Effect of oestrogen during menopause on risk and age at onset of Alzheimer’s disease

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Summary

Background Oestrogen use by postmenopausal women has many health benefits, but findings on the effect of oestrogen in Alzheimer’s disease are conflicting. Oestrogen promotes the growth and survival of cholinergic neurons and could decrease cerebral amyloid deposition, both of which may delay the onset or prevent Alzheimer’s disease. To investigate whether use of oestrogen during the postmenopausal period affects the risk of Alzheimer’s disease, we studied 1124 elderly women who were initially free of Alzheimer’s disease, Parkinson’s disease, and stroke, and who were taking part in a longitudinal study of ageing and health in a New York City community.

Methods Relative risks and age-at-onset distributions were calculated from simple and adjusted Cox proportional hazards models. Standard annual clinical assessments and criterion-based diagnoses were used in follow-up (range 1–5 years).

Findings Overall, 156 (12·5%) women reported taking oestrogen after onset of menopause. The age at onset of Alzheimer’s disease was significantly later in women who had taken oestrogen than in those who did not and the relative risk of the disease was significantly reduced (9·156 (5·8%) oestrogen users vs 158·968 (16·3%) non-users; 0·40 [95% CI 0·22–0·85], p<0·01), even after adjustment for differences in education, ethnic origin, and apolipoprotein-E genotype. Women who had used oestrogen for longer than 1 year had a greater reduction in risk; none of 23 women who were taking oestrogen at study enrolment has developed Alzheimer’s disease.

Interpretation Oestrogen use in postmenopausal women may delay the onset and decrease the risk of Alzheimer’s disease. Prospective studies are needed to establish the dose and duration of oestrogen required to provide this benefit and to assess its safety in elderly postmenopausal women.

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See Commentary page 420

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Introduction

Use of oestrogen by postmenopausal women has many health benefits.1-4 Oestrogen has been used as a treatment5-8 for Alzheimer’s disease, which affects a substantial proportion of elderly women.9 One study reported that oestrogen use was associated with a lower risk of mortality related to Alzheimer’s disease,8 although a subsequent case-control study did not confirm this association.1 Oestrogen promotes the growth of cholinergic neurons,10 stimulates the secretase metabolism of the amyloid precursor protein,11 and may interact with apolipoprotein E.11 All these factors could affect the risk of Alzheimer’s disease.

We examined the effect of a history of oestrogen use on the development of Alzheimer’s disease among elderly women living in New York. Our hypothesis was that oestrogen use might lower the risk of incident Alzheimer’s disease.

Methods

1282 non-demented elderly women were identified in a community-based study of ageing in northern Manhattan, New York City. The Health Care Financing Administration provided access to a random sample of Medicare recipients in the community. Additional potential participants were consecutively identified from records at senior centres and elderly housing sites in the same community. We wrote to potential participants identified by either method explaining that they had been selected to take part in a study of ageing. Participation rates were 77% at the senior centres and housing sites and 72% in the Medicare sample; these rates did not differ by ethnic origin. Each participant underwent a 90 min face-to-face interview then a standard assessment, which included a medical history, physical and neurological examination, and a brief (about 1 h) battery of neuropsychological tests.12,13 The criteria for eligibility were: no evidence of cognitive impairment on detailed psychometric assessment at the initial interview; no history of stroke or Parkinson’s disease; and at least one subsequent annual follow-up assessment.

Information about oestrogen use was available for 1227 (95·7%) women. From this group we excluded 52 (4·2%) women with Parkinson’s disease, 45 (3·7%) with stroke, and six (0·5%) with both disorders. Thus, we restricted the analysis to 1124 women—352 (31%) women identified at the senior centres and housing sites and 772 (69%) from the Medicare sample. The Columbia University Institutional Review Board reviewed and approved this project.

