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Original article

A comprehensive assessment of age at menopause with well-characterized cognition at 70 years: A population-based British birth cohort

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ABSTRACT

Objectives: Associations between age at menopause and cognition post-menopause are examined to determine whether relationships are stronger for certain cognitive domains.
Study design: Women from the Medical Research Council National Survey of Health and Development and its neuroscience sub-study, Insight 46, were included if they had known age at menopause (self-reported via questionnaire) and complete cognitive outcome data at age 69 (n = 746) or at Insight 46 wave I (n = 197). Multivariable linear regression analyses adjusting for life course confounders were run; interactions with menopause type (natural/surgical) and APOE-ε4 status were examined; and the potential contribution of hormone therapy was assessed.
Main outcome measures: Cognitive measures were standardized Addenbrooke's Cognitive Examination - third edition total and sub-domain scores at age 69 (whole cohort) and Preclinical Alzheimer's Cognitive Composite total and sub-test scores at age ~70 (Insight 46).
Results: Older age at menopause was associated with better performance across all outcomes, most strongly for the Addenbrooke's Cognitive Examination memory and visuospatial function sub-domains, and the Preclinical Alzheimer's Cognitive Composite digit-symbol substitution test and face-name associative memory examination sub-tests. Adjusting for early-life factors attenuated all effect estimates, driven by childhood cognition, and accounting for menopause type revealed negative confounding for some outcomes. No significant interactions with menopause type or APOE-ε4 status were detected. Further adjustment for hormone therapy did not meaningfully alter the estimated effects.
Conclusions: Older age at menopause is associated with better later-life cognitive performance, particularly for visual processing and associative learning and memory domains. Childhood cognition was an important contributor.

1. Introduction

Menopause is the female transition to reproductive senescence, typically occurring between ages 45 and 55 years [1]. Endogenous estrogen levels gradually decline during natural menopause, while surgeries to remove the uterus and/or one or both of the ovaries can cause an earlier and sometimes more dramatic decline in estrogen levels [2]. Estrogen has pleiotropic effects influencing both the reproductive axis

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination - third edition; APOE, Apolipoprotein-E; BMI, Body Mass Index; DSST, Digit-Symbol Substitution Test; FNAME-12A, Face-Name Associative Memory Examination; GCSE, General Certificate of Secondary Education; GHQ, General Health Questionnaire; HT, Hormone Therapy; MMSE, Mini-Mental State Examination; MRC, Medical Research Council; MICE, Multiple Imputation by Chained Equations; NART, National Adult Reading Test; NSHD, National Survey of Health and Development; PACC, Preclinical Alzheimer's Cognitive Composite; SEP, Socioeconomic Position; SD, Standard Deviation.

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and higher mental function [3], and menopause is often accompanied by neurological symptoms including cognitive difficulties, particularly with memory and attention [4]. However, our understanding of the longer-term association between menopause and cognitive function in later-life is not yet established. There is conflicting evidence around how age at menopause, or taking menopausal hormone therapy (HT), is associated with dementia risk, cognitive impairment or later-life cognitive function [4,5]. It is important to understand the association between menopause and well characterized cognitive function in later-life, prior to overt dementia symptoms, to help develop a better understanding of female cognitive ageing.

Most studies investigating the association between menopause and later-life cognition are unable to account for childhood cognition, a key confound given higher childhood cognition predicts both later menopause age [6,7] and better cognitive performance in later-life [8,9]. Studies also typically lack prospectively recorded data for pre-menopausal covariables such as BMI and smoking. In addition, most studies have wide age ranges at cognitive testing and short follow-up periods. The British 1946 Birth Cohort (MRC National Survey of Health and Development/NSHD) studies people born in the same week of March and has prospectively recorded data for a range of life course variables, providing a unique opportunity to overcome some of these issues.

Previous NSHD work has investigated associations between menopause age and cognitive performance. Among women who were post-menopause by age 56, positive associations of menopause age with National Adult Reading Test (NART) and verbal memory performance at age 53, but not processing speed, have been detected. Associations attenuated with adjustments for childhood cognition, previous task performance, and additional socioeconomic factors [10]. Small positive associations between age at natural menopause and better verbal memory performance, but not processing speed, from ages 43 to 69 were also found after accounting for lifetime factors, although the effect estimates attenuated with adjustment for childhood cognition [11].

We now expand on previous work by addressing the relationship between age at menopause and performance on clinically relevant cognitive assessments completed in later-life; a test of cognitive state at age 69 (Addenbrooke's Cognitive Examination-third edition/ACE-III) and a composite measure, mainly used in clinical trials (Preclinical Alzheimer's Cognitive Composite/PACC) [12], completed by participants in the NSHD neuroscience sub-study, Insight 46. We assess overall task performance and sub-domain performance to examine which cognitive domains associate more strongly with menopause age. We test whether associations are: independent of a range of relevant confounders including early cognitive and sociodemographic factors, reproductive, and health-related factors; whether associations are modified by menopause type (natural or surgical) and APOE-ε4 status; and the potential contribution of ever using HT.

