Association of earlier age at menopause with risk of incident dementia, brain structural indices and the potential mediators: a prospective community-based cohort study

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eClinicalMedicine 2023;60: 102033
Published Online 8 June 2023
https://doi.org/10.1016/j.eclinm.2023.102033

Summary

Background To date, there is no homogeneous evidence of whether earlier age at menopause is associated with incident dementia. In addition, the underlying mechanism and driven mediators are largely unknown. We aimed to fill these knowledge gaps.

Methods This community-based cohort study included 154,549 postmenopausal women without dementia at enrolment (between 2006 and 2010) from the UK Biobank who were followed up until June 2021. We followed up until June 2021. Age at menopause was entered as a categorical variable (<40, 40–49, and ≥50 years) with ≥50 years taken as a reference. The primary outcome was all-cause dementia in a time-to-event analysis and the secondary outcomes included Alzheimer's disease, vascular dementia, and other types of dementia. In addition, we investigated the association between magnetic resonance (MR) brain structure indices with earlier menopause, and explored the potential underlying driven mediators on the relationship between earlier menopause and dementia.

Findings 2266 (1.47%) dementia cases were observed over a median follow-up period of 12.3 years. After adjusting for confounders, women with earlier menopause showed a higher risk of all-cause dementia compared with those ≥50 years (adjusted-HRs [95% CIs]: 1.21 [1.09–1.34] and 1.71 [1.38–2.11] in the 40–49 years and <40 years groups, respectively; *P* for trend <0.001). No significant interactions between earlier menopause and polygenic risk score, cardiometabolic factors, type of menopause, or hormone-replacement therapy strata were found. Earlier menopause was negatively associated with brain MR global and regional grey matter indices, and positively associated with white matter hyperintensity. The relationship between earlier menopause and dementia was partially mediated by menopause-related comorbidities including sleep disturbance, mental health disorder, frailty, chronic pain, and metabolic syndrome, with the proportion (95% CI) of mediation effect being 3.35% (2.18–5.40), 1.38% (1.05–3.20), 5.23% (3.12–7.83), 3.64% (2.88–5.62) and 3.01% (2.29–4.40), respectively. Multiple mediator analysis showed a combined effect being 13.21% (11.11–18.20).

Interpretation Earlier age at menopause was associated with risk of incident dementia and deteriorating brain health. Further studies are warranted to clarify the underlying mechanisms by which earlier age at menopause is linked to an increased risk of dementia, and to determine public health strategies to attenuate this association.

Funding National Natural Science Foundation of China, the Science and Technology Program of Guangzhou, the Key Area Research and Development Program of Guangdong Province, the China Postdoctoral Science Foundation, and the Guangdong Basic and Applied Basic Research Foundation.

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Keywords: Earlier age at menopause; Dementia; Brain structure; Mediator

Research in context

Evidence before this study

We searched PubMed and Web of Science using the search terms ("cognitive" or "cognition" or "Alzheimer") AND ("early" or "earlier" or "premature") AND ("menopause" or "menopausal") in the title and abstract, up to December 23, 2022. Generally, published findings remained controversial and did not support a consistent link between earlier menopause and incident dementia. Evidence on related changes in brain structure among women with earlier menopause was scarce, and the driving mediators were largely unknown.

Added value of this study

In this large-scale community-based cohort study, earlier age at menopause (before 50 years) was associated with a higher incidence of all-cause dementia compared with those who were aged at least 50 years at menopause. Earlier menopause was negatively associated with brain global and regional grey matter indices, and positively associated with white matter hyperintensity, highlighting the potential pathological basis to dementia. The relationship between earlier menopause and dementia was partially mediated by menopause-related comorbidities, including sleep disturbance, mental health disorder, frailty, chronic pain, and metabolic syndrome.

Implications of all the available evidence

Earlier age at menopause was associated with risk of incident dementia. Our deteriorating brain health findings and the mediating effect of the postmenopausal comorbidities suggest potential pathophysiological processes to cognitive decline. Future studies are warranted to further clarify the underlying mechanisms and to determine public health strategies to attenuate this association.

Introduction

Dementia is a clinical syndrome, characterised by severe loss of cognitive and emotional abilities, that has a negative impact on daily function and quality of life.[1] The most common dementia subtypes are Alzheimer's disease (AD) and vascular dementia (VD).[2,3] An estimated 50 million people worldwide live with dementia.[4] Despite decades of research, its potential aetiologic mechanism has not yet been elucidated, and medical treatments are limited.[5] Emerging evidence has shown that reducing modifiable risk factors may help to prevent and control dementia.[6]

Earlier menopause refers to menopause that occurs before the median age of natural menopause (age 50 years),[7,8] and premature menopause refers to menopause that occurs before age 40 years.[9] Emerging shreds of evidence indicated that earlier menopause, particularly premature menopause, irrespective of its spontaneous or surgery-induced nature, might be associated with increased risks of cardiovascular diseases,[10] sleep disorders,[11] psychiatric diseases,[12] and other sequelae.[13] Most of these findings implicated an oestrogen deficit mechanism leading to tissue or organ dysfunctions.[14] Previous experimental studies indicated that oestrogen improved synaptic plasticity, promoted neuroprotective actions, and enhanced the survival of brain mitochondria.[15] Via these effects, oestrogen deprivation may be a contributor to neurodegenerative disorders, from which it could be inferred that earlier menopause, particularly premature menopause, may be an important risk factor for dementia in menopausal women.

Previous studies, including cohorts from the USA,[16] South Korea,[17] France,[18] Sweden,[19] and other locations,[20] have suggested a possible link between earlier or premature menopause and dementia. However, published findings remain inconsistent. A multinational population-based cohort study that included women aged 65 years and over found no evidence that earlier age at menopause might influence dementia incidence in late life.[21] A systemic review by Georgakis and colleagues[22] included 13 studies (a total of 19,328 women), among which 8 studies were cross-sectional and 5 studies were longitudinal cohort studies, to investigate the association between earlier menopause and dementia. However, the authors failed to draw definitive conclusions on this topic. Previous studies were heterogeneous in the inclusion criteria, the definition of age at menopause, the assessment of outcome, and the possible co-exposure to other covariables. Hence, evidence from a more general population to clarify the relationship between earlier age at menopause and dementia is needed. Although a previous study by Gong and colleagues, based on the UK Biobank cohort, discussed the associations between a wide range of reproductive factors and the risk of incident dementia in both men and women,[23] further work is warranted. Investigations focused on the relationship between earlier age at menopause and dementia in a dose-response manner, based on the prevalent diagnosis criteria for earlier or premature menopause, may provide important implications for clinical practice. In addition, the possible mechanism is not yet clear.

