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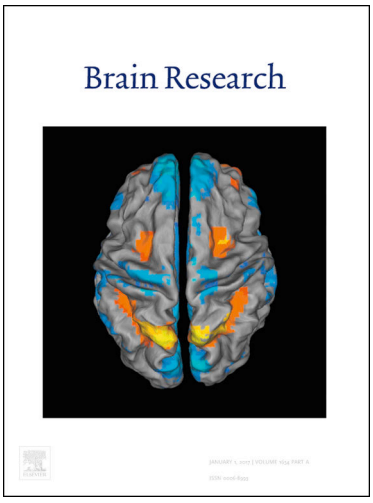

Review

Menopause and Alzheimer's disease susceptibility: Exploring the potential mechanisms

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Menopause and Alzheimer's Disease susceptibility: Exploring the potential mechanisms.

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Abstract

Alzheimer's Disease (AD), responsible for 62% of all dementia cases, is a progressive neurodegenerative condition that leads to cognitive dysfunction. The prevalence of AD is consistently higher in women suggesting they are disproportionately affected by this disease. Despite this, our understanding of this female AD vulnerability remains limited. Menopause has been identified as a potential contributing factor to AD in women, with earlier menopause onset associated with greater AD risk. However, the underlying mechanisms responsible for this increased risk are not fully understood. This review examines the potential role of menopause in the development of Alzheimer's Disease providing a mechanistic overview of the available literature from hormones to pathology. While literature is now emerging that indicates a role of hormonal shifts, gut dysbiosis, lipid dysregulation and inflammation, more research is needed to fully elucidate the mechanisms involved.

Keywords:

Alzheimer's Disease, Ageing, Sex Differences, Menopause, Estrogen, APOE

Introduction

Dementia is an umbrella term used to classify a group of debilitating neurological conditions such as Alzheimer's disease (AD) which influence cognitive function leading to changes in memory and behaviour (1). With age the predominant risk factor for such conditions, the number of dementia cases worldwide is set to increase substantially over the coming decades exceeding 139 million cases per year by 2050 (2). The economic impact of dementia treatment and care is considerable, with current estimates forecasting a $1.6 trillion cost globally by 2050 (3). AD is the most common form of dementia, responsible for approximately 62% of cases. AD is a progressive neurodegenerative condition characterised by distinctive patterns of cognitive dysfunction, memory loss and the neuropathological accumulation of amyloid plaques and neurofibrillary tangles (4).

Dementia prevalence consistently higher in females compared to males (5, 6). This is true for AD, with AD prevalence twice as high in women at the age of 65 (5). This trend is predicted to continue with a female-to-male dementia ratio of 1·67 anticipated for 2050 (6). Although a proportion of this increased prevalence may be attributed to the greater longevity of females, other biological and social factors are likely involved, and are becoming increasingly apparent in the literature (6). The menopause transition has been posited as a contributor to female AD vulnerability, with neuromodulatory hormones (e.g. estrogenic compounds) becoming dysregulated, and therefore resulting in the disruption of various brain systems such as bioenergetics, inflammation, and lipid profile (7-10). The impact of menopause in the development of AD remains largely understudied, likely owing to the fact that neuroscience research is heavily male-skewed (male-to-female ratio of 5.5:1) (11). As a result, the mechanisms connecting menopause and AD are yet to be fully resolved. Newly emerging research is beginning to elucidate the complex molecular mechanisms within the brain in response to menopause. In the present manuscript, we comprehensively review the available literature and summarise the mechanisms by which menopause may influence AD vulnerability.

The Menopausal Transition

Menopause occurs 12 months after a woman's final menstruation. The transition state from premenopausal to menopausal, referred to as perimenopause, is when women may have menopausal symptoms such as hot flushes, irregular monthly cycles, trouble sleeping, depression, irritability and impairment in cognition (12). The menopausal transition typically occurs between the ages of 45 and 55 years and lasts for an average of 7 years, although large inter-individual difference exists (ranging from 4 years to 14 years) (13), likely relating to various lifestyle/circumstantial factors (smoking, perimenopause onset, ethnicity, and race). The menopause transition occurs when a woman loses primary ovarian follicles and oocytes as a result of natural reproductive ageing (13-15). Using a model to predict the ovarian reserves throughout life, Wallace and Kelsey (16) estimate that at age of menarche (average 12.5 years of age) women have 60% of their ovarian reserves remaining, with 100% reserves at pre-birth. At age of perimenopause (40 years) it is predicted that women have only 3% of their ovarian reserves remaining (16). According to the Stages of Reproductive Aging Workshop, the menopause transition consists of five defined stages: −3) Late reproductive stage, -2) early menopausal transition, -1) late menopausal transition, final menstrual period

0), and +1) early post- (17). Throughout these stages, hormone production, particularly estrogen and progesterone, fluctuate. There is a net decline in the plasma concentrations of estrogens and progesterone and a net increase in the concentrations of the gonadotrophins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Perimenopause, has been described as a 'hormonal shock', in which estrogen levels widely fluctuate, producing periods of irregular hormone-receptor interactions (18). The length of this phase has been reported to coincide with aberrant metabolism and immune activation/signalling within the brain (19). These fluctuations in hormonal levels have been shown to exasperate depressive symptoms in premenopausal women (20, 21) as well as impact memory and recall (22).

