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Women's brain health and aging through the lifespan

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Women's brain health and aging through the lifespan

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Hormonal contraception and risk for cognitive impairment or Alzheimer's disease and related dementias in young women: a scoping review of the evidence

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Introduction: Women are significantly more likely to develop Alzheimer's disease and related dementias (ADRD) than men. Suggestions to explain the sex differences in dementia incidence have included the influence of sex hormones with little attention paid to date as to the effect of hormonal contraception on brain health. The aim of this scoping review is to evaluate the current evidence base for associations between hormonal contraceptive use by women and non-binary people in early adulthood and brain health outcomes.
Methods: A literature search was conducted using EMBASE, Medline and Google Scholar, using the keywords "hormonal contraception" OR "contraception" OR "contraceptive" AND "Alzheimer*" OR "Brain Health" OR "Dementia".
Results: Eleven papers were identified for inclusion in the narrative synthesis. Studies recruited participants from the UK, USA, China, South Korea and Indonesia. Studies included data from women who were post-menopausal with retrospective data collection, with only one study contemporaneously collecting data from participants during the period of hormonal contraceptive use. Studies reported associations between hormonal contraceptive use and a lower risk of ADRD, particularly Alzheimer's disease (AD), better cognition and larger grey matter volume. Some studies reported stronger associations with longer duration of hormonal contraceptive use, however, results were inconsistent. Four studies reported no significant associations between hormonal contraceptive use and measures of brain health, including brain age on MRI scans and risk of AD diagnosis.
Discussion: Further research is needed on young adults taking hormonal contraceptives, on different types of hormonal contraceptives (other than oral) and to explore intersections between sex, gender, race and ethnicity.

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1. Introduction

Sex and gender have long been recognized as important influencing factors for Alzheimer's disease and related dementias (ADRD). The lifetime risk for AD at age 45 is estimated at 1-in-5 for women and 1-in-10 for men (1). Female sex is associated with faster hippocampal atrophy (2) and greater pathological phosphorylated tau burden, key hallmarks of AD (3–5). The *APOEε4* gene also confers a greater risk of AD in women compared to men (at least in White populations) (6, 7). Sex hormones may explain some of the differences in risk for ADRD. Indeed, testosterone levels are a potential modifier of tau that may contribute to lower disease burden in males (3). Life-course evidence suggests pregnancy, adverse pregnancy outcomes, age of menarche, cumulative oestrogen exposure and menopause may all have implications for ADRD risk (8, 9). The potential for these biologically driven mechanisms to explain the difference in dementia prevalence by sex justifies the application of a women's health lens to the study of brain health (10).

A number of studies have investigated associations between the use of hormone replacement therapy (HRT) and brain health (9, 11–15). Comparatively less attention has been paid to the associations with hormonal contraception (HC) use. HCs act to simultaneously reduce endogenous sex hormones whilst supplementing synthetic oestrogen and/or progestin. Understanding the links between HC use and cognitive function is of considerable interest given the widespread and long-term use. Globally, over 60% of reproductive-age women use contraceptives, most of which are hormonal methods (16). The average length of time for HC use is five years, although many individuals stop and restart use across their lifespan (17). In addition to avoiding pregnancy, women use HCs for other reasons such as managing a medical condition, such as endometriosis-related pain and menorrhagia (18, 19). A recent study of young transgender individuals assigned-female-at-birth found that 80% were current or previous HC users (20, 21), highlighting the need for studies to be inclusive of this population.

The first use of HCs often occurs in young adulthood (22), a period increasingly acknowledged as a neglected stage in ADRD life-course research (23). Exposure to, and accumulation of, many modifiable risk factors (e.g., alcohol use and mental disorders 24, 25) begins during this life stage. HC use in young adulthood has been linked to changes in functional connectivity, profiled by increases in prefrontal connectivity and decreases in parietal connectivity (26). Studies have also reported changes in areas involved in affective and cognitive processing [e.g., amygdala, hippocampus, and cingulate gyrus (27)]. However, most studies were reported to have major methodological limitations regarding internal validity (27). In addition, most studies focused on short-term exposure to HCs in samples with large age ranges (i.e., 18–45 years 28). Thus, there is a need for further investigation of long-term use, especially regarding young women. Behaviourally, effects of hormone use have been reported in cognitive tasks in women (e.g., mental rotation 29). HC use is also correlated with a first diagnosis of depression, which is a known risk factor for ADRD (30).

The aim of this scoping review was to evaluate the current evidence base for associations between HC use by women, non-binary and transgender people in early adulthood and brain health outcomes.

2. Methods

2.1. Study design

A scoping review methodology was adopted to answer the research question, with a need to identify gaps in the current evidence base (31). A multi-stage approach was taken in line with scoping review methodology; define the research question, apply the PCC framework [as per Joanna Briggs Institute recommendations, the PCC (population, concept, context) framework was used to design the parameters of the scoping review (31)]; identify the databases and search terms and run the search; screen the papers; extract the data; synthesise the findings.

2.2. Population, concept, context

The concept was exposure to HCs. Method of action and mode of delivery included any contraceptive method classified as hormonal and targeted female reproductive systems. This included oral contraceptive (OC) pills, hormonal intrauterine devices (IUD), implant, injection, vaginal rings, and skin patches. Methods of HC were included if they contained oestrogen and/or progestin. The population was identified as female participants (where sex is reported) or women, non-binary, and transgender participants (where gender is reported) who had provided data on use of HCs. The context was selected as cross-sectional or cohort studies. Only studies that reported on the direct associations between HC use and one of the outcomes of interest (risk for dementia, cognitive impairment, other brain health outcomes related to neurodegeneration) were included. No studies that reported on indirect associations (i.e., HC use to depression to neurodegeneration) were included.

2.3. Databases and search terms

A literature search was conducted using EMBASE, Medline and Google Scholar, using the keywords "hormonal contraception" OR "contraception" OR "contraceptive" AND "Alzheimer*" OR "Brain Health" OR "Dementia". Additionally, the following search parameters were added to identify any papers that additionally considered the role of gender in this topic: "women" OR "female" OR "transgender" OR "non-binary". Papers were included if they were written in English or Spanish. No limitations were placed on the year of publication.

2.4. Eligibility criteria and selection

Articles were selected for inclusion in the scoping review if they reported on associations between HC use and brain health outcomes associated with ADRD or risk for ADRD. Although originally designed to only include studies reporting HC use between the ages of 18 to 39, no studies provided sufficient detail to determine this. As the majority of HC use is known to be during this age period (16), reported HC use is assumed to have been during this life stage in the included papers. A single reviewer (SG) assessed eligibility for inclusion, with 10% of papers cross-checked by a second author (KW), as recommended by Mak and Thomas (2022) (32).

2.5. Data extraction

A data extraction tool was created and piloted prior to use. Data extracted included (where provided) paper title, authors, year of publication, number of participants included, sex/gender breakdown, mean age of participants, HC type, duration of HC use, age started/stopped, brain health outcome measure used, and study results.

2.6. Narrative synthesis

A narrative synthesis was used to collate aims, methods and results across the included studies (33). The analysis involved synthesizing and summarizing findings for each outcome identified in the literature. Although we had planned to additionally synthesize results by HC type, most studies reported solely on OC use with the remaining studies providing insufficient detail to determine HC type. We reported effect estimates from studies where available (e.g., hazard ratios with 95% confidence intervals). As a final step, we outlined the broader implications for ADRD risk reduction and prevention, as well as suggestions for future studies. The scoping review was pre-registered on OSF.io (34).

3. Results

A total of 392 papers were identified in the initial search, 381 were not suitable after title and abstract screening with 11 papers included in the narrative synthesis. There was 100% concordance between the lead and secondary reviewer at both screening stages. Studies recruited participants from the UK (35–38), USA (39, 40), Italy (41), Indonesia (42), Singapore (43) and South Korea (13, 44). All studies except one included retrospectively collected data from women who were post-menopausal at the time of study enrolment, with only one study recruiting participants reporting on use during at early adulthood (see **Table 1** for further information). No studies reported on the inclusion of participants who were non-binary or transgender, and as such the results reported relate only to papers that reported on "women" or "female participants". The sample sizes ranged from 99 (40) to 4,696,633 participants (44). Seven studies included in the narrative synthesis reported positive associations between HC use and better brain health (13, 35, 36, 39, 40, 43, 44), whereas four studies reported no significant associations between HC contraceptive use and brain health (37, 38, 41, 42).

3.1. Associations between hormonal contraception and ADRD risk

Four studies reported associations between HC use and a lower risk of ADRD (35, 43, 44), particularly AD (13), whilst three studies found no significant associations between risk of AD diagnosis (38, 41) and subjective memory complaints (42).

In a study of UK Biobank participants, 81% of women reported using OCs. In this population, OC use was associated with a reduced risk of dementia with no evidence of an association between age of first use of OCs and risk of dementia (35). Subgroup analysis identified this association was only seen in women below 65 years of age at study baseline, suggesting OC use may only confer a benefit until a particular stage of life. A study of women from the Singaporean Chinese population similarly found 81% of participants had previously used OCs, with the majority reporting less than 5 years of use. Those who used OCs for less than 5 years were found to have a reduced risk of dementia compared to those who had never used OC, but interestingly, this association was not seen in those with more than 5 years of use (43). In contrast, a study utilising data from the South Korean NHIS found most women (80.6%) had never used OCs. Despite this, the analysis found OC use was significantly associated with approximately 10% lower risk of dementia compared to those who had never used OCs, with no differences between less than or more than a year's use (44).

A second study using both the South Korean NHIS and the National Cancer Screening Programme investigated subtypes of dementia. This study reported similarly low use of OCs (16.4% documented use) and found similar reductions in risk for all-cause dementia. Considering subtypes of dementia there remained a significant association between OC use and decreased risk of AD, however, no significant association with risk for vascular dementia (13).

This specific association between OC use and risk for AD has not been replicated in other studies. In a British cohort study with low OC use rates (26% previous or current users), there was no significant association with the diagnosis of AD (38). This study included a comparatively small sample size with low rates of OC use compared to rates reported in the UK Biobank cohort which limits confidence in interpreting these results. Participants included in this study were recruited between the ages of 70–100 years, therefore many participants included would not have had access to HCs during their early adulthood explaining the low usage rates reported. Another case-control study recruiting

TABLE 1 Table of papers included in narrative synthesis.

Paper	Participants	Hormonal contraception	Menopausal status	Brain health outcome	Results
Associations between hormonal contraception and ADRD risk					
Gong et al. (35).	UK Biobank, 273,240 women and 228,957 men. No information on the inclusion of non-binary or transgender individuals. Mean age of women was 56 years. 94.2% women of White ethnicity; 5.8% women of other ethnicity. Country: UK	Use of OC and age of initiation. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	61% of women included self-reported being postmenopausal by natural menopause (mean age at natural menopause 50.3 years). 19% of women included self-reported having a hysterectomy (mean age 43.9 at hysterectomy years). 8% of women self-reported having an oophorectomy (mean age at oophorectomy 47.4 years).	Incident all-cause dementia.	HR for dementia in those who reported oral contraceptive use was 0.80 (95% CI: 0.72, 0.88), $p < 0.001$. No association with age of starting use of OC. Lower risk only statistically significant in women younger than 65 years at study baseline.
Song et al. (43).	Singapore Chinese Health Study, 8,222 post-menopausal women. No information on the inclusion of non-binary or transgender individuals. Mean age 53.4 years. All women Singapore Chinese (49.8% Cantonese dialect speakers, 50.2% Hokkien dialect speakers). Country: Singapore.	Use of OC for at least one month and duration of use. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	All women self-reported natural menopause. 6.2% menopause before 45 years, 27.9% menopause aged 45–49 years, 53.0% menopause aged 50–54 years, 12.9% menopause aged 54 years and older.	SM-MMSE to determine cognitive impairment (Cut off points determined appropriate to local population; no education: 17/18; primary school education: 20/21; secondary school or more: 24/25).	Women with ≤5 years of OC use had a lower risk of cognitive impairment compared to those who had never used OC HR: 0.74 (95% CI: 0.63, 0.87). Not statistically significant for >5 years (HR 0.87 (95% CI: 0.68, 1.13).
Yoo et al. (44).	Korean National Health Insurance System, 4,696,633 post-menopausal women. No information on the inclusion of non-binary or transgender individuals. Mean age 61.2 years. No information on race or ethnicity available. County: South Korea.	Use of OC. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	Menopausal status self-reported via questionnaire, participants with hysterectomy procedure in general excluded ($n = 17,667$). 1.6% of participants reported menopause prior to 40 years, 5.3% menopause between 40 and 44 years, 25.9% menopaused between 45 and 49 years, 55.4% menopause between 50 and 54 years, 11.8% menopause aged 55 years and older.	Diagnosis of dementia.	Use of OC reduced the dementia risk by 10%, with no differences seen in duration of use: <1 year use HR: 0.91 (95% CI: 0.88, 0.92); ≥1 year use HR: 0.90 (95% CI: 0.88–0.92).
Kim et al. (13).	Korean National Health Insurance System, 209,588 post-menopausal women. No information on the inclusion of non-binary or transgender individuals. Mean age 61.5 years non-dementia group ($n = 179,723$), 70.46 years in dementia group ($n = -29,865$). No information on race or ethnicity available. County: South Korea.	Lifetime use of OC ("never," "use for less than 1 year," "use for more than 1 year," or "unknown."). No information available on type of OC or dosage. Data was retrospectively collected via self-report.	Menopausal status self-reported via questionnaire, participants with history of hysterectomy excluded ($n = 324,425$). Mean age at menopause 49.99 years in non-dementia group, 49.27 years in dementia group.	Diagnosis of dementia, including sub-type analysis (Alzheimer's disease dementia: ADD; vascular dementia: VD).	Dementia (all-cause): OC use <1 year HR: 0.92 (0.88, 0.96). OC use ≥ 1 year HR>: 0.90 (0.86, 0.95). ADD: OC use <1 year HR 0.92 (0.88, 0.97); OC use for ≥1 year HR 0.89 (0.84–0.94). VD: OC use <1 year use HR: 0.96 (95% CI: 0.84, 1.10); OC use ≥1 year use HR: 0.97 (95% CI: 0.84, 1.13)).
Fox et al. (38).	89 women aged 70–100 years. No information on the inclusion of non-binary or transgender individuals. Median age 77 years in control group ($n = 51$), 86 years in the patient group ($n = 38$). All participants were White British, living in England. Country: UK.	OC use. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	Age of experiencing menopause self-reported via interview. Median age at menopause 50 years in control group, 50 years in patient group.	Age at Alzheimer's onset.	No association between OC use and AD risk.
Zucchella et al. (41).	Case control study, 275 women with AD and 276 controls. No information on the inclusion of non-binary or transgender individuals. Mean age 77.6 years in AD patient group, 76.7 years in control group. No information on race or ethnicity. Country: Italy.	History of at least 6 months of HC use. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	Menopause type (physiological or surgical) and age of menopause self-reported via interview. 89% of AD patients and 84.1% of controls had a physiological menopsause. 11% of AD patients and 15.9% of controls hd a surgical menopause.	ADD vs. control.	No differences between groups in history of OC use (χ^2: 1.61, p: 0.20).

(*Continued*)

TABLE 1 Continued

Paper	Participants	Hormonal contraception	Menopausal status	Brain health outcome	Results
Pradono et al. (42).	Prospective cohort study of 2,668 female participants. No information on the inclusion of non-binary or transgender individuals. Mean age 47.4 years. No information on race or ethnicity. Country: Indonesia.	Data on HC use (Yes/No) collected. No information available on type of OC or dosage. Data on current use was collected via self-report.	No information on menopausal status of participants. 2.5% of participants reported using HRT.	Subjective memory complaint based on a positive response to the question: Are you considered forgetful by others (family, friends, etc)?	No significant associations between HC use and with subjective memory complaints in fully adjusted models [OR: 1.30 (95% CI: 0.995, 1.70)].
Associations between hormonal contraception and cognition					
Lindseth et al. (36).	UK Biobank, 221,124 women. No information on the inclusion of non-binary or transgender individuals. Mean age 56.2 years. 95.2%White, 1.5% Asian, 1.5% Black, 0.4% Chinese, 0.8% Other ethnic groups, 0.6% mixed ethnicity. Country: UK.	HC usage (current user, past user, never user) and duration of use and age of initiation. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	75% of participants reported a natural menopause (mean age at natural menopause 50.5 years). 3% of women included self-reported having a hysterectomy (mean age 44.8 at hysterectomy years). 3% of women self-reported having an oophorectomy (mean age at oophorectomy 50.2 years).	Computerised cognitive tests assessing visual memory, working memory, processing speed and executive function.	Both current and past use of HC were significantly associated with higher scores on all cognitive tasks. Longer duration of hormonal contraceptive use was associated with higher performance on all tasks except visual memory. Older age at initiation was associated with lower performance in all cognitive tests.
Egan and Gleason (39).	Wisconsin Registry for Alzheimer's Prevention, 261 women. No information on the inclusion of non-binary or transgender individuals. Mean age 52 years. 98.2% of previous HC users were White, 0.9% Black, 0.4% American Indian and 0.4% Hispanic, whilst 100% of never users were White. Country: USA.	HC use history and duration. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	78% of the previous HC use group self-reported as postmenopausal (no age of menopause available), whilst 64.8% of the never HC use self-reported as post-menopausal.	17 cognitive tests combined into 5 domains: Verbal Ability, Visuo-spatial Ability, Working Memory, Verbal Learning & Memory, and Speed & Flexibility.	Use of HC associated with better visuospatial ability [mean difference: 0.75 (95% CI: 0.23, 1.28)] and speed and flexibility [mean difference: 0.52 (95% CI: 0.14, 0.90), p: 0.007]) compared to those who had never used, with strongest effects seen in those with ≥15 years of use.
Associations between hormonal contraception and MRI measures					
Schelbaum et al. (40).	99 women and 26 men,. No information on the inclusion of non-binary or transgender individuals. Women: Mean age 52 years. Women: 80% White, 6% Asian, 6% Black/African America, 6% Mixed, 4% Hispanic. Country: USA.	Use of HC and duration of use. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	Menopausal status defined by Staging of Reproductive Aging Workshop criteria and laboratory hormone assessments, menopause type categorised as spontaneous or induced. 50% were post-menopausal (74% spontaneous, 26% induced). Mean age at menopause 51 years.	Cognitive tests (verbal memory, executive function, language). MRI parameters (grey matter, white matter).	Positive associations between HC use and grey matter volume were observed in precuneus, fusiform gyrus, superior parietal lobule, angular gyrus, and inferior frontal gyrus of the left hemisphere and in fusiform gyrus of the right hemisphere (all $p < 0.005$). No associations with cognition.
de Lange et al. (37).	UK Biobank, 16,854. No information on the inclusion of non-binary or transgender individuals. Mean age 54.7 years. 97.4% White, 0.7% Asian, 0.6% Black, 0.5% Mixed, 0.5% Other, 0.3% Chinese. Country: UK.	Use of OC and age of initiation. No information available on type of OC or dosage. Data was retrospectively collected via self-report.	50.97% self-reported they had had their menopause, 30.29% reported they had not had their menopause, 21% were not sure and 0.08% preferred not to answer. Amongst HRT users the mean age at menopause was 48.5 years, and amongst non-HRT users the mean age at menopause was 50.6 years.	Brain age.	No significant association between OC status and brain age (β: 0.02, SE: 0.07, p_{corr}: 0.80).

AD, Alzheimer's disease; ADD, Alzheimer's disease dementia; CI, confidence interval; HC, hormonal contraceptive; HR, hazard ratio; HRT, hormone replacement therapy; MRI, magnetic resonance imaging; OC, oral contraceptive.

participants up to their 9th decade of life in Italy with similarly low rates of HC use (3% previous use in patient group, 5% previous use in control group), found no significant associations between HC use and diagnosis of AD (41). Finally, a study in Indonesia recruiting women aged 25 and above (mean ~47 years) with significantly higher HC usage (72% reported use) found no significant association with subjective memory complaint cases (42).

3.2. Associations between hormonal contraception and cognition

Two studies reported associations between HC use and better performance on cognitive tasks. In a study using the UK Biobank (current HC: 2%, previous HC: 78%), both past and current HC use was associated with significantly higher test scores on tasks measuring processing speed, executive

functioning, and visual and working memory. Longer duration of HC use was also associated with better performance on most cognitive tests, whilst an older age of starting HC use was associated with lower performance across all cognitive domains (36). A second study recruiting participants from the USA, with similar high HC usage rates (87% current or previous users), found significantly higher performance on tasks of visual-spatial ability and speed. There were no significant differences by HC use on tasks of verbal ability, working memory and verbal learning and memory (39).

3.3. Associations between hormonal contraception and MRI measures

Only two studies have reported on associations between HCs and MRI measures, with mixed results. A study recruiting participants in the USA (9% current users, 53% past users) reported significant associations between use and larger grey matter volume in the precuneus, fusiform gyrus, superior parietal lobule, angular gyrus and the inferior frontal gyrus of the left hemisphere and in fusiform gyrus of the right hemisphere (40).

A UK Biobank data analysis (86% HC users) found no association between usage and brain age (37). No other studies were identified that reported MRI outcomes and HC use in the context of ADRDs.

4. Discussion

Of the eleven papers included in this narrative review, the majority investigated associations between HC use and risk for dementia. Studies that were typically larger and with higher rates of OC use reported significant associations with decreased risk for dementia, including AD, however smaller studies including older women with lower rates of previous OC use reported no associations with AD risk. One study recruiting women from young adulthood did not find associations between HCs and subjective memory complaints. Two studies reported significant associations with better performance on cognitive tasks with HC use, and whilst one study reported higher grey matter volume amongst HC users, a second MRI study found no association with brain age. There is clearly a need for more research on this topic, with a particular need to focus on data collection within the age group most likely to be using HCs (young adults), more detailed investigation by HC type and an expansion of outcomes of interest to include more specific research around associations with cognitive performance and brain MRI measures relevant to ADRDs.

Studies conducted to date focus exclusively on associations between OCs and brain health or did not define what was meant by HC within their database used, with no studies explicitly considering other HCs such as the implant, injection or hormonal IUD. Understanding the associations between HCs and brain health is critical, as these methods continue to grow in popularity and may exert more localised effects compared to oral contraception. For example, one hormonal IUD has been associated with increased stress reactivity (45), demonstrating the potential for side effects of the contraception outside of the localised effects, and may raise important implications for ADRD given known associations with cortisol (46).

Another potential limitation that must be addressed is the reliance on retrospective data collection, which may be less accurate due to self-reporting events in the past that may not be recalled accurately, leading to potential recall bias (47). Future studies should collect data from participants in early adulthood to understand whether the potential benefits for brain health and ADRD risk reduction can be seen throughout the lifespan. There are also inherent limitations in all observational studies in establishing a direct cause-effect relationship which should be acknowledged. It is also important to consider confounding by indication, such as psychological factors, sexual debut or abstinence and personality that lead to decision to use HCs which may themselves be determined by brain function or structure (27). In addition, the menopausal status of participants included in the individual studies may have influenced the results independent of previous HC use, given known associations between menopause and brain health (48) (including importantly the potentially reversible nature of brain fog experienced in peri-menopause identified in the SWAN studies that may have otherwise influenced cognitive performance in some of these studies 49). Understanding whether exposure to exogenous and synthetic hormones (both as contraceptives and HRT) can modify the risk for future dementia will be important, as evidenced by a recent paper from the UK Biobank which reported significant associations between more prolonged exposure to endogenous hormones and smaller burden of cerebral small vessel disease independent of HC and HRT use (50). Conversely, a study in Sweden found that a longer reproductive period was associated with a higher risk for future dementia, again independent of HC use (51). Slight differences in reproductive periods between the two studies discussed here (37 vs. 34 years on average) as well as different outcomes (small vessel disease on MRI vs. dementia diagnosis) may explain these findings, and highlights the need to develop a more comprehensive literature base in this area to understand the role of HCs, HRT, menopause and lifetime exposure to endogenous sex hormones in relation to brain health and risk for neurodegeneration. Future research could also focus on exploring associations between HC use and more novel and sensitive markers of neurodegeneration, including the use of amyloid and tau positron emission tomography (PET) scans, cerebrospinal fluid (CSF) analysis and blood-based biomarkers (52, 53). As previous research has focused on global cognitive assessments, or the diagnosis of dementia, this would provide evidence on any associations between HCs and the earliest stages of AD in particular, which could help to delineate whether there is an optimal time window where exogenous hormones may confer brain health benefits.

All studies focused exclusively on the dichotomy of sex and did not consider whether gender is relevant to this discussion. Even where studies report on "sex", there are often no documented

definitions for these categories, and as such participants may have chosen whether to self-report sex or gender (54). There is also emerging evidence that there are changes on the brain throughout the menstrual cycle, as demonstrated by a 1.3-year decrease in brain age at ovulation compared to other times (55). This highlights the critical need to consider the role of sex and gender, as well as the use of exogenous hormones, throughout the spectrum of ADRDs, from prevention to detection and treatment. Similarly, studies did not consider race and ethnicity, even though Black women are at the highest risk for ADRD (56). These will be important demographic data points for future studies to consider. Research in ADRD risk factors has long espoused inequitable population representation within their participants, with minority and socioeconomically disadvantaged individuals being underrepresented (57). The research community has typically attributed the under-representation to such groups being naturally "hard to reach" and more challenging to involve (58). A key lesson from previous work is that it is more often the researchers' approach and attitude to engagement that restricts the diversity of public involvement, rather than the enthusiasm and interest of the public concerned (59). Further efforts are needed to systematically evaluate approaches that successfully foster equitable involvement and engagement in research recruitment and retention, including improved methodological standards such as Public and Participant Engagement and Involvement (PPIE) with a focus on under-served populations (60) and involvement with the voluntary and community sector enterprises who support these populations.

An important avenue for future research will be to examine indirect pathways between HCs and ADRD risk, including their impact on modifiable risk factors for ADRD. The Lancet Commission for dementia prevention, intervention, and care lists 12 modifiable risk factors for dementia including hypertension, traumatic brain injury (TBI), depression and diabetes, all of which are affected by HC use (61). For example, HCs increase blood pressure in the majority of women, 5% of whom will develop hypertension (62). Hypertension confers a 2% population attributable fraction (PAF) in high income countries (61), and between 4 and 8% PAF in low- and middle-income countries (LMICs) (63) according to the Lancet Commission, and as such the potential for this indirect association warrants further investigation. Conversely, it has been demonstrated that HCs may reduce the severity of symptoms and duration of recovery following TBI (64). How these indirect influences on known modifiable risk factors affect dementia risk is unknown with more research needed. Given the heterogeneity of women using HCs it is important to consider that associations between HCs and brain health may vary within this group, it is possible that there are subgroups of women where ADRD risk is not reduced and may in fact be increased. It may also be important to consider any interactions between the *APOEe4* gene, HC use and brain health outcomes, given evidence suggesting this gene mediates associations between HRT and cognitive impairment (11). One of the papers included in this scoping review did look at this and reported no interaction between *APOEe4* HC use and cognition (39), with no other studies reporting on this.

Though limited, most studies identified here suggested a positive association between HC use and brain health. The possibility that HCs can confer brain health benefits has significant real-world implications and challenges. Despite efforts to improve women's health, disparities in access and utilization of reproductive services continue to persist. Inequalities have been documented across racial, ethnic, and socioeconomic groups, as well as across geographical regions (65–67). A recent Lancet systematic analysis reported that over 160 million women had an unmet need for contraception in 2019 (67); most of these women resided in sub-Saharan Africa and South Asia. Young women aged 15–24 years had the lowest rates of demand satisfaction. Optimizing any potential benefits of HCs on brain health will therefore require significant efforts to reduce inequities in access and utilization.

In summary, there is a small but growing evidence base suggestive of potential brain health benefits of HCs for women. Further work is needed to address current limitations and work directly with the age group most likely to take these contraceptives, with the goal of understanding if and how these may be used as a tool in ADRD risk reduction and prevention efforts.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

SG: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. LB: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. NJ: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. KB: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. GM: Methodology, Writing – original draft, Writing – review & editing. FF: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cardiometabolic health across menopausal years is linked to white matter hyperintensities up to a decade later

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Introduction: The menopause transition is associated with several cardiometabolic risk factors. Poor cardiometabolic health is further linked to microvascular brain lesions, which can be detected as white matter hyperintensities (WMHs) using T2-FLAIR magnetic resonance imaging (MRI) scans. Females show higher risk for WMHs post-menopause, but it remains unclear whether changes in cardiometabolic risk factors underlie menopause-related increase in brain pathology.

Methods: In this study, we assessed whether cross-sectional measures of cardiometabolic health, including body mass index (BMI) and waist-to-hip ratio (WHR), blood lipids, blood pressure, and long-term blood glucose (HbA1c), as well as longitudinal changes in BMI and WHR, differed according to menopausal status at baseline in 9,882 UK Biobank females (age range 40–70 years, n premenopausal = 3,529, n postmenopausal = 6,353). Furthermore, we examined whether these cardiometabolic factors were associated with WMH outcomes at the follow-up assessment, on average 8.78 years after baseline.

Results: Postmenopausal females showed higher levels of baseline blood lipids (HDL $\beta = 0.14$, $p < 0.001$, LDL $\beta = 0.20$, $p < 0.001$, triglycerides $\beta = 0.12$, $p < 0.001$) and HbA1c ($\beta = 0.24$, $p < 0.001$) compared to premenopausal women, beyond the effects of age. Over time, BMI increased more in the premenopausal compared to the postmenopausal group ($\beta = -0.08$, $p < 0.001$), while WHR increased to a similar extent in both groups ($\beta = -0.03$, $p = 0.102$). The change in WHR was however driven by increased waist circumference only in the premenopausal group. While the group level changes in BMI and WHR were in general small, these findings point to distinct anthropometric changes in pre- and postmenopausal females over time. Higher baseline measures of BMI, WHR, triglycerides, blood pressure, and HbA1c, as well as longitudinal increases in BMI

and WHR, were associated with larger WMH volumes (β range = 0.03–0.13, $p \leq 0.002$). HDL showed a significant inverse relationship with WMH volume ($\beta = -0.27$, $p < 0.001$).

Discussion: Our findings emphasise the importance of monitoring cardiometabolic risk factors in females from midlife through the menopause transition and into the postmenopausal phase, to ensure improved cerebrovascular outcomes in later years.

KEYWORDS

menopause, female health, cardiometabolic health, body anthropometrics, white matter hyperintensities, brain health, UK Biobank

1 Introduction

The menopause is a natural biological process that characterises the change from reproductive to post-reproductive life among females. The phase leading up to the cessation of menstrual cycles, known as perimenopause, involves irregular menstrual cycles, hormonal fluctuations, and a gradual decline in ovarian function. Decreasing endogenous oestradiol levels during the menopause transition have been associated with increased risk for poor cardiometabolic health, including abdominal adiposity, dyslipidaemia, diabetes, and hypertension (1–7). Poor cardiometabolic health is a key risk factor for white matter (WM) lesions or areas of dysmyelination in the brain (8, 9), which can be quantified using WM hyperintensities (WMH) from magnetic resonance imaging (MRI) scans (10, 11). Although WMHs are common with advancing age (9, 12), larger WMH volumes have also been associated with increased risk of dementia (13–16), of which females have higher prevalence (17, 18). Pertinently, a number of studies report greater WMH load in postmenopausal females compared to age-matched males or premenopausal females (19–25). It is however unclear whether changes in cardiometabolic risk across menopausal years and beyond are linked to WMH outcomes.

Both cross-sectional and longitudinal studies indicate that the menopause transition poses a risk for accumulation of abdominal adipose tissue (6, 26–28) and an unfavourable lipid profile (4, 5, 29, 30), beyond the risk related to advancing age. However, higher levels of abdominal adiposity, blood lipids, blood pressure (BP), and blood glucose are generally linked to greater WMH volumes (8, 31–41), and it is challenging to disentangle menopause-specific risks from those linked to increasing age (6). In addition, recent studies show age- and sex-specific associations between cardiometabolic risk factors and brain measures (24, 42, 43), indicating dynamic body-brain relationships across the lifespan. To our knowledge, no population-based studies have yet assessed the relationships between both cross-sectional and longitudinal measures of cardiometabolic risk and WMH outcomes in pre- and postmenopausal females.

In the present study, we aimed to investigate associations between markers of cardiometabolic health, menopause status, and WMH volumes in 9,882 female UK Biobank participants. First, we examined whether females who were pre- and postmenopausal, as categorised based on self-reports at the baseline assessment, differed on baseline measures of body anthropometrics (body mass index (BMI) and waist-to-hip ratio (WHR)), blood lipids (high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides), BP (systolic and diastolic), and long-term glucose levels (glycated haemoglobin; HbA1c). Next, we assessed changes in BMI and WHR between baseline and the imaging timepoint (timepoint 2; mean assessment interval = 8.78 years) by menopause status. Lastly, we examined the relationships of the baseline markers and the longitudinal BMI and WHR changes with WMH volume measured at timepoint 2.

2 Methods and materials

2.1 Sample characteristics

The initial sample was drawn from the UK Biobank cohort (www.ukbiobank.ac.uk), and included 21,930 female participants with data entries across self-reported demographic factors (education, ethnic background, and assessment location), blood lipids (HDL, LDL, and triglycerides), BP (systolic and diastolic), and HbA1c measurements at baseline, WMH volume, hysterectomy (removal of the uterus), and bilateral oophorectomy (removal of both ovaries) at timepoint 2, and body anthropometrics (BMI and WHR), age, and menopausal status at both timepoints. An overview of the variables, including their UK Biobank data-fields, is available in Supplementary Table S1. Participants with missing values ("*Not a Number (NaN)*," "*prefer not to answer*," "*do not know*"), were excluded (missing datapoints = 520 for demographic factors, 2,974 for WMH volume, 8,448 for cardiometabolic risk factors, 4,562 for menopausal status, and 101 for hysterectomy/bilateral oophorectomy, with 10% of all participants having missing values for more than 2 variables). 1,015 participants who had undergone a hysterectomy and/or bilateral oophorectomy were excluded in order to focus the study on variation in natural menopause, as surgical menopause may involve independent risks for cardiometabolic diseases (4, 44), as well as brain ageing and dementia (45–47). 17 participants were excluded due to implausible menopause status data or age at menopause outliers (see Section 2.2 for details). 794 participants with known brain disorders were excluded based on ICD10 diagnoses including Alzheimer's disease and dementia, mild cognitive disorder, neurodegenerative diseases, stroke, mental and behavioural disorders (36, 48). 9,882 participants were included in the final dataset. Sample demographics are provided in Table 1.

TABLE 1 Sample characteristics.

		Premenopausal	Postmenopausal
Number of subjects		3,529	6,353
Age at baseline (years)	Mean ± SD	46.58 ± 3.77	58.39 ± 4.97
	Range	40.00–63.00	41.00–70.00
Assessment interval (years)	Mean ± SD	8.93 ± 1.63	8.71 ± 1.70
	Range	4.33–12.51	4.29–12.41
Education	% University/college degree	51.03	44.23
	% A levels or equivalent	15.95	13.58
	% O levels/GCSE or equivalent	19.95	21.30
	% NVQ or equivalent	8.04	6.34
	% Professional qualification	3.43	6.63
	% None of the above	1.59	7.92
Ethnic background	% White	95.89	98.03
	% Black	0.82	0.35
	% Mixed	0.85	0.30
	% Asian	1.11	0.66
	% Chinese	0.74	0.13
	% Other	0.60	0.54
BMI	Mean ± SD	25.43 ± 4.45	25.93 ± 4.29
	Range	16.23–47.98	15.20–48.91
WHR	Mean ± SD	0.79 ± 0.06	0.81 ± 0.07
	Range	0.59–1.06	0.59–1.12
HDL (mmol/L)	Mean ± SD	1.59 ± 0.33	1.68 ± 0.37
	Range	0.75–3.19	0.74–3.80
LDL (mmol/L)	Mean ± SD	3.27 ± 0.72	3.76 ± 0.82
	Range	1.26–6.89	1.36–7.57
Triglycerides (mmol/L)	Mean ± SD	1.18 ± 0.63	1.46 ± 0.75
	Range	0.35–6.69	0.35–10.38
Systolic BP (mmHg)	Mean ± SD	126.44 ± 16.72	136.17 ± 19.29
	Range	80.00–213.00	85.00–247.00
Diastolic BP (mmHg)	Mean ± SD	77.85 ± 10.43	79.79 ± 10.08
	Range	46.00–131.00	41.00–120.00
HbA1c (mmol/mol)	Mean ± SD	33.06 ± 4.26	35.58 ± 4.45
	Range	20.70–87.10	15.30–148.10

Notes: Mean ± standard deviation (SD) and ranges for age at baseline, assessment interval (years between baseline assessment and imaging timepoint), and cardiometabolic markers at baseline for the premenopausal and postmenopausal group. Percentages for education and ethnic background. GCSE, General Certificate of Secondary Education; NVQ, National Vocational Qualification; BMI, body mass index; WHR, waist-to-hip ratio; HDL, high density lipoprotein; LDL, low density lipoprotein; BP, blood pressure; HbA1c, glycated haemoglobin.

2.2 Menopause status group assignment

All females were classified into two groups based on their self-assessment to the question "*Have you had your menopause (periods stopped)?*". Participants answering "*no*" at baseline were classed as premenopausal, and those answering "*yes*" at baseline were classed as postmenopausal. Premenopausal females who were older than 63 at baseline and postmenopausal females who were younger than 39 at baseline were excluded ($n = 4$), based on outlier estimations for the variable 'age at menopause' conducted on all UK Biobank females in our previous work (36). 13 participants were removed due to implausible menopause status data (e.g., responses indicating postmenopausal status at baseline and premenopausal status at timepoint 2). The final sample consisted of 3,529 premenopausal females and 6,353 postmenopausal females. Supplementary Figure S1 shows the baseline age distributions in the two groups. Due to the minimal age overlap between the groups in this sample, we were unable to use propensity matching [see e.g., (49)] to analyse sub-samples matched on age.

