Reproductive Factors and Risk of Dementia in Natural Postmenopausal Women: a Cross-sectional Study

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Abstract

Background: Women comprise more than half of people suffering cognitive impairment. This study aims to evaluate the association or interaction between reproductive factors and the risk of dementia in Chinese women with natural menopause.

Methods: The cross-sectional study was conducted in 112 community primary health care centers in rural northern China between April 2019 and January 2020. A total of 4,275 women aged ≥ 65 years who had natural menopause were included. Reproductive factors were recorded by self-report. Reproductive period was calculated as age at menopause minus age at menarche.

Results: Compared to those without dementia, women with dementia were significantly older at menarche and younger at menopause; had significantly shorter duration of reproductive period; and had more pregnancies and parities. There were 0.757, 0.698, and 0.708 times to get dementia for women who experienced reproductive periods with 31-33 years, 34-36 years, and ≥ 37 years, respectively, as compared with ≤ 30 years. Reproductive period could positively predict MMSE score (β = 0.112) and negative prediction of the number of parities (β = -0.449); the number of parities could negatively predict MMSE score (β = -0.851) as well.

Conclusions: Longer duration of reproductive period, directly or through lower number of pregnancies/parities indirectly, lowers the risk of dementia in late life.

Background

Epidemiologic studies have for years consistently proved that women comprise more than half of people suffering cognitive impairment (CI), regardless of traditional risk factors we known (age, ethnicity, low education, hypertension, diabetes, dyslipidemia, and alcohol consumption et. al.) [1, 2]. Several pre-clinical and human studies for early prediction for dementia have pointed menopause transition as a major modified factor for females [3].

During the average human menstrual cycle, women experience sharply increase in 17β-estradiol and progesterone [4]. The production of sex hormones surging during pregnancy, particularly [5]. Later in life, women experience a steep decline in sex hormone production during the transition to menopause [6]. Animal studies offer unambiguous evidence that sex hormone regulates the hippocampal morphology and prefrontal cortex pyramidal neurons, which express estrogen receptors (ER-α), to affect memory performance [7]. Meanwhile, neuroprotective and neurotrophic effects of estrogen, including inhibition of amyloid-β (Aβ) formation [8], stimulation of cholinergic activity [9], protection against oxidative stress [10], and increase of cerebral blood flow [11], improve the cognitive performance in human and animals. Numbers of epidemiologic studies identify that reproductive factors play an important role in the cognitive performance in old females. Shorter reproductive period and higher number of parities are associated increase risk of cognitive impairment in late life [12], while the putative associations among longer reproductive period, number of pregnancies and cognitive performance are controversial [13, 14].

Most research has been conducted in the western population, few information on rural elder women in northern China. Previous studies indicate shorter duration of reproductive periods in Chinese women, with older age at menarche and lower age at menopause than that of white women [15]. Two population-based studies in northern China report that longer duration of reproductive period is associated with better cognitive performance [16, 17], the same result is found among Singapore Chinese women [12]. Therefore, studies in rural northern Chinese women are still needed.

Currently, few studies have examined the associations among reproductive period, the number of parities, and risk of dementia in rural northern Chinese females. We conducted a large population-based cross-section investigation from rural northern China to evaluate the association between reproductive factors with the risk of dementia in women who with natural menopause. We hypothesize longer reproductive period is related to lower risk of dementia in late life directly, as well as through lower number of parities indirectly.

Methods

Participants

This cross-sectional study enrolled participants ≥ 65 years of age in 112 community primary health care centers selected from 949 villages in the rural Ji County in northern China between April 2019 and January 2020. The local medical practitioner in each village (who had worked there for over 5 years) was involved in identifying all individuals aged ≥ 65 years based on the date of birth provided on the residence certificate. A face-to-face questionnaire-based survey was conducted by senior MD students or medical staff in the local panel health centers, a neurologist with special expertise in cognitive impairment to re-review the data in each region. All interviewers and experts received the same one-week training on collecting information (consisting demography, lifestyles, medical history, reproductive factors), neuropsychological assessment and diagnosis, and participated in a retraining course every 2 months.