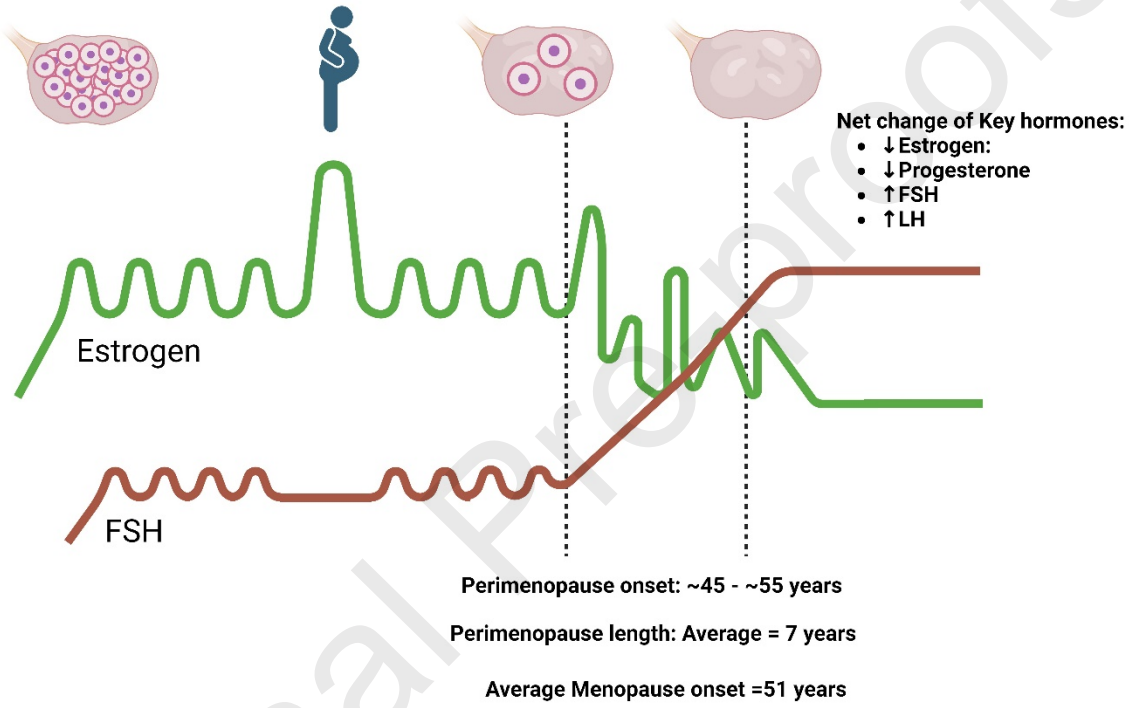


Figure 1: Representation of female hormonal transition across lifespan – During puberty estrogen levels increase, this is followed by the start of the menstrual cycle in which levels of estrogen and FSH fluctuate in a relatively constant manner. This cyclicity continues unless pregnancy occurs and returns shortly after childbirth. Between the ages of 45 and 55 years ovarian reserves become increasingly deplete. This results in a loss of cyclicity and aberrant changes in estrogen and FSH levels. The perimenopause lasts for an average of 7 years with average onset of menopause occurring at 51 years of age. The net change in hormones at menopause is reduced estrogen, progesterone and increased FSH and LH.

Hormonal components of the menopause

In this section we discuss the hormonal components of the menopause transition and provide a brief overview of their potential relationship with AD and cognitive decline. Because these hormones become altered at similar time points in the menopausal transition, and the implication do not necessarily arise until decades later it can be difficult to disentangle the influence of each hormonal component. Preclinical models represent an initial option to tease out this information, providing a mechanistic basis for each. As such we provide a summary of such studies in table 1.

Estrogenic compounds

Estrogen is a gonadal hormone important for female sexual development and regulation of the menstrual cycle. Estrogen is primarily produced in the ovaries, corpus luteum, and placenta, however, other tissues including the liver, brain, and adipose tissue also produce estrogen but to a lesser extent (23). The four main types of estrogen: Estrone (E1), Estradiol (E2), Estriol (E3), and Estetrol (E4) all derive from cholesterol precursors. The synthesis and signalling pathways relating to these forms of estrogen have been extensively reviewed by Baker et al Baker (24). Estradiol is the most potent estrogen during the premenopausal period, whilst estrone plays a larger role after menopause (23). Estrogen has three receptors that mediate estrogen activity, G-protein–coupled estrogen receptor (GPER1) which is a transmembrane receptor, and estrogen receptors -α (ER1) and -β (ER2), which are steroid receptors (25). ER1 levels in hypothalamic neurons are regulated by estradiol. This indicates that estrogen can regulate its membrane signalling. Changes in estrogen receptor (ER) levels can be observed in patients with dementia (26).