2. Methods

2.1. Study design

The NSHD is a cohort originally of 5362 individuals (2547 women) born in mainland Britain during one week in March 1946. Individuals have been followed up 24 times across their lives, with the last whole-cohort assessment at age 69 years. Between ages 43 and 54, 1572 female study members completed annual postal questionnaires for the Women's Health in the Middle Years survey [13]. The neuroscience sub-study, Insight 46, includes detailed neuropsychology cognitive assessments, neuroimaging, and additional biomarkers from 502 NSHD participants (49 % female). Details of recruitment and assessments are outlined in detail elsewhere [8,14,15]. Wave I of Insight 46 data collection was carried out between May 2015 and January 2018, when participants were aged between 69 and 71 years. Women were included in these analyses if they had known age at menopause and available ACE-III data at age 69 (whole-cohort) or available PACC data at age 69–71 (Insight 46 wave 1) (Fig. 1).

Current ethical approval for the MRC NSHD was granted by NRES Queen Square Research Ethics Committee (14/LO/1073) and Scotland A Research Ethics Committee (14/ SS/1009). All study members provided written informed consent. No information is provided in this manuscript that can identify any individual study member.

2.2. Menopause age and type

Age at menopause was ascertained for all menopause types as age at final menstrual period, indicated on self-reported questionnaires [13] as months since birth and later converted into years. Menopause type was recorded as natural if no hysterectomy or oophorectomy surgery was reported prior to the final menstrual period. Women who reported having a hysterectomy and/or unilateral or bilateral oophorectomy before reaching a natural menopause were categorized as having had a surgical menopause. Information on the type of surgeries women reported is presented in Table 1.

2.3. Outcomes: cognitive assessments

NSHD participants completed the ACE-III, a measure of cognitive state, during home visits at age 69, administered by iPad (ACEMobile http://www.acemobile.org). Assessments of five individually scored cognitive domains are summed to generate a total ACE-III score (maximum 100): attention and orientation (scored 0–18), verbal fluency (0–14), memory (0–26), language (0–26), and visuospatial function (0–16). Raw ACE-III total and sub-domain scores were standardized to the analytical sample.

Participants who also took part in Insight 46 completed a comprehensive neuropsychology test battery [8,14] during assessments in a London based research center, aged between 69 and 71. This included a modified version of the PACC [8], comprising of four sub-tests (summarized in Supplementary Material 1): the digit-symbol substitution test (DSST; Wechsler Adult Intelligence Scale-Revised) [16] assessing processing speed, associative learning, attention, and executive function; the 12-item face-name associative memory examination (FNAME-12A) [17] assessing associative, episodic memory; logical memory IIa (Wechsler Memory Scale-Revised) [18] assessing episodic memory; and the mini-mental state examination (MMSE) [19], a 30-point test of overall cognitive state. Raw scores on each sub-test were standardized to the analytical sample and averaged to generate a total PACC score for each participant.

2.4. Covariables

Covariables were selected based on previous analyses and evidence linking variables with menopause age or cognition [7,8,11]. Childhood cognition at age 8 years was the sum of four tests of verbal and non-verbal ability, standardized to the sample at the time of testing. If data were missing for cognition at age 8, we instead used available data for cognition at age 11 (n = 11), or at age 15 years (n = 10). Childhood SEP was manual or non-manual, according to the Registrar General's classification [20] and based on paternal occupation. Education to age 26 was ordinary (GCSE-level or equivalent) or below, or advanced (A-level or equivalent, or above), according to Burnham scale classifications [21]. Age at menarche was recorded as years since birth, reported by a school doctor at age 14–15 years or self-reported at age 48. Parity was indicated by self-reported number of natural-born children. Due to small proportions of nulliparous or single parity women in our sample, this variable was categorized as 0–2 children, or 3 or more children. Menopause type was categorized as natural or surgical. BMI at age 36, negatively associated with cognitive performance at age 60–64 in this cohort [22], was recorded as a continuous value (kg/m^2). Smoking pack years was self-reported at age 36 years. APOE-ε4, linked with an earlier

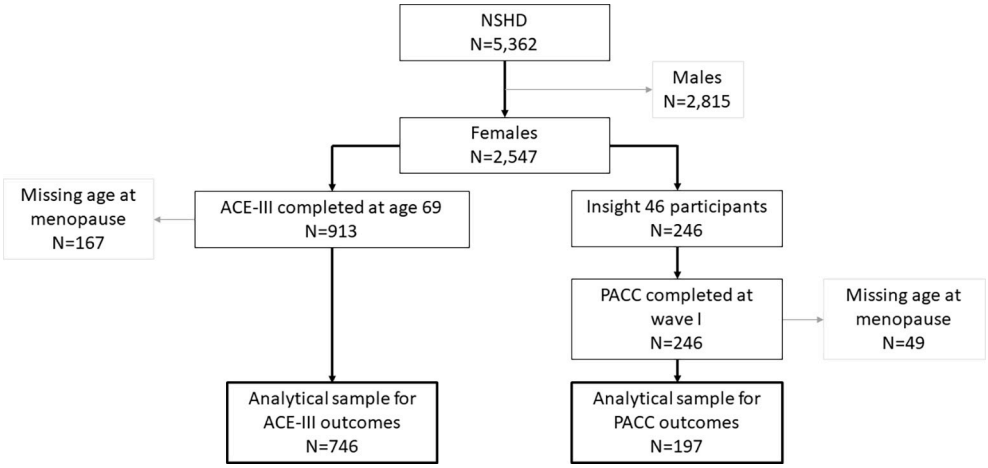

Fig. 1. Flow chart demonstrating sample selection for analyses.

menopause age [23], was categorized as ε4-present or ε4-absent. Affective symptom caseness at age 69 was determined using a cut-off of 5 or more on the 28-item GHQ [24]. Age at cognitive testing for Insight 46 participants was derived from the recorded age, in years, at which participants underwent neuroimaging. Ever or never use of any type of prescribed menopausal HT by age 69 was self-reported by questionnaire.