Figure 1 showed the flow chart of study enrollment and exclusion. The total number of female participants aged ≥ 65 years in these communities was 4,951; however, due to refusal (n = 89), death (n = 5), migration (n = 2), hearing loss (n = 53), aphasia (n = 4) or mental disorders (including definite depression, anxiety, n = 37), totally 4,791 completed the interview. Because of 123 participants with surgical menopause history and 363 participants with uncompleted reproductive information, 486 records were excluded, and 4,275 records were analyzed finally. The study was approved by the Committee for Medical Research Ethics at Tianjin Huanhu Hospital and the Tianjin Health Bureau, and we confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Measures

In this study, all female participants had menopause already. Reproductive factors were collected in the reproductive history section, including age at menarche, age at menopause (natural or surgical), number of pregnancies, and number of parities. Reproductive period was calculated as age at menopause minus age at menarche.
Information on other covariates was collected via the questionnaires, including age, education, marital status (single, married, divorced, widowed), occupation (manual worker, none-manual worker), living states (with spouse, with children, alone, others). History of smoking, drinking, as well as physician's diagnosis of stroke, diabetes mellitus (DM), heart disease, and hypertension.

Cognitive assessment

Cognitive assessment was conducted using the Chinese Mini-Mental State Examination (C-MMSE) [18], the Clinical Dementia Rating (CDR) scale [19], and the Activities of Daily Living (ADL) scale [20]. Participants with C-MMSE score below the cutoff points (17, 20 and 24 points for participants of illiteracy, primary school and higher education) [21]. In this study, we diagnosed dementia based of the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-5) [22]. All dementias underwent physical examination, and neuroimaging examination [magnetic resonance imaging (MRI) or computed tomography (CT)], ^{11}C-PIB PET scan and a ^{18}F-FDG PET scan for those difficult to diagnose if possible. The detailed design was described in a previous study [23].

Data analysis

We calculated descriptive statistics for continuous variables (age, education, and reproductive factors), student t test was used for continuous variables consistent with normal distribution and nonparametric test for non-normal applications. $\chi 2$ tests for categorical variables (marital states, occupation, living status, lifestyles, and comorbidities).

In order to evaluate the crude age-, pregnancy-, and parity- specific prevalence of dementia by reproductive period, we divided age (65–69 years, 70–74 years, 75–79 years, ≥ 80 years), the number of pregnancy (0, 1–2, 3–4, and ≥ 5), the number of parity (0, 1–2, 3–4, and ≥ 5) into categorical variables. To avoid interaction effect, we classified age at menarche (≤ 15, 16–17, ≥ 18), age at menopause (≤ 46, 47–49, 50–52, ≥ 53), and reproductive period (≤ 30, 31–33, 34–36, ≥ 37) as well. Logistic regression and Spearman linear correlation analysis were used to estimate the association or interaction between reproductive factors and dementia. In adjusted models, the age and education were calculated.

All data were analyzed using IBM SPSS Statistics for Windows (Version 25.0; IBM Corp., Armonk, N.Y. USA). P-values < 0.05 were considered statistically significant.

Results

General characteristics of participants

Among the 4275 natural postmenopausal women, the mean (SD) age was 74.21 (5.72) years, and 486 (11.4%) were assessed to have dementia. The general characteristics of participants were presented in Table 1. Compared to those without dementia, women with dementia were significantly older; with lower education; in widowed/divorced; manual workers; fewer living with spouse; more with stroke history; were significantly older at menarche and younger at menopause; had significantly shorter duration of reproductive period; and had more pregnancies and parities.

Table 1
General characteristics of participants

Characteristics	Overall	Dementia		p-value [a]
		Yes	No	
Num.	4275	486	3789	
Age (years, mean, SD)	74.32 ± 5.72	77.32 ± 6.15	73.94 ± 5.54	< 0.001
Education (years, mean, SD)	4.90 ± 4.41	3.50 ± 4.24	5.08 ± 4.40	< 0.001
Marital status (n, %)				< 0.001
Single	7 (0.2)	1 (0.2)	6 (0.2)	
Married	3078 (72.0)	304 (62.6)	2774 (73.2)	
Divorced	48 (1.1)	2 (0.4)	46 (1.2)	
Widowed	1142 (26.7)	179 (36.8)	963 (25.4)	
Occupation (n, %)				0.040
Manual worker	2471 (57.8)	302 (62.1)	2169 (57.2)	
None-manual worker	1804 (42.2)	184 (37.9)	1620 (42.8)	
Living states (n, %)				< 0.001
With spouse	2714 (63.5)	256 (52.3)	2460 (64.9)	
With children	998 (23.3)	167 (34.4)	831 (21.9)	
Alone	521 (12.2)	59 (12.1)	462 (12.2)	
Others	42 (1.0)	6 (1.2)	36 (1.0)	
Lifestyles (n, %)				
Smoking (yes)	296 (6.9)	22 (4.5)	170 (4.5)	0.968
Drinking (yes)	192 (4.5)	12 (2.5)	137 (3.6)	0.194
Comorbidities (yes, n, %)				
Stroke	434 (10.2)	85 (17.5)	349 (9.2)	< 0.001
DM	684 (16.0)	82 (16.9)	602 (15.9)	0.577
Heart disease	755 (17.7)	100 (20.6)	655 (17.3)	0.076

