

https://dspace.org/

Age at menopause and cognitive function and decline among middleaged and older women in the China Health and Retirement Longitudinal Study 20112018

M Guo; Y Wu; A. L Gross; C KarvonenGutierrez; Lindsay Kobayashi

https://hdl.handle.net/10539/46109
WOS

Downloaded from a DSpace repository. https://dspace.org/

Received: 4 November 2024 | Revised: 27 December 2024 | Accepted: 12 January 2025

DOI: 10.1002/alz.14580

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Age at menopause and cognitive function and decline among middle-aged and older women in the China Health and Retirement Longitudinal Study, 2011–2018

Muqi Guo[1,2] | **Yingyan Wu**[3] | **Alden L. Gross**[4] | **Carrie Karvonen-Gutierrez**[5,6] | **Lindsay C. Kobayashi**[5,7,8]

[1]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

[2]Harvard Kenneth C. Griffin Graduate School of Arts and Sciences, Cambridge, Massachusetts, USA

[3]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, USA

[4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[5]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan, USA

[6]Department of Internal Medicine, Division of Metabolism, Endocrinology, and Diabetes, University of Michigan Medical School, Ann Arbor, Michigan, USA

[7]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, Michigan, USA

[8]MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Correspondence
Lindsay C. Kobayashi, Department of Epidemiology, University of Michigan School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109, USA.
Email: lkob@umich.edu

Funding information
Foundation for the National Institutes of Health, Grant/Award Number: R01AG070953; National Institute on Aging, Grant/Award Numbers: R01 AG030153, RC2 AG036619, R03 AG043052; National Institutes of Health, Grant/Award Number: R01 AG070953

Abstract

INTRODUCTION: Chinese women experience higher dementia rates than men, yet sex-specific risk factors are understudied. We examined how menopause age affects cognitive function and decline in aging Chinese women.

METHODS: Data were from 7419 postmenopausal women 45–101 years of age at baseline in the China Health and Retirement Longitudinal Study (CHARLS; 2011–2018). Menopause age was categorized using clinical cutoffs (<40, 40–44, 45–49, 50–55, >55 years). Cognitive function was assessed with neuropsychological tests up to four times over 7 years, and associations were analyzed using multivariable-adjusted linear mixed-effects regression.

RESULTS: Compared to menopause at 50–55 years (3661/7419; 49.3%), premature (<40; 235/7419; 3.2%), early (40–44; 623/7419; 8.4%), and late menopause (>55; 366/7419; 4.9%) were associated with lower baseline cognitive scores. Although the rate of cognitive decline did not differ significantly across menopause age groups, late menopause showed a trend toward faster decline.

DISCUSSION: Cognitive health interventions should consider extreme menopausal age as a risk factor.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2025 The Author(s). *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

KEYWORDS
age at menopause, China, cognitive decline, cognitive function, middle-aged and older women

Highlights

- Extreme menopausal ages—premature (<40), early (40–44), and late (>55)—are linked to lower baseline cognition versus menopause ages 50–55, persisting over 7 years.
- Cognitive disadvantage for late menopause (>55) versus 50–55 tends to increase over time.
- Health interventions should consider extreme menopause ages in women's cognitive health.

1 | BACKGROUND

In China, ≈15 million people 60 years of age or older are living with dementia, and 38.8 million are affected by mild cognitive impairment (MCI), with women impacted disproportionately: dementia prevalence is 3.5% in women versus 2.5% in men, and MCI prevalence is 9.0% in women versus 6.5% in men.[1] Since 1990, China's dementia burden (e.g., deaths, incidence, disability-adjusted life years) has grown, with women at higher risk than men.[2] In addition, Chinese women have a lower life expectancy than women in many high-income countries[3] as well as higher rates of young-onset dementia, with an incidence of 1.87 cases per thousand person-years at ages 55–59.[4,5] There is thus a pressing need to examine risk factors for dementia among Chinese women from younger ages than typically studied in Western and high-income settings.

Multiple social and biological factors may contribute to sex/gender differences in dementia burden, including women's longer life expectancy than men's, lower education access than men, the stronger impact of the apolipoprotein E (*APOE*) genotype and brain injuries on women, and sex-specific risk factors such as pregnancy in women and prostate cancer in men.[6] Given the high and growing dementia burden in women, recent studies increasingly explore estrogen and related reproductive factors in women's risk of dementia. Estrogen may protect women against dementia by supporting neurotransmission, cerebral blood flow, and growth protein regulation.[7] However, menopause leads to a rapid estrogen decline, potentially disrupting brain function and contributing to cognitive decline.[8,9]

Many studies across various global populations have found that a younger age at menopause is associated with a higher risk of dementia,[10–16] as well as poorer cognitive function and accelerated cognitive decline.[17–21] However, a Swedish study found that increased age at menopause was associated with a higher dementia incidence after age 75.[22] Other studies have also reported no association between the timing of menopause and risks of dementia, Alzheimer's disease,[17,23] vascular dementia,[14] or overall cognitive function.[24] Inconsistency in this literature may be due to several factors. Age at menopause has been treated inconsistently, including as a continuous variable[18,23] or with cut points such as the mean age at menopause within the study population.[12] Premature menopause has been categorized as occurring before age 40[20] or early menopause before age 45,[19] or using various age thresholds.[10,11] Furthermore, the limited existing studies in low- and middle-income countries mainly use cross-sectional data,[19,21] which cannot evaluate the relationship between menopause and longitudinal changes in cognition over time. Evidence on this topic is particularly limited for China,[23,25,26] where the age distribution of menopause differs from that in high-income countries,[27,28] and awareness and use of hormone therapy (HT) are low.[29,30] These differences may suggest that the cognitive health effects of menopause in China may differ from those observed in studies from high-income settings.

