14 (0.94 to 1.38)	0.2
3 to <5 years	39; 169	0.84 (0.59 to 1.20)	51; 185	1.24 (0.90 to 1.70)	1.04 (0.82 to 1.32)	0.7
5 to <10 years	126; 398	1.20 (0.98 to 1.48)	84; 405	0.94 (0.74 to 1.19)	1.08 (0.93 to 1.27)	0.3
10+ years	80; 277	1.07 (0.83 to 1.39)	46; 221	0.86 (0.62 to 1.19)	0.99 (0.81 to 1.21)	0.9
Estradiol						
≤1mg						
<1 year	570; 2057	1.03 (0.94 to 1.14)	555; 2467	1.00 (0.91 to 1.11)	1.02 (0.95 to 1.09)	0.6
1 to <3 years	337; 1280	1.01 (0.89 to 1.15)	288; 1419	0.90 (0.79 to 1.03)	0.96 (0.88 to 1.05)	0.4
3 to <5 years	215; 982	0.83 (0.71 to 0.96)	154; 814	0.84 (0.71 to 1.01)	0.84 (0.74 to 0.94)	0.002
5 to <10 years	461; 1799	0.97 (0.88 to 1.08)	271; 1245	0.98 (0.86 to 1.13)	0.98 (0.90 to 1.06)	0.6
10+ years	229; 975	0.89 (0.77 to 1.03)	112; 565	0.94 (0.76 to 1.16)	0.91 (0.80 to 1.02)	0.1

>1mg	40; 167	0.92 (0.65 to 1.30)	67; 266	1.09 (0.82 to 1.43)	1.02 (0.82 to 1.26)	0.9
<1 year	38; 167	0.81 (0.57 to 1.17)	54; 223	1.06 (0.78 to 1.44)	0.95 (0.75 to 1.20)	0.7
1 to <3 years	49; 124	1.45 (1.03 to 2.03)	38; 183	0.87 (0.61 to 1.25)	1.14 (0.89 to 1.46)	0.3
3 to <5 years	107; 352	1.13 (0.91 to 1.41)	81; 321	1.13 (0.88 to 1.46)	1.13 (0.96 to 1.34)	0.1
5 to <10 years	44; 175	0.90 (0.64 to 1.27)	32; 158	0.89 (0.60 to 1.31)	0.90 (0.70 to 1.16)	0.4
10+ years						
oral	304; 1135	1.01 (0.89 to 1.16)	273; 1178	1.03 (0.90 to 1.19)	1.02 (0.93 to 1.12)	0.7
<1 year	134; 609	0.83 (0.68 to 1.00)	121; 505	1.08 (0.88 to 1.33)	0.94 (0.81 to 1.08)	0.4
1 to <3 years	117; 424	1.02 (0.83 to 1.26)	61; 328	0.84 (0.63 to 1.11)	0.95 (0.80 to 1.13)	0.6
3 to <5 years	196; 728	1.00 (0.85 to 1.18)	127; 501	1.15 (0.94 to 1.41)	1.06 (0.93 to 1.20)	0.4
5 to <10 years	69; 328	0.77 (0.59 to 1.00)	45; 194	1.10 (0.79 to 1.54)	0.89 (0.72 to 1.09)	0.3
10+ years						
transdermal	455; 1631	1.04 (0.93 to 1.16)	520; 2257	1.03 (0.93 to 1.14)	1.03 (0.96 to 1.11)	0.4
<1 year	282; 1037	1.05 (0.91 to 1.20)	247; 1281	0.85 (0.74 to 0.98)	0.95 (0.86 to 1.05)	0.3
1 to <3 years	164; 699	0.90 (0.75 to 1.07)	145; 705	0.90 (0.75 to 1.08)	0.90 (0.79 to 1.02)	0.1
3 to <5 years	370; 1411	1.01 (0.90 to 1.14)	222; 1072	0.94 (0.81 to 1.09)	0.98 (0.90 to 1.08)	0.7
5 to <10 years	193; 794	0.93 (0.79 to 1.09)	89; 481	0.86 (0.68 to 1.08)	0.91 (0.79 to 1.03)	0.1
10+ years						
OESTROGEN COMBINED with						
Norethisterone						
oral	1182; 4501	1.00 (0.93 to 1.07)	1033; 5121	0.96 (0.89 to 1.03)	0.98 (0.93 to 1.03)	0.4
<1 year	595; 2234	1.03 (0.93 to 1.13)	485; 2257	1.04 (0.94 to 1.16)	1.04 (0.96 to 1.11)	0.3
1 to <3 years	344; 1424	0.94 (0.83 to 1.06)	277; 1357	0.95 (0.83 to 1.09)	0.94 (0.86 to 1.03)	0.2
3 to <5 years	503; 1892	1.03 (0.93 to 1.14)	299; 1398	1.04 (0.91 to 1.18)	1.03 (0.95 to 1.12)	0.5
5 to <10 years	94; 390	0.90 (0.71 to 1.13)	53; 229	1.07 (0.79 to 1.45)	0.96 (0.79 to 1.15)	0.6
10+ years						
transdermal	415; 1454	1.07 (0.95 to 1.20)	334; 1622	0.99 (0.88 to 1.13)	1.03 (0.95 to 1.12)	0.5
<1 year	218; 902	0.94 (0.80 to 1.09)	111; 667	0.79 (0.64 to 0.97)	0.88 (0.78 to 1.00)	0.04
1 to <3 years	108; 469	0.90 (0.72 to 1.11)	58; 213	1.24 (0.92 to 1.68)	1.00 (0.84 to 1.19)	1

3 to <5 years	155; 603	1.03 (0.86 to 1.24)	48; 211	1.07 (0.78 to 1.48)	1.04 (0.89 to 1.22)	0.6
5 years or more	482; 1771	1.03 (0.93 to 1.15)	351; 1498	1.05 (0.93 to 1.19)	1.04 (0.96 to 1.13)	0.3

[#]Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs.

[α] P-value<0.01; [β] P-value<0.001

eTable 5 Other medications prescribed for menopausal women by database and combined analysis

	QResearch		CPRD		Combined analysis	
	N of cases; controls	Adjusted odds ratio[#] (95% confidence interval)	N of cases; controls	Adjusted odds ratio[#] (95% confidence interval)	Combined odds ratio (95% confidence interval)	P-value
Oestrogen cream						
<1 year	7843; 29494	1.01 (0.98 to 1.03)	3650; 15860	1.03 (0.99 to 1.07)	1.01 (0.99 to 1.04)	0.3
1 to <3 years	1549; 5605	1.03 (0.97 to 1.10)	499; 2476	0.89 (0.80 to 0.98)	0.99 (0.94 to 1.05)	0.8
3+ years	777; 3080	0.96 (0.89 to 1.05)	258; 1118	1.02 (0.88 to 1.17)	0.98 (0.91 to 1.05)	0.5
Vaginal preparations						
<1 year	3286; 12507	0.98 (0.94 to 1.02)	2780; 12754	0.97 (0.93 to 1.02)	0.98 (0.95 to 1.01)	0.1
1 to <3 years	588; 2353	0.93 (0.85 to 1.02)	470; 2022	1.03 (0.92 to 1.14)	0.97 (0.91 to 1.04)	0.4
3+ years	358; 1420	0.93 (0.82 to 1.04)	233; 1084	0.93 (0.81 to 1.08)	0.93 (0.85 to 1.02)	0.1
Clonidine						
<1 year	957; 3711	0.97 (0.90 to 1.04)	1056; 5138	0.96 (0.89 to 1.03)	0.96 (0.91 to 1.01)	0.1
1 to <3 years	221; 750	1.12 (0.96 to 1.31)	234; 1099	1.02 (0.88 to 1.18)	1.07 (0.96 to 1.18)	0.2
3+ years	165; 672	0.94 (0.79 to 1.12)	232; 859	1.19 (1.02 to 1.38)	1.08 (0.96 to 1.21)	0.2

[#]Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs.