Num., the number of samples; SD, standard deviation; DM, diabetes mellitus.

[a] compared between dementia with non-dementia.

Characteristics	Overall	Dementia		p-value [a]
		Yes	No	
Hypertension	2285 (53.5)	265 (54.5)	2020 (53.3)	0.613
Reproductive factors (mean, SD)				
Age at menarche (years)	16.36 ± 2.25	16.64 ± 2.37	16.33 ± 2.24	0.004
Age at menopause (years)	49.33 ± 4.52	48.63 ± 4.70	49.41 ± 4.49	< 0.001
Reproductive period (years)	32.97 ± 5.03	31.99 ± 5.26	33.08 ± 4.99	< 0.001
Num. of pregnancies	3.19 ± 1.45	3.52 ± 1.63	3.15 ± 1.42	< 0.001
Num. of parities	2.60 ± 1.20	3.08 ± 1.45	2.54 ± 1.15	< 0.001
Num., the number of samples; SD, standard deviation; DM, diabetes mellitus.				
[a] compared between dementia with non-dementia.				

Association between reproductive characteristics and dementia

Figure 2 showed age- (Fig. 2A), pregnancy- (Fig. 2B), and parity- (Fig. 2C) specific prevalence of dementia by reproductive period.

After we adjusted for age and education in Table 2, compared with women who had menarche before 15 years old, the odds ratio (OR) (95% Confidence interval, 95% CI) was 1.404 (1.077–1.831) for participants who had menarche after 17 years old. And women with older age of menopause than 46 years showed less likely to be dementia, the ORs were 0.662 (95% CI, 0.483–0.909), 0.740 (95% CI, 0.564–0.972), and 0.584 (95% CI, 0.419–0.813) for the age of 47–49 years, 50–52 years, and ≥ 53 years, respectively. There were 0.757 (95% CI, 0.568–1.009), 0.698 (95% CI, 0.524–0.929), and 0.708 (95% CI, 0.525–0.955) times to get dementia for women who experienced reproductive periods with 31–33 years, 34–36 years, and ≥ 37 years, respectively, as compared with ≤ 30 years. While we didn't find significant difference among pregnancy- and parity- subgroups.

Table 2
Association between reproductive characteristics and dementia

Reproductive characteristics	Overall	Dementia			Crude		Adjusted [b]	
		Yes	No	p-value [a]	OR (95% CI)	p-value	OR (95% CI)	p-value
Age at menarche (years, mean, SD)								
≤ 15	1413 (35.2)	118 (29.8)	1295 (35.8)	0.018	1.00 (Ref.)	–	1.00 (Ref.)	–
16–17	1354 (33.7)	122 (30.8)	1232 (34.0)	0.192	1.087 (0.834–1.416)	0.538	1.046 (0.797–1.372)	0.747
≥ 18	1247 (31.1)	156 (39.4)	1091 (30.2)	< 0.001	1.569 (1.219–2.020)	< 0.001	1.404 (1.077–1.831)	0.012
Age at menopause (years, mean, SD)								
≤ 46	878 (22.2)	112(29.6)	766 (21.4)	< 0.001	1.00 (Ref.)	–	1.00 (Ref.)	–
47–49	859 (21.7)	73 (19.3)	786 (21.9)	0.238	0.635 (0.465–0.867)	0.004	0.662 (0.483–0.909)	0.011
50–52	1395 (35.2)	131 (34.7)	1264 (35.3)	0.807	0.709 (0.542–0.926)	0.030	0.740 (0.564–0.972)	0.044
≥ 53	828 (20.9)	62 (16.4)	766 (21.4)	< 0.001	0.554 (0.400-0.767)	0.001	0.584 (0.419–0.813)	0.002
Reproductive period (years, mean, SD)								
≤ 30	1143 (28.5)	144 (36.4)	999 (27.6)	< 0.001	1.00 (Ref.)	–	1.00 (Ref.)	–
31–33	917 (22.8)	87 (22.0)	830 (22.9)	0.666	0.727 (0.549–0.964)	0.027	0.757 (0.568–1.009)	0.057

