The UK Biobank: what can it tell us about female reproductive factors and dementia risk?

Rose Overton

rao9@st-andrews.ac.uk

Supervised by Professor Peter Donnelly

School of Medicine

University of St Andrews

LAIDLAW SCHOLARS

Contents:

1. Introduction

There are currently over 944,000 people in the UK living with dementia (National Health Service [NHS], 2023). "Dementia" itself is not a single condition, but an umbrella term for diseases that reduce a wide range of brain functions, from memory to movement. It affects daily life, not just for the patient (World Health Organisation [WHO], 2023) but also their carers, family and friends, a demographic it is estimated that around a third of the current population of the UK will one day fall into (NHS, 2023). Not only are the effects of dementia detrimental on a personal level, it has a significant impact on the UK economy with an estimated annual cost of £42 billion in 2024 expected to rise to £90 billion by 2040, according to a study commissioned by Alzheimer's Society (Alzheimer's Society, 2024).

Alzheimer's disease is the most common form of dementia, making up around 60-70% of cases and characterised by a build-up of tau and amyloid proteins in the brain disrupting information exchange between neurons (NHS, 2021; WHO, 2023). Second most common is vascular dementia, where reduced blood flow to the brain, often due to mini strokes or vessel blockage, causes cell death. Dementia with Lewy bodies and frontotemporal dementia are less prevalent. Despite a breadth of knowledge on the biological processes of dementia, there is currently no cure and a limited understanding of risk factors, both modifiable and pre-determined, that influence the condition (Department of Health, 2015).

Additionally, and crucially to this research, there is limited understanding of why there is greater incidence of dementia among women[1] than men, to the extent that 65% of Alzheimer's disease patients in the UK are women (Alzheimer's Research UK, 2022). It is true that, on average, women live longer than men and that age is considered the greatest risk factor for dementia, but there has been a limited amount of research into other factors that may contribute to this, from women's life experiences to the reproductive factors that this report discusses (Beam et al., 2018).

The UK Biobank is a UK-based biological database that operates as a large-scale prospective study of over 500,000 volunteers. Recruited between 2006 and 2010, participants aged 40-69 years initially provided a range of biological samples, answered lifestyle questionnaires, permitted access to their medical records and consequently engaged in follow-up activities. According to its Protocol published in 2006, the UK Biobank aims to "help researchers to

1 The UK Biobank questionnaire and health data reflect societal norms of their time of origin. While sex and gender are now generally distinguished in both academia and society, sex (male, female) generally encompassing reproductive anatomy, sex chromosomes, hormones and secondary sex characteristics, and gender (including man, woman, non-binary) a personal identity and social construct, they have previously been used interchangeably (Office for National Statistics [ONS], 2019; Ackley et al., 2023). The UK Biobank reflects this, with no discrimination between sex and gender (Liao et al., 2023), and subsequent studies using this data generally exclude participants whose self-reported sex did not match sex inferred from their genetic data (Ackley et al., 2023), hence excluding transgender and potentially non-binary volunteers. This review, although acknowledging this, uses the terms "female" and "woman" interchangeably as this is how they are discussed by the literature being reviewed.

understand the causes of diseases better, and to find new ways to prevent and treat many different conditions". Researchers can apply for access to this data, and have so far published over 9,000 peer-reviewed papers (UK Biobank, 2024). Due to the age range of its participants, it is commonly used to investigate conditions such as dementia that are associated with later onset. While still a relatively recent tool, its design is being replicated elsewhere with newer innovations and greater detail, most notably with the launch of Our Future Health in 2022, a new UK-based biobank that aims to recruit 5 million volunteers.

In the context of the personal and economic burden of dementia; the range of investigations into possible causes and risk factors; and the emergence of new databases, this research aims to investigate what the UK Biobank has so far told us about female reproductive health and risks of dementia.

2. Scope and Methodology

The research question posed at the beginning of this project was "Does the UK Biobank have something useful to contribute to research into the causes of dementia?".

The UK Biobank website allows direct searches of publications related to its database: a search of keyword "dementia" yields 54 articles, while "Alzheimer" yields 50 results. (UK Biobank, n.d.). This suggests that a substantial amount of research in the field exists, but is limited by a lack of specificity and Boolean operators.