A standard history of oral oestrogen use was obtained from all women at study entry by a trained interviewer as part of the risk-factor questionnaire. The test-retest reliability of the overall questionnaire had been previously established.14 Questions about oestrogen use had good test-retest reliability (κ=0·65). If a woman had ever taken oestrogen, she was asked the ages at which she began and stopped. She was asked how old she was at the onset of the menopause and whether it occurred naturally or as a result of surgery. We asked the women to name the type of oestrogen preparation they used but not the dosages.

For diagnosis of dementia, medical records and imaging studies were used, as well as data from the initial and follow-up assessments.

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The proportional hazards assumption. The annual incidence rate possible age cohort effect. We used martingale methods to check of developing Alzheimer’s disease than younger women, we Because older women entering the study had a higher probability these covariates were then included in multivariate models. onsets distributions for women who did and did not use oestrogen. and survival analysis was used to plot the age-at- onset distributions for women who did and did not use oestrogen. Subsequent models were stratified to assess the effects ofeducation, APOE genotype, and ethnic origin on the relative risk; these covariates were then included in multivariate models. Because older women entering the study had a higher probability of developing Alzheimer’s disease than younger women, we stratified the analysis by the median age at baseline to reduce a possible age cohort effect. We used martingale methods to check the proportional hazards assumption. The annual incidence rate was estimated and the incidence rate ratio was calculated by standard methods.

Results
The mean age of the participating women was 74-2 years (SD 7-0) and the mean duration of education 9-2 years (SD 4-6). 400 (36%) of the women were African-American, 431 (38%) were Hispanic, and 293 (26%) were Caucasian. During follow-up, which ranged from 1 to 5 years, 156 women entered the study. 156 (14-9%) women developed Alzheimer’s disease. The women who developed Alzheimer’s disease were older than those who did not (78-5 [7-7] vs 73-7 [6-6] years, \( p=0.001 \)) and had had fewer years of education (6-7 [4-2] vs 9-6 [4-5] years, \( p=0.001 \)). Age at menopause was similar for women who did and did not develop Alzheimer’s disease.

156 women reported that they had used oestrogen after the onset of the menopause. The average duration of oestrogen use was 6-8 years (range 2 months to 49 years). Women who had used oestrogen were younger than those who had not (73-0 [6-3] vs 74-4 [7-1] years, \( p=0.01 \)) and had had more years of education (10-2 [4-8] vs 9-0 [4-5] years, \( p=0.005 \)). Fewer African-American women than Caucasian or Hispanic women had used oestrogen (41 [10-3%] vs 115 [15-9%], \( p=0.007 \)). Women who took oestrogen were more likely than those who did not to have had a hysterectomy (78 [50-0%] vs 256 [26-4%], \( p=0.001 \)), and to have had onset of the menopause at an earlier age (45-4 [8-1] vs 47-0 [7-7], \( p=0.06 \)). A greater proportion of women who had undergone hysterectomy than of those who had natural menopauses had used oestrogen for longer than 1 year (23/227 [10-1%] vs 35/897 [4-0%], \( p=0.001 \)). The majority of women used tablets containing conjugated oestrogens (Premarin). The most frequent reasons for discontinuation of oestrogen use were uterine bleeding, fear of cancer, or physician’s advice.

A history of oestrogen use was significantly less common among women who developed Alzheimer’s disease than in women who remained free of the disease (table 1, \( p=0.0006 \)). There was no difference in the use of oestrogen between the women excluded at baseline for Parkinson’s disease or stroke and the disease-free women (Parkinson’s disease 17%, stroke 10%, disease-free 16%, \( p=0.51 \)).

The age at onset for Alzheimer’s disease, stratified by the median age at entry into the study, was significantly later among women who used oestrogen than among women who never used oestrogen (log-rank test \( p=0.01 \)). The relative risk of Alzheimer’s disease associated with a history of oestrogen use was 0.40 (95% CI 0.22–0.85, \( p=0.001 \)). There was no difference in the use of oestrogen between the women excluded at baseline for Parkinson’s disease or stroke and the disease-free women (Parkinson’s disease 17%, stroke 10%, disease-free 16%, \( p=0.51 \)).