In this study, we examined in Chinese older women, the relationship between age at menopause and cognitive function and rate of decline from 2011 to 2018 in a nationally representative cohort study of aging. We hypothesized that extreme ages at menopause (<45 years or >55 years) are associated with worse cognitive function and a steeper rate of cognitive decline over time.

2 | METHODS

2.1 | Study sample

We use data from in-person interviews in China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal cohort study of community-living individuals 45 years of age or older and their spouses in China.[31] The baseline data, collected in 2011, included 17,708 participants from 10,257 households across 450 communities in 150 counties, living in 28 provinces across China. CHARLS has since conducted follow-up interviews every 2 to 3 years among the original participants and recruited a refreshment sample of individuals who were between 39 and 45 years of age in 2011.[31] For this study, we used the harmonized longitudinal CHARLS 2011–2018 data Version D released in June 2021 by the Gateway to Global Aging Data.

CHARLS participants who were eligible for the present analyses included 9833 postmenopausal women, 45 years of age or older, with at least one wave of cognitive assessment data between 2011 and

RESEARCH IN CONTEXT

1. **Systematic review**: The authors conducted a literature search on age at menopause and cognition using databases such as Google Scholar and PubMed. Current findings are mixed, with studies showing either a negative association between younger menopause age and cognitive outcomes or no association. Most research comes from high-income countries, with limited longitudinal studies in China assessing cognitive changes over time in relation to age at menopause.
2. **Interpretation**: The link between age at menopause and cognitive function appears non-linear. Among Chinese women, extreme menopause ages—premature (<40), early (40–44), and late (>55)—are associated with poorer cognitive outcomes in later life.
3. **Future directions**: Further research should explore mechanisms connecting menopause age and cognitive health in older ages, aiding in prevention and intervention strategies for cognitive decline.

2018. We excluded 135 women with a history of ovarian, cervical, or endometrial cancer to avoid confounding the natural timing of menopause; 409 women with missing data on age at menopause; and 796 women with missing cognitive function measures. Of the remaining 8493 women, 1074 were further excluded due to missing covariate data. The final analytic sample included 7419 women, who contributed a total of 18,724 observations from 2011 to 2018 (Figure 1).

2.2 | Measures

2.2.1 | Outcome: Cognitive function

Cognitive function was assessed as a composite score based on performance in several neuropsychological tasks, adapted from those administered in the University of Michigan US Health and Retirement Study (HRS): serial 7's, date naming, picture drawing, and immediate and delayed word recall.[32] In the serial 7's test, participants serially subtract 7 from 100 five times. The final score is the total number of correct subtractions (range: 0–5). Date naming is scored as the sum of correct responses when asked to name the current day of the month, month, year, and day of the week (range: 0–4). The picture drawing task asks participants to copy a picture of two overlapping pentagons and is scored as correct or incorrect (range: 0–1). For immediate and delayed word recall, the interviewer reads a list of 10 brief nouns aloud, asking the participant to recall the words immediately and again after a few minutes. The recall scores reflect the number of words correctly remembered (range: 0–10 each for immediate recall and delayed recall). The composite cognitive function score is the sum of the final scores from each of the neuropsychological tasks listed.

All cognitive tests, except for word recall, were consistent in form and administration across the four waves of data collection. In 2018, CHARLS harmonized their cognitive measures with other aging surveys by changing the word list and the number of trials for the immediate and delayed word recall task.[33] To account for these changes, we applied a weighted equipercentile equating method to adjust the word recall scores in 2018 based on the percentile ranks observed in 2015.[34] The composite cognitive score was calculated at each wave, with participants having up to four waves of observations. We standardized the baseline distribution to have a mean of 0 and standard deviation (SD) of 1, with composite scores at all subsequent waves standardized to the baseline distribution for comparability over time. The distribution of the standardized composite cognitive scores by wave are shown in Figure S1.

2.2.2 | Exposure: Age at menopause

Self-reported age at menopause was collected through responses to the interview question asked at each wave: "When did you begin menopause?" The distribution of age at menopause is shown in Figure S2. We categorized age at menopause into five groups: <40, 40–44, 45–49, 50–55, and >55. Menopause occurring before age 40 is classified as premature menopause, whereas menopause between the ages of 40 and 44 is considered early menopause.[28] We used ages 50–55 as the reference group, as this age range encompassed the highest proportion of women in our study who had experienced menopause. We subsequently considered >55 years as late menopause.[35]

2.2.3 | Covariates

We included potential confounders measured at baseline that are known to be associated with both age at menopause and cognitive function, including demographic characteristics: age (continuous), quadratic function of age (continuous), and ethnicity (Han Chinese vs others); socioeconomic characteristics: rural residence (yes or no, defined by the National Bureau of Statistics of China, recorded based on CHARLS sampling strategy at the community level), educational attainment (lower secondary or less vs upper secondary or more), educational attainment of the most highly educated parent of the participant (lower secondary or less vs upper secondary or more), and marital status (married/partnered, widowed vs separated/divorced/single); and reproductive characteristics: age at menarche (continuous), total number of living biological children (continuous), and experiencing the death of a biological child (yes or no).

2.2.4 | Statistical analysis

Baseline characteristics of the sample were described as mean (SD) for continuous variables and frequencies for categorical variables, both overall and stratified by age at menopause. Given the longitudinal nature of the data with repeated outcome measures, we

