Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Present: Elizabeth Loder (chair); Wim Weber; Nazrul Islam; Di Wang; Tiago Villanueva; Joseph Ross; Gary Collins (statistician)

Decision: Request revisions before final decision

* We agree with reviewers that use of the term "hormone therapy" in place of "hormone replacement therapy" is desirable.

We also agree that the term "hormone replacement therapy" (HRT) is problematic and might better be replaced by "menopausal hormone therapy"(MHT), which is biologically more accurate and exactly describes the type of hormone therapy relevant to our study. We are reluctant to use the simpler "hormone therapy" (HT), as suggested by the reviewers and based on usage conventions in their environments, because it does not clearly identify the hormonal treatments under discussion and could cover many different hormone therapies, including for contraceptive purposes or for transgender patients. In the UK environment, HRT does at least do this and is still the term used in all British guidelines and the one most commonly used by doctors and patients. So we have suggested a compromise, which we hope will satisfy reviewers and the BMJ manuscript committee, and also have a clear meaning to readers inside or outside the UK. We have stated the difference in terminology where the relevant initialisms are defined and from there on throughout the paper used the joint initialism MHT/HRT.

"Although menopausal hormone therapy (MHT) [sometimes referred to simply as hormone therapy (HT) and commonly known within the UK as hormone replacement therapy (HRT)] clearly eases menopausal symptoms …"

* We wondered whether you can explain more about whether this is an important clinical question. Several editors mentioned that they have never thought about HT and dementia.

Doctors require accurate information on risks associated with MHT/HRT use for discussions with patients requiring or requesting treatment. Many women suffering menopausal symptoms are concerned about risks associated with hormonal treatments, no matter how small. A recent Finnish study of MHT/HRT and associated risk of Alzheimer's disease, and published in The BMJ, raised an alert because of suggested increased risks from any use of HRT. In these circumstances – and also in the light of the concerns that have been expressed about the problems caused by the emphasis in many research papers on risks found to be associated with MHT/HRT [BMJ, 367: l5928], we believe it important that evidence from a more definitive study – based on the latest data and with a more rigorous study design – should be disseminated to provide doctors and their patients with the best possible information. This will help women make a better informed decision and may save many women from needless worry or suffering. We have revised the second paragraph of Introduction to highlight this.

"The more recent study suffered from some methodological flaws and had a rather truncated study period, including only cases diagnosed up to 2013. The results suggested possible increased risks of Alzheimer's from MHT/HRT in addition to the known risks of venous thromboembolism or breast cancer. Given concerns expressed by some women's health experts about potential problems caused by over-emphasis on adverse risks from MHT/HRT treatments,[10] and the current National Institute for Health and Care Excellence (NICE) guideline stressing the need for more detailed information on side-effects and adverse outcomes of MHT/HRT,[11] a confirmatory study addressing the problems is appropriate. Our previous studies on venous thromboembolism and breast cancer risks have delivered useful and robust estimates of risk associations with different MHT/HRT preparations, highlighting dydrogesterone as a potentially low risk progestogen.[12][13] In this study we have aimed to provide similar detailed, accurate and robust information with respect to MHT/HRT use and dementia risks."

* Please take care not to emphasize a few positive findings when most findings are negative. Several editors were unsure whether you have adequately controlled for multiple comparisons.

Although our analysis produced many findings, some were to assess biological gradient as one of Hill's principles of causality. A great number of odds ratios in the supplementary data were sensitivity analyses conducted to check our assumptions. We also considered results to be statistically significant only when the p-value was <0.01 (reporting 95% confidence intervals was done – as is our usual practice – only to facilitate comparisons with other studies). Following the advice of the second reviewer we have revised our interpretation of outcomes for oestrogen-dydrogesterone therapy to be sure not to have over-emphasised it as possibly the best available choice. We have also assessed the biological gradient for risks in cases and controls younger than 80 years by running an analysis for exact duration of the exposure and found it statistically significant (p<0.001). This has added confidence to our findings of decreased risk for women younger than 80 years old associated with long-term oestrogen-only therapy.

We have added to Results Additional analysis By age at diagnosis:

"In the younger group, however, exposure to oestrogen-only treatment for more than 10 years was associated with some decreased risk (adjusted odds ratio 0.85, 95% confidence interval 0.76 to 0.94, p-value 0.003) and a linear relationship between duration of the exposure and dementia risk suggested a 1.1% decrease per year of HRT use."

* Can you comment on whether the need to have 10 years of preceding data might introduce selection bias?

