Effects of Female Reproductive Factors on Subjective and Objective Cognitive Function: A Cross-sectional Analysis of the Pingyin Cohort Postprint

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Abstract

Background: Current research conclusions on reproductive factors and cognitive function remain inconsistent, and there is a lack of studies investigating female reproductive factors and subjective cognitive function. Objective: To explore the association between female reproductive factors and both subjective and objective cognitive function, providing a theoretical basis for early prevention and intervention of cognitive decline and dementia. Methods: In July 2023, middle-aged and elderly individuals aged 45-70 years were surveyed in three townships of Pingyin County, Jinan City using multi-stage cluster random sampling, yielding a final valid sample of 2,165 cases. A general information questionnaire was self-developed to collect sociodemographic information, medical history, lifestyle, and female reproductive factors. Subjective and objective cognitive function were measured using the Subjective Cognitive Decline Questionnaire (SCD-Q9) and the Montreal Cognitive Assessment Basic (MoCA-B), respectively. Height, weight, and other information were obtained through anthropometric measurements, and APOE e4 allele genotyping was obtained through blood testing. Multivariate logistic regression was used to explore the effects of female reproductive factors on subjective and objective cognitive function. Locally weighted regression (Loess) was used to analyze the nonlinear association between age at menarche, age at menopause, reproductive span length, and MoCA-B scores. Results: A total of 1,044 women were included, with abnormal SCD-Q9 score rate of 48.37% (505/1,044) and abnormal MoCA-B score rate of 67.43% (704/1,044). Multivariate logistic regression analysis showed that women with three or more children had lower risk of subjective cognitive decline compared to those with one or fewer children (OR=0.59, 95%CI=0.36-0.98); breastfeeding duration 18 years (OR=1.91,

95%CI=1.09-3.35), age at menopause $ $45 years (OR=1.61, 95%CI=1.00-2.62), reproductive span >40 years (OR=1.56, 95%CI=1.07-2.29) or $ $30 years (OR = 2.22, 95 1), shorter breastfeeding duration (18 years, early menopause ($45 years), and reproductive span that is too long or too short were all associated with poorer objective cognitive function. Attention should be paid to the impact of female reproductive factors on cognitive function to delay the progression of cognitive decline.

Full Text

The Association between Female Reproductive Factors and Subjective and Objective Cognitive Function: A Cross-sectional Analysis from the Pingyin Cohort

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Abstract

Background: The association between female reproductive factors and cognitive function remains unclear, and studies on female reproductive factors and subjective cognitive function are lacking. **Objective:** To explore the relationship between female reproductive factors and both subjective and objective cognitive function, providing a theoretical basis for the prevention and intervention of cognitive decline and dementia. **Methods:** In July 2023, a baseline survey was conducted in three townships in Pingyin County, Jinan City, using a multi-stage cluster random sampling method to recruit participants aged 45-70 years, yielding 2,165 valid participants. A self-designed comprehensive questionnaire collected sociodemographic information, medical history, lifestyle factors, and female reproductive factors. Subjective and objective cognitive function were evaluated using the Subjective Cognitive Decline-Questionnaire 9 (SCD-Q9) and Montreal Cognitive Assessment Scale-Basic (MoCA-B), respectively. Anthropometric measurements (height, weight) and blood samples (for APOE e4 allele genotyping) were also obtained. Multivariate logistic regression and locally weighted regression (Loess) were used to analyze the influence of female reproductive factors on cognitive function and to detect potential nonlinear relationships between age at menarche, age

at menopause, length of reproductive period, and MoCA-B scores. **Results:** A total of 1,044 women were included in this study. The prevalence of abnormal SCD-Q9 scores was 48.37% (505/1,044), while the prevalence of abnormal MoCA-B scores was 67.43% (704/1,044). Women who had three or more children had a lower risk of subjective cognitive decline compared with those who had one or fewer children (OR=0.59, 95%CI=0.36-0.98). Women with a breastfeeding duration of less than six months had a higher risk of subjective cognitive decline compared with those with a duration of 6-12 months (OR=3.69, 95%CI=1.03-13.16). Age at menarche >18 years (OR=1.91, 95%CI=1.09-3.35), age at menopause $ $45 years (OR=1.61, 95%CI=1.00-2.62), and reproductive period >40 years (OR=1.56, 95%CI=1.07-2.29) or $ $30 years (OR = 2.22, 95 1) and shorter breastfeeding duration (< 6 months) have a higher risk of subjective cognitive decline. Age at menarche > 18 years, early menopause($45 years), and excessively long or short reproductive periods are all associated with poorer objective cognitive function. Attention should be paid to the influence of female reproductive factors on cognitive function in order to delay the process of cognitive decline.