2.3 Body anthropometric measures and cardiometabolic markers

The primary measures of body anthropometrics included BMI (kg/m^2) and WHR (waist circumference/hip circumference), which were obtained at both timepoints. The other cardiometabolic markers (collected only at baseline) consisted of BP (systolic and diastolic), HbA1c, triglycerides, and cholesterol (LDL and HDL; the latter of which is considered protective (50)). The BP measurements were taken using the Omron Digital BP monitor with the default automated option. All other markers (i.e., HDL, LDL, triglycerides, HbA1c) were obtained through blood assays. Cholesterol (HDL and LDL in mmol/L) were measured by enzyme immunoinhibition analysis on a Beckman Coulter AU5800, and triglycerides (mmol/L) were measured by GPO-POD analysis on the same device. The HbA1c assay was conducted using a Bio-Rad Variant II Turbo analyser, which utilises a High Performance Liquid Chromatography (HPLC) method to obtain a measurement (mmol/mol). Detailed

descriptions of all assessment procedures can be found in the UK Biobank protocol (51). The means, standard deviations, and ranges for each marker are provided in Table 1. Detailed descriptions of the markers can be found in Supplementary Table S2, the distribution plots are provided in Supplementary Figure S2, and the correlations between markers are depicted in Supplementary Figure S3. As some variables did not show a normal distribution, the statistical analyses provided in Section 2.5 were re-run after log-transforming the variables. The results are provided in Supplementary section 6.4.

2.4 MRI data acquisition and processing

Information about the UK Biobank data acquisition protocols is available in Alfaro-Almagro et al. (52) and Miller et al. (53). Total volume of WMH was derived for each participant based on T2 fluid-attenuated inversion recovery (FLAIR) images and T1-weighted data (https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=25781) using the Brain Intensity Abnormality Classification Algorithm (BIANCA) (10), which is part of the FMRIB Software Library FSL (54). BIANCA is a fully automated tool for segmentation of WMH based on the k-nearest neighbour algorithm, and is documented as a reliable method for WMH segmentation in large cross-sectional cohort studies (10). The WMH volume measures were log-transformed to normalise and stabilise the variance (55, 56).

2.5 Statistical analyses

The statistical analyses were conducted using Python 3.8.17. All variables were standardised. Multiple comparisons using false discovery rate (FDR) correction (57, 58) were conducted across all p-values of the four main analyses, and separately across all p-values of the twelve supplementary analyses.

2.5.1 Group differences in baseline cardiometabolic markers

To test for group differences in cardiometabolic markers at baseline, a weighted least squares approach was used by assigning weights based on the number of participants in each group (59) to account for differences in menopause status group size. Menopause status group was used as the independent variable. Due to indications of multicollinearity (see Supplementary section 4 for correlations and variance inflation factors), the analyses were run separately for each of the cardiometabolic markers (dependent variables), whilst adjusting for age at baseline:

$$CM_{marker} = \beta_0 + \beta_1 MP_{status} + \beta_2 Age \quad (1)$$

where CM_{marker} represents the cardiometabolic marker (body anthropometrics, blood lipids, BP, or HbA1c; all measured at baseline), β_0 indicates the intercept, MP_{status} indicates the categorical group assignment based on menopause status, and Age is age measured at baseline.

2.5.2 Longitudinal changes in body anthropometrics by menopause status

To assess age-adjusted changes in BMI and WHR over time, and whether changes depended on menopause status group, we ran two separate linear mixed effects models with *Bodyvar* (BMI and WHR, respectively) as the dependent variable, timepoint and menopause status as categorical predictors, and *timepoint * menopause status group* as an interaction term.

$$Bodyvar = \beta_0 + \beta_1 TP + \beta_2 MP_{status} + \beta_3 TP{*}MP_{status} + \beta_4 Age + b_{0j} + \epsilon \quad (2)$$

In this equation, TP indicates the timepoint of measurement (baseline, timepoint 2), MP_{status} indicates the categorical group assignment based on menopause status, $TP{*}MP_{status}$ indicates the interaction term between time and menopause status, Age represents the age term, b_{0j} is the random intercept term for each participant j, which allows for modeling individual-level variability in the baseline BMI and WHR that is not explained by the fixed effects, and ϵ is the residual error term.

2.5.3 Associations between baseline cardiometabolic markers and WMH volume

To test whether baseline cardiometabolic markers were related to WMH outcomes (measured only at timepoint 2), we ran a series of linear regressions to test for main effects of each marker on WMH volume, respectively:

$$WMH = \beta_0 + \beta_1 CM_{marker} + \beta_2 Age + \beta_3 AssessmentInterval \quad (3)$$

where CM_{marker} represents the cardiometabolic marker (body anthropometrics, blood lipids, BP, or HbA1c; all measured at baseline), Age is age measured at timepoint 2, and $AssessmentInterval$ is the time between baseline and timepoint 2 assessments in years. The models were run separately for each cardiometabolic marker (see section 2.6.1 for models run with all other markers as covariates).

2.5.4 Associations between BMI and WHR changes and WMH volume

To test whether changes in BMI and WHR were associated with WMH volume at timepoint 2, we first regressed the effect of baseline values on the timepoint 2 values to capture changes in BMI and WHR independent of starting point, and used the residuals as independent variables in a linear regression model.

$$WMH = \beta_0 + \beta_1 Bodyvar_{res} + \beta_2 Age + \beta_3 AssessmentInterval \quad (4)$$

Here, $Bodyvar_{res}$ represents timepoint 2 BMI or WHR residualised for baseline values, Age is age measured at timepoint 2, and $AssessmentInterval$ is the time between baseline and timepoint 2 assessments in years.

2.6 Sensitivity analyses

2.6.1 Adjustment for potential confounding factors

To account for potential confounding factors that could influence brain structure, hormone levels, or cardiometabolic health, models 3 and 4 were rerun with the following covariates, in addition to age: lifestyle factors including alcohol use (60–62), and smoking status (63, 64), socioeconomic factors including education level (65–67) and ethnic background (68), and female-specific factors including hormone replacement therapy use (user vs never user) (69, 70), oral contraceptive use (user vs never user) (71), and number of previous childbirths (48, 72). In addition, we included assessment location to adjust for potential effects on the measurements (73, 74). Missing values ("*Not a Number (NaN)*," "*prefer not to answer*," "*do not know*"), were imputed for 71 participants using the SimpleImputer function from the scikit-learn Python library (75) (70 participants had one missing value, and one participant had three missing values). Additionally, model 3 was re-run while including all other markers as covariates in addition to age, to probe independent contributions of each baseline cardiometabolic marker. We also tested if the effects of BMI and WHR change on WMH volume (model 4) persisted when adjusting for baseline cardiometabolic markers, as well as change in systolic and diastolic BP in a subsample of participants who had BP data available at both baseline and timepoint 2 ($n = 8{,}101$).

2.6.2 Additional age adjustments

To evaluate the independence of the group status effect from age-related influences, we report supplementary results from models 1 and 2 both with and without age as a covariate. In addition, the models were repeated including both age and age^2 as covariates, to account for possible non-linear relationships between age and the dependent variables.

2.6.3 Exclusion of participants with values of cardiometabolic markers above healthy levels

To assess if results were consistent when utilising stricter exclusion criteria, we repeated the analyses using a subsample excluding participants whose values for the cardiometabolic markers exceeded established healthy thresholds, as defined by the World Health Organisation (WHO) and the National Cholesterol Education Program Expert Panel (76–80). This included values for BMI above 30, WHR above 0.85, HDL below 1.03 mmol/L, LDL above 4.13 mmol/L, triglycerides above 2.26 mmol/L, Hba1c levels above 48 mmol/mol, in addition to hypertension, determined manually using systolic and diastolic BP measurements with a threshold of 140/90, and a confirmed medical diagnosis of diabetes (see also Supplementary Table S2). 6,019 participants were excluded (3,575 for body anthropometrics, 3,584 for blood lipids, 3,502 for hypertension, and 269 for diabetes and HbA1c, with 48.9% of excluded participants having values above the thresholds for two or more variables). The final subsample consisted of 3,863 participants (n premenopausal = 1,974, n postmenopausal = 1,889).

2.6.4 Separating premenopausal females from menopause-transitioning females

Given the mean age at baseline (46.58 ± 3.77) and the mean assessment interval (8.93 ± 1.63) in the premenopausal group, we separated females in this group who were transitioning to menopause between timepoints from those who remained premenopausal. We classed participants as "transitioning" if their self-reported menopause status changed between baseline and timepoint 2 ("*Have you had your menopause (periods stopped)?*"). Since we did not have data on whether participants were perimenopausal or not, we use the term "transitioning" to describe participants changing from a "premenopausal" status to a postmenopausal one between timepoints. To assess whether this fine-grained group assignment could influence the results, we repeated the analyses testing for group differences of longitudinal changes in body anthropometrics (model 2) and associations with WMHs (model 4) using three groups: premenopausal ($n = 735$), transitioning ($n = 2{,}794$), and postmenopausal ($n = 6{,}353$).

3 Results

3.1 Group differences in baseline cardiometabolic markers

As shown in Table 2, postmenopausal females had significantly higher values for HDL, LDL, triglycerides, and HbA1c compared to premenopausal females, when adjusting for age. BMI, WHR, systolic BP, and diastolic BP did not show significant group differences.

3.2 Longitudinal changes in body anthropometrics by menopause status

Figure 1 shows mean BMI and WHR plotted at both timepoints for each menopause status group. We found significant main effects of time for BMI and WHR, and significant interactions with menopause status group for BMI (Table 3). On average, age-

TABLE 2 Results from the weighted regression models measuring group differences in baseline cardiometabolic factors by menopause status (n premenopausal = 3,529, n postmenopausal = 6,353), with age included as a covariate in the models.

DV	β	SE	t	p-value	Adj. p-value
BMI	0.026	0.034	0.764	0.445	0.490
WHR	0.037	0.033	1.119	0.263	0.303
HDL	0.139	0.033	4.243	**<0.001**	**<0.001**
LDL	0.304	0.032	9.641	**<0.001**	**<0.001**
Triglycerides	0.121	0.032	3.786	**<0.001**	**<0.001**
Systolic BP	-0.063	0.031	−2.014	**0.044**	0.056
Diastolic BP	0.044	0.034	1.298	0.194	0.231
HbA1c	0.239	0.032	7.470	**<0.001**	**<0.001**

Notes: The β values indicate the estimated group difference, with premenopausal status used as the reference group. Adjusted p-values represent FDR-corrected values. Group differences with p–values < 0.05 are marked in bold. DV, dependent variable; SE, standard error; BMI, body mass index; WHR, waist-to-hip ratio; HDL, high density lipoprotein; LDL, low density lipoprotein; BP, blood pressure; HbA1c, glycated haemoglobin.

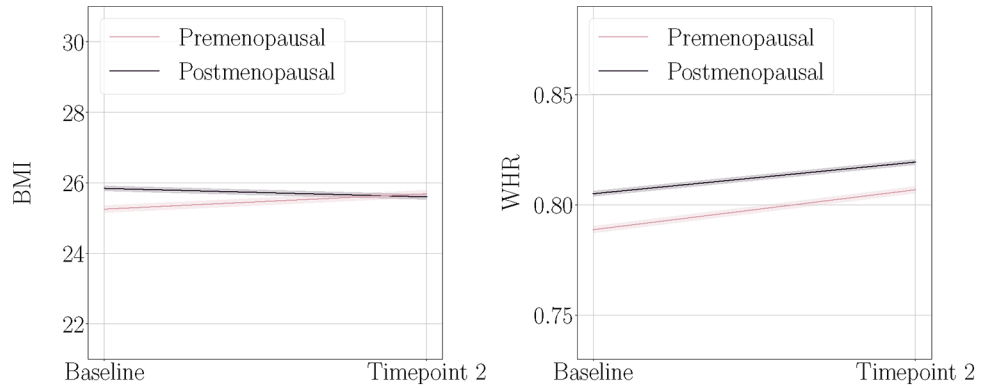

FIGURE 1
Body mass index (BMI) and waist-to-hip ratio (WHR) at baseline and timepoint 2, plotted separately for the premenopausal and postmenopausal groups. The shaded bands indicate 95% confidence intervals. Note that these plots illustrate the raw mean values and are not adjusted for age.

adjusted BMI increased over time in the premenopausal group, while the postmenopausal group showed a decrease; however with small changes at group level. WHR increased on average in both groups over time. To interpret the WHR results in more detail, we ran exploratory analyses utilising waist circumference (WC) and hip circumference (HC) measures in each of the groups (Supplementary section 5). The results showed that premenopausal females had a steeper increase of WC compared to the postmenopausal group, while postmenopausal females had a steeper decrease of HC compared to the premenopausal group.

3.3 Associations between baseline cardiometabolic markers and WMH volume

All baseline cardiometabolic markers except LDL were significantly associated with WMH volume at timepoint 2. Figure 2 displays the associations between baseline cardiometabolic markers and WMH volume. Full results are provided in Table 4.

3.4 Associations between BMI and WHR changes and WMH volume

As shown in Table 5, a greater increase of BMI and WHR between timepoints was significantly related to higher WMH volume at timepoint 2. Figure 3 displays the associations between BMI and WHR changes and WMH volume.

TABLE 3 Results from the mixed linear models for BMI (body mass index) and WHR (waist-to-hip ratio).

DV	Term	β	*SE*	*z*	*p*-value	Adj. *p*-value
BMI	TP	0.048	0.012	4.00	**<0.001**	**<0.001**
	TP × MP status	−0.075	0.015	−5.08	**<0.001**	**<0.001**
WHR	TP	0.133	0.012	11.33	**<0.001**	**<0.001**
	TP × MP status	−0.025	0.015	−1.73	0.083	0.102

Notes: Adjusted *p*-values represent FDR-corrected values. Associations with *p*−values < 0.05 are marked in bold. DV, dependent variable; SE, standard error; TP, timepoint (baseline and timepoint 2); MP status, menopause status.

3.5 Sensitivity analyses

When including the additional covariates specified in (2.7), the results were highly consistent with our main results, as seen in Supplementary section 6.1 and 6.2 (Supplementary Tables S5 and S6, and S8–S13). When adjusting for all other cardiometabolic markers in each model, blood lipids and HbA1c no longer showed statistically significant associations with WMH volume (Supplementary Table S7). Similarly, when excluding participants whose values for the cardiometabolic markers exeeded

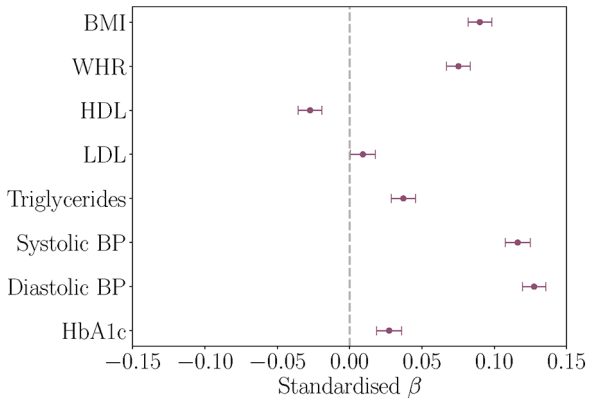

FIGURE 2
Associations between baseline cardiometabolic markers and white matter hyperintensity (WMH) volume at timepoint 2, with age and assessment interval included in the models. The figure shows the standardised β coefficients and their standard errors. Positive β values indicate relationships between higher marker levels and greater WMH volume. BMI, body mass index; WHR, waist-to-hip ratio; HDL, high density lipoprotein; LDL, low density lipoprotein; BP, blood pressure; HbA1c, glycated haemoglobin.

TABLE 4 Results from the linear regression models testing associations between baseline cardiometabolic markers and WMH (white matter hyperintensity) volume at timepoint 2, with age and assessment interval included in the models.

DV	Term	β	SE	t	p-value	Adj. p-value
WMH vol	BMI	0.091	0.008	11.15	**<0.001**	**<0.001**
	WHR	0.078	0.008	9.40	**<0.001**	**<0.001**
	HDL	−0.027	0.008	−3.24	**0.001**	**0.002**
	LDL	0.011	0.009	1.33	0.185	0.223
	Triglycerides	0.040	0.008	4.75	**<0.001**	**<0.001**
	Systolic BP	0.121	0.009	14.06	**<0.001**	**<0.001**
	Diastolic BP	0.128	0.008	15.76	**<0.001**	**<0.001**
	HbA1c	0.030	0.009	3.46	**0.001**	**0.001**

Notes: Adjusted p-values represent FDR-corrected values. Associations with p−values < 0.05 are marked in bold. DV, dependent variable; SE, standard error; BMI, body mass index; WHR, waist-to-hip ratio; HDL, high density lipoprotein; LDL, low density lipoprotein; BP, blood pressure; HbA1c, glycated haemoglobin.

established healthy thresholds, the associations of blood lipids and HbA1c with WMH volume were no longer statistically significant (Supplementary Table S16).

Supplementary section 6.5 shows the longitudinal changes of BMI and WHR in females who remained premenopausal at both timepoints, transitioned between timepoints, and were postmenopausal across timepoints. Premenopausal and transitioning females did not differ significantly in their BMI and WHR slopes over time (Supplementary Figure S6 and Table S19).

4 Discussion

In summary, this population-based study of 9,882 UK Biobank females showed that poorer cardiometabolic health, as indicated by higher baseline levels of blood lipids, BP, and HbA1c, as well as baseline levels and longitudinal increases of BMI and WHR, was associated with larger WMH volume measured up to a decade later. The findings highlight the importance of maintaining cardiometabolic health in females across midlife, during the menopause, and into postmenopausal years, to optimise future cerebrovascular health outcomes.

4.1 Group differences in baseline cardiometabolic markers

Postmenopausal females exhibited significantly higher levels of baseline HDL, LDL, triglycerides, and HbA1c compared to premenopausal females, after adjusting for the effects of age. These results align with prior studies reporting higher levels of blood lipids and blood glucose in post- compared to premenopausal females (3–5, 7, 81–83), and indicate that hormonal changes related to menopause may exacerbate cardiometabolic risks beyond those of advancing age.

However, the postmenopausal group also demonstrated higher levels of HDL, which is typically considered protective (50, 84, 85), and the groups did not differ in baseline BP and body anthropometrics when adjusting for the effects of age. While these results are in contrast to some studies showing group differences in BP (86) and body anthropometrics (4, 87), a population-based study of 908 females found no difference in BP between pre- and postmenopausal females (88), and another study of 3,064 females found no association between change in menopausal status and changes in body anthropometrics (89). Recent reviews and meta-analyses highlight conflicting findings on the links between menopause-related processes and BP (7, 90), body anthropometrics (6), and HDL levels (5, 91), noting that observed differences in some cardiometabolic risk factors may be largely driven by increasing age rather than menopause-specific processes (6, 30), and that discrepancies in methodology and design may also contribute to conflicting findings.

A key challenge in menopause research is to disentangle the effects of chronological vs endocrine ageing given their concurrent progression in females. Although methods such as age-based propensity matching can be useful [see e.g., (49)], they rely on sufficient overlap in age distributions between groups, which was minimal in our sample (Supplementary Figure S1). Given the complex interplay between endocrine and cardiometabolic processes (92, 93), longitudinal menopause research (e.g., (94)) is crucial to clarify how these processes interact in females over time. Moreover, future studies could aim for classifications of menopausal status based on hormonal or symptom profiles (95, 96), which may provide more accurate results than self-assessment (97).

TABLE 5 Results from the linear regression models testing associations between BMI (body mass index) or WHR (waist-to-hip ratio) changes and WMH (white matter hyperintensity) volume at timepoint 2, with age and assessment interval included in the models.

DV	Term	β	SE	t	p-value	Adj. p-value
WMH vol	BMI change	0.038	0.008	4.53	**<0.001**	**<0.001**
	WHR change	0.047	0.008	5.63	**<0.001**	**<0.001**

Notes: BMI and WHR changes were measured using timepoint 2 values residualised for baseline values (see Section 2.5.4). Adjusted p-values represent FDR-corrected values. Associations with p−values < 0.05 are marked in bold. DV, dependent variable; SE, standard error.

4.2 Group differences in longitudinal body anthropometric changes

The premenopausal group demonstrated an average increase in both BMI and WHR between baseline and the imaging timepoint. In this group, the observed change in WHR was driven by an increase in waist circumference (Supplementary Figure S4). Since 79.2% of

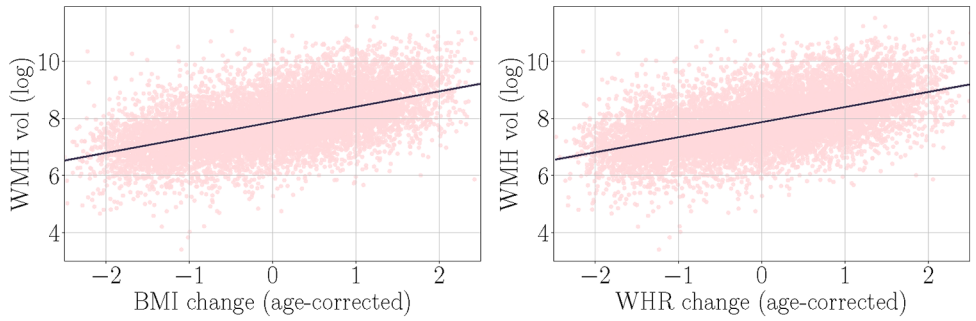

FIGURE 3
Associations between age-adjusted body mass index (BMI) and waist-to-hip ratio (WHR) changes (from baseline to timepoint 2) and white matter hyperintensity (WMH) volume. BMI and WHR changes were measured using timepoint 2 values residualised for baseline values (change independent of starting point, see section 2.5.4). The shaded bands indicate 95% confidence intervals.

the females in the premenopausal group underwent menopause between timepoints (see section 2.6.4), this finding aligns with previous literature highlighting a redistribution of adipose tissue towards the waist during the menopause transition (2–4, 6). For example, a longitudinal study in 1,246 females from the Study of Women's Health Across the Nation (SWAN) showed that the trajectory of fat mass doubled across menopausal years before decreasing two years post-menopause (98). In our study, however, changes in body anthropometrics did not differ between transitioning and premenopausal females (Supplementary section 6.5). Given the lower age limit of our sample (40 years), this could indicate overlapping changes in adipose tissue distribution between transitioning and pre- or perimenopausal females in this cohort.

The years prior to menopause are characterised by changing levels of reproductive hormones such as oestradiol (99–102), with perimenopause often highlighted as a cardiometabolic risk phase (3, 7, 92, 103). Although oestradiol assessments could potentially have clarified the changes observed in premenopausal and transitioning females, these measures were only available for a smaller subset of our sample from the baseline assessment. As previous studies highlight fluctuations and high variability of such reproductive hormones across early and late perimenopause (99, 104, 105), relying on a single baseline measure would prevent definitive conclusions. Given that the years surrounding menopause are characterised by distinct endocrine, menstrual, and ovarian markers that could influence cardiometabolic risk and brain health, future research should aim to include detailed data on hormone levels, menstrual cycle length and regularity, and occurrence of symptoms, in line with criteria established at the Stages of Reproductive Aging Workshop (STRAW) (106).

Importantly, our results might also reflect influences of factors beyond menopause, such as genetic predisposition for cardiometabolic disease (107–109) or lifestyle behaviours in early adulthood and midlife (110, 111). For future studies, it will be crucial to distinguish oestradiol-related effects from other contributing factors to enhance our understanding of cardiometabolic health trajectories in females across menopausal years.

In the postmenopausal group, we found an average decline of BMI, in addition to an increase in WHR that was driven by decreasing hip circumference (Supplementary Figure S4). Lower BMI and sarcopenia (muscle loss) are commonly observed in ageing (112–115), but have also been linked to lower oestradiol levels during menopause (30, 116, 117). Although the group-level changes in body anthropometrics were in general small, these findings could be indicative of processes such as sarcopenia among the postmenopausal participants. Overall, our longitudinal results point to time-sensitive impacts on body anthropometrics in females, and highlight the complexity of the relationships between menopause, ageing, and changes in cardiometabolic factors.

4.3 Associations between markers of cardiometabolic health and WMH volume

Our results showed associations between markers of poor cardiometabolic health at baseline and greater WMH volume measured almost a decade later. This is in line with previous literature linking midlife cardiometabolic health to WMHs, highlighting the long-term implications of cardiometabolic risk factors on brain health (8, 31–41, 56, 118).

Higher systolic and diastolic BP showed prominent associations with larger WMH volume, and the associations persisted when adjusting for other cardiometabolic markers as well as excluding participants whose marker levels exceeded healthy thresholds. This finding corresponds to studies reporting stronger relationships between BP and WMHs compared to body anthropometrics, blood lipids, or HbA1c (119–121), particularly in females (9), and highlights the importance of monitoring and controlling midlife BP levels to protect against cerebrovascular decline (56, 122).

In addition to BP, greater baseline BMI and WHR, as well as increasing levels between timepoints, showed robust associations with larger WMH volume. Previous studies in females have shown associations between increasing BMI and cortical thinning (123, 124), as well as reductions total grey matter volume (125)

and hippocampal volume (126). To our knowledge, the current study is the first to support a link between longitudinal increases in body anthropometric measures and WMH volume in mid- to older-aged females. While a global measure of total WMH volume was used in the current study, future research could aim to investigate periventricular and deep WMHs (127–129) to elucidate their distinct associations with changes in cardiometabolic risk factors [see e.g., (34, 130)], as well as menopause-related processes and vasomotor symptoms (20, 131).

Furthermore, our study measured changes in BMI and WHR independent of starting point, and prospective studies might benefit from characterising differences in trajectories based on initial level (126, 132). While this approach could help to identify individuals at high risk for deteriorating cardiometabolic and brain health, it is important to note that research indicates influences of genetics (133) and early life factors (134) on individual variation in WMHs, as well as age-sensitive variations in body-brain relationships across the lifespan (42, 43). Hence, multifactorial studies with longitudinal designs are needed to map the factors linked to cardiometabolic and microvascular risk across adulthood, the menopause transition, and into older age.

Finally, the demographic context of our study should be taken into account. The UK Biobank cohort is highly homogeneous in terms of "WEIRD" criteria (from Western, educated, industrialised, rich, and democratic societies (135)), and additionally characterized by a "healthy volunteer effect" (136). Consequently, our results offer valuable insights but may not necessarily generalize to other samples. Yet, our study contributes to a critical area in public health, given the rising prevalence of chronic, non-communicable diseases such as cardiometabolic disease and neurodegenerative conditions (137, 138). Despite known sex differences in the aetiology, prevalence, and outcomes of these diseases (139–142), there remains a severe lack of research on female-specific factors and risks (143–145). While our study highlights distinct cardiometabolic patterns in pre- and postmenopausal females and relationships of these with cerebrovascular outcomes, it also underscores the critical need for detailed, longitudinal studies encompassing both midlife and older age in females. Future research should assess the interplay between cardiometabolic health, female endocrine processes, and brain outcomes to lay the groundwork for effective health interventions.

5 Conclusion

This population-based study demonstrates that markers of cardiometabolic health in middle- and older aged females are linked to future cerebrovascular health outcomes. The results highlight the importance of maintaining cardiometabolic health in females across menopausal years, and emphasises the critical need for longitudinal studies addressing cardiometabolic risk and brain health in females throughout adulthood, menopausal years, and into older age.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.ukbiobank.ac.uk/.

Ethics statement

The studies involving humans were approved by National Health Service National Research Ethics Service (ref 11/NW/0382). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LSS: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization; SS: Writing – review & editing, Writing – original draft; AA: Writing – review & editing, Methodology; CB: Writing – review & editing, Methodology; AC: Writing – review & editing; IV: Writing – review & editing; DB: Writing – review & editing; TPG: Writing – review & editing; AT: Writing – review & editing; SS: Writing – review & editing; KPE: Methodology, Project administration, Writing – review & editing; OAA: Methodology, Project administration, Resources, Writing – review & editing; BD: Resources, Supervision, Writing – review & editing; LTW: Methodology, Project administration, Resources, Supervision, Writing – review & editing; AMGL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer FB declared a shared affiliation with the author BD to the handling editor at the time of review.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2023.1320640/full#supplementary-material. Scripts for running the main and supplementary analyses are available at https://osf.io/4ub83/

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Women and the risk of Alzheimer's disease

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Purpose of the review: This review will elucidate reasons to explain why women may be at greater risk for Alzheimer's disease.
Recent findings: Potential mechanisms to explain sex and gender differences in Alzheimer dementia include: differences in risk associated with the apolipoprotein E 4 allele; telomere shortening- which is linked with neurodegeneration, higher incidence of depression and insomnia in women as psychiatric co-morbidities which are linked with an increased Alzheimer disease risk, disorders of pregnancy including gestational hypertension and preeclampsia and psychosocial factors such as educational level which may contribute to differences in cognitive reserve.
Summary: The sex and gender differences in Alzheimer's disease can be explained by biological and psychosocial factors.

KEYWORDS

women, Alzheimer's disease—AD, sex, risk factor, gender

Introduction

Alzheimer's disease (AD) is the most common cause of dementia affecting more than 5.5 million Americans, two thirds of whom are women (1). Age is a known risk factor for development of AD, with the risk doubling for each decade after age 60. It is a well-known fact that women live longer, thereby explaining the difference in prevalence of the disease. Incidence studies examining sex differences in AD are equivocal. A majority of studies do not demonstrate any sex differences in the incidence of AD. See Table 1 (2–8) A meta-analysis of seven population -based studies looking at the incidence of AD found that the increase in the incidence rate slows after age 85. In contrast to this age effect, the meta-analysis showed a significant effect of sex, where the odds ratio of women developing AD compared to men was 1.56 (9). The Framingham study suggests that the difference in disease prevalence is due to a "survivor bias", as men who survive beyond age 65 may have lower cardiovascular risk factors which may explain the lower risk of dementia compared to women after the age of 80 years (10).

There are multiple potential biological mechanisms that may explain the sex and gender differences in AD. These include differences in genetic risk, response to aging, hormonal effects, psychiatric and pregnancy co-morbidities as well as lifestyle/psychosocial factors effecting cognitive reserve. This review will explore these mechanisms.

Apolipoprotein E4-genetic risk

The apolipoprotein E4 (APOE4) allele is the most potent genetic risk factor for late onset sporadic AD. The APOE4 allele generates a dose dependent risk of developing AD, where patients with the E4/E4 genotype have an increased risk of AD compared to the E4/E3 genotype (11). The apolipoprotein E (APOE) protein is widely distributed throughout the

TABLE 1 Summary of studies 1975–2013.

Study location, type	Years	Incidence rates to develop AD women/men
Rochester, MN; Retrospective	1975–1984	Same
Framingham, MA; Prospective	1976–1978 to 1984–1985	Same
Rural area of southwestern Pennsylvania; Prospective	1987–1989 to 1998	Same
Baltimore, MD Prospective	1/1985–5/1998	Insignificant trend towards women having higher incidence rates
East Boston, MA Prospective	1982–12/1992	Same
Seattle, WA Prospective	1994–96 to 1996–98	Same
Cache County, UT Prospective	1995–96 to 1998–99	Greater incidence in women than in men after age 85.
England, Wales- 2 studies Prospective	Study 1 1990–93 to 1993–95 Study 2 2008–11 to 2011–13	Study 1-Women had lower incidence than men Study 2 - Same

human body. In the brain, astrocytes primarily produce APOE (12). The APOE protein in AD plays an important role in amyloid-beta protein transcription, production, aggregation and clearance (13).

The risk of developing AD related to the APOE4 allele effects both sexes equally. However, women who carry the APOE4 allele are more likely to develop mild cognitive impairment (MCI) than men. In addition, among patients with MCI, women with either the *APOE3/3* or *APOE3/4* genotypes, are more likely to develop AD compared to men (14). In a meta-analysis of 27 studies with 58,000 participants, looking at patients with 1 copy of APOE4 allele, women were at a fourfold increased risk to develop AD at younger ages, 65–75 years (15). Further, women carriers had increased total tau in cerebrospinal fluid, a biomarker in AD indicative of neuronal degeneration (16). However, these studies may be confounded by the fact that they did not control for educational level. A study which looked at the longitudinal rates of change from baseline in 398 MCI patients showed women with MCI had greater rates of cognitive and functional progression than men. The effect was greater in APOE4 carriers. In this study educational attainment was statistically greater in men, but the difference was small (17). Available data suggests that the APOE4 may modulate the risk of AD in a sex specific manner.

Telomere shortening and aging

Telomeres are the DNA structures that cap the ends of chromosomes. They are important to protect chromosomes from degradation. Telomere shortening has been associated with limited stem cell function, regeneration and organ maintenance in aging. The enzyme telomerase offsets this reaction by adding repeat telomeres to the terminal DNA. A reduced telomere length is associated with AD especially in females (18). Evidence demonstrates that APOE4 carriers have shorter leukocyte telomere lengths compared to noncarriers (19). This supports the idea that the APOE4 carriers undergo premature aging.

Telomere length demonstrate significant sex differences. In adulthood, women have significantly longer telomere length than men of the same age and this effect appears to be driven by estrogen. Estrogen both increases telomerase activity and decreases oxidative stress (20). In an interesting study, conducted over two years, healthy postmenopausal women who were APOE4 carriers showed significant leucocyte telomere shortening compared to noncarriers. Further the APOE4 carriers who remained on hormonal replacement therapy did not show telomere attrition and this effect was not seen in the noncarriers. Thus, suggesting that hormonal therapy might modulate AD risk for those who are vulnerable (21). Another explanation for this difference may be related to sex differences in educational attainment as this appears to have a protective effect against telomere shortening (22).

Hormonal effects

Initial studies from Cache county Utah supported the idea that there may be a "window of opportunity" for hormonal therapy on cognition. In a population- based study of over 2,000 nondemented women over age 65 (when the covariates of lower education, depression, and *APOE* ∈4 status were controlled) lifetime hormonal replacement therapy (HRT) use was associated with a better baseline mini-mental status exam scores and a slower rate of cognitive decline (23). In another prospective study of 1,889 women from Cache county Utah to look at incidence of dementia those who used HRT had a reduced risk of AD compared with non-HRT users (adjusted HR, 0.59; 95% CI, 0.36–0.96). Risk varied with duration of HRT use, such that the sex-specific increase for women disappeared with more than 10 years of use (24). It appears from these studies that the beneficial effect of HRT is dependent on the timing. However, the generalizability of these studies is unclear as both were performed in a single county and educational and socioeconomic factors may have influenced those who could participate.

In 2003, a large randomized controlled trial, The Women's Health Initiative Memory study (WHIMS) showed that postmenopausal women, ages 65–79, who had not had a hysterectomy, when treated with estrogen and progesterone compared to controls had a doubled risk of dementia. The increased risk of dementia in women treated with hormonal therapy would result in 23 new cases of dementia per 10,000 women/year (25). This well-designed trial clearly demonstrated the negative effects of postmenopausal hormone replacement on cognition.

There have been mixed results in studies to see if there is indeed a therapeutic window for HRT. A prospective cohort study showed that women who used any type of HRT within 5 years of menopause had a 30% less risk of AD. This benefit was also realized in women who used HRT more than 10 years after menopause (26). A 20-year prospective cohort study from Finland following women ages 47–56 did not provide strong evidence that postmenopausal hormone replacement therapy prevents AD. Although, a protective association between long-term (>10 years) self-reported use of HT and AD was observed. This finding indirectly supports the effectiveness of HT if started in the early postmenopausal period (26).

A recent retrospective population- based study demonstrated that women with 5 or more pregnancies had 1.7-fold increased risk of AD compared with women with 1–4 completed pregnancies. In addition, women who had incomplete pregnancies showed half the level of AD risk compared with those who never experienced an incomplete pregnancy (27). Whether these findings are related to hormonal changes, differences in medical comorbidities or education/ socioeconomic status remains to be seen.

Pregnancy complications

Retrospective studies have shown that women who had preeclampsia have higher stroke risks even decades later. See Table 2 Pregnancy related complications unmasks those women at risk for cerebrovascular complications. The increased risk of stroke put these women at risk for vascular dementia and increase risks of cognitive decline. Another study documented those women who had hypertensive disorders of pregnancy had an increased risk of cognitive problems primarily associated with poorer working memory and verbal learning 15 years after pregnancy (28).

Vascular dementia can be caused by either a strategically placed stroke or from small vessel disease. The typical cognitive problems found in patients with vascular dementia are slowed processing speed, impairments in executive function and visual memory, whereas verbal learning is not as affected. This is different from the results of the hypertensive disorder of pregnancy study which showed worsened working memory and verbal learning. Problems which are more in those with seen in with AD. Potentially pregnancy complications may impact cognition by contributing to a mixed dementia. Mixed dementia from both AD and vascular causes is common with small vessel disease of different types underpinning both etiologies (29).

TABLE 2 Preeclampsia and stroke in later life.

Study date	Total no. of subjects	Design	OR-95%CI
Lykke-2009	782,287	Retrospective cohort	1.36–1.66 (1.29–2.14)
Funai-2005	37,061	Retrospective cohort	3.07 (2.18–4.33)
Kestenbaum-2003	124,141	Case control study	2.53 (1.70–3.77)
Irgens-2001	626.272	Retrospective cohort	Preterm preeclampsia 5.0 (2.09–12.35)

Psychiatric co-morbidities-depression and insomnia

Depression increases the risk of AD and women have twice the risk of depression compared to men (30). There is evidence that early life depression can act as a risk factor for later life dementia, and that depression later in life may be a prodromal feature to dementia (31). A meta-analysis of available studies showed a positive correlation between the length of time after a diagnosis of depression and the risk of developing AD, suggesting that depression is a risk factor for AD (30).

In the WHIMS study women with depression were almost twice as likely to develop MCI and AD (32). The risk of developing AD appears to be related to both the severity and timing of the depression. For example, one study demonstrated that patients followed for a mean of 27 months with MCI and active depression within the last 2 years had a 41.7% conversion to AD as compared to 31.6% conversion to AD in patients with a more remote history of depression (33).

