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Pregnancy Life Events as a Modifier to Alzheimer's Disease Risk in Human Females

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Biology

by

Davis Hien Tue Mai

2022

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ABSTRACT OF THE THESIS

Pregnancy Life Events as a Modifier to Alzheimer's Disease Risk in Human Females

by

Davis Hien Tue Mai

Master of Science in Biology

University of California, Los Angeles, 2022

Professor Peter Nicholas Nonacs, Chair

Alzheimer's disease (AD) is a fatal neurodegenerative disease and the most common form of dementia in the world today. In women, reproductive life events help shape their biological systems and, therefore, have been identified as a modifying factor of AD risk. Despite this, the relationship between pregnancy life events and AD risk remains poorly understood. I proposed two original competing hypotheses that may explain this relationship. The first hypothesis, known as the estrogen hypothesis, states that pregnancy life events associated with an increase in estrogen exposure will reduce the risk of AD, as estrogen has neuroprotective properties against AD pathogenesis. The second hypothesis, known as the traditional reproductive pattern hypothesis, believes that because earlier populations were less susceptible to

AD, reproductive patterns that are consistent with the reproduction patterns of earlier populations will reduce the risk of AD. With these two hypotheses in mind, I conducted a review of the known literature on how *parity*, *age of first birth*, and *breastfeeding duration* are related to AD risk and cognition. I found that there is weak association between pregnancy life events that increase baseline lifetime estrogen exposure and AD risk and that most reproductive patterns of earlier populations are not a reliable predictor of AD risk. However, it still needs to be determined whether baseline lifetime estrogen is relevant in modifying AD risk. Overall, the relationship between pregnancy life events and AD is complex, as they modify multiple risk factors associated with the disease.

The thesis of Davis Hien Tue Mai is approved.

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2022

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Introduction

Alzheimer's disease (AD) is the most common form of dementia in the world today and it is primarily observed in individuals over the age of 65[1]. It is a neurodegenerative disease that initially results in loss of cognitive function and progresses to loss in bodily function and eventual death. AD patients observe an extracellular buildup of amyloid beta plaques in the brain and neurofibrillary tangles inside neurons formed from tau hyperphosphorylation. While the exact effects of these pathologies remain unknown, it is believed that they are responsible for weakening neuronal activity and synaptic connections, resulting in progressive brain atrophy and loss of cognitive ability[2]. There is currently no cure for Alzheimer's disease and the exact cause is not fully understood yet. It is a complex disease with many risk factors that span various biological systems, such as the immune, nervous, and endocrine systems.

In women, reproductive life events, such as the age she reaches menarche or the time she spends breastfeeding, are implicated in shaping the function of these systems. Therefore, reproductive life events in women and their association with AD risk have been an area of research interest. Despite this, exactly how these reproductive life events are associated with AD risk remains controversial. In particular, pregnancy life events, such as how many times a woman gave birth, the age a woman has her first child, and the cumulative time she spent breastfeeding, are some of the reproductive life events whose effects on AD risk remain the least understood. Therefore, I summarized the known literature on how *parity*, *age at first birth*, and *breastfeeding duration* are associated with AD risk. Additionally, I propose two competing hypotheses in order to predict how pregnancy life events may be associated with AD risk.

Estrogen and AD Risk

In women, a mediating factor to AD risk is lifetime exposure to the estrogen hormone. Estrogen has an important role in the development and function of multiple body systems in women. While the etiology and pathogenesis of AD are not fully understood, estrogen has an important role in several mechanisms that are linked to the development of AD. Exposure can potentially reduce Alzheimer's disease risk by mediating the immune response and glucose metabolism processes in the brain and altering the levels of known AD pathology[3–5].

Neuroinflammation is an important mediator of AD risk. The inflammatory response in the brain releases pro-inflammatory cytokines that disrupt neuronal activity and synaptic connectivity[6]. When the inflammatory response is too strong, the high levels of these cytokines can be toxic and result in brain dysfunction. Studies have shown that neuroinflammatory markers may potentially contribute to both the increase of amyloid beta deposition and tau hyperphosphorylation[7,8].

The role of estrogen in the immune response is complex, as it is responsible for promoting both pro-inflammatory and anti-inflammatory activity throughout the body[9]. However, exposure to estrogen can potentially reduce inflammation activity in the brain by regulating the inflammatory response of the microglial cells in the brain. It has been demonstrated both *in vivo* and *in vitro* that estrogen exposure was able to inhibit the inflammatory action of these microglia cells, therefore lowering inflammatory activity in the brain[3].

In addition to its anti-inflammatory properties in the brain, exposure to estrogen has an important role in increasing and maintaining glucose metabolism in the brain, which is an

essential process to maintain neuronal function. Estrogen is responsible for maintaining glucose uptake in the brain through potentially regulating the expression of various glucose transporters in the brain[10]. Additionally, estrogen is responsible for increasing ATP production in neurons by improving both glycolytic and mitochondrial processes in these cells[10]. Estrogen upregulates the activity of various enzymes involved in these processes[11].

A buildup of extracellular amyloid beta plaques and tau hyperphosphorylation are observed in the brain of AD patients and has been associated with the pathology of the disease, as it disrupts the function of neurons and promotes neuronal apoptosis[12–14]. A study found that in a mice model, estrogen deficiency in the brain was associated with increased amyloid beta deposition[15]. Exposure to estrogen can decrease the production of amyloid beta, but this has only been observed in primarily neuroblastoma cells[16,17]. However, estrogen has been shown to mitigate the toxic effects amyloid-beta has on the brain, such as protecting neurons against amyloid beta-induced apoptosis[18,19]. Multiple animal model studies have shown that estrogen exposure can reduce tau hyperphosphorylation in the brain[20–22]. While there is no cure for AD yet, estrogen has been shown to help protect and treat AD patients through regulating multiple biological domains associated with its pathology.

Reproductive life events, such as the age a woman reaches menarche and menopause or when a woman first gives birth, alter a woman's estrogen profile. It should be expected that a longer duration and overall greater exposure to estrogen throughout a woman's lifetime should protect her against Alzheimer's disease.

This hypothesis can explain some of the associations observed between the timing of reproductive life events and AD risk. Generally, reproductive life events that extend a woman's exposure to estrogen throughout her life will reduce her risk of developing AD. An earlier age of

menarche, later age of menopause, and use of estrogen replacement therapy in postmenopausal women generally reduce the risk or delay the onset of AD[23–28]. Multiple studies have summarized a woman's lifetime estrogen exposure and found that a longer duration of lifetime estrogen exposure provides more protection against AD or improves cognitive function[29–31].

Pregnancy events, such as *parity*, *age at first birth*, and *breastfeeding duration*, all impact a woman's lifetime estrogen exposure. More parity is associated with a temporary increase in estrogen levels due to the spike in estrogen levels during pregnancy. A later age of first birth is linked to a longer duration of higher baseline estrogen exposure. The duration a woman spends breastfeeding is marked by a period of reduced baseline estrogen levels. Based on the hypothesis above, the pregnancy events that increase a woman's lifetime exposure to estrogen should also trend to providing protection against AD.

Despite these pregnancy events having a clear impact on a woman's lifetime estrogen exposure, the associations with AD risk are mixed. A potential explanation for the inconsistent results is due to these pregnancy events affecting each other. A woman who has a higher parity may observe higher temporary increases in estrogen exposure due to more time spent pregnant, but a higher parity may also be associated with a lower age at first birth and a longer duration spent breastfeeding, which may result in an overall decrease in baseline levels of exposure to estrogen. Additionally, hormonal contraceptive use may further blur the results as they increase the dosage of estrogen exposure in women during periods where they are not pregnant. The variation of control variables used in these studies may explain the deviation in results that we observe.

If the neuroprotective effects of estrogen are a primary factor in mitigating AD risk, then I predict that among parous women, those with more pregnancies are more protected against AD

risk after controlling for breastfeeding duration and age at first birth. Additionally, I predict that nulliparous women have a lower AD risk than parous women due to their higher levels of lifetime baseline estrogen levels. Finally, I predict that a later age of first birth is protective against AD risk when controlling for parity. Through looking at how these pregnancy life events influence AD risk, we can gain a better understanding of how lifetime estrogen exposure and pregnancy may be involved in AD risk.

Traditional Reproductive Patterns and AD Risk

The timing and frequency of pregnancy life events in women have fluctuated throughout history and vary based on geographical regions and cultures. Because of this, certain diseases associated with pregnancy events have been observed to have varying prevalence amongst populations with opposing pregnancy patterns. The most notable example is a comparison of breast cancer risk between the Dogon people of Mali, a West African population that practices natural fertility, and populations where contraceptive use is common. A 1999 study showed that the total fertility rate of the Dogon people is 8.6 ± 0.3, over four times higher than in the United States at that time[32]. The incidence of breast cancer in similar West African populations is 12 times less than women in North America[33]. A review showed that increased parity and other pregnancy patterns resembling those of traditional, natural fertility populations are associated with greater protection against breast cancer, more specially ER+ breast cancer[34].

Because pregnancy events help explain the varying incidence of breast cancer in women for different populations and because the risks of both diseases are dependent on lifetime estrogen exposure, I believe that they can also provide insight into the varying incidence of Alzheimer's disease amongst women into different populations throughout history.

Alzheimer's disease and its risk factors affect different populations differently[35]. However, despite women being more susceptible to developing AD, comparisons on how AD affects women in different populations are less understood. Through understanding how pregnancy events affect a women's risk of Alzheimer's disease, we can paint a clearer picture of how women in different populations, both past and present, were affected by AD.

Additionally, by exploring how women in previous, natural fertility populations may have been affected by Alzheimer's disease, we can improve our understanding of the selective pressure AD may have had on previous generations. AD has a clear genetic risk factor in the e4 allele of the apolipoprotein (APOE) gene. Amongst Caucasians, individuals who carry one or two copies of the e4 allele are at an approximately 3 or 15 times greater risk, respectively, of developing Alzheimer's disease than those who carry two copies of e3, the most common allele[36].

The APOE gene is primarily responsible for regulating lipid transport in the brain, and therefore, modulates many processes associated with AD risk. While estrogen can potentially decrease the inflammatory response in microglial cells, there is evidence that APOE e4 upregulates the inflammatory response of microglial cells and pro-inflammatory cytokines, thus increasing the inflammation in the brain[37]. APOE e4 reduces the glucose uptake in astrocyte cells, in contrast to estrogen, which increases glucose uptake in neurons[39]. Additionally, APOE e4 is associated with reduced total energy expenditure and a reduction of glucose oxidation activity, which is linked to overall lower glucose metabolism[40]. These negative effects of APOE e4 on AD etiology and pathology are in direct contrast to the potential neuroprotective benefits of estrogen.

There is a clear genetic risk factor of AD in the APOE e4 allele, which raises the question as to why the allele frequency for e4 remains as high as it is today with an estimated global frequency of 13.7%[36]. Even though the age of onset for AD occurs primarily after a woman reaches menopause, AD still has negative impacts on a woman's reproductive success. AD places a major burden on those who take care of the AD patients. Additionally, maintaining proper health at a post-menopausal age is important for improving a woman's inclusive reproductive fitness. Known as the "grandmother hypothesis", post-menopausal women taking care of their grandchildren eases the burden of the mothers, therefore allowing them to have more children[41].

