11-Jul-2021
BMJ-2021-066406 entitled "Use of hormone replacement therapy and risk of dementia: nested case-control studies using the QResearch and CPRD databases"

Dear Dr. Vinogradova,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We are interested in proceeding with it provided you are willing and able to revise your paper as explained below in the report from the manuscript meeting.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Sincerely,

Dr Elizabeth Loder

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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 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.

* 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.

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

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where you have dealt with them in the paper.

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.

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The funding for research has been for my PhD students, not for myself.

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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.

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.

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?

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?

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

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

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).

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.

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.

Additional Questions:

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