Insomnia may also be a risk factor for accelerated cognitive decline and AD. Cognitive ability is sleep dependent, especially memory consolidation. Several longitudinal studies confirmed that patients with insomnia were twice as likely to have cognitive decline or a diagnosis of AD (34, 35). Women have a higher prevalence of insomnia. It is not clear if insomnia is an independent risk factor for AD or linked due to its interplay with stress and depression.

Educational status-cognitive reserve

Lower education levels and occupational attainment pose similar risk for AD in both women and men. Women, older than 65 years of age, have had fewer opportunities for higher education and professional achievement, directly affecting their cognitive resilience, thus putting them at risk. Recent population trends indicate that the education gap between women and men is in decline with more women in the workplace. In addition, women are achieving both greater professional success and financial status (36).

Conclusions

Women bear a larger burden of the Alzheimer's disease epidemic. The difference in risks for this disorder can be explained by sex and gender specific variances in genetics, response to aging, hormonal influences, psychiatric conditions as well as psychosocial factors.

Take Home Points

1. Alzheimer's disease is more prevalent in women
2. The risks associated with the APOE allele are stronger in women
3. There are sex differences in how telomeres respond to aging and hormonal changes

4. There may be a beneficial window where estrogen exposure improves cognition for women at risk for AD
5. Hypertensive disorders of pregnancy can contribute to risks of dementia
6. Gender differences in psychiatric co-morbidities especially depression as well as educational status may also impact AD risk

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Publisher's note

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Understanding gender inequity in brain health outcomes: missed stroke as a case study for intersectionality

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Recent attention into sex and gender-based inequities surrounding outcomes for brain health disorders has generated momentum toward addressing what has been called the "brain health gap." Importantly though, "women" are not uniform demographic group. In this perspective piece, we discuss misdiagnosis in stroke as an aspect of access and quality of care within brain health. Drawing on narrative data from a mixed methods study of young stroke survivors we suggest that while missed stroke isn't only an issue of gender, if we are going to understand gender-based gaps in access and navigation through stroke care, we have to understand how intersections of gender with age, ethnoracial identity, nationality, language, (dis)ability, and other aspects of social identity come together to create affordances as well as biases that contribute to stroke outcomes.

KEYWORDS

stroke, gender, intersectionality, misdiagnosis, brain health gap, implicit bias

Introduction

> The one thing I keep going back to is the night of the stroke, in the first hospital, the nurses clearly didn't recognize the symptoms. Or, they didn't recognize the symptoms in a younger female. That, to me, is intensely problematic for very obvious reasons. The whole experience was so bad that I was actually encouraged by one of my neurologists in [that city] to launch a complaint.
>
> (Ms. G, Y-Stroke Needs Participant)

Recent attention into sex and gender-based inequities surrounding outcomes for brain health[1] disorders has generated momentum toward addressing what has been called the

[1]We use the term "brain health disorders" and "brain health gap" in reference to a contemporary discourse around neurological experiences and medical care, but do so with the understanding that *health* is a nebulous and contested concept that often embeds normative assumptions about bodied and minded experiences that are themselves not neutral or based in matters of fact. See, for

"brain health gap". From translational research to health policy and structural change, disparities in understanding the prevalence, detection, and treatment of many forms of brain-related illness that disproportionately impact women have received increased attention (1). Mechanisms for changing these disparities are increasingly called in (2–4). Importantly though, "women" are not uniform demographic group. Various scholarly fields—notably within Black Feminist and critical race scholarship, and more recently what has been termed "crip of colour" critiques from within disability studies[2]—have highlighted the ways in which the intersections *and* interactions of racism, patriarchy, ableism and heteronormativity (amongst other dimensions of social power) are crucial for understanding and addressing health-related inequity (5, 6).

Depending on how they are positioned by virtue of their social identities, some individuals struggle with ableism and expectations of normative embodiment. Navigating medical care can often mean navigating medicalization and ableist assumptions that pathologize diversity in lived experience (7). For others, though, just getting a foot in the door—accessing care *at all*—becomes the issue (6, 8). When lived experiences are shaped by intersections of social power and minoritized group memberships, health care may be withheld, withdrawn, or offered on terms that are low quality or compromise one's values and integrity (9). Understanding how these different dynamics contribute to gender inequity in brain health—the brain health gap—requires an approach oriented within intersectionality. Inequities in relation to access and quality of care within brain health exist not only along lines of gender: we need to consider gender as imbricated with race, ethnicity, sexuality, economic background, (dis)ability, age, geography, and religion, as well as other sources of discrimination and subordination.

Intersectionality is both a theoretical framework and a research praxis that understands inequity in relation to the dynamics of difference and sameness, which impact people by virtue of their membership in social groups; it is an approach explicitly oriented toward social justice (5, 10, 11). An intersectional analysis offers a way of thinking about how social axes of power impact individuals vis a vis their multiple social identities (12, 13). Within the healthcare system, these overlapping (and often mutually constitutive) systems of disadvantage and/or privilege shape experiences of care. In the context of stroke diagnosis and post-stroke care, these overlapping identities can result in clear markers of advantage for some, while manifesting disparities in outcome due to bias and structural forms of disadvantage for others (14).

Drawing on our own mixed-methods research exploring the care needs of young stroke survivors (*Y-Stoke Needs* study; funded by the Canadian Institutes of Health Research and approved by University Health Network research ethics board), we turn to the narrative of Ms. G: a woman in her early forties with a missed diagnosis of stroke. Ms. G's symptoms were ignored or challenged by medical professionals because she did not fit the template of who a stroke patient was and because some aspects of her identity delimited the extent to which her testimony about her symptoms was taken as credible. And yet, Ms. G's social position was also marked, at least in some ways, by privilege. Her story provides a foundation for helping us to think about the complexities of the brain health gap in stroke.

More women than men suffer cerebrovascular accidents (CVAs) and women's outcomes are often worse—they are treated less aggressively for primary and secondary prevention; they are more likely to have lower quality of life post-stroke as well as higher prevalence of post stroke psychiatric comorbidities (15–17). But as we argue, we need to think intersectionally to understand the ways in which nuances, contexts, and multi-level factors come together to shape these broad-based inequity findings. Missed stroke isn't *only* an issue of gender—if we are going to understand gender-based gaps in access and navigation through stroke care, we have to understand how intersections of gender with age, ethnoracial identity, nationality, language, (dis)ability, and other aspects of social identity come together to create affordances as well as biases that contribute to stroke outcomes.

The case

When our team met her, Ms. G was a single woman in her early forties, a well-educated scientist working in a provincial public service position. She had been away on a work trip when, three days into the trip, she experienced a sudden onset of gastrointestinal symptoms late one night. As she described to us, she realized something was "very wrong" when what seemed like typical nausea and vomiting was suddenly accompanied by a rapid and progressive loss of sensation and motor control in her right leg.

> The day of the stroke, I had felt off. Off, in the sense that I felt like maybe I was getting sick, that something was coming… I felt so rundown that I declined going out with [my colleagues] and I thought I would just have a quiet night. I continued to not feel terribly well throughout the course of the night and I ended up going to bed a little bit early, around 10:00. Then, I woke up at 11:00, with an intense need to vomit… Then, around 2:00, I started to realize that something was very, very wrong, because I had lost feeling in my right leg. It started as a tingle and then it progressed into full paralysis of my right leg… I was starting to suspect I was having a stroke, I ended up calling 911. I told the ambulance attendant that I couldn't move my right leg and we went to the hospital. That's where the story gets really bad. The

instance, *Against Health: How Health Became the New Morality*. Metzl and Kirkland, editors. NYU Press (2010).

[2]The concept of "crip" (invoked within the notion of "crip of colour critique") makes reference to an orientation in critical disability studies that attends to insights from queer theory, exploring how gender/sexuality norms intersect with social pressures and norms relating to ability. Crip-of-colour scholarship further layers intersections of critical race theory within this orientation.

> nurses that I was assigned did not believe me when I told them that I had lost feeling in my right leg. They thought that I was lying to them and were refusing care to me. (Ms. G)

Our team met Ms. G less than one year from her stroke and she was doing well, all things considered. She had access to rehabilitation, she was supported with workplace accommodations, she was managing mood and cognitive symptoms with multidisciplinary supports.

The *Y-Stroke Needs* study aims to understand the challenges facing young stroke survivors, from the onset of symptoms, through acute care and the rehabilitation process, to long-term survivorship (UHN REB #17-6092; all study participants provided written informed consent). Ms. G participated in the qualitative arm of the project, sharing with us her narrative of the experiences she had as she moved through the post-stroke pathways within the Canadian healthcare system. Even for as much as her outcomes were positive, overall, the experience of accessing stroke care had been marked by distress.

> At one point in time, I was so desperate for water, and I knew that the water fountain was directly next to my bay, I decided to try and walk there. Forgetting, of course, that my right leg was paralyzed. As soon as I tried to stand up, I hit the ground. That's when one of the nurses told me outright that I was lying, that she had seen me move my leg and since I had put myself onto the ground, I could get myself back up. So, I tried to do that, and I ended up falling backwards and dislocating my thumb. Which she then accused me of lying about. She told me my thumb was just double-jointed and that it could move back. I was in the ER of [the general hospital] from 4:00 in the morning until noon. At noon, I was transferred out to the designated stroke hospital in [that city's] system. (Ms. G)

Despite symptoms typical of public education campaigns and infographics on stroke (e.g. sudden onset of unilateral weakness), her symptoms were minimized, unrecognized, and mischaracterized, putting Ms. G well beyond the optimal window for acute stroke identification and initial management. The challenges and issues prompted by her experience are not simply related to a misdiagnosis through the inevitabilities of human error or the subtleties and evolution of clinical signs and symptoms.

Ms. G had articulated and displayed physical signs and symptoms of stroke: these were interpreted by healthcare providers through a lens that could not make sense of these *as* stroke symptoms, because of her intersecting social identities. A younger, single, white woman, her exam findings were read as anxiety at best and manipulation at worst—a throwback to categorizations of hysteria that continue to impact the uptake of women's embodied experiences in the healthcare system (18). The enduring legacy of hysteria as a label for women's health concerns highlights the persistent gender biases within the healthcare system. Relegating symptoms to historic stereotypes risks overlooking legitimate health issues, perpetuating a cycle of disbelief that can impact the quality and timeliness of care. Acknowledging this historical context is crucial for dismantling stereotypes and ensuring a more equitable and compassionate approach to women's health, rooted in evidence-based medicine and a genuine understanding of diverse experiences.

Epidemiology of misdiagnosis in stroke: a case for intersectionality

> I literally told the EMT who picked me up, and this is a quote, "it's like my brain is sending signals that my foot isn't responding to". And I don't know how that information didn't get to the nurses who were responsible for my care. It seems to me that was pretty self-explanatory what it meant. But I think the one thing, people really need to understand the signs of stroke in younger women. My nurses, I know I told you this, but they not only didn't believe me—they accused me of lying about my symptoms. And that, to me, is unconscionable. (Ms. G)

Like Ms. G, women who present with stroke are more likely to have their symptoms go unrecognized; variations exist in the timeframe at which women receive standardized and evidence-based care and the type of care offered compared to men, including being less likely to be seen by a stroke specialist or receive diagnostic testing (19, 20). The interplay between gender and adherence to guidelines is also rapidly evolving: in 2018, two-thirds of heart and stroke clinical research was reported to be based on symptoms in men; 28% of women received ECG within 10-min period in contrast to 38% of men; clot-dissolving therapy (within the recommended 30-min period) was offered to 32% of women in contrast to 59% of men (21). More recently though, we see significant geographic differences and a multiplicity of factors underlying in gender inequity in the detection of stroke (22) as well as increasing sex-based parity within time trends in endovascular therapy (23). Gender bias-based "knowledge gaps" (24) are variable in how they translate to clinical disparities in prevention, diagnosis, post-stroke care and secondary outcome within the dynamic relationships between age, gender, ethnoracial identity, language and nationality (25, 26).

Social ecological models of disparities relating to access to stroke care and functional outcomes from stroke are particularly demonstrative of the ways that gender, ethnoracial minoritization and class/socioeconomic status are mutually constitutive of increased barriers and worsened outcomes (27). Epidemiological data relating to inequity and health disparities in stroke are well-documented, but understanding underlying causes has been more lacking, often due to the complex and multi-level nature of the phenomena: intra- and interpersonal factors including implicit bias and stereotype threat; institutional and organizational factors such as the number of care transitions that take place in stroke pathways; multidirectional neighborhood and community factors that influence predisposing factors in addition to accessibility of care, referral pathways, and functional supports; and larger policies and practices that can embed structural forms of racism amongst other discriminatory practices in health settings (27).

> I had to wait until the ER doctor came to see me, which was, to the best of my recollection, was about 9:00 a.m. The ER doctor did a quick reactivity test on my foot, realized that there was absolutely no reaction and immediately sent me for a CT scan. That's when they found the two bleeds. He also attempted to push my thumb back into place, without anaesthetic, which caused me to scream very loudly. It was quite dislocated. So, I certainly hadn't made up that injury. To this day, I still don't have full functionality back in my thumb. (Ms. G)

While the interpersonal factors that Ms. G cogently described are notable within this particular case, we also have to consider how larger systems and structures facilitate (or alternatively can correct) implicit biases. It is inadequate to attend only to individual-level factors in understanding what hinders timely and accurate diagnosis and treatment. Her younger age and a combination of typical as well as "atypical" symptoms decreased attention to stroke as a possibility. Young people have higher occurrence of less typical stroke symptoms and greater heterogeneity in stroke etiology; this is especially true for women (28, 29). But rather than consider that age and gender might lead to the presence of less typical stroke symptoms, in this case the intersection (particularly with gender) contributed to the characterization that Ms. G was not straightforward or was mistaken in her depiction of these symptoms. This reflects how "typical" symptoms have been determined based on older (usually male) bodied experiences, which get set as the unmarked norm; it also reflects what Maya Dusenbery has termed the "trust gap" that operates in healthcare settings (24). The "trust gap" refers to a tendency to treat particular group members as less credible in their testimony or interpretation of their own experiences, contributing to a dismissal or minimization of symptoms, under-treatment, and misdiagnosis.

The "trust gap" is lockstep with knowledge gaps and can be understood as contributing to what has been termed *epistemic injustice*—a form of injustice in which particular group members are regarded as less credible or knowledgeable about their own situation due to their social position qua group member (30). Epistemic injustice exacerbates negative psychosocial impacts of medical experiences, affecting a person's sense of self, their ability to trust their own judgments, and their recovery process (31), while further contributing to asymmetries of knowledge/power within medical contexts (32).

> Once I was transferred to the designated stroke hospital, my care improved significantly… I was [also] in rehab for about a month… My stay [in rehab] was great, everyone there was fantastic… At the point when I was discharged, I was walking with a cane. Then, about a week after I was discharged, I was able to stop using the cane completely. At this point in time, my leg is completely recovered. I still have a little bit of the frozen arm thing happening. I can almost get my arm up, but not quite yet. But, it's improved quite a lot. The only other major effect that I'm feeling is a bit of short-term memory loss…
>
> I'd say, there needs to be more understanding, awareness and recognition of what stroke looks like in younger people. They let me sit in the ER department for five hours, without doing any sort of neurological assessment. Had I had a clot-based stroke, my outcome would be very different right now. I'm extremely lucky that it was a hemorrhagic stroke. (Ms. G)

Importantly, Ms. G *also* occupied social positions of privilege—white, fluent in the language, higher socioeconomic group, employed—and so she was also able to advocate for herself once out of the emergency area. Her experience of being misdiagnosed and experiencing the trust gap about her symptoms was certainly distressing but was not repeated in numerous other health contexts she interfaced with. It did not stop her from accessing further rehabilitation services. Care transitions are an identified area where stroke survivors from historically disadvantaged groups are likely to face challenges (33). Ms. G's social identities contributed to misdiagnosis, but they became assets as she transitioned out of the initial healthcare setting, reflecting the dynamic nature of intersectionality.

What does intersectional brain health look like?

Our discussion illuminates a number of different issues, if the "brain health gap" relating to stroke is going to be addressed (Figure 1). First, a more nuanced understanding of challenges entering stroke pathways is needed, including the ways that misdiagnosis in stroke among minoritized groups impacts downstream care. The field needs to move beyond incidence rates for discrete demographic groups and understand differences *within* groups are being mediated by aspects of identity that are impacted by structural disadvantage (26, 34). The tendency to misdiagnose a stroke does not necessarily stem from a lack of technological advancements or incompetency among healthcare professionals. Rather, it arises from a range of institutional and structural factors that may include implicit biases, knowledge gaps surrounding who is impacted by less typical stroke symptoms and in what ways, *why* certain symptoms are considered less typical, and the systemic propensity to overlook or downplay symptoms in marginalized groups. The ongoing disparities amongst minoritized groups in stroke reflect an urgent need for an awareness and understanding of how intersectionality impacts clinical acumen, differential diagnosis, and access to high quality care.

Second, understanding and addressing the broader impact of stroke on women, younger adults, and people racialized as minorities extend beyond the initial misdiagnosis challenge that intersectional frameworks can inform. Stroke survivors are confronted with a complex array of health outcomes impacting their physical well-being, mental health and cognition (14), which increase a person's interfacing with medical care and the need for care transitions. Barriers and facilitators of recovery need an intersectional framework for research and care delivery given that ethnoracial minoritization, gender, age, language, (dis)

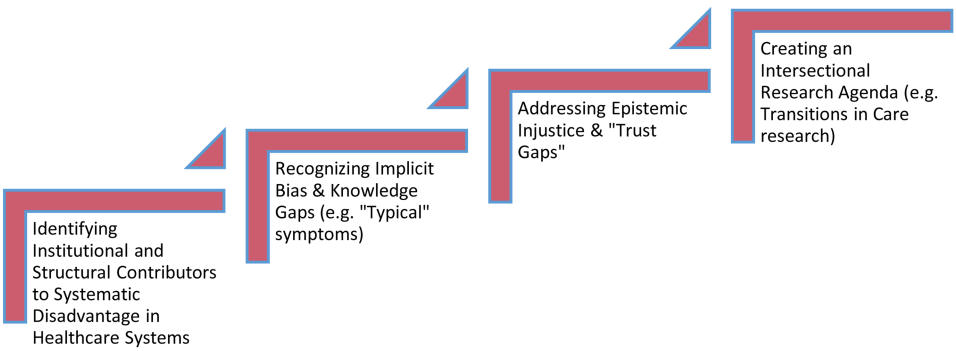

FIGURE 1
Agenda for intersectional practices in stroke care.

ability, geography and nationality are all implicated as meaningful and context dependent. To that end, it is relevant that Ms. G was seen in the Canadian healthcare context—a (mostly) universal health system where acute care has substantive financial investment and where there is a degree of geopolitical stability. Understanding that the Canadian context is but one location, which will shift the valence of different social identities and their impact on stroke care is also crucial for ensuring that findings from one time and space are not erroneously generalized.

Finally, intersectionality calls us in to social change: research that is merely descriptive will not shift us toward a more inclusive model of healthcare that can reduce the incidence of misdiagnosis, improve treatment outcomes, and improve quality of life from a biopsychosocial perspective. Biases that contribute to misdiagnosis, lack of evidence-based intervention, and worsened longer-term outcomes are often more impactful for stroke patients who are minoritized along multiple social axes of power (14). Given that age-related biases are mutually constitutive with other forms of biases that influence stroke care (including gender bias), we need to ensure that attention is not merely paid to interpersonal processes and knowledge gaps, but rather that the larger underlying structural causes of these knowledge gaps are addressed (e.g., long-standing research practices that marginalize research into the health of minoritized groups as "special interest" rather than good science). When we fail to identify and name structural injustices *as* structural (for instance, by focusing on the individual encounter), epistemic marginalization takes place that furthers worse outcomes and the systems that contribute to inequity (35–37).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University Health Network Research Ethics Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SB: Conceptualization, Methodology, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. SH: Data curation, Writing – original draft, Writing – review & editing. AP: Conceptualization, Funding acquisition, Project administration, Data acquisition, Investigation, Writing – review & editing, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Neurovascular coupling is altered in women who have a history of brain injury from intimate partner violence: a preliminary study

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Introduction: Intimate partner violence (IPV) is a global health crisis with 30% of women over the age of 15 experiencing at least one event in their lifetime. Brain injury (BI) due to head impacts and/or strangulation is a common but understudied part of this experience. Previous research has shown BI from other injury mechanisms can disrupt neurovascular coupling (NVC). To gain further insight into whether similar changes occur in this population, we assessed NVC responses in women with a history of IPV-BI.

Methods: NVC responses were measured for the middle and posterior cerebral arteries (MCA, PCA) using transcranial Doppler ultrasound while participants performed a complex visual search task. The lifetime history of previous exposure to IPV-BI was captured using the Brain Injury Severity Assessment (BISA) along with measures of post-traumatic stress disorder (PTSD), anxiety, depression, substance use, and demographic information. Initial analyses of NVC metrics were completed comparing participants who scored low vs. high on the BISA or did or did not experience non-fatal strangulation followed by a stepwise multiple regression to examine the impact of PTSD, anxiety, and depression on the relationship between the NVC metrics and IPV-BI.

Results: Baseline and peak cerebral blood velocity were higher and the percentage increase was lower in the PCA in the low compared to the high BISA group whereas no differences between the groups were apparent in the MCA. In addition, those participants who had been strangled had a lower initial slope and area under the curve in the PCA than those who had not experienced strangulation. Finally, the stepwise multiple regression demonstrated the percentage increase in the PCA was significantly related to the BISA score and both depression and anxiety significantly contributed to different components of the NVC response.

Abbreviations

AD, Alzheimer's disease; AUC_{30}, area under the curve to 30 s; BAI, Beck's Anxiety Inventory; BDI, Beck's Depression Inventory; BP, blood pressure; BI, brain injury; BISA, brain injury severity assessment; CBv, cerebral blood velocity; CTE, chronic traumatic encephalopathy; CAPS, clinician-administered PTSD scale; ECG, electrocardiogram; $P_{ET}CO_2$, end-tidal pressure of carbon dioxide; IPV, intimate partner violence; MAP, mean arterial pressure; MCA, middle cerebral artery; NVC, neurovascular coupling; NFS, non-fatal strangulation; PCA, posterior cerebral artery; PTSD, post-traumatic stress disorder; SRC, sport-related concussion; TCD, transcranial Doppler ultrasound; WEB, Women's Experiences with Battering Scale.

Conclusions: This preliminary study demonstrated that a lifetime history of IPV-BI leads to subtle but significant disruptions to NVC responses which are modulated by comorbid depression and anxiety. Future studies should examine cerebrovascular function at the acute and subacute stages after IPV episodes to shed additional light on this experience and its outcomes.

KEYWORDS

intimate partner violence, brain injury, strangulation, neurovascular coupling, cerebrovascular physiology, mental health

Introduction

Intimate partner violence (IPV) is an international public health crisis as, on average, 30% of women over the age of 15 report an incident of IPV in their lifetime (1–3). The prevalence of IPV varies extensively based on geographical region, with some areas of the world reporting rates as high as 66% (2). A systematic review by Stöckl *et al.* (2013) examining intimate partner homicide reported one in seven homicides are committed by an intimate partner and the proportion of women homicide victims killed by an intimate partner is six times higher than it is for men (4). In 2009, 335,697 Canadians experienced a total of 942,000 violent encounters at the hands of their intimate partner; the associated economic impact of this violence is estimated at $7.4 billion per year (5), with the COVID-19 pandemic unfortunately exacerbating this issue (6). Women who have experienced IPV commonly report injuries to the head, face and neck sustained during a violent event—Jackson *et al.* (2002) found 92% of women recruited from women's shelters or emergency rooms were hit in the head or face by their partner (7). Thus it stands to reason that a significant portion of this population are at risk of suffering a brain injury (BI) (8). Further, as many as 76% of women who have experienced an IPV event report experiencing non-fatal strangulation (NFS), a method of violence that can lead to unconsciousness within seconds and brain death within minutes and, for women surviving an IPV event, chronic symptoms including, but not limited to, depression, anxiety and posttraumatic stress disorder (PTSD) (9–11). Researchers have examined the incidence of IPV-BI and found it is especially prevalent in this population, as 35%–88% of women who have experienced IPV are diagnosed with a BI, and more than half of women who experience IPV-related injuries suffer multiple partner-related BIs (12–17). To put the endemic nature of this into perspective, this means up to 296,000 women suffer a BI at the hands of an intimate partner each year in Canada. This number does not reflect the true weight of this issue, as most women do not seek medical attention for abuse-related injuries (12).

Little is known about both the short- and long-term consequences of IPV-BI from both a physiological and psychological perspective. A BI results in tissue deformation and direct damage to vascular, neuronal and glial structures due to biomechanical forces (18). As a result, IPV survivors are subject to both acute and chronic mental and physical health consequences including PTSD, increased suicidality, anxiety, depression, decreased cognitive function, substance use and physical injury (12, 19–23). Despite the high incidence of IPV-BI, there has been relatively little quantitative analysis on the associations between the severity and frequency of BI and the resulting pathophysiological and psychopathological consequences. Indeed, the sequelae resulting from a single or multiple IPV-BI events may be compounded by the fact most women do not report their injuries for fear of retribution or because the woman does not recognize the BI (24).

Accurate identification of the presence and severity of BI is contingent on early screening and requires a multidisciplinary approach; however, current clinical exams used in the detection of BI rely heavily on reported symptoms during an interview (18). Missed diagnosis of BI may lead to the exacerbation of symptoms, prolonged neurological and physiological impairments, and a lengthened recovery period. The Brain Injury Severity Assessment (BISA) tool was created in 2003 and involves a semi-structured interview that identifies the history of non-partner and partner-related BI (12). It results in a score from 0 to 8 where lower scores (i.e., 0–4) represent little to no previous exposure to potential BIs resulting from episodes of IPV and higher scores (i.e., 5–8) represent significant exposure to IPV-BI with episodes happening more frequently, more recently, and with more severe consequences including potential loss of consciousness and post-traumatic amnesia. The BISA has been shown to be related to disruptions to neurocognitive function, white matter integrity, and functional connectivity (12, 25).

Finally, BIs experienced by women surviving IPV are associated with an increased risk of developing Alzheimer's disease (AD) and may have the potential to lead to chronic traumatic encephalopathy (CTE) analogous to that experienced by many former collision sport athletes (26, 27). Thus, a better understanding of the physiology surrounding IPV-BI is of vital importance to improving long-term health outcomes in this underserved population. It has been suggested alterations in cerebrovascular regulation induced by BI can lead to an increased risk of developing the cognitive impairment underlying dementia and AD later in life (28, 29). Hence, in the current study we examined cerebrovascular regulation in women who have experienced IPV-BI.

Transcranial Doppler ultrasound (TCD) has shown remarkable value in the assessment of multiple domains of cerebrovascular function, including elevations in cerebral blood velocity (CBv) due to increases in cerebral neuronal metabolism (activation of neural tissue), referred to as neurovascular coupling (NVC) (30,

31). In particular, NVC reflects the maintenance of appropriate levels of nutrient and oxygen supply to relevant brain regions during functional activation (30). Alterations to cerebral blood flow regulatory mechanisms are associated with hypertension and AD, and it has been postulated that NVC is useful in quantifying the degree of vascular and metabolic decoupling in these conditions (32–34). We have previously examined NVC metrics following acute sport-related concussion (SRC) and found altered CBv responses in athletes up to two weeks following injury compared to non-injured controls (35). Determining whether cerebral blood flow changes are the cause or consequence of alterations in functional activation following BI is challenging. Preclincial animal models offer perhaps the clearest insight into this issue and have shown both immediate effects of head impacts on neurovascular structure and function most likely due to cerebral vascular injury/disruption as well as mid- and long-term alterations in cerebral blood flow and brain activation that are interrelated and, therefore, difficult to disentangle [reviewed in (30)].

Previous work has shown that the cumulative effects of BI may make an individual more susceptible to subsequent injury, leading to lingering symptoms and a lengthier recovery period (36). As most women who have experienced IPV endure numerous events before seeking shelter, it is important to identify the presence and severity of symptoms and brain dysfunction to direct appropriate treatment and rehabilitation strategies. Assessment of NVC through TCD may provide further evidence for the challenges these individuals are working to overcome on a daily basis. No previous study has investigated the extent to which NVC metrics are altered in the context of IPV-BI, the influence on BI severity and occurrence of NFS on the magnitude of NVC alterations, and the prospective role of TCD in identifying the history, presence and severity of BI in this population. Thus, the objective of this study were to evaluate the effects of IPV-BI on NVC dynamics. It was hypothesized (i) NVC responses would be disrupted in women who have experienced IPV-BI, (ii) NFS would affect NVC responses above and beyond that due to head impacts alone; and (iii) comorbid factors (PTSD, depression, anxiety) would modulate these effects.

Materials and methods

Participants

The principal criterion for study inclusion was at least one reported incident of IPV. Participants were not excluded if they had experienced any form of BI outside the context of IPV. As such, 37 women were recruited from local community partner sites (demographic information can be found in Table 1). All aspects of the study were described to the women prior to written informed consent being provided, with all questions about the study being explained prior to participation. The study was approved by the Clinical Research Ethics Board at the University of British Columbia.

TABLE 1 Participant demographics and clinical characterisics ($N = 37$).

Characteristics	Mean ± SD or *n* (%)
Age, years	37.42 ± 8.49
Education, years	13.36 ± 2.11
Ethnicity, % (*n*)	
Caucasian	22 (59.45)
Indigenous	10 (27.03)
Other/Did not disclose	5 (13.51)
WEB, total score	47.47 ± 13.58
BISA, total score	3.70 ± 2.17
Time since last IPV-BI episode, months	18.39 ± 22.49
Duration of substance use, years	15.97 ± 9.84
CAPS, total score	177.67 ± 71.04
BAI, total score	23.45 ± 13.78
BDI, total score	22.91 ± 13.06
History of non-IPV-related BI, % (*n*)	
Yes	23 (62.2)
No	14 (37.8)

SD, standard deviation; BISA, Brain Injury Severity Assesment; WEB, Women's Experiences with Battering Scale; CAPS, Clinician Administered PTSD Scale for DSM-IV; BAI, Beck's Anxiety Inventory; BDI, Beck's Depression Inventory; IPV, Intimate partner violence; BI, brain injury.

All participants were tested over 2 sessions separated by 3–7 days. Psychopathological assessments and a brief demographic questionnaire were completed during the first session by the research coordinators (KEJ, KR) who are trained clinical social workers with experience working with women who have survived IPV. The assessments included indices of PTSD [Clinician-Administered PTSD Scale (CAPS)] (37), depression [Beck's Depression Inventory (BDI)] (38), anxiety [Beck's Anxiety Inventory (BAI)] (39), history of substance use [Initial Substance Use Scale (40)], history of previous abuse (Women's Experiences with Battering scale (WEB) (41), and the BISA. The second session consisted of laboratory assessments of cerebrovascular, sensorimotor, neurocognitive, and blood biomarker measures. The current paper focuses on the NVC aspect of cerebrovascular function. All women were familiarized to the testing procedures prior to participation and did not exercise or consume caffeine/alcohol 12 h prior to testing (42). Current symptom burden and other data were reported on a subset of this sample in a previous publication (17).

Transcranial Doppler ultrasound

The posterior cerebral artery (PCA) and middle cerebral artery (MCA) were insonated using two 2-MHz TCD probes (ST3; Spencer Technologies, Seattle, WA, USA) through the temporal acoustic window on the side of the head to record PCA and MCA velocity. The P-1 PCA and M-1 MCA segments were identified and the signals optimized corresponding to the depth of each vessel, velocity of blood flow and waveform produced (31, 43). Participants were fitted with a three-lead electrocardiogram (ECG). Blood pressure (BP) was measured using finger photoplethysmography with a brachial cuff to adjust for height differences between the finger and brachial artery

(Finometer PRO; Finapres Medical Systems, Amsterdam, Netherlands). End-tidal pressure of carbon dioxide ($P_{ET}CO_2$) was sampled with a mouthpiece and monitored with an inline gas analyzer (ML206; ADInstruments, Colorado Springs, CO, USA), calibrated with a known gas concentration prior to each collection. All data were time-aligned and collected at a sampling frequency of 1,000 Hz via an 8-channel PowerLab (ADInstruments) and stored for offline analysis using commercially available software including LabChart (ADInstruments) and Microsoft Excel (Microsoft Corporation; Redmond, WA, USA).

Experimental protocol

NVC metrics were quantified using a complex visual search task (Where's Waldo) that has been shown to elicit robust changes in PCA velocity (44, 45). Resting physiological data were recorded while sitting quietly for at least 4 min, while baseline CBv was quantified during a 2-min eyes open and a 2-min eyes closed period. Participants were seated in front of the screen (27" Apple iMac, Apple, Cupertino, California, USA) and completed 6–8 cycles of 20 s with their eyes closed followed by 40 s with their eyes open performing the visual search (46). Screen settings were consistent across all subjects. None of the screen parameters were altered between trials or between participants.

Data processing

Data processing was completed in the same manner as in previous studies from our group examining NVC coupling (44). Briefly, mean BP and CBv traces were calculated following extraction of beat-to-beat heart rate, peak systolic and end diastolic blood pressure, and peak systolic and end diastolic PCA velocity and MCA velocity using the R-R intervals from the electrocardiogram for gating. $P_{ET}C_{O2}$ was measured from extracted breath-to-breath peak expired carbon dioxide values. The resulting signals were visually inspected for artefacts or noise and corrected by cubic spline interpolation and downsampled to 10 Hz and subsequently filtered with a dual-pass, 4th order digital Butterworth filter with a 2 Hz cut-off frequency. Data from each trial were aligned to stimulus onset (eyes open), and then averaged to generate one response per subject for both the PCA velocity and MCA velocity. From these averaged responses the following dependent variables were measured: (i) area under the curve to 30 s (AUC_{30}); (ii) baseline CBv; (iii) initial slope of the CBv response; (iv) peak CBv (v) % increase in CBv; and (vi) time to peak CBv (35, 44).

Statistical analyses

Paired-sample *t*-tests were initially performed to determine potential differences in each dependent variable for groups of participants who scored low on the BISA (0–4) vs. high on the BISA (5–8) or did or did not experience strangulation. A stepwise multiple linear regression analysis was subsequently completed to determine the impact of the psychopathological factors (e.g., PTSD, anxiety, and depression) on the relationship between the dependent variables and the experiences of IPV-BI as assessed with the BISA. All statistical tests were performed using SPSS, version 27 (IBC Corporation, Armonk, New York, USA). Data are presented as mean ± standard deviation, with *a priori* significance set at $p = 0.05$.

Results

Table 1 outlines the demographic and clinical information of the participants. Participants were 37.42 ± 8.49 years old and had 13.36 ± 2.11 years of education. The majority (~59%) were Caucasian, and a significant minority (~27%) were Indigenous. Given ~6% of the population in this region of Canada is Indigenous, this finding is consistent with the overrepresentation of Indigenous women experiencing IPV (47). Most of the participants (~95%) scored above 20 on the WEB scale fulfilling the criteria for having experienced IPV. The average BISA score was 3.7 ± 2.17 with only 2 participants scoring 0 indicating that approximately 95% of participants experienced at least one episode of IPV resulting in signs and symptoms consistent with BI. The average time since the most recent IPV-BI episode was 18.39 ± 22.49 months with a very broad range (4–117 months) indicating all of the episodes were remote in time and none of the participants were in the acute/subacute stage after a potential BI. Finally, as a group, the participants had been engaged in substance use for 15.97 ± 9.84 years with the majority of them (~73%) limiting this use to alcohol and/or tobacco. With respect to psychopathology, consistent with previous work (12, 19–23), most of the participants (~93%) had elevated levels of PTSD and ~49% had moderate or severe levels of depression and anxiety. Finally, in addition to a history of IPV-BI, many of the participants (~62%) also had a history of one or more brain injuries from other causes.

Analysis of the NVC metrics demonstrated that they were normally distributed as determined by Shapiro–Wilk's test ($p > 0.05$). Initially, we were interested in whether there were any differences between participants who scored low on the BISA (0–4) ($n = 22$) and those who scored high on the BISA (5–8) ($n = 15$). Figure 1 shows the averaged NVC coupling responses in these two groups for the PCA velocity and MCA velocity and the associated time course of mean arterial pressure (MAP). The most obvious differences are in the NVC response in the PCA which shows a lower CBv at both baseline and peak for the high BISA group relative to the low BISA group. These differences were not apparent in the MCA. In addition, the magnitude of the response to opening the eyes and starting the visual search is substantially more muted overall in the MCA relative to the PCA consistent with previous work using this paragidm (35, 44). Finally, MAP did not vary during task performance relative to

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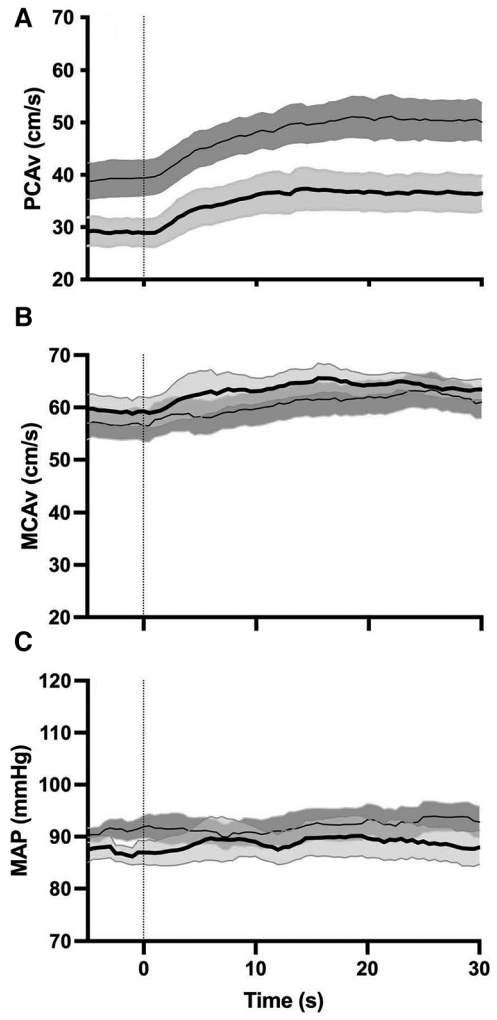

FIGURE 1
Group averages ($N = 37$ female IPV survivors) for NVC response in the PCA (A) and MCA (B) and corresponding MAP response (C) thin solid line and dark grey shaded region: average NVC response and intrasubject SEM for low BISA group. Thick solid line and light grey shaded region: average NVC response and intrasubject SEM for the high BISA group. Dashed vertical line: onset of opening eyes and visual search task.

