ORIGINAL ARTICLE

Later age at menopause was associated with higher cognitive function in post-menopausal women

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ABSTRACT

BACKGROUND

Menopause is a condition in which the menstrual periods have stopped for the last 12 months due to cessation of ovarial functions causing estrogen hormones to decrease. Various studies find that many factors affect cognitive function at post-menopausal age among others the decrease in estrogens, age at menopause, duration of menopause, and education. However, the effects have been subject to controversy. The aim of this study was to determine the relationship of age, age at menopause, estradiol level, and education with cognitive function among healthy post-menopausal women.

METHODS

A cross-sectional study was conducted involving 31 post-menopausal women between 50 to 75 years old. Data on age, age at menopause, and education were collected using a questionnaire. The estradiol levels were measured using an electrochemiluminescent immunoassay (ECLIA). The Indonesian version of the Montreal Cognitive Assessment (MoCA INA) was used to assess the cognitive function. Multiple linear regression was used to analyze the data. A $p<0.05$ was considered statistically significant.

RESULTS

Age (β=-0.086; 95% C.I.=-0.263-0.090; p=324) and estradiol levels (β=0.106; 95% C.I.=-0.018 -0.230; p=0.092) were not significantly associated with cognitive function. However, education (β=1.537; 95% C.I.=0.176-2.898; p=0.028) and age at menopause (β=0.364;0.056-0.671; p=0.022) were significantly associated with cognitive function. Age at menopause was the most influential factor of cognitive function (Beta=0.402) compared to education (Beta=0.394).

CONCLUSION

Later age at menopause could increase cognitive function in post-menopausal women. Our findings are that modifiable factors that delay age at menopause should receive attention, in order to promote cognitive function.

Keywords: Age at menopause, estrogens, cognitive function, post-menopausal women

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INTRODUCTION

The advances in the medical and healthcare sciences have an impact on increased life span of the Indonesian population. This is apparent from the data issued by the Central Statistics Agency *(Badan Pusat Statistik)*, stating that there is an increase in the life span of Indonesians, from 69.09 years in the period of 2005-2010 to 70.5 years in the period of 2010-2015.[1] This increase in life span indirectly also carries its own age-associated health problems, particularly in women.

In menopause there is a decrease in estrogens, which are steroid hormones with wide-spread influence in the whole body, including the central nervous system. Therefore estrogens affect various types of behavior, such as mood, cognitive function, and consciousness,[2,3] and sexual behavior in mammals. This influence is due to its role on various neurotransmitter systems, particularly those involving acetylcholine, serotonin, noradrenaline, and gamma-butyric acid (GABA). estrogen receptors can be detected in various parts that comprise cognitive processes such as learning and memory, including in the hippocampal group, amygdala, and cerebral cortex.[2,4]

Menopause is that point in time when permanent cessation of menstruation occurs, after loss of ovarial activity. The term "menopause" comes from the Greek word "men" (month) and "pausis" (cessation). The term "menopause" refers to the time point at which menstruation has ceased for one year. Post-menopause refers to the time after that point.[5]

The decrease in estrogens in postmenopausal women causes various complaints, changes in the limbic system associated with mood changes, anxiety, depression, insomnia, headaches /migraine and changes in cognitive function.[5]

Disturbances in cognitive function are classified into 3 types, i.e. i) cognitive aging; ii) mild cognitive impairment (MCI); and iii) dementia. Cognitive aging is a physiological condition with symptoms such as forgetfulness and complaints of reduced ability to do something. Mild cognitive impairment is episodic loss of memory without dementia, in which memory is disturbed but other cognitive abilities and daily activities are still normal. Subjects with MCI are at risk for dementia, so that its prevention is very important.[4]

A systematic review and meta-analysis showed that age at menopause was not associated with the risk of dementia in postmenopausal women.[6] However, another study showed differing results, in that verbal memory increases after menopause.[7] Various studies have been conducted to determine the effect of estrogen replacement therapy with or without progesterone on cognitive function. One study showed that the use of long-term hormonal replacement therapy did not improve cognitive function in women.[8] In younger women with bilateral oophorectomy, estrogen administration can improve episodic memory for verbal information. In addition to the influence of estrogens, there are other factors that influence cognitive function in post-menopausal women, such as age at menopause, duration of menopause, life style, nutrition, medical conditions such as hypertension and diabetes mellitus, and education.[5]

The inconsistent study reports on the relationship between age at menopause and cognitive function in postmenopausal women point to the need for further studies. The aim of the present study was to determine the relationship of age at menopause, estradiol level, and education with cognitive function in postmenopausal women.