Num., the number of samples; SD, standard deviation; ORs, odds ratios; CI, confidence interval; Ref., reference.

a compared between dementia with non-dementia; b adjusted age and education.

Reproductive characteristics	Overall	Dementia			Crude		Adjusted [b]	
		Yes	No	p-value [a]	OR (95% CI)	p-value	OR (95% CI)	p-value
34–36	1042 (25.9)	88 (22.2)	954 (26.4)	0.075	0.640 (0.484–0.846)	0.002	0.698 (0.524–0.929)	0.014
≥ 37	914 (22.8)	77 (19.4)	837 (23.1)	0.098	0.638 (0.477–0.854)	0.003	0.708 (0.525–0.955)	0.024
Num. of pregnancies (n, %)								
0	42 (1.0)	7 (1.5)	35 (1.0)	0.281	NA		NA	
1–2	1395 (34.2)	165 (35.5)	1230 (34.1)	0.540	1.00 (Ref.)	–	1.00 (Ref.)	–
3–4	1998 (49.0)	212 (45.6)	1786 (49.4)	0.118	NA		NA	
≥ 5	642 (15.7)	81 (17.4)	561 (15.5)	0.293	NA		NA	
Num. of parities (n, %)								
0	58 (1.4)	9 (1.9)	49 (1.3)	0.319	NA		NA	
1–2	2195 (53.5)	256 (54.8)	1939 (53.4)	0.555	1.00 (Ref.)	–	1.00 (Ref.)	–
3–4	1557 (38.0)	160 (34.3)	1397 (38.5)	0.079	NA		NA	
≥ 5	290 (7.1)	42 (9.0)	248 (6.8)	0.086	NA		NA	

Num., the number of samples; SD, standard deviation; ORs, odds ratios; CI, confidence interval; Ref., reference.

a compared between dementia with non-dementia; b adjusted age and education.

Table 3 showed the correlation coefficients between reproductive factors and MMSE score. Larger number of pregnancies (r = -0.123) or parities (r = -0.217), older age of menarche (r = -0.092), younger age of menopause (r = 0.103) and shorter duration of reproductive period (r = 0.131) were correlated with lower MMSE scores, as well as poorer cognitive performance. Reproductive period could positively predict

MMSE score (β = 0.112, p < 0. 001) and negative prediction of the number of parities (β = -0.449, p < 0. 001); the number of parities could negatively predict MMSE score (β = -0.851, p < 0. 001) as well. The results indicated that the number of parities had mediating effect on MMSE scores (Fig. 3A). Similarly, the number of pregnancies also established mediating effect on MMSE score (Fig. 3B).

Table 3
Correlation coefficients of reproductive factors and MMSE score

	Num. of pregnancies	Num. of parities	Age at menarche	Age at menopause	Reproductive period	MMSE
Num. of pregnancies	–					
Num. of parities	0.737**	–				
Age at menarche	0.032*	0.130**	–			
Age at menopause	− 0.038*	− 0.077**	0.018	–		
Reproductive period	− 0.055**	− 0.137**	− 0.447**	0.859**	–	
MMSE score	− 0.123**	− 0.217**	− 0.092**	0.103**	0.131**	–

MMSE, Mini Mental State Examination; *$p < 0.05$; **$p < 0.001$

Discussion

Consistent with our original hypothesis, the longer duration of reproductive period, directly or through lower number of pregnancies/parities indirectly, was positive related to lower risk of dementia in late life.