The age at menopause was similar for women who did and did not develop Alzheimer’s disease (table 2). 31 (20%) oestrogen users did not recall their duration of oestrogen use. The association with Alzheimer’s disease among these women (unknown group in table 2) was not significantly different from that in non-users, which suggests that they may not have used oestrogen at all or for only a brief period. Women who took oestrogen for 1 year or less (average 4 months) had a lower risk of Alzheimer’s disease than never-users, of borderline statistical significance (\( p=0.06 \)). The relative risk of Alzheimer’s disease for women who took oestrogen for longer than 1 year (average 13-6 years) was significantly reduced (0-13 [0-02–0-92], \( p=0.01 \)). There was a significant linear trend in the effect of duration of oestrogen use on disease risk (log-rank test, \( p=0.0034 \), figure). 23 women were still taking oestrogen at enrolment in the study, and none has developed Alzheimer’s disease during the study period.

To check the assumptions of the Cox regression model, we plotted the martingale residuals against age at onset. Data for all but three subjects fell within the predicted horizontal band around 0, satisfying the assumptions of proportional hazards.

Among women whose data satisfied criteria for
The annual incidence rates are within [0.09–0.69]; incidence rate oestrogen 1.2% [0.25–0.9], p=0.04) as was the incidence rate ratio (0.24). Results of the Cox model were similar (relative risk the relative risk of more advanced disease (n=99), but the relative risk of more advanced disease was less than one. That study had sufficient power to detect a reduction in risk similar to that in our study but the study design may explain why the outcomes differ. Brennan and colleagues' main comparison was of the odds that patients with Alzheimer's disease used oestrogen and the odds that controls used oestrogen. By contrast, we classified women on the basis of a history of oestrogen use and compared the cumulative risk that Alzheimer's disease would develop among oestrogen-users and never-users. Our results (figure) show that oestrogen use does not prevent Alzheimer's disease, but that it seems to delay the onset of the disease. The case-control design used by Brennan et al would not allow examination of differences in the age-at-onset distribution. Toran-Allerand and colleagues identified colocalisation of oestrogen-receptor binding sites with the mRNA for nerve growth factors and their receptors in developing neurons of rodent basal forebrain. The degeneration of these regions in Alzheimer's disease may cause the loss of memory and other cognitive functions. Their findings imply that oestrogen and nerve growth factors influence synthesis and release of nerve growth factors or alternatively promote survival, differentiation, regeneration, and plasticity. In a study of rats that had undergone oophorectomy, those treated with 17β-oestradiol did better on a memory task than those deprived of oestradiol; these animals also showed preservation of neurons in the basal forebrain as well as a return to near-normal concentrations of mRNA for nerve growth factors.

Oestrogen protects hippocampal neurons in culture exposed to excitotoxins, oxidative stress, or amyloid β. Cells cultured with 17β-oestradiol accumulate a soluble form of the amyloid precursor protein by enhancing the amount or activity of α-secretase. An exogenous source of oestrogen in postmenopausal women, even for a limited time, might foster the survival of neurons and limit the amount of amyloid β deposition, thus delaying the onset of overt manifestations of Alzheimer's disease.

The association between APOE ε4 and Alzheimer's disease has been extensively investigated and our results are similar to other population estimates. Oestrogen use was associated with a reduction in the risk of Alzheimer's disease among women heterozygous for ε4 and among women with other APOE genotypes, but we were unable to assess the effect of oestrogen among women homozygous for ε4.

This study has limitations because the design was observational. Oestrogen use was assessed by history. Oestrogen use was less common among African-American
women and more likely among better-educated women. Although we adjusted for some of these factors in our analyses, we cannot exclude the possibility that oestrogen use reflects a lifestyle characteristic or an as yet unidentified exposure or bias that accounts for the effect observed. We therefore believe that a prospective trial of oestrogen in perimenopausal women to delay the onset of Alzheimer’s disease is justified, once more data on the safety, dosage, and duration of oestrogen treatment required become available.

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