APOE e4 carriers also observe higher levels of plasma LDL cholesterol, or "bad" cholesterol, which can be associated with worse cardiovascular outcomes[42]. Because of this, APOE e4 carriers potentially are at a genetic predisposition to higher coronary heart disease risk[43]. However, due to the higher levels of physical activity and dietary practices of previous populations, it is unlikely that this had a major impact on the negative selection of APOE e4.

One explanation for why the frequency remains high despite the negative effects it has on reproductive fitness is that there are some fitness-enhancing benefits for e4 carriers. There is some evidence that carriers of the e4 allele have improved fertility. A study of Polish women found that APOE e4 carriers have a higher level of mean luteal progesterone during their menstrual cycle, a potential indicator of improved fertility[44]. Another study found that APOE e4 carriers had higher fertility than non-APOE e4 carriers if they were exposed to a highly pathogenic environment, which resembles the pathogenic profile of previous populations[45]. However, the effects of APOE genotype and fertility remain mixed, as another study found that the e3 allele was associated with higher fertility in a rural Italian population[46]. Considering that

these studies came from populations that used contraceptives, it is difficult to interpret how the varying APOE genotypes may influence fertility. Another potential fitness benefit for APOE e4 carriers is that they may be at an advantage in highly pathogenic environments. There is evidence that individuals who carry the APOE e4 allele and live in a highly pathogenic environment perform better on cognitive tests than non-APOE e4 carriers in the same environment[47,48]. In a Brazilian shanty town, a study found that children who carried the APOE e4 allele had lower diarrheal burden, which impacts their cognitive and physical development[49]. Therefore, it is worth noting that APOE e4 carriers can potentially confer some fitness-enhancing benefits in the form of improved childhood development and fertility when exposed to a high pathogenic load.

A novel explanation I propose for the APOE e4 allele maintaining its global frequency today is the reproductive patterns of previous populations potentially diminishing the risk of AD that the APOE e4 allele conferred, reducing the negative selection of APOE e4. Although we do not know the exact mechanism of how APOE e4 increases AD risk, it is possible that the protective effects of the reproductive patterns may mitigate the negative effects APOE e4 has on AD risk because of how the pregnancy life events affect multiple domains of AD etiology.

The distribution of the e4 allele across the world is disproportionate, with the e4 allele being most common in African and Oceanic regions[50]. Natural fertility populations, such as the aboriginals of Malaysia and Australia, have the highest frequency of the e4 allele, with some populations having a frequency three times higher than that of the global population[51,52]. I believe that this trend may be partially due to these populations being less susceptible to AD because of their reproductive patterns.

Therefore, if traditional and previous populations were less susceptible to selective pressure against the APOE e4 allele due to their reproductive patterns promoting protection

against AD, then we should also expect the events that reduce AD risk to be reflective of the reproductive patterns of these populations. For parity, the traditional reproductive pattern hypothesis will predict that higher parity should be associated with decreased risk of AD. Higher parity was more common in previous populations and is associated directly with higher dosages of estrogen exposure. Because breastfeeding practices highly vary between different cultures throughout history, it is difficult to predict how breastfeeding may affect AD risk using the traditional reproductive pattern hypothesis. However, because fertility in previous population was higher, earlier populations most likely had higher durations of breastfeeding. Additionally, studies on breastfeeding duration in hunter-gatherer populations showed that women in these populations had higher breastfeeding duration per child relative to women in industrialized populations[53]. Therefore, higher breastfeeding duration should be associated with a decreased risk for AD. Finally, age of first birth was lower in earlier populations, therefore, it should be associated with a decreased risk of AD.

If previous populations were truly at a reduced risk of AD, then there would be minimal to zero negative selection against the APOE e4 allele, considering the potential positive effects it has on fitness. This would be consistent with the high global frequency of the e4 allele observed today.

Estrogen Hypothesis vs. Traditional Reproduction Pattern Hypothesis

The traditional reproductive pattern and estrogen hypothesis share similar predictions with parity but have competing predictions for breastfeeding and age of first birth. Through conducting this review and comparing these two hypotheses, we hope to gain better insight not only into how estrogen and pregnancy events are associated with AD risk, but also into the evolutionary history of the disease itself.

Material and Methods

I accessed relevant articles from the PubMed database between February 2019 and February 2022. In order to include as many relevant articles as possible in this review, I also included studies that compared the relationship of these reproductive events to dementia and cognitive function. Key terms for each of the pregnancy events were used to search for articles that had those terms in the title, abstract, MeSH, and/or any other key description of the study. Additionally, each of the articles had to include either the words "Alzheimer's", "dementia", "cognitive", and/or "cognition" in any of the sections listed above. The search terms used for each of the pregnancy events can be found in Table 1 and the specific PubMed search input can be found in Table 2. Because many of the variables of interests are control variables or secondary analyses and may not be included in the aforementioned sections, I also conducted a search using other reproductive events to account for this. In addition to accessing the PubMed database, snowballing was also done in order to include as many studies as possible from this search. A small number of articles used in this review were obtained through personal academic references, which include articles that were already known to me or referred to me by an academic advisor. Reviews, case reports, meta-analyses, and studies that did not study a human female population were excluded from this review. If multiple articles analyzed the same study population, both studies were only included if their analysis of that population was unique. If not, only the original study was used in this review. Results coming from the same study cohort are clearly identified. Using these criteria, a total of 1913 unique articles were accessed from the entire PubMed search result and 43 unique articles were included in this review. A breakdown of the search process can be found in *Figure 1*.

The variable definition of pregnancy events for each of the listed studies was included. In the age of first birth results, the age of first pregnancy was also included under this event. In the parity results, studies that included the total number of pregnancies or the total number of children were included. If a study measured both completed pregnancies and total pregnancies, the completed pregnancy result was prioritized over total pregnancies. This was done to increase the number of relevant studies included in the review.

The operationalization for each of the studied variables was included for every finding. The measure that had a significant result was in bold, and the non-significant result was non-bolded. In addition to the operationalization and variable definition, the location of the study population, name or noteworthy details of the cohort, study population size, covariates, and how they defined cognitive performance and AD/dementia cases were also included for each listed result.

It is important to note that I considered some studies used in this review to hold more weight than others due to having ideal study designs. These studies include those with a study size of at least 300 participants and, at the minimum, controlled for age, education and/or income, and other health outcomes. Additionally, if a study controlled for other reproductive life events, they were also identified as ideal study designs regardless of the other control variables as long as they had an adequate study population size. The studies with robust study designs were clearly identified in the various tables in the results section.

When reporting studies, I set up specific rules to account for varying covariates within the same studies, as well as across different studies. If a study had done multiple analyses for the same variable using different covariates, the result that came from an analysis that included some covariates was always prioritized over a result with no or unknown covariates. An analysis from

a study with no or unknown covariates was only listed when there was no further analysis done. In the case that a study completed multiple analyses of the same variable where each analysis contained its own set of covariates, the analysis that contain covariates we categorized as having a robust study design was always prioritized. If a study had multiple models that meet the criteria for covariates with a robust study design, the analysis with the significant finding was always prioritized over the result with the non-significant finding. The covariates in each reported study correspond to the result that was listed.

If a study only found a significant result when stratifying their study population with a certain characteristic, such as race or APOE e4 status, the significant result from this subset of this cohort was listed over the non-significant result of the main study population. This was done due to consideration of the fact that some studies entire sample size had a specific characteristic already.

For each of the pregnancy events, two tables were produced. The first table compares the relationship between pregnancy events and AD risk. The studies that also examined dementia cases were also included under this category and are clearly identified in the table. If a study analyzed both AD and dementia risk, the AD result was prioritized over the dementia result. There were several different definitions we defined as a case of AD or dementia. Studies that used clinical interviews, tests done by clinicians to specifically diagnose AD or dementia, and medical records to define their AD or dementia cases group were included in the analysis. A higher prevalence of AD/dementia and/or an earlier age of AD onset were considered as a proxy for an increased risk of AD.

The second table compared the relationship between pregnancy events and reduced cognitive performance. Any cognitive assessment administered by appropriately trained researchers was considered in the analysis. Brain activity measured by imaging techniques was not considered as a measure of cognitive performance. The cognitive tests used were listed for each of the studies. If a study did not include results for each cognitive test they used, the cognitive domains or test batteries for which they reported results were listed instead. A clinical diagnosis of mild cognitive impairment was also considered as reduced cognitive performance in this review. For each study, the measure(s) of cognition that correlated to a significant finding are bolded, and non-significant measure(s) are non-bolded. In the case a study had both significant and non-significant results for multiple cognitive measures, the finding was listed as "(+ or -)/0" in the "Correlation…" column.

Table 1: List of reproductive life events and the specific search terms that were used to obtain the articles in PubMed.

Reproductive Event	**Search Terms**
Age at First Birth	Primiparous, primiparity, first birth, first pregnancy
Parity	Parity, number of children, gravidity, gravid, number of pregnancies, time spent pregnant, cumulative pregnant, total pregnant
Breastfeeding	Breastfeed, breastfeeding, lactation
Other Reproductive Events (Menarche, Menopause, Menstrual Cycles, Reproductive Span, Estrogen Exposure)	Menarche, menopause, reproductive span, reproductive length, estrogen exposure, menstrual cycles

Table 2: List of reproductive life events and the exact input that was used to search for articles in PubMed.