[α] P-value<0.01; [β] P-value<0.001

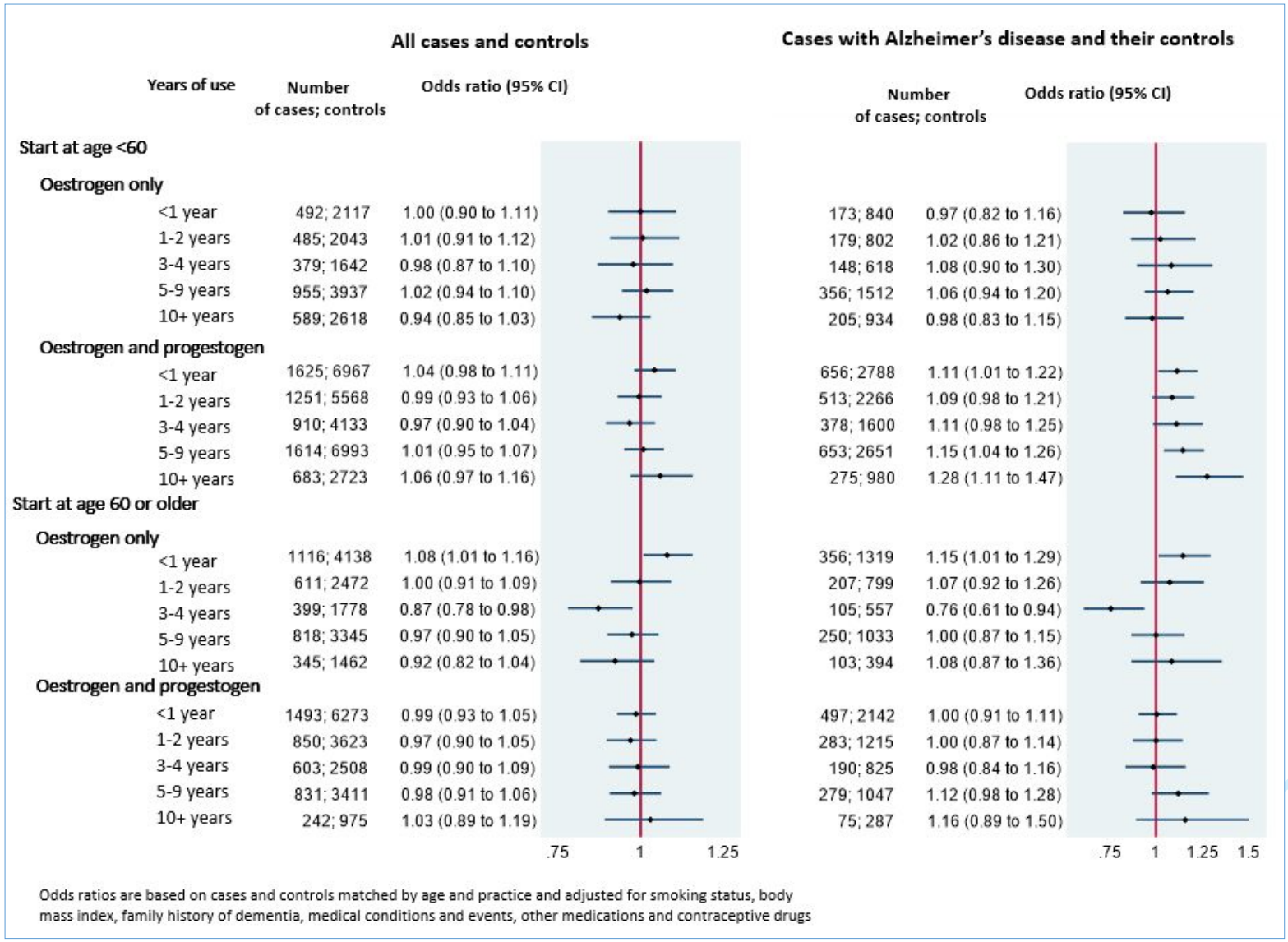
eTable 6 ***All cases and controls:*** *Gap since the last use of different hormones of HRT by database.*

	QResearch		CPRD		Combined analysis	
	N of cases; controls	Adjusted odds ratio# (95% confidence interval)	N of cases; controls	Adjusted odds ratio# (95% confidence interval)	Combined odds ratio (95% confidence interval)	P-value
HRT						
3 to <5 years	1119; 4412	0.96 (0.89 to 1.03)	826; 3662	0.97 (0.89 to 1.05)	0.96 (0.91 to 1.02)	0.2
5 to <10 years	2042; 7414	1.06 (1.01 to 1.12)	1513; 6419	1.06 (1.00 to 1.13)	1.06 (1.02 to 1.11)	0.004
10 years or more	6135; 24017	0.98 (0.95 to 1.02)	4656; 22802	0.97 (0.93 to 1.01)	0.98 (0.95 to 1.00)	0.08
OESTROGEN ONLY						
3 to <5 years	523; 2112	0.92 (0.83 to 1.01)	350; 1693	0.88 (0.78 to 1.00)	0.90 (0.84 to 0.98)	0.01
5 to <10 years	884; 3133	1.08 (0.99 to 1.16)	616; 2624	1.03 (0.94 to 1.13)	1.06 (0.99 to 1.12)	0.07
10 years or more	2162; 8405	0.98 (0.93 to 1.03)	1654; 7585	0.99 (0.94 to 1.06)	0.98 (0.95 to 1.02)	0.5
Conjugated equine oestrogen						
3 to <5 years	216; 916	0.87 (0.74 to 1.01)	143; 657	0.93 (0.77 to 1.12)	0.89 (0.79 to 1.00)	0.06
5 to <10 years	425; 1500	1.07 (0.96 to 1.20)	291; 1182	1.06 (0.93 to 1.21)	1.07 (0.98 to 1.16)	0.1
10 years or more	1348; 5207	0.99 (0.93 to 1.06)	966; 4401	1.00 (0.92 to 1.08)	1.00 (0.95 to 1.05)	0.9
Estradiol						
3 to <5 years	315; 1248	0.94 (0.83 to 1.07)	212; 1075	0.84 (0.72 to 0.98)	0.90 (0.82 to 0.99)	0.04
5 to <10 years	532; 1885	1.08 (0.98 to 1.19)	389; 1671	1.03 (0.92 to 1.16)	1.06 (0.98 to 1.14)	0.1
10 years or more	1243; 4945	0.95 (0.89 to 1.02)	1051; 4915	0.97 (0.90 to 1.05)	0.96 (0.91 to 1.01)	0.1
OESTROGEN COMBINED with						
any progestogen						
3 to <5 years	498; 1950	0.98 (0.89 to 1.09)	405; 1609	1.09 (0.97 to 1.23)	1.03 (0.95 to 1.11)	0.5
5 to <10 years	1080; 3993	1.05 (0.98 to 1.13)	825; 3489	1.09 (1.00 to 1.18)	1.07 (1.01 to 1.13)	0.02
10 years or more	4149; 16250	0.99 (0.95 to 1.03)	3145; 15883	0.97 (0.92 to 1.01)	0.98 (0.95 to 1.01)	0.2
Medroxyprogesterone						
3 to <5 years	138; 609	0.87 (0.72 to 1.05)	117; 481	1.04 (0.84 to 1.29)	0.94 (0.82 to 1.09)	0.4
5 to <10 years	396; 1425	1.09 (0.97 to 1.23)	280; 1184	1.05 (0.92 to 1.21)	1.08 (0.98 to 1.18)	0.1