This population-based cross-sectional study of rural females with natural menopause, were generally consistent with previous studies that have examined the relationship of the reproductive period on cognitive profile [24, 25]. Traditionally, the duration of reproductive period was defined as the period extending from age at menarche to age at menopause in years. We found that the average age at menarche in rural old females was 16.36 (2.25), which was consistent with old women in Eastern China (16.8 ± 1.7 years old) [17]. While the age of menarche was younger in developed countries. French women showed younger age at first menses (13.1 ± 1.6 years old), older age at menopause (49.5 ± 5.4 years old), and average 36.6 (5.6) years of reproductive period [26]. The Japanese women with CI began menstruating at 14.4 (1.7) years old, which was later than normal women [14] whereas earlier than rural women in northern China. The international age at natural menopause was 44.6–55 years [27], several reports suggested the age was 54 in Europe, 51.4 in North America, and 48.6 in Latin America, and 51.1 in Asia [15]. In our study, the average age at menopause (49.33 ± 4.52 years of age) was consistent with previous studies in Eastern China (49.3 ± 4.2 years of age) and France (49.5 ± 5.4). It was reported that

the mean age of natural menopause among Jordanian women was younger (48.5 ± 5.0) [28], with 7.8% of the women experienced early menopause (40–44 years of age), and 21.1% with late menopause (> 52 years of age). What's more, later age at menarche and younger age at menopause were associated with poor cognitive performance [13, 16], and our findings were generally consistent with these studies.

Most previous studies had been conducted among Western females to investigate the relationship between reproductive periods with risk of cognitive function and dementia, while evidence among Asian populations is limited. Reproductive period, an indicator of endogenous estrogen exposure, lasted shorter in Chinese women (32.97 ± 5.03 in our study; 34.5 ± 4.3 in Guangzhou province; and 32.5 ± 4.7 in Zhejiang province) than those living in dependent countries (36.6 ± 5.6 in ESPRIT study from France, 35.1 ± 5.2 in the Rotterdam Study from Netherlands, and 34.9 ± 4.5 in the Prospective Population Study of Women from Gothenburg, Sweden). In other words, old females in rural northern China had shorter period of endogenous estrogen exposure, which might lead to poor cognitive performance and increase the risk of dementia. Three population-based studies had supported that shorter reproductive period was significantly associated with worse cognitive function among Chinese women [12, 16, 17]. The Japan Public Health Center-based Prospective Study also showed longer exposure to endogenous estrogen may have a protective effect against cognitive impairment. Women with a reproductive period ≥ 38 years had a significantly lower risk of cognitive impairment (OR = 0.62, 95% CI, 0.40–0.96) compared with those with ≤ 33 years [14].

The putative association between hormones and cognitive performance is controversial. An observational study in Switzerland, including 44 women receiving IVF, showed that estradiol didn't have a significant short-term effect on cognitive function [29]. While in a retrospective analysis with 164 surgical-menopause women (the mean time since menopause was 11.3 ± 7.4 years) performed frontal lobe dysfunction and couldn't be improved by hormone therapy usage [30]. A Cochrane systematic review of clinical trials concluded that hormone replacement therapy (HRT) did not prevent cognitive decline in postmenopausal women[31], and some observational studies also reported null or opposite [13, 32, 33] associations[34]. In a population-based prospective cohort (The Singapore Chinese Health Study), women with < 35 reproductive years were 1.28 (95% CI, 1.11–1.48) times to get cognitive impairment compared with women with 35–39 reproductive years (Ref.), whereas no significant findings among women with > 39 years. When comparing to women with 39–44 years reproductive period, women with 35–38 years had no significant difference on the increased risk of dementia [35]. In ESPRIT study, longer reproductive period had association with better verbal fluency, instead of better global cognition, though the age at first menses was negatively associated with visual memory and psychomotor speed performance [26]. Longer reproductive period was associated with increased risk of all-cause dementia and Alzheimer's disease in all models, particularly in aging people [34].