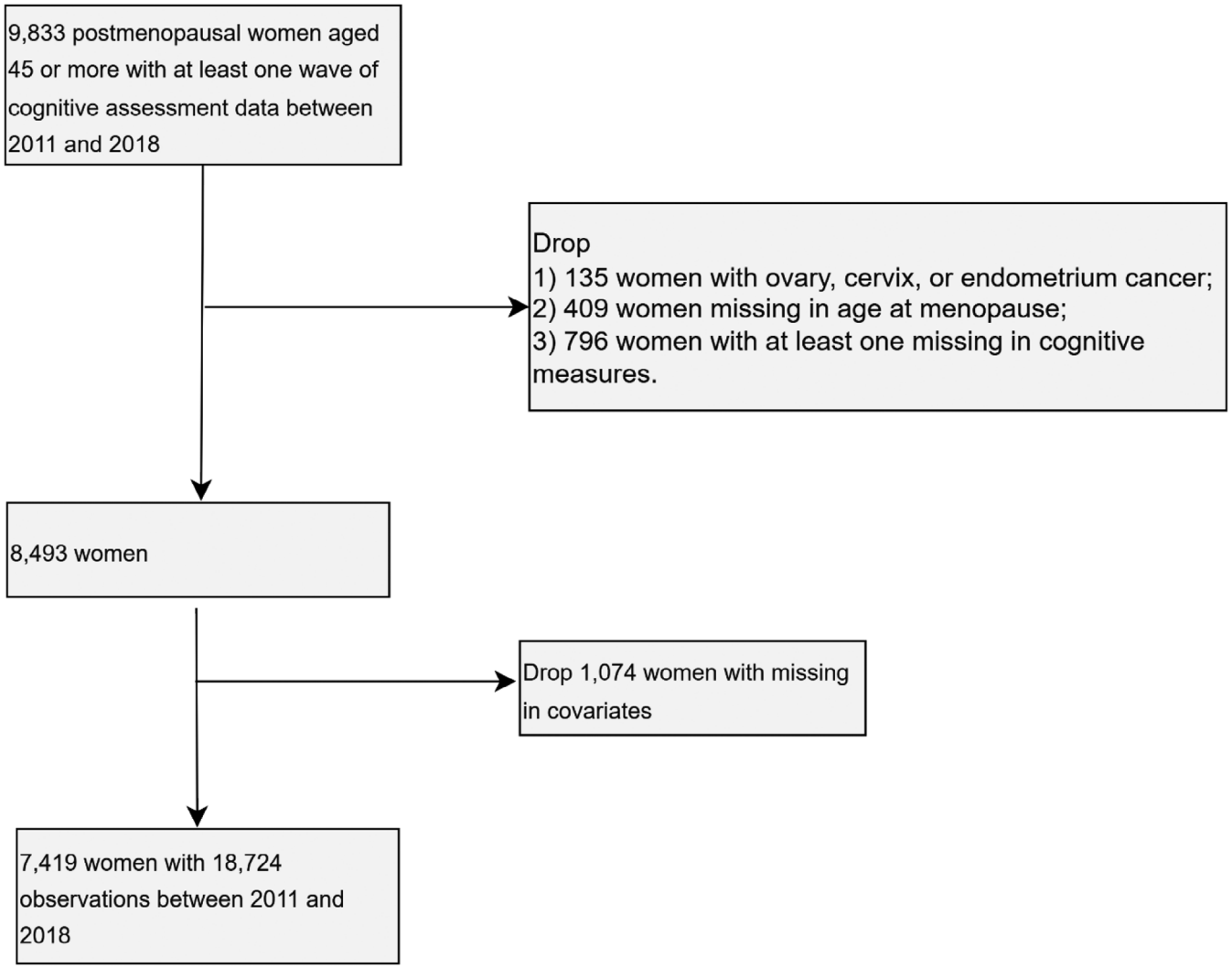

FIGURE 1 Study flow chart.

applied a multivariable-adjusted mixed-effects linear regression model with random intercepts to estimate the associations between age at menopause and cognitive function at baseline and rate of cognitive change (slope) over time. Follow-up time (in years) was used as the time scale. Random slope effects were excluded due to their minimal variance. We developed four models by adding different categories of covariates step by step, to assess the confounding impacts from each of demographic characteristics, socioeconomic characteristics, age at menarche, and biological children. To account for confounders influencing the rate of cognitive change over time, we tested the statistical significance of interaction terms between years since baseline and each covariate, retaining those with $p < 0.05$.

To better understand whether the associations under study differed across women of varied sociodemographic groups, we conducted a set of sensitivity analyses by performing the regression Model 4 stratified by the median age at menarche (16 years), rural residence, education level, marital status, and the median number of years of postmenopausal experience prior to the baseline interview (8 years). In addition, we performed further sensitivity analyses designed to further assess the robustness of our results, including (1) excluding women who experienced menopause before age 30 ($n = 50$; <1%), (2) excluding women <55 years of age at baseline ($n = 3008$), and (3) using individual cognitive tests as the outcome variable (e.g., serial 7's to represent executive function, and the composite immediate and delayed recall score to represent episodic memory). The distribution of age at menopause across sub-analysis samples is shown in Table S1.

3 | RESULTS

Table 1 presents the baseline characteristics of postmenopausal women in the study. The mean age of the sample at baseline was 58.5 years (SD: 9.0 years, range: 45–101). Overall, 235 women (3.2%) experienced premature menopause (before age 40), 623 (8.4%) experienced early menopause (between 40 and 44 years of age), and 366 (4.9%) experienced late menopause (after age 55) (Table 1). Over 90% of the women were Han Chinese, and the majority had lower secondary education or less. More than 70% of the women resided in rural areas, with

TABLE 1 Baseline characteristics, overall and by age at menopause, China Health and Retirement Longitudinal Study (CHARLS), China, 2011–2018.