The menstruation influence on dementia may be reflected in brain structure. Previous studies have shown that important changes in the brain structure, including brain atrophy and white matter hyperintensity (WMH) on magnetic resonance (MR), might lead to cognitive decline and have a role in the aetiology of dementia.[24,25] Alteration in oestrogen may change brain structure, which may, in turn, lead to dementia. Evidence on related changes in brain structure among women with earlier menopause, which provides insight into the mechanisms of earlier menopause contributing to dementia, is scarce. Furthermore, the driving mediators in the chain of the menopause-dementia causality remain largely unknown. As women traverse the menopause transition, they may experience multiple menopause-related comorbidities such as sleep disturbance, mental health disorder, frailty, chronic pain, and metabolic syndrome (MetS).[10,26,27] Nevertheless, few studies have explored the mediating effects of these influential factors on the relationship between earlier menopause and the risk of dementia.

We aimed to conduct a large-scale study of UK Biobank data to address whether earlier or premature menopause would increase the risk of all-cause dementia and its subtypes in a general community population, to investigate the relevant changes in brain structure measured by MR with earlier menopause, and to explore the potential underlying driven mediators.

Methods

Data source and participants

For this community-based cohort study, data were extracted from the public UK Biobank Resource (https://www.ukbiobank.ac.uk/). The UK Biobank is a prospective cohort study with over 500,000 community-dwelling participants across the UK aged 37–73 years when recruited between 2006 and 2010.[28] The present study was conducted under application number 70109 of the UK Biobank resource.

Participants who were 37–73 years old at baseline were included in our study. We excluded those who were 1) reported previous dementia, 2) male participants, 3) premenopausal women without self-report menopause or with unknown menopause status. The flow chart is shown in Fig. 1.

Sex of participants in the study was determined by a mixture of the NHS record and the self-reported questionnaire. In the sensitivity analysis, we excluded participants with unknown genetic sex or mismatch information in self-reported and genetic sex. Methods of data collection at baseline are detailed in the Supplementary Methods.

Ethics

The UK Biobank Study's ethical approval was granted by the National Information Governance Board for Health and Social Care and the National Health Service (NHS) North West Multicentre Research Ethics Committee. All participants provided informed consent through electronic signature at baseline assessment.

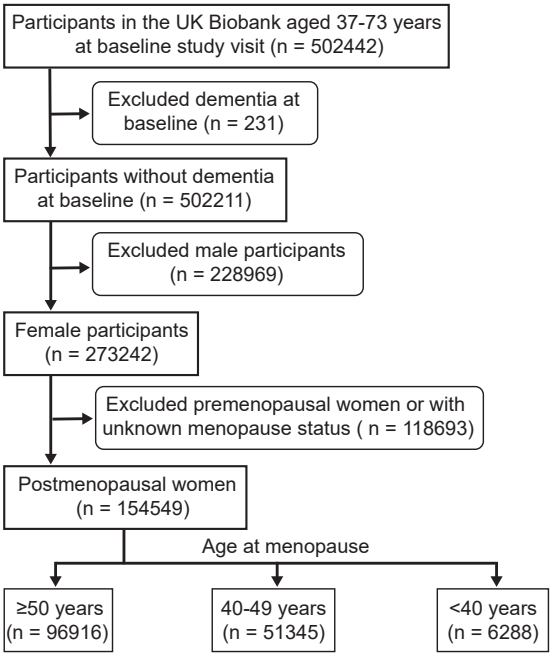

Fig. 1: **Study profile, showing creation of the study sample from women in the UK Biobank.**

Age at menopause

Participants were asked "How old were you when your periods stopped?" about the age at menopause at baseline. In this study, unless otherwise mentioned, age at menopause was entered as a categorical variable (<40, 40–49, and ≥50 years) with ≥50 years taken as a reference. These age categories were pre-specified in the WHI OS study.[29] Clinically speaking, these age categories distinguished women who experienced menopause later than the natural median age (≥50 years) from those at earlier ages (including premature menopause). Premature menopause was defined as menopause that occurred before age 40 years.[9] Reproductive period was defined as the time interval from menarche to menopause. Interval of menopause-baseline was defined as the time interval from menopause to the baseline assessment.

Type of menopause

Natural menopause was defined as the absence of menstruation without experience of hysterectomy and/or bilateral oophorectomy prior to this. Surgical menopause was defined by report of either hysterectomy or bilateral oophorectomy.

Outcomes

The primary outcome was all-cause dementia in a time-to-event analysis, and the secondary outcomes included AD, VD, and other types of dementia. The electronic health records (EHRs), a data linkage to hospital inpatient admissions and death registries, include primary or secondary events in England, Scotland, and Wales. A previous comparison between EHRs and expert clinical adjudicators in the UK Biobank showed that the overall positive predictive value for dementia diagnosis is 82.5%,[30] suggesting that the EHRs were effective to assess the association between risk factors and dementia. We used the algorithms provided by UK Biobank to identify dementia cases, which were generated based on EHRs, using the International Classification of Diseases (ICD) 9 and ICD-10 codes (Table S1). In the time-to-event analysis, the date of incident dementia during follow-up was set as the earliest date of dementia codes recorded regardless of the source used. At the time of analysis, as hospital admission data were available until June 30, 2021. We, therefore, censored the disease-specific outcome analysis at this date or the date of the first disease incidence or death, whichever occurred first. Mortality data were available for participants until May 31, 2021.

Partial participants were invited back for brain MR imaging after a median of 8.88 years (2.11–13.82) since the baseline assessment. As a post-hoc analysis, the brain structural imaging data measured by MR were processed by the UK Biobank team and made available to approved researchers as imaging-derived phenotypes (IDPs). IDPs used in this study included global brain structure indices: grey matter volume (GMV), white matter volume (WMV) and WMH; and regional brain structure indices: area, volume, and mean thickness in 68 cortical regions based on the Desikan-Killiany atlas[31] and volume in 35 subcortical regions based on the segmentations by Fischl and colleagues.[32] WMH was log transformed due to its log normally distribution.

Covariates, confounders, and mediators

Derivation of synthetic variables including healthy diet, low physical activity and MetS were detailed in the Supplementary Methods. Directed acyclic graph (DAG) was applied to state the rationale in selecting covariates as confounders and mediators on the relationship between earlier menopause and dementia, based on biological plausibility and previous literature (Fig. S1). The covariates considered as the primary confounding factors[10,33] included: age at baseline (used as a continuous variable unless otherwise specified); ethnicity (white or others); education (higher or others); socioeconomic deprivation (SED), categorised as high, medium and low deriving from the Townsend deprivation index terciles; smoking status (never or previous/current); alcohol intake (non-drinker or drinker); physical activity, categorised into age-specific and sex-specific quintiles, in which the lowest quintile was classified as low physical activity; healthy diet. These factors were supposed to linked with both earlier menopause and dementia. We focused and considered menopause-related comorbidities including sleep disturbance (minimal/mild or moderate/severe),[10] mental health disorder,[10] frailty (a proxy-based version of the Fried frailty phenotype, see Supplementary Methods),[26] chronic pain,[27] and MetS[10] as mediators in this study, since these factors affected a postmenopausal woman's quality of life and were known for their association with dementia. In the sensitivity analysis to test the robust of the association, we also further adjusted covariates: a) polygenetic risk score (PRS) category for dementia, which was classified into low, middle and high, with constructing information on the 23 selected SNPs[34] listed in Table S2; b) cerebrovascular risk factors[10,33] including body mass index (BMI), categorised into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obesity (≥30.0 kg/m^2) based on their BMIs[35]; hypertension; Type 2 diabetes; hypercholesterolemia; coronary heart disease; stroke; c) other female reproductive factors[10,23] including age at menarche, oral contraceptive use, number of live births, type of menopause (natural or surgical), and hormone-replacement therapy (HRT). In addition to self-report HRT, we also considered drug-coded HRT use by medication codes (shown in Table S3) collected during the verbal interview.