Keywords: Female; Reproductive factors; Cognitive function; Subjective cognitive function; Objective cognitive function; Cross-sectional study

Introduction

Subjective cognitive decline (SCD) refers to increased frequency of self-reported memory loss or mental confusion [1], which occurs earlier than mild cognitive impairment (MCI) [2] and may represent a preclinical stage of Alzheimer's disease (AD) [3]. Previous studies have shown that women are more susceptible to SCD and MCI than men [4-6], and postmenopausal women face higher risks of both subjective and objective memory decline compared with men [7]. The neuroprotective mechanism of estrogen has long been established [8], and insufficient ovarian estrogen secretion during perimenopause is considered a cause of cognitive dysfunction and SCD in women [1].

Female reproductive factors—including age at menarche and menopause, number of children, and length of reproductive period—are closely related to estrogen levels. However, research on the association between female reproductive factors and subjective cognitive function remains scarce, and existing studies on reproductive factors and cognitive function have yielded inconsistent conclusions. Both the "Healthy China Action (2019-2030)" and the "14th Five-Year Plan for Healthy Aging" have explicitly proposed specific tasks for dementia prevention. In light of this, the present study utilizes data from the Pingyin cohort to explore the association between female reproductive factors and both subjective and objective cognitive function from a gender-specific perspective, providing evidence for sex-specific precision prevention of cognitive decline.

Methods

Study Participants

The baseline survey of the Pingyin cohort was initiated in July 2023. A multi-stage cluster random sampling method was used to select participants. Based on geographic location, one township each was selected from the northern, central, and southern parts of Pingyin County in Jinan, totaling three townships. From each township, administrative villages with permanent populations exceeding 1,500 were identified, and two villages were randomly selected as sample villages, yielding six villages total. If insufficient sample size was obtained, a third village was randomly selected, resulting in a final sample of seven villages.

Inclusion criteria were: (1) permanent residents of the area (living locally for six months or more); (2) aged 45-70 years; (3) provision of informed consent by the participant or their family. Exclusion criteria were: (1) severe schizophrenia, existing Alzheimer's disease, or other types of dementia; (2) severe hearing, vision, or communication impairments; (3) inability to cooperate with investigators or complete the questionnaire for other reasons. The baseline survey included 2,187 participants, with 2,165 valid samples (complete questionnaires without missing or erroneous items), yielding a response rate of 98.9%. This study included only postmenopausal women from the baseline population, with 1,044 women ultimately included after excluding those with missing covariates. The baseline survey included physical examinations, epidemiological questionnaires, brain MRI scans, and blood sample collection and testing. The study was approved by the Ethics Committee of Shandong University (LL20220319).

Survey Methods

Questionnaires were administered through face-to-face interviews. Professional equipment was used to collect anthropometric data including height, weight, and blood pressure. Fasting blood samples were collected the day after questionnaire completion.

Measurements

General Information Questionnaire: A self-designed questionnaire collected sociodemographic information (age, gender, occupation, marital status, education level), medical history (hypertension, diabetes, coronary heart disease), family history, lifestyle factors (smoking, alcohol consumption, diet, physical activity), self-reported visual and hearing status, psychological status, and female reproductive factors. Reproductive factors included number of children, age at first and last childbirth, age at menarche, age at menopause, length of reproductive period, and breastfeeding status.

Subjective Cognitive Decline-Questionnaire 9 (SCD-Q9): This study used the SCD-Q9 to assess subjective cognitive function. The scale has a Cronbach's α coefficient of 0.870-0.881 [9] and comprises two dimensions with nine

items: overall memory function and temporal comparison (six items) and daily activity ability (three items), with a total score of 9 [9]. Following previous literature, scores $ $5 were classified as abnormal [10].

Montreal Cognitive Assessment Scale-Basic (MoCA-B): Objective cognitive function refers to comprehensive cognitive function measurable by scales, in contrast to subjectively reported cognitive function. Common tools include the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment Scale (MoCA). Considering the relatively low education level in rural areas, this study used the more accessible MoCA-B, which assesses domains including executive function, language, orientation, calculation, abstract thinking, memory, visual perception, attention, and concentration (Cronbach's α=0.807) [10]. The maximum score is 30, with cut-off scores adjusted for education: 19/20 ($ $6 years of education; $ $20=normal, $ $19=abnormal), 22/23 (6-12 years), and 24/25 (>12 years) [11]. Scores below the cut-off were classified as abnormal.