Baseline characteristics	<40, premature (*N* = 235, 3.2%)	40–44, early (*N* = 623, 8.4%)	45–49 (*N* = 2534, 34.2%)	50–55 (*N* = 3661, 49.3%)	>55, late (*N* = 366, 4.9%)	Total (*N* = 7419)
Age in years, mean (SD)	60.3 (9.4)	61.0 (9.6)	57.4 (9.1)	58.2 (8.7)	62.5 (7.1)	58.5 (9.0)
Ethnicity						
Other Chinese	7 (3.0%)	28 (4.5%)	128 (5.1%)	210 (5.7%)	35 (9.6%)	408 (5.5%)
Han Chinese	228 (97.0%)	595 (95.5%)	2406 (94.9%)	3451 (94.3%)	331 (90.4%)	7011 (94.5%)
Rural residence						
Urban	45 (19.1%)	108 (17.3%)	485 (19.1%)	865 (23.6%)	77 (21.0%)	1580 (21.3%)
Rural	190 (80.9%)	515 (82.7%)	2049 (80.9%)	2796 (76.4%)	289 (79.0%)	5839 (78.7%)
Education level of parents						
Lower secondary or less	225 (95.7%)	602 (96.6%)	2423 (95.6%)	3506 (95.8%)	351 (95.9%)	7107 (95.8%)
Upper secondary or more	10 (4.3%)	21 (3.4%)	111 (4.4%)	155 (4.2%)	15 (4.1%)	312 (4.2%)
Education level						
Lower secondary or less	226 (96.2%)	587 (94.2%)	2329 (91.9%)	3303 (90.2%)	343 (93.7%)	6788 (91.5%)
Upper secondary or more	9 (3.8%)	36 (5.8%)	205 (8.1%)	358 (9.8%)	23 (6.3%)	631 (8.5%)
Marital status						
Married/partnered	190 (80.9%)	497 (79.8%)	2171 (85.7%)	3169 (86.6%)	288 (78.7%)	6315 (85.1%)
Widowed	41 (17.4%)	120 (19.3%)	335 (13.2%)	450 (12.3%)	74 (20.2%)	1020 (13.7%)
Separated/divorced/single	4 (1.7%)	6 (1.0%)	28 (1.1%)	42 (1.1%)	4 (1.1%)	84 (1.1%)
Age at menarche, mean (SD)	16.5 (2.8)	16.4 (2.7)	16.1 (2.2)	16.2 (2.4)	16.7 (2.2)	16.2 (2.4)
Number of biological children alive, mean (SD)	3.3 (2.1)	3.5 (2.0)	3.0 (1.8)	3.1 (1.8)	3.5 (1.9)	3.1 (1.8)
Ever experienced the death of a biological child						
No	225 (95.7%)	575 (92.3%)	2417 (95.4%)	3470 (94.8%)	346 (94.5%)	7033 (94.8%)
Yes	10 (4.3%)	48 (7.7%)	117 (4.6%)	191 (5.2%)	20 (5.5%)	386 (5.2%)
Years of follow-up, mean (SD)	4.0 (2.5)	4.2 (2.5)	4.1 (2.5)	3.7 (2.6)	3.7 (2.6)	3.9 (2.6)

Abbreviation: SD, standard deviation.

the proportion of rural residents increasing among those who experienced menopause earlier. Approximately 4.5% of women across all menopause age groups reported their parents having an upper secondary education or higher. Widowhood was more common among women with premature or early menopause or late menopause, compared to the overall average of 13.7%. The mean age at menarche was 16.2 years, with higher mean age at menarche among women with premature menopause (16.5 years) and late menarche (16.7 years). Women with late menopause had slightly more biological children on average, and women with early menopause were more likely to have experienced the death of a biological child (Table 1). On average, women participants were followed for 3.9 years (SD: 2.6 years).

Table 2 presents the results from the multivariable-adjusted linear mixed-effects models estimating the associations between age at menopause and cognitive function and rate of change over time. Premature, early, and late menopause were consistently linked to poorer baseline cognitive performance across all models. Although cognitive function declined over time, the rate of decline did not differ significantly across menopause age categories. Compared to controlling demographic characteristics alone (Model 1), including socioeconomic status (Model 2) weakened the association between menopause age and cognitive performance. Further adjustment for age at menarche (Model 3) slightly reduced these associations. However, adding characteristics related to biological children slightly strengthened the associations, except for attenuating the link between early menopause and baseline cognitive scores (Table 2).

In the fully adjusted model (Model 4), women who experienced premature menopause (before age 40) had a cognitive score at baseline that was, on average, 0.201 SD units lower (95% confidence interval [CI]: −0.313 to −0.090) than those who had menopause at ages 50–55 (Table 2). Women with early menopause (ages 40–44) had a baseline cognitive score that was 0.083 SD units lower (95% CI: −0.155 to −0.011), representing 10.9% lower scores than those who had menopause at ages 50–55 (Table 2). Late age at menopause (>55 years) was also associated with lower cognitive function at baseline (−0.130 SD units; 95% CI: −0.222 to 0.038; Table 2), representing 17%

TABLE 2 Multivariable-adjusted mixed-effects linear regression results for the association between age at menopause and standardized composite cognitive function score, China Health and Retirement Longitudinal Study (CHARLS), China, 2011–2018.

	Model 1: demographic controls only	Model 2: Model 1 + socioeconomic characteristics	Model 3: Model 2 + age at menarche	Model 4: Model 3 + biological children (births and death)
Cognitive function score at baseline: menopause at 50–55 years (reference group; SD units)[a]	0.459 (−0.297, 1.214)	0.590 (−0.104, 1.283)	0.655 (−0.039, 1.349)	0.764* (0.074, 1.454)
Difference for with menopause at <40 years (premature)	−0.264*** (−0.387, −0.141)	−0.199** (−0.312, −0.087)	−0.196** (−0.308, −0.084)	−0.201*** (−0.313, −0.090)
Difference for those with menopause at 40–44 years (early)	−0.152*** (−0.231, −0.072)	−0.088* (−0.160, −0.015)	−0.087* (−0.159, −0.015)	−0.083* (−0.155, −0.011)
Difference for those with menopause at 45–49 years	−0.035 (−0.083, 0.012)	0.007 (−0.037, 0.050)	0.006 (−0.037, 0.049)	0.006 (−0.037, 0.049)
Difference for those with menopause at >55 years (late)	−0.162** (−0.263, −0.060)	−0.133** (−0.226, −0.040)	−0.128** (−0.220, −0.035)	−0.130** (−0.222, −0.038)
Rate of cognitive change over time: menopause at 50–55 years (reference group; SD units/year)	−0.100*** (−0.117, −0.083)	−0.086*** (−0.105, −0.068)	−0.038* (−0.069, −0.007)	−0.037* (−0.068, −0.006)
Difference for those with menopause at <40 years (premature)	−0.002 (−0.024, 0.019)	0.001 (−0.021, 0.022)	0.001 (−0.020, 0.022)	0.002 (−0.020, 0.023)
Difference for those with menopause at 40–44 years (early)	0.005 (−0.009, 0.018)	0.006 (−0.008, 0.019)	0.007 (−0.007, 0.020)	0.007 (−0.007, 0.020)
Difference for those with menopause at 45–49 years	−0.005 (−0.013, 0.004)	−0.003 (−0.011, 0.006)	−0.003 (−0.012, 0.005)	−0.003 (−0.011, 0.005)
Difference for those with menopause at 55 years (late)	−0.017 (−0.035, 0.001)	−0.014 (−0.033, 0.004)	−0.013 (−0.031, 0.005)	−0.013 (−0.031, 0.006)