Statistical analysis

For baseline characteristics, continuous variables were visually assessed for normality by histograms (Table S4). Those conforming to normal distribution were described by their means and standard deviations (SD), while those not conforming to normal distribution were described by medians and interquartile ranges (IQR). Categorical variables were described by counting numbers and calculating percentages. Univariate comparisons between groups were performed using Student's *t*, Mann–Whitney, or χ^2 tests according to the types and distributions of variables.

In the primary analysis, Kaplan–Meier survival analysis of cumulative incidence for all–cause dementia was plotted based on groups of age at menopause. Log-rank test was used to compare the survival distributions between groups. Time-to-event analysis for dementia was performed using the Cox proportional hazard regression model, and we constructed several models that included different covariates to estimate hazard ratios (HR) and their 95% confidence intervals (95% CI). Model 1 was only adjusted for age at baseline. Model 2 was adjusted for age at baseline, ethnicity, education, and SED. Model 3 was adjusted for covariables in Model 2, smoking status, alcohol intake, low physical activity, and healthy diet. Model 3 was chosen as the primary model based on model comparison using the Akaike

information criterion and the Bayesian information criterion (Table S5), and the collinearity among predictor variables was assessed through Spearman's correlation coefficients and the condition number (kappa) (Fig. S2). Tests for trend across groups were examined using ordinal values in separate models. In addition, we applied restricted cubic spline (RCS) regression to flexibly model the association of earlier age at menopause, reproductive period, and interval of menopause-baseline with risk of dementia.

In order to assess the robustness of our findings, we conducted several sensitivity analyses. First, we further adjusted some covariates. Model 4 was adjusted for terms in Model 3 and PRS category. Model 5 was adjusted for terms in Model 3, and cerebrovascular risk factors including BMI category, hypertension, type 2 diabetes, hypercholesterolemia, coronary heart disease and stroke. Model 6 was adjusted for terms in Model 3, and other female reproductive factors including age at menarche, oral contraceptive use, number of live births, type of menopause and self-reported HRT. Model 7 was adjusted for all the covariables. Second, we adjusted the model for BMI taken as a continuous variable. Third, we analysed the impact of earlier age at menopause on dementia using Fine–Gray methods accounting for death as a competing risk. Fourth, we performed the same analysis in the dataset containing 92,834 participants with complete information on all covariables and in the whole dataset containing 154,549 participants using multiple imputations (Supplementary Methods, information about frequencies of missing data between groups by age at menopause was shown in Table S6, and missing data pattern by correlation matrix was shown in Fig. S3). Fifth, we included participants who were ≥55 years old at baseline to avoid immortal time bias. Sixth, we excluded 2131 women with any prevalent gynaecological cancer at enrolment. Seventh, we excluded participants with unknown genetic sex or mismatch information in self-reported and genetic sex. Finally, we excluded participants with a prior hysterectomy but no history of a bilateral oophorectomy to assess the potential effect of hysterectomy on the menopause-dementia association.

In the subgroup analysis, which was set out to explore whether the impact of earlier menopause on dementia varied in the subgroups defined according to age at baseline, the follow up period, longitudinal age defined as age at the time of analysis, ethnicity, education, SED, smoking status, alcohol intake, low physical activity, healthy diet and PRS strata, the *P* value for interaction was calculated by the tests of exposure-by-covariate interaction in the Cox models. Associations between earlier menopause and incident dementia, stratified by cardiometabolic factors including obesity, hypertension, type 2 diabetes, hypercholesterolemia, coronary heart disease, and MetS were also studied. In additional exploratory analysis, hazard for incident dementia associated with type of menopause, self-report or drug-coded HRT was compared in the earlier and normal menopausal women, using the Cox models. We also investigated whether the timing of HRT initiation was associated with dementia.

All continuous brain structural indices (ie, IDPs) were standardised (mean = 0, standard deviation = 1), and the standardised effect size (ie, the standardised beta) and 95% CIs resulting from earlier menopause vs normal menopause were calculated using a linear regression model adjusting for covariates in Model 3 as well as height and the assessment centre of the imaging. The false discovery rate (FDR) was obtained using the Benjamini–Hochberg (BH) method to correct for multiple comparisons. Associations between earlier menopause and global brain indices including GMW, WMV, and WMH stratified by cardiometabolic factors were also studied.

Lastly, we performed mediation analyses to investigate the potential underlying driven mediators impacting the menopause-dementia relationship. The regression-based approach using the R 'CMAverse' package[36] was conducted for both single and multiple analyses. In addition, as a sensitivity analysis, the model-based framework using the R 'Mediation' package was also conducted[37] for the single mediation analysis. These had been explained in detail in the Supplementary Methods. Finally, considering some mediators such as frailty and MetS and the adjusting confounders were collinear,[38] we additionally performed a sensitivity analysis for frailty and MetS without adjustment for latent overlapping factors (Supplementary Methods).

All *P* values were reported as two-sided tests with significance defined as $P < 0.05$. Statistical analyses were performed in the R software (Version 4.0.3, R Core Team, https://www.r-project.org).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analyses, interpretation, or writing of the report.

Results

Baseline characteristics

Fig. 1 has illustrated the participants' selection. Among totally 502,442 participants in the UK Biobank aged 37–73 years, after sequentially excluding 231 individuals who reported previous dementia, 228,969 male individuals, 118,693 individuals without either self-report menopause or specific menopause status, finally 154,549 individuals were enrolled in the study. Of the eligible participants, 96,916 (62.7%) individuals experienced menopause ≥50 years, 51,345 (33.2%) individuals experienced menopause at 40–49 years, and 6288 (4.1%) individuals experienced menopause at <40 years. Baseline characteristics were displayed in Table 1.