A search was conducted of Ovid Medline and Embase on 12th June 2024 with the following terms:

Ovid MEDLINE(R) ALL <1946 to June 12, 2024>

1	exp Dementia/	215830
2	dementia*.mp.	171194
3	exp Alzheimer Disease/	125956
4	Alzheimer*.mp.	215573
5	1 or 2 or 3 or 4	340915
6	exp UK Biobank/	288
7	uk biobank.mp.	8395
8	6 or 7	8395
9	risk*.mp.	3572992
10	associat*.mp.	6040890
11	9 or 10	8102728
12	5 and 8 and 11	662

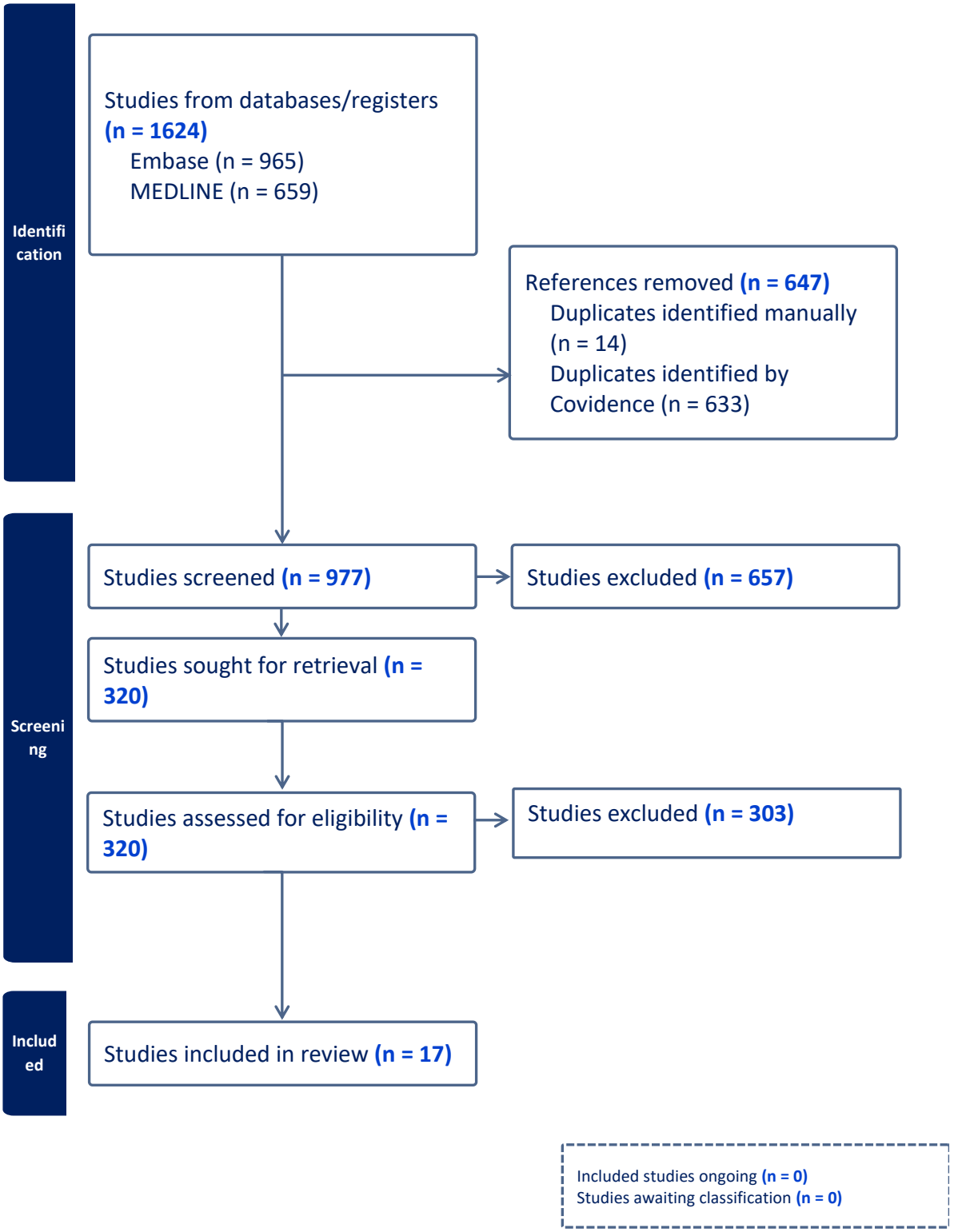
Embase <1974 to 2024 June 12>

1	exp dementia/	467277
2	dementia*.mp.	268064
3	exp Alzheimer Disease/	262237
4	Alzheimer*.mp.	321853
5	1 or 2 or 3 or 4	546423
6	uk biobank.mp.	12617
7	risk*.mp.	5401575
8	associat*.mp.	8564966
9	7 or 8	11611687
10	5 and 6 and 9	976