[a]The estimates for menopause age between 50 and 55 years represent a woman with a reference value for all covariates. 95% Confidence intervals are in parentheses. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. A random effect of the intercept was used for each model. Covariates include characteristics at baseline. Model 1 includes age, quadratic function of age, Han Chinese, and its interaction with time. Model 2 includes all covariates in Model 1 plus rural residence and its interaction with time, respondent education and its interaction with time, parental education, and marital status. Model 3 includes all covariates in Model 2 plus age at menarche and its interaction with time. Model 4 includes all covariates in Model 3 plus total number of biological children, and ever experiencing the death of a biological child.

lower scores than those who had menopause at ages 50–55 (Table 2). Cognitive scores at baseline were similar for women who experienced menopause at 50–55 years and 45–49 years. With respect to cognitive decline, each additional year since baseline was associated with a decline in cognitive score by 0.037 SD units (95% CI: −0.068 to −0.006) for those who had menopause at ages 50–55 (Table 2). The rate of cognitive decline was not significantly different by age at menopause. However, women with menopause after age 55 had a trend of faster decline compared to women who experienced menopause at ages 50–55 (−0.013 SD units, 95% CI: −0.031 to 0.006). Figure 2 visualizes the rates of cognitive change over time by age at menopause estimated from Model 4. The rate of cognitive decline among women who experienced late menopause (>55) surpassed that of women with premature menopause (<40 years) after 4 years of follow-up, ultimately resulting in the lowest predicted cognitive scores among all menopause age groups (Figure 2).

The association between age at menopause and cognitive function and decline appeared stronger among women who experienced menarche after age 16, who lived in rural areas, who were married, who had lower secondary education or less, or more than 8 years of being postmenopausal prior to baseline interview (Tables S2–S6). However, the reduced sample sizes of subgroups used in these analyses limit the statistical power of these analyses, and the results should be interpreted with caution (Table S1). Results of the sensitivity analyses excluding women with menopause before age 30, excluding women younger than age 55, and restricting the outcome to individual cognitive test items were similar to the results of the main analysis (Tables S7–S10).

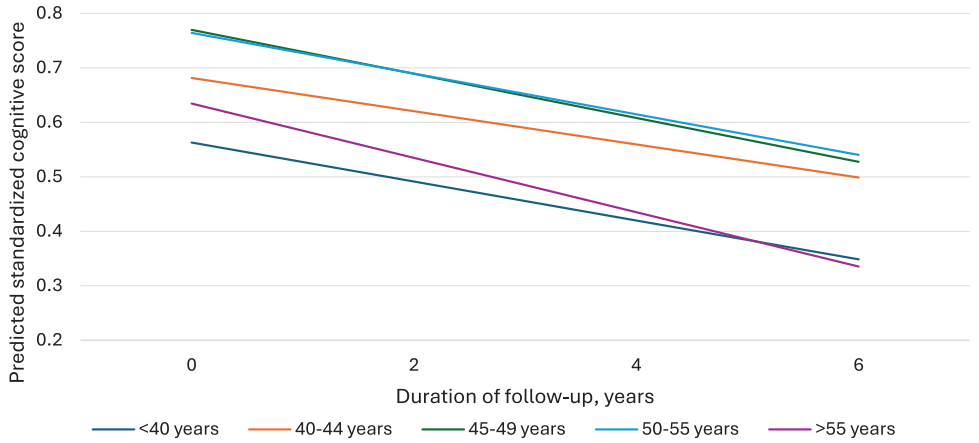

FIGURE 2 Predicted standardized cognitive score by age at menopause during follow-up years. Values are estimated based on the multivariable-adjusted mixed-effects linear regression presented in Table 2. A random effect of the intercept was used. Covariates include characteristics at baseline: age, quadratic function of age, Han Chinese, and its interaction with time, rural residence and its interaction with time, respondent education, and its interaction with time, parental education, marital status, age at menarche and its interaction with time, the total number of biological children, and ever experiencing the death of a biological child.

4 | DISCUSSION

Using nationally representative longitudinal data from China, we found a non-linear relationship between menopause age and cognitive function among middle-aged and older women. Premature, early, and late menopause were all linked to lower cognitive function, indicating that extreme ages of menopause may be a salient risk factor for later-life cognitive health in this study setting. In addition, premature and early menopause affected just over 1 in 10 Chinese women in this study, slightly higher than that observed in high-income countries, highlighting the disproportionate cognitive risks associated with earlier menopause faced by Chinese women.[28] Late age at menopause was additionally marginally associated with a faster rate of cognitive decline over time, with a magnitude that was equivalent to 0.35 years of chronological aging. Future studies should confirm and replicate our findings in this and other populations with longer follow-up periods to better understand the association of extreme menopause ages with later-life cognitive outcomes.