Characteristics	Age at menopause		
	≥50 years (n = 96,916)	40–49 years (n = 51,345)	<40 years (n = 6288)
Age at baseline, years	60.7 ± 4.7	59.0 ± 6.3	58.8 ± 7.2
Ethnicity (white)	88,856 (91.9)	46,500 (90.8)	5774 (92.1)
Education (higher)	49,916 (51.5)	26,159 (50.9)	3108 (49.4)
SED category			
High	34,846 (36.0)	16,601 (32.4)	1795 (28.6)
Medium	33,753 (34.9)	17,212 (33.6)	2032 (32.4)
Low	28,220 (29.1)	17,476 (34.1)	2450 (39.0)
Smoking status (previous/current)	38,744 (40.1)	22,983 (44.9)	3135 (50.1)
Alcohol intake (drinker)	88,236 (91.1)	45,715 (89.1)	5335 (84.9)
Low physical activity	14,658 (19.6)	8084 (20.4)	991 (21.2)
Healthy diet	73,882 (76.2)	37,465 (73.0)	4398 (69.9)
BMI category			
Normal weight	36,361 (37.7)	19,015 (37.2)	1879 (30.1)
Underweight	625 (0.7)	420 (0.8)	57 (0.9)
Overweight	37,563 (38.9)	19,395 (38.0)	2349 (37.6)
Obesity	21,955 (22.8)	12,260 (24.0)	1959 (31.4)
Waist circumference, cm	85.0 ± 12.2	85.1 ± 12.4	87.3 ± 13.2
SBP, mmHg	139 ± 19.1	137 ± 19.4	137 ± 19.6
DBP, mmHg	81.2 ± 9.9	80.9 ± 10.0	81.1 ± 10.1
TG, mmol/L	1.40 (0.93)	1.40 (0.96)	1.54 (1.07)
HDL, mmol/L	1.63 ± 0.38	1.61 ± 0.38	1.55 ± 0.38
Fasting glucose, mmol/L	5.13 ± 1.05	5.12 ± 1.12	5.18 ± 1.29
Hypertension	44,285 (45.7)	23,037 (44.9)	3114 (49.5)
Type 2 diabetes	2932 (3.03)	1785 (3.48)	338 (5.38)
hypercholesterolemia	11,472 (11.8)	6272 (12.2)	1028 (16.3)
Coronary heart disease	2419 (2.5)	1623 (3.2)	415 (6.6)
Stroke	1375 (1.4)	841 (1.6)	212 (3.4)
Sleep disturbance	12,825 (13.4)	7583 (15.0)	1318 (21.3)
Mental health disorder	36,826 (38.3)	20,644 (40.5)	3098 (49.6)
Frailty	3348 (4.68)	2256 (6.0)	486 (11.0)
Chronic pain	42,208 (43.6)	24,457 (47.6)	3772 (60.0)
MetS	27,603 (33.6)	14,721 (34.0)	2290 (43.2)
PRS category			
Low	31,915 (33.9)	16,338 (32.9)	1931 (31.9)
Middle	31,153 (33.1)	16,627 (33.5)	2089 (34.5)
High	31,024 (33.0)	16,683 (33.6)	2033 (33.6)
Age at menarche, years	13.0 (2.0)	13.0 (2.0)	13.0 (3.0)
Oral contraceptive use	75,250 (77.8)	40,133 (78.3)	4790 (76.4)
Number of live births	2.00 (2.00)	2.00 (1.00)	2.00 (2.00)
Type of menopause			
Natural menopause	96,235 (99.3)	50,563 (98.5)	6104 (97.1)
Surgical menopause	681 (0.7)	782 (1.5)	184 (2.9)
HRT (ever/current)	40,960 (42.3)	25,137 (49.0)	4550 (72.4)

Continuous data presented as mean ± SD for normal distribution variables, or median (IQR) for non-normal distribution variables. Categorical variables presented as number (%). SED: Socioeconomic deprivation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglycerides; HDL: High-density lipoprotein; MetS: Metabolic syndrome; PRS: Polygenetic risk score; HRT: Hormone replacement therapy; SD: Standard deviation; IQR: Interquartile range.

Table 1: **Baseline characteristics of the included female participants by age at menopause.**

Participants who had earlier menopause, particularly those with premature menopause, were more likely to be younger, have a lower education or SED level, be smokers, be non-drinkers, have lower physical activity, have less healthy diet, have a higher prevalence of unnormal weight, hypertension, type 2 diabetes, hypercholesterolemia, coronary heart disease, stroke, sleep disturbance, mental health disorder, frailty, chronic pain and MetS, have higher waist circumference, triglyceride (TG), and fasting glucose, have lower high-density

lipoprotein (HDL), use less oral contraceptive, be surgical menopause, and use HRT. In our study, 11,604 participants had available brain image data. Sample baseline characteristics of individuals with and without available brain data were shown in Table S7.

Age at menopause and risk of incident dementia

The incidence of the primary and secondary outcomes was shown in Table 2. We observed 2266 incident dementia cases during a median follow-up period of 12.3 years, of whom 1327 (1.37%), 788 (1.53%) and 151 (2.40%) were in the ≥50 years, 40–49 years and <40 years group, respectively. The incidence per 100,000 person-years in these groups were 113.35, 127.23 and 201.37 respectively. Women with earlier menopause, particularly premature menopause had a higher incidence of all-cause dementia compared with those ≥50 years (unadjusted-HR [95% CI] were 1.12 [1.03–1.23] and 1.79 [1.51–2.11] in the 40–49 years and <40 years group respectively; Fig. 2). After adjusting for confounders including age at baseline, ethnicity, education, SED, smoking status, alcohol intake, low physical activity, and healthy diet, the higher risk of all-cause dementia among earlier menopause remained (adjusted-HR [95% CI] were 1.21 [1.09–1.34] and 1.71 [1.38–2.11] in the 40–49 years and <40 years group respectively; *P* value for trend <0.001; Table 2). In Fig. 3, RCS visualised the relation of age at menopause, reproductive period, and interval of menopause-baseline with incidence of all-cause dementia. With age at menopause and reproductive period decreasing, the risk of all-cause incidence was relatively flat until around 50 and 40 years respectively, and then started to increase rapidly afterwards (age at menopause: *P* for non-linearity = 0.211, *P* for linearity <0.001; reproductive period: *P* for non-linearity = 0.015, *P* for linearity <0.001). By contrast, interval of menopause-baseline was positively correlated with incident dementia at the turning point of around 10 years (*P* for non-linearity = 0.465, *P* for linearity <0.001). The RCS confidence intervals in the