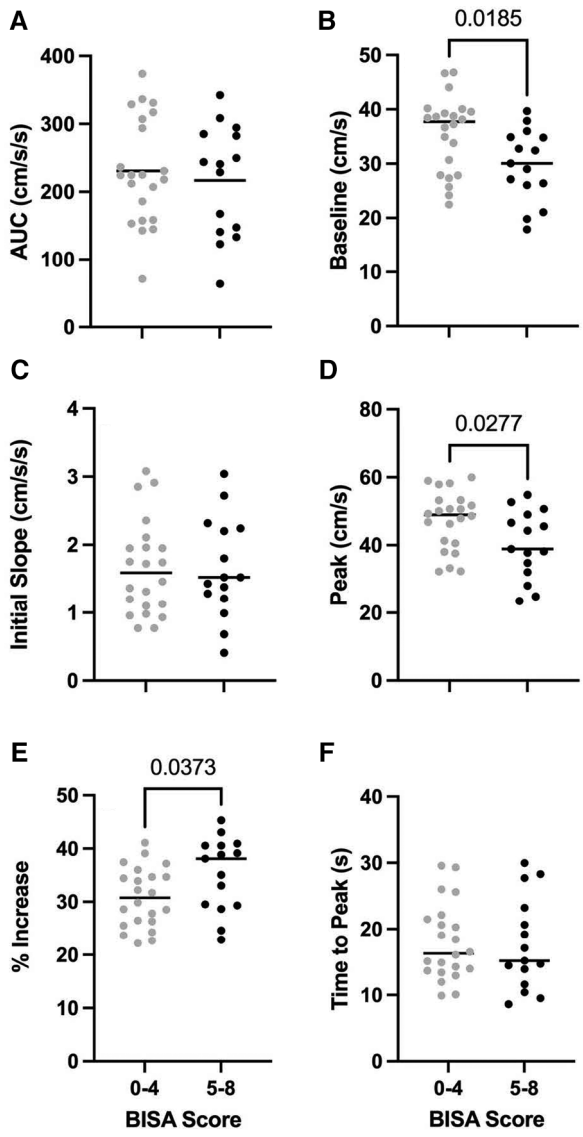

FIGURE 2
Group averages ($N = 37$ female IPV survivors) for PCA NVC metrics for AUC_{30} (A), baseline PCA velocity (B), initial slope (C), peak PCA velocity (D), % increase in PCA velocity (E), and time to peak PCA velocity (F) light grey circles: low BISA group. Black circles: high BISA group. Horizontal lines: median values for each group.

baseline indicating the changes in CBv were not affected by alterations in systemic blood pressure.

Figure 2 shows the NVC metrics for PCA velocity across the low and high BISA groups. Consistent with the observations from the average NVC responses in the PCA velocity shown in Figure 1, differences between the groups were observed for the baseline PCA velocity (t-test = 2.47, $p = 0.0185$) and the peak PCA velocity (t-test = 2.297, $p = 0.0277$). In addition, the % increase in PCA velocity was greater in the high BISA group than the low BISA group (t-test = 2.165, $p = 0.0373$). None of the other metrics were significantly different for PCA velcoity and there were no differences between the groups for the MCA velocity or for MAP.

Next we asked what impact NFS had on the NVC metrics in the PCA. Given that NFS tends to be associated with elevated BISA scores,[1] we restricted this analysis to a subset of participants who differed in whether they experienced NFS or not but overlapped in their scores on the BISA. The group that had not experienced NFS ($n = 8$) had an average BISA score of

[1]Adhikari SP, Maldonado-Rodriguez N, Daugherty JC, Molinares NQ, Wallace C, Smirl J, et al. A four country study of strangulation-related alterations in consciousness in women who have experienced intimate partner violence: co-occurrence with traumatic brain injuries and measures of psychological distress. (2023).

10.3389/fgwh.2024.1344880

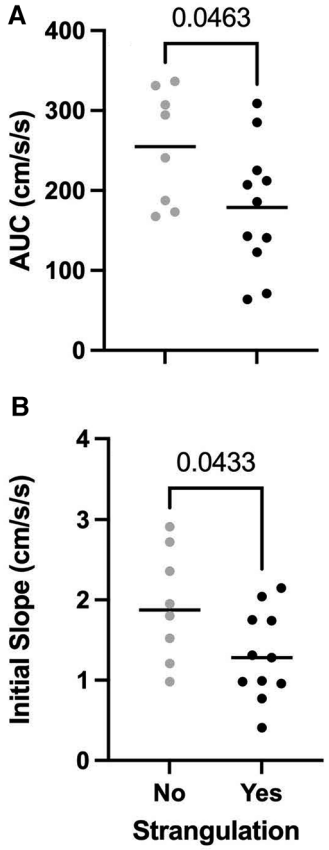

FIGURE 3
Group averages ($N = 37$ female IPV survivors) for PCA NVC metrics for AUC_{30} (**A**) and initial slope (**B**) for participants who did (black circles) or did not experience strangulation (light grey circles). Horizontal lines: median values for each group.

4 ± 2.12 whereas the group that had experienced NFS ($n = 11$) had an average BISA score of 4.18 ± 3.54 (t-test = 0.382, $p > 0.38$). Comparison of these two groups on the NVC metrics demonstrated those who had experienced NFS had smaller AUC_{30} (t-test = 2.149, $p = 0.0463$) and initial slope (t-test = 2.184, $p = 0.0433$) values (Figure 3). None of the other NVC metrics differed between the two groups.

Finally, in an effort to better understand the contributions of comorbid psychopathological and demographic factors in modulating the relationship between the NVC metrics and BISA scores we completed stepwise multiple linear regression analyses using 3 models (i) in Model 1, PTSD scores were included as a covariate; (ii) in Model 2, depression and anxiety scores were included as covariates; and (iii) in Model 3, demographic variables (age, ethnicity, education, substance use and non IPV-related BI) were included as covariates. Because the only differences in the preliminary analysis were observed for the PCA and not the MCA, we restricted the regression analysis to NVC metrics from the PCA. Moreover, the analysis was limited to a subset of the participants ($n = 24$) for whom we had complete datasets for all the variables of interest. Table 2 shows the results of this analysis. For Model 1, the only significant

TABLE 2 Stepwise multiple linear regression, models 1 and 2 for PCA ($N = 24$).

		R^2	B	β	Sig.	95% CI	
AUC (cm/s/s)							
Model 1	BISA	0.05	5.605	.160	.496	−11.227	22.436
	CAPS total		−.350	−.228	.335	−1.087	.387
Model 2	BISA	0.29	.076	.002	.991	−14.390	14.542
	BAI total		2.449	.432	.062	−.139	5.037
	BDI total		−4.148	−.568	.013*	−7.336	−.960
Baseline velocity (cm/s)							
Model 1	BISA	0.08	−.977	−.251	.281	−2.814	.860
	CAPS total		−.010	−.060	.793	−.091	.070
Model 2	BISA	0.14	−.938	−.241	.282	−2.706	.831
	BAI total		−.010	−.016	.946	−.327	.306
	BDI total		−.203	−.251	.289	−.593	.186
Initial Slope (cm/s/s)							
Model 1	BISA	0.09	.061	.193	.403	−.088	.210
	CAPS total		−.004	−.321	.170	−.011	.002
Model 2	BISA	0.32	.022	.068	.729	−.107	.151
	BAI total		.012	.227	.305	−.011	.035
	BDI total		−.041	−.619	.007*	−.069	−.013
Peak velocity (cm/s)							
Model 1	BISA	0.04	−.725	−.143	.545	−3.174	1.724
	CAPS total		−.019	−.086	.716	−.126	.088
Model 2	BISA	0.13	−.811	−.160	.474	−3.133	1.510
	BAI total		.059	.072	.770	−.356	.474
	BDI total		−.359	−.340	.159	−.870	.153
% Increase in velocity							
Model 1	BISA	0.20	1.652	.481	.033*	.144	3.160
	CAPS total		−.015	−.098	.646	−.081	.051
Model 2	BISA	0.42	1.164	.339	.074	−.125	2.452
	BAI total		.271	.487	.024*	.040	.501
	BDI total		−.295	−.413	.042*	−.579	−.011
Time to peak (s)							
Model 1	BISA	0.07	−.353	−.129	.578	−1.652	.946
	CAPS total		.034	.287	.222	−.022	.091
Model 2	BISA	0.06	−.239	−.087	.706	−1.540	1.063
	BAI total		.079	.179	.485	−.153	.312
	BDI total		.070	.122	.617	−.217	.357

Model, "Stepwise" method in SPSS Statistics; B, unstandardized regression coefficient; β, standardized regression coefficient; CI, confidence interval; LL, lower limit; UL, upper limit; R^2, coefficient of determination.
*$p < 0.05$.

effect was found for the % increase in PCA velocity which was associated with the BISA score. In particular, for every 1 unit change in the BISA score, the % increase in PCA velocity was increased by 1.65 units ($p = 0.03$) and this relationship was not modulated by the level of PTSD experienced by the participants. This result is consistent with the significant difference between the low and high BISA groups for this variable in the preliminary analysis (Figure 2E). By contrast, several significant effects were found for Model 2. In particular, although none of the NVC metrics were significantly affected by the BISA score in this model, AUC_{30}, initial slope, and % increase in PCA velcoity were all modulated by the levels of depression, whereas the % increase in PCA velcoity was further modulated by the levels of anxiety. Finally, for Model 3 (not shown), no significant effects were observed.

Discussion

This study provides the first examination of NVC characteristics in women who have experienced IPV-BI. We demonstrated (i) the NVC response is muted in women who have had more exposure to IPV-BI; (ii) experiencing NFS modulated the NVC response above and beyond that observed due to head impacts alone; and (iii) these effects were associated with the levels of comorbid depression and anxiety. The fact this aspect of cerebrovascular function is affected by the combination of the head impacts and NFS occurring during IPV as well as the psychological distress associated with this experience is consistent with previous work in this population (12, 13, 17, 25, 48) and reflects the complex interaction between the physical injuries and the mental health consequences resulting from episodes of IPV.

Previous work has demonstrated BI from other injury mechanisms (e.g., sport-related concussion, accidents, military) is associated with disruptions to the NVC response. Our group has shown that NVC metrics are elevated for up to two weeks following sport-related concussion compared to non-injured controls (35), as well as following a controlled bout of soccer heading (49), but not after a season of subconcussive head impacts in collision sport athletes (50), with this difference likely due to the potential protective effects associate with physical activity (51, 52). Interestingly, and more directly relevant to the current study, Roby and colleagues (53) reported that military personnel with a history of 3 or more previous BIs displayed a reduced NVC response compared to those with 1–2 previous BIs. Analogous results have recently been demonstrated using functional near infrared spectroscopy in retired collision sport athletes with a history of BI (54). Thus, the acute/subacute increase in the NVC response, likely linked to aspects of the neurometabolic cascade following BI (55), evolves over time into a muted NVC response in those who have been exposed to multiple BI events including, as shown by the results from the current study, women who have survived IPV-BI. Because of the nature of the Where's Waldo search task, we did not formally assess task performance. Indeed, most participants were unsuccessful in locating Waldo during the time spent searching. As a result, we were unable to determine if the reduced NVC response in those women with greater exposure to IPV-BI was associated with reduced task performance. Although the present study did not allow us to mechanistically examine the implications of this reduced NVC response, it suggests those women with greater exposure to IPV-BI would require a larger delivery of oxygen and nutrients to accomplish a task with the same degree of success as women with less exposure to IPV-BI (31, 56). Interestingly, this may explain why BI symptoms such as fatigue, low energy, drowsiness, and difficulty concentrating are amongst the most common and highly correlated with the BISA in women experiencing IPV-BI (17). Future studies should be designed to address the links between changes in NVC responses and task performance in participants who have experienced IPV-BI by using behavioural protocols in which response accuracy and timing can be measured.

Research directly examining cerebrovascular function in women who have experienced IPV is remarkably limited. However, there are studies which have indirectly shed light on this potential link. For example, it has been shown IPV leads to an increased risk of hypertension (57) and this relationship is exacerbated in those who have also suffered a BI (58). Moreover, comorbid mental health factors associated with IPV, including PTSD, depression, and anxiety, are also known to be associated with hypertension (59). Finally, hypertension has been linked to alterations in NVC (32, 33, 60). Thus, given these intersecting set of factors, it is perhaps not surprising we found the NVC response was disrupted in IPV-BI in the present study.

Finally, because IPV tends to be a cyclical/repetitive process, there is growing concern around the potential cumulative impact of repeated BIs or subconcussive blows to the head, face, and neck on longer term neurodegenerative disease processes including chronic traumatic encephalopathy (CTE) and AD and related dementias. Although there are case reports of putative CTE in survivors of IPV-BI (27, 61), a recent more in depth case series found consistent neuropathological evidence of white matter disruption consistent with BI as well as vascular damage but, importantly, no evidence meeting the criteria for CTE (62). Moreover, the women whose brains were included in this case series had complex histories of comorbid factors including substance use, epilepsy, cerebrovascular, and psychiatric conditions reinforcing the need to take such factors into account in research in this population. With respect to IPV-BI being a risk factor for AD, the evidence is still very much in its infancy. One study examined this association and found women who had a self/family-reported history of head trauma from IPV were more likely to have AD than those without such a history. Previous work has demonstrated that BI from other injury mechanisms is a known risk factor for AD (63). Importantly with respect to the findings from the current study, NVC responses have been shown to be altered in hypertension and AD (32–34). A potential mechanism for the altered NVC responses reported in these populations could be that associated with disruptions to the glymphatic system as it plays a vital role in the removal of waste/by-products from the NVC response and maintenance of the white matter within the brain (64). Furthermore, the links between NVC and removal of metabolic waste by the glymphatic system (65) have been shown to be disrupted in neurodegenerative pathology (66, 67) and are likely contributing to the challenges facing survivors of IPV (68, 69). Finally, there is evidence that BI-induced cerebrovascular dysregulation contributes to the cognitive impairments associated with AD (28, 29). Taken together, the results from the current study, when considered in the context of this previous work suggests that IPV-BI may increase the risk of developing AD, however, a more definitive answer awaits further more in depth epidemiology and neuropathological work. Over the longer term, the links between altered NVC responses and exposure to IPV-BI highlight the potential for pharmacological and non-pharmacological treatment targets designed to improve cerebral blood flow responses. Although such treatments are still under development, some preliminary

evidence suggests they may be effective following BI from other injury mechanisms (reviewed in 30) and, therefore, may be useful in the context of IPV-BI.

Limitations

The current study does have its limitations. First, the sample size is relatively small and, thus, we may lack the power needed to detect subtle but potentially important effects. Second, recruitment was limited to several key community organizations serving women who have experienced IPV. Because of this, the extent to which we can generalize our findings to the broader population experiencing IPV is limited. Third, there was wide variation in the time since the most recent IPV-BI episode potentially introducing substantial variability in our measures of NVC responses. Fourth, because we used a cross-sectional approach and the participants had numerous comorbid factors, we can not draw causal links between IPV-BI and the observed effects on NVC.

Conclusions

This study is the first to our knowledge to characterize a component of cerebrovascular function in women who have experienced IPV-BI. We demonstrated several important NVC metrics were affected by the extent of previous exposure to IPV-BI and associated NFS and these effects were modulated by the levels of depression and anxiety. Taken together, these results show cerebrovascular function is affected by a history of BI resulting from IPV. This indicates there are functional changes in the neurons of IPV survivors following BI, which reduces the efficiency of their brain metabolism during task performance. This key finding suggests this may place women who survive this experience at increased risk of developing longer-term neurodegenerative disorders.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Clinical Research Ethics Board, UBC. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CW: Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. JS: Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. SA: Formal Analysis, Methodology, Writing – review & editing. KJ: Data curation, Investigation, Methodology, Writing – review & editing. MR: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. KR: Data curation, Investigation, Methodology, Writing – review & editing. PvD: Conceptualization, Funding acquisition, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The impact of informant-related characteristics including sex/gender on assessment of Alzheimer's disease symptoms and severity

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Alzheimer's disease (AD) is a debilitating neurological disorder affecting millions of people worldwide. Early and accurate diagnosis of AD is crucial for accessing treatments (including clinical trials), planning for the future, and obtaining necessary services. Unfortunately, AD and other neurodegenerative diseases associated with cognitive impairment or behavioral changes, are frequently misdiagnosed or diagnosed at later stages. Experts recommend a multifaceted approach that integrates performance, informant, and self-report data to properly assess patients with neurodegenerative diseases (1). This approach allows clinicians to assess the presence and severity of cognitive disorders, establish a differential diagnosis, and formulate an effective treatment plan. Caregivers play a pivotal role in recognizing early signs of the disease, such as memory loss and behavioral changes. They provide valuable insights to healthcare providers, assisting in diagnosis and treatment (2). In contrast to conditions where self-reporting is standard, caregiver input is instrumental in AD assessments, especially in clinical trials where disease severity is a critical criterion and endpoint.

Integral to an accurate ascertainment of a patient's severity of disease, which is focused on functional abilities, is a dementia rating scale. In the Clinical Dementia Rating Scale (CDR), a semi-structured interview format is used to collect detailed information from an informant regarding the patient's ability to function in various domains (3). The CDR (either the global score, from 0 (no impairment) to 3 (severe dementia), or the sum of boxes, CDR-SB) is thought to reflect the impact of neurodegeneration on everyday global function based on six cognitive and behavioral domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Currently, this is the most widely used scale for assessing severity/staging of AD (4, 5). The CDR-SB is commonly used as the primary endpoint in clinical trials of AD, in addition to several cognitive measures.

Given the importance of the CDR, it is imperative to consider the informant's characteristics that may influence scoring. Prior research highlights the significance of caregiver input in diagnosing and classifying AD and other neurodegenerative diseases (2). Psychosocial factors, including cultural background (6), ethnicity (7–9), and sex/

gender (10) can influence the diagnosis of neurodegenerative diseases (11). However, it's reasonable to hypothesize that additional informant characteristics such as their relationship with the patient, time spent with the patient, their gender/sex, and cultural and socioeconomic factors may also impact diagnosis and severity scores. It's essential to consider these factors when analyzing caregiver reports, as they can introduce biases in patient diagnosis and staging, particularly since severity assessments are primary endpoints in clinical trials. Examples of such factors include:

1. The informant's *relationship with the patient* can significantly affect their perception of the patient's health status, potentially influencing severity scores. One study has shown that wives tend to be more optimistic about the progression of the disease compared to husbands (12), potentially affecting patient staging in informant-based assessments. The amount of time informants spend with the patient may also impact severity assessments. Caregivers who are closely involved with the patient might have a better understanding of their condition, but their assessments may be colored by factors such as caregiver stress or habituation to symptoms (13, 14). Alternatively, caregivers who are not living with the patient, such as children or friends, may not accurately assess the patient's functioning, especially in the early stages of the disease. Additionally, the nature of the relationship between the informant and the patient, whether a spouse, child, or in-law, may affect assessment accuracy. They may underestimate or overestimate their function based on their limited knowledge of previous functional ability in certain areas such as finances or household management.
2. *The sex/gender* of the informant can also influence dementia assessments in significant ways. Gender influences the awareness and likelihood of caregivers to report symptoms about patients with AD. Women often have a key role in detecting and reporting symptoms in their partners due to their close relationships and caregiving responsibilities. They tend to be more perceptive of subtle changes in cognition, behavior, and daily functioning, leading to early detection and intervention for AD (15). Previous research has shown that female caregivers are more likely to notice and report symptoms of depression in patients (16), which may be a risk factor for dementia as well as a prodromal symptom (17–19). Given that approximately 67% of family caregivers are women, with 80%–90% of them being adult children [National Alliance for Caregiving and AARP (20)], caregiver gender should be considered when interpreting reports. Additionally, gender stereotypes may unintentionally influence the evaluation scale used to assess AD symptoms, affecting the interpretation of caregiver reports.
3. *Cultural and socioeconomic characteristics* can influence how caregivers assess AD symptoms and severity (21, 22). These factors can include language barriers, cultural beliefs, and financial constraints. An investigation into behavioral and psychological symptoms in AD patients underscored the significance of caregiver attributes, including their education level, age, gender, co-residence with the patient, and time spent caregiving, in relation to the severity ratings on the Neuropsychiatric Inventory (23).

In summary, informants and caregivers are instrumental in identifying and assessing cognitive and behavioral deficits in AD and other neurodegenerative diseases, owing to their close connection with the patient. Informant attributes, such as gender, relationship to the patient, the amount of time spent with the patient, and cultural and socioeconomic factors, may impact the evaluation process. Given the importance of assessments in recruiting patients for clinical trials and tracking disease progression, understanding these factors is crucial. Incorporating caregiver characteristics allows clinicians to account for potential biases in reports, improving the accuracy of dementia staging and response to therapy.

There is an urgent need for the development of precise assessment tools that address the limitations of current scales. By advancing scale development, including caregiver characteristics, incorporating biomarkers and digital technologies, we can obtain objective measures, enhance early detection, and enable personalized interventions. This comprehensive approach will significantly improve patient care and outcomes in neurodegenerative disease.

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Conflict of interest

LC-A is the scientific project manager of the Women's Brain Project. ASC is the co-founder and pro bono CEO of the WBP. ASC is also the pro bono Euresearch Vice President.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Insights into neurosteroids and their role in women with epilepsy

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Epilepsy, is a serious neurological condition, characterized by recurring, unprovoked seizures and affects over 50 million people worldwide. Epilepsy has an equal prevalence in males and females, and occurs throughout the life span. Women with epilepsy (WWE) present with unique challenges due to the cyclical fluctuation of sex steroid hormone concentrations during their life course. These shifts in sex steroid hormones and their metabolites are intricately intertwined with seizure susceptibility and affect epilepsy during the life course of women in a complex manner. Here we present a review encompassing neurosteroids—steroids that act on the brain regardless of their site of synthesis in the body; the role of neurosteroids in women with epilepsy through their life-course; exogenous neurosteroid trials; and future research directions. The focus of this review is on progesterone and its derived neurosteroids, given the extensive basic research that supports their role in modulating neuronal excitability.

KEYWORDS

women, neurosteroids, epilepsy, seizure, progesterone, sex steroids, oestrogen, GABA-A receptor

1 Neurosteroids

1.1 Neurosteroid synthesis

1.1.1 Distant synthesis

Traditionally sex steroids are produced by endocrine regulation and feedback by the hypothalamic-pituitary-ovarian axis. The hypothalamus is involved with regulation, production, and pulsatile secretion of gonadotropin-releasing hormone (GnRH), which then controls the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. These hormones induce ovulation, stimulating estradiol and progesterone production that provides feedback to neuronal cells, in particular the temporo-limbic system (amygdala, hippocampus) (1). This is a well-established pathway whereby steroids synthesized in the distant endocrine glands, cross the blood brain barrier, and then act directly in the brain.

1.1.2 Local synthesis

There is a second mechanism which is *de novo synthesis* in the brain. French endocrinologist Etienne-Emile Baulieu first introduced the term neurosteroids in 1981 to describe steroids produced in the brain '*de novo*" (2), based on the identification of steroids accumulating in rat brain, independent of the traditional endocrine pathway. Animal models demonstrated neurosteroid concentrations higher in the nervous system compared with plasma concentrations. It has been well established with animal models

that the neurosteroid biosynthetic enzymes are also present within the human brain and that precursor steroids are produced *de novo* in glial cells and neurons (3). There is complexity of neurosteroid biosynthetic enzymes, with regards to region and cell type-specific expression as well as developmental regulation of these enzymes (4).

There are 3 distinct steps in *de novo* synthesis of neurosteroids (NS). The first is that cholesterol is directed to the outer mitochondrial membrane by the steroidogenic acute regulatory (StAR) protein; StAR is complexed with the translocator protein (TSPO) on the outer membrane of the mitochondria, which then mediates cholesterol transport from the outer mitochondrial membrane to the inner membrane; and finally the cytochrome P450 side-chain cleavage (P450scc) enzyme on the inner mitochondrial membrane creates the precursor pregnenolone (5).

The term "neuro-active steroids" has been utilised for locally synthesized steroids, which can be brain derived or from systemic precursors (6). For the scope of this review, we will refer to all sex steroids and their derivatives, produced both distally and locally in the brain, as "neurosteroids" (NS), as their combined actions are of interest from a clinical perspective.

Figures 1A,B demonstrates the sites of production of NS.

1.2 Neurosteroid regulation

Synthesis of NS occurs in neurones and glia and is controlled by the translocator protein (TSPO) (3). From vertebrate studies, it is thought that neuropeptide control, such as gonadotropin-releasing hormone (GnRH) may also regulate NS biosynthesis as GnRH is expressed in the brain, outside of the hypothalamus and pituitary (5). In females, pulsatile GnRH secretion regulates estradiol synthesis in ovaries and NS in the hippocampus, highlighting the basis for the cyclical nature of NS production in women (7) and why NS production fluctuates with the ovarian cycle (8). The GnRH-induced rise in estradiol establishes a connection between the hypothalamus and the hippocampus, potentially underpinning the cyclical modulation of spine density in the female hippocampus (9).

Figure 2 demonstrates the NS pathway and the most common enzymes involved as well as differing modulation on the GABA-A receptor. The neurosteroids derived from deoxycorticosterone are tetrahydrodeoxycorticosterones (THDOC), which are part of the hypothalamic-pituitary-adrenal axis. This represents a more distant pathway compared with the direct progesterone-derived neurosteroids. Also of note is the reduction of testosterone by aromatase leads to the generation of 17-β estradiol.

1.3 Neurosteroid mechanisms of action

The mechanism of action differs for each NS. One mechanism being non-genomic mechanisms where the sex steroids act on membrane ion channels/receptors (rapid action, within minutes) and the other mechanism being genomic, where the sex steroid hormones act in the nucleus and alter mRNA transcription (delayed action) (6).

1.3.1 Progesterone

The largest body of literature is on progesterone-derived NS and their action on the GABA-A receptor (membrane action). The GABA A-type receptor represents a pentameric protein` with five protein units, including 2α and 2β sub-units and one subunit of either δ, γ and ϵ, θ, π. Some of the protein subunits have multiple isoforms (α1–α6, β1–β3 and γ1–γ3) (11). The α1, β2 γ2 is the most common subunit within the brain and different sub-unit compositions are observed in different brain regions (11).

The opening of the GABA ion channel allows for movement of chloride ions across the cell membrane following a gradient and this may lead to hyperpolarization, pending movement of the chloride ions. This receptor modulates most of the inhibitory neurotransmission in the brain through synaptic (phasic) and extrasynaptic (tonic) inhibition (3). The extra-synaptic GABA-A receptors are the key target for NS (12).

NS are the most potent modulators of δ-GABA-A receptors (13). If a specific NS binds to the δ-GABA-A receptors, this can lead to an increased affinity for GABA, termed a positive allosteric modulator. Higher NS concentrations can also lead to activation of GABA-A receptors in the absence of GABA. There are positive, allosteric modulators of the GABA-A receptor (allopregnanolone, THDOC, and androstanediol), which enhance the GABAergic response and negative, allosteric modulators (DHEA, pregnenolone) which suppress the GABAergic response. Figure 2 shows that NS can be positive or negative modulators of the GABA-A receptor pending on the steroid molecule structure. Positive modulators of GABA-A receptors are anti-convulsant whilst negative modulators are pro-convulsant.

Progesterone also activates the progesterone receptors (genomic mechanism), isoforms A and B, expressed in the brain, and especially in the hippocampal neurons, and their expression is regulated by estrogen (14). Joshi and colleagues demonstrated that progesterone receptor activation also increased expression of GluA1 and GluA2 subunits of AMPA receptors in the hippocampi (15). These findings shifted the dominant paradigm of progesterone as a solely anticonvulsant agent and reveals that it has dual actions on the brain: inhibition via NS and excitation via the progesterone receptor.

1.3.2 Estrogen

There also exists rapid, membrane-initiated, 17*β*-estradiol mediated actions in addition to the classic nuclear signaling pathway. 17β-estradiol acts as a posttranscriptional modulator of excitatory NMDA receptors (16). Estrogen activates estrogen receptors, isoforms α and β, and enhances the expression of the GluA1 subunit of AMPA receptors via activation of estrogen receptor β (17). Compared to progesterone metabolites that act predominantly on GABA-A receptors, membrane-mediated effects of 17β-estradiol trigger various intracellular cascade

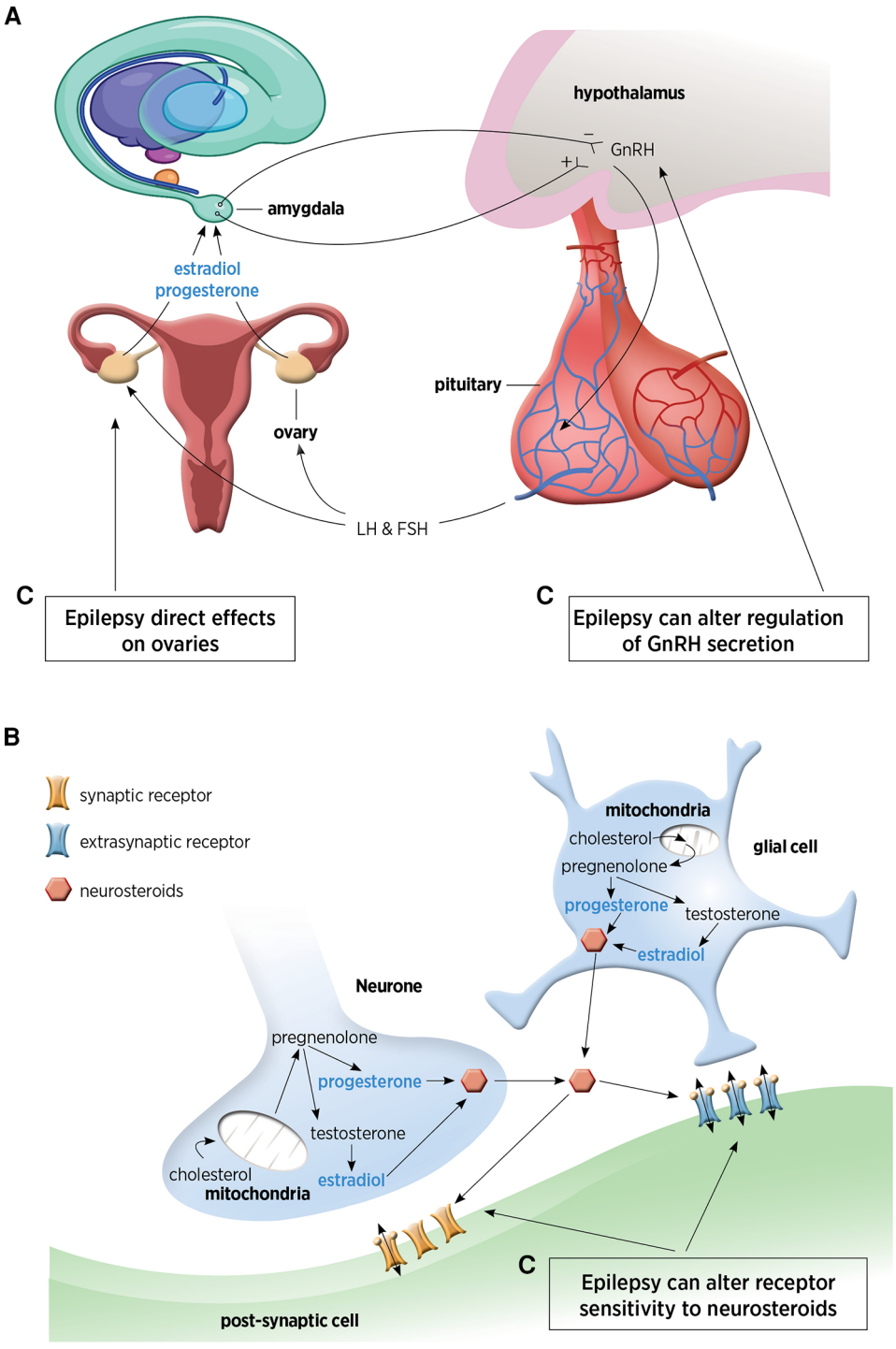

FIGURE 1
(A) Hypothalamic-pituitary-ovarian axis responsible for distal steroid hormone production. This figure has been adapted from Tauboll et al. (1). (B) Neuronal and glial pathways for local neurosteroid production within the brain. (C) The complex inter-relationship between epilepsy and neurosteroids. GnRH, gonadotrophin releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

pathways, leading to changes in ion channel regulation and neuronal excitability (18).

17β-estradiol also facilitates neuroprotection, synaptic and cognitive preservation, has anti-inflammatory effects and regulates microglial activation and function (19). The is evidence for interactions between 17β-estradiol and the signalling molecule brain-derived neurotrophic factor (BDNF) (20). Experimental models have also demonstrated increased concentrations of BDNF in the hippocampus, has both a protective effect as well as increased excitability (21).

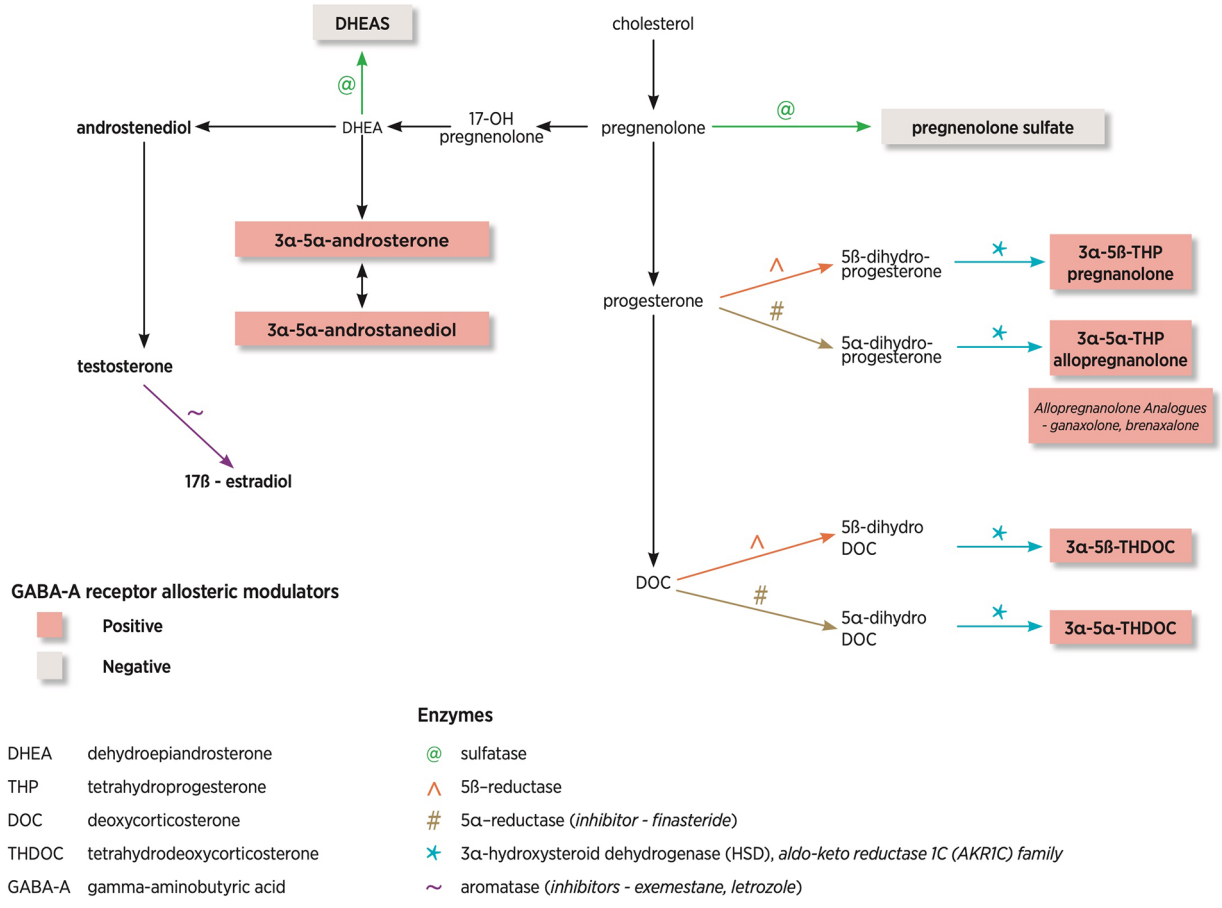

FIGURE 2
Neurosteroid pathway and enzymes involved. This diagram has been adapted from Finn and Jimenez (10).

A potential mechanism to explain the effect of estradiol on hippocampal excitability was demonstrated in a rat model, where spine density in excitatory postsynaptic synapses positively correlated with estradiol concentrations (22). This work could have implications for cognitive performance not only during the menstrual cycle but also during the menopausal transition and later in life.

1.4 Neurosteroids and epilepsy

1.4.1 Altered expression of GABA-A receptors due to seizures

Multiple studies have similarly concluded that altered GABA-receptor expression in epileptic animals is the basis for the reduced NS sensitivity, evidenced by reduction in δ and α1 subunits and increased α4 and γ1 sub-units (23). This has been demonstrated by NS at physiological concentrations failing to lead to increased synaptic and tonic inhibition in epileptic animals. Joshi demonstrated reduced δ- subunit-containing GABA-A expression and upregulation of γ2 subunit following status epilepticus (23).