Anthropometric Data: Height and weight were measured to calculate BMI (kg/m^2).

Blood Sample Data: Apolipoprotein e4 (APOE e4) allele genotyping was performed.

Quality Control

Quality management was implemented across design, implementation, analysis, and reporting phases. During the design phase, a rigorous questionnaire was developed based on domestic and international literature and expert opinions, and refined after pilot testing. Before implementation, the research team underwent two unified training sessions to ensure standardized instructions for participants, reducing information bias. After collection, questionnaires were reviewed by designated personnel, and incomplete or obviously unreasonable responses were excluded to ensure data integrity and reliability.

Statistical Analysis

Data were analyzed using SAS 9.4 and R 4.3.3. Categorical data were expressed as relative frequencies, with between-group comparisons using ^{2} tests. Using abnormal SCD-Q9 scores and abnormal MoCA-B scores as dependent variables, multivariate logistic regression was used to examine associations between female reproductive factors and cognitive outcomes. Locally weighted scatterplot smoothing (Loess) was further used to analyze nonlinear associations between age at menarche, age at menopause, reproductive period length, and MoCA-B scores, with fitted regression curves and confidence intervals. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics and Reproductive Factors

This study included 1,044 postmenopausal women aged 47-70 years. The prevalence of abnormal SCD-Q9 scores was 48.37% (505/1,044), while abnormal MoCA-B scores occurred in 67.43% (704/1,044). Significant differences in abnormal SCD-Q9 and MoCA-B scores were observed across age, income, education level, hypertension history, and diabetes history (P<0.05). Abnormal SCD-Q9 scores also differed significantly by number of leisure activities, arrhythmia history, and estrogen use history (P<0.05), while abnormal MoCA-B scores differed by occupation (P<0.05) .

Among participants, 57.18% (597/1,044) had two children, 63.31% (661/1,044) experienced menarche at age 15-18, and 44.25% (462/1,044) underwent menopause at age 46-50. Abnormal SCD-Q9 scores differed significantly by age at menarche (P<0.05), while abnormal MoCA-B scores differed significantly by number of children, age at menarche, age at menopause, and reproductive period length (P<0.05) .

Association Between Reproductive Factors and Abnormal SCD-Q9 Scores

Using abnormal SCD-Q9 scores as the dependent variable (normal=0, abnormal=1) and reproductive factors as independent variables, multivariate logistic regression showed that women with three or more children had lower odds of abnormal SCD-Q9 scores compared with those with one or fewer children (OR=0.59, 95%CI=0.36-0.98, P<0.05). Among women who breastfed, those with duration <6 months had higher odds of abnormal SCD-Q9 scores compared with those with 6-12 months duration (OR=3.69, 95%CI=1.03-13.16) .

Association Between Reproductive Factors and Abnormal MoCA-B Scores

Using abnormal MoCA-B scores as the dependent variable (normal=0, abnormal=1), multivariate logistic regression revealed that women with menarche after age 18 had increased odds of abnormal MoCA-B scores compared with those with menarche at age 13-14 (OR=1.91, 95%CI=1.09-3.35, P<0.05). Women with early menopause ($ $45 years) had higher odds of abnormal MoCA-B scores compared with those with menopause at age 51-54 (OR=1.61, 95%CI=1.00-2.62, P<0.05). Compared with women with reproductive period length of 31-35 years, those with length $ $30 years (OR=1.56, 95%CI=1.07-2.29, P<0.05) or >40 years (OR=2.22, 95%CI=1.05-4.72, P<0.05) had increased odds of abnormal MoCA-B scores .

Non-linear Association Between Reproductive Factors and MoCA-B Scores

Loess analysis revealed an approximate inverted J-shaped relationship between age at menarche, age at menopause, reproductive period length, and MoCA-B scores. Women with menarche at age 13-14 had higher MoCA-B scores, with later menarche associated with lower scores. Women with menopause at age 51-54 had higher scores, with earlier menopause associated with lower scores; scores declined markedly when menopause occurred after age 55. Women with reproductive period length of 36-40 years had higher scores, with both shorter and longer periods associated with lower scores, particularly when exceeding 40 years [Figure 1: see original paper].