	Age at menopause			*P* value for trend
	≥50 years (n = 96,916)	40–49 years (n = 51,345)	<40 years (n = 6288)	
All-cause dementia				
Person-years at risk	1,170,727	619,332	74,986	–
Crude cumulative incidence, cases (%)	1327 (1.37)	788 (1.53)	151 (2.40)	–
Incidence per 100,000 person-years	113.35	127.23	201.37	–
Model 1	Reference	1.24 (1.13–1.35)	1.93 (1.63–2.28)	<0.001
Model 2	Reference	1.22 (1.11–1.33)	1.87 (1.58–2.21)	<0.001
Model 3	Reference	1.21 (1.09–1.34)	1.71 (1.38–2.11)	<0.001
AD				
Person-years at risk	1,172,418	620,443	75,218	–
Crude cumulative incidence, cases (%)	636 (0.66)	332 (0.65)	60 (0.95)	–
Incidence per 100,000 person-years	54.25	53.51	79.77	–
Model 1	Reference	1.08 (0.95–1.23)	1.58 (1.21–2.06)	0.005
Model 2	Reference	1.06 (0.93–1.22)	1.53 (1.17–1.99)	0.012
Model 3	Reference	1.14 (0.98–1.34)	1.38 (0.98–1.93)	0.022
VD				
Person-years at risk	1,173,255	620,867	75,299	–
Crude cumulative incidence, cases (%)	249 (0.26)	164 (0.32)	35 (0.56)	–
Incidence per 100,000 person-years	21.22	26.41	46.48	–
Model 1	Reference	1.35 (1.11–1.65)	2.33 (1.64–3.32)	<0.001
Model 2	Reference	1.34 (1.10–1.63)	2.27 (1.59–3.24)	<0.001
Model 3	Reference	1.28 (1.10–1.63)	2.25 (1.48–3.44)	<0.001
Other dementia				
Person-years at risk	1,171,886	620,001	75,147	–
Crude cumulative incidence, cases (%)	899 (0.93)	564 (1.10)	91 (1.45)	–
Incidence per 100,000 person-years	76.71	90.97	121.10	–
Model 1	Reference	1.31 (1.17–1.45)	1.71 (1.38–2.12)	<0.001
Model 2	Reference	1.28 (1.15–1.42)	1.64 (1.32–2.04)	<0.001
Model 3	Reference	1.25 (1.10–1.42)	1.45 (1.10–1.91)	<0.001

Model 1 are adjusted for age at baseline. Model 2 are adjusted for covariables in Model 1, ethnicity, education, and SED. Model 3 are adjusted for covariables in Model 2, smoking status, alcohol intake, low physical activity, and healthy diet. Data in Model 1, Model 2 and Model 3 are presented as HR (95% CI). AD: Alzheimer's disease; VD: Vascular dementia; HR: Hazard ratio; CI: Confidence interval.

Table 2: **Hazard ratios for outcomes associated with age at menopause.**

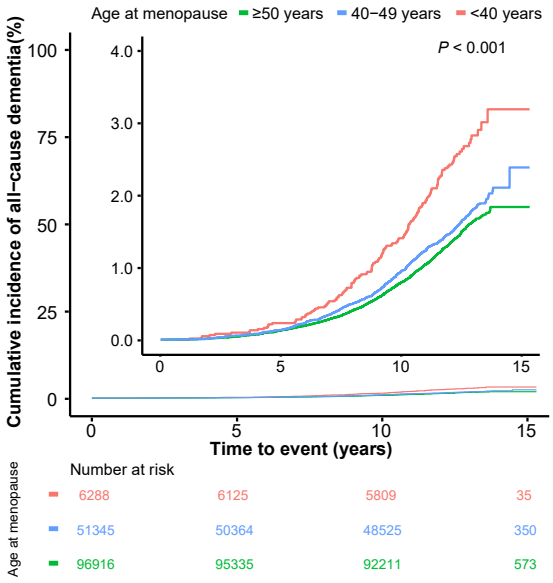

Fig. 2: **Kaplan–Meier survival analysis for all-cause dementia between groups based on age at menopause**.

lower range of age-at-menopause (Fig. 3A) and reproductive period (Fig. 3B), and the higher range of interval of menopause-baseline (Fig. 3C) were large, owing to the relatively small sample in the menopause age <40 y group.

Similar results were observed for the secondary outcomes of dementia subtypes. The earlier menopause effect estimates on HR were highest among participants with VD outcome (adjusted-HR [95% CI] was 2.25 [1.48–3.44]). A significant association was also observed between earlier menopause and other types of dementia (adjusted-HR [95% CI] were 1.25 [1.10–1.42] and 1.45 [1.10–1.91] in the 40–49 years and <40 years group respectively). Despite the risk of AD did not reach a statistical significance (adjusted-HR [95% CI] were 1.14 [0.98–1.34] and 1.38 [0.98–1.93] in the 40–49 years and <40 years group respectively), a trend for the inverse relationship persisted (*P* for trend = 0.022). Hazard ratios for outcomes associated with age at menopause by dividing the 40–49 years group into 45–49 years and 40–44 years subgroups were shown in Table S8. The difference of incidence between the 45–49 years and 40–44 years subgroups did not reach a significance (Table S9).

Sensitivity analysis

We conducted several sensitivity analyses to assess the robustness of our findings. The results showed no substantial change of the impact of earlier age at menopause on dementia (Tables S10–S18).

Subgroup analyses

As shown in Table S19, the impact of earlier menopause on dementia did not differ among participants who were in the low-, intermediate-, or high-PRS subgroups (*P* for interaction = 0.988). Similarly, no significant interaction was observed in the subgroups of age at baseline, the follow up period, longitudinal age, ethnicity, education, SED, smoking status, alcohol intake, low physical activity, and healthy diet strata (Table S19). We found no significant interactions between earlier menopause and cardiometabolic factors (Table S20).

Impact of type of menopause and HRT

In additional exploratory analysis, surgical menopause was not associated with a significant increased risk for all-cause dementia, as compared to natural menopause among either earlier nor normal menopausal women, whether partially or fully adjusted for confounders (Tables S21–S23). Detailed frequency and proportions of surgical menopause including bilateral oophorectomy

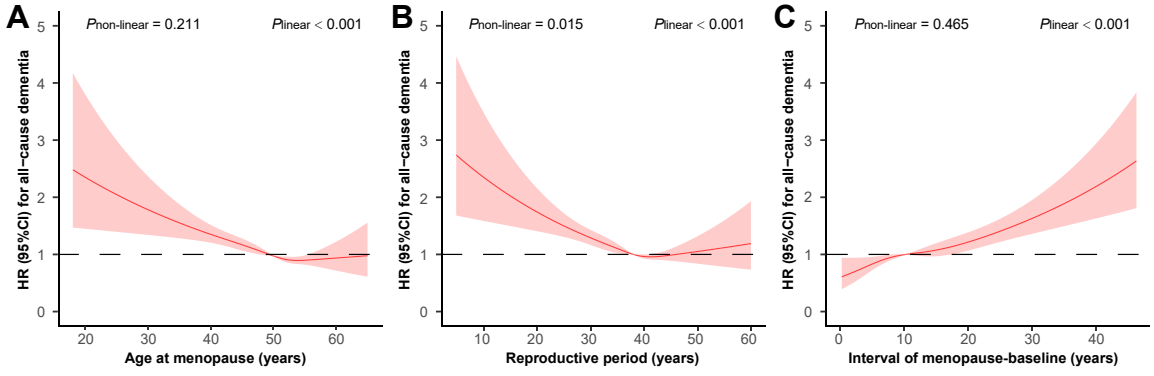

Fig. 3: **Dose–response associations between age at menopause, reproductive period, and interval of menopause-baseline with all-cause dementia**. Note: HR (95% CI) adjusted for age at baseline, ethnicity, education, SED, smoking status, alcohol intake, low physical activity, and healthy diet. Shaded areas represent 95% CIs. Non-linear relationships were estimated using restricted cubic splines and linear relationships were estimated using Cox-proportional hazards regression analysis. HR: hazard ratio; SED: socioeconomic deprivation; CI: confidence interval.