2.5. Statistical analyses

All analyses were conducted using Stata version 17.0.

Associations between menopause age and z-score standardized cognitive outcomes (ACE-III total and sub-domains, and PACC total and sub-tests) were assessed using multivariable linear regression analyses, cumulatively adjusting for covariables. Unadjusted models (model 0/M0) were followed by adjustments for early cognitive and sociodemographic factors (M1:childhood cognition, childhood SEP, education), reproductive factors (M2:M1 plus age at menarche, parity, menopause type), and health-related factors (M3:M2 plus BMI, smoking, affective symptoms, APOE-ε4 status, and age at cognitive testing [Insight 46 only]).

The potential moderating role of menopause type was examined by testing for menopause age-by-type interactions on standardized ACE-III total and PACC total scores in fully adjusted models (M3). Similarly, menopause age-by-APOE interactions were added to fully adjusted models to examine whether associations were modified by APOE-ε4 status.

We considered whether HT use contributed to associations of menopause age with cognitive outcomes by further adjusting for HT (M3 plus HT). We also examined whether HT use was associated with ACE-III total and PACC total scores without adjustments, and after accounting for menopause age.

In sensitivity analyses, ran for ACE-III total and PACC total, we excluded participants who scored <82 on the ACE-III (whole-cohort n = 50; Insight 46 n = 5), a threshold indicative of possible cognitive impairment [25]. Additionally, since the surgical removal of both ovaries results in the cessation of all ovarian estrogen production, in contrast to surgeries in which at least one ovary is conserved [2], we excluded women who had bilateral oophorectomy (whole-cohort n = 83; Insight 46 n = 24).

Multiple imputation by chained equations (MICE) was used to account for missing data in the covariables and, where applicable, in outcomes (PACC FNAME-12A only; missing n = 2). For outcomes which were skewed (ACE-III total, all ACE-III sub-domains, MMSE), non-parametric bootstrap confidence intervals were used for inference. Supplementary Material 1 provides more detail on the imputation and bootstrapping procedures used.

3. Results

3.1. Participant characteristics

1378 women had available menopause age data. Of these, 746 were still in the cohort and completed the ACE-III at age 69, and 197 Insight 46 participants completed the PACC (Fig. 1). Two participants did not complete the FNAME-12A assessment due to technical problems and lack of time; multiple imputation was applied to account for these missing data (Supplementary Material 1).

Table 1 displays participant characteristics. Mean age at menopause was comparable between the whole-cohort (mean = 49.81 years, range 28.75–62.50 years) and the Insight 46 samples (mean = 49.89 years, range 30.25–60.50 years). Women who had a surgical rather than natural menopause experienced menopause at a younger age (7.70 and 8.06 years younger, on average, for the whole-cohort and Insight 46 samples, respectively). Surgical menopause and HT use were more common among Insight 46 participants than in the whole-cohort. Consistent with previous work [15], cognitive scores were also generally higher in Insight 46 participants, as was childhood SEP and education.

Most women included in these analyses had ever used HT (57.72 % and 69.63 % in the whole-cohort and Insight 46, respectively; Table 1). Of the women who had used HT, most started taking HT between age 46 and 51 years (whole-cohort = 60.16 %; Insight 46 = 67.42 %; Table 1), and <5 years was the most common length of HT use (whole-cohort = 48.54 %; Insight 46 = 46.92 %; Table 1).

3.2. Associations of menopause age with later-life cognitive performance

Among women from NSHD who completed the ACE-III at age 69, we detected positive associations for later menopause age with better task performance on the ACE-III total and across all ACE-III sub-domains (n = 746; Fig. 2; Supplementary Material 2). In the unadjusted model, each 1-year increase in age at menopause associated with a 0.024 SD increase in standardized ACE-III total score (95 % CI 0.012, 0.036), equating to 0.02 additional points for the ACE-III total raw score (maximum 100). Attention and orientation was the only ACE-III outcome measure for which the unadjusted effect estimate was not significant.

As shown in Fig. 2 and Supplementary Material 2, the effect estimates for all ACE-III outcomes were attenuated after adjustments for early cognition and sociodemographic factors in model 1. Adjustments for reproductive factors in model 2 increased the effect estimates for ACE-III total and the language, verbal fluency, and visuospatial sub-domains. With further adjustment for health-related factors in model 3, no significant associations of menopause age with any ACE-III

Table 1
Characteristics for women with available data on age at menopause and cognitive home assessment at age 69 (ACE-III), and Insight 46 sub-study neuropsychology assessment (PACC). The descriptive data included in this table have not been imputed.