Results were uploaded to Covidence set to individual reviewer mode. 657 duplicates were automatically removed and the remaining titles were screened for relevance according to predefined inclusion and exclusion criteria.

Criterion	Inclusion	Exclusion
Population	UK Biobank cohort only	Consideration of any other large prospective studies
Time period	Publication 2006-2024	Publication prior to 2006
Language	Text in English	Text in languages other than English
Content	investigating association or causal link between factor and dementia	focus on diagnoses, natural history or risk scores
Publication type	Journal article	Poster, abstract only

Studies identified as relevant for retrieval were grouped by theme to allow a more specific factor to be isolated. Based on the number, quality and diversity of articles available; the unique insight provided by the UK Biobank; and the potential for additional future research, “female reproductive factors” were identified as the specific dementia risk to be investigated by this literature review and 17 articles were extracted.


Identification
Studies from databases/registers
(n = 1624)
Embase (n = 965)
MEDLINE (n = 659)
References removed (n = 647)
Duplicates identified manually
(n = 14)
Duplicates identified by
Covidence (n = 633)
Screening
Studies screened (n = 977)
Studies excluded (n = 657)
Studies sought for retrieval (n =
320)
Studies assessed for eligibility (n =
320)
Studies excluded (n = 303)
Included
Studies included in review (n = 17)
Included studies ongoing (n = 0)
Studies awaiting classification (n = 0)

This review assesses the literature produced using data from the UK Biobank, summarising the findings of the following risk factors and their influence on dementia incidence:

1. Endogenous hormone exposure
2. Exogenous hormone exposure
3. Pregnancy
4. Brain imaging

It discusses the impact of these findings; discrepancies and similarities between methodologies; and the advantages and limitations of the UK Biobank as a resource.

3. Results

a) Endogenous hormone exposure

Menarche refers to the onset of menstrual periods alongside other puberty-related changes that affect females (Law & Martin, 2020). The average age of menarche in the UK has decreased over recent decades and is currently 12.7 years (Morris et al., 2010). Studies using the UK Biobank are in consensus that compared to a reference age of 12 or 13 years depending on the study, an increased age at menarche is associated with an increased risk of dementia in later life (Park et al., 2024; Gong et al., 2022). Gong et al. further identified a U shaped relationship between age at menarche and dementia, with onset before 12 years of age also associated with increased risk.

Menstrual cycles occur on average every 28 days from menarche until menopause is reached, when ovaries cease to produce eggs (Naish & Court, 2019). Liao et al. (2023) outline how this typically occurs naturally during middle age, with menopause occurring before the median age of 50 classed as “earlier menopause”, and menopause before the age of 40 considered “premature menopause”. Results from the UK Biobank agree that a lower age at natural menopause is associated with increased risk of all-cause dementia particularly if premature compared to the average or later age (Liao et al., 2023; Constantino et al., 2023; Hao et al., 2023; Gong et al., 2022). Liao et al. (2023) additionally concluded that the risk for vascular dementia in particular due to earlier menopause was the most significant, while the risk for Alzheimer’s disease was not statistically significant. Additionally, later menopause was strongly associated with reduced dementia risk (Hao et al., 2023; Constantino et al., 2023; Park et al., 2024).

While the above studies focused on age at menarche or menopause, others considered cumulative lifetime exposure to oestrogen as a risk factor, oestrogen being the primary sex hormone in females and its levels helping regulate the menstrual cycle. Oestradiol is the primary oestrogen during reproductive years (Tulchinsky et al., 1972), and is thought to have a neuroprotective role through a variety of mechanisms including myelin protection and synaptic plasticity maintenance (Park et al., 2024). Cumulative oestrogen exposure was taken either as reproductive span – the time from menarche to menopause – or

reproductive span plus length of hormone replacement therapy (Park et al., 2024). These specific results agreed with the hypothesis of the neuroprotective role of oestrogen, with shorter oestrogen exposure associated with an increased risk for all-cause dementia among UK Biobank participants (Park et al, 2024; Gong et al., 2022).