Reproductive Event	Search Terms
Age at First Birth	**(alzheimer's[Title/Abstract] OR alzheimer[Title/Abstract] OR dementia[Title/Abstract] OR cognitive[Title/Abstract] OR cognition[Title/Abstract] OR memory[Title/Abstract] OR OR "executive function"[Title/Abstract] OR "problem solving"[Title/Abstract] OR alzheimer's[Mesh:NoExp] OR alzheimer[Mesh:NoExp] OR dementia[Mesh:NoExp] OR cognitive[Mesh:NoExp] OR cognition[Mesh:NoExp] OR memory[Mesh:NoExp] OR "executive function"[Mesh:NoExp] OR "problem solving"[Mesh:NoExp] OR alzheimer's[Tw] OR alzheimer[Tw] OR dementia[Tw] OR cognitive[Tw] OR cognition[Tw] OR memory[Tw] OR "executive function"[Tw] OR "problem solving"[Tw]) AND (“first birth”[Title/Abstract] OR “first birth”[Mesh:NoExp] OR “first birth”[Tw] OR “first pregnancy”[Title/Abstract] OR “first pregnancy”[Mesh:NoExp] OR “first pregnancy”[Tw] OR “primipara*”[Title/Abstract] OR “primipar*”[Mesh:NoExp] OR “primipar*”[Tw]) AND ("humans"[Mesh:NoExp]) NOT ("review"[Publication Type] OR "review literature as topic"[Mesh:NoExp] OR "review"[Title/Abstract]) NOT ("meta-analysis"[Publication Type] OR "meta-analysis as topic"[Mesh:NoExp] OR "meta-analyses"[Title/Abstract])**
Parity	**(alzheimer's[Title/Abstract] OR alzheimer[Title/Abstract] OR dementia[Title/Abstract] OR cognitive[Title/Abstract] OR cognition[Title/Abstract] OR memory[Title/Abstract] OR OR "executive function"[Title/Abstract] OR "problem solving"[Title/Abstract] OR alzheimer's[Mesh:NoExp] OR alzheimer[Mesh:NoExp] OR dementia[Mesh:NoExp] OR cognitive[Mesh:NoExp] OR cognition[Mesh:NoExp] OR memory[Mesh:NoExp] OR "executive function"[Mesh:NoExp] OR "problem solving"[Mesh:NoExp] OR alzheimer's[Tw] OR alzheimer[Tw] OR dementia[Tw] OR cognitive[Tw] OR cognition[Tw] OR memory[Tw] OR "executive function"[Tw] OR "problem solving"[Tw]) AND (“parity”[Title/Abstract] OR “parity”[Mesh:NoExp] OR “parity”[Tw] OR “number of children”[Title/Abstract] OR “number of children”[Mesh:NoExp] OR “number of children”[Tw] OR “time spent pregnant”[Title/Abstract] OR “cumulative pregnant”[Title/Abstract] OR "total pregnant"[Title/Abstract] OR “time spent pregnant”[Mesh:NoExp] OR “cumulative pregnant”[Mesh:NoExp] OR "total pregnant"[Mesh:NoExp] OR “time spent pregnant”[tw] OR “cumulative pregnant”[tw] OR "total pregnant"[tw] OR “gravid*”[Title/Abstract] OR “gravid*”[Mesh:NoExp] OR “gravid*”[Tw] OR “number of pregnancies”[Title/Abstract] OR “number of pregnancies”[Mesh:NoExp] OR “number of pregnancies”[Tw])) AND ("humans"[Mesh:NoExp]) NOT ("review"[Publication Type] OR "review literature as topic"[Mesh:NoExp] OR "review"[Title/Abstract]) NOT ("meta-analysis"[Publication Type] OR "meta-analysis as topic"[Mesh:NoExp] OR "meta-analyses"[Title/Abstract])**
Breastfeeding	**(alzheimer's[Title/Abstract] OR alzheimer[Title/Abstract] OR dementia[Title/Abstract] OR cognitive[Title/Abstract] OR cognition[Title/Abstract] OR memory[Title/Abstract] OR OR "executive function"[Title/Abstract] OR "problem solving"[Title/Abstract] OR alzheimer's[Mesh:NoExp] OR alzheimer[Mesh:NoExp] OR dementia[Mesh:NoExp] OR cognitive[Mesh:NoExp] OR cognition[Mesh:NoExp] OR memory[Mesh:NoExp] OR "executive function"[Mesh:NoExp] OR "problem solving"[Mesh:NoExp] OR alzheimer's[Tw] OR alzheimer[Tw] OR dementia[Tw] OR cognitive[Tw] OR cognition[Tw] OR memory[Tw] OR "executive function"[Tw] OR "problem solving"[Tw]) AND (“miscarriage*”[Title/Abstract] OR “miscarriage*”[Mesh:NoExp] OR “miscarriage*”[Tw]) AND ("humans"[Mesh:NoExp]) NOT ("review"[Publication Type] OR "review literature as topic"[Mesh:NoExp] OR "review"[Title/Abstract]) NOT ("meta-analysis"[Publication Type] OR "meta-analysis as topic"[Mesh:NoExp] OR "meta-analyses"[Title/Abstract])**
Other Reproductive Events (Menarche, Menopause, Menstrual Cycles,	**(alzheimer's[Title/Abstract] OR alzheimer[Title/Abstract] OR dementia[Title/Abstract] OR cognitive[Title/Abstract] OR cognition[Title/Abstract] OR memory[Title/Abstract] OR OR "executive function"[Title/Abstract] OR "problem solving"[Title/Abstract] OR alzheimer's[Mesh:NoExp] OR alzheimer[Mesh:NoExp] OR dementia[Mesh:NoExp] OR cognitive[Mesh:NoExp] OR cognition[Mesh:NoExp] OR memory[Mesh:NoExp] OR "executive function"[Mesh:NoExp] OR "problem solving"[Mesh:NoExp] OR alzheimer's[Tw] OR alzheimer[Tw] OR dementia[Tw] OR cognitive[Tw] OR**

Reproductive Span, Estrogen Exposure)	**cognition[Tw] OR memory[Tw] OR "executive function"[Tw] OR "problem solving"[Tw]) AND (menarche[Title/Abstract] OR menarche[Mesh:NoExp] OR menarche[Tw] OR menopause[Title/Abstract] OR menopause[Mesh:NoExp] OR menopause[Tw] OR "reproductive span"[Title/Abstract] OR "reproductive span"[Mesh:NoExp] OR "reproductive span"[Tw] OR "reproductive length"[Title/Abstract] OR "reproductive length"[Mesh:NoExp] OR "reproductive length"[Tw] OR "estrogen exposure"[Title/Abstract] OR "estrogen exposure"[Mesh:NoExp] OR "estrogen exposure"[Tw] OR "menstrual cycles"[Title/Abstract] OR "menstrual cycles"[Mesh:NoExp] OR "menstrual cycles"[Tw]) AND ("humans"[Mesh:NoExp]) NOT ("review"[Publication Type] OR "review literature as topic"[Mesh:NoExp] OR "review"[Title/Abstract]) NOT ("meta-analysis"[Publication Type] OR "meta-analysis as topic"[Mesh:NoExp] OR "meta-analyses"[Title/Abstract])**

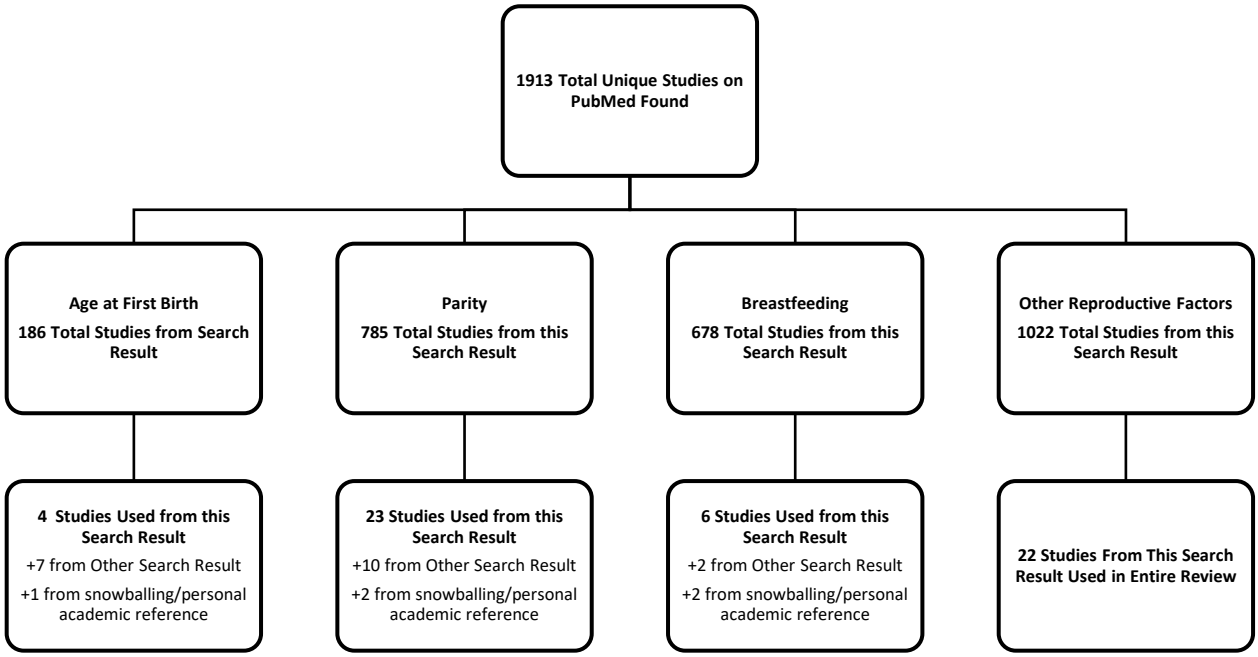

Figure 1: Breakdown of PubMed search results. The top row is the total number of unique studies on PubMed using all of the search terms. The middle row represents each pregnancy event category and additional reproductive factors and how many search results appeared from using the search terms for each of the four categories separately. The bottom row represents how many studies from each search result (except for "Other Reproductive Factors") were listed in their respective category in this review. For each category, studies that were discovered from another category's PubMed search were identified in addition to studies obtained through snowballing or personal academic references.

Results

I divided the pregnancy events into the following three categories: parity, age of first birth, and breastfeeding. From these 43 studies, I summarized the results that compared the relationship of these three events to AD risk or reduced cognitive performance. The findings from each of these events can be found in Tables 3-8.

Table 3: The relationship between parity and Alzheimer's Disease risk.

Legend	
	Study with Non-Robust Study Design
	Study with Robust Study Design

Reference	Variable Definition	Operationalization	Correlation to AD Risk	Covariates	Measure of AD	Study Location	Population	Sample Size
Baldereschi 1998	number of children	0 vs. 1-2, >2	0	None	clinical diagnosis of AD from NINDCDS-ADRA criteria	Italy	women aged 65-84, Italian women participating in ILSA	2,816
Ptok 2002	number of children	nulliparity vs **any parity;** continuous	+	Age, years of formal education	SIDAM	Bonn and Mainz, Germany	women, aged unclear	189
Kim 2003	number of children	Unreported	0	None	Korean MMSE and Korean DRS. Diagnosis of dementia, AD, and vascualar dimentia made according to SDM-IV, NINCDS,ADRDA, and NINDS-AIREN criteria respectively (a)	Kwangju, South Korea	women, Community residents > 65 years of age, urban and rural	438
Jang 2018	number of completed pregnancies	1-4 vs 0, vs **≥5**	+	Age, education, SES, diabetes melllitus, hypertension, hyperlipidemia, depression, age at menopause, length of reproductive period, previous HRT, breastfeeding history, CRS history	clinical diagnosis of AD from NINCD-ADRDA	South Korea and Greece	women aged 60+ from two different population-based cohorts(e)	3,549
Fox 2018	number of completed pregnancies	Continuous	0	age at first birth, reproductive span, and history of breastfeeding, marriages, occupation, and cumulative months pregnant	CDR-SOB > 0	UK	British women aged 70 - 100 years	95 (39 cases, 56 control)
Prince 2018	number of children	nulliparity vs any parity; **continuous**	+	age, education, household assets, marital status	Geriatric Mental State, CSI-D COGSCORE, CERAD , CSI-D RELSCORE (a)	Central/South America and China	10/66 study of multiple population-based cohorts , women age 65+	8,466
Bae 2020	number of completed pregnancies in 6 cohorts,	1-4 vs **nulliparity**, ≥5	- (c)	age, educational level, hypertension, diabetes mellitus	AD by NINCDS-ADRDA or DSM-IV criteria	Europe, Asia, Latin America	1 1 population-based cohorts, women 60 years+	14,792

	number of children in 5 cohorts							
Corbo 2007	number of children	nulliparity vs parity	+ (d)	none or unclear	DSM-IV, NINCDS-ADRDA, MMSE	Verona, Italy	women with sporadic form of AD, age 56+	176
Yoo 2020	number of children	Nulliparity vs **1**, ≥2	-	duration of fertility, duration of breastfeeding, duration of HRT, duration of oral contraceptive use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes mellitus, dyslipidemia and cancer	Clinical diagnosis of AD	South Korea	Post-menopausal women using the Korean National Health Insurance System	4,696,633
Jung 2020	number of completed pregnancies	0-4 vs ≥5	+	age, education, APOE4 positivity, cognitive status, VRS, income level at early adulthood, level of lifetime occupation, age at menarche age and age at menopause	AD-type regional cortical atrophy patterns	South Korea	Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease(b)	237
Bove 2014	number of surviving children (unclear if this meant alive at time of interview or number of live births)	Continuous	0	age at enrollment[for clinical diagnosis only] or age at death[for pathology diagnosis only], years of education, study (ROS vs MAP), and smoking (pack-years at study baseline)	Clinical interview using NINCDS-ADRDA criteria and AD neuropathology	Chicago, IL, USA	2 longitudinal cohorts-Religious Orders Study and Rush Memory and Aging Project, women mean age 78 (b)	1,884
Beeri 2009	number of children	Continuous	`+	age at death and Clinical Dementia Rating	Neurotic plaques (NP) and Neurofibrillary Tangles (NFTs) in Hippocampus, Entorhinal Cortex, Amygdala, Cerebral Cortex, and Total. General Neuropathology score (NPs and NFTs in hippocampus, entorhinal cortex, amygdala, and cerebral cortex)	Manhattan and Bronx, NY, USA	the brain of 42 women at a Jewish hospital, average age of death = 80	42
Sobow and Kloszewska 2004 (f)	number of pregnancies (unclear if this included incomplete pregnancies)	continuous	+	age, age at menopause, education, and smoking behavior	AD diagnosis	Poland	women hospital patients	65 cases