	ACE-III completed (NSHD)		PACC completed (Insight 46)	
Variable	N	Mean(SD);range/%	N	Mean(SD);range/%
Age of period cessation (years since birth) (mean (SD); range)	746	49.81 (5.95);28.75–62.50	197	49.89 (5.71);30.25–60.50
Natural menopause (mean (SD); range)	541	51.95 (4.06);34.50–61.92	134	52.47 (3.22);40.50–59.50
Surgical menopause (mean (SD); range)	205	44.18 (6.44);28.75–62.50	63	44.41 (5.98);30.25–60.50
ACE-III total raw score (mean(SD); range)	746	91.79 (6.01);62–100	167	93.28 (5.27);70–100
ACE-III attention & orientation raw score (mean(SD); range)	746	16.61(1.95);5–18	167	16.74(1.90);8–18
ACE-III language raw score (mean(SD); range)	746	25.28(1.13);16–26	167	25.49(0.99);19–26
ACE-III memory raw score (mean(SD); range)	746	23.79(2.66);12–26	167	24.50(1.97);15–26
ACE-III verbal fluency raw score (mean(SD); range)	746	11.09(22.04);2–14	192	11.5(1.87);2–14
ACE-III visuospatial function raw score (mean(SD); range)	746	15.01(1.30);8–16	167	15.13(1.34);8–16
PACC total raw score[a] (mean(SD); range)	167	39.62 (6.59);13.50–52	197	39.8 (6.62);13.50–52.75
PACC DSST raw score (mean(SD); range)	167	48.80 (10.24);24–76	197	49.15 (10.11);24–76
PACC FNAME-12A raw score (mean (SD); range)	165	68.78(18.36);3–95	195	69.18(18.16);3–95
PACC logical memory delayed raw score (mean (SD); range)	167	12.17(3.27);0–20	197	12.39(3.41);0–23
PACC MMSE raw score (mean(SD); range)	167	29.23(1.10);23–30	197	29.28(1.04);23–30
Childhood cognition z-score age 8[b] (mean(SD); range)	693	0.16(0.80);-2.11–2.39	197	0.40(0.77);-1.59–2.47
Childhood social class	702		192	
Manual (%)	377	53.70	94	48.96
Non-manual (%)	325	46.30	98	51.04
Education (to age 26)	709		192	
Ordinary (GCSE-level or below) (%)	462	65.16	95	49.48
Advanced (A-level or higher) (%)	247	34.84	97	50.52
Age at menarche (years since birth) (mean(SD); range)	598	13.02 (1.19);9–18.50	172	12.88 (1.20);9.92–17.50
Number of natural-born children	642		177	
0–2 children (%)	420	65.42	115	64.70
3 or more children (%)	222	34.58	62	35.03
Menopause type	746		197	
Natural (%)	541	72.50	134	68.02
Surgical (%)	205	27.50	63	31.98
Type of surgery	205		63	
Hysterectomy only (%)	101	49.27	34	53.97
Unilateral oophorectomy (with/without hysterectomy) (%)	21	10.24	5	7.94
Bilateral oophorectomy (with/without hysterectomy) (%)	83	40.49	24	38.09
BMI at age 36 years (kg/m^2) (mean (SD); range)	690	23.18 (3.31);16.23–40.39	183	23.10 (3.27);17.16–39.16
Smoking pack years at age 36 years (mean(SD); range)	679	1.12(2.01);0–10	183	0.84(1.72);0–7.50
APOE-ε4 status	665		197	
ε4 present (%)	195	29.32	54	27.41
ε4 absent (%)	470	70.68	143	72.59
Affective symptoms age 69 (GHQ caseness)	744		192	
Yes (%)	140	18.82	24	12.50
No (%)	604	81.18	168	87.50
Age at Insight 46 cognitive testing (mean(SD); range)	N/A	N/A	184	70.68 (0.68);69.27–71.86
Ever use of HT	667		191	
No (%)	282	42.28	58	30.37
Yes (%)	385	57.72	133	69.63
For HT users, age at first use	384		132	
≤45 years (%)	83	21.61	23	17.42
46–51 years (%)	231	60.16	89	67.43
≥52 years (%)	70	18.23	220	15.15
For HT users, length of HT use	377		130	
<5 years (%)	183	48.54	61	46.92
5–10 years (%)	139	36.87	48	36.92
>10 years (%)	55	14.59	21	16.15

ACE-III = Addenbrooke's Cognitive Examination; PACC = Preclinical Alzheimer's Cognitive Composite; NSHD = National Survey of Health and Development; SD = standard deviation; DSST = Digit-Symbol Substitution Test; FNAME = Face-Name Associative Memory Examination; MMSE = Mini-Mental State Examination; GHQ = General Health Questionnaire; HT = Hormone Therapy.

[a] PACC total raw score is the mean of scores across the four PACC sub-tests (DSST, FNAME-12A, logical memory delayed recall, MMSE) calculated for each participant. Where FNAME-12A data was missing, PACC total was calculated as the mean of scores across DSST, logical memory delayed recall and MMSE.

[b] *Z*-score standardized to the sample at the time. If data are missing for cognition at age 8, values from age 11 (n = 11) or age 15 (n = 10) years were used instead.

outcomes remained, but the largest effect estimates were for ACE-III total (β = 0.010; 95 % CI −0.004, 0.024) and the memory (β = 0.009; 95 % CI -0.006, 0.023) and visuospatial function (β = 0.013; 95 % CI −0.004, 0.026) sub-domains.

For women in the Insight 46 sub-sample, later menopause age associated with better task performance on the PACC total and across all PACC sub-tests (n = 197; Fig. 3; Supplementary Material 2). In the unadjusted model, each 1-year increase in menopause age associated with a 0.029 SD increase in PACC total z-score (95 % CI 0.011, 0.048), equating to 0.01 additional points on the PACC total raw score. MMSE was the only PACC sub-test which for which the unadjusted effect estimate was not significant.