Menopause, however, can also be induced surgically via a bilateral oophorectomy, surgical removal of both ovaries, resulting in a faster decrease in hormone production than natural decline (Constantino et al., 2023). Similar surgeries that can affect female reproduction and hormone production include a unilateral oophorectomy and hysterectomy, the latter involving partial or complete removal of the uterus (Law & Martin, 2020). While several articles using UK Biobank data considered surgical menopause as a risk factor for dementia, there was little overlap in the specific type or combination of surgeries studied. While Hao et al. (2023) suggested "surgical menopause" conferred a 10% greater all-cause dementia risk than natural, Liao et al. (2023) found no such relationship. Bilateral oophorectomy alone was also shown to have no association with dementia (Park et al., 2024; Gong et al., 2022). Elsewhere, age at general surgical menopause or oophorectomy and the associated risk for dementia was found to be U shaped, with both extremes of age associated with increased risk compared to a baseline (Hao et al., 2023; Gong et al., 2022). Hysterectomy was also considered independently: ever hysterectomy alone was identified as a risk factor (Park et al., 2024; Gong et al., 2022), and hysterectomy before 40 years of age had the greatest associated risk compared to later ages (Park et al., 2024). Most specifically, Gong et al. (2022) identified the greatest risk factor in this category to be hysterectomy following an oophorectomy.

b) Exogenous hormone exposure

Exogenous oestrogen, environmental sources of the hormone, is primarily from HRT (hormone replacement therapy) and oral contraceptives. HRT, as it is labelled in the UK Biobank, is also referred to broadly – and interchangeably by some of the discussed literature - as menopausal hormone therapy (MHT) or hormone therapy (HT). There exists a "critical window hypothesis", a theory suggesting that HRT use initiated within 5 years of menopause is neuroprotective, while detrimental thereafter (Maki, 2013). Data from the UK Biobank would suggest otherwise, with no association found between ever HRT use and all-cause dementia (Park et al., 2024; Liao et al., 2023; Hao et al., 2023; Gong et al., 2022), and no association with risk and timing of onset related to menopause (Gong et al., 2022). Regardless of menopause, while there was additionally no identified risk with duration of HRT (Gong et al., 2022; Constantino et al., 2023; Lange et al., 2020), there were conflicting findings with the age of initiation of HRT and dementia risk. Gong et al. (2022) suggested an older age of initiation - therefore prolonged exposure to oestrogen and its suggested neuroprotective effects - was associated with a decreased risk, while Liao et al (2023) found no such relationship and Lange et al. (2020) suggested later onset of HRT use was associated with more apparent brain aging than earlier use.

Use of oral contraceptive pills identified in the UK Biobank, which can contain oestrogen with or without progestin, was associated with a slightly reduced risk of all-cause dementia

compared to never users (Gong et al., 2022), yet greater general brain atrophy in women aged over 65 years (Lange et al., 2020).

c) Pregnancy

Pregnancy is associated with significant changes in oestrogen levels, with oestradiol becoming the primary hormone and levels potentially increasing 300-fold during pregnancy before falling 100-1000 fold postnatally (Schock et al., 2016; Nott et al., 1976). High parity therefore results in more dramatic changes in endogenous oestrogen level, and several studies that evaluated this as a risk factor for dementia were identified with varying conclusions. Two UK Biobank studies identified that a greater number of live births was associated with an increased risk of dementia, Fu et al. (2023) identifying the relationship with vascular dementia as particularly significant, and Park et al. (2024) citing the lower oestrogen after pregnancy as a potential mediator of this. When data from male UK Biobank participants was analysed in conjunction, however, the increased risk of dementia associated with a greater number of children was similar for both men and women, suggesting that physical childbearing might not be the greatest female-specific risk factor responsible for a greater incidence of dementia among women than men (Gong et al., 2022). This same study further found that while a history of stillbirth and miscarriage were not associated with dementia risk, both ever pregnant and abortion were associated with a decreased dementia risk.