Estrogen influences numerous processes such as lipid regulation, carbohydrate metabolism, skeletal homeostasis, as well as the cardiovascular system. Interestingly, females with AD have been found to have significantly reduced levels of 17β-estradiol levels in the brain but not in the serum, indicating that female AD patients may have a brain-specific estrogens deficit (27), which may relate to the impairment of local estrogen synthesis in the brain (27). The depletion of estrogen has been shown to increase Aβ depositions, neuroinflammation, and tau pathology. It is also shown to increase obesity and to reduce the effectiveness of mitochondria as estrogenic compounds protect the mitochondrial toxicity of amyloid-β (28). Estrogen suppresses inflammatory reactions by blocking the adhesion of leukocytes in the brain. Furthermore, estrogen upregulates the enzymes α and γ secretase while down regulating β-secretase. The initial cleavage of the β site on the amyloid precursor protein (APP) by the β-secretase accelerates the formation of Aβ plaques in the brain, however, subsequent cleavage of APP by both α and γ secretases assist with the clearance of the plaques therefore, protecting neuronal cells from being damaged by the toxicity of Aβ (29-31).

Progesterone

Progesterone is a hormone derived from cholesterol that increases before ovulation and peaks during pregnancy as it functions to promote uterine growth (32). Progesterone is produced in the gonads or the adrenal cortex and is vital for the maintenance of the uterus during pregnancy (33). Progesterone impacts inflammatory mediators, for instance T-cells within the uterine cavity (33). Whilst research exploring progesterone in the context of memory and cognitive function is sparse and contradictory, some studies suggest a potential beneficial relationship (34, 35), while others suggest progesterone disrupts cognitive ability (32, 36).

Follicle-stimulating hormone

Produced in the pituitary gland, follicle-stimulating hormone (FSH) is a glycoprotein polypeptide important for menstrual cycle regulation which alongside the luteinizing hormone (see next paragraph) ensures that the mature ovarian follicles will proceed to

ovulation (37). The menopause transition arises when the ovarian follicle reserve starts to deplete. FSH stimulates follicles to enlarge and produce estrogen, but diminishing follicle counts reduce follicle stimulation and in turn estrogen production. This loss of estrogen feedback leads to unrestricted FSH production. Rodent studies are beginning to provide some evidence for FSH in the development of AD and cognitive decline. Increasing levels of FSH in OVX mice increases the expression in the C/EBPβ–AEP/δ-secretase pathway, leading to increased Aβ deposition, tau pathology and impaired cognition, which can be nullified via FSH blockade (38). Similarly, reduction of Follicle-stimulating hormone receptor expression subsequently improves cognition in AD mice (39). Intriguingly, the impact of FSH on cognition appears to be somewhat increased by the AD risk gene *APOE4* (40).

Luteinizing hormone

Luteinizing hormone (LH) is a glycoprotein hormone that is co-secreted along with FSH by the gonadotrophin cells in the anterior pituitary. LH release is stimulated by gonadotropin-releasing hormone (GnRH) and inhibited by estrogen (41). As with FSH, levels of LH increase throughout the menopausal transition (42). Emerging evidence now suggests that LH also plays an important role in CNS function (43) with higher levels of LH being linked with neuroplasticity impairment, cognitive dysfunction, and increased risk of AD (43, 44). Similarly in ovariectomised mice, decreasing LH levels via pharmacological intervention reduced cognitive impairment (45, 46), whilst injection of LH exacerbated behavioural impairment, neuronal damage and Aβ deposition in AD mice (47). The mechanistic basis for LH's role in cognitive decline and neurodegenerative disease remains nonetheless in its infancy.

Table 1. Hormonal influence on rodent models of menopause

Hormone	Influence/relationship with AD	Reference
Estrone (E1)	1. ↑Estrone ↓Hippocampal neurogenesis in OVX rat, No change in Morris water maze performance 2. ↑Estrone ↓Spatial working memory in OVX rats	1. McClure, Barha and Galea (48) 2. Engler-Chiurazzi, Talboom (49)
Estradiol (E2)	1. ↓ Estradiol ↓ learning and recollection memory ↑ depressive and anxious behaviour in OVX mice 2. ↓estradiol ↓Mitochondrial function in OVX rats 3. ↓ Estradiol ↑inflammation, apoptosis, gliosis, ↓ neurogenesis in OVX mice 4. ↑Estradiol has no impact on AD pathology in APP/PS1 OVX mice 5. ↑ Estradiol ↑ spatial memory and BDNF in OVX rats	1. Kang, Lee (50) 2. Wang, Wang (51) 3. De La Torre, Cerbón (52) 4. (46) 5. Bohm-Levine, Goldberg (53) 6. Wada, Sameshima (54) 7. Uzum, Bahcekapili (55) 8. McClure, Barha and Galea (48) 9. Kang, Ahn (56) 10. Feng and Zhang (57)