Colucci 2006	number of pregnancies (unclear if this included incomplete pregnancies)	≤ 3 vs **>3**; continuous	+	none	diagnosis of probable AD according to NINCDS-ADRDA criteria	Italy	women mean age 75.3 ± 6.8 yrs in cases, women mean age 74.3 ± 6 yrs in control	405 (204 cases, 201 control)
Najar 2020	number of total pregnancies	continuous	0	reproductive period, months of breastfeeding, birth year, exogenous estrogen, physical activity,WHR, hypertension, ischemic heart disease, and psychological stress	diagnosis of dementia from neuropsychiatric examinations based on DSM-III-R criteria	Gothenburg, Sweden	women who went through natural menopause followed for 44 years beginning from age 38-60 from Gothenburg H70 Birth Cohort Study (e)	1462
Paganini-Hill 2020	number of children	0 vs. 1,2,3+ (a)	0	age, education	in-person evaluation, neurological exam, or MMSE (a)	Laguna Hills, CA, USA	The 90+ study, originally from the Leisure World Cohort Study, women all currently aged 90+	424 (209 dementia cases, 215 control)
Waring 1999	number of completed pregnancies	Unreported	0	None	Diagnostic clinical interview based on DSM-III-R	Rochester MN, USA	postmenopausal women identified through medical linkage system.	222

(a) - Combined both dementia and AD cases into one group or only looked at any dementia.
(b) - Study looked at both cognition and AD risk in the same cohort. The study is listed twice.
(c) - when stratified by Asian regions only
(d) - when stratified by non - APOE e4 carriers
(f) - Data from this study obtained from accessing a review. An attempt was made to contact the authors from the original study. However, I was unable to get in contact with the authors.
Under the "operationalization" column, if a study included multiple operational variables, the variable(s) that corresponds to a significant result are in bold in order to distinguish it from the non-significant variables. The results highlighted in green meet the criteria for what I identified as having robust study designs. Robust study designs have a sample size of at least 300 participants and, at the minimum, controlled for age, education and/or income, and other health outcomes. If a study controlled for other reproductive life events, they were also identified as ideal study designs regardless of the other control variables as long as they had an adequate study population size.

Table 4: The relationship between parity and lower performance on various cognitive measures.

Legend	
	Study with Non-Robust Study Design
	Study with Robust Study Design

Reference	Variable definition	Operationalization	Correlation to Reduced Cognitive Performance	Covariates	Measure of cognition	Study Location	Population	Sample Size
Bender 2013	number of pregnancies (unclear if this included incomplete pregnancies)	**continuous**	+/- (g)	age and estimated verbal intelligence	visual learning and memory (Rey Complex Figure Test and Cambridge Neuropsychological Test Automated Battery [CANTAB] Paired Associate Learning Test), executive function (Delis Kaplan Color Word Interference and Verbal Fluency Tests and Trail Making Test-B)**, verbal learning and memory (Rivermead Behavioral Memory Test Story Recall and Rey Auditory Verbal Learning Test)**, attention (CANTAB Stockings of Cambridge and Spatial Working Memory Tests and Digit Vigilance Test), **psychomotor efficiency (Grooved Pegboard and Digit Symbol Substitution Test)**, and visual sustained attention (CANTAB Rapid Visual Information Processing mean latency and total hits)	Pittsburgh, PA, USA	women with breast cancer who were matched with healthy women aged <75	264 breast cancer patients, 95 healthy controls
Ilango 2019	number of pregnancies (unclear if this included incomplete pregnancies)	2 vs 0, 1, 3, ≥4; nulliparity vs. **parity;** continuous	+/0	education and marital status	MMSE, trail making test part B, Animals Naming Category Fluency Test, **Buschke-Fuld Selective Reminding Test**	Rancho Bernardo, CA, USA	prospective cohort study that enrolled participants from 1972 to 1974, women (mean 73.1 ± 9.6)	1025
Karim 2016	number of total pregnancies	1 vs 2, >2, **no full-term pregnancies**, nulliparous	-/0	Age at cognitive testing, race or ethnicity, income and education	**global cognition, verbal memory,** executive function	Los Angeles, CA, USA	Natural Postmenopausal women from Women's Isoflavone Soy Health (WISH) and the Early vs Late Intervention Trial of Estradiol (ELITE)	830

Hesson 2012	number of completed pregnancies	Continuous	0	Index of Cumulative Estrogen Exposure, IQ, education	Logical Memory I and II subtests from the Wechsler Memory Scale – Third Edition ; time-based prospective memory task	Newfoundland, Canada	postmenopausal women with mean age 69.3 years	50
Mclay 2003	whether they had given birth to a live infant	Nulliparity vs **any parity**	+	age, education, race, surgical versus natural menopause, use of birth control pills, and baseline MMSE score	**MMSE**	Baltimore, MD, USA	community sample of postmenopausal women with mean age 63.4 ± 14.3	361
Heys 2011	number of children	**Continuous**	+	age, education, childhood and adulthood socio-economic position and physical activity	**immediate and the delayed 10-word recall score, MMSE**	Southern China	Postmenopausal Chinese Women Aged 50+ from Guangzhou Biobank Cohort Study	11,094
Jung 2020	number of completed pregnancies	0-4 vs **≥5**	+	age, education, APOE4 positivity, cognitive status, VRS, income level at early adulthood, level of lifetime occupation, age at menarche age and age at menopause	**MMSE**	South Korea	Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease(b)	237
Jang 2018	number of completed pregnancies	1-4 vs 0, ≥5	0	Age, education, SES, diabetes melllitus, hypertension, hyperlipidemia, depression, age at menopause, length of reproductive period, previous HRT, breastfeeding history, CRS history	MMSE, clinical diagnosis of AD from NINCD-ADRDA and MCI diagnosis from IWGMCI	South Korea and Greece	women aged 60+ from two different population-based cohorts(e)	3,549
Low 2005	number of children	Continuous	0	Age, education and Spot-The-Word, SF-12 physical health, depression, BMI, diabetes, smoking history, alcohol use, exercise level	verbal learning test (immediate recall and 1-minute delay), the Mini- Mental State Examination (MMSE), digit span backwards, the Symbol-Digit Modalities Test and simple and choice reaction time tests.	Canberra, Australia	naturally postmenopausal aged 60-64, PATH Through Life Study	760
Rasgon 2006	number of children	1-2 vs 0, 3-4, **≥5**	+	age and education	**TELE**	Sweden	women aged 65-84 from HARMONY Study from Swedish Twin Registry	6604
Ryan 2009	number of children	0 vs 1,2-3, >3; nulliparity vs parity	0	age, education level, marital status, depressive symptoms, high caffeine intake, physical incapacities and comorbidity	5-word Test of Dubois, with both immediate and delayed recall tasks, Isaacs Set Test, Benton's visual retention test, Trail Making Tests A and B, MMSE	Montpellier, France	65+ aged women, ESPRIT study (e)	996
Henderson 2003	number of children	**continuous**	-	age, education, employment, marital status, smoking history, alcohol use, exercise, and mood.	**supraspan word list recall task.**	Melbourne, Australia	Women aged 52-63 years, Melbourne Women's Midlife Health Project	326

Glynn 2012	number of pregnancies	primiparous vs **multiparous; continuous**	+(h)	race/ ethnicity, education level, age, lactation status, depressive symptoms and sleep quality	**verbal recall task**	CA, USA	pregnant and postpartum women	254
Zhang 2020	number of completed pregnancies	continuous	0	menopause or not, age, level of education, soya products, daily exercise intensity, daily exercise amount, smoking, alcohol consumption, HRT, higher age at menarche	**"cognitive symptoms" from database**	China	perimenopausal and postmenopausal women (mean age 50.69 $\pm$6.49)	4595
Ning 2020	number of completed pregnancies	Nulliparity vs **1,2,3 $\geq$4**	-	age, education, body mass index (BMI), average total house- hold income, past tobacco smoking frequency, alcohol intake frequency, sleep duration, living alone or with others, diabetes, and hypertension disease status	**response time and visual memory test**	United Kingdom	women (mean age =56.7) from UK biobank	160,077
Chou 2021	birth times	continuous	0	age, cerebrovascular disease, education level, living alone, BMI, total cholesterol, LDL-cholesterol, age at menarche, reproductive period, breath times and breastfeeding period	MMSE	Taiwan	women (mean age = 63.7 $\pm$ 2.9) from Taiwan Biobank	520
Song 2020	number of children	1-2 vs. 0, 3-4, and **>5; continuous**	+	MMSE measurement, year of baseline interview, dialect group, marital status, and education level, smoking status, tea intake, coffee intake, sleep duration, physical activity, body mass index, total energy intake, alternate Mediterranean dietary pattern score, baseline history of hypertension, diabetes, cardiovascular disease, and cancer. Age at menarche, number of children, use of oral contraceptives, age at menopause and use of hormone replacement therapy	**Singapore Modified MMSE**	Singapore	postmenopausal Singapore Chinese Health Study- women aged 45-74	8,222
Rote 2021	number of children	0 -1 vs >**5**	+	education, cardiovascular disease, diabetes	**MMSE**	Texas, New Mexico, Colorado, Arizona, and California, USA	Mexican American women aged 65+ from Hispanic Established Populations for the Epidemiological	1,642