Our requirement for 10 years of data was not based on a particular condition or on drug prescribing practice, but only on the administrative issue of a possible lack of recorded data because of the point at which a women had joined or left a practice and/or the practice had started or stopped providing data to the databases. This requirement was particularly applied to minimise any under recording bias for women who joined the practice not long before receiving their diagnosis for dementia. We compared age distribution between the cases with at least 1 year of data (this to exclude temporary patients) and the subgroup of cases with at least 10 years of data. The table below is based on CPRD data before applying exclusion criteria and demonstrates how close the distributions were. We

think the figures show it to be very unlikely that the need to have 10 years of preceding data introduced selection bias.

Age @ diagnosis	>1yr of records		>10yrs of records	
	Freq.	Percent	Freq.	Percent
55-59	757	0.7	331	0.7
60-64	1,425	1.3	629	1.2
65-69	3,271	3.0	1,478	2.9
70-74	8,178	7.5	3,945	7.8
75-79	17,143	15.8	8,072	15.9
80-84	26,890	24.7	12,555	24.8
85-89	28,383	26.1	13,295	26.3
90-94	16,915	15.5	7,790	15.4
95-99	5,214	4.8	2,279	4.5
100-104	610	0.6	253	0.5
105-114	35	0.0	17	0.0
Total	108,821	100	50,644	100

Comments from Reviewers

Reviewer: 1

Comments:
This case control study used data from two research databases (QResearch and CPRD), covering the 22.5-year period 1998-2020. Cases were women with a dementia diagnosis and for each case five controls were chosen from the same practice, matched on year of birth of the case.

Exposure to hormone therapy was assessed according to oestrogen-only and combined therapy, oral and non-oral administration, length of use, estrogen type, and type of progestogen included in the combined regimens. A user in a certain year was defined as a person with at least one prescription of systemic hormones in that year.

Confounder control included smoking, BMI, family disposition, medical comorbidity, other medications, and use of hormonal contraception. Sometimes also

The results were stratified according to regimen, length of use, oestrogen types, progestogen types, and age of the dementia diagnosis.

Generally, only few significant results were demonstrated. Among 104 specific odds ratios calculated seven protecting results were significant and four were significantly increased. With 95% CI you should expect by random five significant results. Six of seven protecting results were found for oestrogen only therapy and one for combined regimens. No systematic trend was found with length of use of oestrogen, while for combined therapy and tibolone the risk of dementia increased slightly but significantly by increasing duration of use.

Comments

It is complicated to make long-term follow-up for clinical end points in women according to use of different types of hormones taken for different periods and often shifting from one regimen to another and with substantial fluctuations in the overall use of hormone therapy during the study period, different routes of administration, and different types of oestrogen and progestogens in the combined products. At the same time potential confounding factors might have changed their influence by time and many are likely to have influence on the end point. Of methodological importance is the adjustment for family disposition for dementia, and the exposure "wash out" period of 1-3 years before the diagnosis index date.

All these obstacles are handled according to sensible algorithms, and results are reported in comprehensive main and supplementary tables.
Main limitation was lack of data on length of education, but adjustment for other lifestyle habits such as smoking and BMI, and for degree of affluency (Townsend quintile) are likely to have catched most of any confounding influence from length of education.

The authors have made a clear presentation of design, methods, results, and have discussed the limitations of the study appropriately in the discussion. Also, absolute risk estimates are delivered at the end of the result section.
An interesting online supplementary delivers relevant basic data for detailed differences between the different exposure groups, unadjusted estimates, results stratified for the two data sources and for different routes of hormone administration.

One principal point: When women go into premature menopause, their missing hormone production is generally replaced by exogenous hormones until age of normal menopause. Such a treatment is by some referred to as hormone replacement therapy (HRT) because the exogenous hormones replace hormones which normally is present. Hormone therapy in and after menopause, on the other hand, is an addition of hormones to women who would by nature be almost without natural sex-hormone production. I think, therefore, it is more logic to call this therapy for hormone therapy (HT) as it does not replace something but add something. I know this has been debated, but in Scandinavia we generally stick to this distinction, and I suggest HRT being replaced by HT in this paper. Perhaps editors might think otherwise.

Otherwise I have not further suggestions to this high standard transparent observational study. It is difficult to imagine how we could achieve more reliable data for a study like this, which therefore bring clarification to an issue which has been intensively debated through decades. Due to the high external validity I consider results like these at least as credible as results from much smaller randomized studies with (by choice) highly selected included women.