10 years or more	1298; 4867	1.03 (0.96 to 1.11)	817; 4282	0.93 (0.85 to 1.00)	0.99 (0.94 to 1.04)	0.6
Levonorgestrel						
3 to <5 years	100; 427	0.91 (0.73 to 1.14)	77; 294	1.08 (0.83 to 1.41)	0.98 (0.82 to 1.16)	0.8
5 to <10 years	332; 1157	1.13 (1.00 to 1.29)	213; 907	1.05 (0.89 to 1.23)	1.10 (0.99 to 1.21)	0.07
10 years or more	2628; 10062	1.02 (0.96 to 1.07)	1991; 9630	1.03 (0.98 to 1.10)	1.02 (0.99 to 1.06)	0.2
Norethisterone						
3 to <5 years	279; 1003	1.07 (0.93 to 1.22)	227; 887	1.07 (0.91 to 1.25)	1.07 (0.96 to 1.18)	0.2
5 to <10 years	579; 2250	1.00 (0.90 to 1.10)	491; 2033	1.08 (0.97 to 1.20)	1.03 (0.96 to 1.11)	0.4
10 years or more	2355; 9172	0.98 (0.93 to 1.04)	1743; 8950	0.94 (0.89 to 1.00)	0.97 (0.93 to 1.00)	0.08
Dydrogesterone						
3 to <5 years	60; 283	0.73 (0.55 to 0.97)	72; 308	1.07 (0.81 to 1.40)	0.89 (0.73 to 1.09)	0.3
5 to <10 years	247; 972	0.97 (0.84 to 1.13)	154; 834	0.90 (0.75 to 1.08)	0.94 (0.84 to 1.06)	0.3
10 years or more						
TIBOLONE						
3 to <5 years	159; 652	0.94 (0.79 to 1.13)	136; 580	1.03 (0.85 to 1.25)	0.98 (0.86 to 1.12)	0.8
5 to <10 years	336; 1328	0.98 (0.87 to 1.11)	300; 1163	1.19 (1.04 to 1.35)	1.07 (0.98 to 1.17)	0.1
10 years or more	1280; 4766	1.03 (0.96 to 1.10)	1068; 5344	0.97 (0.90 to 1.04)	1.00 (0.95 to 1.05)	0.9

[#]Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs.

eFigure 2 Adjusted odds ratios for cases and controls with initiated HRT at different ages, main analysis and analysis restricted to cases with Alzheimer's disease



eTable 7 ***All cases and controls:*** *Duration of use for different types and hormones of HRT across the databases, by age at the index date*

	Age between 55 and 79		Age 80 and older	
	N of cases; controls	Combined adjusted odds ratio# (95% confidence interval)	N of cases; controls	Combined adjusted odds ratio# (95% confidence interval)
Total number of women	32010; 139845		86491; 357571	
OVERALL USE				
HRT	9587; 40604	0.99 (0.96 to 1.02)	6704; 28122	0.98 (0.95 to 1.01)
Oestrogen only	3203; 13269	0.95 (0.91 to 1.00)	2986; 12283	0.99 (0.95 to 1.04)
Combined therapy	6384; 27335	1.02 (0.98 to 1.06)	3718; 15839	0.97 (0.93 to 1.02)
DURATION OF EXPOSURE				
HRT				
<1 year	2258; 9475	1.02 (0.97 to 1.08)	2082; 8374	1.03 (0.98 to 1.09)
1 to <3 years	1932; 8107	1.01 (0.96 to 1.07)	1163; 5099	0.94 (0.88 to 1.00)
3 to <5 years	1448; 6345	0.95 (0.89 to 1.01)	839; 3742	0.92 (0.85 to 1.00)
5 to <10 years	2751; 11530	1.00 (0.95 to 1.05)	1694; 7122	0.97 (0.91 to 1.02)
10+ years	1198; 5147	0.94 (0.87 to 1.01)	926; 3785	1.01 (0.93 to 1.09)
OESTROGEN ONLY				
<1 year	689; 2714	1.01 (0.93 to 1.11)	919; 3541	1.06 (0.99 to 1.15)
1 to <3 years	593; 2479	0.96 (0.87 to 1.06)	503; 2036	1.02 (0.92 to 1.12)
3 to <5 years	444; 1900	0.91 (0.81 to 1.02)	334; 1520	0.89 (0.79 to 1.00)
5 to <10 years	1000; 4009	0.99 (0.91 to 1.07)	773; 3273	0.96 (0.89 to 1.04)
10+ years	477; 2167	0.85 (0.76 to 0.94)*	457; 1913	0.98 (0.88 to 1.09)
Conjugated equine oestrogen				
<1 year	494; 1963	1.00 (0.90 to 1.12)	528; 2099	1.03 (0.93 to 1.13)
1 to <3 years	363; 1389	1.07 (0.94 to 1.21)	263; 1140	0.94 (0.82 to 1.08)
3 to <5 years	236; 956	0.99 (0.85 to 1.15)	185; 787	0.94 (0.80 to 1.11)
5 to <10 years	463; 1940	0.95 (0.85 to 1.06)	408; 1724	0.96 (0.86 to 1.08)
10+ years	221; 945	0.89 (0.76 to 1.04)	228; 920	1.01 (0.87 to 1.17)
Estradiol				

<1 year	579; 2411	0.97 (0.88 to 1.07)	653; 2546	1.04 (0.95 to 1.14)
1 to <3 years	388; 1786	0.86 (0.76 to 0.96)	329; 1303	1.07 (0.94 to 1.21)
3 to <5 years	266; 1218	0.85 (0.74 to 0.98)	190; 885	0.87 (0.74 to 1.02)
5 to <10 years	546; 2121	1.01 (0.91 to 1.12)	374; 1596	0.96 (0.85 to 1.07)
10+ years	214; 1010	0.83 (0.71 to 0.97)	203; 863	0.97 (0.83 to 1.14)
OESTROGEN COMBINED with				
any progestogen				
<1 year	1802; 7778	1.02 (0.96 to 1.08)	1316; 5462	1.00 (0.94 to 1.07)
1 to <3 years	1415; 5967	1.04 (0.97 to 1.11)	686; 3224	0.88 (0.81 to 0.96)*
3 to <5 years	1006; 4422	0.99 (0.91 to 1.06)	507; 2219	0.95 (0.86 to 1.05)
5 to <10 years	1596; 6870	1.01 (0.95 to 1.08)	849; 3534	0.98 (0.91 to 1.06)
10+ years	565; 2298	1.03 (0.94 to 1.14)	360; 1400	1.07 (0.95 to 1.21)
Medroxyprogesterone				
<1 year	767; 3335	0.98 (0.90 to 1.07)	487; 2006	1.00 (0.90 to 1.12)
1 to <3 years	512; 2139	1.05 (0.94 to 1.16)	223; 992	0.93 (0.80 to 1.09)
3 to <5 years	342; 1420	1.04 (0.91 to 1.17)	177; 733	1.00 (0.85 to 1.19)
5 years or more	319; 1344	1.00 (0.88 to 1.14)	219; 879	1.02 (0.88 to 1.19)
Levonorgestrel				
<1 year	1335; 5560	1.04 (0.97 to 1.12)	679; 2907	1.00 (0.91 to 1.09)
1 to <3 years	828; 3625	0.98 (0.90 to 1.07)	436; 1957	0.96 (0.86 to 1.08)
3 to <5 years	537; 2173	1.08 (0.97 to 1.19)	276; 1096	1.10 (0.96 to 1.27)
5 to <10 years	618; 2633	1.00 (0.91 to 1.10)	383; 1497	1.10 (0.98 to 1.24)
10+ years	143; 601	1.04 (0.86 to 1.26)	106; 428	1.03 (0.83 to 1.28)
Norethisterone				
<1 year	1496; 6616	0.97 (0.91 to 1.03)	928; 3789	1.01 (0.93 to 1.09)
1 to <3 years	898; 3731	1.05 (0.97 to 1.13)	389; 1846	0.87 (0.77 to 0.97)
3 to <5 years	536; 2354	0.97 (0.88 to 1.07)	248; 1053	0.97 (0.84 to 1.12)
5 to <10 years	642; 2690	1.05 (0.95 to 1.15)	335; 1335	1.01 (0.89 to 1.14)
10+ years	138; 526	1.03 (0.85 to 1.25)	64; 355	0.73 (0.56 to 0.96)