							Study of the Elderly	
Shimizu 2019	number of completed pregnancies, including stillbirths	1 vs 2, 3, ≥4; continuous	0	age at mental health examination, baseline BMI, educational background, smoking, sports or leisure-time physical exercise , and past medical history of any of hypertension, diabetes mellitus, or depression	current cognitive impairment by clinical diagnosis	Nagano Prefecture, Japan	women aged 40-59 in Japan Public Health Center-based Prospective Study	670
Tierney 2013	Number of children	continuous	0	age, years of education, total numbers of months spent breastfeeding, years since menopause, and previous OC and HT use	RCFT immediate recall, RCFT delayed recall, CVLT immediate recall, CVLT short delay recall, Digit span backwards	Toronto, Canada	nondemented, natural menopause women aged 60-89	126
Tsai 2020	number of pregnancies	0-1 vs 2-4, **5-11; continuous**	+	age, race/ethnicity, education, family, systolic blood pressure, body mass index, age at menarche, age at menopause, C-reactive protein, total cholesterol, serum folate, history of coronary heart disease, time to complete a 20-ft walk, smoking, history of diabetes, and vigorous activity over the past 30 days	**digit symbol substitution test**	USA	postmenopausal women (mean age 70.79 ± 7.84) from Nutrition Examination Survey dataset	1,093
Sujarwoto 2020	number of biological children	continuous	-	age, premature menopause, early onset menarche, number of stillbirths, number of miscarriages, marital status, education, household expenditure, number of cigarettes consumed per day, grams of tobacco consumed per day, obesity, mental depression, and living in urban areas	**Indonesia Family Life Survey 2014**	Indonesia	1031 postmenopausal women aged 60+	1,031
Read 2017	number of living children	2 vs **0, 1,** 3, 4	-	age, education, occupational status, tenure status, wealth, limiting long-term illness, physical activity, smoking depressive symptoms,	**composite score from world list recall task (immediate recall; delayed recall) verbal fluency test**	England	English Longitudinal Study of Ageing, women aged 50+	6,123
Li 2016	number of completed pregnancies	1-4 vs 0, **≥5**	+	age, race , education level, marital status , economic status, smoking , alcohol	**MMSE**	Eastern China	postmenopausal women from Zhejiang Major	4,796

				drinking , exercise, hypertension, diabetes, coronary heart disease , and depressive symptom			Public Health Surveillance Program	
Harville 2020	number of completed pregnancies	Any parity vs **Nulliparity** ; <3 vs ≥3; <4 vs ≥4	-/0	age at interview, menopausal status, race, smoking (ever), marital status, depressive symptoms, BMI	**logical memory 1** , **logical memory 2, logical recognitive**, **digit coding score**, **trail A time**, trail B time, trail B/A ratio, digit span forward , digit span backward, **summary score**	Bogalusa, LA, USA	mid-life aged women (mean 47.7)Bogalusa Heart Study	730
Bove 2014	number of surviving children (unclear if this meant alive at time of interview or number of live births)	Continuous	0	age at enrollment[for clinical diagnosis only] or age at death[for pathology diagnosis only], years of education, study (ROS vs MAP), and smoking (pack-years at study baseline)	Composite of following tests: Word List Memory, Recall, and Recognition and immediate and delayed recall of story A from Logical Memory and the East Boston Story, 15-item version of the Boston Naming Test, Verbal Fluency, and a reading recognition test, Digit Span For- ward and Backward plus Digit Ordering, oral version of the Symbol Digit Modalities Test and Number Comparison, 15-item version of Judgment of Line Orientation and an 11-item version of Standard Progressive Matrices	Chicago, IL, USA	2 longitudinal cohorts- Religious Orders Study and Rush Memory and Aging Project, women mean age 78 (b)	1884

(e) - Population from cohort is also included in 1 of the 11 cohorts in the analysis in Bae 2020.
(b) - Study looked at both cognition and AD risk in the same cohort. The study is listed twice.
(g) - more children reduces psychomotor efficiency performance, more children increases verbal learning and memory performance
(h) - when stratified by >16 weeks gestational age and 3 months postpartum
Under the "operationalization" column, if a study included multiple operational variables, the variable(s) that corresponds to a significant result are in bold in order to distinguish it from the non-signficant variables. Under the "measure of cognition" column, the measure of cognition that corresponds to the significant result are in bold to distinguish it from the non-signficant measures of cognition. The results highlighted in green meet the criteria for what I identified as having robust study designs. Robust study designs have a sample size of at least 300 participants and, at the minimum, controlled for age, education and/or income, and other health outcomes. If a study controlled for other reproductive life events, they were also identified as ideal study designs regardless of the other control variables as long as they had an adequate study population size.

Parity Results

A total of 43 results listed in this review explored the relationship between various measures of parity and AD risk or cognitive performance. Some studies operationalized parity as number of children, some compared women with no children versus any children, some used both operationalizations, and there were also other variations on these.

When looking at both robust and non-robust studies that measured the relationship between parity and AD risk, a majority of them found that higher parity was associated with either an increase or no effect on AD risk, although a few studies found higher parity to decrease AD risk. Eight studies found that higher parity was associated with increased risk of AD[54–61], while 7 studies found no association[28,62–67] and 2 studies found parity to decrease the risk[25,55].

For studies with robust study designs, the relationship between parity and AD risk becomes mixed, with an equal number of studies finding that parity was associated with an increased risk, no change, or decreased risk. Evidence from the robust studies leans more towards decreased risk than the full list of studies implies. Two robust studies found that overall higher parity was associated with an increased AD risk[55,56], but the effect appears weak on closer inspection. One of these studies, *Prince et al.2018*, looked at any dementia and looked at a total of 11 different population-based cohorts across Central/South America and China for a total sample size of 8,466. Out of these cohorts, only one cohort (with a sample size of 1,156) found that higher parity was significantly associated with an increased risk of AD. The other ten cohorts found no association between higher parity and AD risk. The other robust study that found higher parity was associated with a higher risk of AD was *Jang et. al 2018*, but they found that women with five or more completed pregnancies, or grand multiparity, were associated with an increased risk of AD when compared to women with one to four completed pregnancies.

There was no significant association between AD risk in nulliparous women when compared to primiparous women and they did not compare nulliparous women to grand multiparous women. Two robust studies found no association between parity and AD risk. In one of these studies, *Bove et. al 2014*, the primary focus was to compare cognitive function in women who went through natural menopause versus surgical menopause. It was unclear whether they controlled for this factor when measuring the effects of parity on cognition and Alzheimer's risk.

Two robust studies found that overall higher parity was associated with a decreased risk of AD. *Bae et.al 2020* found that nulliparity was associated with a higher risk of AD when compared to women with 1-4 completed pregnancies. However, this association was only found when they stratified their sample population in Asian regions. There was no association between parity and AD risk in European and Latin American regions. Additionally, they found no association between AD risk and grand multiparity in any of the other regions. *Yoo et al. 2020* found that primiparous women had a significantly lower risk of AD when compared to nulliparous women. This association was lost for any women with additional parity.

For the studies that looked at the relationship between parity and cognitive performance, the effects become slightly more mixed than AD risk. When I factor in studies with both robust and non-robust study designs, 11 studies found that higher parity and similar factors were correlated to a decrease in performance on various cognitive measures[31,57,68–76], another 12 studies reported no effect on cognitive abilities[55,64,68,77–85], and 7 studies finding that parity increased the performance on various cognitive measures[76,77,85–89]. It is worth noting that 5 studies that found that higher parity was associated with worse cognitive performance found this association only in women who had over four completed pregnancies[31,57,73–75]. There were 3 studies that found no association between cognitive performance and having over four completed

pregnancies[55,68,83] and 1 study that found having over four completed pregnancies was associated with improved cognitive performance[88]. When we only consider the studies with a robust study design, the distribution of results remained mixed.

When looking at all studies that compared parity with AD risk or cognition performance, none of them controlled for age at first birth, but there were several studies with a robust study design that controlled for some form of breastfeeding. From these robust studies, 1 study, *Jang et al. 2018,* found that parity was associated with an increase in AD risk, and 1 study, *Yoo et al. 2020,* found it to decrease the risk[25]. Both of these studies were discussed earlier; however, it is worth noting that *Jang's* population cohort is from Greece and South Korea while *Yoo*'s study consisted exclusively of a South Korean population. Additionally, *Jang*'s study consisted of 3,549 women while *Yoo*'s study size was much larger with 4,696,633 women. Four studies, which include both robust and non-robust study designs, controlled for breastfeeding and showed no association between parity and AD risk[63,65] or cognitive performance[55,84]. Of these 4 studies, 2 of these studies did not have a large sample size[63,84]. The other 2 studies did have a large sample size, however, one of these studies was *Jang*'s study, and they found higher parity to be associated with increased AD risk but found no association for mild cognitive impairment in that same cohort.

A total of 14 studies with robust study design compared AD risk and cognitive performance between nulliparous women with parous women and the results primarily showed no association or that nulliparity was associated with worse AD risk or cognitive performance, i.e., parity was protective. Out of these 14 studies, 5 of them found that nulliparity was associated with a higher AD risk[25,90] or lower cognitive performance[85,86,88]. Only 2 of those 5 studies found that nulliparity was associated with higher AD risk or worse cognitive function

compared to any parity[85,88]. The other two studies only found this association when comparing nulliparity to a lower parity (4 or less) but not higher parity (e.g. 5 or more) or did not compare this to women with higher parity[25,90]. Only 1 study with a robust study design found that nulliparity was linked to better cognitive performance[19], and this study compared nulliparity to any parity. All of these studies found this association when comparing nulliparity with any parity. The remaining 8 studies found no association between nulliparity and AD risk[56] and cognitive performance[31,55,72,75,77,80,85].

Table 5: The relationship between age at first birth and Alzheimer's Disease risk.

Legend	
	Study with Non-Robust Study Design
	Study with Robust Study Design

Reference	Variable Definition	Operationalization	Correlation to AD Risk	Covariates	Measure of AD	Study Location	Population	Sample Size
Fox 2013	Age at first birth	<21 vs >21	-	Age, (Age)2, education history, family history of dementia, COC use	CDR-SOB > 0	UK	British women aged 70 - 100 years	89 (51 controls, 38 cases)
Kim 2003	Age at first birth	Continuous	0	None	Korean MMSE and Korean DRS. Diagnosis of dementia, AD, and vascular dementia made according to SDM-IV, NINCDS,ADRDA, and NINDS-AIREN criteria respectively (a)	Kwangju, South Korea	Community residents > 65 years of age, urban and rural	746 (110 dementia cases, 636 no dementia)
Paganini-Hill 2020	Age at first birth	<20 vs 21-24, 25-29, 30+, no child	0	age, education	in-person evaluation, neurological exam, or MMSE (a)	Laguna Hills, CA, USA	The 90+ study, originally from the Leisure World Cohort Study, women all currently aged 90+	424 (209 dementia cases, 215 control)
Fox 2018	Age at first birth	Continuous	0	None	CDR-SOB > 0	UK	British women aged 70 - 100 years	95 (39 cases, 56 control)

Combined both dementia and AD cases into one group or only looked at any dementia.

Under the "operationalization" column, if a study included multiple operational variables, the variable(s) that corresponds to a significant result are in bold in order to distinguish it from the non-significant variables. The results highlighted in green meet the criteria for what I identified as having robust study designs. Robust study designs have a sample size of at least 300 participants and, at the minimum, controlled for age, education and/or income, and other health outcomes. If a study controlled for other reproductive life events, they were also identified as ideal study designs regardless of the other control variables as long as they had an adequate study population size.

Table 6: The relationship between age at first birth and lower performance on various cognitive measures.