We would like to thank the reviewer for this positive overview, which emphasises the clinical importance and methodological transparency of our study. As noted in our response to the support from The BMJ manuscript committee above, we are sympathetic to the view that the established UK term "hormone replacement therapy"(HRT) does not correctly reflect the biological effect of what is hormone addition. However, perhaps the only advantage that HRT has as a descriptor over the simpler proposed HT, is its identification (at least within the British context!) of the specific hormonal treatments under consideration. We have suggested, therefore, using the term "menopausal hormone therapy" (MHT) as a more exact alternative to both. Because 'HRT' is still used all UK national guidelines and is common terminology between doctors and patients, however, we have also proposed that the dual initialisation MHT/HRT should be used after the alternative

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Reviewer: 2

Comments:
Thank you for the opportunity to review the manuscript by Vinogradova et al., which describes two nested case-control studies investigating the possible association between postmenopausal hormone therapy (HT) use and the risk of incident dementia.

The study is important, because the existing literature on the subject is still conflicting with some studies indicating that HT has a neuroprotective effect, some showing no effect and others indicating an increased risk of dementia in HT users. Some of the previous studies are rather small in size, and furthermore, there are differences in the age at the start of HT, in the preparations used as well as in the dementia diagnoses. However, due to the long gap between HT exposure and the usual age at dementia diagnosis, an RCT setting is impossible to conduct.

The study protocol has been ambitious. Cases were women aged 55 years and over with dementia diagnosis between 1998 and 2020. The data came mainly from general practices. Risk associated with HT use, including analyses related e.g. to duration, routes and age at start have been analysed.

The results support a recent Finnish finding that prolonged use of HT (especially EPT for over 5 years) is associated with a slightly increased risk for Alzheimer's disease. On the other hand, regarding other dementia types, e.g. vascular dementia, the effect of HT may even be protective. This may reflect the overall neutral effect of HT on dementia overall.

Our findings did not suggest any protective effect for vascular dementia. In fact, the odds ratio for 10+ years of oestrogen-progestogen therapy was 1.09 (95% CI 0.93-1.28), but we think that this apparent small increase most likely simply reflects elements of uncertainty about the type of dementia. We believe that all increased risks of overall dementia (in our study it was odds ratio 1.05, 0.97-1.13 for 10+ years of use oestrogen-progestogen therapy) are primarily attributable to Alzheimer's disease.

The strengths of the manuscript include its large size and a more comprehensive adjustment for various demographics, than in some previous studies. My major concerns regard the adequate diagnoses of dementia and the different dementia subtypes.

There are still major concerns related to the use of postmenopausal HT. The findings of the present study support the prevailing opinion on the associations between HT and dementia, and may offer support for doctors giving information for women with menopausal symptoms.

Major comments:

Are dementia diagnoses done in general practices, what is the diagnostic process like? How reliable are the different dementia diagnoses? For example it is mentioned that only part of the practices (45%) were linked to hospital and mortality data. Moreover, over half of the cases had no dementia type specified.

NHS memory clinics, staffed by specialists (psychiatrists, neurologists, etc.) are central to dementia diagnoses in the UK. These clinics, usually commissioned and run by secondary care teams, may be located in hospitals or in community clinics, but the specialist diagnoses are always fed back to GPs. In some places, the diagnostic process has been handed back to GPs following a set of guideline, investigations and with access to CT scans and oversight from specialist services. Where drugs are prescribed, prescribing also starts and is stabilised in a memory clinic, before the responsibility for care is handed over to the GP.

In all cases, it is the responsibility of the practice to enter the diagnosis on the patient record. The lack of linkage to hospital data for all records should not be too much of an issue because a letter will have been sent from secondary to primary care with the diagnosis information. Transferring this into the primary care record is essentially a manual process so only as good as the staff performing it. However, all practices contributing to these databases offer high quality services and it is generally very unlikely that an important diagnosis like dementia would be missed from a coding perspective whatever the information source.

Specialists will usually give an opinion as to the subtype of dementia though this may not necessarily pass into the records in the same way. Historically older diagnoses are more likely simply to state 'dementia' without giving a subtype. This is shown in figure 1, where the proportion of non-specific codes has decreased over time from 65% to 25%. A proportion of diagnoses are likely to be made only in general practice and based on clinical findings. This would happen if a patient had not yet had a diagnosis and had presented to a GP with obvious moderate or severe dementia. These are likely to be older patients or care home residents, where it may be felt that referral to and a review from a memory clinic would not be in the patient's best interests or have any therapeutic benefit. In these cases, lack of specific labelling might simply reflect the practical circumstances. This seems also to be reflected in the data because the proportion of diagnoses without a specific dementia code has consistently been higher in the older population – decreasing from 71% to 27% during the study period in women 80-120 years old, and from 53% to 21% in women 55-79 years old) [fig 1].