1.4.2 Altered expression of GABA-A receptors due to neurosteroids

In late diestrus cycle of the mouse (high-progesterone phase), there was increased δ subunit-containing GABA-A receptors and decreased γ2 subunit-containing GABA-A receptors (24). This enhanced expression of δ subunit-containing GABA-A receptors increased tonic inhibition, reducing neuronal excitability and decreased seizure susceptibility (24). This study also found that by eliminating the cycling of δ GABA-A receptors by antisense RNA treatment or gene knockout, changes in excitability were prevented and hypothesized that cyclical seizures (as seen in catamenial epilepsy) maybe due to abnormalities in regulation of the normal cycling of δ subunit-containing GABA-A receptors (24).

1.4.3 The complex interplay of neurosteroids and seizures

There is a complex inter-relationship between NS and epilepsy, with epilepsy affecting multiple sites in the NS biosynthesis process (as shown in Figure 1C). Epilepsy has direct effects on the ovaries, can alter GnRH regulation (1, 9) and can also alter receptor sensitivity to NS (as described earlier).

1.4.4 Animal studies

Over the past few decades, there has been extensive research into NS using preclinical models to explore their implications in depression, anxiety, and excitability disorders. Miziak and colleagues provide a comprehensive table summary of animal models demonstrating the anticonvulsant and proconvulsant actions of the different NS, based on their particular chemical structure (25).

2 The role of neurosteroids in women with epilepsy across their life-course

2.1 Pre-puberty

In Protocadherin 19 in female epilepsy (PCDH19-FE), seizure onset and offset coincides with periods of changes in NS (26). Seizure onset occurs after mini-puberty (around 8 months of age), which seems to start after the fall of *in utero* NS concentrations. The median age of onset was 8 months old, while the median age of offset was 12 years old, when NS are elevated in association with puberty (26).

This landmark publication reviewed transcriptomics in PCDH 19-FE patients and identified 94 dysregulated genes, involved with NS metabolism. Interestingly, nearly half of the genes demonstrated gender-biased expression when compared with transmitting males (26).

Of particular interest within the dysregulated gene set were the genes *AKR1C2* and *AKR1C3*, members of the aldo-keto reductase 1C (AKR1C) family (AKR1C1-4), of which only *AKR1C1-3* is expressed in the brain (26). These enzymes are responsible for reducing NS into downstream metabolites such as allopregnanolone. AKR1C3 gene encodes steroid hormone-metabolizing enzyme, 3α-HSD. Figure 2 demonstrates the location of this enzyme in the biosynthetic pathway. They found that *AKR1C3* mRNA and 3α-HSD protein levels were significantly reduced in PCDH19-FE (26). To further support their hypothesis, they reviewed blood allopregnanolone concentrations, which were also reduced, highlighting the potential role of NS in PCDH19-FE (26).

2.2 Childbearing Age

There is growing evidence for the key role of NS in catamenial seizure exacerbation. It is the cyclical changing balance of sex hormone concentrations that drives an increased seizure frequency with certain menstrual/ovarian cycle phases. There are three common patterns C1 (around menstruation); C2 (ovulation); C3 (anovulatory cycles from mid-cycle to menstruation). Building upon clinical observations, the concept of treatment with cyclical progesterone was conceived leading to the only NIH-approved clinical trial to-date to test a hormonal treatment for catamenial epilepsy (27). This study, led by Herzog, yielded inconclusive results for women with focal catamenial epilepsy overall. However, sub-group analysis demonstrated superior efficacy in women with a prominent C1 pattern (3-fold increase in seizure frequency around menstruation) (27, 28). Herzog's subsequent investigation implicated allopregnanolone as the mediator of seizure reduction in progesterone-treated women (29). Notably, the trial employed progesterone and not allopregnanolone. The previously describer proconvulsant effect via the progesterone-derived NS nuclear action may play a role in seizure exacerbation (15). A more recent pilot study of 173 menstrual cycles from 23 women with epilepsy demonstrated that 52.2% of women met the criteria for one or more catamenial pattern (30), further supporting the role of NS in seizure exacerbation.

2.3 Pregnancy

A novel study during pregnancy study demonstrated that lower allopregnanolone concentrations were associated with increased seizure frequency (31).

2.4 Peri-menopausal and menopause

Harden reviewed the effect of menopause and perimenopause on the course of epilepsy and in women with a history of catamenial epilepsy, seizures increased during perimenopause in and decreased at menopause (32). This data re-affirming the role of fluctuating hormones on seizure control during perimenopause and then reduction in seizures when hormones no longer fluctuate during menopause.

3 Exogeneous neurosteroid trials

3.1 Aromatase inhibitors- exemestane and letrozole

The enzyme aromatase and where it acts in the biosynthetic pathway is shown in Figure 2. A clinical case report demonstrated seizure reduction with tamoxifen and complete seizure freedom with the aromatase inhibitor exemestane (given for the management of breast cancer in a post-menopausal woman), highlighted the link between hormones and seizure control (33).

Harden and MacLusky reported a case report of a 61-year-old man with temporal lobe epilepsy who was commenced on letrozole (aromatase inhibitor) off-label to improve libido and energy levels. There was sustained improvement in seizure control, seizure exacerbation with withdrawal of letrozole and subsequent improvement with re-commencement, once again highlighting the link between hormones and seizure control (34).

3.2 Reductase inhibitor- finasteride

Finasteride is a 5α reductase enzyme blocker, which blocks the conversions of progesterone and deoxycorticosterone to

pregnanolone, allopregnanolone and THDOC. Figure 2 highlights where in the biosynthetic pathway this enzyme plays a role. A case report of a woman by Herzog and Frye demonstrated that finasteride (commenced for male pattern baldness) increased seizures, which had been controlled with progesterone (35).

3.3 Ganaxolone (3β-methylated analog of allopregnanolone)

Natural NS such as allopregnanolone have low bioavailability due to rapid inactivation, however synthetic NS, such as ganaxolone may overcome these limitations (3). Ganaxolone (ZTALMY®; Marinus Pharmaceuticals) is a positive allosteric modulator of the GABA-A receptor (36). Phase 1 trials were undertaken in 1994 and orphan drug status was achieved for PCDH19-FE, status epilepticus and fragile X syndrome (36).

A phase II trial of two patients were given oral ganaxolone from day 21 of their menstrual period until 3 days after their menstrual period for 4 months demonstrated a decrease in total seizure burden with cessation of perimenstrual seizure activity. This promising outcome is yet to be replicated with a larger sample size and longer follow-up (37).

Safety and efficacy of galaxolone was demonstrated in a double-blind phase of the randomized, placebo-controlled phase III trial in patients with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder, leading to the first FDA approval of ganaxolone (38).

3.4 Brenaxolone (aqueous formulation of allopregnanolone)

A phase III trial of brenaxolone was undertaken for refractory status epilepticus. The primary endpoint did not differ significantly from placebo at the end of the double-blind period (39). During the open label extension, 37% of patients on brexanolone achieved treatment response (39).

3.5 PF-06372865 (selective GABA-A receptor positive allosteric modulator)

This is a positive allosteric modulator of α2/3/5 subunit-containing GABA-A receptor. A phase 2A double-blind study of seven patients with photoparoxsymal response demonstrated a statistically significant suppression of the photosensitivity response compared with placebo, with similar responses to lorazepam, highlighting the potential of a selective GABA-A positive allosteric modulator (40).

3.6 Hormone replacement therapy

A randomized, double-blind, placebo-controlled study limited in numbers ($n = 21$), due to the outcomes from the Women's Health Initiative, reviewed women taking Prempro (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate) daily, or double-doses for a 3-month treatment period (41). The outcomes demonstrated a dose-related increase in seizure frequency in post-menopausal women (41).

4 Further research directions

There is solid evidence that NS modulate neuronal excitability. Yet, there is much to be understood about their complex actions in the brain and the inter-relationship between NS and epilepsy. While there are many research avenues to pursue, this relationship is easier to measure in WWE during their life course. There are the cyclic monthly fluctuations during reproductive years; the extreme effects of high NS concentrations during pregnancy; and low NS concentrations at menopause.

There is an enormous knowledge gap at the clinical level. We hypothesize the potential role of exogenous NS administration to improve cyclical seizure exacerbation in patients with catamenial epilepsy; for the pregnant women to reduce seizure and medication burden to the mother and foetus; and for peri- and post-menopausal women to reduce seizure burden and improve cognition.

At the basic science level, we hypothesize that seizure susceptibility can be influenced by: (1) NS concentrations, influenced by multiple variables: synthesis capacity, genetics, biological stage; (2) GABA-A receptor expression and sensitivity, with a different degree of influence based on the location of the epileptogenic focus.

From a clinical science perspective, the only placebo-control blinded study employed a pulse progesterone treatment in a population of women with catamenial seizure exacerbation. It failed to show an impressive benefit, except for patients with significant perimenstrual worsening, yet the timing of the treatment in this trial would not be expected to clearly be helpful for other catamenial patterns. Moreover, the lack of an impressive response is not surprising now that we learned about the progesterone dual actions on excitability. However, there are already synthetic allopregnanolone analogues available and some are FDA-approved for other indications. The trials to assess for their efficacy in epilepsy were not tailored to a patient population where one would expect a benefit (for example catamenial epilepsy), but rather to status epilepticus patients where seizures are provoked by different factors or to very heterogenous groups of refractory epilepsy patients. In the absence of a dedicated treatment option, many clinicians employ continuous progestins or combined contraceptive pills to suppress sex hormone fluctuation, a strategy that they know works for many, despite the lack of solid clinical evidence for it.

At the other end of the life-course, peri-menopause and menopause remain a largely unmapped territory. The essence is to better understand the complex relationship between changing NS concentrations and seizure burden. This will enable greater insights into the pros and cons of exogenous hormone replacement in women with epilepsy.

The role of NS in epilepsy, particularly in the context of women's health, represents a fascinating and uncharted field of research. The potential for advancements in understanding NS

molecular underpinnings holds great promise for developing more personalized treatments, to enhance clinical outcomes for women with epilepsy.

Author contributions

LV: Conceptualization, Writing – original draft, Writing – review & editing. DPA: Writing – original draft, Writing – review & editing. PV: Conceptualization, Writing – review & editing.

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Conflict of interests

LV has received honoraria and consulting fees from UCB and Eisai Pharmaceuticals. LV is on the Advisory Board of the Raoul Wallenberg Australian Pregnancy Register. Grants in the last 3 years include Royal Brisbane and Women's Hospital (RBWH) Foundation Project Grants, UCB collaborative research grant, Medical Research Future Fund Stem Cell Therapies Mission-Stream 3, The University of Queensland, Brain Foundation and Queensland Genomics. PV has received honoraria from Neurodiem, Physician's Education Resource and Philippines League Against Epilepsy. Grant in the last 3 years include NIS—NINDS, Brigham and Women's Hospital, American Epilepsy Society and Epilepsy Foundation of New England. PV is a member of the scientific advisory board for North American AED Pregnancy Registry. She is the Board Chair for My Epilepsy Story and the Executive Director of Epilepsy in the Childbearing through menopause (ECAM) consortium.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Predictors of cognitive change in cognitively healthy older women in Panama: the PARI-HD study

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Background: Evidence suggests that a combination of biological and social factors influence risk of dementia differently for women and men. In healthy older women, several factors may contribute to changes in cognition.
Objective: Describe the characteristics associated with variation in cognition in a sample of cognitively healthy older Panamanian women.
Methods: The study includes cross-sectional analyses of cognitive domains at baseline (n = 357) and 17-month (SD = 2.0) follow-up (n = 200) for women aged 60 years and older enrolled in the Panama Aging Research Initiative-Health Disparities (PARI-HD) study. Instruments included clinical questionnaires, physiological measures, and a neuropsychological test battery assessing global cognition and seven cognitive domains. Multiple regression analyses examined the associations between demographic and clinical characteristics and cognition at baseline. Repeated measures analyses were used to investigate changes in cognition from baseline to follow-up.
Results: On average, participants were 68.6 years of age (SD = 5.9) with 16.1 years of education (SD = 4.7). Age, income, and education showed robust associations with baseline cognition. Subjective cognitive impairment was associated with lower performance in global cognition, verbal learning, and memory domains. Only performance in the attention domain decreased at follow-up, and subjective health state and depressive symptoms significantly predicted the change in attention.
Discussion: Our study findings contribute to the investigation of cognitive health in older Hispanic women and to the understanding of sociodemographic and health-related factors associated with cognitive decline and the progression to cognitive impairment and dementia.

KEYWORDS

Hispanic, cognition, cardiovascular, depressive symptoms, health behaviors, older adults, Latin America, longitudinal studies

1 Introduction

Population aging is occurring in all countries of the world, but with a more rapid rate of increase in low- and middle-income countries (LMIC) (1). Countries in the Latin American and Caribbean (LAC) region are experiencing one of the fastest rates of population aging (2, 3). Estimates show that by 2050, the number of adults over 60

years of age in the LAC region will double (1). An increase in the number of aging individuals is associated with a rise in mild cognitive impairment (MCI) and dementias such as Alzheimer's disease (AD). The prevalence of dementia in LAC has been estimated at 10% (4) analogous to more developed regions but with a more accelerated growth. Projections indicate that by 2050, the number of people living with dementia will increase by 449% (reaching 978,000 cases). In Central America, Panama is projected to have the 3rd highest percentage increase in dementia cases (273%) due to socioeconomic and health factors (5). Although Panama is classified as a middle-high income country, it is globally ranked as one of the most unequal nations in terms of wealth distribution and is the third most unequal country in the LAC region (6, 7). A large proportion of the population cannot access high quality public services, such as health care, education, and sanitation. Furthermore, Panama's public education and healthcare systems are constrained by limited funding, precarious infrastructure, and frequent shortages of workers. These factors are implicated in the high prevalence of chronic illnesses, such as hypertension, diabetes, and obesity, as well as health disparities across the population, given that many people do not receive timely and effective healthcare services or adequate health education (6, 8, 9).

Aging is a normal process involving physiological and psychological changes. Research has shown that although most cognitive functions decline with age, these can decrease at different rates (10). Cognitive domains such as episodic memory, processing speed, executive function, and verbal fluency tend to decline more rapidly and at an earlier age (11–13), whereas other aspects of cognition such as vocabulary and general knowledge, remain more stable and can even improve over time (14, 15). Moreover, there is interindividual variability regarding cognitive trajectories and decline. Some individuals exhibit high cognitive performance, comparable to younger adults, while others experience a steeper and more rapid decline, that could progress to cognitive impairment and dementia (14). Changes in cognition also vary between women and men. In dementia-free women, some studies reveal that cognition levels remain stable for longer periods of time relative to men (16–18), in line with cross-sectional studies that suggest women perform better in some cognitive tasks than men (18–20). Nonetheless, the overall estimated prevalence for dementia is higher for women than men (5), although sex differences in the incidence of dementia are less clear, and may vary across geographical regions (21, 22). These contradictory findings call for further research in women's cognitive health.

Evidence suggests that a combination of biological and social factors influence risk of dementia differently for women and men (23, 24). In healthy older women, several factors may contribute to changes in cognition. Longitudinal studies show that sociodemographic characteristics (e.g., age, and sex), socioeconomic status (e.g., education, income, employment), physical and mental health-related determinants (e.g., chronic illnesses, BMI, depression) and daily habits (e.g., sleeping, physical activity, and smoking) contribute to maintenance or decline of cognitive function (25, 26). Depression and stress in women are also notable risk factors associated with cognitive decline (27, 28). Several studies show that depression is associated with poorer cognitive functioning and faster cognitive decline over time, even for individuals with low to moderate symptoms (29–33). In addition, some research suggests that cardiovascular risk factors (e.g., high systolic blood pressure, obesity) decrease cognitive function (34–37). However, most research has been carried out in predominantly Caucasian populations, which limits the generalizability of the results to other populations (38). In LAC countries, where the prevalence of chronic vascular diseases is increasing (39) these risk factors are of special relevance.

Research on aging women is particularly limited in LAC countries. Some studies that include both men and women tend to overlook gender differences in their analyses, therefore limiting findings on women's cognitive health (4, 40). In Panama, women face unique economic, educational and health obstacles (41). Women perform twice as much domestic labor, earn lower wages, and are less likely to be employed full-time compared to men. This may stem, in part, from the fact that more than 80% of caregivers in Panama are women, which constrains women's career prospects. Consequently, women are more likely to pursue informal and part-time employment, characterized by lower wages and job insecurity (42). Furthermore, many women experience barriers to accessing and completing education due to poverty, early pregnancies, and gender-based violence (43, 44). The Panama Aging Research Initiative- Health Disparities (PARI-HD) program has studied cohorts of older adults for over a decade, and established the first longitudinal aging study in the country as well as one of the few in the broader LAC region. In the present study, the main objective was to examine the characteristics associated with variation in cognition using a sample of cognitively healthy older Panamanian women assessed at two time points.

2 Methods

2.1 Participants and procedure

The study included women aged 60 years and older enrolled in the PARI-HD study, an ongoing community-based longitudinal study of the factors affecting cognitive aging in older adults in Panama. Participants were recruited from the community using convenience sampling. The research team used advertisements on social media platforms that included a description of the study objectives and inclusion criteria. The study was also divulged in public outreach events. Interested adults who met inclusion criteria were recruited. At baseline, participants were literate, dementia-free and community-dwelling, as per inclusion criteria, and enrolled after providing informed consent. The study protocol was approved by the Institutional Bioethics Committee of the Caja del Seguro Social (P-083-16). Participants underwent clinical interviews, physical and cognitive assessments. Data included in this manuscript were collected between October 2016 and March 2020. The first follow-up visit began April 2018. All in-person visits were suspended due to the COVID-19 pandemic. Here we include cross-sectional data for female participants at baseline ($n = 357$) and those who had complete evaluations at first follow-up ($n = 200$). The time elapsed between visits was 17 months (SD = 2.0).

2.2 Measures

2.2.1 Clinical interviews and instruments

Evaluations were conducted in Spanish by health professionals as well as medical, undergraduate, and graduate students trained by a multidisciplinary group of health specialists. A questionnaire based on the 15-item Subjective Memory Complaints Questionnaire (45) was used to assess subjective memory complaints. The European Quality of Life Health Questionnaire (EQ-5D-3l) (39, 46) was used to evaluate subjective health status. The measure includes a visual analogue scale where health is rated on a scale from 0 (worse imaginable health) to 100 (best imaginable health). Independence in instrumental (IADL) and basic (BADL) activities of daily living was measured with Lawton and Brody (47) and Katz Index (48), respectively. For both IADL and BADL higher scores indicate higher function and independence. The Spanish version of the 15-item Geriatric Depression Scale (GDS-15) (49) was used to screen for depressive symptoms.

Other measures included waist circumference, body mass index (BMI; kg/m^2) and blood pressure. A cardiovascular risk (CVR) score (range 0–4) was calculated based on four common risk factors (50, 51): BMI with a cutoff score of less risk ≤30 kg/m or more risk >30 kg/m; blood pressure (systolic) with a cutoff of ≤140 mm Hg or >140 mm Hg; smoking (current or ever smoked) with a score of 0 (never smoked) or 1 (current/past smoker); and physical activity, which was measured through self-reported responses to the question: "Which of the following best describes your level of physical activity" and given the following options: (a) vigorous activity for at least 30 min 3 times a week; (b) moderate activity at least 3 times a week; and (c) rarely active, prefers sedentary activities (52). This item was scored positive if participants selected the last option.

2.2.2 Neuropsychological testing

The neuropsychological test battery included measures of global cognition and seven cognitive domains: (1) attention, (2) executive function, (3) verbal learning, (4) memory, (5) language, (6) visuospatial abilities and (7) processing speed. Test scores were converted to *z* scores and averaged for each of the cognitive domains. Global cognition was measured by the 30-item Spanish version of the Mini-Mental State Examination (MMSE) (53) adjusted for age and education. The attention domain comprised the Trail Making Test Form A (TMT A) (54), and direct and inverse digit span (55). Executive function was evaluated with the TMT Form B (54), Phonetic Verbal Fluency Test (56), and INECO Frontal Screening (57). To assess verbal learning, the Consortium to Establish a Registry for Alzheimer's Disease Word List Memory Task (CERAD) (58) and the immediate recall for the Logical Memory subtest from the Wechsler Memory Scale (59) were used. The memory domain was measured with the recall forms of CERAD (58) and the Wechsler Memory Scale subtest on Logical Memory (59). Language was assessed with Semantic and Phonetic Verbal fluency tests (56) and Boston Vocabulary Test (60). Visuospatial abilities were measured with Clock Drawing Test (CDT) (61) in both forms, copy and draw to the order. Lastly, the time taken to complete the TMT A (seconds) was used as a measure of processing speed.

2.2.3 Statistical analyses

Analyses were conducted using SPSS version 29. Descriptive analyses examined sample characteristics in relation to baseline and follow-up. Means and standard deviations were calculated for variables using a continuous scale of measurement, and frequencies and percentages were used to summarize categorical variables. Repeated measures analyses, McNemar's tests, or marginal homogeneity tests compared individuals at baseline and follow-up for each variable. A series of linear regressions explored the associations between demographic and clinical factors, and neuropsychological test scores for eight cognitive domains at baseline. Repeated measures analyses of covariance (ANCOVA) were used to investigate changes in cognition from baseline to follow-up. Eight simultaneous multiple regression analyses examined the associations between demographic and clinical characteristics and cognition at baseline. Cases with missing data were excluded from statistical analyses via listwise deletion.

3 Results

3.1 Descriptive analyses

Demographic and clinical characteristics are summarized in Table 1. At baseline, participants were 68.6 years of age (SD = 5.9) with 16.1 years of formal education (SD = 4.7). Most participants (60.1%) reported incomes in the upper quartile (*M* = 1,201–1,600 USD). Overall subjective health ratings were high (*M* = 86.3/100, SD = 12.6), although many participants reported subjective cognitive impairment (43.4%). BMI measurements (*M* = 27.3 kg/m^2, SD = 4.9) indicated that many participants were overweight (40%) or obese (27%), and the most reported chronic illness was hypertension (51.5%). According to the Fried criteria (45) most participants were pre-frail (59.3%) and 9% were frail. The total number of chronic illnesses, medications, and the prevalence of subjective cognitive decline increased at follow-up. Moreover, performance declined in global cognition, learning, long-term memory, attention, and executive function from baseline to follow-up (see Table 2).

Independent samples *t*-tests comparing the 157 participants who did not complete the second interview with the 200 participants who completed both interviews revealed that those who did not return were, on average, older (*M* = 70.0 vs. 68.6 years old, $p = .041$) and had lower learning (*M* = −.34 vs. .27, $p < .001$), long-term memory (*M* = −.30 vs. .25, $p = .004$), attention (*M* = −.39 vs. .32, $p < .001$), and processing speed (*M* = 55.87 s vs. 45.26 s, $p < .001$) scores than those who completed the follow-up visit.

3.2 Multiple regression analyses

For each statistical model, cognitive domains were regressed on to age, educational attainment, income, subjective health state,

TABLE 1 Demographic and clinical characteristics of study participants.

Variable	Visit 1 ($n = 357$)	Visit 2 ($n = 200$)	*P* value
	n (%)/*M* (SD)	*n* (%)/*M* (SD)	
Age (years)	68.6 (5.9)	70.0 (5.9)	$p < .001$
Age group			$p < .001$
60–69	221 (61.9%)	116 (58.0%)	
70–79	111 (31.1%)	72 (36.0%)	
>80	25 (7%)	12 (6.0%)	
Marital status			$p = .375$
Partnered	197 (55.2%)	121 (60.8%)	
Not partnered	160 (44.8%)	78 (39.2%)	
Education (years)	16.1 (4.7)	16.2 (4.7)	$p = .463$
Highest education attained			$p = .048$
Incomplete primary school	4 (1.1%)	1 (0.5%)	
Completed primary school	44 (12.3%)	43 (21.5%)	
Completed high school	96 (26.9%)	33 (16.5%)	
University or higher	213 (59.7%)	123 (61.5%)	
Monthly income (USD)	4.3 (1.8)	4.1 (1.8)	$p = .003$
Subjective health state	86.3 (12.6)	86.7 (13.5)	$p = .656$
BMI	27.3 (4.9)	27.2 (4.8)	$p = .615$
Underweight	8 (2.3%)	5 (2.5%)	$p = .873$
Normal	109 (30.7%)	58 (29.0%)	
Overweight	142 (40.0%)	91 (45.5%)	
Obese	96 (27.0%)	46 (23.0%)	
Chronic illnesses (sum)	1.8 (1.2)	2.2 (1.5)	$p < .001$
Asthma (% yes)	40 (11.2%)	25 (12.5)	$p = .727$
Diabetes (% yes)	56 (15.7%)	32 (16.0%)	$p = .999$
Hypertension (% yes)	184 (51.5%)	111 (55.5%)	$p = .180$
Cardiovascular disease (% yes)	39 (10.9%)	21 (10.6%)	$p = .999$
Stroke (% yes)	13 (3.6%)	10 (5.1%)	$p = .727$
Chronic lung disease (% yes)	24 (6.7%)	24 (12.1%)	$p = .052$
Arthritis (% yes)	54 (15.1%)	27 (13.6%)	$p = .999$
Cancer (% yes)	36 (10.1%)	22 (11.0%)	$p = .250$
Liver disease (% yes)	10 (2.8%)	11 (5.6%)	$p = .227$
Osteoporosis (% yes)	142 (39.8%)	96 (48.5%)	$p = .248$
Systolic blood pressure	137.3 (20.6)	142.1 (19.0)	$p < .001$
Cardiovascular risk score	1.2 (1.0)	1.2 (0.9)	$p = .773$
Systolic blood pressure (% at risk)	164 (45.9%)	104 (52.0%)	$p = .004$
Physical activity (% frail)	117 (32.8%)	42 (21.0%)	$p = .005$
Past/current tobacco use (% yes)	85 (23.8%)	51 (25.5%)	$p = .388$
BMI classification (% at risk)	96 (27.0%)	48 (24.0%)	$p = .999$
Medications (sum)	2.5 (2.0)	2.8 (2.2)	$p = .021$
Polypharmacy status (% ≥5 medications)	61 (17.1%)	39 (19.5%)	$p = .216$
Falls			$p = .930$
No falls	259 (72.6%)	141 (70.5%)	
One fall	60 (16.8%)	38 (19.0%)	
≥2 falls	38 (10.6%)	21 (10.5%)	
Overall frailty[a]			$p = .821$
Not frail	113 (31.7%)	77 (38.5%)	
Pre-frail	212 (59.3%)	107 (53.5%)	
Frail	32 (9.0%)	16 (8.0%)	
IADL	7.9 (0.6)	7.9 (0.5)	$p = .893$
BADL	5.8 (0.4)	5.9 (0.3)	$p = .045$
Difficulty sleeping (% yes)	139 (38.9%)	67 (33.8%)	$p = .525$
Depression symptoms (GDS-15)	1.8 (2.1)	1.6 (2.0)	$p = .146$
Subjective cognitive impairment (% yes)	155 (43.4%)	106 (53.0%)	$p = .006$

M, mean; SD, standard deviation; USD, U.S. dollars; monthly income was measured using a Likert-scale (0 = ≤ 250$, 1 = 251$–500$, 2 = 501$–850$, 3 = 851$–1,200$, 4 = 1,201$–1,600$, 5 = 1,601$–2,000$, 6 = > 2,000$). BMI, body mass index; GDS-15, geriatric depression scale-15 items; IADL, instrumental activities of daily living; BADL, basic activities of daily living.

[a]Frailty was assessed using the five components proposed by Fried.

TABLE 2 Composite scores of cognitive domains.

	Visit 1 *n*, *M* (SD)	Visit 2 *n*, *M* (SD)	*P* value
Global cognition	27.3 (1.9)	27.9 (1.6)	$p < .001$
Verbal learning[a]	0.3 (1.5)	0.0 (1.7)	$p = .002$
Long-term memory[a]	0.3 (1.6)	0.0 (1.8)	$p = .002$
Attention[a]	0.3 (1.5)	0.0 (1.7)	$p < .001$
Executive function[a]	0.6 (1.9)	0.4 (1.9)	$p = .027$
Visuospatial abilities[a]	0.0 (1.7)	−0.002 (1.7)	$p = .794$
Language[a]	0.1 (2.3)	0.0 (2.4)	$p = .208$
Processing speed (sec)	45.3 (17.5)	46.5 (19.2)	$p = .257$

M, mean; SD, standard deviation. Global cognition was measured using the raw score of the mini-mental state examination (MMSE). Processing speed was measured using the raw score of the trail making test A (seconds).

[a]Scores for cognitive domains represent standard z scores.

diabetes diagnosis, CVR score, symptoms of geriatric depression, and subjective cognitive decline (see Table 3).

3.3 Model 1: global cognition

The omnibus test was significant [F (8, 345) = 2.43, MSE = 1.88, $R^2 = 0.05$, $p = 0.015$] and results showed an effect of income ($\beta = .14$, $t = 2.40$, $p = .017$) and subjective cognitive decline ($\beta = -.13$, $t = -2.37$, $p = .018$) on global cognition. Higher income was associated with higher global cognition scores, and individuals who reported subjective cognitive decline scored lower on global cognition.

3.4 Model 2: verbal learning

The omnibus test was significant [F (8, 344) = 11.75, MSE = 1.53, $R^2 = 0.22$, $p < 0.001$] and results showed an effect of age ($\beta = -.21$, $t = -4.20$, $p < .001$), educational attainment ($\beta = .18$, $t = 3.42$, $p < .001$), income ($\beta = .19$, $t = 3.60$, $p < .001$), cardiovascular risk ($\beta = .13$, $t = 2.62$, $p = .009$), and subjective cognitive decline ($\beta = -.11$, $t = -2.17$, $p = .031$) on learning. Older age and subjective cognitive decline were associated with lower learning scores, whereas higher educational attainment, income, and cardiovascular risk were associated with higher scores on learning.

3.5 Model 3: long-term memory

The omnibus test was significant [F (8, 343) = 10.74, MSE = 1.59, $R^2 = 0.20$, $p < 0.001$] and results showed an effect of age ($\beta = -.23$, $t = -4.54$, $p < .001$), educational attainment ($\beta = .18$, $t = 3.41$, $p < .001$), income ($\beta = .18$, $t = 3.26$, $p < .001$), and subjective cognitive decline ($\beta = -.11$, $t = -2.17$, $p = .029$) on long-term memory. Higher educational attainment and income were associated with higher long-term memory scores. Older age and subjective cognitive decline were associated with lower long-term memory scores.

TABLE 3 Multiple linear regression analysis by cognitive domain at time of first visit ($n = 357$).

Model	Dependent variable	*b*	Standard error	*β*	*t*
1. Global cognition ($n = 354$)					
	Age	.02	.02	.05	.92
	Years of education	−.03	.03	−.07	−1.14
	Income*	.15	.06	.14	2.40
	Subjective health state	.003	.01	.02	.36
	Diabetes	−.15	.28	−.03	−.54
	Cardiovascular risk	.18	.10	.10	1.79
	Depression symptoms	.09	.05	.11	1.76
	Subjective cognitive decline*	−.50	.21	−.13	−2.37
2. Verbal Learning ($n = 353$)					
	Age***	−.06	.01	−.21	−4.20
	Years of education**	.07	.02	.18	3.42
	Income***	.18	.05	.19	3.60
	Subjective health state	.003	.01	.03	.51
	Diabetes	.16	.23	.03	.70
	Cardiovascular risk**	.22	.08	.13	2.62
	Depression symptoms	−.03	.04	−.04	−.69
	Subjective cognitive decline*	−.38	.17	−.11	−2.17
3. Long-term Memory ($n = 352$)					
	Age***	−.06	.01	−.23	−4.54
	Years of education**	.07	.02	.18	3.41
	Income**	.17	.05	.18	3.26
	Subjective health state	.004	.01	.04	.63
	Diabetes	.22	.24	.05	.94
	Cardiovascular risk	.10	.09	.06	1.17
	Depression symptoms	.002	.04	.003	.06
	Subjective cognitive decline*	−.40	.18	−.11	−2.20
4. Attention ($n = 353$)					
	Age***	−.05	.01	−.19	−3.95
	Years of education***	.08	.02	.20	3.83
	Income***	.19	.05	.21	3.97
	Subjective health state	.01	.01	.11	2.00
	Diabetes	−.34	.22	−.08	−.158
	ardiovascular risk**	.22	.08	.13	2.75
	Depression symptoms	.02	.04	.03	.50
	Subjective cognitive decline	−.16	.17	−.05	−.94
5. Executive Function ($n = 320$)					
	Age***	−.08	.02	−.23	.4.39
	Years of education***	.13	.03	.24	4.31
	Income*	.15	.07	.12	2.16
	Subjective health state	.01	.01	.04	.63
	Diabetes	−.31	.31	−.05	.98
	Cardiovascular risk	.17	.11	.08	1.60
	Depression symptoms	.01	.05	.01	.15
	Subjective cognitive decline	−.36	.22	−.09	−1.62
6. Visuospatial ($n = 354$)					
	Age*	−.03	.02	−.13	−2.36
	Years of education	.01	.02	.03	.59
	Income	.06	.05	.06	1.07
	Subjective health state	−.003	.01	−.03	−.47
	Diabetes	−.47	.25	−.10	−1.93
	Cardiovascular risk	−.09	.09	.05	1.03
	Depression symptoms**	−.14	.04	−.20	−3.24
	Subjective cognitive decline	.14	.19	.04	.74
7. Language ($n = 354$)					
	Age**	−.07	.02	−.17	−3.37
	Years of education***	.11	0.3	.21	3.80
	Income*	.18	.07	.14	2.47
	Subjective health state	.001	.01	.004	.07
	Diabetes	−38	.33	−.06	−1.16
	Cardiovascular risk	.24	.12	.10	1.96
	Depression symptoms	−.06	.06	−.06	−.97
	Subjective cognitive decline	−.29	.25	−.06	−1.15
8. Processing speed ($n = 353$)					
	Age***	.69	.18	.19	3.89
	Years of education***	−1.03	.27	−.21	−3.84
	Income**	−1.93	.67	−.16	−2.89
	Subjective health state	.14	.09	.09	1.54
	Diabetes	−3.81	3.00	−.06	−1.27
	Cardiovascular risk*	−2.65	1.09	−.12	−2.42
	Depression symptoms	−.83	.52	−.09	−.59
	Subjective cognitive decline	1.10	2.28	.03	.49

Diabetes and subjective cognitive decline were coded as 0 = no, 1 = yes. *$p < .05$, **$p < .01$, ***$p < .001$.

3.6 Model 4: attention

The omnibus test was significant [F (8, 344) = 13.09, MSE = 1.45, $R^2 = 0.23$, $p < 0.001$] and results showed an effect of age ($\beta = -.19$, $t = -3.95$, $p < .001$), educational attainment ($\beta = .20$, $t = 3.83$, $p < .001$), income ($\beta = .21$, $t = 3.97$, $p < .001$), and cardiovascular risk ($\beta = .13$, $t = 2.75$, $p = .006$) on attention. Older age was associated with lower attention scores. Higher educational attainment, income, and cardiovascular risk were associated with higher attention scores.

3.7 Model 5: executive function

The omnibus test was significant [F (8, 311) = 8.63, MSE = 1.89, $R^2 = 0.18$, $p < 0.001$] and results showed an effect of age ($\beta = -.23$, $t = -4.39$, $p < .001$), educational attainment ($\beta = .24$, $t = 4.31$, $p < .001$), and income ($\beta = .12$, $t = 2.16$, $p = .031$) on executive function. Older age was associated with lower executive function scores, and higher educational attainment and income were associated with higher executive function scores.

3.8 Model 6: visuospatial abilities

The omnibus test was significant [F (8, 345) = 3.95, MSE = 1.65, $R^2 = 0.08$, $p < 0.001$] and results showed an effect of age ($\beta = -.13$, $t = -2.36$, $p = .019$) and depression symptoms ($\beta = -.20$, $t = -3.24$, $p < .001$) on visuospatial abilities, such that older age and having more depression symptoms was associated with lower visuospatial scores.

3.9 Model 7: language

The omnibus test was significant [F (8, 345) = 8.82, MSE = 2.20, $R^2 = 0.17$, $p < 0.001$] and results showed an effect of age ($\beta = -.17$, $t = -3.37$, $p < .001$), educational attainment ($\beta = .21$, $t = 3.80$,

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$p < .001$), and income ($\beta = .14$, $t = 2.47$, $p = .014$) on language. Older age was associated with lower language scores, while higher educational attainment and income were associated with higher language scores.

3.10 Model 8: processing speed

The omnibus test was significant [F (8, 344) = 11.34, MSE = 20.07, $R^2 = 0.21$, $p < 0.001$] and results showed an effect of age ($\beta = .19$, $t = 3.89$, $p < .001$), educational attainment ($\beta = -.21$, $t = -3.84$, $p < .001$), income ($\beta = -.16$, $t = -2.89$, $p = .004$), and cardiovascular risk ($\beta = -.12$, $t = -2.42$, $p = -.016$) on processing speed. Years of education, income, and cardiovascular risk were associated with faster processing speed, and older age was associated with slower processing speed.

3.11 Repeated measures analyses of covariance

For global cognition and the seven cognitive domains, a repeated measures ANCOVA was conducted to assess changes in cognition from baseline to the follow-up while controlling for demographic and clinical factors. Age, educational attainment, income, subjective health state, diabetes diagnosis, cardiovascular risk, symptoms of geriatric depression, and subjective cognitive decline were entered as covariates.

The overall results revealed that only scores on the attention domain differed significantly between time points [F (1, 189) = 5.08, MSE = 3.12, $\eta^2 = 0.03$, $p = .025$], and a *post hoc* analysis ($p < .001$) showed that attention scores decreased significantly from baseline ($M = .34$) to follow-up ($M = .04$). No significant differences were observed between visits for the remaining domains (all p-values > .05).

3.12 Exploratory multiple regression analysis

An exploratory regression analysis was performed to examine demographic and clinical factors at baseline that predict change in attention scores over time (see Table 4). The change score was created by computing the difference between the attention scores at first visit and second visit. Change in attention was then regressed on to age, educational attainment, income, subjective health state, diabetes diagnosis, cardiovascular risk, depression symptoms, and subjective cognitive decline.