Legend
Study with Non-Robust Study Design
Study with Robust Study Design

Reference	Variable definition	Operationalization	Correlation to Reduced Cognitive Performance	Covariates	Measure of cognition	Study Location	Population	Sample Size
Heys 2011	age at first pregnancy	Continuous	+/0	age, education, parental possession, occupation, and physical activity	immediate and the delayed 10-word recall score, MMSE	Southern China	Postmenopausal Chinese Women Aged 50+ from Guangzhou Biobank Cohort Study	11,094
Karim 2016	age at first pregnancy	<24 vs >24	-/0	none	global cognition, verbal memory, executive function	Los Angeles, CA, US	Natural Postmenopausal women from Women's Isoflavone Soy Health (WISH) and the Early vs Late Intervention Trial of Estradiol (ELITE)	830
Ryan 2009	age at first birth	<20 vs 21-29, >30	-/0	age, education level, marital status, depressive symptoms, high caffeine intake, physical incapacities and comorbidity	5-word Test of Dubois, with both immediate and delayed recall tasks, Isaacs Set Test, Benton's visual retention test, Trail Making Tests A , Trail Making Tests B, MMSE	Montpellier, France	65+ aged women, ESPRIT study	996
Song 2020	age at first birth	<20 vs 21-25, 26-30, >30; continuous	-	age at MMSE measurement, year of baseline interview, dialect group, marital status, and education level. ,smoking status, tea intake, coffee intake, sleep duration, physical activity, body mass index, total energy intake, alternate Mediterranean dietary pattern score	Singapore Modified MMSE	Singapore	postmenopausal Singapore Chinese Health Study- women aged 45-74	8,222
Harville 2020	age at first pregnancy	<16 vs >16; <18 vs >18	-/0	age at interview, menopausal status, race, smoking (ever), marital status, depressive symptoms, BMI	logical memory 1 , logical memory 2, logical recognitive, digit coding score, trail A time, trail B time, trail B/A ratio, digit span forward , digit span backward, summary score	Bogalusa, LA, USA	mid-life aged women (mean 47.7)Bogalusa Heart Study	730

Shimizu 2019	age at first birth (including stillbirths)	<22 vs 23-25, >26; continuous	0	age at mental health examination, baseline BMI, educational background, smoking, sports or leisure-time physical exercise, and past medical history of any of hypertension, diabetes mellitus, or depression	current cognitive impairment by clinical diagnosis	Nagano Prefecture, Japan	women aged 40-59 in Japan Public Health Center-based Prospective Study	670
Read 2017	age at entry to parenthood	>20 vs <20	-	age, education, occupation status, tenure status, wealth	composite score from world list recall task (immediate recall; delayed recall) verbal fluency test	England	English Longitudinal Study of Ageing, women aged 50+	6,123
Ilango 2019	age at first pregnancy	20-24 vs <20, 25-29, ≥30; continuous	0	education, ever married, retest	MMSE, trail making test part B, Animals Naming Category Fluency Test, Buschke-Fuld Selective Reminding Test	Rancho Bernardo, CA, USA	prospective cohort study that enrolled participants from 1972 to 1974, women (mean 73.1 + 9.6)	1025

Under the "operationalization" column, if a study included multiple operational variables, the variable(s) that corresponds to a significant result are in bold in order to distinguish it from the non-significant variables. Under the "measure of cognition" column, the measure of cognition that corresponds to the significant result are in bold to distinguish it from the non-significant measures of cognition. The results highlighted in green meet the criteria for what I identified as having robust study designs. Robust study designs have a sample size of at least 300 participants and, at the minimum, controlled for age, education and/or income, and other health outcomes. If a study controlled for other reproductive life events, they were also identified as ideal study designs regardless of the

Age at First Birth Results

There was a total of 12 studies, including both robust and non-robust study designs, that explored the relationship between the age of first birth and AD risk or cognitive performance. Overall, a majority of studies show that a later age of first birth correlates to reduced AD risk and better cognitive performance or no association. This does not change when we consider the studies that are categorized as having robust study designs. From the full list of 12 studies, 4 of them measured the association between the age of first birth and AD risk. Out of these 4 studies, 1 found that an older age of first birth was correlated to a decrease in AD risk[91] and 3 found no association[62,63,66]. However, 2 of these studies did not include any covariates when looking at this relationship[62,63] and 2 of them combined both AD cases and other dementia cases in the same group[62,66]. 8 studies measured the relationship between age of first birth and performance on various cognitive measures, and 5 of them found that an older age of first birth was associated with better performance on various cognitive measures[72,77,80,85,86], 1 study found older age at first birth was associated with worse performance on various cognitive measures[70], and 6 studies found no association on performance on various cognitive measures[68,70,77,80,83,85]. None of these studies adjusted for parity in their analysis, which is important to consider as age at first birth may be a proxy to parity, which affects AD risk and cognitive performance.

Table 7: The relationship between breastfeeding and Alzheimer's Disease risk.

Legend	
	Study with Non-Robust Study Design
	Study with Robust Study Design

Reference	Variable Definition	Operationalization	Correlation to AD Risk	Covariates	Measure of AD	Study Location	Population	Sample Size
Fox 2013	BFSUM (Lifetime sum of months spent breastfeeding), BFMEAN (the mean breastfeeding per full-pregnancy), BFSUM/PMONTHS (Number of months spent breastfeeding divided by number of months spent pregnant in lifetime), BFANY (any breastfeeding)	No breastfeeding vs. BFANY; BFSUM/PMONTHS(below cohort median) vs. BFSUM/PMONTHS(above cohort median); continuous	-	age at interview, education, occupation, ERT use, oophorectomy, age at first birth, and age at menopause	AD risk defined as time between age 50 and a transition from CDR-SOB = 0 to 0.5	UK	women over the age of 70	81
Yoo 2020	cumulative breastfeeding duration (months)	Never breastfed vs <6 months , 6-12 months, > 12 months	+/- (i)	duration of fertility, parity, duration of HRT, duration of oral contraceptive use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes mellitus, dyslipidemia and cancer	Clinical diagnosis of AD	South Korea	Post-menopausal women using the Korean National Health Insurance System	4,696,633
Fox 2018	cumulative breastfeeding duration (months)	continuous	0	none	CDR-SOB > 0	UK	British women aged 70 - 100 years	95 (39 cases, 56 control)
Najar 2020	cumulative breastfeeding duration (months)	continuous	0	reproductive period, number of pregnancies, birth year, exogenous estrogen, physical activity, hypertension, ischemic heart disease, and psychological stress	diagnosis of dementia from neuropsychiatric examinations based on DSM-III-R criteria	Gothenburg, Sweden	women who went through natural menopause followed for 44 years beginning from age 38-60 from Gothenburg	1462

							H70 Birth Cohort Study	

(i) - <6 month decreases risk, >12 increases risk
Under the "operationalization" column, if a study included multiple operational variables, the variable(s) that corresponds to a significant result are in bold in order to distinguish it from the non-signficant variables. The results highlighted in green meet the criteria for what I identified as having robust study designs. Robust study designs have a sample size of at least 300 participants and, at the minimum, controlled for age, education and/or income, and other health outcomes. If a study controlled for other reproductive life events, they were also identified as ideal study designs regardless of the other control variables as long as they had an adequate study population size.

Table 8: The relationship between breastfeeding and lower performance on various cognitive measures.

Legend
Study with Non-Robust Study Design
Study with Robust Study Design

Reference	Variable definition	Operationalization	Correlation to Reduced Cognitive Performance	Covariates	Measure of cognition	Study Location	Population	Sample Size
Hesson 2012	cumulative breastfeeding duration (months)	continuous	+	Index of Cumulative Estrogen Exposure, IQ, education	Logical Memory I and II subtests from the Wechsler Memory Scale – Third Edition ; time-based prospective memory task	Newfoundland, Canada	postmenopausal women with mean age 69.3 years	50
Chou 2021	cumulative breastfeeding duration (months)	continuous	0	age, cerebrovascular disease, education level, living alone, BMI, total cholesterol, LDL-cholesterol, age at menarche, reproductive period, birth times	MMSE	Taiwan	women (mean age = 63.7 + 2.9) from Taiwan Biobank	520
Shimizu 2019	ever breastfed	never breastfed vs ever breastfed; continuous	0	age at mental health examination, baseline BMI, educational background, smoking, sports or leisure-time physical exercise (leisure-time physical exercise), and past medical history of any of hypertension, diabetes mellitus, or stroke	current cognitive impairment by clinical diagnosis	Nagano Prefecture, Japan	women aged 40-59 in Japan Public Health Center-based Prospective Study	670
Tierney 2013	cumulative breastfeeding duration (months)	continuous	0	age, years of education,number of children, years since menopuase, and previous OC and HT use	RCFT immediate recall, RCFT delayed recall, CVLT immediate recall, CVLT short delay recall, Digit span backwards	Toronto, Canada	nondemented, natural menonpuase women aged 60-89	126
Fox 2021	ever breastfed, cumulative breastfeeding duration (months)	never breastfed vs breastfed ;0 vs 1-12, >12 months breastfeeding; 1-12 vs > 12; continuous	-	age, education, ethnicity, and depression status	Learning (California Verbal Learning Test-II (CVLT-II) [Trial 1 through 5 Total] or Hopkins Verbal Learning Test (HVLT) [Total Recall], Rey–Osterrieth Complex Figure Test (ROCF) [3-minute recall]); Delayed Recall (CVLT-II [long delayed free recall] or HVLT [Delayed Recall], ROCF [30-minute delayed recall]); Executive Functioning (Trail Making Test B (TMT), Controlled Oral Word Association test (FAS)); and Processing Speed (TMT A, Stroop Color Naming [Kaplan version])	Los Angeles, CA, USA	women aged 50+ "Brain Connectivity and Response to Tai Chi in Geriatric Depression" and "Reducing risk for Alzheimer's Disease in High risk women through Yoga or	115

							Memnory Training" study	
Harville 2020	ever breastfed, cumulative breastfeeding duration (weeks)	never breastfed vs ever breastfed; continuous	-/0	age at interview, menopausal status, race, smoking (ever), marital status, depressive symptoms, BMI	logical memory 1 , logical memory 2, logical recognition, digit coding score, trail A time, trail B time, trail B/A ratio (log), digit span forward (total), digit span backward (total), summary score	Bogalusa LA, USA	mid-life aged women (mean 47.7)Bogalusa Heart Study	730
Heys 2011	average duration of breast feeding per child (years)	continuous	+	age (continuous), education, parental possessions(categorized by possession of sewing machine, watch, and bike. This is a proxy of childhood SEP) , occupation and physical activity	delayed 10-word recall, immediate 10-word recall, MMSE	Southern China	Postmenopausal Chinese Women Aged 50+ from Guangzhou Biobank Cohort Study	11,094

Under the "operationalization" column, if a study included multiple operational variables, the variable(s) that corresponds to a significant result are in bold in order to distinguish it from the non-significant variables. Under the "measure of cognition" column, the measure of cognition that corresponds to the significant result are in bold to distinguish it from the non-significant measures of cognition. The results highlighted in green meet the criteria for what I identified as having robust study designs. Robust study designs have a sample size of at least 300 participants and, at the minimum, controlled for age, education and/or income, and other health outcomes. If a study controlled for other reproductive life events, they were also identified as ideal study designs regardless of the other control variables as long as they had an adequate study population size.

Breastfeeding Results

There was a total of 11 studies, including both robust and non-robust study designs, that compared various measures of breastfeeding duration to AD risk and cognitive measures, and the results were mixed. When considering only the studies with robust study designs, the results still remain mixed. Overall, 4 studies found that overall higher rates of breastfeeding were associated with a lower risk of AD[25,91] and better performance on various cognitive measures[85,92]. All 4 of these studies observed this association when they compared no breastfeeding to breastfeeding. Additionally, *Fox et. al 2013*, *Fox et. al 2021*, and *Harville 2020* took into consideration the possibility that no breastfeeding may be a proxy for nulliparity in their analysis through controlling for nulliparity or only including parous women in their analysis.

From those 11 studies, there were 3 studies that found that more breastfeeding was associated with an increased risk of AD[25] or reduced cognitive performance[70,78] and 6 studies found no association between more breastfeeding and AD risk[63,65] or cognitive performance[82–85]. It is worth noting that a majority of the studies found that more breastfeeding was associated with worse outcomes or no difference operationalized breastfeeding duration as a continuous variable. There were only 2 studies that compared no breastfeeding to some breastfeeding and found no association or that breastfeeding was associated with worse outcomes. *Shimizu et. al 2019* found no association between current cognitive impairment among parous Japanese women who never breastfed to those who did breastfeed.