As shown in Fig. 3 and Supplementary Material 2, adjusting for early cognition and sociodemographic factors in model 1 attenuated the

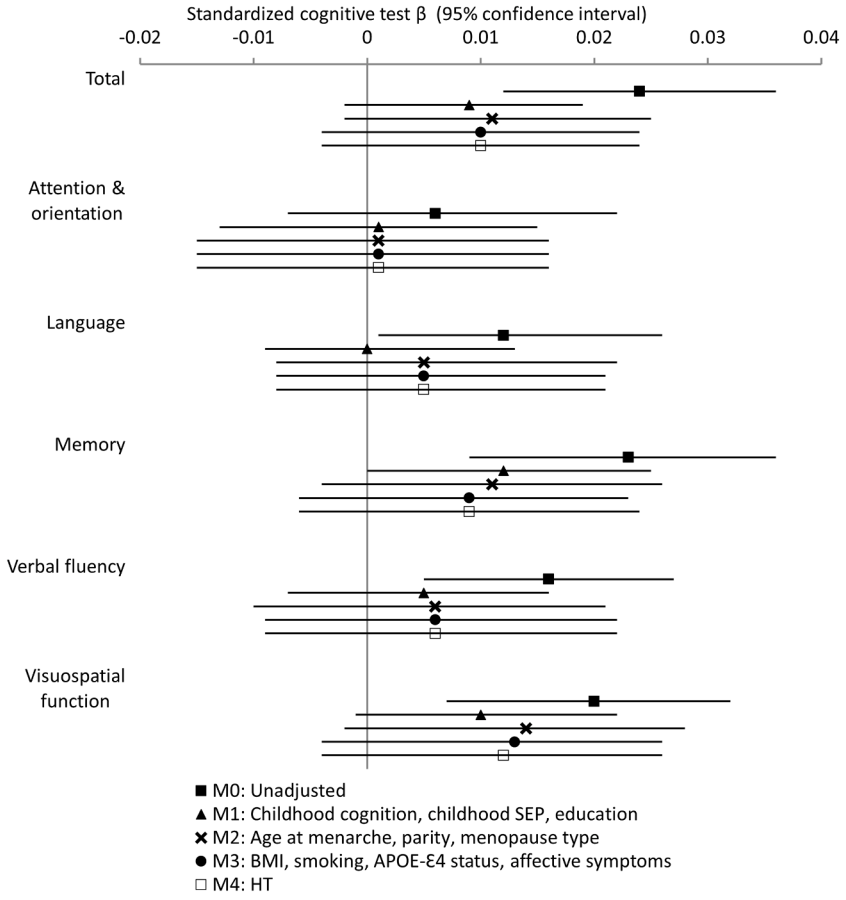

Fig. 2. Model estimates and bootstrap 95 % confidence intervals for the effect of 1-year increase in age at menopause on standardized z-scores for the Addenbrooke's Cognitive Examination (ACE-III; total score and sub-domains) at age 69 in the National Survey of Health and Development (NSHD) whole-cohort. N = 746.

associations with PACC outcomes; no associations remained significant. Additionally adjusting for reproductive factors in model 2 increased the effect estimates for PACC total, DSST, and FNAME-12A. With full adjustments (M3) the largest effects were for FNAME-12A performance, remaining significant (β = 0.037; 95 % CI 0.005, 0.069), and for DSST, although non-significant (β = 0.031; 95 % CI −0.001, 0.062). No significant associations remained for PACC total, logical memory delayed, nor MMSE performance.

3.3. Effect modification by menopause type and APOE-ε4 status

We did not detect interactive effects of menopause age-by-menopause type on standardized ACE-III total (95 % CI −0.03, 0.02) nor PACC total (p = 0.243; 95 % CI −0.073, 0.019) performance (Supplementary Material 2). Additionally, no interactive effects of menopause age-by-APOE-ε4 status on ACE-III total (95 % CI −0.009, 0.006) nor PACC total (p = 0.949; 95 % CI -0.039, 0.037) were detected (Supplementary Material 2).

3.4. The role of menopausal hormone therapy

Compared with fully adjusted models (M3), further adjusting for HT use (M4) had little impact on the effect estimates for any outcomes (Figs. 2 and 3; Supplementary Material 2). We did not find any evidence of associations between HT use and ACE-III total nor PACC total performance (Supplementary Material 2).

3.5. Supplementary and sensitivity analyses

Individually adjusting for each model 1 covariable (childhood cognition, childhood SEP, education) revealed that the attenuation of effect estimates was driven by childhood cognition (Supplementary Material 3).

Where negative confounding in model 2 was observed (ACE-III: total, language, verbal fluency, visuospatial function; PACC: total, DSST, FNAME-12A), individually adjusting for reproductive covariables (age at menarche, parity, menopause type) showed that the negative confounding was driven by menopause type (Supplementary Material 3). No menopause age-by-menopause type interactions were detected on these outcomes (Supplementary Material 3). Regressing menopause type on cognitive outcomes, we found unadjusted negative associations for surgical compared with natural menopause which were negatively confounded when adjusting for menopause age (Supplementary Material 3).

Excluding women with possible cognitive impairment (total ACE-III score < 82) did not substantially change the effect estimates for the association of menopause age with ACE-III total, although the estimates for PACC total were slightly attenuated (Supplementary Material 3). Similarly, excluding women with bilateral oophorectomy did not substantially change the effect estimates for the ACE-III total outcome, while the estimates for PACC total were slightly attenuated (Supplementary Material 3).