Research on the relationship between age at menopause and cognitive aging in China is limited. A longitudinal cohort study based on ≈1000 older women in China found no linear association between menopause age and dementia incidence within 5 years.[23] Similarly, a cross-sectional study in Hebei province (1760 participants) observed no association between age at menopause and cognitive impairment.[36] In contrast, a more recent cross-sectional study of 4275 women ≥65 years of age in northern China found later menopause associated with better cognition and reduced risk of cognitive impairment.[25] Our study adds to this research by identifying a non-linear relationship between menopause age and cognitive outcomes in a younger, nationally representative sample. Given that dementia, particularly Alzheimer's disease, includes a prodromal phase that may extend up to 10 years, there is a need for longer follow-up to fully capture the long-term relationship between menopause age and cognitive health.

Our findings align with studies conducted in regions near China, such as Singapore,[26] India,[19] Indonesia,[21] and Korea.[11] These studies consistently show that earlier menopause is linked to higher risks of cognitive impairment or dementia. Our findings are also consistent with most studies from high-income Western countries, which find that earlier menopause is associated with a higher risk of dementia.[10,12–16] In the 1946 British Birth Cohort, increasing age at natural menopause was positively linearly associated with verbal memory performance among women 43 to 69 years of age.[18] In our study, the associations between age at menopause with cognitive function and decline was more nuanced, despite the similar age range of the study sample. The 1946 British Birth Cohort study[18] accounted for childhood cognitive ability, a previously identified risk factor for earlier menopause,[37–39] which is not available in our data. In addition, a French study found that premature menopause was linked to poorer cognitive performance and faster cognitive decline later in life.[20] In contrast, our study did not find significant differences in cognitive decline across women of different age at menopause categories. However, women with late menopause had much faster cognitive decline, although this association was not statistically significant.

Several mechanisms have been proposed to explain why younger age at menopause is associated with worse later-life cognitive outcomes. Gonadal steroids, such as estradiol, play a critical role in brain function by promoting the growth of nerve cells and facilitating the formation of new neural connections, which enhance memory and thinking; and estradiol may also protect against the loss of key neurotransmitters, helping to preserve cognitive performance.[8,17] Earlier menopause shortens the lifetime duration of exposure to estrogen, which could impair cognitive functions like verbal memory and executive function, as they are particularly sensitive to changes in estrogen levels.[8,9] Indeed, an urban Indian cohort study found that menopause before age 45 was associated with reduced total gray matter volume, particularly in the left middle and superior frontal regions.[10,19]

In addition, younger age at menopause has been associated with increased white matter hyperintensity, a marker linked to cognitive decline and dementia risk in older adults.[10] These mechanisms provide a possible explanation for our findings, particularly given that verbal memory and executive function were key components of the cognitive measures used in our study.

We also found that late menopause was associated with worse cognitive performance at baseline and had a trend toward a faster rate of cognitive decline over time. This is a new finding compared to existing studies. One study based on women in the UK found that age at natural menopause after 55, compared to ages 46–50, was associated with a lower risk of dementia, whereas surgical menopause after age 55 was linked to a higher risk of dementia.[14] Our study may include women who experience surgical menopause after age 55. However, due to data limitations, we were unable to differentiate between surgical and natural menopause. To mitigate this issue, we excluded women with a history of ovarian, cervical, or endometrial cancer as a precautionary measure to minimize the likelihood of including individuals who underwent surgical menopause. Another study based on women in Singapore did not find a significant association of menopause at age 54 or older with cognition, although there was a trend of increased risk of cognitive impairment among women with menopause ≥54.[26] The current body of research is still investigating the potential explanations for the role of late menopause in later-life cognition. One plausible theory is the "healthy cell bias" hypothesis, which suggests that the beneficial effects of estrogen depend on the health of neurons and the timing of exposure; estrogen exposure is thought to be beneficial only when neurons are healthy, but it may become detrimental when neurons are compromised.[22,40] At older ages, neurons are more likely to be compromised, so maintaining premenopausal estrogen levels as one ages beyond the typical age at menopause could negatively affect brain health. In addition, women experiencing menopause at older ages may be more vulnerable due to immune system changes that occur during menopause, potentially contributing to accelerated cognitive decline.[8] Further research is needed to explore these mechanisms in more detail.

This study has limitations. We attempted to distinguish between natural and surgical menopause by excluding women with a history of ovarian, cervical, or endometrial cancer, as these women are more likely to have experienced surgical menopause. However, this method may still result in misclassification, meaning our findings reflect age at menopause in general rather than exclusively age at natural menopause. We relied on self-reported age at menopause, which may introduce recall bias. However, the existing literature suggests that self-reported age at menopause is generally reliable,[41] and misclassification bias may be more likely among women with natural menopause, older ages,[42,43] or less education.[43] We adjusted for those factors in our analyses. Furthermore, the CHARLS questionnaire does not provide a clear definition of menopause. Typically, menopause is defined as the absence of menstrual periods for at least 12 consecutive months, excluding non-natural causes such as surgical removal of the uterus, pregnancy, or breastfeeding.[28] Without this definition, participants may misreport their age at menopause, particularly younger women whose last menstrual period may have occurred less than 12 months ago. To help address this, we adjusted for baseline age and its quadratic form in our regression analyses, although some measurement errors may still be present. Due to data limitations, we could not adjust our analysis for certain variables that are known to influence both the timing of menopause and cognitive function in later life, such as *APOE* genotype[20,24] and childhood cognitive ability.[18] We also did not have data on HT use, which can alter estrogen levels and potentially affect cognitive aging trajectories.[20] However, the influence of HT is likely limited in our sample given its low awareness and use among Chinese women.[30]

Strengths of this study include its large, nationally representative sample of middle-aged and older women in China. The sample includes Chinese women living in rural areas and with low early-life access to education, which expands representation in the evidence base on menopause and cognitive aging to these rapidly aging yet underrepresented global population groups. We had longitudinal data over a 7-year follow-up period to help establish the temporality and validity of the associations under study, with repeated measures of an in-depth neuropsychological assessment harmonized with that used in the HRS and several of its international partner studies around the world.