	6. ↑Estradiol improves anxiety like behaviour in mouse model of postmenopausal obesity 7. ↑Estradiol ↑Working and Reference Memory in Ovariectomized Rats 8. ↑Estradiol ↑Hippocampal neurogenesis in OVX rats 9. ↑Estradiol ↑occluding mRNA levels in OVX mice 10. ↑Estradiol ↓oxidative stress in OVX rats	
Estriol (E3)	No evidence available	
Estetrol (E4)	No evidence available	
Progesterone	1. ↑Progesterone ↑Performance on object placement task in OVX control rats 2. ↓ progesterone ↑ spatial learning in OVX rats 3. ↑ progesterone ↓ Cognitive abilities 4. ↑Progesterone ↑Learning and memory abilities	1. Frye, Duffy and Walf (58) 2. Bimonte-Nelson, Singleton (59) 3. Bimonte-Nelson, Singleton (36) 4. Chesler and Juraska (60)
FSH	1. ↓FSH signalling ↑ spatial and recognition memory deficits in AD mice 2. ↑ FSH ↑ AD pathology in *APOE4* mice 3. ↓FSH through FSH blocking ↑ cognition in AD mice.	1. Frolinger, Korkmaz (39) 2. Xiong, Kang (40) 3. Xiong, Kang (61)
LH	1. ↓LH in OVX AD mice ↓cognitive impairment 2. ↑LH ↑ Cognitive impairment ↑ Aβ depositions in AD mice	1. Zhang, Chen (46) 2. Jia, Du (47)

	3. ↓LH ↑ spatial memory and BDNF in OVX rats 4. ↑LH in OVX mice and rats ↓cognitive impairment ↓ spatial memory dysfunction 5. ↑LH in OVX mice ↓ neuronal spine density ↓ cognitive ability	3. Bohm-Levine, Goldberg (53) 4. Burnham, Sundby (62) Casadesus, Milliken (45) 5. Blair, Palm (63)

Menopause and AD risk

Hormone dysregulation associated with the menopausal transition may contribute to female AD vulnerability. It is increasingly clear that changes in the hormone profile directly influence brain function and can be used as a predictor of cognitive decline (estrogen: FSH ratio predicts Mild Cognitive Impairment (MCI)) (64). The evidence relating to early menopause and increased cognitive decline/AD risk is particularly strong. It has been observed that females who develop menopause at an earlier age have an increased risk of developing AD and display greater cognitive decline later in life (Verbal fluency odds ratio: 1.51, visual memory odds ratio: 1.43, psychomotor speed hazard ratio: 1.36, global decline hazard ratio: 1.35) (65). This is in line with Xi, Gan (66), who reported that longer reproductive periods and later menopause onset reduces AD risk (OR = 0.960 = 0.949 respectively). Furthermore, two recent studies utilising the UK biobank data set similarly support this interaction (67, 68), reiterating that earlier menopause onset (40-49 HR = 1.21, <40 HR = 1.71 compared to ≥50 years) or reduced estrogen exposure (34-37 years = 28% decrease in dementia compared to <33 years) (67) increases dementia risk.

A similar trend is observed when investigating the impact of surgical menopause in relation to Alzheimer's, Dementia and cognitive decline. Indeed, bilateral ovariectomy prior to natural menopause massively increases MCI risk (adjusted OR = 2.21 P < .001) (69). Intriguingly Bove et al. report that earlier age at surgical menopause results in a steeper decline in cognitive function, specifically episodic memory and semantic memory, which is accompanied by increased AD neuropathology (70).

Menopause and genetic risk factors for AD (*APOE4**menopause interaction)

Genetic factors associated with AD may have altered penetrance in females that may be explained in part by menopausal interactions. Although this is yet to be explored across the majority of genetic AD risk factors, it appears to be true for *APOE*4 carriers. Apolipoprotein E4 (*APOE4)* is one of three common isoforms (*APOE2*, *APOE3* and *APOE4*) that encode a 299 amino acid protein APOE. *APOE4* is the most common genetic risk factor for the development of sporadic late-onset AD and appears to be modulated by sex (71). Indeed, Altmann et al. reported that female *APOE4* carriers were more likely to convert from healthy individuals to MCI/AD (female hazard ratio = 1.81, male hazard ratio: 1.27) and from MCI to AD (female hazard ratio: 2.17 and male hazard ratio: 1.51) (72). A similar effect was later reported in a large meta-analysis study (73), in which this increased AD risk emerged between the ages of