Global brain structure indices	Standardized beta (95% CI)	*P* value
GMV	−0.107 (−0.147, −0.067)	<0.001
WMV	−0.116 (−0.157, −0.075)	<0.001
WMH	0.046 (0.007, 0.086)	0.022

WMH was log transformed. Standardized beta and 95% CIs were calculated from earlier menopause vs normal menopause using a linear regression model adjusting for age at baseline, ethnicity, education, SED, smoking status, alcohol intake, low physical activity, healthy diet, height, and the assessment centre of the imaging. Sample size: menopause at the age ≥50 years, n = 7623, menopause at the age <50 years, n = 3981. GMV: Grey matter volume; WMV: White matter volume; WMH: White matter hyperintensity.

Table 3: **Associations between earlier menopause and global brain structure indices.**

and hysterectomy was shown in Table S24. Likewise, HRT or its initiation time was not associated with a decreased risk of dementia (Tables S25–29).

Relationship between earlier menopause, global and regional brain structure indices

Table 3 summarised the results, revealing that earlier menopause was associated with reduction of the global brain structure IDPs including GMV (standardised beta, –0.107; 95% CI, –0.147 to –0.067) and WMV (standardised beta, –0.116; 95% CI, –0.157 to –0.075). Meanwhile, earlier menopause was associated with increasing WMH (standardised beta, 0.046; 95% CI, 0.007–0.086). Further sensitivity analysis adjusting for the baseline-image time interval yielded similar results (Table S30). To investigate whether the reduction in global GMV derived from relationships in specific regions, we estimated the same regression model to quantify the association of earlier menopause with regional brain structure indices. Of the 239 regional GMV IDPs, 143 (59.8%) were significantly associated with earlier menopause (Fig. 4, Table S31, and Table S32). We observed the strongest associations in the frontal, parietal, temporal lobes, the putamen, pallidum, thalamus, hippocampus, and the brain stem (Fig. 4, Fig. S4, Table S31, Table S32). Most associations were negative, except that involving the area in the left para-hippocampal gyrus; thickness in the right temporal pole; volume in the right middle temporal gyrus, right supramarginal gyrus, right inferior lateral ventricle, central corpus callosum and mid-anterior corpus callosum. These effect sizes were positive but very small (FDR corrected *P* value ≥ 0.05). We found no significant interactions between earlier menopause and cardiometabolic factors on the relationship with global brain structure indices (Tables S33–S35).

Mediation analyses of the menopause-dementia association

After adjustment for potential confounders, menopause-related comorbidities including sleep disturbance, mental health disorder, frailty, chronic pain, and MetS showed partial mediating effects on the association between earlier menopause and all-cause dementia, with the significant proportion (95% CI) of mediation effect being 3.35% (2.18–5.40), 1.38% (1.05–3.20), 5.23% (3.12–7.83), 3.64% (2.88–5.62) and 3.01% (2.29–4.40), respectively (Table 4). The multiple mediator analysis showed that, the significant combined effect of all the mediators was 13.21% (11.11–18.20) (Table 4). Detailed regression coefficients were presented in Table S36. Sensitivity analysis using the model-based method yielded similar result (Table S37). Mediation sensitivity analysis for frailty and MetS without adjustment for latent overlapping factors also yielded similar results (Table S38).

Discussion

In this large-scale community-based cohort study in the UK Biobank, involving 154,549 menopausal female participants without dementia at baseline, we found the potential inverse relationship between earlier age at menopause and risk of all-cause dementia and its subtype including AD and VD. The definition of earlier or premature menopause in the study was based on the prevalent clinical diagnosis criteria,[7–9] providing important implications to clinical practice. Given that most previous studies had recruited age-specific participants, and were limited to case series or retrospective cohort studies with relatively small sample sizes, this work is a notable advance upon existing literature.

A previous study by Gong and colleagues[23] observed that certain reproductive factors (including age at menarche, age at menopause, pregnancy, birth, and abortion) were associated with incident dementia. Notably, we extended Gong and colleagues' study by investigating the dose–response relationship between earlier menopause and dementia. The result suggested that earlier age at menopause 40–49 years and premature menopause <40 years had a respectively 21% and 71% increased risk of all-cause dementia as compared with those ≥50 years during a median follow-up period of 12.3 years. We also extended the previous study by examining the relation of earlier menopause to the quantitative brain morphological structure measured by MR. Furthermore, we added evidence in the potential driven mediators on the menopause-dementia association. A vast set of sensitivity and exploratory analyses were also conducted. Our findings had important public health implications in terms of the need for effective public measures to reduce the risk of dementia in order to improve the quality of life and health of women with earlier menopause.

In the present study, linear trends between age at menopause, reproductive period, interval of menopause-baseline and dementia were observed from an RCS analysis, also indicating a dose-dependent effects of oestrogen exposure on brain health.