UK Biobank data was also used to gain insight into age of first birth and potential dementia risks. An inverse trend was generally identified, with earlier age at first birth associated with an increased risk of all-cause dementia (Gong et al., 2022; Park et al., 2024) and most significantly vascular dementia, with the relationship only greater when there was an increased number of total subsequent live births (Fu et al., 2023).

It is also worth considering health impacts of pregnancy itself, aside from oestrogen fluctuations. Gestational diabetes mellitus is the most common pregnancy complication, affecting around 14% of pregnancies globally (Wang et al., 2021). Data from the UK Biobank shows that a history of gestational diabetes results in an increased risk of all-cause dementia, with a nearly twofold increase in incidence of all-cause dementia among affected women who are physically inactive (Zhang & Gao et al., 2024). The same study further suggested this relationship is mediated by type 2 diabetes and other comorbidities that arise following GDM.

d) Brain imaging

Alongside raw data, the UK Biobank contains information on cognitive testing and medical imaging. Although covering a lesser number of participants, this information can provide additional insights to complement data analysis and has been used by a number of studies to determine the impact of the above reproductive factors not only on dementia cases, but

previously identified symptoms and brain changes. For example, Fu et al. (2023) found that both low and high parity (compared to a reference value of 2 children) were associated with poorer cognitive function. Elsewhere, a longer reproductive span, older age at menopause (both factors associated with longer cumulative oestrogen exposure) and older ages at first and last birth were positively associated with cognitive performance (Lindseth et al., 2023).

MRI can also be used to investigate white and grey matter volume, with reduced volume indicative of cell death and possible irreversible brain damage, as well as ultimately types of dementia such as Alzheimer's disease (Mercadente & Tadi, 2023). Nabulsi et al. (2020) found ever HRT use to be associated with worse white matter aging. Longer HRT duration was found to have a small positive effect on the volume of parahippocampal gyri (Steventon et al., 2023), while earlier menopause was associated with grey matter volume loss in multiple areas including the hippocampus and amygdala (Steventon et al., 2023; Liao et al., 2023).

4. Discussion

While there may be slight discrepancies between the findings of the above literature, it seems conclusive that there are several female reproductive factors that increase the risk of dementia. In particular, and in accordance with other research, factors associated with reduced oestrogen exposure are identified as risk factors, in line with theories about the neuroprotective effects of oestrogen dependent on the time of exposure (Dubal & Wise, 2002). These studies are not in isolation, but the scale of the UK biobank as a population database is yet unmatched. While there is widespread consensus that further research into this topic is needed to determine causal relationships (Hill, 1965), this research may be crucial to the design and implementation of public health strategies with the intention to reduce dementia risk or shape clinical practice (Zhang & Gao et al., 2024; Liao et al., 2023).

In general, where similar literature exists, the articles included in this review agree with results from large cohort studies with participants of similar age (Gong et al., 2022). There is heterogeneity often with small studies with limited populations, and existing research is frequently inconclusive with conflicting definitions, confounders and selection criteria for participants.

Most of the included UK Biobank studies used a proportional hazards model to take into account covariates that may also act as risk factors for dementia, such as BMI, blood pressure, smoking status and physical activity. There was a significant range of factors included and methods of measurement, in particular for socioeconomic status, but the impact of this upon the results is unclear. It is only due to the large database of the UK biobank that such a wealth of information is available for consideration, alongside additional sensitivity and subgroup analyses that other studies may lack. Therefore, while addressed differently by different researchers it is an overall advantage of the resource that allows isolated consideration of factors.

On the other hand, there are considerable limits to the UK Biobank. Despite the available information being wide-ranging, some questions crucial to understanding specific health

issues lack appropriate depth. For example, the initial questionnaire asked participants "Have you had your menopause (periods stopped)?" (University of Oxford, n.d.) whereas natural menopause is clinically defined by the WHO (2022) as 12 consecutive months after last menstruation. This self-reporting may also be vulnerable to recall bias.