Dydrogesterone				
<1 year	234; 1017	0.97 (0.83 to 1.13)	87; 373	0.97 (0.76 to 1.23)
1 to <3 years	93; 485	0.83 (0.66 to 1.04)	42; 156	1.09 (0.76 to 1.55)
3 years or more	57; 278	0.89 (0.66 to 1.20)	20; 88	0.80 (0.48 to 1.33)
TIBOLONE				
<1 year	845; 3545	1.02 (0.94 to 1.10)	746; 3064	1.03 (0.95 to 1.13)
1 to <3 years	347; 1521	0.97 (0.86 to 1.10)	289; 1205	1.04 (0.91 to 1.18)
3 to <5 years	214; 883	1.04 (0.89 to 1.21)	162; 697	0.98 (0.82 to 1.17)
5 to <10 years	258; 1175	0.93 (0.81 to 1.07)	256; 1070	1.04 (0.90 to 1.19)
10+ years	76; 292	1.15 (0.89 to 1.50)	86; 381	0.95 (0.75 to 1.20)

[#]Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs; [α] P-value<0.01; [β] P-value<0.001

eTable 8 ***Cases with Alzheimer's disease and with Vascular dementia and controls:*** *Duration of use for different types and hormones of HRT and gap since the last use, across the databases*

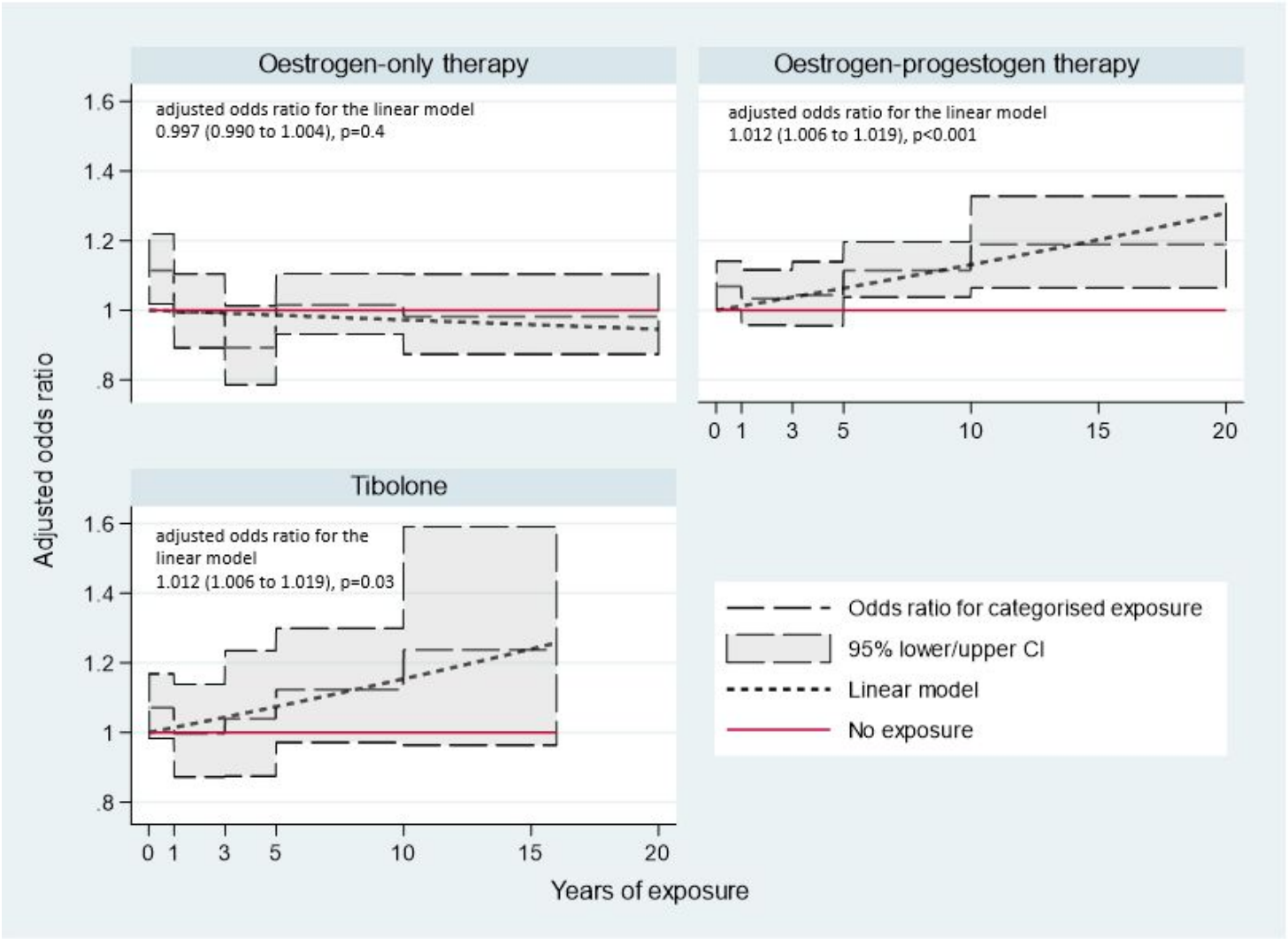
	Alzheimer's disease			Vascular dementia	
	N of cases; controls	Combined adjusted odds ratio# (95% confidence interval)	P-value	N of cases; controls	Combined adjusted odds ratio# (95% confidence interval)
Total number of women	43502; 187311			28493; 121571	
OVERALL USE					
HRT	7332; 30129	1.05 (1.01 to 1.09)	0.005	3773; 16248	0.95 (0.91 to 0.99)
Oestrogen only	2612; 10861	1.01 (0.96 to 1.07)	0.7	1525; 6086	0.96 (0.90 to 1.03)
Combined therapy	4720; 19268	1.08 (1.03 to 1.12)	<0.001	2248; 10162	0.95 (0.89 to 1.00)
DURATION OF EXPOSURE					
HRT					
<1 year	1901; 7661	1.09 (1.03 to 1.15)	0.003	1010; 4329	0.96 (0.89 to 1.03)
1 to <3 years	1379; 5914	1.01 (0.95 to 1.08)	0.7	719; 3099	0.94 (0.86 to 1.03)
3 to <5 years	1028; 4424	0.99 (0.92 to 1.07)	0.8	536; 2364	0.92 (0.83 to 1.02)
5 to <10 years	2047; 8264	1.06 (1.00 to 1.12)	0.04	1027; 4384	0.96 (0.89 to 1.04)
10+ years	977; 3866	1.08 (1.00 to 1.17)	0.05	481; 2072	0.94 (0.85 to 1.05)
OESTROGEN ONLY					
<1 year	665; 2558	1.11 (1.02 to 1.22)	0.02	417; 1536	1.03 (0.92 to 1.16)
1 to <3 years	463; 1962	0.99 (0.89 to 1.10)	0.9	272; 1072	0.98 (0.85 to 1.13)
3 to <5 years	318; 1472	0.89 (0.79 to 1.01)	0.08	203; 808	0.96 (0.82 to 1.13)
5 to <10 years	772; 3184	1.01 (0.93 to 1.11)	0.7	412; 1708	0.93 (0.82 to 1.04)
10+ years	394; 1685	0.98 (0.87 to 1.10)	0.8	221; 962	0.88 (0.76 to 1.03)
Conjugated equine oestrogen					
<1 year	407; 1672	1.03 (0.92 to 1.15)	0.6	268; 986	1.04 (0.90 to 1.20)
1 to <3 years	264; 1055	1.05 (0.91 to 1.21)	0.5	161; 601	1.03 (0.86 to 1.24)
3 to <5 years	165; 727	0.94 (0.79 to 1.11)	0.5	115; 404	1.09 (0.87 to 1.35)
5 to <10 years	371; 1588	1.00 (0.89 to 1.12)	1.0	217; 870	0.97 (0.83 to 1.14)