METHODS

Design of study

This study was of cross-sectional design and was conducted in *Kelurahan* Duren Sawit, East Jakarta, from January to March 2018.

Study sample

The subjects participating in this study were postmenopausal women, aged from 50 to 75 years, who resided in *Kelurahan* Duren Sawit, East Jakarta.

The sample size was calculated based on the correlation value (r) of 0.76 between estradiol concentration and cognitive function in postmenopausal women,[9] and α of 0.05 and β of 0.2. Therefore the optimal sample size required in this study was 24. Subjects were recruited by consecutive non-random sampling. The inclusion criteria were postmenopausal women aged 50-75 years, agreeing to participate in this study by signing an informed consent form, capable of active communication, able to read and write and to walk unaided. The exclusion criteria were consumption of estrogens, suffering from diabetes mellitus, renal disease, ovarial tumors, heavy smokers, receiving steroid therapy or phenothiazines, having neurological disorders such as cerebrovascular disease and epilepsy, or not participating in this study to the end.

Data collection

A questionnaire was used to collect the data on age, education, and age at menopause.

Laboratory analysis

Blood samples for biochemical examination were obtained by venepuncture after an overnight fast of 12–14 hours. The blood was collected in plain tubes and left to clot for 30-45 minutes, then centrifuged at 3000 rpm for 15 minutes, after which the separated serum was stored at -70^0C until required for examinations. Measurement of estradiol concentration was performed with an electrochemiluminescent immunoassay (ECLIA), using an Elecsys 2010/ Cobas E601 analyzer and Cobas Roche Estradiol II reagent. Estradiol in the sample binds to biotinylated anti-estradiol antibody. The estradiol-anti-estradiol complex is immobilized in the solid state and bombarded by electrons so as to induce a chemiluminescent emission, the intensity of which is measured and indicates the estradiol concentration in the sample. The detection range for serum estradiol was 5 – 4300 pg/mL.

Measurement of cognitive function

Measurement of cognitive function was performed using the Montreal Cognitive Assessment (MoCA) questionnaire that had been adapted for Indonesian subjects, namely MoCA-INA. MoCA-INA is used for evaluation of various areas of cognitive function, comprising (i) short-term memory; (ii) visuospatial memory; (iii) executive functions; (iv) attention; (v) language, and (vi) spatial and temporal orientation. MoCA is an extremely good screening method for mild cognitive impairment (MCI). [10] The normal score for MoCA-INA is >24.

Data analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of the collected data and showed that the data were normally distributed. The distribution of all collected variables was expressed as mean ± standard deviation. Multiple linear regression analysis was performed to determine the variable with the greatest effect on cognitive function. The statistical analysis used SPSS for Windows version 17 (SPSS Chicago), and $p < 0.05$ was declared statistically significant.

Ethical clearance

The present study obtained ethical clearance from the Ethics Commission, Faculty of Medicine, Trisakti University, under No. 122/ KER/FK/XII/2017. The participants provided written informed consent.

RESULTS

A total of 31 postmenopausal women were successfully recruited for this study. The mean age of the subjects was 64.03 ± 6.52 years, and mean age at menopause was 51.23 ± 3.61 years.

Table 1. Distribution of several important characteristics of the study subjects (n=31)

Characteristic	
Age (years)	64.03 ± 6.52
Education (years)	15.30 ± 4.80
Age at menopause (years)	51.23 ± 3.61
Estradiol concentration (pg/mL)	19.57 ± 8.73
MoCA-INA*	22.84 ± 3.27

MoCA-INA= Montreal Cognitive Assessment Indonesian version

Mean duration of education was 15.30 ± 4.80 years and mean estradiol concentration was 19.57 ± 8.73 pg/mL (Table 1).

The results of the multiple regression analysis showed that age at menopause (β=0.364;95% C.I.=0.056-0.671; p=0.022) and duration of education (β=1.537;0.176-2.898; p=0.028) were significantly associated with cognitive function (Table 2). However, age and estradiol concentration were not significantly associated with cognitive function. Age at menopause was the most influential factor on cognitive function in postmenopausal women (Beta =0.402). The later the age at menopause the higher the cognitive function in postmenopausal women.