TABLE 4 Multiple linear regression analysis of the change in attention from baseline to follow-up ($n = 198$).

	b	Standard error	*β*	*t*
Age	.02	.01	.09	1.22
Years of education	−.01	.02	−.04	−.52
Income	−.04	.05	−.06	−.79
Subjective health state***	.03	.01	.27	3.41
Diabetes	.05	.23	.02	.22
Cardiovascular risk	−.01	.08	−.01	−.17
Depression symptoms***	.14	.04	.26	3.30
Subjective cognitive decline	−0.5	.17	−.02	−.27

Criterion variable was measured using the total score of the trail making test A and digit span (direct and inverse). Diabetes and subjective cognitive decline were coded as 0 = no, 1 = yes. *$p < .05$, **$p < .01$, ***$p < .001$.

Results indicated a significant omnibus test [F (8, 189) = 2.41, MSE = 1.11, $R^2 = 0.09$, $p = 0.017$] and showed a main effect of subjective health state ($\beta = .27$, $t = 3.41$, $p < .001$) and depression ($\beta = .26$, $t = 3.30$, $p < .001$) on the change in attention. Higher self-rated health and more geriatric depression symptoms at baseline were associated with greater changes in attention scores at follow-up.

4 Discussion

The main objective of this study was to examine the characteristics associated with variation in performance across cognitive domains in a sample of cognitively healthy older Panamanian women. We compared performance across seven cognitive domains at baseline and follow-up. First, a cross-sectional analysis was conducted to determine the health, clinical and social factors associated with different cognitive domains. Our cross-sectional analyses were consistent with studies on cognitive function in older women (10, 61). Older age was associated with worse performance across domains except global cognition and processing speed. Social determinants such as years of education and income were associated with most cognitive domains. Evidence shows that women experience social inequalities including lower income, lower educational attainment and limited stimulating activities that are related to diminished cognitive reserve and may explain worse cognitive outcomes (21, 23, 62). Research studies in other LAC countries reveal that education provides a larger cognitive reserve due to the cognitive stimulation and intellectual engagement (63–65). Additionally, education is often associated with better access to resources and healthcare, which can also influence cognitive health (66, 67).

Moreover, depression was associated only with the visuospatial domain at baseline. Although the relationship between depression and attention is not clear, depression has been linked to several factors that can contribute to cognitive impairment (29, 68), including changes in brain structure, inflammation, and vascular risk factors such as diabetes, hypertension, and obesity (68). Performance in nonverbal tests, such as visuospatial tasks, tends to decrease more quickly in older adults diagnosed with depression (69). Older adults with depression experience more difficulty analyzing and discriminating visual stimuli, and show deficits in perceptual organization (70). Some research suggests that visuospatial deficits are useful to determine the progression of subjects to AD (71).

Counterintuitive results were observed with cardiovascular risk showing positive associations with verbal learning, attention, and processing speed at baseline. The inclusion of women whose cardiovascular risk scores lie within healthy ranges may explain the relationships we observed between these markers of risk and cognition at baseline prior to the presence of cognitive impairment. There are different mechanisms that can explain the association

between vascular alterations and cognitive decline that have been studied in cross-sectional (72, 73) and longitudinal studies (74, 75). Vascular risks, such as smoking or having a sedentary lifestyle, can provoke narrowing of the arteries, therefore reducing blood circulation and disruption of the flow of nutrients to the brain (76–78). Also, vascular alterations such as atherosclerosis are associated with lower cognitive performance (79, 80). All these vascular pathologies have been associated with deficits in memory, processing speed and executive function (73, 80). Studies in LAC countries have shown that prevalent chronic illnesses such as hypertension, diabetes, cerebrovascular disease, and obesity impact cognition and are associated to a higher risk of dementia (81, 82). Moreover, in women, hormonal imbalance can have diverse effects on cardiovascular health and cognitive function. For instance, the decrease in estrogen can contribute to cognitive decline (83, 84).

Subjective cognitive impairment (SCI) at baseline was associated with worse global cognition, verbal learning, and verbal long-term memory. Studies have shown that in preclinical stages of AD, objective cognitive deficits are not present, though individuals may note subtle changes in cognition that could be considered a risk factor of cognitive impairment (85) and may reflect early neurodegeneration (86, 87). Neuroimaging studies have reported an association between subjective cognitive impairment and brain atrophy, particularly in frontal and temporal lobes (88). This is consistent with memory deficits present in people with SCI. Currently, SCI is being studied as an intermediate state between normal cognition and mild cognitive impairment, and, therefore, can be a useful tool in early diagnosis of MCI and AD (89).

Attention was the only cognitive domain that showed significant changes over time. In addition, higher self-rated health and more depression symptoms were associated with greater changes in attention. Changes in attention in the elderly are not fully understood (90). Some studies indicate that more complex attention processes such as selective and alternating attention tend to decrease more than sustained attention (91), while other studies show an impact in all attention processes. In our sample, changes were associated with sustained attention. In cognitive impairment, attention deficits can appear before alterations in other cognitive functions, and poor performance in attention tasks is observed in preclinical phases of AD (92–94). Multiple studies have shown depressive symptoms are associated with cognitive decline (27, 28, 95). Depression impacts brain systems that can contribute to difficulties processing information (96), and has been associated with lower volume in frontal gray matter including the orbitofrontal cortex and the cingulate gyrus (97, 98). Further, greater subjective health state was associated with worse attention. One possible explanation for this result is that participants were relatively healthy at baseline. Approximately 75% of individuals rated their health above 80/100, which may have limited the range of subjective health scores, and therefore the ability to detect a meaningful association with cognition.

4.1 Strengths and limitations

This study has several limitations. First, participants had a higher level of education and income relative to the national and regional average, which may limit the generalizability of our findings. Second, the self-reported variables, such as depressive symptoms, physical activity, and subjective health may be subject to response bias. Nonetheless, evidence suggests that self-report provides accurate estimates of disability and disease comorbidity and predicts mortality and other clinical health measures (99). Third, the 17-month follow-up timeline may have been too short to observe noticeable changes in cognition, particularly in cognitively healthy individuals. Lastly, the sample size was limited due to participant attrition, which minimized statistical power at follow-up.

This study also has several strengths. We recruited a relatively large community-based cohort from an under-represented population, and implemented neuropsychological tests that measure diverse cognitive domains. The study also included detailed clinical interviews and several objectively measured variables, such as BMI and blood pressure (i.e., two important components of cardiovascular risk). Hence, our analyses accounted for potential sociodemographic, lifestyle, and health-related confounders known to impact cognition.

4.2 Conclusions

Age, income, and education level showed the most robust associations with cognition in our sample. In addition, subjective cognitive impairment and impaired cognition were observed across global cognition, verbal learning, and memory domains. Our study findings contribute to the investigation of cognitive health in older Hispanic women and may help to inform health professionals about predictors of cognitive decline in this population. Future studies with more extended longitudinal follow-up would contribute to our understanding of how social determinants of health and other biological and health-related markers shape cognitive trajectories in older women.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Bioethics Committee of the Caja del Seguro Social (P-083-16). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DO: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft. AT: Formal Analysis,

Writing – review & editing. SR-A: Methodology, Project administration, Writing – review & editing. AV: Writing – review & editing. GR: Writing – review & editing. MC: Writing – review & editing. GB: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Imaging phenotypic differences in multiple sclerosis: at the crossroads of aging, sex, race, and ethnicity

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Clear sex differences are observed in clinical and imaging phenotypes of multiple sclerosis (MS), which evolve significantly over the age spectrum, and more specifically, during reproductive milestones such as pregnancy and menopause. With neuroimaging being an outcome measure and also a key subclinical biomarker of subsequent clinical phenotype in MS, this comprehensive review aims to provide an overview of sex and hormone differences in structural and functional imaging biomarkers of MS, including lesion burden and location, atrophy, white matter integrity, functional connectivity, and iron distribution. Furthermore, how therapies aimed at altering sex hormones can impact imaging of women and men with MS over the lifespan is discussed. This review also explores the key intersection between age, sex, and race/ethnicity in MS, and how this intersection may affect imaging biomarkers of MS.

KEYWORDS

aging, hormone therapy, magnetic resonance imaging, multiple sclerosis, race, sex

1 Introduction

There are clinical sex differences affecting aspects of multiple sclerosis (MS) from susceptibility to disease course, and from relapse recovery to progression. MS is more common in women (1) and women often have an earlier disease onset than men (2). Women have more frequent relapses early in the disease course (3), but with better relapse recovery potential than men (4). Although men have fewer relapses (3), they usually have faster disability worsening early on (5) due to lower relapse recovery potential with higher likelihood of entering the progressive phase earlier (6), possibly partly associated with age-related decline of androgens in men (7). However, once women enter the progressive phase (around the fifth decade), they accumulate disability faster and consequently can catch up to men (8). Along with aging, menopause results in a more dramatic sex hormone drop compared to men and thus likely contributes to this alteration in the MS disease course.

In addition to sex, race/ethnicity is also closely related to MS susceptibility, course, and progression. There is a similar prevalence of African Americans to White Americans with MS in California (9). African American women have a higher risk of MS than White American women (9). African Americans have more aggressive clinical disease than White Americans (10) and African American men are more likely to have primary progressive MS (PPMS) than White American men (11). Little to no work has been

conducted looking at how sex and race/ethnicity impact imaging findings, individually or together, in MS.

It is imperative to incorporate the role of aging into sex and racial/ethnic differences in MS imaging as aging is a key determinant of the phenotypic and radiological variability in MS (12, 13). Central nervous system (CNS) reserve decreases with aging, not only in the general population, but also in MS (14). With aging, inflammatory activity and therefore new relapse and lesion formation frequency tend to decrease in MS, but the recovery potential from relapses decreases with aging as well (15). Most importantly, transition to the progressive phase of MS increases with aging (16), which often overlaps with changes in age-related sex hormone levels during menopause and andropause.

Imaging biomarkers in those of diverse races/ethnicities differ from those in White persons. African Americans have earlier brain atrophy, lower cortical thickness, and higher WM lesion load than White Americans (17, 18). Latin Americans with MS have higher T2 lesion volume, and lower brain volume, white matter volume, and cortex volume than non-Latin American White persons with MS (19). Japanese persons with MS have greater T2 lesion volume per lesion, and lower total brain volume, white matter volume, thalamic volume, and deep grey matter volume compared to White persons with MS (20). Magnetic resonance imaging (MRI) differences between diverse racial/ethnic groups worldwide with MS has been comprehensively reviewed (21). Less is known about sex differences in diverse populations. However, men generally have greater brain atrophy than women (22) with a higher rate of decreasing cortical thickness (23).

Similarly, there are sex and racial/ethnic differences in laboratory biomarkers of MS such as vitamin D, cerebrospinal fluid (CSF) kappa free light chain, oligoclonal bands, and neurofilament light chain (NfL). Vitamin D supplementation seems to be more effective at reducing CD4+ *T*-cell proliferation in women than in men with MS (24). With respect to diverse racial/ethnic groups, African Americans have lower vitamin D levels than non-Latin American White Americans and Mexican Americans in the general population (25). In persons with MS, vitamin D levels were found to be higher in White Americans compared to Black Americans and Hispanic Americans, with the association of higher vitamin D levels with reduced risk of MS being significant only in White Americans (26). On the other hand, the CSF biomarkers of kappa free light chain (27) and oligoclonal bands (28) do not appear to differ between the sexes, while some studies have shown that men are more likely to have negative CSF oligoclonal bands (29–31). Moreover, CSF neurofilament light chain levels are higher in men than women (29, 32, 33). Regarding biomarkers in diverse racial/ethnic groups, Black persons with MS are more likely to have CSF oligoclonal bands than White persons with MS (34). However, overall, knowledge of the interaction of sex and race in laboratory biomarkers remains limited, similar to what has been observed in imaging metrics of MS.

As the focus of this review, imaging metrics can serve both as an outcome and a biomarker. To better understand and explain sex and racial/ethnic differences in MS clinical findings, identification of sex and racial/ethnic differences in imaging biomarkers of MS in the age spectrum is essential. As many of the differences on imaging are expected to precede differences observed clinically, evaluating the impact of sex and race/ethnicity on imaging phenotypes provides an opportunity to intervene and optimize MS management in a timely manner. Investigating the interaction of sex with race/ethnicity in imaging in MS is important to target and reduce disparities.

This comprehensive review provides an overview of sex and hormone differences in imaging biomarkers of MS, and highlights how reproductive milestones (pregnancy, menopause) along with hormone therapy (HT) may impact MS imaging differences in the age spectrum. The review also focuses on the key interactions of age, sex, and race/ethnicity in MS and how this intersection may affect imaging biomarkers of MS.

2 How do sex and hormones impact lesion load and location in MS?

Women generally have a greater number of gadolinium-enhancing lesions compared to men (35–37), though a few studies have not found a significant sex difference (38, 39). More gadolinium-enhancing lesions in women is indicative of a more inflammatory phenotype, related either to abnormally low testosterone levels in women (36) or due to high estradiol and low progesterone levels (40). A small study of eight women showed that the ratio of progesterone/17-beta-estradiol during the luteal phase was associated with the number and volume of gadolinium-enhancing lesions (41). These MRI results align with a large study including over 6,000 women and 3,000 men with MS, demonstrating that women have more relapses up to menopause than men, indicative of more inflammatory disease in premenopausal women than men (42), likely related to changes associated with sex hormone levels and aging. Aging in MS is generally associated with decreased inflammatory activity regarding relapses (8) and new enhancing and/or T2 lesions on MRI (43), and thus, interactions between sex and age warrant further investigation to determine the relative contribution of each variable to inflammatory activity in MS.

With respect to T1 hypointense lesions related to more severe axonal/neuronal damage, men with progressive MS have higher T1 lesion volume and higher T1/T2 ratio compared to women (44), which has been replicated in another study showing higher T1/T2 ratio in men compared with women in both relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) (35). T2 hyperintense lesion area was increased in women compared to men with MS as well (45).

Regarding lesion location, men with RRMS had a much greater likelihood of having exclusively infratentorial lesions than women, a relationship that did not hold in progressive MS (39). This study did not find any difference between sexes regarding spinal cord lesions (39), though another study showed that men have more spinal cord lesions than women (46). Men also have more cortical GM lesions than women (47) which has been confirmed by a neuropathological study (48).

3 How do sex and hormones impact atrophy in MS?

Brain atrophy occurs with aging in the general population, but the atrophy rate is faster in those with MS (14). Sex differences contribute to clinical phenotypic variability in MS, both independently and in association with aging (49). Sex differences also impact imaging biomarkers of atrophy in MS across the lifespan.

Although CNS atrophy occurs in both sexes in MS, men show more significant whole brain and GM atrophy compared to women, especially during the early and midlife periods of the disease. Regional GM atrophy, including localized cortical thinning and deep GM atrophy, independent of age and disease duration, occurs more extensively in men (50–52). In parallel, higher bifrontal GM atrophy in men compared to women with MS persisted even after the groups were matched for IQ, education level, cognitive performance and physical disability in addition to age and disease duration (53). Moreover, men showed more prominent central atrophy, with larger third and lateral ventricle volumes than age-matched women, indirectly reflecting deep GM damage (38, 50). There is also a stronger association between thalamic atrophy and clinical metrics such as 9-hole peg test (52) and cognitive function (51) in men than women with MS.

Data on sex differences in spinal cord atrophy in MS is limited. In a study of early RRMS patients, although not statistically significant, women exhibited a smaller cervical spinal cord cross-sectional area than men (54). In another study, women had smaller cervical spinal cord areas compared to men in the control group, whereas cervical spinal cord areas were similar between women and men in the MS group (55). In parallel, a postmortem pathology study found similar lateral column cross-sectional areas at C3 and T2 between the sexes, but that the nerve fiber layer density was significantly lower in men, suggesting greater axonal damage in men than women (56).

In contrast to multiple unfavorable structural imaging findings in men, one study found that women had more advanced WM atrophy in the brain compared to men with MS (38). This could relate to higher inflammatory activity with a higher number of WM lesions in women, discussed in the previous section, leading to more accelerated WM loss.

4 How do sex and hormones impact non-conventional imaging metrics in MS?

Sex differences in WM integrity, functional connectivity, microglia, and iron deposition warrant attention since these advanced imaging techniques could enlighten the underlying mechanisms better and may correlate more strongly with clinical outcomes.

A diffusion tensor imaging (DTI) study showed that diffuse and regional WM damage was significantly higher in men, while disease duration, disability, and WM lesion load were similar between sexes with MS (57). The normal appearing WM was the main driver of more extensive and severe WM integrity loss in men. The region-wise WM integrity loss was specifically more severe in the thalamus, which was associated with faster deterioration in cognition in men (57). Another DTI study found a significant difference in the microstructural change rate of chronic stable demyelinating WM lesions, with men having a faster rate of ongoing inflammation, demyelination, and axonal loss in lesions compared to women, which was associated with progressive brain atrophy (58).

In a resting-state functional MRI (fMRI) study on early-stage MS, men exhibited greater GM atrophy but also increased functional connectivity compared to women (53). However, in a similar group of patients with MS, in the caudate, men had lower functional connectivity to the posterior cingulate cortex compared to women (59). In another fMRI study, MS patients had impaired functional connectivity within the male group, whereas no difference was found between MS patients and controls in the female group (60). Additionally, a decline in functional connectivity and network efficiency was associated with a decline in visuospatial memory only in men with MS (60).

Women with MS have a more clustered hippocampal network organization with an increase in hippocampal connectivity, despite more widespread hippocampal atrophy than men with MS (61). It is hypothesized that in men, increased functional connectivity seen earlier in the disease course may be due to a compensatory mechanism aiming to overcome increased structural tissue damage, but it seems to evolve into a more maladaptive mechanism as the disease progresses. In contrast, women start to demonstrate greater functional connectivity and re-organization as the disease continues since women may have better functional preservation and reserve, resulting in lower rates of disability worsening (29, 53). However, how this relates to aging and menopause remains unknown.

Quantitative susceptibility mapping (QSM) has been used to identify chronic active lesions in MS with one study determining that men are more likely to have QSM-visible lesions with rims, indicative of chronic active inflammation compared to women (62). This finding has been replicated in neuropathology studies that showed an increase in smoldering lesions (63) and more mixed active/inactive lesions in men than women with MS (48).

Positron emission tomography (PET) is an emerging advanced imaging technique in MS targeting various underlying mechanisms such as demyelination and neuroinflammation, based on which radioligand is used (64, 65). For example, microglia can be evaluated using radioligands that bind to 18kDA translocator protein (TSPO). In a recent study, men showed higher TSPO binding on PET compared to women, both in MS and healthy individuals, and this sex difference in TSPO-expressing microglia was suggested to contribute to the higher likelihood of progression in men with MS (66).

5 How do reproductive milestones affect imaging biomarkers in MS?

With respect to reproductive milestones for women, studies in MS using MRI have been conducted during pregnancy, in the

postpartum period, and with the transition to menopause. The impact of pregnancy on new MRI activity has been demonstrated even at the earliest phase of MS, radiologically isolated syndrome (RIS), a form of asymptomatic MS, where a significant increase in the number of T2 lesions and T2 lesion volume was seen in individuals with RIS who became pregnant compared to those who did not (67).

In the same vein, a study conducted on women with MS with 2 MRIs completed before pregnancy and 2 MRIs completed after delivery demonstrated higher T2 lesion volume and greater annualized T2 lesion volume increase as compared to the pre-pregnancy period (68). Of note, in this study, MS was deemed to be mild, with only 6% of participants on moderate to high efficacy DMTs and 81% on low efficacy DMT (68). This study paradigm was interesting in that each MS patient served as their own internal control with multiple scans, enabling for comparisons within a single individual over 4 MRIs. An increase in brain T2 lesion volume postpartum has been replicated by other studies (69), with one of these studies also finding an increase in brain T1 lesion volume (69).

Other studies have compared MRI gadolinium-enhancing lesions before and after pregnancy, which have shown a significant increase in the number of gadolinium-enhancing lesions on brain MRI postpartum compared to pre-pregnancy (70, 71), even in the absence of clinical attacks (70, 71).

Regarding breastfeeding, one study noted a protective effect of breastfeeding on MRI activity (70), while another did not (71). Most of the aforementioned studies did not include spinal cord MRIs, or if they did, did not provide separate analyses for spinal cord. This is noteworthy, as the development of new spinal cord lesions are more likely to be symptomatic than new brain lesions and thus to contribute to disability worsening (72). Interestingly, in the postpartum period, breastfeeding duration of >6 months was associated with lower WM volume, though this could be linked to increased inflammatory disease activity in the postpartum period rather than the independent effect of breastfeeding (73). The postpartum inflammatory activity was also associated with shorter breastfeeding duration (73).

Upon entering menopause, the MS disease course and MRI features change for women into a less inflammatory form. Menopausal women have lower annualized relapse rate and MRI activity than women not in menopause (74). Although women have more benign volumetric outcomes and men have faster atrophy rates early in the MS disease course, this trend starts to change with aging and possibly with menopause.

In an MS cohort with a mean age of 30 years, while the initial normalized deep GM volumes were greater in men, the follow-up volumes became similar between two sexes after 5 years (75). Moreover, compared to men, greater total brain, cortical and brainstem volumes were observed in women with MS onset before menopause, whereas no difference was found in women with MS onset after menopause (76). In parallel, another study found greater GM and central atrophy rates in men compared to age-matched women in earlier decades of life, but this difference was nullified after age 60 (50). This suggests a potential role of menopause and change in sex hormone levels contributing to increased atrophy rates in women, resulting in women catching up to men. This aligns with what is observed clinically; after progressive MS onset, disability worsening rate increases in women, catching up to men (8). Additionally, women with an earlier age at menopause onset tend to transition to the progressive phase earlier (77) and disability worsening increases after menopause (78).

Anti-Mullerian hormone (AMH) can be used as a biomarker of ovarian aging, as plasma AMH levels associate with oocyte and leukocyte telomere lengths as well as antral follicle counts and start to decrease with ovarian aging (79). In contrast, the levels of gonadal sex hormones such as estrogen and progesterone often start to drop later on during the perimenopausal transition. Although AMH may not necessarily have similar pleiotropic effects on the brain like gonadal sex hormones, in a study on women with MS, lower AMT levels correlated with greater GM atrophy and disability independent of age and disease duration in women with MS (80). The impact of this decline in reproductive hormone levels on brain atrophy is also seen in the general population. Premenopausal women who underwent bilateral salpingo-oophorectomy had smaller amygdala volumes, thinner parahippocampal-entorhinal cortex, and lower entorhinal WM integrity compared to controls (81). Whether abrupt or relatively gradual, reproductive hormone changes may lead to regional structural abnormalities in the brain, possibly preceding cognitive decline in cognitively unimpaired women (81) and disability worsening in women with MS (80).

6 How does hormone therapy affect imaging biomarkers in MS?

The above arguments point to clear sex differences in MS, suggesting a potential for reversal of these trends with HT in both men and women. As deficiency in sex hormones is associated with deterioration of imaging metrics in MS, patients may benefit from HT.

In a pilot study, the effect of testosterone supplementation was evaluated in 10 men with relapsing-remitting MS (82). Patients first had a 6-month pretreatment period, followed by a 12-month period of 100 mg daily testosterone gel treatment. After one year of treatment, participants showed an increase in lean body mass without any significant adverse effects, as well as a significant improvement in Paced Auditory Serial Addition Task (PASAT) scores. There was no significant change in the number or volume of gadolinium-enhancing lesions with treatment. However, compared to the first half of the study (6 months of pretreatment, 3 months of testosterone treatment), in the second half of the study (9 more months of testosterone treatment), the annualized rate of brain volume loss was reduced by 67%. Therefore, in addition to the improvement in cognition, men with MS experienced a slowing in brain atrophy after using testosterone treatment for 12 months. Although a potential anti-inflammatory effect of testosterone was not detected in this group of patients with low level of baseline inflammatory activity, the findings of this small study suggested a potential neuroprotective impact of testosterone supplementation in men with MS, which would merit further exploration (82).

In women with MS <50 years, after 24-months of estriol treatment (along with glatiramer acetate), the voxel-based morphometry showed localized GM sparing, particularly in the frontal cortex, correlating with cognitive improvement (83). This is supported by animal studies demonstrating an increase in remyelination and decrease in microglial activation with estrogen treatment (84). This is also consistent with HT study findings in healthy women, such as the Kronos Early Estrogen Prevention Study (KEEPS) (85). In recently menopausal women treated with transdermal estradiol or oral conjugated equine estrogen (CEE), the WM hyperintensity volume increased in both groups, which was different from the rate of WM hyperintensity increase in the placebo group in the oral CEE group, but not in the transdermal estradiol group. Furthermore, the transdermal estradiol group had preservation of prefrontal cortex volume over 7 years of longitudinal MRI compared to the placebo group (85). However, the increase in WM hyperintensity in the oral CEE group compared to the placebo group did not persist 10 years after the end of KEEPS in the KEEPS continuation study. No differences in WMH was identified when the treatment groups (transdermal estradiol, oral CEE) were compared to placebo 10 years after the end of hormone therapies (14 years after randomization) (86).

Few studies have used therapies aimed at altering a woman's hormones, either as oral contraceptive pill or HT, with MRI lesion load as an outcome measure. One study used a combination of interferon beta-1a and oral contraceptive pill (containing ethinylestradiol and desogestrel), finding that more patients did not develop gadolinium-enhancing lesions compared to those treated with interferon beta-1a alone (87). Similarly, another study showed a longer time to the next gadolinium-enhancing lesion in women on continuous oral contraception compared to women who were not (88). There was also a randomized clinical trial using either the combination of glatiramer acetate and estriol or glatiramer acetate and placebo in women ages 18–50 with MS, finding a decrease in relapse rate but no change to MRI lesions (89). Lastly, one study (POPARTMUS) used a combination of nomegestrol acetate and 17-beta-estradiol in post-partum women with MS, finding no difference in annualized relapse rate compared to placebo at 12 weeks, and no difference between groups with respect to volume or number of gadolinium-enhancing or T2 lesions on MRI (90).

In a study on 14 peri/postmenopausal women with MS and 13 controls, the use of HT (estradiol and cyclical dydrogesterone) for 12 months improved vasomotor and depressive symptoms at 3 and 12 months in both groups and showed no change to MRI lesion burden with respect to gadolinium-enhancing or T2-FLAIR lesions at 12-months (91). In a follow-up study on 16 peri/postmenopausal women with MS, lower baseline estradiol correlated with lower whole brain volume on MRI independent of age. Lower baseline estradiol also correlated with higher brain white matter lesion load and higher serum NfL (sNfL) and serum glial fibrillary acidic protein (sGFAP) levels (92). Over one year of menopausal HT, there was no significant change in white matter lesion load, whole brain volumes, sNfL and sGFAP. In another pilot study on 24 peri/postmenopausal women with MS treated with bazedoxifene plus conjugated estrogen for 2 months, hot flashes were improved (93). Of the 12 participants who underwent MRI, only one in the placebo group, who was not on DMT, developed new gadolinium enhancing lesions in 8 weeks, whereas none of the 8 in the hormone treatment group, who were all on DMTs, developed new lesions (93). Other than the aforementioned studies, there is a dearth of studies on HT use in menopausal women, which would be important given the higher propensity for disability worsening upon entering menopause.

Transgender individuals also warrant mention here, though data is very limited. One study has shown that MS risk is higher in transgender individuals having undergone male-to-female transition (94). The specific effects of HT on clinical and imaging outcomes in these individuals with MS is unknown. However, in transgender individuals without MS, those undergoing male-to-female transition receiving estradiol and anti-androgen treatment developed volume decreases in total brain (95), hypothalamus (95), and hippocampus (96), as well as reduction in cortical thickness (97).

7 How does the intersection of sex and race/ethnicity affect imaging biomarkers in MS?

Most studies above do not report on the racial/ethnic makeup of the participants, nor do they analyze differences between diverse racial/ethnic groups in conjunction with age and sex. This is an unmet need in MS, and of great importance given African Americans tend to have more aggressive disease, both clinically and radiologically, than White Americans (21, 98, 99).

Few studies exist on international populations with MS looking at sex differences on imaging. A study using the Argentine MS Registry (RelevarEM) (39) did not report on the race/ethnicity makeup of their participants. Other registries with diverse racial/ethnic groups with MS include the National African Americans with MS Registry (NAAMSR) (100) and the North American Research Committee on Multiple Sclerosis (NARCOMS) (101). These are promising avenues for further exploration of the interactions between sex and race/ethnicity and MS, including MRI outcomes.

With the lack of MS studies looking at the intersection between sex and race/ethnicity, one can turn to other systemic autoimmune conditions where this has been studied more extensively, including systemic lupus erythematosus (SLE) and sarcoidosis, for insight. In SLE, African American men fare worse than African American women with a higher likelihood of end organ damage and death (102). Similar to MS, the prevalence of SLE in African American women is higher than that in White American women (103) as is the prevalence in Latin American women compared to non-Latin American White women (104). Furthermore, African Americans with SLE have more severe disease compared to White Americans (105). The presence of focal brain lesions in SLE is associated with African American ethnicity, with analysis of sex not revealing an additional association (106).

Sarcoidosis is more common in African Americans than White Americans, with African Americans having earlier age of onset and being more likely to die from the disease (107). In neurosarcoidosis specifically, African Americans are less likely to show resolution of abnormalities on MRI than other races/ethnicities (108).

The extent of interaction between race/ethnicity and sex in other disorders is not limited to the immune activation and its measures. As the other component of pathobiology of MS is neurodegeneration, one can investigate such interactions in other neurodegenerative disorders. In dementia, age-standardized incidence of Alzheimer's disease (AD) was found to be higher in women than men, and AD risk was higher in African Americans and Native Hawaiians, whereas the risk was similar in Latin Americans, and lower in Asian Americans compared to White Americans (109). High exposure to statins correlated with a lower risk of AD among White women, White men, Latin American women, Latin American men and Black women, but not in Black men (110). Given the clinical and imaging interactions between sex and race/ethnicity noted in these studies of other systemic autoimmune and neurodegenerative diseases, more work needs to be done using imaging biomarkers as an outcome measure to study the intersection of sex and race/ethnicity in the clinical, imaging, and laboratory immunophenotypes of MS in the age spectrum.

8 Discussion

There are clear sex differences in MS seen with imaging, with women tending to have a higher number of T2 hyperintense and gadolinium-enhancing lesions, as well as greater WM atrophy. Both T2 hyperintense and gadolinium-enhancing lesions tend to increase in the postpartum period but decrease after menopause. In contrast, men are likely to have more T1 hypointense, cortical GM, infratentorial, and spinal cord lesions. Men also demonstrate lower diffuse and regional WM integrity as well as decreased functional connectivity and re-organization in the brain than women, which suggests better functional preservation and CNS reserve in women. Moreover, men have a higher number of chronic active WM lesions with rims and lower WM integrity in chronic stable WM lesions than women. Men exhibit greater whole brain and GM atrophy than women, especially early in the disease course. However, with aging, and potentially with menopause, no significant difference in brain volume is seen between the sexes, especially after around the sixth decade. In parallel, a decrease in T2 hyperintense and gadolinium-enhancing lesions along with decrease in brain atrophy rates were observed in women who received HT (Figure 1).

Based on imaging study findings, neuronal and axonal loss is overall more extensive in men with MS, leading to a more neurodegenerative disease process early on (49, 111) in a region-specific manner (52). Chromosomal differences between sexes and how they affect the nervous and immune systems are one of the main drivers of sex differences observed in CNS atrophy metrics of MS. The XX genotype exhibits a more proinflammatory immune response (112) whereas the XY genotype exhibits a more neurodegenerative response to an immune system attack (49, 111).

Differences in sex hormone patterns also play a main role in the sex variability in imaging metrics through their relationship with nervous and immune systems, as sex hormones have both neuroprotective and anti-inflammatory effects (113–115). The gradual decline in sex hormones with aging and menopause is associated with immuno-senescence and decreased neuronal repair, and appears to result in enhancement of neurodegenerative outcomes including increase in brain atrophy in MS.

From the work reviewed here, while there is a higher number of studies looking at impact of sex on clinical and imaging phenotypes of MS, such studies are less common with race/ethnicity. Similarly,

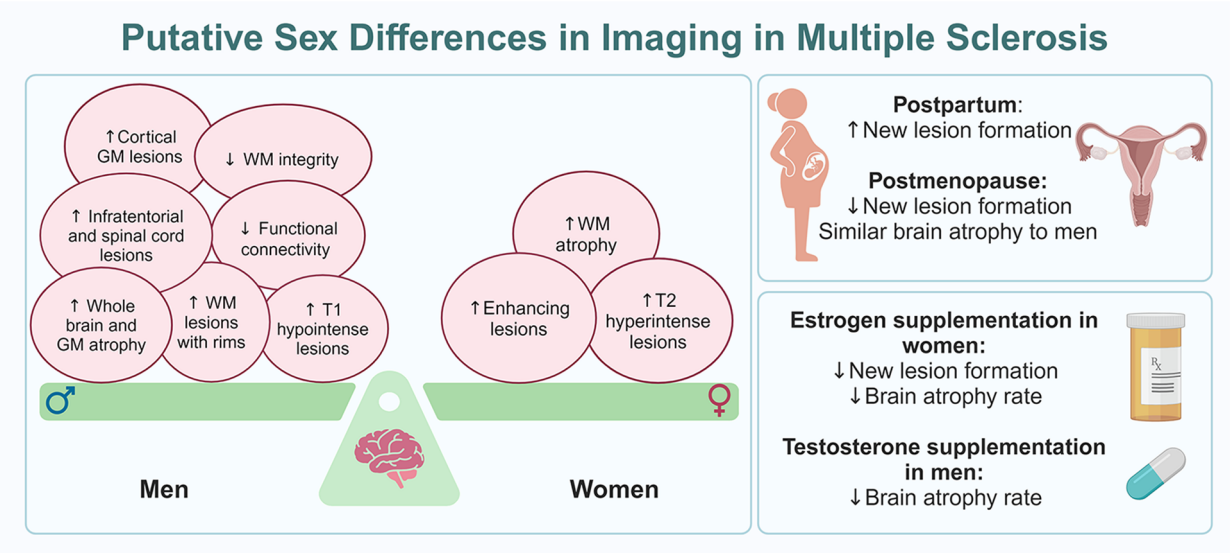

FIGURE 1
Putative sex differences in imaging in MS. The panel on the left shows the balance of imaging findings between women and men with MS, with women having more MRI markers of inflammatory disease while men have more MRI markers of neurodegeneration, often early in the disease course. The panels on the right outline MRI changes seen at reproductive milestones for women with MS (top) and how hormone therapy can impact MRI findings in both women and men with MS (bottom).

with imaging biomarkers, the interactions with race/ethnicity have not been studied. The paucity of studies with race/ethnicity as opposed to sex is somewhat understandable given the easier definition of sex as a variable rather than race/ethnicity in studies, along with the fact that many centers may not have enough representation of different ethnicities across the globe.

While single variable studies are helpful in answering focused questions in MS, genetic and hereditary variables such as sex and race/ethnicity, along with the impact of socioeconomic status and disparities directly tied into these variables, cannot be separated into single variable silo studies. Our review highlights the significant unmet need in studying how age, sex and race/ethnicity interact in predicting imaging and clinical outcomes in MS. Such studies need to be conducted with significant effort across multiple centers with sufficient power to come up with better predictive models to individualize health care in discrepant MS populations.

Author contributions

NNa: Conceptualization, Writing – original draft, Writing – review & editing. NNe: Data curation, Visualization, Writing – review & editing. OK: Conceptualization, Writing – review & editing. BZ: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The absence of formal work experience may affect the rate of cognitive decline in older adult women: findings from the health and retirement study

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Objective: This study investigated the relationship between years of employment and cognitive health among older non-Latinx Black, Latinx, and non-Latinx White women. We hypothesized that women who had never been formally employed (i.e., zero years of formal work experience) would exhibit a pronounced cognitive decline.

Methods: Our study included 5,664 older adult women from the Health and Retirement Study (2010–2016) aged 65–101 ($M = 75.41$). Out of 5,664 participants, 850 identified as non-Latinx Black, 475 identified as Latinx, and 4,339 identified as non-Latinx White. Furthermore, 5,292 women indicated having a professional employment history of at least one year, whereas 372 women reported no formal work experience. The Telephone Interview for Cognitive Status-27 (TICS-27) was used to assess cognitive performance. Linear mixed effects models were conducted to assess whether employment history was associated with the rate of cognitive decline.

Results: In all three racial and ethnic groups, lower age, higher education, greater number of years worked, fewer chronic conditions, and greater household income were associated with better cognitive performance at baseline ($p < .05$). Additionally, women who had not worked in any formal capacity had a lower baseline cognitive performance ($p < .001$) and a more extreme decline in cognitive performance over time ($p = .04$).

Conclusion: In conclusion, we found that women without any formal work experience performed lower at baseline and experienced a steeper cognitive decline over time. These findings underscore the need to further explore the complex interrelationships between employment duration and cognitive trajectories, especially among older women and those from different racial and ethnic backgrounds.

KEYWORDS

cognitive reserve, occupation, gender norms, socioeconomic factors, ethnic minority, aging

Introduction

Cognitive decline remains one of the world's most burdensome chronic health conditions. Rates of Alzheimer's disease and related dementias (ADRD) have risen in recent years (1), and disproportionately across marginalized racial and ethnic groups. Non-Latinx Black and Latinx older adults have an increased risk of receiving an ADRD diagnosis when compared to their non-Latinx White counterparts (2–4), and this higher rate of ADRD is largely due to the effects of systemic racism on health and educational, occupational, and social opportunities. Additionally, women have an increased risk of developing ADRD (5). This greater risk may be linked to several factors: women are more likely than men to live into older age (6), there are sex differences in ADRD neuropathology and changes in hormones during menopause may affect risk (1, 5), and gender discrimination in education and work opportunities may result in lower cognitive reserve (CR) (7, 8).