10+ years	179; 751	1.01 (0.85 to 1.20)	0.9	100; 428	0.89 (0.71 to 1.12)
Estradiol					
<1 year	527; 2086	1.08 (0.98 to 1.19)	0.1	323; 1178	1.06 (0.93 to 1.21)
1 to <3 years	304; 1434	0.89 (0.78 to 1.01)	0.08	155; 692	0.86 (0.72 to 1.04)
3 to <5 years	188; 923	0.85 (0.72 to 1.00)	0.05	119; 492	0.95 (0.77 to 1.18)
5 to <10 years	409; 1637	1.03 (0.91 to 1.15)	0.7	204; 865	0.90 (0.77 to 1.06)
10+ years	189; 777	0.99 (0.84 to 1.17)	0.9	102; 457	0.86 (0.69 to 1.08)
OESTROGEN COMBINED with					
any progestogen					
<1 year	1412; 5836	1.07 (1.00 to 1.14)	0.05	682; 3188	0.90 (0.82 to 0.99)
1 to <3 years	972; 4186	1.03 (0.96 to 1.12)	0.4	462; 2133	0.91 (0.81 to 1.02)
3 to <5 years	708; 2982	1.04 (0.96 to 1.14)	0.3	342; 1529	0.96 (0.84 to 1.09)
5 to <10 years	1179; 4621	1.11 (1.04 to 1.20)	0.003	553; 2470	0.96 (0.87 to 1.07)
10+ years	449; 1643	1.19 (1.06 to 1.33)	0.002	209; 842	1.09 (0.93 to 1.28)
Medroxyprogesterone					
<1 year	603; 2328	1.08 (0.98 to 1.18)	0.1	284; 1244	1.00 (0.87 to 1.15)
1 to <3 years	368; 1458	1.06 (0.94 to 1.19)	0.4	146; 729	0.90 (0.75 to 1.09)
3 to <5 years	245; 984	1.05 (0.91 to 1.22)	0.5	107; 471	1.01 (0.81 to 1.26)
5 years or more	278; 1025	1.11 (0.96 to 1.27)	0.1	102; 499	0.90 (0.72 to 1.13)
Levonorgestrel					
<1 year	926; 3827	1.04 (0.96 to 1.13)	0.3	443; 2002	0.99 (0.89 to 1.11)
1 to <3 years	583; 2515	1.00 (0.91 to 1.10)	1.0	278; 1282	0.97 (0.84 to 1.12)
3 to <5 years	406; 1470	1.18 (1.05 to 1.32)	0.006	179; 791	1.03 (0.87 to 1.22)
5 to <10 years	450; 1826	1.05 (0.94 to 1.17)	0.4	238; 985	1.10 (0.94 to 1.28)
10+ years	125; 433	1.25 (1.02 to 1.54)	0.03	55; 244	1.03 (0.76 to 1.39)
Norethisterone					
<1 year	1146; 4688	1.02 (0.95 to 1.10)	0.6	516; 2413	0.91 (0.82 to 1.01)
1 to <3 years	601; 2543	1.01 (0.92 to 1.11)	0.9	278; 1295	0.93 (0.81 to 1.07)

3 to <5 years	360; 1524	1.00 (0.88 to 1.12)	0.9	185; 800	0.99 (0.83 to 1.17)
5 to <10 years	470; 1757	1.14 (1.03 to 1.27)	0.02	233; 963	1.06 (0.91 to 1.23)
10+ years	94; 392	0.98 (0.78 to 1.23)	0.9	48; 189	1.11 (0.80 to 1.54)
Dydrogesterone					
<1 year	170; 634	1.09 (0.91 to 1.30)	0.4	60; 315	0.81 (0.61 to 1.09)
1 to <3 years	62; 289	0.90 (0.68 to 1.19)	0.5	32; 127	1.17 (0.78 to 1.77)
3 years or more	40; 162	0.98 (0.68 to 1.40)	0.9	18; 86	0.84 (0.49 to 1.42)
TIBOLONE					
<1 year	726; 2881	1.07 (0.98 to 1.17)	0.1	381; 1531	1.06 (0.94 to 1.20)
1 to <3 years	285; 1215	1.00 (0.87 to 1.14)	1.0	145; 652	1.02 (0.84 to 1.23)
3 to <5 years	170; 695	1.04 (0.87 to 1.23)	0.7	74; 379	0.89 (0.69 to 1.15)
5 to <10 years	242; 936	1.12 (0.97 to 1.30)	0.1	118; 552	0.96 (0.78 to 1.18)
10+ years	82; 286	1.24 (0.96 to 1.59)	0.10	45; 158	1.23 (0.87 to 1.74)
GAP AFTER THE LAST EXPOSURE					
OESTROGEN ONLY					
3 to <5 years	370; 1573	0.94 (0.84 to 1.06)	0.3	197; 809	0.95 (0.80 to 1.12)
5 to <10 years	617; 2449	1.04 (0.94 to 1.14)	0.5	396; 1423	1.08 (0.96 to 1.22)
10 years or more	1625; 6839	1.02 (0.96 to 1.08)	0.6	932; 3854	0.92 (0.85 to 1.00)
***OESTROGEN COMBINED with* any progestogen**					
3 to <5 years	442; 1543	1.19 (1.06 to 1.33)	0.002	183; 813	0.92 (0.78 to 1.10)
5 to <10 years	934; 3275	1.23 (1.14 to 1.34)	<0.001	418; 1784	1.01 (0.90 to 1.13)
10 years or more	3344; 14450	1.03 (0.98 to 1.08)	0.3	1647; 7565	0.93 (0.87 to 1.00)

[#]Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs. No statistically significant associations were found for Vascular dementia.

eFigure 3 Adjusted odds ratios for linear model of HRT and tibolone exposures in cases with Alzheimer's disease and their controls



Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs

eTable 9 ***Cases and controls registered before their 50th birthday:*** *Duration of use for different types and hormones of HRT and gap since the last use, by database*

	QResearch		CPRD		Combined analysis	
	N of cases; controls	Adjusted odds ratio# (95% confidence interval)	N of cases; controls	Adjusted odds ratio# (95% confidence interval)	Combined odds ratio (95% confidence interval)	P-value
Total number of women	942; 3071		1689; 8329			
OVERALL USE						
HRT	499; 1636	0.98 (0.82 to 1.16)	836; 3814	1.31 (1.16 to 1.48)*	1.18 (1.07 to 1.31)	0.001
Oestrogen only	141; 426	1.07 (0.79 to 1.45)	212; 1035	1.18 (0.91 to 1.53)	1.13 (0.93 to 1.38)	0.2
Combined therapy	358; 1210	0.96 (0.80 to 1.17)	624; 2779	1.40 (1.22 to 1.61)*	1.23 (1.10 to 1.37)	<0.001
DURATION OF EXPOSURE						
HRT						
<1 year	91; 286	0.90 (0.68 to 1.20)	200; 920	1.28 (1.07 to 1.54)*	1.16 (0.99 to 1.35)	0.06
1 to <3 years	84; 251	1.07 (0.79 to 1.45)	193; 847	1.43 (1.18 to 1.73)*	1.32 (1.12 to 1.55)	<0.001
3 to <5 years	69; 247	0.85 (0.63 to 1.17)	137; 599	1.38 (1.11 to 1.72)*	1.18 (0.99 to 1.41)	0.07
5 to <10 years	166; 565	0.99 (0.78 to 1.25)	216; 1025	1.36 (1.13 to 1.64)*	1.20 (1.04 to 1.39)	0.01
10+ years	89; 287	1.02 (0.76 to 1.36)	90; 423	1.37 (1.06 to 1.79)	1.20 (0.99 to 1.46)	0.07
OESTROGEN ONLY						
<1 year	21; 51	1.22 (0.67 to 2.21)	37; 212	0.93 (0.62 to 1.41)	1.02 (0.73 to 1.43)	0.9
1 to <3 years	21; 52	1.18 (0.66 to 2.12)	44; 201	1.33 (0.89 to 1.97)	1.28 (0.92 to 1.78)	0.1
3 to <5 years	15; 49	0.99 (0.51 to 1.93)	33; 147	1.30 (0.83 to 2.04)	1.20 (0.83 to 1.74)	0.3
5 to <10 years	50; 171	0.94 (0.63 to 1.42)	67; 307	1.33 (0.93 to 1.89)	1.15 (0.88 to 1.50)	0.3
10+ years	34; 103	1.14 (0.71 to 1.82)	31; 168	1.16 (0.73 to 1.82)	1.15 (0.83 to 1.59)	0.4
OESTROGEN COMBINED with **any progestogen**						
<1 year	82; 262	0.89 (0.66 to 1.21)	195; 824	1.42 (1.17 to 1.72)*	1.24 (1.05 to 1.46)	0.01
1 to <3 years	73; 229	1.06 (0.76 to 1.48)	155; 679	1.44 (1.17 to 1.77)*	1.32 (1.10 to 1.58)	0.002
3 to <5 years	55; 204	0.84 (0.59 to 1.19)	101; 459	1.37 (1.07 to 1.75)	1.16 (0.94 to 1.42)	0.2
5 to <10 years	104; 362	1.02 (0.78 to 1.34)	129; 633	1.32 (1.05 to 1.65)	1.19 (1.00 to 1.41)	0.05
10+ years	44; 153	0.95 (0.65 to 1.39)	44; 184	1.55 (1.08 to 2.21)	1.23 (0.95 to 1.59)	0.1