HRT in particular lacks detail in the UK Biobank, with no information on the duration or regimen used. This is of importance not only as the combination of hormones taken may affect the brain differently (Steventon et al., 2023), but also because dosages and formulation have changed over time (Hampson, 2020) and a decline in prescriptions has occurred after 2002 (Zbuk & Anand, 2011). Similarly due to the age and timing of their recruitment, many UK Biobank volunteers had their first live births years before gestational diabetes mellitus screening became commonplace, so the true prevalence may be underrepresented in the data (Danilenko-Dixon et al., 1999; Zhang & Gao et al., 2024).

There are many other ways in which the UK Biobank is not representative of the wider UK – or global – population: participants are relatively healthier, better educated and less deprived than general population (Hao et al., 2023), and the vast majority are of white ethnicity, making up 94.6% of the biobank cohort (Fry et al., 2017) and only 81.7% of the England and Wales population in 2021 (ONS, 2022).

As initial data was collected from 2006-2010 with participants aged 40-69 at this time, the use of the UK Biobank as a prospective study of aging is ongoing. This is important to consider when assessing risks for an age-related condition such as dementia, as it takes time for cases to develop. Indeed, Fu et al (2023) found women included in their study had a mean age of 68.3 years at last follow up, while the risk of dementia doubles every five years after the age of 65 (National Institute on Aging, 2019).

This, however, is why this review is significant. The use of this biobank is just beginning, meaning it is crucial to understand its usefulness and limitations alongside the extent of existing research in order to ensure the future of its use is effective and insightful. By understanding risk factors of conditions such as dementia, more progress can be made towards reducing its effects.

5. References

Ackley, S. F., Zimmerman, S. C., Flatt, J. D., Riley, A. R., Sevelius, J., & Duchowny, K. A. (2023). Discordance in chromosomal and self-reported sex in the UK Biobank: Implications for transgender- and intersex-inclusive data collection. *PNAS*, *120*(18). https://doi.org/10.1073/pnas.2218700120

Alzheimer's Research UK. (2022, May 15). *Why women are bearing more of the impact of dementia*. Alzheimer's Research UK. https://www.alzheimersresearchuk.org/news/why-women-are-bearing-more-of-the-impact-of-dementia/#:~:text=It

Alzheimer's Society, & Carnall Farrar. (2024). *The economic impact of dementia Module 1: Annual costs of dementia*. https://www.alzheimers.org.uk/sites/default/files/2024-05/the-annual-costs-of-dementia.pdf

Beam, C. R., Kaneshiro, C., Jang, J. Y., Reynolds, C. A., Pedersen, N. L., & Gatz, M. (2018). Differences Between Women and Men in Incidence Rates of Dementia and Alzheimer's Disease. *Journal of Alzheimer's Disease*, *64*(4), 1077–1083. https://doi.org/10.3233/jad-180141

Costantino, M., Pigeau, G., Parent, O., Ziolkowski, J., Devenyi, G. A., Gervais, N. J., & M. Mallar Chakravarty. (2023). *Menopause, Brain Anatomy, Cognition and Alzheimer's Disease*. https://doi.org/10.7554/elife.91038.1

Danilenko-Dixon, D. R., Van, J. T., Nelson, R. M., & Ogburn, P. (1999). Universal versus selective gestational diabetes screening: Application of 1997 American Diabetes Association recommendations. *American Journal of Obstetrics and Gynecology*, *181*(4), 798–802. https://doi.org/10.1016/s0002-9378(99)70304-2

Department of Health. (2015). *Prime Minister's Challenge on Dementia 2020*. https://assets.publishing.service.gov.uk/media/5a80d3ce40f0b62302695b8c/pm-dementia2020.pdf

Dubal, D., & Wise, P. (2002). Estrogen and neuroprotection: from clinical observations to molecular mechanisms. *CNS Aspects of Reproductive Endocrinology*, *4*(2), 149–161. https://doi.org/10.31887/dcns.2002.4.2/ddubal

Fry, A., Littlejohns, T. J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., & Allen, N. E. (2017). Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *American Journal of Epidemiology*, *186*(9), 1026–1034. https://doi.org/10.1093/aje/kwx246

Fu, C., Hao, W., Ma, Y., Shrestha, N., Virani, S. S., Zhu, D., & Mishra, S. R. (2023). Number of Live Births, Age at the Time of Having a Child, Span of Births and Risk of Dementia: A Population-Based Cohort Study of 253,611 U.K. Women. *Journal of Women's Health*, *32*(6), 680–692. https://doi.org/10.1089/jwh.2022.0396