DISCUSSION

In the present study there was a significant relationship between duration of education and cognitive function. Low educational level was significantly associated with performance on continuous visual attention, episodic memory and spatial work, and reaction time.[11]

The theoretical concept of brain reserve refers to the ability for tolerating changes in the brain associated with aging as well as disease pathology without exhibiting clinical manifestations. The majority of investigators agrees that a number of factors, including education, complexity of work, social networks, duration of activity, and relaxation, can contribute to the amount of brain reserve that influences the survival of cognitive function in old age.[12] The higher the education and intellectual capacity of an individual, the greater the protection against various brain diseases.[13] There are more individuals of low educational level who are diagnosed with dementia as compared with those of high educational level.[14] Gholizaleh et al.[18] also found that education influences cognitive function in menopausal women.

In the present study a significant relationship was also found between age at menopause and cognitive function, in that the later the age at menopause the higher the cognitive function. Similar results were found in the study of Kuh et al.[7] who state that delayed natural menopause results in better memory than does early menopause, due to a longer exposure to estrogens. Similar results were found in the study of McLay et al.[16] who state that early menopause and low education decrease cognitive function, due to lesser exposure to estrogen. Bove et al.[17] and Kurita et al.[18] conducted studies on subjects who had bilateral oophorectomy before the onset of natural menopause, in which the subjects had a more rapid decrease in global cognitive functions. However, differing results were obtained in the study by Ryan et al.[22] who state that they did not find any significant differences in cognitive function between older postmenopausal women with surgical menopause and those with non-surgical menopause.

Table 2. Multiple regression analysis of age. age at menopause, duration of education and estradiol concentration with cognitive function (n=31)

Variable	Reg coeff (β)	95% CI	p value	Beta
Age	-0.086	-0.263-0.090	0.324	-0.172
Age at menopause	0.364	0.056-0.671	0.022	0.402
Duration of education	1.537	0.176-2.898	0.028	0.394
Estradiol concentration	0.106	-0.018-230	0.092	0.283

Reg coeff: regression coefficient; CI: Confidence Interval

Estrogen is a neuroprotective agent and acts to improve synaptic plasticity, axonal growth, hippocampal neurogenesis, and physiologic processes comprising episodic memory formation. Estrogen also protects against apoptosis and counteracts nerve injury, including toxicity induced by excitatory neurotransmitters, β-amyloid, oxidative stress, and ischemia. Estrogen influences various neurotransmitter systems, such as those involving acetylcholine, serotonin, noradrenalin and glutamate. Acetylcholine is important in the memory processes. Estrogen receptors are present in the basal portion of the forebrain and it is these pathological neurons that are particularly pathologically affected in Alzheimer disease.[4]

In the study of Sherwin et al.[20] it was found that estrogen administration can prevent decrease in verbal memory when given to patients after oophorectomy. The study by Cutter et al.[21] also stated that decreases in estradiol level impair cognitive function. Yoon et al.[22] stated that hormonal therapy in menopausal women for one month improves the test results of MoCA-K and the Korean-Mini-Mental Status Examination (K-MMSE) as compared with administration of placebo. The increased in dementia in the control group was 52.9% whereas in the intervention group it was 44.4%. Similar results were also encountered in the study by Ryan et al.[23] who stated that decreased estradiol concentration causes disturbances in cognitive function, since estradiol acts as a neuroprotector by preventing atherosclerosis, particularly in the ventral hypothalamus. However, another study did not support the hypothesis that estrogen or menopausal status affects cognitive performance in middle-aged women.[24] The limitation of this study was that it was a cross-sectional community-based study, so that it cannot allow conclusions to be drawn about the cause-and-effect relationship of age at the onset of menopause and the duration of menopause versus cognitive function. Data on administration of hormone replacement therapy that have yet to be collected may also affect cognitive function.

The clinical implication of the present study is that hopefully individuals having a family history of early menopause and vascular risk factors may train their cognitive functions as early as possible so that these may be adequately preserved. Another implication of our findings is that modifiable factors that delay reproductive aging, such as physical exercise, should be promoted.

There is a need for further studies to be conducted using a better study design, e.g. a cohort design using a number of cognitive function tests to determine cognitive function.

CONCLUSION

A later age at menopause may substantially increase cognitive function in postmenopausal women.

CONFLICT OF INTEREST

The investigators state that they had no conflict of interest in this study.

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CONTRIBUTORS

IR and LMS contributed to the study design and data collection. RAN performed the analysis. IR revised the manuscript. YI contributed to preparation of the final manuscript for publication. All authors have read and approved the final manuscript.

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