Cognitive reserve

CR helps explain the discrepancies between neuropathology and clinical functioning. Individuals with high CR may not show symptoms of ADRD, despite significant brain atrophy and network disruption (9). CR has been linked to a 47% reduction in the risk of progressing to Mild Cognitive Impairment (MCI) or ADRD, independent of structural pathology and Alzheimer's biomarkers (10). CR enables alternative neuronal networks and cognitive strategies to maintain performance despite brain changes (11). However, operationalizing CR is complex due to varying definitions that influence the perceived risk of MCI or ADRD. Proxies like educational attainment, occupational complexity, and participation in intellectually enriching activities are often used as indirect measures of CR, assuming that higher levels indicate greater reserve (12). Another approach uses residual cognitive performance after adjusting for AD neuropathology to measure CR (10).

CR is significantly shaped by social determinants of health (SDoH), including education, occupational history, and socioeconomic status (SES). Education strengthens and creates neural networks (13–15) and serves as a proxy for higher SES. Those with higher educational attainment often secure better-paying jobs, leading to health-promoting behaviors, reduced social stressors, and a lower risk of cognitive decline (7, 16, 17). Occupation, as a core SES indicator, supports health maintenance by contributing to economic, cultural, or social capital (16, 18) and may directly influence cognitive outcomes (19).

The role of occupational history on cognitive reserve

Adulthood is largely occupied with work-related activities that demand significant time and energy (20). Jobs involving monotonous, low-skill tasks (low job complexity) and limited autonomy (low job control) are associated with poorer cognitive performance (21). In contrast, roles requiring higher cognitive engagement and complex social interactions are linked to better cognitive performance (22–27), reduced risk of ADRD (28), and a slower rate of cognitive decline post-retirement (29, 30), and roles with high autonomy correlate with increased hippocampal volume and a slower reduction in this volume over time (31, 32). Additionally, the cognitive benefits of job complexity appear to be moderated by leisure activity, especially social activities (22).

Racial discrimination's impact on occupation and cognitive reserve

Simons et al. (33) suggest a possible role of SES and discrimination on accelerated biological aging through the accrual of chronic illnesses. The impacts of racial discrimination and chronic stress due to socioeconomic hardship, substandard education quality, and neighborhood disadvantages are linked to cognitive impairment and an increased risk of ADRD (2–4). Differences in SDoH account for 39% of the non-Latinx Black-non-Latinx White disparity and 76% of the Latinx- non-Latinx White disparity in cognitive performance (34), with years worked explaining 6% and 10% of these disparities, respectively. However, the protective effects of higher education or occupational complexity on cognitive decline may not apply equally across non-Latinx Black, Latinx, and non-Latinx White adults (18, 35–38), in part due to poorer educational quality and limited opportunities for occupational mobility among marginalized groups (39).

Gender norms impact on occupation and cognitive performance

Gender disparities shape how occupational history impacts cognitive performance in older adulthood (40, 41). Occupational roles, often limited by historical gender norms, significantly influence cognitive health in later life (8, 42). Women, especially those from older birth cohorts, were subject to lower expectations for educational attainment and occupational status, often confined to roles with less cognitive complexity that could impact the rate of cognitive decline years later (22, 41). This effect is even more pronounced in women of color, who have faced compounded challenges due to intersecting sexism and racism, further limiting their educational and occupational opportunities and, thus, influencing their cognitive health (22, 43).

This study examined the impact of formal work experience on cognitive decline in older women, focusing on non-Latinx Black, Latinx, and non-Latinx White women to understand how years of formal employment affected cognitive trajectories. We hypothesized that having greater formal employment history would affect the rate of change on the TICS-27 over time (i.e., the interaction of employment duration by time) and that this effect would differ among non-Latinx Black, Latinx, and non-Latinx

White women. Furthermore, we hypothesized that women who had never been formally employed (i.e., zero years of formal work experience) would exhibit a pronounced rate of cognitive decline.

Methods

Participants and study design

This is a retrospective cohort study examining a sample of older adult women (>65 years) from the Health and Retirement Study (HRS). The present study utilizes longitudinal data from the following four consecutive assessments: wave 10 (2010), wave 11 (2012), wave 12 (2014), and wave 13 (2016). The HRS is a collaboration between the National Institute of Aging (U01AG009740) and the University of Michigan, started in 1992. Managed by the University of Michigan's Survey Research Center, the study has maintained response rates between 81.7% and 89.1% since inception (49).

Inclusion criteria were: (1) aged ≥ 65 years at wave 10 and (2) identified as non-Latinx Black, Hispanic/Latinx, or non-Latinx White. Participants that identified as "other," or were missing race and ethnicity data were excluded. Outcome: The Telephone Interview for Cognitive Status-27 (TICS-27) was used to assess cognitive performance. The TICS-27 is a 27-item measure of global cognition, scored using the Langa-Weir composite scoring approach (44). This method allocates 20 points to short-term and long-term memory and 7 points to processing speed and executive functions, with total scores ranging from 0 to 27.

Covariates

The following covariates were included to control for possible confounding contributors to cognitive decline: age (years), education (years), body mass index, annual household income (natural-logged U.S. dollars), and number of chronic health conditions, including high blood pressure, diabetes, cancer, lung disease, heart problems, stroke, psychological problems, and arthritis. All covariates were estimated at participants' 2010 (wave 10) assessment which functioned as a baseline for our analyses.

Statistical analysis

Linear mixed effects models (LMMs) were conducted to assess the impact of employment duration on the rate of cognitive decline (i.e., change in cognitive performance over time). In this multilevel LMM framework, cognitive performance at each wave (Level 1) was nested within each participant (Level 2) to determine how women performed over time. Models were stratified by race and ethnicity (non-Latinx Black, Latinx, and non-Latinx White). The main independent variable of interest was employment duration (number of years worked), and the main outcome variable of interest was performance on the TICS-27 score measured consecutively over four waves. The coefficient for employment duration describes the average change in cognitive performance at baseline for each additional year of formal work experience. The coefficient for time describes the average change in cognitive performance over each wave (in roughly 2-year increments). An interaction term of time by employment duration describes the impact of each additional year of formal work experience on the average rate of change in cognitive performance. LMMs included a random intercept to capture interindividual differences at baseline. A random slope capturing intraindividual differences could not be estimated due to low within-person variance over time (i.e., the rate of change was largely homogeneous).

An additional LMM using the full sample (all three race and ethnicity groups) was constructed to examine cognitive decline in women with some vs. no formal work experience. In this model, employment duration was dummy coded as a categorical variable (zero years worked vs. one or more years work). An interaction term of time by the categorical employment duration variable assessed the impact of having no formal work experience on the average rate of change in cognitive performance. Due to significant differences in education between the two employment duration groups (i.e., a large effect size difference), models with education and without education are presented. As a sensitivity analysis, all models were reconducted with the TICS-20 memory component subscore (10 points immediate recall; 10 points delayed recall).

Results

The final sample included 5,664 women aged 65–101 ($M = 75.41$, $SD = 7.22$), of which 850 identified as non-Latinx Black, 475 identified as Latinx, and 4,339 participants identified as non-Latinx White. 5,292 women (93%) indicated having a professional employment history of at least one year, whereas 372 women (7%) reported no formal work experience. See Table 1 for baseline demographic information stratified by race and ethnicity.

In all three racial and ethnic groups, lower age, higher education, greater number of years worked, fewer chronic conditions, and greater household income were significantly associated with higher TICS-27 scores (indicating better cognitive performance) at baseline ($p < .05$). In the non-Latinx Black and non-Latinx White groups, higher body mass index was also significantly associated with higher TICS-27 scores at baseline. No significant interactions were observed between duration of employment and slope of cognitive performance in any of the racial and ethnic groups ($p > .05$; Table 2). Removing educational attainment as a covariate from the race and ethnicity stratified analyses did not appreciably change the results.

In the full sample, women with some work experience ($M = 12.41$, $SD = 2.84$) compared to women with none ($M = 10.08$, $SD = 3.73$) had significantly higher levels of education, ($p < .001$, Cohen's $d = -0.80$). When excluding education as a covariate, having no formal work experience was significantly associated with lower TICS-27 scores at baseline ($p < .001$) and a greater rate of decline in cognitive performance over time ($p = .04$) compared to having one or more years of formal work experience. Compared to non-Latinx White women, non-Latinx Black and Latinx women

TABLE 1 Demographic characteristics by race and ethnicity group.SD, standard deviation; TICS-27, telephone interview for cognitive status–modified 27-item.

Variables	Full sample (n = 5,664)		Non-Latinx black (n = 850)		Latinx (n = 475)		Non-Latinx white (n = 4,339)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	75.41	7.22	74.31	6.76	74.20	6.42	75.75	7.36
Education (years)	12.25	2.97	11.72	2.98	8.26	4.53	12.80	2.33
Employment duration (years worked)	29.78	16.66	32.86	15.89	21.36	17.27	30.09	16.45
Annual household income	$43,836.49	$68,247.68	$26,536.52	$27,846.32	$23,019.94	$28,136.51	$49,504.35	$75,524.32
Body mass index	27.63	6.12	29.90	6.83	28.80	6.19	27.06	5.85
Chronic health conditions	2.46	1.40	2.68	1.35	2.46	1.44	2.42	1.40
TICS-27 total score at baseline/wave 10	14.21	4.62	11.91	4.82	11.81	4.67	14.93	4.34
TICS-27 total score at wave 11	14.05	4.66	11.94	4.72	11.43	4.74	14.74	4.41
TICS-27 total score at wave 12	13.90	4.77	11.45	4.84	11.08	4.66	14.67	4.49
TICS-27 total score at wave 13	13.62	4.75	11.40	4.64	10.65	4.73	14.41	4.49
TICS-20 memory component subscore at baseline/wave 10	9.26	3.48	8.17	3.50	8.20	3.37	9.59	3.42
TICS-20 memory component subcore at wave 11	9.14	3.49	8.10	3.44	7.78	3.39	9.49	3.43
TICS-20 memory component subcore at wave 12	8.98	3.59	7.73	3.49	7.45	3.40	9.38	3.53
TICS-20 memory component subscore at wave 13	8.74	3.53	7.66	3.32	7.12	3.37	9.14	3.50

TABLE 2 Linear mixed effects models assessing the association of employment duration, covariates, and cognitive decline assessed via TICS-27 total score stratified by race and ethnicity.

	Model 2 Non-Latinx black			Model 3 Latinx			Model 1 Non-Latinx white		
	B	CI	p	B	CI	p	B	CI	p
Age (years)	−.201	(−.237, −.165)	<.001	.298	(−.236. −.134)	<.001	−.215	(−.229, −.200)	<.001
Education (years)	.588	(.509, .668)	<.001	−.185	(.222, .373)	<.001	.462	(.417, .506)	<.001
Employment duration (years worked)	.031	(.011, .051)	.003	.049	(.023, .074)	<.001	.019	(.010, .027)	<.001
Annual household income (log-transformed)	.233	(.115, .350)	<.001	.151	(.014, .289)	.031	.455	(.346, .563)	<.001
Body mass index	.041	(.007, .076)	.019	.037	(.015, .090)	.164	.050	(.033, .068)	<.001
Chronic health conditions	−.314	(−.485, −.143)	<.001	−.374	(−.596, −.152)	<.001	−.338	(−.411, −.264)	<.001
Slope	−.551	(−.800, −.302)	<.001	−.538	(−.738, −.338)	<.001	−.531	(−.622, −.441)	<.001
Employment duration* slope	.001	(−.005, .008)	.738	.000	(−.007, .007)	.942	.001	(−.002, .004)	.454

Asterisk denotes an interaction term.

performed lower at baseline ($p < .001$). When adjusting for education, differences between women with and without formal work experience were no longer significant, suggesting that disparities in educational attainment partially attenuated the relationship between formal work experience and cognitive decline. See Table 3 for full model details.

When repeating the above analyses with the TICS-20 memory component subscore as the outcome variable, results largely remained the same. However, in the full sample, having no formal work experience was associated with lower performance on the TICS-20 memory component scores at baseline, and this effect persisted after adjusting for education ($p = .04$). See Tables 4, 5 for full details.

Discussion

This study was primarily focused on elucidating the impact of formal work experience on the cognitive trajectories of older women (≥65), with a particular emphasis on historically marginalized groups, including non-Latinx Black, Latinx, and non-Latinx White women. We examined the impact of employment duration on cognitive decline over time, considering potential variations across different racial and ethnic backgrounds. Our results did not substantiate the first hypothesis. The number of years of employment did not affect the rate of cognitive decline, nor was there a differential impact by race and ethnicity among the women in our study. However, years worked did positively impact baseline performance, with each of the racial and ethnic groups having better TICS-27 and TICS-20 performance with greater employment history.

Discrimination based on race and ethnicity significantly influences employment opportunities and cognitive health trajectories. For non-Latinx Black Americans, the effects of institutional racism result in reduced access to high quality education, lower job attainment, and diminished income compared to other racial and ethnic groups (33). non-Latinx Black Americans disproportionately experience socioeconomic stressors, including financial precarity, lower-status jobs, periods of unemployment, inadequate housing, and the compounded

TABLE 3 Linear mixed effects models assessing the association of categorical employment duration, covariates, and cognitive decline assessed via TICS-27 total score in the full sample.

	Model 4a Full sample (without education as a covariate)			Model 4b Full sample (with education as a covariate)		
	B	CI	*p*	B	CI	*p*
Age (years)	−.229	(−.243, −.215)	<.001	−.214	(−.223, −.201)	<.001
Education (years)	–	–	–	.470	(.434, .505)	<.001
Race/Ethnicity						
White (ref)	–	–	–	–	–	–
Non−Latinx black	−2.873	(−3.143, −2.603)	<.001	−2.501	(−2.761, −2.240)	<.001
Latinx	−2.822	(−3.167, −2.476)	<.001	−1.004	(−1.374, −.635)	<.001
Annual household income (log-transformed)	.512	(.440, .583)	<.001	.356	(.278, .435)	<.001
Body mass index	.033	(.017,.049)	<.001	.050	(.034, .066)	<.001
Chronic health conditions	−.445	(−.514, −.376)	<.001	−.364	(−.431, −.297)	<.001
Slope	−.500	(−.538, −.463)	<.001	−.495	(−.533, −.457)	<.001
Work experience (yes/no)						
Yes (ref)	–	–	–	–	–	–
No	−1.290	(−1.80, −.774)	<.001	−1.005	(−2.096, .087)	.071
Work experience (yes/no) * slope						
Yes (ref)	–	–	–	–	–	–
No	−.172	(−.338, −.005)	.043	−.178	(−.532, .176)	.324

Asterisk denotes an interaction term. Ref: reference category.

TABLE 4 Linear mixed effects models assessing the association of employment duration, covariates, and cognitive decline assessed via TICS−20 memory component subscore stratified by race and ethnicity.

	Model 2 Non-Latinx black			Model 3 Latinx			Model 1 Non-Latinx white		
	B	CI	*p*	B	CI	*p*	B	CI	*p*
Age (years)	−.164	(−.189, −.139)	<.001	−.144	(−.180, −.107)	<.001	−.183	(−.194, −.172)	<.001
Education (years)	.316	(.260, .372)	<.001	.137	(.083, .191)	<.001	.278	(.245, .312)	<.001
Employment duration (years worked)	.026	(.010, .042)	.001	.031	(.011, .051)	.002	.010	(.004, .017)	.002
Annual household income (log-transformed)	.111	(.027, .196)	.010	.090	(−.008, .187)	.073	.293	(.212, .376)	<.001
Body mass index	.016	(−.008, .040)	.197	.016	(−.023, .054)	.423	.031	(.018, .044)	<.001
Chronic health conditions	−.128	(−.248, −.007)	.038	−.232	(−.392, −.072)	.005	−.209	(−.265, −.153)	<.001
Slope	−.357	(−.569, −.145)	<.001	−.480	(−.655, −.305)	<.001	−.424	(−.501, −.346)	<.001
Employment duration * slope	−.001	(−.007, .004)	.624	.000	(−.006, .006)	.971	.001	(−.001, .003)	.304

Asterisk denotes an interaction term.

challenges of food deserts and elevated crime rates (45). These factors hinder professional advancement and may negatively affect cognitive reserve. Additionally, it is well-known that chronic conditions may cluster among racial, ethnic, geographic, or cultural groups due to differences in health behaviors, access to healthcare, systemic inequities, and the numerous impacts of social determinants of health. Future work should consider whether specific chronic conditions uniquely affect the rate of cognitive decline in older women from different backgrounds and identities.

Educational attainment was included and excluded from certain models to determine whether the effect of years worked on cognitive performance was fully or partially explained by educational attainment. Given that educational attainment can confound the relationship between years worked and cognitive performance, it was essential to assess its attenuating effect. Although women without formal work experience performed worse at baseline and over time, these findings were attenuated by the inclusion of educational attainment. A larger sample would be needed to determine if educational attainment and formal work experience independently affect cognitive performance at baseline and over time or if these factors are interdependent.

We hypothesized that older women with no formal employment history would demonstrate a more pronounced rate of cognitive decline, supported by existing literature that highlights the role of job complexity in mitigating cognitive decline and reducing the risk of ADRD (22–28). Historically, women in the United States were restricted from fully participating in the formal workforce due to gender norms and legal discrimination until the Civil Rights Act of 1964. As a result, older cohorts of women (e.g., Silent Generation, Greatest Generation) often assumed demanding, unpaid roles as homemakers and caregivers, while their daughters (e.g., Baby Boomers) were encouraged to pursue "feminine" roles in the

TABLE 5 Linear mixed effects models assessing the association of categorical employment duration, covariates, and cognitive decline assessed via TICS-20 memory component subscore in the full sample.

	Model 5a Full sample (without education as a covariate)			Model 5b Full sample (with education as a covariate)		
	B	CI	*p*	B	CI	*p*
Age (years)	−.190	(−.120, −.180)	<.001	−.183	(−.193, −.173)	<.001
Education (years)	–	–	–	.269	(.244, .294)	<.001
Race/Ethnicity						
White (ref)	–	–	–	–	–	–
Non-Latinx black	−1.467	(−1.66, −1.272)	<.001	−1.313	(−1.502, −1.125)	<.001
Latinx	−1.455	(−1.70, −1.205)	<.001	−.424	(−.683, −.165)	.001
Annual household income (log-transformed)	.305	(.253, .357)	<.001	.187	(.136, .238)	<.001
Body mass index	.019	(.007, .031)	.001	.026	(.015, .037)	<.001
Chronic health conditions	−.279	(−.329, −.229)	<.001	−.230	(−.278, −.182)	<.001
Slope	−.392	(−.424, −.360)	<.001	−.390	(−.422, −.358)	<.001
Work experience (yes/no)						
Yes (ref)	–	–	–	–	–	–
No	−.743	(−1.149, −.337)	<.001	−.421	(−.821, −.021))	.039
Work experience (yes/no) * slope						
Yes (ref)	–	–	–	–	–	–
No	−.124	(−.266, .018)	.086	−.106	(−.247, .036)	.143

Asterisk denotes an interaction term. Ref: reference category.

economy, such as teachers, nurses, administrative assistants, wait staff, and beauticians. These generational gender norms and legal segregation led to disparities in educational attainment, occupational status, and work complexity for women, which may have influenced their cognitive functioning and trajectory in later life (8, 42). This hypothesis aligns with the broader narrative that women are at an elevated risk for ADRD, a disparity that may be partly attributable to gender-based differences in CR stemming from historical discrimination in educational and occupational opportunities (5, 7, 8).

The Latinx cohort performed similarly at baseline to the non-Latinx Black cohort, despite having worked fewer years (21.36 vs. 32.68) and having lower educational attainment (8.26 vs. 11.72) on average. Age does not appear to be a confound, as these two groups were similar (74.20 vs. 74.31). If educational attainment was fully attenuating the relationship between formal work experience and cognitive performance, we might expect a significantly lower performance from our Latinx cohort. Because we do not see this (TICS-27: 11.81 vs. 11.91), it suggests that other factors such as education quality, cognitive reserve, test-wiseness, or a variety of other factors may be preserving our Latinx cohort's performance, at least on a univariate level.

Educational attainment is not solely a measure of knowledge or skill acquisition; it is often indicative of a broader spectrum of socioeconomic advantages. Higher education is correlated with higher-paying occupations, which may be a reflection of or a pathway to generational wealth. Such economic stability can afford an individual the luxury of engaging in health-promoting activities, accessing superior healthcare services, or reducing exposure to chronic social stressors—all of which are linked with preserving cognitive function (7, 16, 17). Moreover, prior literature has highlighted that education can enhance the brain's resilience to neuropathological damage by strengthening existing neural networks and facilitating the development of new ones (14). This reserve allows individuals to better cope with the structural changes associated with aging and potentially delays the onset of clinical manifestations of ADRD. However, older women with no formal work experience had fewer years of education on average in our study. It is possible that educational attainment and formal work experience impact cognitive health through similar processes for some women (e.g., cognitive reserve), but this is not likely to be true for all women. There may be a variety of reasons why a woman chooses to or is forced to abstain from the workforce (e.g., preference and economic ability to do so; health concerns; experiences of discrimination; gender roles and expectations), and each of these groups may have a different level of education and risk for cognitive decline in later life. Clearly, more work needs to be conducted along these lines.

Furthermore, despite our initial hypotheses, we did not observe an effect of employment duration on cognitive decline across non-Latinx Black, Latinx, or non-Latinx White older women. Several SDoH are known to impact cognitive health and risk of ADRD (46, 47), yet determinants especially prominent among historically underserved groups remain understudied (e.g., experiences of discrimination, exclusion from the formal workforce, nativity status; disparities in education quality) (34, 48). In our study, formal work experience affected cognitive performance and the rate of decline uniformly across non-Latinx Black, Latinx, or non-Latinx White women, which differs from the previous findings by Jester et al. (34) in which the number of years worked explained a sizeable proportion of the non-Latinx Black- non-Latinx White (6%) and Latinx- non-Latinx White (10%) disparities in cognitive performance at baseline. It is important to consider the possibility that a SDoH like work experience may influence performance at baseline, but not necessarily differences in longitudinal trajectories. Alternatively, it

may be that when measuring cognitive trajectories by race and ethnicity, education simply explains more of the variance, thus attenuating the relationship. Although our findings paint an unclear image of the relationship between the number of years worked and cognitive decline across racial and ethnic groups, it highlights the need for ongoing research into the SDoHs that impact cognitive health.

Our findings are subject to methodological limitations, primarily stemming from the structure and availability of variables within the HRS. The HRS's classification of racial and ethnic groups is limited, which may not capture the full diversity within each category. It does not include individuals who do not fit into the predefined classifications or have missing race and ethnicity data. This categorization limitation could lead to a lack of representation and an incomplete understanding of the cognitive trajectories across a more diverse population. Furthermore, the variables available in the HRS allowed us to consider the quantity of education, but not the quality. The quality of education is a critical factor that can influence cognitive outcomes and varies based on several factors, such as socioeconomic status, school resources, and geographic location. The absence of data on the quality of education means that our analysis may only partially reflect the nuanced ways in which educational experiences impact cognitive health. Unfortunately, the reason for being absent from the formal workplace was not registered in the HRS dataset. Work is needed to understand how education and formal work experience influence each other, and how/whether they explain the same or different aspects of cognitive performance and cognitive decline. Furthermore, residual confounding may exist in our models despite our attempts at controlling for a variety of demographic, social, and health factors. Finally, this study's outcome variable was limited to the TICS-27. While TICS-27 is a widely used and validated measure for assessing global cognitive performance in the HRS, it does not capture the various domains of cognition in sufficient detail. Given that our sensitivity analysis utilizing the TICS-20 memory component subscore yielded slightly differing results, future work should include a full cognitive battery when possible.

In addition to its limitations, this study has several strengths. One of the main strengths is the substantial sample size of older women, which allows for more robust and generalizable findings. The richness of the HRS data is another significant strength, providing comprehensive information on a wide range of variables, including demographic, socioeconomic, and health-related factors. Furthermore, the longitudinal design of the HRS allows for examining changes over time, adding depth to our understanding of cognitive decline.

In conclusion, the relationship between formal work experience, education, race and ethnicity, and cognitive decline in older women is complex and multifaceted. Our study adds to the growing body of literature recognizing educational disparities' crucial role in cognitive health outcomes. While our study points to educational disparities as a significant factor in cognitive decline, we recognize that education is intertwined with broader social issues, including gendered expectations and roles. The historical underrepresentation of women in higher education and the workforce, often due to caregiving responsibilities or cultural norms, especially in developing countries, merits further investigation to determine its impact on cognitive health. Moreover, gender discrimination and societal expectations have differentially shaped the educational and occupational opportunities available to women. As such, future studies should examine how these gendered experiences intersect with race and occupation to influence cognitive outcomes.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://hrsdata.isr.umich.edu/data-products.

Ethics statement

Ethical approval was not required for the studies involving humans because publicly available data sets were analyzed in this study. The studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

DG: Conceptualization, Writing – original draft, Writing – review & editing. MP: Formal Analysis, Methodology, Writing – review & editing. VL-J: Conceptualization, Supervision, Writing – review & editing. MA: Supervision, Writing – review & editing. DJ: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Unexplored avenues: a narrative review of cognition and mood in postmenopausal African women with female genital circumcision/mutilation/cutting

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Recent ageing research has projected the lifespan and proportion of postmenopausal women living in low- and middle-income countries to substantially increase over the years, especially on the African continent. An important subgroup within the African postmenopausal population is those with female genital circumcision/mutilation/cutting (FGC). Practised across 31 African nations, FGC holds cultural significance as it is deemed essential to marriage and successful womanhood. Perhaps because of this, most FGC studies have primarily focused on women's reproductive functioning and their mood experiences. These studies also usually exclude postmenopausal women from their cohorts. Consequently, cognition and age-related cognitive decline and preservation remain understudied. Therefore, we investigated what is known about mood and cognition in local and immigrant postmenopausal African women with FGC. To do this, we carried out a narrative review searching PubMed, PsycInfo, and Google Scholar databases. Boolean combinations of keywords related to FGC, cognition, ageing, and mood were used, with a focus on cognition and ageing-related terms. Only studies published in English, those that recruited African women with FGC aged 50 years and older, and those that investigated cognitive and/or mood-related experiences were included. Ten studies were found; these included quantitative, qualitative, and case reports. The age range of cohorts across included studies was 13–90 years; women who were likely postmenopausal formed a minority within the cohorts (4.5%–25%). There were no studies assessing memory or cognition beyond those looking at FGC-related memories, which were vivid, especially if women had type III FGC (Pharaonic) or were older at the time of FGC. Although most of these women reported experiencing negative emotions concerning FGC, quantitative reports showed that only a minority of women experienced post-traumatic stress disorder, anxiety, or depression. Thus, there remains an urgent need to bring this understudied group into ageing and dementia research. Future research should adopt mixed-methods with culturally sensitive methodologies to

investigate the lived experience of ageing as well as cognitive changes. A holistic understanding of ageing women from the Horn of Africa's experiences and needs will support an improvement in the quality of care delivered to this cohort in both local and immigrant contexts.

KEYWORDS

female genital cutting, cognition, mood, postmenopausal women, African women, ageing, memory

1 Introduction

Greater than any other region worldwide, recent reports and population ageing studies have shown a dramatic increase in the average life expectancy in Africa (1); epidemiological research has shown that approximately 212 million adults 60 years and older will be living on the continent by 2050 (2). Concomitantly, mixed-sex and community-based studies have already shown evidence of cognitive decline in Africans over 2 years of follow-up (3) and increasing rates of dementia (4). Postmenopausal women form an important part of the African population, given that, by the late 2020s, the proportion of postmenopausal women living in developing countries is estimated to become 76% (5), with approximately 5 million of them living in sub-Saharan Africa (6). Some studies on sub-Saharan African women have shown the transition into the postmenopausal phase to be associated with a decline in cognitive function (6, 7). Outside of African contexts, studies have also shown that Alzheimer disease (AD) and related dementias (ADRDs) may disproportionately affect African American populations with increasing age (8). Moreover, African persons' experiences with racial discrimination in new Western contexts may predict a myriad of challenges with age, such as a higher risk of ADRDs (9) and accelerated rates of cognitive decline relative to their White counterparts (10).

In certain African countries, studies have indicated the presence of an increasing mental health burden among the ageing population (11). In general, ageing can be accompanied by an increased risk of depression; additionally, depression increases health problems and rates of mortality among older adults (12, 13). Multiple systematic reviews and meta-analyses have established a bi-directional relationship between depression and frailty (14), where one is associated with an increased incidence in the other, or one may be a risk factor for the development of the other (15–17). Similarly, research has also shown various mood disorders (e.g., major depressive disorder, bipolar disorder) to be major risk factors for AD, with this risk doubled among older adults (18, 19). This is likely because both mood disorders and AD have shared biological mechanisms (18). Mixed sex studies have shown faster rates of ageing for African Americans at risk of depression due to racial discrimination relative to those not at risk of depression (20), highlighting an undeniable influence of mood on their ageing experiences. Studies on postmenopausal local African women have also shown a high prevalence of depressive mood, irritability, and anxiety (21). An important subgroup of postmenopausal women in Africa includes those that have experienced female genital cutting/circumcision/mutilation (FGC); however, the links between menopause, FGC, cognition, and mood remain understudied.

FGC is a practice involving partial or total cutting/removal of the external female genitalia (22). There are variations in the type of FGC performed both within and across countries. Based on the extent of the cut/removal, a widely accepted classification system has been devised, consisting of four major FGC types (23). Type I FGC involves the partial or complete removal of the clitoral glans and/or the clitoral head, type II FGC involves partial or complete removal of the clitoral glands and labia minora (with or without removal of the labia majora), type III FGC involves the narrowing of the vaginal opening by cutting the labia minora/majora and suturing them (Pharaonic), and type IV FGC includes all other procedures done to the female genitalia for non-medical reasons (e.g., pricking, cauterization, piercing, etc.). Across 31 countries, at least 200 million girls and women have FGC, with the practice being most widespread in Northern Africa (24). Indeed, some of the highest FGC prevalence rates worldwide have been found in African countries such as Somalia, Djibouti, and Mali (25, 26). FGC is practised in diverse ways both between and within different ethnoracial groups (27).

Despite the ongoing debate about the ethical implications of FGC (28, 29); at present, the World Health Organization has recognised the practice as a form of violation of human rights, discrimination based on gender, and violence against girls (30). However, it is important to embed the practice in an African cultural context, given that it holds paramount significance in the lives of many African women, both locally and for those who immigrate. FGC marks their initiation into womanhood, instantiates femininity, and inscribes several values of comportment and aesthetics. The ritual allows them to physically resemble other members of their community and thus, be considered more marriageable, beautiful, hygienic, and pure

Abbreviations

AD, Alzheimer's disease; ADRDs, Alzheimer's disease and related dementias; CAPS-1, clinical rating scale for assessing current and lifetime post-traumatic stress disorder; CFV, checklist of childhood familial violence; FGC, female genital cutting; GAD-2, generalized anxiety disorder scale-2; HADS, hospital anxiety and depression scale; HSCL-25, Hopkins symptom checklist-25; HTQ-30, Harvard trauma questionnaire-30; IES, impact of event scale; M.I.N.I., mini-international neuropsychiatric interview; MINI, McGill illness narrative interview; PC-PTSD-5, primary care post-traumatic stress disorder screen for Diagnostic and Statistical Manual of Mental Disorders-5th Edition; PDS, post-traumatic stress diagnostic scale; PHQ-2, patient health questionnaire-2; PRISMA, preferred reporting items for systematic reviews and meta-analysis; PSS-I, post-traumatic stress disorder symptom scale-interview; PTSD, post-traumatic stress disorder; MCI, mild cognitive impairment; RHS-13, refugee health screener-13; SSGS, state shame and guilt scale.

(31–34). Moreover, many members of their community emphasise upholding the long-standing tradition to maintain their cultural heritage (35). If lacking FGC, these women may face sexual dishonour and risk being ostracised by members of their community (27, 36). Specific traditional components of FGC (e.g., age, environmental, and social factors) tend to vary based on different regions in Africa (37, 38); however, where practised, culture gives meaning and importance to the practice. Given that women live with FGC for the rest of their lives, it is critical for their health to understand the cognitive and mood experiences of ageing with FGC.

To date, most literature investigating the lived experiences of local and immigrant women with FGC has primarily focused on their reproductive health outcomes (39). Systematic reviews and meta-analyses have found factors such as prolonged labour, caesarean sections, difficult delivery, menstruation challenges, and pain during intercourse to be associated with FGC (40–42). Articles focusing on long-term complications post-FGC have also mainly investigated gynaecological, perinatal, and postnatal complications (43, 44). To our knowledge, only two papers focus on the possibility of long-term chronic pain and one on heart disease, independent of reproduction - all from our research group (45–47). Due to this narrow focus on reproduction, most studies tend to recruit women with FGC in their reproductive or childbearing years, often ranging from 15 to 49 years (e.g., 48, 49). Thus, there still remains a scarcity of research conducted on any other health aspect beyond women with FGC's reproductive health (47).

Previous reviews focusing on women with FGC's mental health outcomes reported that they often have high incidences of affective disorders or post-traumatic stress disorder [PTSD; (50)]. Similarly, a systematic review found that women with FGC tend to report a higher burden of adverse mental health outcomes relative to women without FGC (51). In relation to cognition, there was only one pilot study that investigated the mental health status and memory of local Senegalese women of reproductive age with and without FGC. They found a diagnosis of PTSD to be associated with the presence of significant memory problems among young women with FGC relative to those without FGC (52). However, these findings are controversial since some studies have not found significant differences in psychological consequences between women with FGC and those without (53). None of these reviews or the one pilot study looked at cognition in the absence of some pathology purportedly linked with FGC. Since FGC may well affect the nervous system beyond the reproductive tract (45, 46), it may be that as they age, cognition and mood are further affected.

Thus, there is a need to bring this understudied subgroup of postmenopausal African women with FGC into cognitive ageing research, specifically. By better understanding their cognitive ageing experiences along with their mood, we will be better able to assure their health as they age. The current review aimed to investigate what is already known about the cognitive and mood experiences of postmenopausal African women with FGC aged 50 years and above. Our primary research question was: *What is known about cognition and mood in postmenopausal African women with FGC?* We conducted a review of the literature to obtain the broadest perspective on what is currently known. Our work aims to highlight the gaps in the literature, opportunities for future research and the importance of evidence-based research in this population to strengthen health, community and systems that care for women with FGC.

2 Methods

2.1 Literature search strategy

We searched across three databases: PubMed, APA PsycInfo, and Google Scholar. PubMed was chosen for its extensive biomedical and life sciences literature and PsycInfo for its broad view of literature within the behavioural and social sciences (54, 55). Google Scholar was used to pick up any grey literature or qualitative studies missed by PubMed and PsycInfo (56, 57). Including grey literature in reviews has been shown to highly reduce publication bias, increase their comprehensiveness, and contribute to a more balanced overview of existing evidence on a topic (58). We included all results obtained from each search on PubMed and PsycInfo, even if they yielded beyond 50 articles. However, if one Boolean search on Google Scholar retrieved over 100 results, only the first 50 results were included for screening. Given that Google Scholar is known to return a large volume of information for most searches (57), including only the first 50 is standard practice for many reviews that have used the search engine to date. Overall, Google Scholar formed a powerful supplementary addition to our search strategy (59).

Boolean combinations of keywords related to FGC, cognition and its broad domains, mood, and ageing were used to identify relevant studies. Altogether, we used combinations of the following keywords: "female genital cutting", "female genital circumcision", "female genital mutilation", "aging", "ageing", "Alzheimer's disease", "mild cognitive impairment", "attention", "cognition", "cognitive function", "cognitive functioning", "dementia", "executive function", "memory", and "mood". We used "mood" as a broad category representing affective states that encompass widespread forms of emotional and/or psychological conditions, such as depression or anxiety (60). We avoided the use of any keywords (e.g., "psychological disorders") that may potentially bias our search to yield papers potentially pathologising the experiences of women with FGC. By including only one keyword for mood and multiple types for cognition and its main domains, we focused our review primarily on cognition and ageing, while also accounting for studies that have explored mood-related cognitive experiences of women with FGC [e.g., (61)] or any age-related mood experiences. Across all three databases, each Boolean combination was applied to search the full text to obtain a broad search, instead of searching by article title alone.

2.2 Study selection criteria & screening process

Inclusion criteria were: women with FGC, study cohorts including women aged 50 and older, local and/or immigrant African women, articles published in English, and all papers

published before June 30, 2023. We did not limit our search based on whether their cognitive and mood experiences were explored qualitatively and/or quantitatively, article type/design, FGC type, or the age at which FGC was experienced. For any review articles obtained during our search, we further searched their included studies to screen more papers. Papers were excluded if they: did not include women with FGC aged 50 or over, investigated only/a majority of non-African FGC cohorts, published research studies without clear abstracts or summaries, were not written in English, or had broken Google Scholar links.

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method (62) to document the search and screening processes as this method has been shown to improve the quality of literature reviews and aid in reducing bias [(63); Figure 1]. The abstracts of empirical research articles were first screened independently by two authors (R.K. & N.C.) before their full texts. For specific publication types and grey literature without abstracts (e.g., book chapters, commentaries, online blog posts, e-news articles), their full texts were directly assessed.

2.3 Data extraction

During the abstract screening process, the following information was extracted and put in table format using Microsoft Excel (65): article reference, study type and design, study focus, participant characteristics, age at FGC (in years), FGC type, relevant outcome measures, and relevant results. Upon compiling the information, all three authors resolved discrepancies in the extracted information and selected the final articles. All figures and tables were created using Microsoft Word (66).