We also found that more pregnancies and parities were associated with lower MMSE scores, especially among women with shorter duration of reproductive period. Previous studies indicated that parous women had shorter reproductive periods and lower level of estradiol than nulliparous women, and thus greater parity could lead to an overall lower levels of lifetime estrogen exposure [36, 37]. These findings

had been proved in many studies [38–41]. Women with higher number of pregnancies had indirectly relate to higher estro-progestinic exposure. We proposed that it is the increase of progesterone or estrogens level – and not the estrogens decrease, in other words, the dramatic changes in estrogen and progesterone during and after parity, play a role in cognitive impairment. Women with greater parity might lead to lower circulating estrogen over lifetime than women with fewer parity or nulliparity. In our analysis of interaction among the number of pregnancies/parities, reproductive period and dementia, reproductive period positively predicted cognitive performance. And the number of pregnancies/parities, as part of a mediation model, played negative predictive role on cognition; that is, reproductive period would be mediated by the number of pregnancies/parities, had indirect effects of cognitive performance for older women. The shorter reproductive period could increase the risk of dementia by non-parous or greater pregnancies/parities in elderly women. Later age at menarche (≥ 17 years), earlier age at menopause (< 40 years), shorter reproductive span (< 30 years) increased the risks of fractures [42] and age-related hearing decline [43] as well.

The main strength of our study was the large population in rural northern China, and detailed collection of information on participants (demographic, dietary, lifestyle factors, and medical history) to investigate the association and interaction between reproductive and dementia. Nevertheless, several limitations should be noted. As research on reproductive factors and dementia continues, more and more risk factors needed to be investigated, including those affecting dementia and reproduction. The second is recall bias. Because of the self-report information was retrospective, the information of participants might be inaccurate due to their age, while previous studies suggested that age at menarche, age at menopause, the number of brain fast /parities could still be reliable over many years [44, 45]. Another is the lack of objective biomarkers. In this cross-sectional study, hormone levels and Aβ levels were not measured, and dementia was not classified as subtypes, which required further analysis and exploration of the data.

Conclusions

The duration of reproductive period is shorter for women living in rural northern China. Longer duration of reproductive period, directly or through lower number of pregnancies/parities indirectly, lowers the risk of dementia in late life. We call for more awareness for the adverse effects of reproductive factors on women's brain health, particular in rural regions.

Declarations

Acknowledgments

Not applicable.

Authors’ contributions

JG: Conceptualization, Formal analysis, Investigation, Writing-original draft, Writing - review & editing. SL: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, and Funding. XW:

Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. ZC, XD, FW, WH, and HZ: Investigation. ZS: Resources, Supervision. YJ: Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, and Funding. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was approved by the Committee for Medical Research Ethics at Tianjin Huanhu Hospital and the Tianjin Health Bureau (ID: 2019-40). And all subjects gave written informed consent before enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