4. Discussion

Our findings support previous evidence for positive associations between age at menopause and cognitive outcomes [5,7,10], with prolonged exposure to the neuroprotective benefits of endogenous estrogen a hypothesized mechanism [3]. Additionally, our findings are consistent with previous evidence of small positive associations between

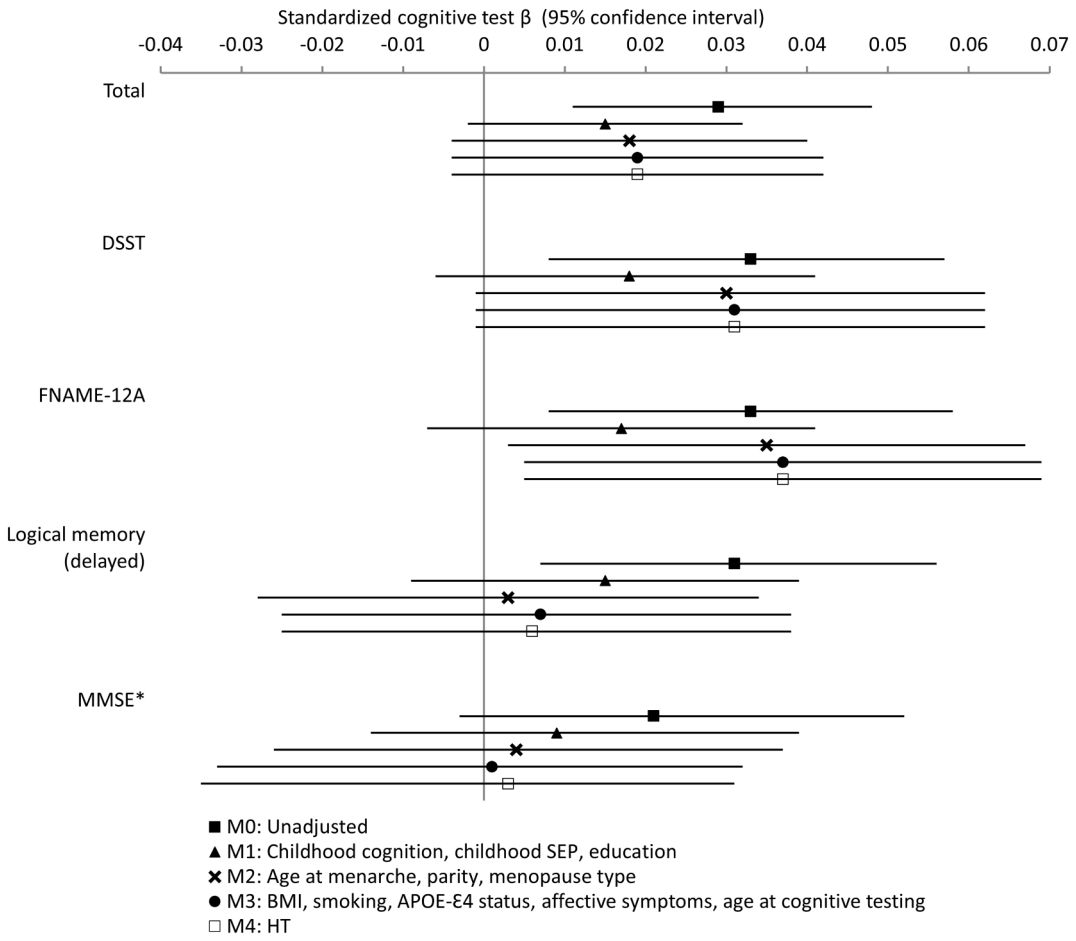

Fig. 3. Model estimates and 95 % confidence intervals for the effect of 1-year increase in age at menopause on standardized z-scores for the Preclinical Alzheimer's Cognitive Composite (PACC; total score and sub-tests) at age 69 to 71 in the Insight 46 sample. N = 197.
DSST = Digit-Symbol Substitution Test; FNAME = Face-Name Associative Memory Examination; MMSE = Mini-Mental State Examination
*Bootstrap confidence interval.

menopause age and verbal memory performance in NSHD [7]. During the menopause transition, women often report memory problems [4], and estrogen receptors are found in high concentrations within the hippocampus, a brain region important for learning and memory [3]. However, the associations of menopause age with memory performance were not consistent across different memory assessments; the association with delayed episodic memory (logical memory delayed recall) in the Insight 46 sample was not particularly strong compared with other outcome measures. There are several memory types (e.g. episodic, associative, verbal) each differently assessed in the sub-tests included in these analyses. Associations between menopause age and memory performance could differ according to the type of memory task assessed.

The association with a measure of processing speed in the Insight 46 cohort contrasts with previous evidence from NSHD where associations with processing speed were not detected [7,10]. However, the processing speed measure completed by Insight 46 participants (DSST) differs from the letter cancellation task completed between age 43 and 69 in the whole-cohort [7,10]; the DSST includes an associative learning component. The relationship with a measure of associative memory (FNAME-12A) in the Insight 46 cohort might also suggest that menopause age links with associative learning in later-life. Additionally, both the DSST and FNAME-12A are reliant on visual processing, in agreement with the whole-cohort association with visuospatial function.

As previously shown [7,10], most associations were not independent of life course covariables and childhood cognition was a particularly important factor. Adjustment for childhood cognition, which predicts both menopause age [6,7] and later-life cognitive performance [8,9], most strongly attenuated the associations compared with other covariables such as SEP and education. Upstream, developmental factors giving rise to childhood cognition could therefore link the timing of menopause with later-life cognitive outcomes. For example, genetic factors, pre-natal exposures and early life experiences might be important [7,26].