Yoo et. al 2020 report on breastfeeding is worth noting due to breastfeeding duration being associated with both an increase and decrease in AD risk. Women who had a cumulative duration of breastfeeding of over 12 months were at a higher risk of AD when compared to women who never breastfed. On the other hand, women who breastfed for a cumulative duration

of less than 6 months had a lower risk of AD when compared to women who never breastfed. Those who had a cumulative duration of breastfeeding of 6-12 months had no significant association of AD risk when compared to women who never breastfed. It is worth noting that they included nulliparous women in the breastfeeding analysis and that they found that nulliparity was also associated with an increased risk of AD in this same cohort. This can potentially be an issue as women who never breastfed may be a proxy for nulliparity, which can impact AD risk.

Discussion

After looking through all the relevant articles on this topic, at a first glance, there is no clear picture of the relationships between the pregnancy life history events and AD risk and cognitive function. The results are either mixed or there are not enough studies that explored these topics. However, there are some points that can be made from the summarized information.

Parity Analysis

Beginning with parity, the majority of the studies found that higher parity increased the risk of AD or lowered cognitive performance or had no difference. To my surprise, this is in contrast to both the estrogen and traditional reproductive pattern hypotheses that I proposed. For the estrogen hypothesis, I predicted that higher parity would be associated with a reduced risk of AD because pregnancy is defined by a period of a significantly higher dosage of estrogen exposure. Therefore, I expected that the more pregnancies a woman has, the more protected she should be against AD. However, no studies found that parity was associated with reduced AD risk, and only one study found that parity was associated with increased performance on various cognitive measures[87].

Additionally, there is a trend where parity was associated with an increased risk of AD risk and worse cognitive performance primarily in women who experience grand multiparity, or five or more completed pregnancies.

These two points are in direct conflict with both hypotheses. During pregnancy, estrogen levels gradually rise and peak in the third trimester, where they can be over 300 times higher than what they are at baseline levels[1]. However, the higher estrogen exposure seen with more pregnancies did not seem to confer protection against AD despite the evidence that estrogen is protective. This may be due to the possibility that at some dosage, the neuroprotective effects of estrogen become negligible, i.e., a ceiling effect. Studies that compared the effects of varying dosages of estrogen replacement therapy on AD risk and cognition found that lower doses of estrogen replacement therapy had better outcomes for cognitive performance than higher doses[31,93]. Another study found that there was no difference in cognitive function among various dosages of estrogen use[94]. However, one study found that an increasing dosage of estrogen replacement therapy was able to confer better protection against AD risk versus a lower estrogen dosage[23]. Because of the conflicting results on the effects of estrogen dosage on AD risk and cognitive function, more research needs to be done before determining whether the estrogen high levels observed during pregnancies confer any additional neuroprotective effects than what is observed at baseline.

This finding of grand multiparity primarily being associated with an increased risk of AD and worse cognitive performance is also in direct conflict with the traditional reproductive pattern hypothesis. In order to estimate the reproductive patterns of earlier populations, we can use the reproductive patterns observed in contemporary hunter-gatherer populations. While there are still flaws to this approach due to limited sample sizes, these populations are useful for

gaining insight into reproductive patterns of earlier populations as modern advancements, such as contraceptives, that impact reproductive patterns do not or only slightly influence these populations. The total fertility rate (TFR) in three contemporary hunter-gatherer populations is observed to be between 4.7 to 8.2, while the TFR in the United States in 2019 is much lower at approximately 1.7[95,96]. As grand multiparity was much more common in earlier populations, it is unlikely that the higher parity associated with earlier populations conferred any significant neuroprotective benefits against AD and reduced the selective pressure of AD.

The results found that nulliparity primarily had no effect or increased the risk of AD when compared to parous women. This is in direct contrast to the rest of the parity studies, as an increase in parity generally trends towards increasing the risk of AD, especially in the case of grand multiparity. For the estrogen hypothesis, we would expect nulliparity to be protective against AD risk due to nulliparous women having approximately 22% higher baseline estrogen levels in contrast to women who are parous[97]. An explanation for why we don't see this is that these studies did not account for women who may be infertile or have other health reasons that are associated with them being nulliparous. Infertility may be caused by abnormally low levels of baseline estrogen, which can potentially lead to an increased AD risk. Additionally, nulliparity is associated with a higher risk of endometriosis and an earlier age of menopause, which are both linked to a potential increased risk of AD[98–100]. Because of the lack of studies that accounted for the possible health outcomes associated with a woman's nulliparity status, there may still be a possibility that the higher baseline estrogen levels associated with nulliparous women may be protective against AD.

The finding of nulliparity being associated with an increase in AD risk is consistent with the traditional reproductive pattern hypothesis. Because nulliparity was rare in earlier

populations, women in earlier populations may have had less selective pressure against AD due to nulliparity being rarer. However, it is important to note that no studies compared nulliparity to grand multiparity directly. Both of these reproductive statuses are associated with an increase in AD risk. Grand multiparity was more common among parous women in earlier populations, so it is unlikely that parous women in earlier populations were significantly more protective against AD than nulliparous women. Additionally, it is unclear whether another medical condition mediated the association between nulliparity and an increase in AD risk. Combining these factors together, it is highly unlikely that the finding that protection against AD in parous women when compared to nulliparous women conferred a significant reproductive advantage where they were able to affect the APOE e4 allele frequency.

Age at First Birth Analysis

I predicted that higher parity should ultimately protect against AD due to it being associated with higher estrogen exposure. However, I established that a higher parity may be a proxy for other reproductive life events that are associated with lower estrogen exposure. One of these reproductive life events that higher parity can be a proxy for is an earlier age of first birth. Once a woman gives birth for the first time, her baseline estrogen levels decline for the rest of her reproductive period[97]. Therefore, the estrogen hypothesis predicts that an earlier age of first birth should be associated with an increased risk of AD. There is weak evidence that supports this claim, as most of the studies found that an earlier age of first birth was associated with an increased risk of AD or lower cognitive function or no effect. Therefore, there is evidence that a longer duration of higher baseline estrogen levels may be protective against AD.

It is important to note that, similar to women who have a late age of first birth, nulliparous women are also associated with a higher baseline duration of estrogen exposure.

However, despite these two trends both increasing the duration of baseline estrogen exposure, we did not see a reduction of risk in nulliparous women. As stated earlier, this may to due to their nulliparity status potentially being associated with estrogen deficiency such as earlier age of menopause[100]. In contrast to nulliparity, the age of first birth is not related to the age of menopause[101].

While the results provide some evidence that a higher baseline duration of estrogen exposure may be protective of estrogen, it is important to keep in mind the points of women's reproductive life that are spent experiencing "baseline" estrogen. Populations that do not use contraceptives and have higher fertility, referred to as "natural" fertility populations, will be in a constant state of being pregnant and breastfeeding. Therefore, they will not experience "baseline" estrogen exposure as much, and this type of estrogen exposure may not be relevant in predicting their risk of AD. On the other hand, populations who do have contraceptive use and lower fertility will be more exposed to longer periods of "baseline" estrogen and their AD risk may be influenced by their baseline estrogen levels.

An early age of first birth may also be associated with an increased risk of cardiovascular disease, which is associated with an increased risk of AD[102,103]. *Song et al. 2020* found that when they controlled for cardiovascular disease, an earlier age of first birth was no longer associated with cognitive impairment[72]. In contrast, *Ryan et al. 2009* controlled for cardiovascular diseases and found that an earlier age of first birth was still associated with lower performance on some cognitive tests[80]. More research needs to be done in order to draw a conclusion on whether the age of first birth is an important predictor of cardiovascular risk.

As it is unclear whether cardiovascular disease can mediate the interaction between age of first birth and AD risk, it is still worth noting that a majority of them found that earlier age of

first birth was associated with an increased risk of AD/lower cognitive performance or no effect. Furthermore, none of these studies controlled for parity, which is important to consider as an early age of first birth may be associated with higher parity. Higher parity is associated with periods of high estrogen dosages, which I predicted to be protective. Therefore, this reinforces the idea that the estrogen dosage at high levels during pregnancy is not relevant to protecting against AD and that the slight decline of baseline estrogen levels associated with the first birth may be a better predictor of AD risk in lower fertility populations. On the other hand, because none of the parity studies controlled for age of first birth, higher parity may be a proxy for earlier age of first birth, which may help explain why grand multiparity is associated with an increase in AD risk and lower cognitive performance.

As opposed to the estrogen hypothesis, this finding goes against the traditional reproductive pattern hypothesis, as earlier populations often observed an earlier age of first birth. Especially in earlier populations, which have a higher total fertility rate, the relationship between an early age of first birth and increased AD risk may be due to an early age of first birth being a proxy for higher parity. Therefore, it is unlikely that the earlier population's reproductive pattern of an early age of first birth conferred any significant protection against AD and impact the APOE e4 allele frequency.

Breastfeeding Analysis

Similar to age of first birth, breastfeeding duration is also a proxy for parity. Generally, higher parity is associated with a longer cumulative breastfeeding duration due to more children a woman can potentially breastfeed. However, while estrogen peaks are much higher during pregnancy, the time spent breastfeeding after a pregnancy is a period when estrogen levels are lower than baseline. When looking at lifetime estrogen exposure, these two events are in direct

conflict with one another. The estrogen hypothesis predicted that longer cumulative breastfeeding duration will be related to an increased AD risk, due to the estrogen decline associated with this event. However, when looking at the results, this was not the case as the results were mixed, with most studies finding that breastfeeding and AD risk were unrelated.

A potential explanation for this is how the breastfeeding variable is being measured. It is difficult to measure breastfeeding duration accurately. Breastfeeding durations in all of these studies were categorized in total weeks, months, or years spent breastfeeding. They do not account for the possibility that breastfeeding duration can highly vary depending on whether breastfeeding is exclusive or given alongside infant formula. Breastfeeding only continues to suppress sex steroid levels beyond the first few weeks postpartum if it is intensive, and infrequent breastfeeding allows for sex steroids to be expressed again and menstrual cycling to resume. For example, a woman who breastfeeds for two months may only breastfeed one time per day if she is supplementing with formula while a woman who exclusively breastfeeds for one month may breastfeed 10 times per day. The woman who breastfeeds 10 times a day for one month will have a longer period of estrogen deprivation despite being defined as having a lower overall breastfeeding duration.

While still flawed, a more accurate measure of breastfeeding duration is comparing women who never breastfed to women who have. When we consider studies with both robust and non-robust study designs that measured breastfeeding this way, there is a weak association between breastfeeding and reducing the risk of AD. However, when we consider only studies with robust designs, that association becomes less clear. Because estrogen suppression is still observed in post-partum women for a few weeks regardless of whether or not they breastfed, and breastfeeding extends duration, it is unclear whether the time spent breastfeeding in women who

do breastfeed has such a significant enough difference in duration of estrogen exposure where it can affect AD risk.