65 and 75 years (Female OR: 4.37 and Male OR: 3.14), which given the known latency in AD development (~10 years +), may pertain to a menopausal involvement. A recent study consisting of 105,796 multi-ethnic participants found that females with one copy of the *APOE4* allele had increased AD risk (Female HR: 2.22, Male HR:1.70). Interestingly, this risk was reversed in individuals with two copies of the *APOE4* allele (HR Female: 3.43 HR Male: 5.20), adding further complexity to this *APOE4**sex interaction. When investigating the *APOE**sex interaction Balu, Valencia-Olvera (74) found that in aged mice (18 months old) female *APOE4* carriers had the highest levels of Aβ deposition when compared to female *APOE3* carriers and male *APOE3* and *APOE4* carriers, with female *APOE3* carriers having similar levels of Aβ deposits as male *APOE4* carriers. This trend is also seen in the reactive microglia, with female *APOE4* carriers having the greatest levels of neuroinflammation than female *APOE3* carriers and male *APOE3* and *APOE4* carriers, with female APOE3 carriers having similar levels of neuroinflammation as male *APOE4* carriers (74). Evidence suggests that this increased risk in female *APOE4* carriers may relate to the changes that occur in and throughout the menopause transition (19, 73, 75). Indeed, we (75), and others have reported on an *APOE4*-menopausal interaction (19, 73), which is consistent with greater cognitive decline, decreased synaptic plasticity and brain lipid dysregulation. Given this potential *APOE4*-menopause interaction one would speculate there may be a subsequent *APOE4*-hormone replacement therapy (HRT) interaction, however the current evidence remains mixed. Some studies suggest the possibility of this *APOE4*-HRT interaction (67, 76, 77) whilst others failed to find such an interaction (78, 79). Despite this, our understanding of how this relationship directly relates to AD progression remains limited and should be a focus for future research. Additionally, the existence of this *APOE4**sex/menopause interaction should encourage further investigation into other AD susceptibility genes to evaluate their impact across both sexes.

Brain dysregulation during the menopause transition

Brain Bioenergetics and Metabolism during Menopause

Neuroimaging has revealed that the menopause transition has a profound impact on brain structure, with areas responsible for higher-order cognitive processes most affected (80). Multi-modal brain imaging has revealed dysregulation of brain bioenergetics during the menopausal transition, resulting in subsequent increases in Aβ deposition and grey matter loss, particularly in the posterior cingulate cortex (81). In line with these observations, mitochondrial function is reportedly dysregulated during the menopause transition, due to Aβ toxicity, which is no longer prevented/protected due to the loss of estrogenic compounds (28). Together this emphasises the importance of the mitochondria in female AD vulnerability. Given that the mitochondrial dysfunction associated with menopause may relate to Aβ toxicity, it is interesting to note that estrogens can influence APP processing (82). One way in which this can occur is via the regulation of brain-derived neurotrophic factor (BDNF) which possesses an estrogen response element. BDNF is a neuroprotective agent and promotes/supports neuronal growth and synaptic plasticity but additionally can modulate APP processing via the modulation of alpha-secretase activity. Furthermore, it has been reported that estrogen upregulates mitochondrial genes, with menopausal women presenting with AD showing excessive mutations on the mitochondrial gene malonyl-CoA-Acyl carrier protein transacylase (*MCAT*) which links with the bioenergetic state transition

hypothesis and the subsequent metabolism deficits in the brains of post-menopausal women (9, 83). Unsurprisingly, it has also been well reported that estrogen regulates glucose homeostasis within the brain (reviewed extensively by Rettberg, Yao and Brinton (84), influencing glucose transport (via glucose transporters) and metabolism (via mitochondrial modulation).

Neuroinflammation

Neuroinflammation likely has a causal role in AD pathogenesis, with key immune receptors (e.g., TREM2) closely associated with the disease onset and progression. The inflammatory response within the brain is conducted by the microglia (the resident phagocytes of the CNS) and astroglia and is mediated through cytokines, chemokines, caspases, reactive oxygen species, and secondary messengers (85). In addition, peripheral immune activation can have consequences on the brain. Whilst some degree of neuroinflammation can be beneficial, for instance, in processes related to learning and memory development, uncontrolled neuroinflammation (as seen in AD development) has deleterious implications (86). Estrogen is believed to possess anti-inflammatory properties (87). Ovariectomised rats display higher levels of interleukin-1-beta (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), which leads to decreased long-term potentiation in the hippocampus (88, 89). This is also observed in humans with postmenopausal women showing increased pro-inflammatory markers attributed to estrogen deprivation (90). Indeed, Interleukin-8 (IL-8), TNF-α, IL-6, and interferon-gamma (IFN-γ), are all found to be expressed at higher levels in blood plasma and serum of post-menopausal women (91-93).