Finally, with respect to labelling, figure 1 also shows that specific coding for rare diagnoses have remained stable, while specific coding for Alzheimer's and vascular dementia have increased. This possibly reflects the fact that specific labelling can be difficult and is contingent on circumstance.

Labelling has, however, clearly improved over time, presumably due to a better diagnostic process – access to specialist memory clinics and to scans.

Figure 1 Proportion of women in different age groups with different types of dementia in GP CPRD records by calendar year
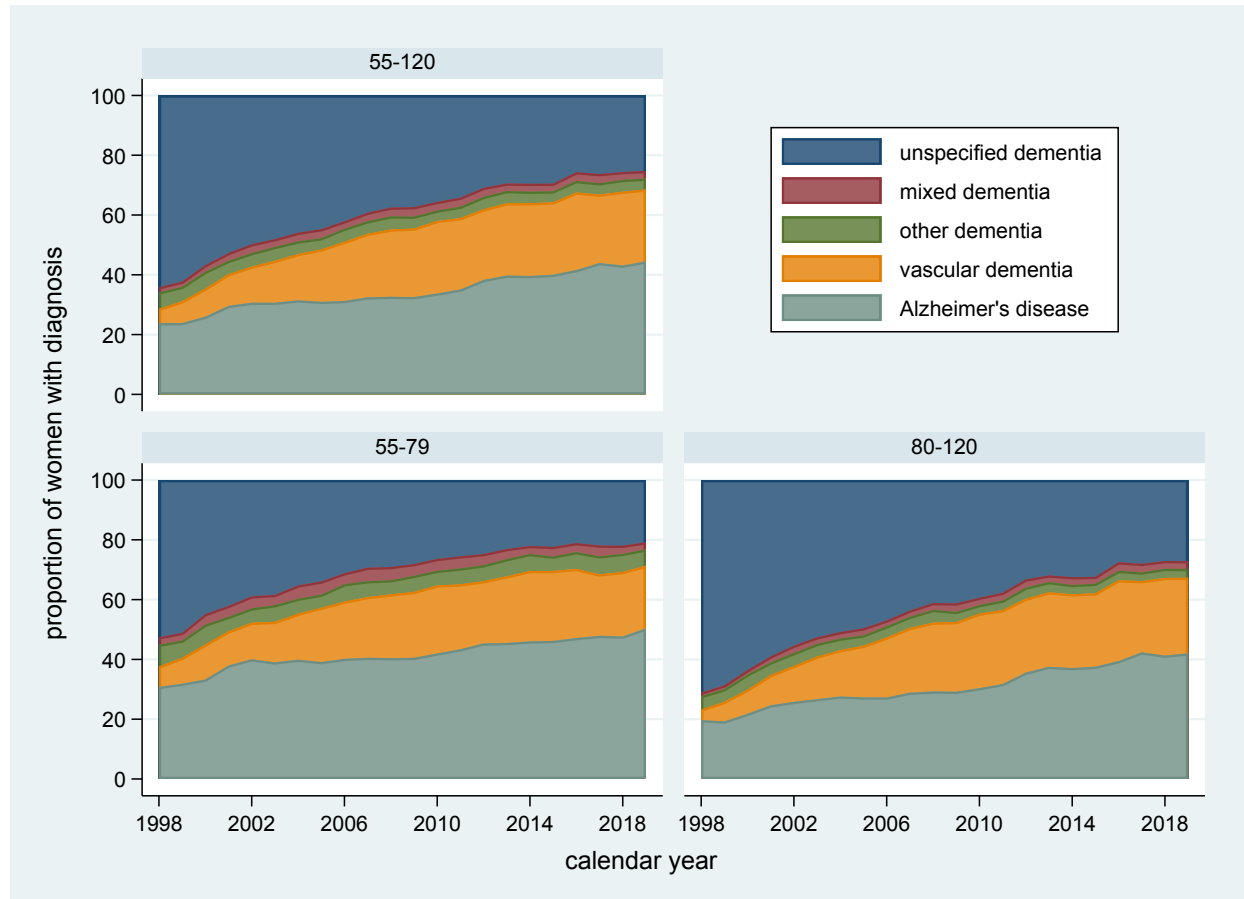
We have added the following text to Methods Selection of cases and controls and the figure 1 to Supplementary material:

