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Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women

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Summary The effect of estrogen on Alzheimer's Disease (AD) risk has received substantial research and media attention, especially in terms of hormone replacement therapy. But reproductive history is also an important modifier of estrogenic exposure, and deserves further investigation. Importantly, there is wide variation in reproductive patterns that modifies estrogen exposure during the reproductive span, which previous AD studies have not incorporated into their calculations. We measured degree of Alzheimer's-type dementia in a cohort of elderly British women, and collected detailed reproductive and medical history information, which we used to estimate number of months with estrogen exposure and number of months with menstrual cycles. Using Cox proportional-hazards models, we find that longer duration of estrogen exposure may have a protective effect against AD risk, such that for every additional month with estrogen, women experienced on average a 0.5% decrease in AD risk ($N = 89$, $p = 0.02$). More menstrual cycles may also have a protective effect against AD risk, although this result was of borderline statistical significance ($p < 0.10$). These results build upon previous methodologies by taking into account a variety of parameters including oral contraceptive use, breastfeeding, post-partum anovulation, abortions, and miscarriages. Additionally, Cox models revealed that longer reproductive span, age > 21 at first birth, and more months in lifetime spent pregnant had protective effects against AD risk.

1. Introduction

Estrogen has been implicated in Alzheimer's Disease (AD) risk and etiology. Various aspects of reproductive history determine the cumulative duration of estrogen exposure a woman

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experiences in her lifetime. Because there is substantial variation between women's reproductive histories and use of hormone-containing therapies, there is substantial variation in lifetime exposure to estrogen. Here, we investigate whether differences in cumulative exposure to estrogen and differences in specific aspects of reproductive history influence risk of AD in a cohort of elderly British women.

A range of studies have demonstrated estrogen's role in inhibiting and reversing AD-specific brain insults. In in vitro and animal model studies, estrogen has been shown to inhibit amyloid-β formation, promote amyloid-β clearance, inhibit neuronal apoptosis pathways, inhibit tau hyperphosphorylation, and reduce brain oxidative stress and inflammation, among other neuroprotective functions (see Supplementary Material section 2 for list of references). Nonetheless, a range of medical and epidemiological studies indicate possible heterogeneous effects of estrogen or confounders, so we present a literature review on this topic in Section 4.

1.1. Combined reproductive history features

Two studies have attempted to combine estrogen-altering life-history traits to calculate their cumulative effects in comparison to AD risk. Rasgon et al. (2005) added the duration of reproductive span (years between menarche and menopause) with the duration of time spent using hormone replacement therapy (HRT). They found that those with a higher composite number of years of estrogen exposure exhibited less cognitive decline.

Smith et al. (1999) created a more complex measurement for determining lifetime estrogen exposure. The effects of age at menarche, age at menopause, parity, duration of estrogen replacement therapy (ERT) use, postmenopausal weight, and years since menopause were given standardized (z) scores, which were then accumulated to create an estrogen exposure index. They found a correlation between their estrogen exposure index and cognitive function, which was stronger after they corrected for age and depression.

2. Methods

We propose an original method for a more comprehensive determination of lifetime exposure to estrogen based on number of months spent with exposure to estrogen. Women ages 70—100 along with family member(s) and/or carer(s) were recruited for participation through nursing homes, churches, community centers, the Alzheimer's Society, and a retired employee community. Participants received a modest gift voucher. The protocol was approved by the University of Cambridge Human Biology Research Ethics Committee.

Each session consisted of an interview collecting information about reproductive history, medical history, and factors that would potentially confound the relationship between AD and hormone exposure, or could obscure determination of dementia status. Exclusionary criteria included non-Alzheimer's-type dementia (e.g. vascular) or possible brain injury (e.g. head impact injury, brain tumor). Ten cases were excluded from analysis post-interview because of these criteria. Dementia status was measured by the Clinical Dementia Rating (CDR) scale, consisting of a 60—90 min interview conducted in two parts, one with the proband and the other with an informant (her relative or carer). Interviews were conducted by a researcher certified in CDR rating by the Washington University School of Medicine, a credential that requires high inter-rater reliability between the trainee and "gold standard" (Morris, 1997). In the CDR, probands are evaluated in six categories: memory; orientation; judgment and problem solving; home and hobbies; community affairs; personal care. The "sum of boxes" was used as a continuous variable, as has become standard in clinical trials (Coley et al., 2011; O'Bryant et al., 2008), computed from the sum of each category score, creating a scale from 0 to 18.

2.1. Variable calculations

2.1.1. Total lifetime duration of estrogen exposure

To estimate the number of months women spent in their lifetimes exposed to estrogen, we measured reproductive span as menopausal minus menarcheal age, subtracted the number of months spent breastfeeding, and for those pregnancies after which there was no breastfeeding, 1.5 months were subtracted to approximate the typical delay before ovulatory cycling resumes in such cases (Tulchinsky, 1980). Duration of post-menopause ERT use was added.

Rasgon et al. (2005) previously investigated the effect of total duration of estrogen exposure on AD risk, which they estimated by adding reproductive span to duration of ERT use after menopause. Given their significant results, we tested the same parameter ("Rasgon variable").

2.1.2. Number of menstrual cycles

No previous study known to the authors has investigated the relationship between number of menstrual cycles and AD risk. Cancer studies have estimated number of menstrual cycles by considering different combinations of the following variables: reproductive span, full-term pregnancies, abortions, miscarriages, breastfeeding, oral contraceptive (OC) use, infertility, period regularity (see Supplementary Material section 2 for list of references). Our methods are similar to these techniques, employing more variables at once than previous studies.

The number of months with menstrual cycles was computed as reproductive span, in months, minus months spent pregnant (including miscarriages, abortions, stillbirths, and child-bearing pregnancies), months spent breastfeeding, and months spent using OC. For pregnancies followed by no breastfeeding, cycling was assumed to resume 1.5 months post parturition (Tulchinsky, 1980).

2.1.3. Age at first birth

Age at first birth was taken as a woman's age at her first childbearing pregnancy, including stillbirths. This dataset did not contain nulliparas. While it would have been possible to instead utilize information for any pregnancy including incomplete ones, there is not biological evidence that incomplete pregnancy produces the equivalent long-term decrease in estrogen levels as full-term pregnancies. Additionally, recall of age at miscarriage or abortion was often vague and difficult to verify through family interview.

Ryan et al. (2009) found a relevant trend based on whether women had their first child in their twenties versus earlier. Our cohort contained only three individuals who had