GAP AFTER THE LAST EXPOSURE						
OESTROGEN ONLY						
3 to <5 years	65; 198	1.29 (0.91 to 1.83)	147; 740	1.23 (1.00 to 1.52)	1.25 (1.04 to 1.50)	0.02
5 to <10 years	100; 356	0.92 (0.70 to 1.23)	208; 939	1.36 (1.12 to 1.64)*	1.21 (1.03 to 1.41)	0.02
10 years or more	334; 1082	0.93 (0.76 to 1.12)	481; 2135	1.41 (1.21 to 1.64)*	1.20 (1.07 to 1.35)	0.003
***OESTROGEN COMBINED with* any progestogen**						
3 to <5 years	19; 63	1.16 (0.63 to 2.12)	38; 225	0.91 (0.60 to 1.39)	0.99 (0.70 to 1.39)	0.9
5 to <10 years	25; 99	0.76 (0.45 to 1.29)	56; 279	1.09 (0.76 to 1.57)	0.97 (0.72 to 1.31)	0.8
10 years or more	97; 264	1.13 (0.81 to 1.59)	118; 531	1.34 (1.00 to 1.80)	1.25 (1.00 to 1.56)	0.05

[#]Odds ratios are based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of dementia, medical conditions and events, other medications and contraceptive drugs; [α] P-value<0.01; [β] P-value<0.001

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***
Re: Use of hormone replacement therapy and risk of dementia: nested case-control studies using the QResearch and CPRD databases

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	7
		(*b*) For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8-11
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how matching of cases and controls was addressed	7
		(*e*) Describe any sensitivity analyses	10-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic,	13,

		clinical, social) and information on exposures and potential confounders	28-29
		(b) Indicate number of participants with missing data for each variable of interest	28-29
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	13-14, 30
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	17
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22-23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Hormone replacement therapy and dementia risk: nested case-control studies using CPRD and QResearch

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East Midlands Research into Ageing Network (EMRAN) is a research collaboration across the East Midlands to facilitate applied research into ageing and the care of older people. EMRAN was set up with support from National Institute of Health Research Applied Research Collaboration East Midlands (NIHR ARC-EM)

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ABSTRACT

Introduction

Research from clinical trials of hormone replacement therapy (HRT) has produced conflicting findings about possible risks of dementia after receiving these treatments, and further research on HRT and dementia risk has been identified as a priority. This study will investigate risks of incident dementia associated with different types of hormone replacement therapy (HRT), using data from two primary care databases (CPRD and QResearch).

Method

The study design is two nested case-control studies, one in each database. Cases will be women aged 55 years and over with incident dementia diagnosed between 1998 and 2020, matched with up to 5 controls by age, practice and calendar year. Cases of dementia will be identified in each database using general practice clinical and other linked data. The outcome for analysis is incident dementia. The exposure will be having received prescriptions for HRT.

Analysis

Exposure to different HRT treatments will be defined as at least one prescription for that treatment excluding the three years prior to the index date (date of diagnosis of dementia or equivalent date in matched controls). Conditional logistic regression will be used to assess the risks associated with different types of oestrogen and progestogen. The effects of duration, length of any gap since the last use, different application routes and the age at which treatment started will be analysed for the most common types of hormones used. All analyses will be adjusted by available data for potential confounding variables.

Analysis using this same protocol will be carried out using data from each of two primary care databases (CPRD and QResearch). Adjusted odds ratios from the conditional regression analyses of the two datasets will be pooled using a fixed effect model with inverse variance weights.

Discussion

The study findings will show whether receipt of HRT is associated with either an increased or decreased risk of subsequent incident dementia. These results will inform future national and international guidance for women and for prescribers.

Key words: Hormone replacement therapy, dementia, incidence, risk, primary care

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INTRODUCTION

In November 2015, NICE published its first ever guidance on the menopause [1]. The menopause occurs when a woman stops having periods – usually a gradual process, during which women experience perimenopause before reaching postmenopausal status. The average age of menopause in the UK is 51 years but this varies widely, and 1 in 100 women experience premature ovarian insufficiency (menopause occurring before the age of 40 years). Oestrogen depletion associated with menopause causes irregular periods and has many other effects on the body such as hot flushes, night sweats, mood changes, memory and concentration loss, vaginal dryness, reduced libido, headaches, and joint and muscle stiffness. Quality of life may be severely affected. Most women (8 out of 10) experience some symptoms, typically lasting about 4 years after the last period, but continuing in about 10% of women for up to 12 years. Prolonged lack of oestrogen affects the bones and cardiovascular system, and postmenopausal women are at increased risk of a number of long-term conditions, such as osteoporosis. A central theme to the NICE guideline is the need for clinicians to provide information on the short and longer term risks and benefits of different treatments for menopausal symptoms. This includes the effects of non-hormonal treatment such as clonidine as well as different types of HRT for women (principally oestrogen and progestogen for women with a uterus, and oestrogen alone for women without a uterus). The guidance distinguishes different age groups, such as those under the age of 40, who have had a premature menopause due to premature ovarian insufficiency; those undergoing the menopause as a result of medical or surgical treatment (including women with cancer); and older women experiencing the menopause naturally.

A woman's decision to take medication for menopausal symptoms is often influenced by high profile studies reported in the media. The use of HRT halved following the publication of two large studies: the Women's Health Initiative in 2002 [2] and the Million Women study in 2003 [3], which found associations between HRT and increased risks of breast cancer. Evidence had also emerged that HRT, rather than having a protective effect on the risk of cardiovascular disease as previously thought, might in fact be associated with increased risk [4], and the NICE guidance on the menopause was developed to respond to concerns about this issue. Concern about the prospect of dementia in older age is growing, so clear information on the associations between future risk of dementia and use of HRT will be increasingly important to women considering such treatments. The guideline therefore highlighted investigation into associations between the risk of dementia and HRT use as one of its key research

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recommendations[1]. Media reports about HRT and risks are not always well founded, so providing healthcare professionals and women with a robust body of information on risk is essential. While evidence has been improving on some of the risks and benefits of HRT (for example, relating to venous thromboembolism[5] and breast cancer[6]), hard evidence on how HRT treatments might affect the risk of developing dementia is still very uncertain.