The bioenergetic dysregulation discussed above and the inflammatory profile associated with menopause may be linked. In addition to reduced mitochondrial function, a key characteristic of AD is the decreased uptake of glucose in the brain. Positron Emission Tomography (PET) studies have indicated that regional patterns of brain glucose deficits can be observed in the entorhinal cortex and parietal lobes, which can be identified even before a diagnosis of AD (94). Declining glucose metabolism in the brain causes a shift to ketone body utilization for ATP generation which is associated with increased microglial and astrocytic reactivity (95). Ketones are the main alternative fuel when glucose is not available, particularly in adults observing restricted diets such as calorific or carbohydrate restrictions, and ketogenic diets (96). During AD progression, the reduction in white matter in the brain reflects the decreased synthesis of the protective myelin, with myelin being broken down to provide glucose for brain functioning, which is seen more in women than in men (97). Menopause is associated with deteriorating brain glucose metabolism and inefficient mitochondria, as shown in rats; those that underwent OVX surgery displayed an increase in ketones in blood plasma, and a decrease in white matter and myelin volumes which indicate the switch to utilising brain lipids for ATP generation (98, 99).

Blood-Brain Barrier integrity

The blood-brain barrier (BBB) is formed from endothelial cells, astrocyte end-feet and pericytes and is critical for brain homeostasis restricting and regulating the movement of matter between the blood and the brain. Intriguingly, estrogen has been posited as a regulator of BBB integrity, leading to subsequent implications for menopause. Loss/reduction in estrogen or ovariectomy typically increases BBB impairment, evidenced by increased

permeability and accumulation of BBB breakdown products (100-102). While an increase in estrogen is preventative (101-103). The ability of estrogen to modulate BBB integrity is believed to be mediated through the estrogen receptors, with ERα- and ERβ-specific agonists similarly reducing TJ disruption (104). There is some evidence to suggest that estrogen can influence cell-cell adhesion through the modulation of TJ proteins (56, 105-107), offering one route as to which estrogen mediates these effects. Alternatively, the anti-inflammatory properties of estrogen may also contribute. Indeed, estrogen has been shown to prevent inflammation-induced tight junction breakdown through the enhancement of well-known anti-inflammatory protein annexin A1 (103). However, the interaction may be more complex than initially conceived with evidence suggesting the effects to be age-dependant (i.e. Protective for BBB in young, and deleterious for BBB in old) with age-dependant loss of ERα offered as a mechanistic rationale for this (105, 108-110). In addition to this, the effects on BBB exerted by estrogen may be brain region-specific (109). Furthermore, others have highlighted the potential involvement of other hormones (e.g. gonadotropins) (100), as well as ERα and Erβ independent effects adding further complexity to this interaction. As such, further exploration is warranted to address these added complexities.

Dysregulation of lipid metabolism

Weight gain, increased visceral fat, and adipose remodelling are reported during menopause (111) and may relate to estrogen receptor expression (112). This may be indicative of menopause-induced lipid dysregulation. Ovariectomy in rats causes a shift in the lipid profile to an atherogenic state with increases total cholesterol and decreases triglycerides, and is associated with increased oxidative stress, cell death and neurodegeneration of the hippocampus (113). Furthermore, changes in HDL quantity and quality are observed during menopause with HDL cholesterol decreasing dramatically (114). This may relate to apolipoprotein A-I (ApoA-I)-mediated HDL particle-formation impairment and may be ameliorated by omega-3 consumption (114). This is supported by a recent randomised control trial which reported favourable effects on the lipid profile in postmenopausal women (115). There is evidence to suggest that such dysregulation also occurs within the brain, although this has been predominantly studied in preclinical models. For example, lipid peroxidation products are increased within the cortex of OVX rats (116) whilst systemic total antioxidant potential is decreased (117). Additionally, estradiol appears to modulate cholesterol and DHA within the brain (8, 118). Indeed, administration of the menopause mimic VCD in *APOE*-TR mice resulted in lower levels of DHA in the brains of all animals regardless of genotype with expression of the DHA transporter *Acsl6* significantly reduced (75). Together these studies suggest that the menopause transition alters lipid transport and metabolism within the brain with cholesterol and DHA appearing to be particularly affected.