In conclusion, this study identified a non-linear relationship between women's age at menopause and cognitive function and decline over time among middle-aged and older Chinese women. Extreme ages at menopause were associated with lower cognitive function, and late age at menopause may be associated with a faster rate of cognitive decline over time. Future health interventions should consider extreme ages at menopause as an important risk factor for women's later-life cognitive health in this population. Future studies should replicate these findings in other global populations and settings and with longer follow-up periods to better understand the complex relationship between women's menopause and cognitive aging.

ACKNOWLEDGMENTS

This analysis uses data or information from the Harmonized China Health and Retirement Longitudinal Study (CHARLS) data set and Codebook, Version D, as of June 2021, developed by the Gateway to Global Aging Data. The development of the Harmonized CHARLS was funded by the National Institute on Aging (R01 AG030153, RC2 AG036619, R03 AG043052). For more information, please refer to https://g2aging.org/. This work was made possible by funding from the National Institute on Aging at the U.S. National Institutes of Health, under grant number R01 AG070953 (Kobayashi, Gross). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Written or verbal informed consent was obtained from all study participants.

ORCID

Lindsay C. Kobayashi https://orcid.org/0000-0003-2725-3107

REFERENCES

1. Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. *Lancet Public Health*. 2020;5:e661-e671. doi:10.1016/S2468-2667(20)30185-7
2. Li R, Qi J, Yang Y, et al. Disease burden and attributable risk factors of Alzheimer's disease and dementia in China from 1990 to 2019. *J Prev Alzheimers Dis*. 2022;9:306-314. doi:10.14283/jpad.2021.69
3. Cao X, Hou Y, Zhang X, et al. A comparative, correlate analysis and projection of global and regional life expectancy, healthy life expectancy, and their GAP: 1995-2025. *J Glob Health*. 2020;10:020407. doi:10.7189/jogh.10.020407
4. Yuan J, Zhang Z, Wen H, et al. Incidence of dementia and subtypes: a cohort study in four regions in China. *Alzheimer's & Dementia*. 2016;12:262-271. doi:10.1016/j.jalz.2015.02.011
5. Hendriks S, Peetoom K, Bakker C, et al. Global incidence of young-onset dementia: a systematic review and meta-analysis. *Alzheimers Dement*. 2023;19:831-843. doi:10.1002/alz.12695
6. Mielke MM. Sex and gender differences in Alzheimer's disease dementia. *Psychiatr Times*. 2018;35:14-17.
7. Genazzani AR, Pluchino N, Luisi S, Luisi M. Estrogen, cognition and female ageing. *Hum Reprod Update*. 2007;13:175-187. doi:10.1093/humupd/dml042
8. Conde DM, Verdade RC, Valadares ALR, Mella LFB, Pedro AO, Costa-Paiva L. Menopause and cognitive impairment: a narrative review of current knowledge. *World J Psychiatry*. 2021;11:412-428. doi:10.5498/wjp.v11.i8.412
9. Sochocka M, Karska J, Pszczołowska M, et al. Cognitive decline in early and premature menopause. *Int J Mol Sci*. 2023;24:6566. doi:10.3390/ijms24076566
10. Liao H, Cheng J, Pan D, et al. Association of earlier age at menopause with risk of incident dementia, brain structural indices and the potential mediators: a prospective community-based cohort study. *eClinicalMedicine*. 2023;60:102033. doi:10.1016/j.eclinm.2023.102033
11. Yoo JE, Shin DW, Han K, et al. Female reproductive factors and the risk of dementia: a nationwide cohort study. *Eur J Neurol*. 2020;27:1448-1458. doi:10.1111/ene.14315
12. Gilsanz P, Lee C, Corrada MM, Kawas CH, Quesenberry CP, Whitmer RA. Reproductive period and risk of dementia in a diverse cohort of health care members. *Neurology*. 2019;92:e2005-e2014. doi:10.1212/WNL.0000000000007326
13. Fu C, Hao W, Shrestha N, Virani SS, Mishra SR, Zhu D. Association of reproductive factors with dementia: a systematic review and dose-response meta-analyses of observational studies. *EClinicalMedicine*. 2022;43:101236. doi:10.1016/j.eclinm.2021.101236
14. Hao W, Fu C, Dong C, et al. Age at menopause and all-cause and cause-specific dementia: a prospective analysis of the UK Biobank cohort. *Hum Reprod*. 2023;38:1746-1754. doi:10.1093/humrep/dead130
15. Gong J, Harris K, Peters SAE, Woodward M. Reproductive factors and the risk of incident dementia: a cohort study of UK Biobank participants. *PLoS Med*. 2022;19:e1003955. doi:10.1371/journal.pmed.1003955
16. Han S-L, Liu D-C, Tan C-C, Tan L, Xu W. Male- and female-specific reproductive risk factors across the lifespan for dementia or cognitive decline: a systematic review and meta-analysis. *BMC Med*. 2023;21:457. doi:10.1186/s12916-023-03159-0
17. Georgakis MK, Kalogirou EI, Diamantaras A-A, et al. Age at menopause and duration of reproductive period in association with dementia and cognitive function: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2016;73:224-243. doi:10.1016/j.psyneuen.2016.08.003
18. Kuh D, Cooper R, Moore A, Richards M, Hardy R. Age at menopause and lifetime cognition. *Neurology*. 2018;90:e1673-e1681. doi:10.1212/WNL.0000000000005486
19. Mensegere A, Singh S, Stezin A, Sundarakumar JS, Issac TG. Effect of early menopause on cognition and brain morphology in an Urban Indian Cohort. *Alzheimers Dement*. 2024;20:5607-5616. doi:10.1002/alz.14069
20. Ryan J, Scali J, Carrière I, et al. Impact of a premature menopause on cognitive function in later life. *BJOG*. 2014;121:1729-1739. doi:10.1111/1471-0528.12828
21. Sujarwoto S, Tampubolon G. Premature natural menopause and cognitive function among older women in Indonesia. *J Women Aging*. 2020;32:563-577. doi:10.1080/08952841.2019.1607679
22. Najar J, Östling S, Waern M, et al. Reproductive period and dementia: a 44-year longitudinal population study of Swedish women. *Alzheimers Dementia*. 2020;16:1153-1163. doi:10.1002/alz.12118
23. Prince MJ, Acosta D, Guerra M, et al. Reproductive period, endogenous estrogen exposure and dementia incidence among women in Latin America and China; a 10/66 population-based cohort study. *PLoS One*. 2018;13:e0192889. doi:10.1371/journal.pone.0192889
24. Whalley LJ, Fox HC, Starr JM, Deary IJ. Age at natural menopause and cognition. *Maturitas*. 2004;49:148-156. doi:10.1016/j.maturitas.2003.12.014
25. Xi H, Gan J, Liu S, et al. Reproductive factors and cognitive impairment in natural menopausal women: a cross-sectional study. *Front Endocrinol*. 2022;13:893901. doi:10.3389/fendo.2022.893901
26. Song X, Wu J, Zhou Y, et al. Reproductive and hormonal factors and risk of cognitive impairment among Singapore Chinese women. *Am J Obstet Gynecol*. 2020;223:410.e1-410.e23. doi:10.1016/j.ajog.2020.02.032
27. Wang M, Kartsonaki C, Guo Y, et al. Factors related to age at natural menopause in China: results from the China Kadoorie Biobank. *Menopause*. 2021;28:1130. doi:10.1097/GME.0000000000001829
28. Mishra GD, Pandeya N, Dobson AJ, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. *Hum Reprod*. 2017;32:679-686. doi:10.1093/humrep/dew350
29. Chu K, Song Y, Chatooah ND, et al. The use and discontinuation of hormone replacement therapy in women in South China. *Climacteric*. 2018;21:47-52. doi:10.1080/13697137.2017.1397622
30. Zhu Y, Yang X, Wang Y, Zhu X. Assessment of knowledge, understanding and awareness of Chinese women clinical staff towards menopause hormone therapy: a survey study. *J Obstet Gynaecol*. 2023;43:2171779. doi:10.1080/01443615.2023.2171779
31. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China health and retirement longitudinal study (CHARLS). *Int J Epidemiol*. 2014;43:61-68. doi:10.1093/ije/dys203
32. Zhao Y, Strauss J, Chen X, et al. *China Health and Retirement Longitudinal Study Wave 4 User's Guide*. National School of Development, Peking University; 2020.
33. Meng Q, Wang H, Strauss J, et al. Validation of neuropsychological tests for the China health and retirement longitudinal study harmonized cognitive assessment protocol. *Int Psychogeriatr*. 2019;31:1709-1719. doi:10.1017/S1041610219000693
34. Wu Y, Zhang YS, Kobayashi LC, Mayeda ER, Gross AL. How to assess cognitive decline when test administration changes across study waves? Harmonizing cognitive scores across waves in the China health and retirement longitudinal study. *J. Alzheimer's Dis. Rep.*. 2024;8:1661-1669. doi:10.1177/25424823241302759