The negative confounding by menopause type likely reflects negative associations of surgical, compared with natural, menopause and cognitive outcomes [27], which contrasts the positive associations between menopause age and cognitive performance. We did not detect differential differences in menopause age-cognition associations by menopause type. However, beyond a generally earlier age at menopause, surgical menopause leads to more rapid declines in estrogen levels than during natural menopause. Surgery to remove both ovaries results in the most acute cessation of ovarian estrogen production [2], although excluding women who had a bilateral oophorectomy did not substantially change our results. Women with surgical menopause are also more likely to use HT, and to have poorer overall health and lower SEP than women who have a natural menopause [28,29]. Whether and how the associations of menopause age with later-life cognitive outcomes might differ by menopause type is a complex topic which requires further investigation utilizing different and larger cohorts.

4.1. Strengths and limitations

The main strength of this work is the use of longitudinal, prospective life course data which allows us to uniquely account for early life confounds, such as childhood cognition. The age homogenous cohort is particularly beneficial given that our exposure variable is age dependent. However, the generalizability of our results to other generations could be limited given secular changes in women's access to education and in HT use, for example. While we have considered the potential contribution of HT use in relation to associations between menopause age and later-life cognition, we could not differentiate the different types of HT used. We recognize a need for more in-depth analyses of HT and cognition beyond the scope of this analysis, which might benefit from the inclusion of additional data sets, given potential variations according to dosage, formulation, duration of use, and age when HT is initiated [30]. Sample attrition is also acknowledged as a limitation given that participants from more disadvantaged backgrounds are more likely to withdraw from longitudinal studies, as are participants with poorer general health which could induce survivor bias. While the effects we report are small, these are consistent with other research, and we still detect some residual associations after adjustments. In future research, follow-up cognitive assessments will facilitate further examination of associations between menopause and cognitive decline, and the availability of neuroimaging data within Insight 46 will enable us to examine the potential neural mechanisms underlying these associations.

4.2. Conclusions

We provide further evidence that later age at menopause is associated with better cognitive performance in later-life and identify that the associations are most notable for visual processing and associative learning and memory domains. However life course covariables, particularly childhood cognition, contribute to associations. Such factors are important to consider when examining the potential mechanisms underlying relationships between menopause and female cognitive ageing.

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Contributors

Louisa P Needham conceived and designed the study, performed the analyses, wrote the first draft of the manuscript, contributed to the interpretation of the results and critically revised the manuscript.

Kirsty Lu contributed to the interpretation of the results and critically revised the manuscript.

Jennifer M Nicholas supervised the statistical analyses, contributed to the interpretation of the results and critically revised the manuscript.

Jonathan M Schott contributed to the interpretation of the results and critically revised the manuscript.

Marcus Richards conceived and designed the study, contributed to the interpretation of the results and critically revised the manuscript.

Sarah-Naomi James conceived and designed the study, wrote the first draft of the manuscript, contributed to the interpretation of the results and critically revised the manuscript.

All authors acknowledge full responsibility for the analyses and interpretation of the report. All authors read and approved the final manuscript.

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Ethical approval

Current ethical approval for the MRC National Survey of Health and Development was granted by NRES Queen Square Research Ethics Committee (14/LO/1073) and Scotland A Research Ethics Committee (14/ SS/1009). All study members provided written informed consent.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data used in this publication are available to bona fide researchers on request to the National Survey of Health and Development Data Sharing Committee via a standard application procedure. Further details can be found at http://www.nshd.mrc.ac.uk/data. doi:https://doi.org/10.5522/NSHD/Q101; doi:https://doi.org/10.5522/NSHD/Q102; doi:https://doi.org/10.5522/NSHD/Q103.

Declaration of competing interest

JMS has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), has consulted for Roche Pharmaceuticals, Biogen, and Eli Lilly, given educational lectures sponsored by GE, Eli Lilly and Biogen, and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE. The funding bodies did not have any role in the study design or in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. All other authors report no conflicts with any product mentioned or concept discussed in this article.

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References

[1] B.S. Hulka, O. Meirik, Research on the menopause, Maturitas 23 (1996) 109–112, https://doi.org/10.1016/0378-5122(95)00967-1.
[2] W.H. Utian, Menopause-related definitions, Int. Congr. Ser. 1266 (2004) 133–138, https://doi.org/10.1016/j.ics.2004.01.102.
[3] S. Zárate, T. Stevnsner, R. Gredilla, Role of estrogen and other sex hormones in brain aging. Neuroprotection and DNA repair, Front. Aging Neurosci. 9 (2017) 430, https://doi.org/10.3389/fnagi.2017.00430.
[4] P.M. Maki, V.W. Henderson, Cognition and the menopause transition, Menopause 23 (2016) 803–805, https://doi.org/10.1097/GME.0000000000000681.
[5] M.K. Georgakis, et al., Age at menopause and duration of reproductive period in association with dementia and cognitive function: a systematic review and meta-analysis, Psychoneuroendocrinology 73 (2016) 224–243, https://doi.org/10.1016/j.psyneuen.2016.08.003.
[6] M. Richards, D. Kuh, R. Hardy, M. Wadsworth, Lifetime cognitive function and timing of the natural menopause, Neurology 53 (1999) 308–314, https://doi.org/10.1212/wnl.53.2.308.
[7] D. Kuh, et al., Childhood cognitive ability and age at menopause: evidence from two cohort studies, Menopause 12 (2005) 475–482, https://doi.org/10.1097/01.GME.0000153889.40119.4C.
[8] K. Lu, et al., Cognition at age 70: life course predictors and associations with brain pathologies, Neurology 93 (2019) e2144–e2156, https://doi.org/10.1212/WNL.0000000000008534.