Yoo et al. *2020* found that women who had a cumulative breastfeeding duration of over 12 months were at a greater risk of AD when compared to women who did not breastfeed in a very large population cohort of 4.6 million individuals. However, this association was not found in women who breastfed for 6-12 months when compared to women who did not breastfeed. Additionally, they found that women who breastfed for less than 6 months had a decreased risk of AD when compared to women who did not breastfeed. This supports the estrogen hypothesis as a longer state of estrogen deprivation may be associated with an increase in AD risk. An explanation to why we see this trend could be because the estrogen deprivation in women who breastfed for less than 12 months may not be significant enough to be associated with an increase in AD risk. It is possible that women who breastfed for less than 6 months experienced a small period of estrogen deprivation and, in turn, were at a lesser risk of AD than women who breastfed for longer. Additionally, this study did not account for the possibility that women who never breastfed may be nulliparous, which I found earlier to potentially be associated with an increase in AD risk. Therefore, when compared to women who did not breastfeed, it is possible they were at a lesser risk of AD because of their parous status and having a negligible period of estrogen deprivation.

On the other hand, *Fox et al. 2021* found that women who breastfeed for a cumulative duration of over 12 months had better cognitive function than women who never breastfed, which is in direct contrast to *Yoo et al. 2020*'s finding. However, this cohort is a very small sample size and should not be weighted to the same degree as *Yoo et al. 2020*'s finding.

Therefore, there is potentially a weak association between breastfeeding duration and an increase in AD risk, especially in women who have a cumulative breastfeeding duration of over 12 months, as this may be associated with an extended period of post-partum estrogen deprivation. This is consistent with the estrogen hypothesis. However, due to the lack of studies and ambiguous measuring of the breastfeeding duration variable, there is a lot more research that needs to be done before drawing any conclusion on how breastfeeding may be involved in AD risk.

The traditional reproductive pattern hypothesis supports the idea that longer duration of breastfeeding will be protective against AD. Even though breastfeeding patterns varied throughout history, and factors, such as higher infant and maternal mortality rates, may have shifted those patterns, traditional populations generally had higher duration of cumulative breastfeeding as well as higher parity. A meta-analysis found that in a non-industrialized population, women on average breastfeed for 29 months per child, which is much higher than in the U.S. in the 21st century where only 35.3% of women breastfeed their children for more than one year[53,104]. While more evidence needs to be presented, it is unlikely that the increased breastfeeding duration reduced the selective pressure traditional populations may have faced due to AD. This is due to longer breastfeeding durations also being associated with higher parity and that an extended period of reduced estrogen levels defined by longer breastfeeding duration may be associated with an increase in AD risk.

Evidence Supporting the Hypotheses?

Based on the results I collected, there is weak evidence supporting that lifetime estrogen exposure is neuroprotective against AD and that the traditional reproductive patterns did not confer protection against AD.

Estrogen Hypothesis Reflection

For the estrogen hypothesis, only certain estrogen exposures may be relevant to protecting against AD risk. High levels of estrogen over short periods of time are not important to protecting against AD risk, while changes in baseline estrogen levels throughout one lifetime may serve as a potential predictor of AD. As stated earlier, this may be because, at a certain estrogen level, the neuroprotective effects of estrogen become diminished.

However, this does not explain why grand multiparous women are associated with an increased risk of AD. There are multiple explanations as to why this may be the case. The first explanation is that higher parity is a proxy for other reproductive events that are associated with a reduction in baseline estrogen level, such as earlier age of first birth and longer cumulative breastfeeding duration, which may be better predictors of AD risk. An alternative explanation could be that the factor mediating the relationship between parity and AD risk is not estrogen exposure. A major marker of AD pathology is reduced glucose metabolism in the brain, which is observed during pregnancy due to the increased insulin resistance associated with pregnancy[105]. While often times after pregnancy, the insulin sensitivity returns to normal, it is possible for these pregnancy-induced metabolic changes to linger in women, particularly in women with gestational diabetes mellitus[106]. Additionally, the association with more sedentary habits and a poorer diet during and after pregnancy may also contribute to an increase in AD risk[107]. Because of these factors, higher parity is associated with an increased risk of Type II Diabetes, which is a major risk factor for AD[108,109]. Therefore, it is likely that estrogen exposure is not mediating the relationship observed with parity and AD risk, but rather it is the metabolic changes associated with pregnancy that is. Another explanation is that grand multiparous women are also responsible for taking care of many children, which can place a heavy social and financial

burden on them. Women who live in settings that lack that proper support may experience high amounts of stress, which may also be associated with AD risk[110].

Based on the results, higher lifetime baseline estrogen exposure can be beneficial in protecting against AD, which supports the estrogen hypothesis. However, it is important to be skeptical about whether or not these minor changes in dosage are relevant in the context of other AD risks. From the results, I saw that the major spikes in estrogen dosages observed during pregnancy were not protective of AD, or at least not protective in the context of the other risk factors of AD associated with pregnancy. Therefore, it would be difficult to believe that the subtle change in dosage of baseline estrogen exposure may be relevant for AD risk. However, it is important to mention that modern women spend more time in a state of baseline estrogen exposure than pregnancy-level estrogen exposure. The longer duration of being exposed to baseline estrogen exposure may mean that the effects of baseline estrogen exposure on AD risk may be more relevant than the estrogen exposure during pregnancy. In order to better understand whether extended periods of increased estrogen exposure confer any significant protection against AD, we can compare how different dosages of estrogen replacement therapy affect AD risk. As stated earlier, data on this topic is limited, and it must be studied further before any decision on the relevancy of baseline estrogen exposure and AD risk is made.

Traditional Reproductive Pattern Hypothesis Reflection

The fact that I was unable to find a clear association of AD risk with any of the pregnancy events demonstrates that no single pregnancy event is a strong indicator of AD risk. Therefore, it is unlikely that traditional reproductive patterns are protective against AD. The reproductive events that we did find some association for, such as grand multiparity and early age of first birth being associated with an increased AD risk, went against the hypothesis that

traditional reproductive patterns were protective against AD risk. While pregnancy life events do modify known factors of AD risk, these factors are shaped by a woman's life story beyond pregnancy. Alzheimer's modifying factors, such as estrogen exposure, glucose metabolism, and inflammation, are also shaped by a woman's lifestyle and environment, and the lifestyle and environment of a traditional population could be protective against AD.

Relative to modern women, women in traditional populations had higher overall levels of physical activity and diets that are lower in the glycemic index. However, the rapid industrialization in the 19th and 20th centuries quickly changed the diet to more processed sugar and people became more sedentary. Because of the rapid change in lifestyle and environment, modern women's metabolic regulatory systems are unable to adjust to this rapid shift, which increases their susceptibility to metabolic dysfunction such as Type II Diabetes. The increased risk of Type II Diabetes and other metabolic problems were associated with an increased risk of AD[109]. Additionally, increased physical activity and an overall active lifestyle were associated with a decreased risk of AD through reducing neuroinflammation[111]. Because women in traditional populations had better metabolic functions and higher physical activity, they were less susceptible to AD and, therefore, faced less selective pressure against AD and the fitness-reducing effects of APOE e4.

In addition to higher levels of physical activity reducing neuroinflammation in traditional populations, the rapid shift from a highly pathogenic to a primarily sterile environment brought upon by the rapid industrialization of the world during the 18th and 19th centuries made modern populations more susceptible to immune dysregulation and high rates of neuroinflammation. Because humans lived in an environment in which they had constant exposure to diverse microbiota for the most part of human history, their immune system developed in this setting.

Therefore, the immune system of a human is optimized to function in this environment. When the environment shifted to a sterile environment that is missing these microbes, this altered the immune system's function as it is not used to working in this environment[112]. In turn, autoimmune diseases and allergies become more common due to advancements in hygiene, and because neuroinflammation is implicated in AD risk, AD risk may also have increased due to these advancements[113]. The pathogenic environment traditional populations lived in reduced inflammation-associated AD risk in women, which reduces the selective pressure of AD that previous populations have faced.

Because there is evidence that the environment and lifestyle of women in traditional populations reduce AD risk, it is likely that these are the factors that allowed traditional populations to face less selective pressure from AD and therefore, mitigate the fitness-reducing effects of being an APOE e4 carrier. The pregnancy life events are involved in mediating the biological mechanisms implicated in AD risk, but based on the results from this review, there is no clear association that warrants the idea that these pregnancy life events impacted the selective pressure of AD these populations may have faced. Combined with the potential fitness-enhancing benefits of APOE e4, such as improved fertility and cognition in a pathogenic environment, traditional pregnancy patterns most likely did not have a significant impact on the APOE e4 allele frequency. It is likely that the environment and lifestyle factors of traditional populations that promoted a healthy metabolic and immune system allowed the APOE e4 allele frequency to maintain its frequency and is responsible for the variation we see in today's world.

However, while the environment and lifestyle of previous populations established better metabolic and immune systems that protect against AD, women in traditional populations have a lower overall estrogen exposure. Their baseline estrogen levels are lower due to physical activity

reducing circulating estrogen levels[114] and advancements, such as postmenopausal hormone replacement therapy, that are able to extend a woman's estrogen exposure after she reaches menopause. If estrogen exposure is a primary factor that reduces AD risk, women in previous populations should be at a higher risk of AD than women in modern populations due to having an overall lower average duration and dosage of lifetime estrogen exposure. However, this is clearly not the case. A healthy metabolic and immune system that were associated with the environment and lifestyle habits of traditional populations potentially reduced the selective pressure these populations faced from AD despite having overall lower estrogen exposure. While the data collected shows that changes in lifetime baseline estrogen levels potentially may be protective against AD, the weak association shows us that estrogen exposure alone cannot be viewed as a sole mediator of AD risk.

Limitations

There are several limitations to this review. While I was able to summarize and collect the relevant articles, the use of one database and the fact that this review was conducted by one person may result in some articles being inadvertently missed. For one study, the data were only accessible through a review due to the inability to reach the original author[59]. Therefore, some details may have been left out from this study. The variation in operationalization of both the pregnancy life events and AD risk and cognition may result in difficulties with comparison between the studies. Because a lot of these reported results were not the primary focus of these papers, important information, such as the covariates and pregnancy variable definitions, were often left out.

Conclusion

Overall, pregnancy life events alone are not a reliable predictor of AD risk. The changes in lifetime estrogen exposure associated with pregnancy life events primarily had no effect on AD risk and that traditional pregnancy patterns are not protective against AD. For the estrogen hypothesis, despite the pregnancy events having a clear relationship with how they impact estrogen exposure, there was no strong association between AD risk and any of the pregnancy events. These pregnancy events also alter other mediating factors of AD, such as glucose metabolism and stress, which may overpower estrogen's neuroprotective properties. Therefore, when taking into consideration other modifying factors of AD, lifetime estrogen exposure is not a viable predictor of AD risk.

The strongest evidence of changes in estrogen exposure associated with pregnancy events being a mediating factor of AD risk is its potential association with changes in baseline estrogen levels. However, because of the lack of data on dosage changes in estrogen exposure and AD risk, this topic would need to be addressed before baseline estrogen exposure can be viewed as a relevant mediator of AD risk.

From the estrogen hypothesis, I established that other risk factors, such as stress and glucose metabolism, may be more relevant mediators of AD risk than estrogen. These factors are influenced by life events and environmental factors outside of pregnancy, and because no single pregnancy event was able to clearly predict AD risk, traditional reproductive patterns are not likely to affect the selective pressure of AD. Rather, other lifestyle factors, such as diet and physical activity, are more likely to protect women from selective pressure of AD, which allows the APOE e4 allele frequency to remain high today. While there is no strong trend between any pregnancy life patterns and AD risk, changes in dosages of prolonged estrogen exposure induced

by these pregnancy events can be a potential area worth studying to better understand the specific relationship between estrogen and AD risk in women.

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