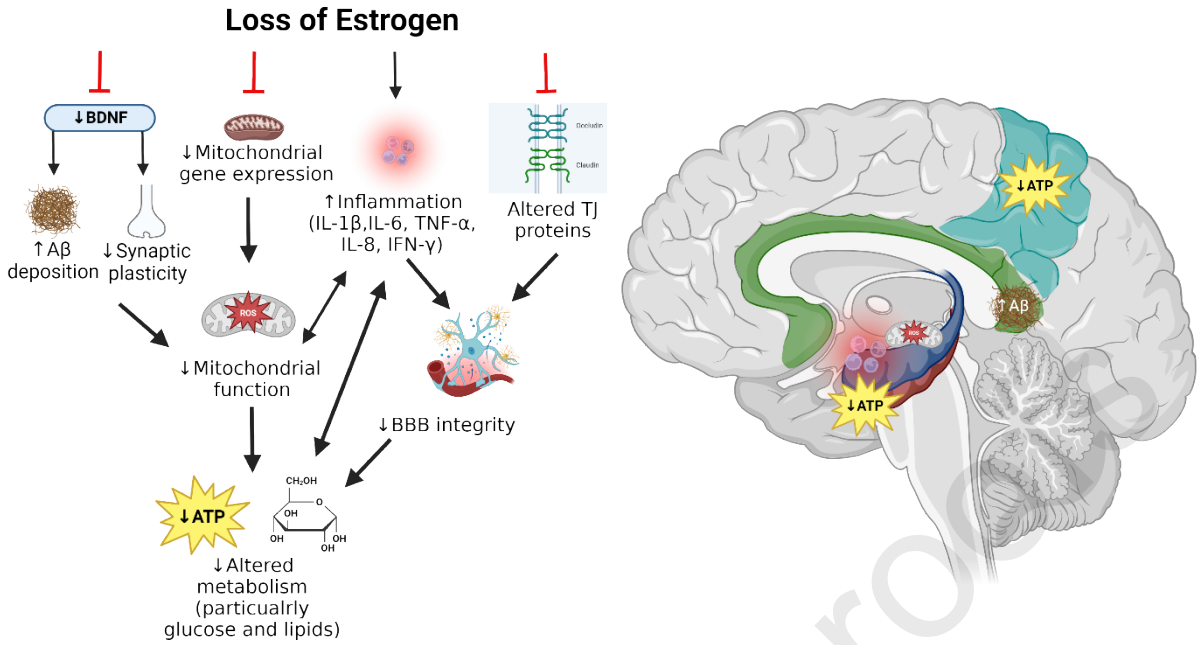


Figure 2 A mechanistic overview of menopause mediated AD risk. Overview of pathways and processes influenced by menopause. Regional specificity is depicted in the diagram if stated in literature Blue = hippocampus, Red = entorhinal cortex, teal = parietal lobe, green = cingulate cortex

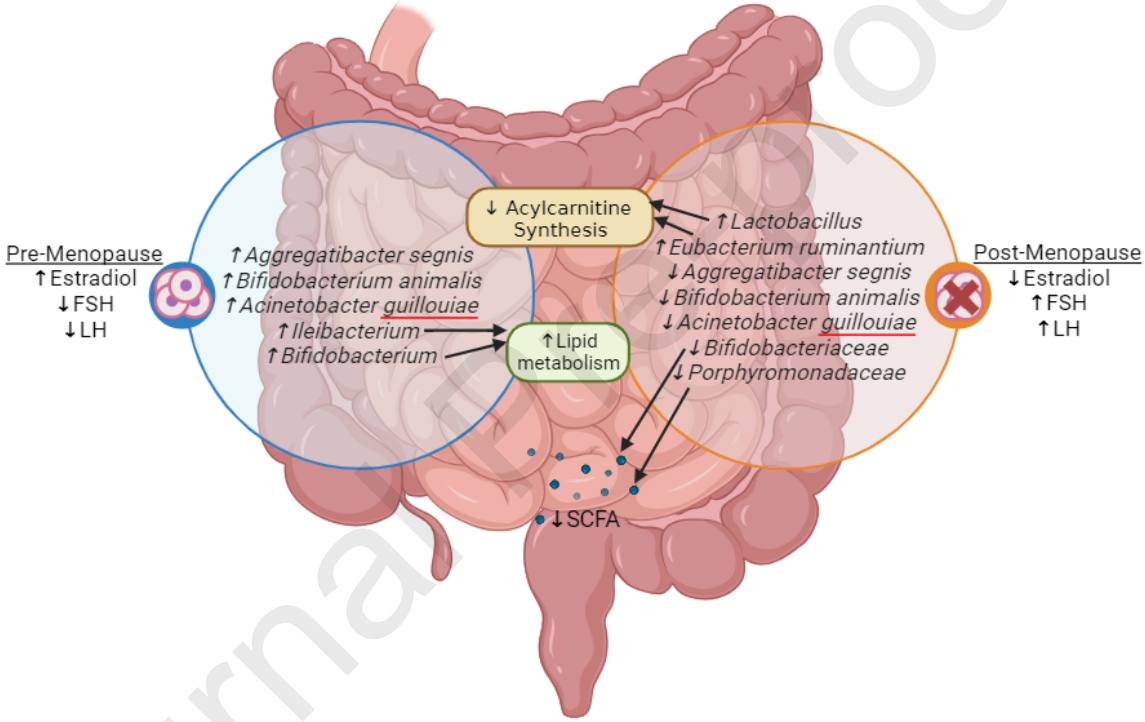
Gut Microbial dysregulation.