[9] M. Richards, et al., Identifying the lifetime cognitive and socioeconomic antecedents of cognitive state: seven decades of follow-up in a British birth cohort study, BMJ Open 9 (2018), e024404, https://doi.org/10.1136/bmjopen-2018-024404.
[10] H.S. Kok, et al., Cognitive function across the life course and the menopausal transition in a british birth cohort, Menopause 13 (2006) 19–27, https://doi.org/10.1097/01.gme.0000196592.36711.a0.
[11] D. Kuh, R. Cooper, A. Moore, M. Richards, R. Hardy, Age at menopause and lifetime cognition: findings from a british birth cohort study, Neurology 90 (2018) E1673–E1681, https://doi.org/10.1212/WNL.0000000000005486.
[12] M.C. Donohue, et al., The preclinical alzheimer cognitive composite: measuring amyloid-related decline, JAMA Neurol. 71 (2014) 961–970, https://doi.org/10.1001/jamaneurol.2014.803.
[13] D. Kuh, R. Hardy, Women's health in midlife: findings from a British birth cohort study, J. Br. Menopause Soc. 9 (2003) 55–60, https://doi.org/10.1258/136218003100322206.
[14] C.A. Lane, et al., Study protocol: insight 46 - a neuroscience sub-study of the MRC National Survey of health and development, BMC Neurol. 17 (2017) 75, https://doi.org/10.1186/s12883-017-0846-x.
[15] S.N. James, et al., Using a birth cohort to study brain health and preclinical dementia: recruitment and participation rates in insight 46, BMC Res. Notes. 11 (2018) 885, https://doi.org/10.1186/s13104-018-3995-0.
[16] D. Wechsler, Wechsler Adult Intelligence Scale, revised edition, 1981.
[17] K.V. Papp, et al., Development of a psychometrically equivalent short form of the face-name associative memory exam for use along the early alzheimers disease trajectory, Clin. Neuropsychol. 28 (2014) 771–785, https://doi.org/10.1080/13854046.2014.911351.
[18] D. Wechsler, Wechsler Memory Scale, revised edition, 1987.
[19] M.F. Folstein, S.E. Folstein, P.R. Mchugh, "Mini-mental state". A practival method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198, https://doi.org/10.1016/0022-3956(75)90026-6.
[20] R. Bland, Measuring 'social class' a discussion of the registrar-general's classification, Sociology 13 (1979) 283–291. https://www.jstor.org/stable/42861234.
[21] Department of Education and Science, Burnham Further Education Committee Grading Courses, 1972.
[22] S. Masi, et al., Patterns of adiposity, vascular phenotypes and cognitive function in the 1946 British Birth Cohort, BMC Med. 16 (2018) 75, https://doi.org/10.1186/s12916-018-1059-x.
[23] J. Koochmeshgi, S.M. Hosseini-Mazinani, S.M. Seifati, N. Hosein-Pur-Nobari, L. Teimoori-Toolabi, Apolipoprotein E genotype and age at menopause, Ann. N. Y. Acad. Sci. 1019 (2004) 564–567, https://doi.org/10.1196/annals.1297.105.
[24] M. Sterling, General health Questionnaire-28 (GHQ-28), J. Physiother. 57 (2011) 259, https://doi.org/10.1016/S1836-9553(11)70060-1.
[25] S. Hsieh, S. Schubert, C. Hoon, E. Mioshi, J.R. Hodges, Validation of the Addenbrooke's cognitive examination III in frontotemporal dementia and Alzheimer's disease, Dement. Geriatr. Cogn. Disord. 36 (2013) 242–250, https://doi.org/10.1159/000351671.
[26] R. Hardy, D. Kuh, Social and environmental conditions across the life course and age at menopause in a british birth cohort study, BJOG An Int. J. Obstet. Gynaecol. 112 (2005) 346–354, https://doi.org/10.1111/j.1471-0528.2004.00348.x.
[27] M.K. Georgakis, T. Beskou-Kontou, I. Theodoridis, A. Skalkidou, E.T. Petridou, Surgical menopause in association with cognitive function and risk of dementia: a systematic review and meta-analysis, Psychoneuroendocrinology 106 (2019) 9–19, https://doi.org/10.1016/j.psyneuen.2019.03.013.
[28] L.L. Sievert, L. Murphy, L.A. Morrison, A.M. Reza, D.E. Brown, Age at menopause and determinants of hysterectomy and menopause in a multi-ethnic community: the Hilo Women's health study, Maturitas 76 (2013) 334–341, https://doi.org/10.1016/j.maturitas.2013.08.007.
[29] C. Secoşan, et al., Surgically induced menopause-a practical review of literature, Medicina (Kaunas). 55 (2019) 482, https://doi.org/10.3390/medicina55080482.
[30] A.C. McCarrey, S.M. Resnick, Postmenopausal hormone therapy and cognition, Horm. Behav. 74 (2015) 167–172, https://doi.org/10.1016/j.yhbeh.2015.04.018.