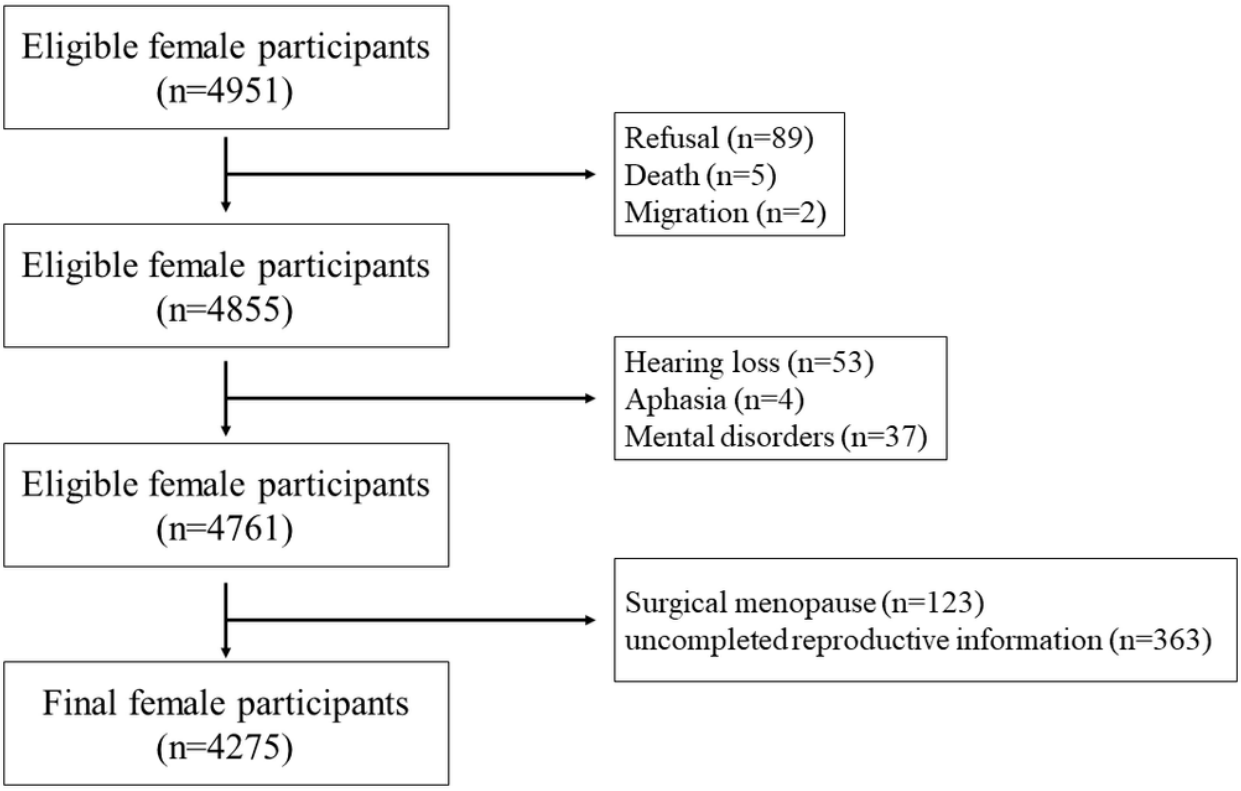

Figure 1

Flowchart of this study.