35. Eckhardt S, Wellons M. Defining menopause: what is early, what is late? In: Santoro NF, Cooper AR, eds. *Primary Ovarian Insufficiency: A Clinical Guide to Early Menopause*. Springer International Publishing; 2016:1-17. doi:10.1007/978-3-319-22491-6_1
36. Song M, Wang Y-M, Wang R, et al. Prevalence and risks of mild cognitive impairment of Chinese community-dwelling women aged above 60 years: a cross-sectional study. *Arch Womens Ment Health*. 2021;24:903-911. doi:10.1007/s00737-021-01137-0
37. Kuh D, Butterworth S, Kok H, et al. Childhood cognitive ability and age at menopause: evidence from two cohort studies. *Menopause*. 2005;12:475. doi:10.1097/01.GME.0000153889.40119.4C
38. Mishra G, Hardy R, Kuh D. Are the effects of risk factors for timing of menopause modified by age? Results from a British birth cohort study. *Menopause*. 2007;14:717. doi:10.1097/gme.0b013e31802f3156
39. Richards M, Kuh D, Hardy R, Wadsworth M. Lifetime cognitive function and timing of the natural menopause. *Neurology*. 1999;53:308-308. doi:10.1212/WNL.53.2.308
40. Brinton RD. Investigative models for determining hormone therapy-induced outcomes in brain: evidence in support of a healthy cell bias of estrogen action. *Ann NY Acad Sci*. 2005;1052:57-74. doi:10.1196/annals.1347.005
41. Lucas R, Azevedo A, Barros H. Self-reported data on reproductive variables were reliable among postmenopausal women. *J Clin Epidemiol*. 2008;61:945-950. doi:10.1016/j.jclinepi.2007.11.001
42. Hahn RA, Eaker E, Rolka H. Reliability of reported age at menopause. *Am J Epidemiol*. 1997;146:771-775. doi:10.1093/oxfordjournals.aje.a009353
43. Schmidt-Pokrzywniak A, Kluttig A. Reliability of self-reported weight, age at menarche and menopause, and reason for absence of menses: a cohort study. *JWHIC*. 2016;5(4). doi:10.4172/2325-9795.1000240

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Guo M, Wu Y, Gross AL, Karvonen-Gutierrez C, Kobayashi LC. Age at menopause and cognitive function and decline among middle-aged and older women in the China Health and Retirement Longitudinal Study, 2011–2018. *Alzheimer's Dement*. 2025;21:e14580. https://doi.org/10.1002/alz.14580