The human microbiome represents a complex community of microbes that live in a mutualistic relationship with their host. Gut microbial composition is increasingly recognized as a central factor in health and disease, protecting the intestinal gut barrier and preventing the establishment of pathogenic microorganisms (119, 120). Over the last 15 years there has been increasing evidence of a bidirectional communication system between the CNS and the gastrointestinal tract, more commonly referred to as the 'gut-brain axis' (121). Liu, Zhou (122) investigated the relationship between the menopause transition and dysbiosis in the gut microbiome using the faecal samples from 77 menopausal women and 24 healthy female controls. The results of this study show that menopausal women had reduced *Aggregatibacter segnis*, *Bifidobacterium animalis*, and *Acinetobacter guillouiae*. These bacteria are positively correlated with estradiol but negatively correlated with FSH and LH, which is indicative of the hormonal changes that occur during the menopausal transition (122). In ovariectomised rats, *Bifidobacteriaceae* and *Porphyromonadaceae* were reduced which led to a reduction in the microbial short-chain fatty acid (SCFA), formate, and an increase in isobutyrate, and deficits in spatial working memory (123) Guo, Cao (124) examined menopause and estradiol benzoate (estrogen medication) treatment on lipids and the gut microbiome in ovariectomised mice by supplementing the mice with. The authors report that ovariectomised mice had an increase in *Lactobacillus* and *Eubacterium ruminantium* that are significantly negatively associated with acylcarnitine synthesis, which synthesises lipids and alters membranes. However, there was an increase in bacteria *Ileibacterium* and *Bifidobacterium* in the estradiol benzoate supplementation; these microbes are significantly positively associated with acylcarnitine synthesis (124). As with

many explorations of gut-brain interactions, it can be difficult to disentangle direct causal effects, and this is particularly true in the context of menopause. Future endeavours should attempt to elucidate the contribution of the microbiota in menopause physiology. To achieve this more sophisticated experimentation is required.

Sex, menopause, and AD pathology

Figure 3 Gut-brain axis is there a menopausal interaction? Menopause transition (orange) alters gut microbial profile which may influence lipid metabolism, Acylcarnitine synthesis and short chain fatty acid production.



Neuroimaging studies have revealed more extensive brain atrophy in women with mild cognitive impairment (MCI) or possible AD in comparison to age matched men (125, 126). Additionally, women show a faster rate of cognitive decline across both MCI and AD (126). Proteomic analysis of the temporal lobe of AD patients indicates that the severity of white matter pathology is greater in women, with myelin basic protein (MBP) found to be hyper-citrullinated. MPB activation is thought to increase protein degradation, via citrullination of arginine and deamidation of glutamine and asparagine, which suggests that females have greater accumulation of dysfunctional proteins within the brain (7). This is further exacerbated in menopausal women, particularly when women develop menopause at an earlier age as they exhibit greater white matter hyperintensity fractions when compared to those who developed menopause at a later age (127). The entorhinal cortex is one of the first structure to be affected by AD pathology. Whilst Aβ deposition in the entorhinal cortex is comparable across males and females, women have greater tau pathology (128). This was also investigated by Coughlan, Betthauser (129), who found that seven regions across the temporal, parietal, and occipital lobes had elevated levels of tau. This was exacerbated by an

earlier onset of menopause and later intervention with hormone replacement therapy (129). Mosconi, Rahman (81) noted changes in Aβ deposition in response to menopause with perimenopausal women displaying significantly higher levels of Aβ in the frontal cortex (81).

Wang, Zhou (130) reported that in female MCI *APOE4* carriers', episodic memory declined more sharply than their male counterparts, highlighting a cognitive domain and perhaps brain region sensitive to *APOE4* in females. Indeed, dysregulation and deterioration of the entorhinal cortex are often reported in response to *APOE4* insult (131, 132) and may be exacerbated to some extent in female carriers (75, 76). Deterioration of white matter, temporal lobes, ventricle volume, and hippocampal volume have also been reported to be exacerbated in *APOE4* female carriers (7, 125, 126). From a pathological perspective, it has been reported that CSF tau-pathology is elevated in female carriers of *APOE4*, whilst male *APOE4* carriers have greater Aβ burden. In EFAD mice (which expresses both the 5XFAD mutations and human APOE), microglial interactions appear to be dysregulated in *APOE4* female mice leading to greater amyloid burden (133).

Conclusion

The menopause transition causes widespread dysregulation of numerous processes within the brain predisposing females to AD development. Although the underlying mechanisms appear complex and multifactorial, common themes, such as the decreased levels of estrogen, the increased levels of FSH, microbiome dysbiosis, and neuroinflammation, which we have outlined in this review, are beginning to emerge within the literature (31, 32, 40). Determining which processes are critical (i.e., precede the others), and unravelling the complexities relating to region specificity will be necessary in the future to complete the mechanistic picture, but if achieved this could lead to the identification of novel targets to mitigate the deleterious effects of menopause on the brain.

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1. Females have a greater AD prevalence.
2. Females who develop menopause earlier have increased AD risk.
3. Deleterious effects broadly relate to dysregulation of immune-metabolic processes.
4. Interestingly such features within the brain may be region specific.
5. Further elucidation of the underlying mechanisms is still required.