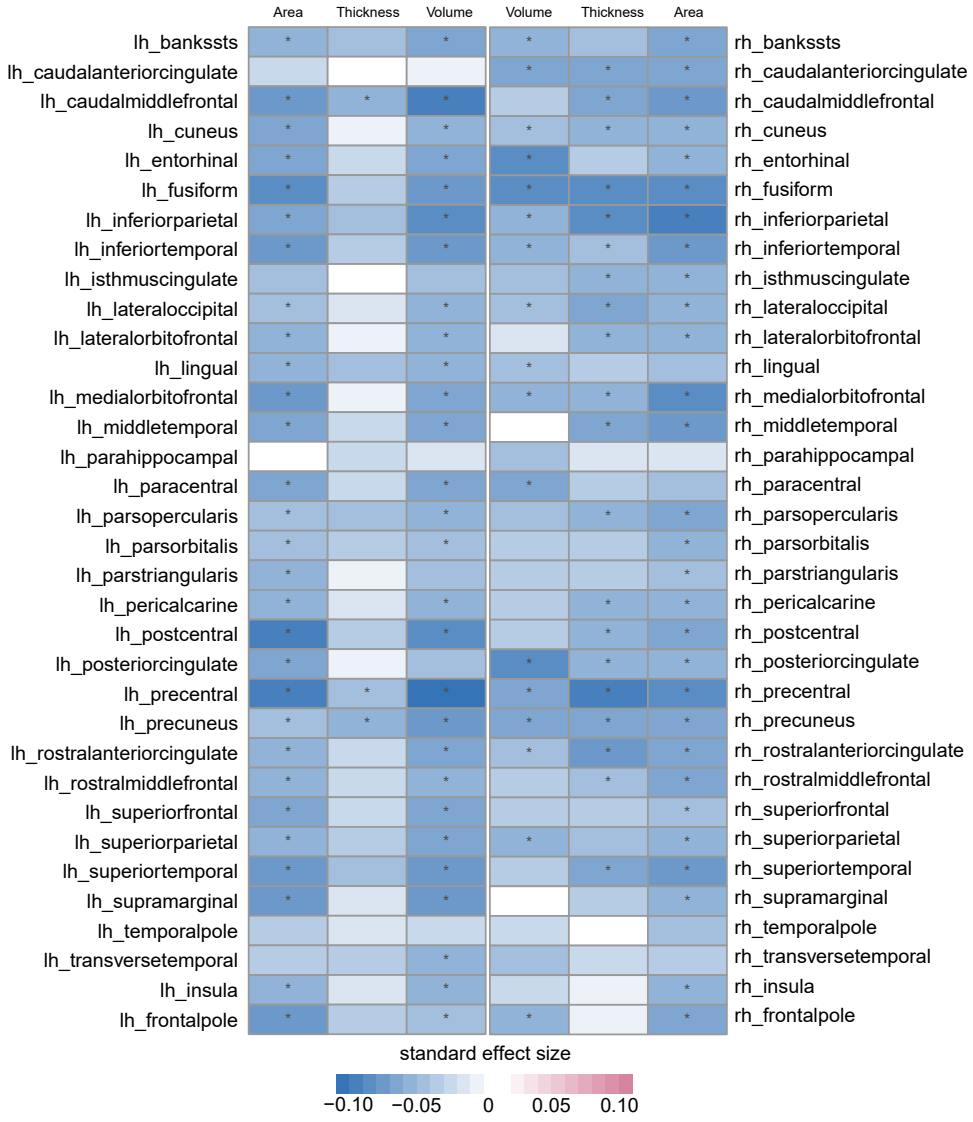

Fig. 4: **Associations between earlier menopause and regional brain structure indices**. Note: Asterisks denote statistically significant effects, with Benjamini–Hochberg (BH) FDR corrected *P* values < 0.05. Colours represent the standardised beta resulting from earlier menopause vs normal menopause at the age ≥50 years. r: right; l: left.

Nonetheless, no significant difference was found between the menopause age at 40–44 years and 45–49 years groups. The most profound hazard for dementia was within the premature individuals, which was consistent with other earlier menopause-related comorbidities.[10]

Extensive sensitivity analyses assessing the robustness of our findings had all yielded similar results, and subgroup analyses found that the risk of dementia associated with earlier menopause did not significantly differ among participants in different risk strata (ie, PRS, age at baseline, ethnicity, etc.) of dementia. Besides, we also performed sensitivity study by excluding women with any prevalent gynaecological cancer at enrolment to eliminate its influence on the association between earlier age at menopause and risk of dementia.

Few studies investigated how earlier menopause caused dementia, and the underlying mechanisms remained unclear. Most studies inferred the rationality of oestrogen deprivation theory from natural perimenopause influence on dementia.[39] Previous study had suggested that the neuropathological changes of brain structure were the basis of the pathogenesis of dementia.[40] Bove and colleagues quantitatively measured the pathological changes in 600 women's brain autopsies, and found that earlier age at menopause was associated

Mediators	Total association		Direct association		Indirect association		Proportion mediated, %	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	Percent mediated (95% CI)	*P* value
Sleep disturbance	1.26 (1.16, 1.34)	<0.001	1.25 (1.15, 1.33)	<0.001	1.01 (1.00, 1.01)	<0.001	3.35 (2.18, 5.40)	<0.001
Mental health disorder			1.25 (1.16, 1.34)	<0.001	1.00 (1.00, 1.01)	<0.001	1.38 (1.05, 3.20)	<0.001
Frailty			1.24 (1.15, 1.32)	<0.001	1.01 (1.01, 1.01)	<0.001	5.23 (3.12, 7.83)	<0.001
Chronic pain			1.25 (1.16, 1.34)	<0.001	1.01 (1.01, 1.01)	<0.001	3.64 (2.88, 5.62)	<0.001
MetS			1.25 (1.15, 1.33)	<0.001	1.01 (1.00, 1.01)	<0.001	3.01 (2.29, 4.40)	<0.001
All mediators			1.22 (1.14, 1.27)	<0.001	1.03 (1.02, 1.04)	<0.001	13.21 (11.11, 18.20)	<0.001

All the effects were presented as HR (95% CI). The effects were estimated as a combination of the regression coefficients obtained from the mediator model and the outcome model. Regression equations for the two models were provided in the Supplementary Methods. More detailed statistical results were provided in Table S36. The total effect was decomposed into direct effect (DE, not through mediator/s) and indirect effect (IDE, through mediator/s). The proportion of the association by the mediator (IDE/[DE + IDE]) was estimated to quantify the magnitude of mediation. SED: Socioeconomic deprivation; HR: Hazard ratio; CI: Confidence interval; DE: Direct effect; IDE: Indirect effect. Sample size: menopause at the age ≥50 years, n = 96,916, menopause at the age <50 years, n = 57,633.

***Table 4*: Mediation analysis of the association between earlier menopause and risk of incident dementia.**

with increased AD neuropathology, in particular neurotic plaques.[41] Here, we extended those prior findings by examining the relation of earlier menopause to the quantitative brain morphological structure measured by MR. Specifically, earlier menopause was negatively associated with global and regional grey matter indices, and positively associated with WMH. These brain structure indices changes might underlie cognitive decline related to earlier menopause. In our study, individuals with earlier menopause had greater global and cortical GMV loss (especially in the frontal, parietal, and temporal lobes), as well as subcortical GMV loss (especially in the hippocampus). These regional changes were sensitive to significant cognitive effects.[42] Besides, WMH was suggested to be a key marker of cerebrovascular burden in the ageing brain and a predictive marker of cognitive decline progression.[43] The time of the brain imaging was a median of 8.88 years (2.11–13.82) after the baseline assessment, rendering the MR data not representative of the brain structural status at baseline. However, sensitivity adjusting for the baseline-image time interval did not alter our result.

Cardiometabolic complications might dramatically arise at the menopausal transition,[44] imposing the effect of ageing onto the risk of a series of comorbidities. Epidemiologic evidence indicated that cardiometabolic risk factors might be associated with an increased breast cancer risk, particularly among postmenopausal women.[45] Postmenopausal individuals with more cardiometabolic factors generally had poorer brain health outcomes.[46] While the results of our study indicated that earlier menopause was associated increased risk of dementia and deteriorating brain health, we found no significant interactions between earlier menopause and cardiometabolic factors, implying that earlier menopause seemed to be an additive risk factor. The inconsistent results of our findings might be inferred to the different definitions of cardiometabolic factors, the different interest outcomes of dementia, and the different biological significance of menopause status to age at menopause. Future longitudinal studies enabling more in-depth investigation on metabolism–menopause interaction are warranted.

