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

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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

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

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

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

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).

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

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.

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.

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.

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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