Discussion

This cross-sectional analysis based on the Pingyin cohort explored relationships between female-specific reproductive factors and both subjective and objective cognitive function, complementing and extending previous research.

Few studies have examined associations between reproductive factors and subjective cognitive function. Our research team previously analyzed data from the China Health and Retirement Longitudinal Study but found no statistically significant associations between age at menarche, age at menopause, reproductive period length, and SCD [7]. The current study found that shorter breastfeeding duration was associated with abnormal SCD-Q9 scores, adding to the existing evidence base.

Researchers have extensively investigated relationships between reproductive factors and objective cognitive decline, but findings remain inconsistent. A large cross-sectional study in rural northern China found that higher parity was associated with lower cognitive function scores (r=-0.07, P<0.001) [12]. Similar results were reported by SONG et al. [13] in Singaporean Chinese women and HEYS et al. [14] in Guangzhou women. However, a U.S. study found that women with 1-3 births (HR=0.75, 95%CI=0.56-0.99) or $ $4 births (HR=0.71, 95%CI=0.53-0.96) had lower risks of MCI and dementia compared with nulliparous women [15]. These studies did not adjust for APOE e4, a major susceptibility gene for dementia [16]. After adjusting for APOE e4 and other covariates, our study did not observe an association between number of children and abnormal MoCA-B scores, possibly because most participants' reproductive years fell under the one-child policy period, resulting in concentrated parity distribution.

Consistent with previous research [12,17-18], we found that later age at menarche was associated with more pronounced declines in MoCA-B scores, with women experiencing menarche after age 18 showing higher odds of abnormal scores. Menarche typically marks the beginning of high-level endogenous estrogen secretion, which has neuroprotective effects [8]; delayed menarche means later exposure to high estrogen levels, potentially contributing to lower MoCA-B scores. We observed an association only for

early menopause ($ 45 $years$) $and abnormal $MoCA - B$ scores. A recent meta-analysis also showed that early menopause (45 $years$) $ significantly increased risks of cognitive impairment and dde 1.22, 95 54 $years$) $ was associated with reduced risk ($RR = 0.93$, 95 $54 years) and objective cognitive function remains insufficient.

The association between reproductive period length and objective cognitive decline is unclear. XI et al. [12] and HEYS et al. [14] found that longer reproductive periods reduced MCI risk in Chinese populations. SHIMIZU et al. [19] reported that women with reproductive periods $ $38 years had 38% lower odds of cognitive impairment compared with those $ 33 $years$ ($OR = 0.62$, 95 $30 years) and longer (>40 years) reproductive periods increased odds of abnormal MoCA-B scores by 56% and 22%, respectively. Notably, while previous research focused on linear relationships, our study explored non-linear associations, finding that both short and long reproductive periods were associated with lower scores. Short-term endogenous estrogen exposure (e.g., shorter reproductive periods) is associated with poorer cognitive function, but long-term estrogen exposure may also cause cognitive decline. Studies suggest that estrogen supplementation to extend overall exposure may not benefit cognition [21].

Despite controversial findings, the influence of reproductive factors on cognitive function cannot be ignored. Our study provides new evidence for future research. Large-scale, multi-center prospective cohort studies are needed to assess how race and geography affect relationships between reproductive factors and cognitive decline.

Our findings can inform targeted prevention and intervention strategies for female cognitive health. However, limitations include: (1) cross-sectional design precludes causal inference; (2) reproductive factor data were self-reported, potentially introducing recall bias; (3) abnormal SCD-Q9 and MoCA-B scores were used as indicators rather than confirmed SCD and MCI diagnoses; (4) participants were rural residents from a single region, limiting generalizability.

Conclusion

In summary, female reproductive factors are associated with both subjective and objective cognitive function. Having fewer children ($ 1) $ and shorter breastfeeding duration ($<$ 6 $months$) $ correlate with poorer subjective cognitive performance, while later menarche ($>$ 18 $years$), early menopause (45 $years$), and excessively long ($>$ 40 $years$) $ or short ($30 years) reproductive periods correlate with poorer objective cognitive performance. These findings provide a theoretical basis for precise prevention and control of cognitive decline.

Author Contributions: FU Chunying and YU Ruihong were responsible for field data collection and organization, study implementation and design, statistical analysis, figure preparation, and manuscript drafting. WANG Qi, LI Meiling, and WANG Xiaoyi participated in field data collection and preliminary processing. ZHU Dongshan conceived the study, provided quality control and review, and was responsible for final version revision and overall accountability.

Conflict of Interest: None declared.

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