A better understanding of the mechanism of earlier age at menopause in dementia would inform targeted evidence-based interventions achieving more favourable outcomes. Therefore, we aimed to examine this association and identify potential mediators. We chose potential mediators including sleep disturbance, mental health disorder, frailty, chronic pain, and MetS, which were supposed to be subsequently followed by earlier menopause[10,26,27] and associated with the risk of dementia.[47–51] Links between many of these menopause-related symptomatology and cardiovascular disease risk have been found.[10] Our results showed that the mediating proportion ranged from 1.38% to 5.23% for each single mediator and reached 13.21% for all mediators combined, indicating a latent mechanism between earlier menopause and dementia. Nonetheless, the modest mediation proportion, though significant, indicated the multi-factorial nature of menopause and that substantial reductions of incident dementia could not be achieved through promoting a single mediator alone. In the present mediation study, the exposure to earlier menopause was prior to the baseline assessment. Though the mediators were investigated and existed at enrolment, we could not ensure their sequential order with earlier menopause, which might lead to a potential reverse-causality. In fact, the mediators we focused were postmenopausal related comorbidities and were known for their association with dementia. This consideration was based on biological plausibility and previous literature.[10,26,27] Future prospective cohort studies with a longitudinal design should include data with the starting dates of the mediators to provide more accurate results. In addition, some mediators and confounders used in analysis might be collinear and likely overlapping. Putting highly correlative variables into the regression

model may bias the result towards the null or lead to an underestimation of effect size, which was indeed a limitation of our study. However, mediation sensitivity analysis for frailty and MetS without adjustment for latent overlapping factors did not change the significance of our results.

In our exploratory analyses, there was no significant difference in the risk of dementia by type of menopause, suggesting that the association between earlier menopause and dementia was robust, regardless of whether earlier menopause was spontaneous or surgically induced. Our study suggested the necessity to consider these findings to make risk assessment prior to gynaecological surgery. It is uncertain whether hysterectomy had an impact on the oestrogen depletion.[10,52,53] We have further conducted a sensitivity analysis by excluding participants with a prior hysterectomy but no history of a bilateral oophorectomy, which did not alter our primary results. Besides, our study suggested that HRT or its initiation time was not associated with a decreased risk of all-cause dementia and any secondary outcomes. The result was consistent with the North American Menopause Society guideline that HRT should not be used at any age for preventing or treating dementia.[54]

Our study has several major strengths. First, the large sample size and the wealth of information on lifestyle, and other covariates of UK Biobank participants, enabled comprehensive sensitivity analyses and subgroup analyses in this study. Second, we found linear trends between age at menopause and dementia from an RCS analysis. Third, our study was restricted to postmenopausal women. Eligible participants who had already experienced the outcome of dementia, or who had not undergone menopause at the time of enrolment, were excluded. Exclusion of these women may result in "immortal time bias".[55] Acknowledging the risks of this approach, we included participants who were ≥55 years old at baseline to effectively control for age at baseline and avoid immortal time bias.

There were also several limitations in our study. First, the study was a retrospective analysis of data from the UK Biobank, thus confounders that were included in the multivariable Cox model were based on available variables in the database and there might be some unknown or unmeasured (such as chemotherapy) biases confounding the association between earlier menopause and dementia. Second, the low response rate in the UK Biobank cohort and healthy volunteer bias[56] may still contribute to an underestimation of the impact of menopause on dementia, which needs to be further assessed in future studies. Similarly, participants who attended the brain MR assessment were also likely to be heathier and have normal menopause than those who did not have the brain image data (Table S7). However, given that the UK Biobank has a tremendous sample size and a median follow-up time of over 10 years, it still has the capacity to detect and identify risk factors.[56] Third, dementia might be misdiagnosed or underdiagnosed, and participants with dementia usually are more likely to be lost to follow-up, hence some dementia cases might not be captured by EHRs. Fourth, although most large-scale epidemiological studies rely on self-reported questionnaires, some variables in our study, including age at menopause and the confounders/mediators, may lead to recall bias. Especially, we could not ensure whether menopause lasted longer than 12 months, which meet with the WHO menopause definition.[57] Fifth, an accurate measure of gender as a social construct was not available in the UK Biobank. We were therefore unable to discriminate between the potential effects of sex (a biological construct) and gender (a social construct) on the associations we found. Finally, participants recruited by UK Biobank were mostly white British, which may limit the extrapolation of our findings to other ethnicities, such as Asians and Africans.

In conclusion, earlier age at menopause was associated with a higher incidence of all-cause dementia and its subtypes including AD and VD compared with those ≥50 years. The increased incidence of dementia in earlier menopause did not differ between participants in different risk strata for dementia. Earlier menopause was negatively associated with brain global and regional grey matter indices, and positively associated with WMH, underlying the potential pathological basis to cognitive decline. The relationship between earlier menopause and dementia was partially mediated by menopause-related comorbidities including sleep disturbance, mental health disorder, frailty, chronic pain, and MetS. Our findings have public health implications for the primary prevention of dementia, but studies are still warranted to future clarify the underlying mechanisms and to determine the strategy in preventing earlier menopause which would in turn contribute to lowering the risk of incident dementia.

Contributors

H. Liao, J. Cheng, D.P., Z.D., and Y.T. conceptualised and designed the study. H. Liao, J. Cheng, D.P., Z.D., and Y.T. acquired, analysed, and interpretated the data. H. Liao, J. Cheng and Y.T. drafted the manuscript. H. Liao and D.P. accessed and verified the underlying data. H. Liao, J. Cheng, D.P., Z.D., Y. Liu, J.J., J. Cai, B.H., M.L., H. Li, Y. Li, Y.X., and Y.T. critically revised of the manuscript for important intellectual content. Y.T. supervised the study. All authors approved the final version of the paper.

Data sharing statement

All data relevant to the study were acquired from the UK Biobank Resource under application number 70109. We have included all available outputs in the main text or the Supplementary Material. Further enquiries could be sent to the corresponding author.

Declaration of interests

We declare no competing interests.

Acknowledgements

The present study was conducted under application number 70109 of the UK Biobank resource. We are thankful to the staff of UK Biobank for data collection and participants follow-up. This study was supported by

grants from the National Natural Science Foundation of China, China (81925031, 81820108026, 81872549, 82003389, 81801229), the Science and Technology Program of Guangzhou, China (202007030001), the Key Area Research and Development Program of Guangdong Province, China (2018B030340001), the China Postdoctoral Science Foundation, China (2020TQ0374, 2020M683095) and the Guangdong Basic and Applied Basic Research Foundation, China (2021A1515111102).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102033.

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