From clinical trials and biological studies, there is evidence that oestrogen may have a neuroprotective effect [7] and that HRT initiated soon after the menopause may prevent degeneration in crucial brain regions of women at increased risk of dementia (for example, those with a history of major depression or with a family history of Alzheimer's disease) [8, 9]. One trial randomised post-menopausal women to either continue or discontinue HRT, following them for an average of 2 years use [8]. Of the 54 women who remained in the study, 30 stayed on HRT and 24 stopped using HRT. Comparisons of brain images taken at outset and after two years indicated that metabolic activity in the medial prefrontal cortex, essential to decision making, seemed better preserved in women who had remained on hormone therapy [8]. Of the two HRT drugs taken by women in the study (estradiol in pure form and Premarin, a branded drug partly comprising estradiol) pure estradiol showed the larger effect in preserving metabolic activity [9]. The study size, however, was very small and none of the women in the study experienced cognitive decline, making it difficult to draw any firm conclusions [8, 9]. Conversely the Women's Health Initiative Study recruited women aged 65 and older and found an increased risk of dementia with conjugated equine oestrogen compared with placebo as well as an increased risk with combined oestrogen and progestogen [10, 11]. A recent study used a genomic approach to show that oestrogen loss at menopause is likely to contribute to Alzheimer's disease vulnerability [12]. Some researchers have suggested that different types of oestrogen studied may explain this discrepancy while others have speculated that there may be a "window of opportunity" for initialisation of HRT around the time of the menopause [13].

The fact that trial research has so far produced only conflicting findings on the benefits or risks of HRT with respect to the development of dementia appears to have inhibited further research in the area. Whatever the reason, the most promising current route for investigation seems to be well-powered observational studies – as recommended by NICE. A recent Finnish case-control study, which identified 84,739 women diagnosed with Alzheimer's disease and compared their exposure to HRT with women without a diagnosis, found a 9-17% increased risk of Alzheimer's in HRT users, with no difference

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between different types of hormones [14]. This study, however, used data from a national register, which contained no information about important confounders. Since both general and mental health as well as other drug exposure are related to the development of dementia [15, 16], and aspects of these may also be indications for HRT prescribing, the overall increased risk of Alzheimer's disease found in the study might reflect confounding due to the association between overall health and indication for HRT prescribing.

The time is ripe, therefore, for a large observational study, which has access to data containing as many known risk factors as possible, and which is powered sufficiently to consider all the complexities of drug variety, treatment regimes, exposures and patient characteristics as possible. Our proposed study clearly fits these requirements.

METHODS

Study design

We will undertake two nested case control studies with cases of dementia and matched controls using two primary care databases QResearch (Version 44) and CPRD (GOLD June 2020). QResearch accumulates records from approximately 1500 English general practices, all linked to hospital episode statistics (HES) and Office for National Statistics (ONS) mortality data. CPRD contains information from 771 UK practices (GOLD only) with 422 linked to HES and ONS mortality data.

Information collected by the databases is very similar and contains records for consultations, diagnoses and symptoms, tests and prescriptions. It is, however, recorded using different computer systems – EMIS for QResearch and VISION for CPRD GOLD. Although both systems use READ codes for clinical records, recording of ethnicity and family history and evaluation of Townsend deprivation scores between the databases differ. Different sets of codes are also used for prescription records.

Information from these databases is also stored in different locations and cannot be pooled. Two separate studies will therefore be conducted – as similar as possible, selecting the same confounders and running the same procedures. All observations will be from general practices in the UK, from the same time period, having similar exposures and using similar methods for recording outcomes.

Definition of the study population

We will include all practices which have contributed to the databases for at least 10 years. The study population will consist of two underlying cohorts of women aged 55

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and over during the study period (1st January 1998 to 30th June 2020) without a diagnosis of dementia at study entry. This age range reflects the mean age of menopause in the UK (51 years) to exclude women receiving HRT earlier in life for various medical or surgical indications. The study entry date will be defined as at the latest of: the study start date (1st January 1998); the practice up to standard date; the patient's date of registration with the practice plus 10 years; the woman's 55th birthday. The cohort will be followed until the earliest of: diagnosis of dementia date; the study end date (30th June 2020); the transfer out date; the practice last collection date; patient death.

Selection of cases and controls

Cases will be women in the cohort who have a first incidence of dementia during the observation period, acquired on the earliest date from either the GP record, the hospital record or the mortality record. The diagnosis of dementia will be identified using Read and ICD-10 codes for dementia used in previous studies [16]. Linked hospital (HES) and mortality data will also be used to identify additional cases with ICD10 diagnoses of dementia recorded on hospital records or death certificates. Additional cases included will be those who have received prescriptions for acetylcholinesterase inhibitors licensed only for patients with dementia (donepezil, galantamine, memantine, and rivastigmine).

We will match each case with up to 5 controls, who were alive and registered with the same practice at the time of the dementia diagnosis of the case. Controls will be matched with cases by practice, age, and calendar time using incidence density sampling. Each control will be allocated an index date which will be the date of first diagnosis for the matched case. Cases and controls will be included only if they have at least 10 years of recorded data at the index date, so that exposure to HRT can be assessed over a minimum of 7 years (because HRT exposure in the 3 years before diagnosis is not being considered).

Exposures

We will extract all prescriptions for HRT in cases and controls from the date of patient's registration with the practice up to one year before the index date. Prescriptions in the three years before the index date will not, however, be included for the main analysis to reduce protopathic bias. This is because early symptoms of dementia such as depression and sleep disorders might be mistaken for menopause symptoms. A woman will be defined as an HRT user if she has had at least one prescription containing

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systemic (oral, subcutaneous or transdermal) oestrogen indicated for menopausal treatment. The types of HRT to be included have been identified using the British National Formulary section 6.4.1.

We will consider the types of HRT most commonly prescribed in the UK [6] and categorise the exposure by: type of oestrogen (conjugated equine oestrogen or estradiol); type of progestogen (medroxyprogesterone, dydrogesterone, norethisterone or levonorgestrel/norgestrel); and regimen of use (oestrogen only (or unopposed oestrogen) or oestrogen combined with progestogen). Two types of oestrogen (conjugated equine oestrogen and estradiol) will be analysed separately for women using oestrogen-only therapy. Four types of progestogen (medroxyprogesterone, dydrogesterone, norethisterone and levonorgestrel/norgestrel) may be prescribed either in combination with one of the oestrogens or in addition to an oestrogen-only preparation. The type of oestrogen will not be specified for oestrogen-progestogen users.

We will also categorise HRT by route of delivery – oral or transdermal/subcutaneous. Women will be defined as users of oral preparations if they used a tablet formulation of HRT, and as users of transdermal/subcutaneous preparations if they used a patch, gel formulation or injection of oestrogen, with or without a progestogen. To account for more than one route for a treatment (such as a tablet and a patch) we will have a separate variable for each. There is no evidence of increased dementia risk associated with other routes of administration (such as cream or vaginal), but they will be included into the analysis for consistency and to provide further information on possible risks associated with these routes. Other drugs used for treatment of menopausal symptoms – tibolone and clonidine – will also be included as separate variables.

We will consider the dose for oestrogen which will be categorised into low dose (≤ 0.625mg for oral equine oestrogen or ≤ 1mg for oral estradiol or ≤ 50 micrograms of transdermal estradiol) and high dose (otherwise). We will analyse the median dose across all relevant prescriptions for a woman if she was exposed to both levels.

Duration of use will be assessed by calculating the number of days of exposure. If the gap between the end of one prescription and the start of the next is 90 days or fewer, we will consider exposure as continuous [17, 18] and combine the duration of the prescriptions. We will classify duration as: short-term (up to 1 year); medium-term (1 to 4 years); long-term (5 to 9 years); very long-term (10 or more years).

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To address existing speculations that initialisation of HRT around the time of the menopause may be beneficial for dementia prevention [13], we will analyse exposures by age when HRT treatment was started (<50 years, 50-59 years, 60+ years).

To investigate the effect of stopping HRT on dementia risk we will assess recency of use by calculating the gap in days between the estimated date for last use of HRT and the index date, categorising it as either recent use (used between 3 and 5 years before the index date) and past use (last use was earlier than 5 years before the index date).