"Current practice is that cases are normally diagnosed in specialist secondary care memory clinics staffed by specialists or in general practices, following a set of guideline investigations including CT scans and supported by specialists. Where patients present late with evident moderate or advanced dementia, and where circumstances mean that a patient is unlikely to benefit from referral to or review by specialists in a memory clinic, case diagnosis may be made by the GP based on clinical findings. Whatever the process, diagnostic information is available within the practice, whose responsibility it is to enter the information into patient records. The type of dementia, however, was not always available or may not have been transferred. The data showed that this was more pronounced earlier in the study period and among older patients, probably because of improvements in the diagnostic process over time and differing patient circumstances at the time of diagnosis. [Supplementary eFig 1]"

Dementia has been diagnosed between 1998 and 2020. From which year was the HT use recorded? If I understood right, the cases and controls were selected only if at least 10 years of medical records before the index date were included. Does that also include data on HT use?

Practices in the UK have been computerised from the 1980s. Prescribing rates of MHT/HRT were very low in the early years, so older cases and controls were less likely to have been exposed. We are confident that we have captured virtually all prescribing data. The requirement for "at least 10 years of data" was applied to ensure we captured all clinical information for included patients well before they received a diagnosis of dementia.

HRT treatments will be defined as at least one prescription for the treatment. For how long use is one prescription usually intended, is it certain that the women bought the medication and also used it?

We use exact prescription information for the number of days (median duration 84 days, inter-quartile range 56 to 100). Less than 1% of users had missing data and we imputed these using 84 days – in line with the recommendations of the British National Formulary, where hormonal therapy is usually prescribed for 84-90 days. We noted in our limitations that there was no information about actual use of the therapy but all our conversations with MHT/HRT users have suggested high levels of compliance.

Statistical analysis: it is mentioned that a small proportion of the demographic data were missing, could you specify this?

We had already noted that *"A small proportion of data for body mass index, smoking and alcohol consumption were missing."* but have now added a reference to Table 1, where we provide the proportion of patients with complete data for these confounders.

It seems that the risk ratio for dydrogesterone is not statistically significant. The sentence could be softened.

We have followed this advice and replaced the previous statement:

"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."

with:

"Although the findings for oestrogen-dydrogesterone appear to be associated with lowest risks among oestrogen-progestogen combinations, the confidence intervals were too broad for definite conclusions to be drawn."

Since the etiology and pathology of dementia types is at least to some extent different, it is good that the analyses have been done also in different subgroups, such as vascular dementia and Alzheimer's disease. However, it remained a bit unclear if the power of the analyses remained in the subgroups as well (including dementia subtypes and different HRT preparations).

Because of the power requirements necessary to draw conclusions, we could consider only vascular dementia and Alzheimer's disease for our subgroup analyses – and then only main exposures. We could not analyse different doses or applications for any other dementia type subgroups because of the low numbers. We have clarified this in Methods / Additional analyses.

To me it is not clear why clonidine, a non-hormonal treatment was included in the study. There might be differences between countries in the use of non-hormonal medications for hot flushes, but at least in some European countries the use of SSRI/SNRI is much more common than clonidine. Of course, it might be difficult to identify when SSRI was indicated for menopausal symptoms and not for some other reason.

Clonidine was added only because it is also used as a menopausal treatment. However, to respond to the concern of the reviewer and reinforce our focus on hormonal treatments, we have rearranged the text and clonidine is now described as a confounder along with other relevant medications. Antidepressants have also been included into analyses.

Discussion, page 23 "relation to other studies": it is good to notice that in the Finnish register study, analyses were done both with accurate knowledge on the HT exposure and with some assumptions on the HT initiation date, with no differences between those analyses. Time from HT initiation to AD diagnosis was shorter than 5 years in only 5.6% of the cases.

Thank you for drawing our attention to the results of the sensitivity analysis in the Finnish study. We have removed the point about assumption of exposure periods from Discussion. It is, however, not clear from the paper how many women stayed on MHT/HRT in the last 3 years before the diagnosis. It is possible therefore that, as symptoms of Alzheimer's disease were getting more pronounced, a women might still have tried to ease them by using MHT/HRT. Including all exposures up to diagnosis can introduce protopathic bias, shifting odds ratios away from unity.

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