Gong, J., Harris, K., Peters, S. A. E., & Woodward, M. (2022). Reproductive factors and the risk of incident dementia: A cohort study of UK Biobank participants. *PLOS Medicine*, *19*(4), e1003955. https://doi.org/10.1371/journal.pmed.1003955

Hampson, E. (2020). A brief guide to the menstrual cycle and oral contraceptive use for researchers in behavioral endocrinology. *Hormones and Behavior*, *119*, 104655. https://doi.org/10.1016/j.yhbeh.2019.104655

Hao, W., Fu, C., Dong, C., Zhou, C., Sun, H., Xie, Z., & Zhu, D. (2023). Age at menopause and all-cause and cause-specific dementia: a prospective analysis of the UK Biobank cohort. *Human Reproduction*, *38*(9), 1746–1754. https://doi.org/10.1093/humrep/dead130

Hill, A. B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*, *58*(5), 295–300. https://doi.org/10.1177/003591576505800503

Lange, A. G., Barth, C., Kaufmann, T., Maximov, I. I., Meer, D., Agartz, I., & Westlye, L. T. (2020). Women's brain aging: Effects of sex-hormone exposure, pregnancies, and genetic risk for Alzheimer's disease. *Human Brain Mapping*, *41*(18), 5141–5150. https://doi.org/10.1002/hbm.25180

Law, J., & Martin, E. (Eds.). (2020). *Concise Medical Dictionary.* (10th ed.). Oxford Univ Press.

Liao, H., Cheng, J., Pan, D., Deng, Z., Liu, Y., Jiang, J., Cai, J., He, B., Lei, M., Li, H., Li, Y., Xu, Y., & Tang, Y. (2023). Association of earlier age at menopause with risk of incident dementia, brain structural indices and the potential mediators: a prospective community-based cohort study. *EClinicalMedicine*, *60*, 102033–102033. https://doi.org/10.1016/j.eclinm.2023.102033

Lindseth, L. R. S., de Lange, A.-M. G., van der Meer, D., Agartz, I., Westlye, L. T., Tamnes, C. K., & Barth, C. (2023). Associations between reproductive history, hormone use, APOE ε4 genotype and cognition in middle- to older-aged women from the UK Biobank. *Frontiers in Aging Neuroscience*, *14*, 1014605. https://doi.org/10.3389/fnagi.2022.1014605

Maki, P. M. (2013). Critical window hypothesis of hormone therapy and cognition. *Menopause*, *20*(6), 695–709. https://doi.org/10.1097/gme.0b013e3182960cf8

Mercadante, A., & Tadi, P. (2023). *Neuroanatomy, Gray Matter*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK553239/

Morris, D. H., Jones, M. E., Schoemaker, M. J., Ashworth, A., & Swerdlow, A. J. (2010). Determinants of age at menarche in the UK: analyses from the Breakthrough Generations Study. *British Journal of Cancer*, *103*(11), 1760–1764. https://doi.org/10.1038/sj.bjc.6605978

Nabulsi, L., Lawrence, K. E., Vigneshwaran Santhalingam, Zvart Abaryan, Boyle, C. P., Villalon-Reina, J. E., Nir, T. M., Iyad Ba Gari, Zhu, A. H., Haddad, E., Muir, A. M., Jahanshad, N., & Thompson, P. M. (2020). Exogenous Sex Hormone Effects on Brain Microstructure in Women: A diffusion MRI Study in the UK Biobank. *BioRxiv (Cold Spring Harbor Laboratory)*. https://doi.org/10.1101/2020.09.18.304154

Naish, J., & Syndercombe Court, D. (Eds.). (2019). *Medical sciences* (3rd ed.). Elsevier. (Original work published 2018)

National Institute on Aging. (2019, December 24). *What causes Alzheimer's disease?* National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-causes-alzheimers-disease

NHS England. (2015). *Dementia*. NHS England. https://www.england.nhs.uk/mental-health/dementia/

NHS. (2021, July 5). *Causes - Alzheimer's Disease*. NHS. https://www.nhs.uk/conditions/alzheimers-disease/causes/

NHS. (2023, July 20). *What is dementia*. Nhs.uk. https://www.nhs.uk/conditions/dementia/about-dementia/what-is-dementia/