We will assess exposure at different times by combining duration with recency using the categories defined for each. If the numbers of patients in some category combinations are too low, we may collapse some categories.

For all analyses, no use prior to three years before the index date will be a reference category.

Covariates

Analyses will be adjusted for patient characteristics, chronic conditions and use of other medications which are either risk factors for dementia [15] or indications for HRT use. Data for time-related confounders will be extracted at the closest date to 10 years before the index date, when they might be more closely associated with initial HRT use.

Patient characteristics will include: self-assigned ethnicity (using HES and GP data); body mass index (continuous); Townsend deprivation score (for the main analysis in QResearch and for sensitivity analyses only for CPRD); smoking status (non-smoker; ex-smoker; light (light smoker (<10/day), moderate smoker (10-19/day), heavy smoker 20+/day)); alcohol consumption (non-drinker, ≤1 unit/day, 2-3 units/day, 4-6 units/day, 7+ units /day); family history of dementia (yes/no); oophorectomy/ hysterectomy (yes/no); premature menopause (yes/no). Chronic conditions will include any record of: anxiety; cancers; coronary heart disease; depression; diabetes; hearing loss; hypertension; Parkinson's disease; stroke. Use of other medications will be considered if prescribed at least once at any time before 10 years prior to the index date and include: anticholinergic drugs (in particular antidepressants, antiparkinson, antipsychotics, antiepileptics and bladder antimuscarinics); antihypertensive; benzodiazepines; oral contraceptive; statins.

Data analysis

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Main analysis

The main analyses will be run separately on all practices contributing to CPRD and to QResearch. We will use the CPRD study population cohort to calculate incidence rates of dementia by dividing the number of incident dementia cases in the cohort by the number of person years. We will present rates by both 5-year age-band and calendar year. We will describe characteristics of cases and controls in both cohorts using appropriate summary statistics.

We will use conditional logistic regression in the nested case-control study to estimate odds ratios with 95% confidence intervals for the HRT exposure variables. We will calculate unadjusted odds ratios and odds ratios adjusted for potential confounding variables listed above.

To account for missing values, we will use multiple imputation to create ten imputed datasets with multiple chained equations, applying Rubin's rules to combine effect estimates and standard errors [19]. The imputation model will include all potentially important covariates, outcome status, and years of records [20]. To test our assumption that data were missing at random, we will run a sensitivity analysis using only records with complete data.

Adjusted odds ratios from the conditional regression analyses of the two datasets will be pooled using a fixed effect model with inverse variance weights. We will also run a sensitivity analysis using a random effect model to allow for any heterogeneity. Designing a two database study will not only provide more precise estimates but will also increase statistical power to facilitate investigation of less common exposures.

Using incidence rates in the unexposed CPRD cohort and combined odds ratios, we will estimate the absolute and excess risks associated with exposure to different types of HRT and for different subgroups of women (55 to 79 years old and 80 years and older). To assess incidence rates in unexposed women, we will use the CPRD study population cohort but exclude women with prescriptions for HRT before the study entry and follow the rest until their first prescription of HRT.

A 1% level of statistical significance will be used to allow for multiple comparisons. Stata 16 will be used for all the analyses.

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Additional analyses

To compare the prevalence rate of HRT captured by routinely collected data with existing evidence [21], we will assess the prevalence of HRT exposure in the CPRD study population for each year by dividing the number of women with at least one HRT prescription by the total number of women, all being registered for the whole year of the interest. The prevalence rates will be presented by 5-year age-band (55-59, 60-64, 65-69, 70-74, 75 and over) and calendar year.

To assess whether risks of different types of dementia associated with HRT use vary – and to facilitate comparisons with other studies – we will repeat the analyses with two subgroups, one restricted to cases diagnosed with Alzheimer's disease and the other to cases with vascular dementia. We will also run a sensitivity analysis omitting cases identified only by prescription for a dementia drug.

To address consistency in capturing HRT exposure in women of advanced age, we will run subgroup analyses for women younger than 80 years and for women 80 years or older (at the date of diagnosis of dementia or index date). We will also run an additional analysis on the subgroup of women who had been registered with a practice from their 50th birthday or earlier.

For the main analysis, we will include HRT prescriptions recorded up to 3 years before the index date, but in a sensitivity analysis we will use all records up to 1 year before the index date. This analysis will be included to investigate the effects of a form of selection bias caused by possible under-sampling of exposed cases and controls in the main analysis.

For the main analysis we will assess confounders at 10 years before the index date. Since the recording of some of these confounders could be from some time ago, and so not be as consistent as more recent data, we will also run a sensitivity analysis where confounders will be assessed at three years before the index date.

For the main analysis we will use all records from QResearch and CPRD. Because not all patients in the CPRD are linked to HES, ONS mortality data and patient-level Townsend deprivation index, we will repeat the main analysis on the subgroup of CPRD patients linked to these sources of data, also adjusting for the deprivation data.

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Sample size considerations

We have interrogated CPRD GOLD using the December 2019 version. We considered patients with first diagnosis of dementia or prescription for dementia aged 55 and over between 1 January 1998 and 31st December 2019. There were 39,862 (18,325 linked) such patients with at least 10 years of up to standard (UTS) data.

To detect an odds ratio of 0.9 with 90% power at the 1% significance level, and assuming an exposure prevalence of 10% in controls [6] and correlation of exposure between cases and control of 0.1, 19,511 cases would be required, with 5 matched controls per case. To detect an odds ratio of 1.1, 21,814 cases will be required. For rarer exposures of 5%, we will need 37,178 cases for an odds ratio of 0.9 and 41,108 cases for an odds ratio of 1.1.

To detect an odds ratio of 0.8 with 90% power at the 1% significance level, and assuming a low exposure prevalence of 1% in controls and correlation of exposure between cases and control of 0.1, 42,572 cases would be required, with 5 matched controls per case. For an odds ratio of 1.2, 51,181 cases will be required.

Using QResearch as well as CPRD GOLD will mean that we have easily the required number of available cases. This will provide sufficient power to run the proposed analyses.

DISCUSSION

The study findings will provide important information as to whether HRT is associated with either an increase, a decrease or no clinically relevant change in the rate of subsequent incident dementia. This will be important for future guidance of women considering HRT and for their doctors. The results will have international importance.

The study will have several strengths. It will be the largest single study, be based on the UK general population and will assess risks over a wide range of ages. Including all eligible women – alive or deceased – will make this study free from selection bias. Because the information is collected prospectively, the study will be free from recall bias. It will use the most recent information on all prescribed HRT treatments available in the UK over the last 20 years. Long durations of prescribing available in routinely collected information will allow the investigation of dosage effects for different types of HRT.

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The limitations of the study will include the lack of formal adjudication of dementia diagnoses. There might be some false positives for cases and some false negatives for controls and it is worth noting that, over time, the number of false negatives is likely to decrease over time because of improved dementia diagnosis rates. The likelihood of misclassification is much higher for cases than for controls because of the low incidence of dementia in the general population. A systematic review, however, has reported that on average 83% of diagnoses of mental and behavioral disorders recorded in general practice electronic records were confirmed by other data sources [22]. Also using hospital and mortality data for identifying cases will allow us to capture most women with dementia diagnoses.

Another limitation is the potential misclassification of exposure to HRT. Women can access HRT through online prescribing services without seeing their own doctor, but at a cost more than three times greater than the prescription fee. We also do not know with certainty whether a woman with a prescription had it filled or whether/when she started taking the medication. Another source of exposure misclassification will mostly affect older women, who had their menopause before their practice started contributing to the database. We do not see, however, any reason why these instances should differ between cases and controls. The effects of these potential misclassifications are likely to be small, but might shift the odds ratios towards unity.

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Approvals

The project has been reviewed in accordance with the QResearch® agreement with NRES Committee East Midlands – Derby [reference 18/EM/0400]. The protocol for CPRD has been approved by The Independent Scientific Advisory Committee for MHRA Database Research (N 20_139R).

Competing Interests

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