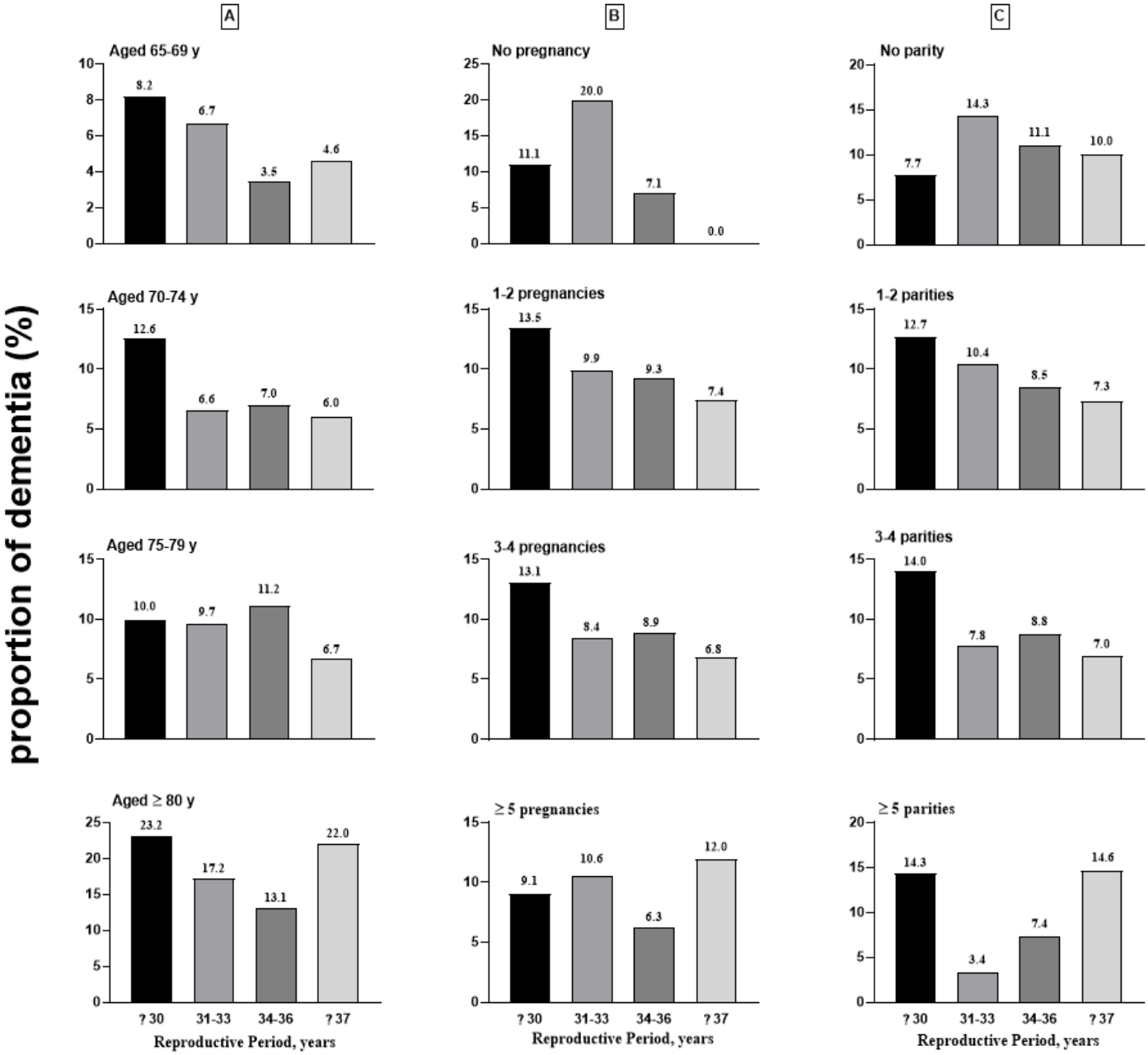

Figure 2

Specific prevalence rates of dementia by quartile of reproductive period

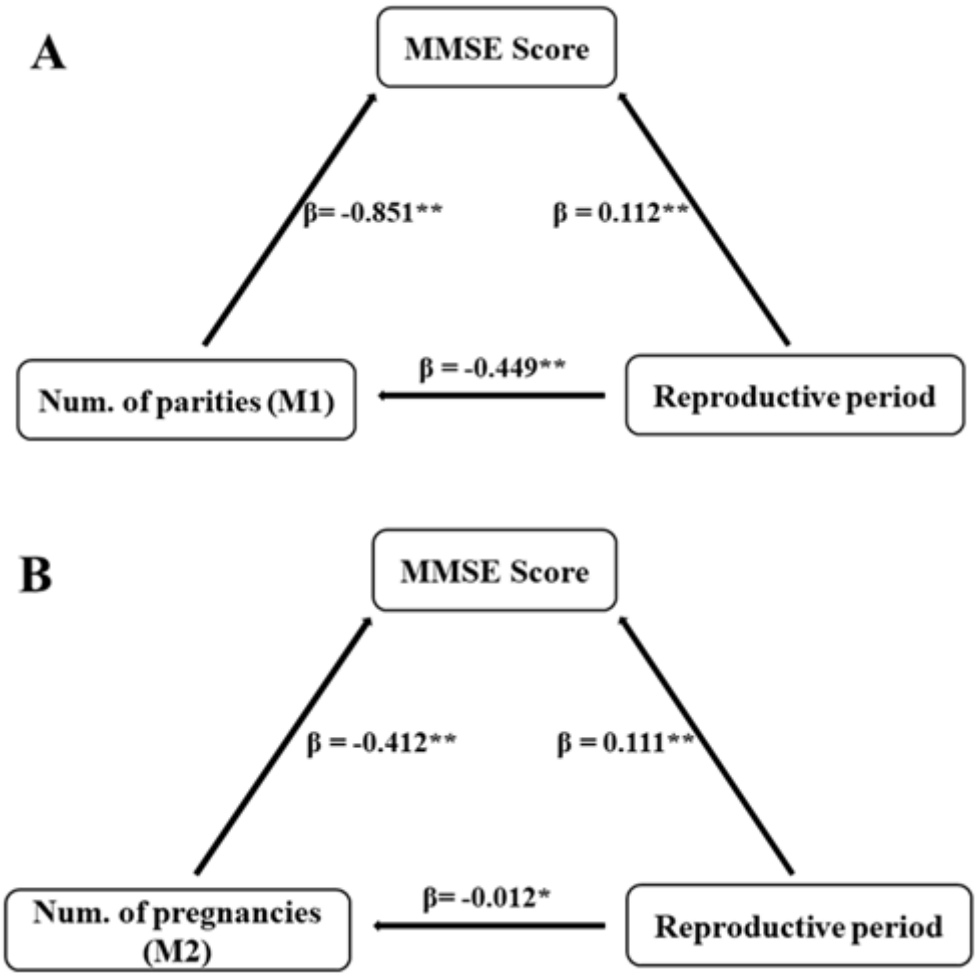

Figure 3

Mediating effect models of pregnancy/parity between reproductive period and dementia in elderly women
MMSE, Mini Mental State Examination; *p < 0.05; **p < 0.001