3 Results

3.1 Overview of included records

Across the three databases, 2,003 records were identified. Upon removing duplicate records within and between databases, 1,231 records were then independently screened for titles by two

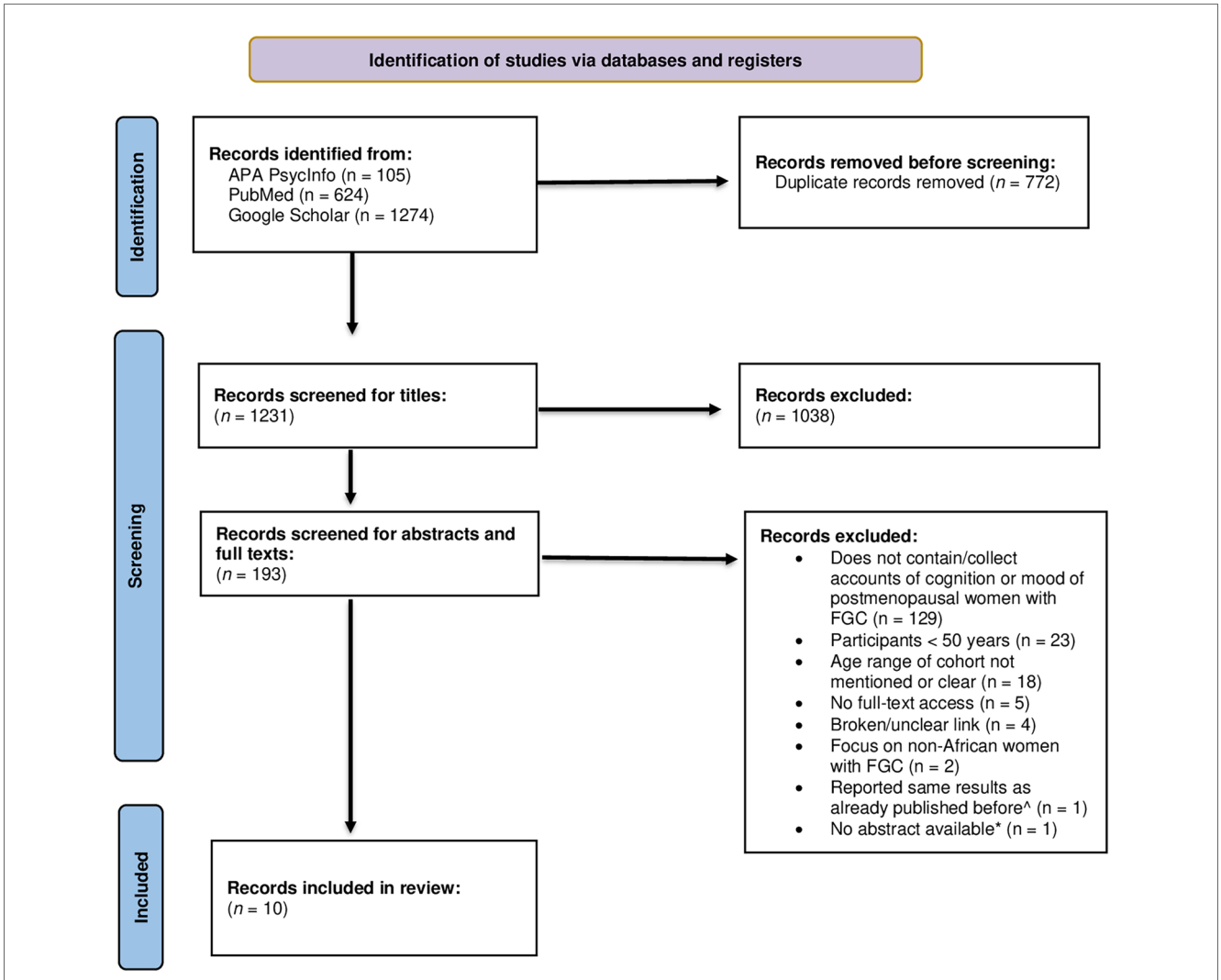

FIGURE 1
PRISMA flow diagram of the study selection process. APA, American Psychological Association; FGC, female genital cutting; ^, repeated the same results from the same cohort originally recruited in Vloeberghs et al. (64); *, only relevant for empirical research articles.

authors (R.K. & N.C.). Any discrepancies in the independent title screenings were resolved by the same two authors, after which 1,038 articles were excluded, leaving 193 records. Next, the abstracts of those 193 records were screened using the eligibility criteria for the review. Once again, any discrepancies following these independent screenings were discussed and resolved, while bringing in the third author's (G.E.) input as necessary. After completing full-text screening in the same manner, 183 articles were deemed ineligible, leaving a final 10 papers included in our review (Figure 1). The summary characteristics of all included studies are compiled in Table 1 and relevant study-specific information is compiled in Table 2. Among the 10 records included, publication years ranged from 1980 to 2022, with 6 published in the last 10 years. The majority were qualitative studies with cross-sectional research designs; however, 3 were quantitative studies with either cross-sectional or case-control research designs. One article consisted of participant case reports.

Across all the studies, the number of African women investigated (with FGC, without FGC, or both) ranged from 9 to 879, with ages ranging from 13 to 90 years. Five studies clearly indicated the number of postmenopausal women with FGC; in these, they ranged from 4.5% to 25% of the total study cohort. In the other five studies, it was impossible to discern who was and was not postmenopausal. Although they constituted a minority of their cohorts, 6 studies included women aged approximately 50–69 years. Five studies reported the mean age at FGC as between 3 and 8.25 years. One reported their median age at FGC to be 7 years, one reported the age range at FGC to be 10–15 years, and three did not report age at FGC. Among studies that collected participants' age at FGC, only one reported the ages at FGC for each included participant.

In six studies, a majority of the FGC cohort had Type III FGC. Women across these studies hailed from a total of 16 African countries: Somalia, Sierra Leone, Sudan, Eritrea, Ethiopia, Egypt, Kenya, Nigeria, Gambia, Guinea, Burkina Faso, Senegal, Ivory Coast, Liberia, Chad, and Djibouti. Six studies investigated the experiences of immigrant African women with FGC living in Western countries, while four investigated their experiences within their local African contexts.

Five studies investigated mood and memory experiences related to their FGC experiences. Among those investigating memory, all focused on the affective quality of FGC memories and did not focus on other aspects of cognition (e.g., memory *per se*, attention, or executive function). Nine studies conducted interviewer-administered questionnaires assessing their physical or psychological health symptoms or semi-structured interviews about their FGC event, experiences, and feelings. Altogether, seven studies aimed to investigate how FGC affected the lives of African women and collected details about their FGC event; two collected information on the FGC event and the immediate emotional impact it had on them, and one collected information on the FGC event and explored their views/attitudes towards the practice.

Across most studies, it was unclear whether the cognition- and/or mood-related experiences and findings also applied to women with FGC aged 50 and above. The results from the included studies are listed according to study type and design below.

TABLE 1 Overview of characteristics of included articles.

Article Characteristics (n = 10)	Proportions (n)
Published within the last 10 years (2013–2023)	6
Qualitative studies with cross-sectional design	4
Quantitative studies with cross-sectional design	3
Quantitative studies with case-control design	2
Case reports	1
Study cohort included women aged	
~50–69	8
~70–80	1
~90	1
Majority FGC type within cohort	
Type III	6
Unreported	4
Cohort from	
The United States	2
The Netherlands	1
The United Kingdom	1
Norway	1
Germany	1
Egypt	1
Nigeria	1
Kenya	1
Ethiopia	1
Assessed	
Memory-related[a] and mood-related experiences	5
Only memory-related[a] experiences	4
Only mood experiences	1
Measures	
Interviewer-administered questionnaires about health symptom experiences	3
Semi-structured interview(s) about FGC event and experience	3
Both interviewer-administered questionnaires about health symptom experiences and semi-structured interviews about FGC experience	1
Structured interview schedule about FGC experience	1
Semi-structured interview schedule about health symptom experience	1
Self-reported questionnaires about health symptom experiences	1

[a]Assessed the affective quality of cognition, but not cognition exclusively.

3.2 Qualitative studies with cross-sectional research designs

A total of four studies analysed the experiences of African women with FGC using qualitative methods. One study (73) analysed the experiences of 20 African immigrant women with FGC living in Norway (aged 32–60 years) using semi-structured interviews to capture details about their FGC experience. Although no descriptive statistics was reported, the authors indicated that most women in their cohort had Type III FGC. The interviews revealed that all participants vividly recalled the

TABLE 2 Synopsis of findings of relevant articles.

Reference	Study type & design	Study focus	Participants	Age at FGC (years)	Type of FGC	Relevant outcome measures	Relevant results
Michlig et al. (67)	Quantitative, case-control	Psychological distress among Somali-American women via memories of FGC	879 immigrant Somali women with and without FGC living in the U.S. (15–90 years)[a]	*Range:* 0–15 *Mean:* 7.09	Type I = 25.37% Type II = 15.81% Type III = 27.65% Unknown FGC Type = 9.33% None = 18.32% Unknown = 3.53%	Questionnaires about adverse physical or psychological reactions during or immediately after FGC or any previously experienced traumatic event, and RHS-13; memory assessed by asking to recall	• Types I and III FGC associated with less distress symptoms. The same not found for Type II FGC • No association between the age of FGC and distress symptoms • 12% of the FGC cohort and 27% of the non-FGC cohort showed distress symptoms • 73.3% of the FGC cohort could not recall any adverse events related to FGC • If recalled, associated with distress • 63.6% of women who could recall any adverse event with FGC had experienced Type III FGC
Wulfes et al. (68)	Quantitative, cross-sectional	Physical and mental health of women with FGC in Germany seeking reconstructive surgery	112 immigrant women with FGC living in Germany (14–63 years)	*Range:* 0–21 *Mean:* 7.33	Type I = 18.75% Type II = 31.25% Type III = 50%	Questionnaires PHQ-2, GAD-2, PC-PTSD-5, SSGS shame and guilt subscales; memory assessed by asking to recall	• 36.6% suspected depression • 48.2% suspected anxiety • 55.4% suspected PTSD • Feelings of guilt and age of FGC significant predictors for PTSD symptoms • Current age and FGC type not significant predictors for PTSD symptoms
Assaad (69)	Case reports	Egyptian women's views on how FGC affects them, their attitudes toward it, and how their attitudes may be changing	4 local Egyptian women with FGC (22–60 years)	*Range:* 8–9 *Mean:* 8.25	Type I = 25% Type II = 25% Unknown = 50%	Structured interview of 57 questions, including about FGC; memory assessed by asking to recall	• One 60-year-old participant with Type II FGC at 8 years had vivid autobiographical memory of her FGC event • Could provide detailed accounts of her experiences a week before, the day of, and a week after FGC • Recalled feeling deceived by her mother and by woman performing FGC • Reported intense fear during and immediately after event
Gacheru (70)	Qualitative, cross-sectional	Kenyan Kikuyu women's experiences and perceptions of FGC in the context of its emotional impact	12 local Kikuyu (Kenyan) women with FGC (35–55 years)	*Range:* 10–15	NR	Semi-structured interviews with open-ended questions asking to: describe their experience with FGC, investigate whether they can recollect their FGC event, see what they remembered, and what their current feelings are; memory assessed by asking to recall	• Vivid memories of FGC event • Recall of its effect before, during, and immediately following the event • Subsequent feelings of loss of trust, unworthiness, and incompleteness
Omigbodun et al. (71)	Qualitative, cross-sectional	Nigerian women with FGC's psychological experiences	38 local Izzi (Nigerian) women with FGC (18–60 years)	NR	NR	Interviews (1–2 h) questions from the adapted MINI; memory assessed by asking to recall	• Majority remembered their FGC experience • Feelings of anger, sadness, shame, and embarrassment before their FGC. • Happy anticipation closer to the day of their FGC event. • During FGC, feelings of intense fear. • Immediately following event, some expressed eventual happiness, while others expressed intense emotional turmoil reminiscent of PTSD symptoms.

(*Continued*)

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TABLE 2 Continued

Reference	Study type & design	Study focus	Participants	Age at FGC (years)	Type of FGC	Relevant outcome measures	Relevant results
Lockhat (72)	Quantitative, cross-sectional	Prevalence rate of psychological distress, physical challenges, complications, and other variables in immigrant Sudanese and Somali women with FGC	55 immigrant Sudanese and Somali women with FGC living in the U.K. (21–60 years)	*Range:* 2–13 *Median:* 7	Type I = 18.18% Type II = 20% Type III = 61.82%	Questionnaire about stressful life events HADS, IES, CAPS-1, semi-structured questionnaire asking questions about the FGC event; memory assessed by asking to recall	• 96.36% participants remembered their FGC event • Vivid accounts of their experience before, during, and following the event: almost half reported as negative, others reported as positive • 3.63% reported as neutral • Type III FGC; more likely to have anxiety and depression • 7.2% met criteria for current PTSD • 27.3% met criteria for lifetime PTSD • More than half did not report their FGC as a stressful life event.
Schultz & Lien (73)	Qualitative, cross-sectional	Type of quality of psychological care provided to African girls before, during and after FGC. Description of the beliefs systems underlying FGC-related care provided in Gambia	20 immigrant African (Gambia, Somalia, and other unnamed neighbouring countries) women with FGC living in Norway (32–60 years)	NR	Most had Type III, others unknown	Semi-structured interviews about childhood experiences and FGC narratives; memory assessed by asking to recall	• Clear recollections of their FGC event. • Painful memories of FGC. • Recalled forming short-lived negative relationships with their mothers if they played an active role in FGC event. • Negative emotions at the time: such as fear, numbness, disbelief, betrayal, sadness, loss of trust, and anger • Some recount happiness and pride.
Dahlen (74)	Qualitative, cross-sectional	Life experiences of first-generation Ethiopian immigrant mothers in the US in the context of FGC	9 immigrant Ethiopian women with and without FGC living in the U.S. (late 20s-mid 50s)	NR	Unknown FGC Type = 77.78% None = 22.22%	Three in-depth semi-structured interviews exploring their current lived experiences and narratives about FGC; memory assessed by asking to recall	• 44.44% could not recall their FGC event. • 33.33% could recall the event in detail. • 11.11% recalled it vividly. • One (in her mid-50s) with vivid memory recalled feeling upset, helpless, screaming, and crying during FGC event. • Another (in her mid-50s) had limited memory but stated not feeling proud of her parents for having her experience FGC.
Köbach et al. (75)	Quantitative, case-control	Psychopathological sequelae of FGC in Jijiga, in the context of stress-related variables	165 local African women with and without FGC living in Jijiga, Ethiopia (13–80 years)	*Type I FGC Mean:* 3.1 *Type II/III FGC Mean:* 7.6	Type I = 36.36% Type II = 4.85% Type III = 47.88% None = 10.91%	Questionnaires administered: 45-item checklist about FGC, CFV, PDS, PSS-I, HSCL-25, and M.I.N.I.; memory assessed by asking to recall	• 18% of women with Type II/III FGC and 6% of women without FGC met PTSD criteria. • 12% of women with Type II/III FGC met major depressive disorder criteria. • Significant association between Type II/III FGC and PTSD, depression, and anxiety symptoms. • 92% of participants who remembered their FGC event reported experiencing intense fear and/or helplessness during the event.

(*Continued*)

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TABLE 2 Continued

Reference	Study type & design	Study focus	Participants	Age at FGC (years)	Type of FGC	Relevant outcome measures	Relevant results
Vloeberghs et al. (64)	Quantitative, cross-sectional	Psychosocial and relational challenges of African immigrant women with FGC living in the Netherlands	66 immigrant women from Somalia, Sudan, Eritrea, Ethiopia, and Sierra Leone with FGC living in the Netherlands (18–69 years)	*Range:* 8 months–16 years *Mean:* 6.4	Type I = 31.82% Type II = 13.64% Type III = 53.03% Unknown FGC Type = 1.52%	Questionnaires administered: HTQ-30 and HSCL-25, semi-structured interviews including questions about FGC event; memory assessed by asking to recall	• 50% had vivid memory of their FGC event. • 19.69% had some memory. • 21.21% had no memory. • Vivid memories and those with Type III FGC more likely to report higher PTSD symptoms, and anxiety and depression symptoms. • Those older at the time of FGC had significantly more PTSD symptoms, but not more anxiety or depression symptoms. • 17.5% had an indication of PTSD. • 31.7% met the cut-off for anxiety. • 34.9% met the cut-off for depression. • Independent of African community, recurrent bad memories, and nightmares in relation to FGC event reported. • Independent of African community, feelings of fear, powerlessness, anger, shame, and guilt in relation to their FGC event reported. • Pride post-FGC rarely reported.

CAPS-1, clinical rating scale for assessing current and lifetime post-traumatic stress disorder; CFV, checklist of childhood familial violence; FGC, female genital cutting; GAD-2, generalized anxiety disorder scale-2; HADS, hospital anxiety and depression scale; HSCL-25, Hopkins symptom checklist-25; HTQ-30, Harvard trauma questionnaire-30; IES, impact of event scale; M.I.N.I., mini-international neuropsychiatric interview; MINI, McGill Illness narrative interview; NR, not reported; PC-PTSD-5, primary care post-traumatic stress disorder screen for diagnostic and statistical manual of mental disorders - 5th edition; PDS, post-traumatic stress diagnostic scale; PHQ-2, patient health questionnaire-2; PSS-I, PTSD symptom scale-interview; PTSD, post-traumatic stress disorder; RHS-13, refugee health screener-13; SLE, stressful life events; SSGS, state shame and guilt scale.

[a]69.5% were born in Somalia, 19.0% in Kenya, 6.3% in other African or Middle Eastern countries, and 5.2% in the U.S. or Europe.

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series of events that took place on the day of their FGC. One participant stated "…it is all recorded down to every detail as if it was a film. My problem is not remembering but trying to forget" (p. 212). Few also remembered their mothers playing an active role in their FGC experience and recalled their relationships with their mothers being negatively affected in the initial weeks post-FGC. Specifically, they described experiencing negative reactions such as anxiety, fear, numbness, disbelief, betrayal, and anger towards their mother. Many also reported feeling frustration, sadness, and loss of trust. However, they reported these negative reactions as being short-lived. In contrast, some participants reported positive reactions to certain aspects of FGC, such as happiness when receiving gifts and praises, and pride once they completed the ritual.

Similarly, four of nine first-generation Ethiopian immigrant mothers reported being unable to recall their FGC experience (74). This inability to recall the event was attributed to their FGC being performed during infancy, though their exact ages at FGC were not reported. Three participants could recall their experience, though in sparse detail, estimating that their FGC occurred between the ages of three to nine. One participant in their mid-50s (pseudonym "Mulu") was able to recall her experience with only some detail and reported experiencing it as a young child. However, whatever she could recall held negative connotations. She mentioned that she did not feel heard as a child when she tried to voice her opinion on the ritual. She stated, "If they had asked me, I wouldn't have let them do it" (p. 71) and later said, "I'm not proud of my parents doing that to me" (p. 131). One participant in her mid-50s (pseudonym "Telile"), who also experienced FGC as a young child, did recall her FGC experience quite vividly and said, "You remember in your ears what happened" (p. 69). She also remembered feeling upset, screaming, and crying during her FGC experience, and said, "I know it was going to happen…that's why I refuse and I fight" (p. 131). She also recalled feeling helpless.

A qualitative study (70) examining the psychological and emotional experiences of 12 local Kenyan women (aged 35–55 years) found that their memories of FGC were fresh. A vividness was observed across participants, despite experiencing FGC at different ages ranging from 10 to 15 years. Some expressed extreme fear before their ritual; though only one participant (P5) in their study, who was between 55 and 60 years old, recalled feeling excited beforehand. Many participants also described experiencing intense and long-term loss of trust, and feelings of unworthiness and incompleteness later in life.

A qualitative study (71) used an adapted version of the McGill Illness Narrative Interview Schedule [MINI; (76)] to understand the embodied psychological experiences of 38 local Nigerian women with FGC (aged 18–60 years). Virtually all participants experienced intense negative psychological feelings such as anger, sadness, shame, and embarrassment before their FGC, as they recalled being mocked and humiliated for not being cut during this period. On the other hand, some recalled experiencing positive emotions, particularly happy anticipation closer to the day of their FGC. During the ritual, many described feeling intense fear. After FGC, participants described emotions ranging from positive (e.g., happiness from escaping stigma and gaining a respectful status), negative (e.g., betrayal, anger, and fear of dying), and mixed emotions. In terms of their long-term experiences post-FGC, some experienced happiness due to not facing any complications following FGC; whereas others experienced intense emotional turmoil linked to their complications.

3.3 Qualitative case reports

One article (69) described case reports of four local Egyptian women with FGC (aged 22–60 years) via individual structured interviews. The case report of one 60-year-old Egyptian woman (pseudonym "Camilia") who had FGC at age 8, revealed that she remembered her FGC experience "as if it happened yesterday" (p. 11) and was able to provide detailed accounts of her experience, starting from the week before her cutting, the day of her ritual, and approximately a week post-cutting. She also remembered what others around her (specifically, her mother and the woman who performed the practice) remarked about the practice and vividly recalled feeling deceived by them. She also detailed other negative emotions, particularly fear, that she experienced during and immediately after FGC.

3.4 Quantitative and mixed-method studies with cross-sectional research designs

Three studies used quantitative methods to investigate FGC and related experiences among a cross-sectional cohort. One mixed-methods (64) study assessed the long-term psychological and relational consequences of FGC among 66 immigrant African women with FGC living in the Netherlands (aged 18–69 years) using semi-structured interviews and two interviewer-administered questionnaires about their PTSD, depression, and anxiety symptoms, namely: the Harvard Trauma Questionnaire-30 [HTQ-30; (77)] and the Hopkins Symptom Checklist-25 [HSCL-25; (78)]. The findings revealed differences in FGC recollection; 33 participants had a vivid memory, 13 had some memory, and 14 had no memory. Those who recalled their FGC event and those who experienced Type III FGC reported significantly more PTSD, anxiety, and depression symptoms. Those older at the time of FGC reported significantly more PTSD symptoms, but not more anxiety or depression symptoms. All women with FGC hailing from different African communities in the study cohort reported experiencing recurrent bad memories and nightmares of their FGC events, as well as fear, feelings of powerlessness, tension, apathy, exclusion, anger, shame, and guilt. Only one participant reported experiencing pride after FGC. Eleven participants showed an indication of PTSD, 20 met the cutoff for anxiety, and 22 met the cutoff for depression. There were no significant differences in these outcomes based on age.

Another study (72) looked at the experiences and feelings of 55 immigrant Sudanese and Somali women with FGC living in the U.K. (aged 21–60 years). The authors used the following set of mood-related questionnaires: the Hospital Anxiety and Depression

Scale to measure stressful life events [HADS; (79)], the Impact of Event Scale [IES; (80)] to measure the intrusions and avoidance symptoms of PTSD, the Clinical Rating Scale for Assessing Current and Lifetime PTSD-1 [CAPS-1; (81)], and a semi-structured questionnaire asking about their FGC event. Two participants in the study were unable to recall any aspect of their FGC event: one experienced Type I FGC (Sunna), and the other experienced Type III FGC (Pharaonic). Among the 53 who remembered their FGC experience, most were able to provide vivid accounts of events that took place and their feelings before, during, and directly after the ceremony. Their feelings before FGC widely varied, including excitement and/or fear. Immediately after FGC, there was ample variation in their overall memories of thoughts and feelings about the FGC experience, ranging from contentment and pride to indifference, anger, sadness, and confusion. The authors' qualitative analyses of those who remembered their FGC event revealed that 26 participants reported their overall experience to be negative, 25 as positive, and two as neither negative nor positive. In terms of their mood-related experiences, they found that women with Type III FGC were more likely to have higher anxiety and depression scores relative to others with Type I. Twenty-nine participants did not report FGC as a stressful life event and 26 did. Only four participants met the criteria for current PTSD and 15 met the criteria for lifetime PTSD.

Finally, another study (68) examined the physical and mental health characteristics associated with PTSD symptoms among 112 immigrant women with FGC living in Germany (aged 14–63 years). Authors administered the following relevant self-report screening instruments via the Patient Health Questionnaire-2 [PHQ-2; (82)] to measure depression symptoms, the Generalized Anxiety Disorder Scale-2 [GAD-2; (83)] to measure anxiety symptoms, and the Primary Care PTSD Screen for the Diagnostic and Statistical Manual of Mental Disorders-5th Edition [PC-PTSD-5; (84)] to screen for PTSD. One hundred and seven participants hailed from Africa, while the remaining were from Qatar, Great Britain, and Iraq. Scores obtained above the cutoff on these screening tools were said to show 'suspected' symptomatology for those disorders. They also assessed trauma-associated shame and guilt by using some subscales within the State Shame and Guilt Scale [SSGS; (85)]. Their findings showed that 41 participants had suspected depression, 54 had suspected anxiety disorder, and 62 had suspected PTSD. The age at FGC was a significant predictor for PTSD symptoms, such that older age at FGC was associated with higher PTSD symptomatology. Feelings of guilt were found to be a significant predictor of PTSD symptoms, while feelings of shame were not. No significant differences in PTSD symptomatology were found based on current age and FGC type.

3.5 Quantitative studies with case-control research designs

Two quantitative studies used case-control research designs to investigate the experiences of African women with FGC relative to those without FGC. One of these studies (67) analysed whether FGC was associated with psychological distress among 879 Somali immigrant women with FGC living in the United States. The control group consisted of Somali American women without FGC. All participants ranged from 15 to 90 years. The FGC group was also asked if they could recall any adverse physical or psychological reactions at the time of or immediately following their FGC event. Their distress symptoms were recorded using the Refugee Health Screener-13 [RHS-13; (86)]. Participants' ages were controlled across all statistical analyses conducted. Findings showed that most women with FGC did not recall any adverse events experienced either during or immediately after their FGC; though they found that a majority of women who were able to recall any adverse events had experienced Type III FGC. However, those with Types I and III FGC reported significantly fewer distress symptoms than Somali American women without FGC. There was no significant association between experiencing Type II FGC and distress symptoms. Only 12% of participants from the FGC cohort showed clinically significant distress symptoms, whereas the non-FGC cohort had slightly more participants showing distress symptoms (27%). No association between the age at FGC and distress symptoms was found. Moreover, participant's ability to recall any adverse events during FGC was strongly associated with experiencing clinically significant symptoms of distress.

Using a case-control design and a mixed methods approach (75), PTSD and other stress-related variables were investigated among 165 local African women with and without FGC living in Ethiopia (13–80 years). The following were verbally administered: traumatic experiences using the Checklist of Childhood Familial Violence [CFV; (87)] and the event checklist within the Post-Traumatic Stress Diagnostic Scale [PDS; (88)], PTSD symptoms using the PTSD Symptom Scale-Interview [PSS-I; (89)], depression and anxiety symptoms using the HSCL-25 (78), and the diagnostic status of major depression, suicidal ideation, drug abuse, and psychotic disorders using the Mini-International Neuropsychiatric Interview [M.I.N.I.; (90)]. In addition, the FGC cohort's experiences with the ritual were also explored via a 45-item checklist constructed by the authors. Women with FGC who could not remember specific details about their FGC experience were excluded from analyses. This was found to be the case for women who experienced FGC at 3 years old, for one participant with Type I FGC, and two participants with Type II/III FGC. Ninety six women with FGC who remembered their FGC experience, regardless of FGC type, reported experiencing intense fear and/or helplessness during the ritual. Sixteen women with Type II/III FGC and one without FGC met the criteria for PTSD. Eleven women with Type II/III FGC met the criteria for major depressive disorder. All women without FGC did not meet the criteria for depression, and all except one did not meet criteria for PTSD. Women with Type I FGC neither met the criteria for PTSD nor depression. The authors also found a significant association between having Type II/III FGC and a greater vulnerability to PTSD symptoms, depression, and anxiety symptoms.

4 Discussion

The current review aimed to identify and summarise what is already known about the cognition and mood experiences of local and immigrant postmenopausal African women with FGC. Upon completion of the screening process, 10 articles were included in the current review. No studies to date have exclusively investigated the experiences of a postmenopausal African FGC cohort aged 50 years and above. Likewise, no study has explored cognition, ageing, or memory in any context beyond their FGC experience. Participants were specifically asked to recount or answer questions about their FGC ceremony and often, those were paired with questionnaires about pathological conditions like anxiety, depression, and PTSD. In terms of cognition, qualitative accounts revealed that African women with FGC tend to hold vivid episodic autobiographical memories of the ceremony, including the series of events that took place, their feelings about other people involved, and their feelings leading up to, during, and after FGC. Among those who remembered the ceremony, feelings of anger, guilt, shame, fear, and helplessness were common, while feelings of indifference, happiness, or pride were less reported. Despite these negative feelings and high levels of psychological distress- and disorder-related symptoms reported, only a minority had PTSD, anxiety, depression, or psychological distress when interviewer-administered measures were used. In general, those who had more severe FGC types or were older at the age of FGC were more likely to have higher PTSD and psychological distress symptoms.

We aimed to capture different aspects of cognition with our review (i.e., memory, executive function, and attention). However, our searches only yielded articles that focused on autobiographical memory via qualitative retrospective accounts and did not analyse them in the context of memory research. No quantitative cognitive, neuropsychological, and/or neuroimaging measures were used to complement these results and further analyse participants' memories. Indeed, no study has analyzed other aspects of memory such as verbal episodic memory or associative memory which are impacted by dementia. Qualitative retrospective accounts, although valuable in capturing the nuances of individual lived experiences, can be prone to recall bias or misclassification bias if used alone (91). Currently, the only study to date using a neuropsychological assessment tool is a study investigating cognition in young African women with FGC aged 15–40 years (52). In this study, they found that a diagnosis of PTSD among African women with FGC was significantly associated with the presence of significant memory problems, relative to those without FGC.

The vast majority of studies found in our larger search focused on FGC's reproductive outcomes. Once these were excluded, the included studies investigating the memory experiences of older women with FGC still focused on the affective quality of their FGC memories and adverse psychological outcomes. Although they included older cohorts within their study cohorts, we found that no studies were conducted with postmenopausal women exclusively. Of the 10 studies included, older women formed a minority of the study cohort. There were none or unclear categorisations of these women's ages in most of the studies. Due to this, it was also unclear whether the cognition- and/or mood-related findings found also generalised to older women with FGC and were similar to those in the cohort that were of reproductive age. Therefore, future studies should prioritise investigating the cognitive experiences of postmenopausal African women with FGC to holistically understand how the practice might affect their cognition as they age.

This lack of cognitive ageing studies of local and immigrant postmenopausal African women with FGC is a serious gap in the literature, especially since existing research shows that some, at least, have the markers of early cardiovascular disease, depression, and possibly, chronic pain – all associated with late-life cognitive decline (45–47, 92, 93). Longitudinal studies to date have shown that sub-Saharan women tend to have substantially worse cognitive health and a significantly steeper age gradient in cognitive ability, relative to sub-Saharan men, over time (94). Similarly, studies have found that African American women tend to experience steeper rates of cognitive decline relative to White and Hispanic women and men (95). Thus, there is a dire need to study cognitive ageing in postmenopausal women with FGC to fully determine the prevalence of neurodegenerative diseases, healthcare needs, and quality of life.

Our search did not find articles on cognition. Rather, the focus was on memory of the FGC ceremony and events before and after which were vivid, suggesting that their autobiographical memory is intact. This was especially the case for women older than age three when they had FGC or had Type III FGC. This is consistent with existing literature showing that by the age of three children can start to retain autobiographical episodic memories (96, 97). This trend is also consistent with general ageing research demonstrating that both male and female older adults tend to subjectively report high levels of vividness for remote autobiographical memories, sometimes even higher, relative to young adults (98). Reviews have shown that while there is an age-related decline in the level of detail provided by older adults, their overall gist representation of the event remains (99, 100).

Among the included studies that reported their cohort's FGC type, most women, regardless of FGC type, tended to remember strong feelings of either fear, anger, excitement, or happiness. Thus, their FGC event was likely an emotionally charged memory for them and likely, an emotionally charged event. Mixed-sex studies on memory in older adults reveal that although they tend to produce greater semantic details and fewer episodic details for emotionally charged autobiographical events relative to younger adults, the overall number of details recalled for such events remains strong with age (101).

While episodic autobiographical memories were related, much of the focus of the 10 studies was on women's FGC subjective memories, particularly their affective experiences. Specifically, they reported high levels of negative emotions such as anger, shame, fear, helplessness, and guilt, in relation to their FGC. Although in one study, as many as half of the participants reported positive or neutral emotions related to their FGC event. To date, mixed-sex ageing research has shown evidence for individuals' tendency to pay attention to positive information and avoid negative information as they age (102, 103). Interpreted in the context of this "positivity effect", women in the reported studies were specifically asked about FGC and not

about general recollection of life events, so it is unclear whether the "positivity effect" pertains to them. Mixed-sex studies have shown that older adults with MCI and dementia tend to experience more negative emotions (104, 105); however, again, there is no way of knowing the cognitive state of the participants in the studies cited here as it was not exclusively explored. Using relevant quantitative measures, future studies should investigate whether there is actually a positivity or negativity bias in FGC-related recall. This is especially important given that experiencing intense negative emotions increases the risk of developing depression, which in turn is a risk factor for dementia (106, 107). There may be more cause for concern, given that older women, in general, are more likely to be at risk of developing depression than older men (106, 108, 109). Furthermore, future studies should also aim to analyse the valence of this cohort's qualitative accounts using well-validated quantitative measures and, accordingly, report what proportions of their cohorts recalled experiencing positive, negative, and/or neutral emotions to various aspects of their FGC as the negative bias may be built into the study, itself, much like studies of menstruation (110).

In addition to memories of FGC, studies included measures of psychological distress. These revealed little to no findings of psychological distress, PTSD, depression, and anxiety among women with FGC, regardless of study type and design. When control groups were present, the outcomes of women with FGC did not significantly differ from women without FGC. Given that research has shown increased levels of depression, anxiety, and clinical distress to be strongly associated with lower levels of cognitive health as individuals age (111, 112), with the decline in cognitive health often being substantially worse for women (94), future research should continue to explore age-related changes in the mood experiences of postmenopausal women with FGC and correlate those with cognitive outcomes. It is, however, critical to do this research without pathologising women's mood experiences and instead, attempting to uphold consistency with each African population's local terms, concepts, and views of mental health (113).

In sum, we have found a dearth of knowledge about ageing women with FGC whether locally or in countries to which they have immigrated. For their health, it is important to bring this radically understudied group of postmenopausal African women with FGC into ageing and dementia research. Doing this will lead to a better understanding of their evolving age-related cognition, potential etiologies of dementia, and cognitive health needs. Receiving evidence-based, sensitive ageing care may also serve to reduce the known barriers they have with accessing and/or receiving appropriate healthcare in Western contexts. Further research is needed to analyze the crucial implications on policy and practice related to aging with FGC.

5 Limitations

The main limitation of this review is that the dearth of literature on ageing women with FGC in any context, as well as the primary focus on FGC and reproductive health, drastically limited the number of papers recovered. This is an important finding since it opens the necessity of including these women in studies of health beyond the reproductive system, including cognitive ageing. Given that there were no studies on our topic, we did not conduct a systematic review and/or a meta-analysis. Instead, we reached more broadly for any study that included older women with FGC and asked them about their memories; a narrative review facilitated a wider search on this topic. Another limitation is that we used Google Scholar as one of our search databases. Research has shown Google Scholar to be inappropriate as a principal search engine for reviews as it lacks reproducibility and transparency in its search algorithm as well as around the size of its database (59, 114). Nonetheless, studies evaluating the search engine have shown that although it is considered unsuitable for primary review searches, it is a suitable and often helpful supplementary source of evidence, especially for grey literature (57). Thus, Google Scholar allowed for the widest search possible. Indeed, seven out of the ten papers, some of which were published theses/dissertations, included in our review were obtained from our Google Scholar searches. Using it and not finding any other reports underscores the dearth of any kind of study on cognition in ageing women with FGC. A strength of this review is that it is the first to search the literature for cognitive ageing studies in older women with FGC, marking the first step to organising existing literature on this topic. We also used the PRISMA methodology in our search to improve rigour and avoid bias (62).

6 Conclusion

The current review revealed some evidence for the cognitive and mood experiences of local and immigrant postmenopausal African women with FGC, primarily around their FGC experience. To date, no studies have exclusively investigated cognitive ageing in this group of women. Instead, ageing women with FGC have been integrated into cohorts consisting of a wide range of ages with the older women constituting a minority. The questions asked of them only reveal their accounts of autobiographical memory, specifically with respect to FGC. These studies reveal that most, but not all, older women with FGC report vivid memories of FGC. However, since the studies do not focus on capturing memory *per se*, studies do not report details about their memory abilities, leaving open how much of their cognition is actually affected. When these studies include questions about mood, they reveal low incidences of PTSD, depression, and anxiety symptoms in the face of reported feelings of anger, guilt, and shame. With increasing life expectancy, AD is becoming a concern in Africa as well as in the countries to which Africans have immigrated (8). This demands that international health care policy begin to consider the cognitive health of Africans; and especially, female Africans with early life adversity, so that we can determine the earliest, most efficacious times for treatment. In this sense, future research should explore their cognitive health in-depth using culturally sensitive and mixed-method approaches.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

RK: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. NC: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. GE: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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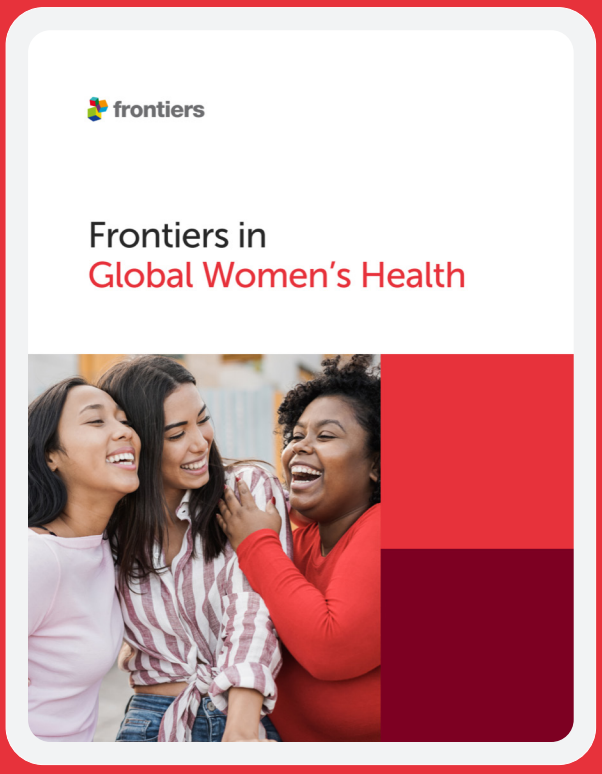

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