Nott, P. N., Franklin, M., Armitage, C., & Gelder, M. G. (1976). Hormonal Changes and Mood in the Puerperium. *British Journal of Psychiatry*, *128*(4), 379–383. https://doi.org/10.1192/bjp.128.4.379

ONS. (2019). *People and places: Sex, gender and gender identity – Content style guide – Service manual – Office for National Statistics*. Service Manual. Retrieved July 2, 2024, from https://service-manual.ons.gov.uk/content/language/sex-gender-and-gender-identity

ONS. (2022, November 29). *Ethnic group, England and Wales - Office for National Statistics*. Www.ons.gov.uk. https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/bulletins/ethnicgroupenglandandwales/census2021

Park, H. K., Marston, L., & Mukadam, N. (2024). The Effects of Estrogen on the Risk of Developing Dementia: A Cohort Study Using the UK Biobank Data. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*, *32*(7), 792–805. https://doi.org/10.1016/j.jagp.2024.01.025

Schock, H., Zeleniuch-Jacquotte, A., Lundin, E., Grankvist, K., Lakso, H.-Å., Idahl, A., Lehtinen, M., Surcel, H.-M., & Fortner, R. T. (2016). Hormone concentrations throughout uncomplicated pregnancies: a longitudinal study. *BMC Pregnancy and Childbirth*, *16*(1). https://doi.org/10.1186/s12884-016-0937-5

Steventon, J. J., Lancaster, T. M., Baker, E., Bracher-Smith, M., Escott-Price, V., Ruth, K. S., Davies, W., Caseras, X., & Murphy, K. (2023). Menopause age, reproductive span and hormone therapy duration predict the volume of medial temporal lobe brain structures in postmenopausal women. *Psychoneuroendocrinology*, *158*, 106393–106393. https://doi.org/10.1016/j.psyneuen.2023.106393

Tulchinsky, D., Hobel, C. J., Yeager, E., & Marshall, J. R. (1972). Plasma estrone, estradiol, estriol, progesterone, and 17-hydroxyprogesterone in human pregnancy. I. Normal pregnancy. *American Journal of Obstetrics and Gynecology*, *112*(8), 1095–1100. https://doi.org/10.1016/0002-9378(72)90185-8

UK Biobank. (2024, June 24). *About us*. Www.ukbiobank.ac.uk. https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us

UK Biobank. (n.d.). *Publications*. Www.ukbiobank.ac.uk. https://www.ukbiobank.ac.uk/enable-your-research/publications

University of Oxford. (n.d.). *UK Biobank touch-screen questionnaire: final version 1 UK Biobank touch-screen questionnaire: final version*. Retrieved July 2, 2024, from https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/TouchscreenQuestionsMainFinal.pdf

Wang, H., Li, N., Chivese, T., Werfalli, M., Sun, H., Yuen, L., Hoegfeldt, C. A., Elise Powe, C., Immanuel, J., Karuranga, S., Divakar, H., Levitt, Na., Li, C., Simmons, D., & Yang, X. (2021). IDF Diabetes Atlas: Estimation of Global and Regional Gestational Diabetes Mellitus Prevalence for 2021 by International Association of Diabetes in Pregnancy Study Group's Criteria. *Diabetes Research and Clinical Practice*, *183*(109050), 109050. https://doi.org/10.1016/j.diabres.2021.109050

World Health Organization. (2022, October 17). *Menopause*. WHO. https://www.who.int/news-room/fact-sheets/detail/menopause

World Health Organization. (2023, March 15). *Dementia*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/dementia

Zbuk, K., & Anand, S. S. (2011). Declining incidence of breast cancer after decreased use of hormone-replacement therapy: magnitude and time lags in different countries. *Journal of Epidemiology and Community Health*, *66*(1), 1–7. https://doi.org/10.1136/jech.2008.083774

Zhang, Y., Gao, D., Gao, Y., Li, J., Li, C., Pan, Y., Wang, Y., Zhang, J., Zheng, F., & Xie, W. (2024). Gestational diabetes mellitus is associated with greater incidence of dementia during long-term post-partum follow-up. *Journal of Internal Medicine*, *295*(6), 774–784. https://doi.org/10.1111/joim.13787