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Review Article

Association between estrogen and female patients with Alzheimer's disease: a meta-analysis

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Abstract: Objective: A number of studies have evaluated the estrogen level in female Alzheimer's disease (AD) patients with controversial conclusions. We conducted a meta-analysis to investigate the correlation between estrogen level and female AD patients. Methods: Studies on estrogen level in female AD patients were identified by searching of PubMed, EMBASE, Web of Science databases and Chinese database till May, 2016. The standard deviation of difference (SMD) and corresponding 95% confidence interval (CI) were to assess the strength of association. Results: 11 studies with a total of 577AD patients and 824 controls were included in this meta-analysis. The results showed that there was no difference of estrogen level between two groups. The standard deviation of difference (SMD) was -0.05 (95% CI: -0.41-0.31, random effect model). In addition, among these studies, 4 studies evaluated the correlation between testosterone and Alzheimer's disease, and the result demonstrated that higher level of testosterone was found in the Alzheimer patients, the SMD were 0.20 (95% CI: 0.06-0.35, fixed effect model). No significant publication bias was found in the studies. Conclusions: No significant difference of estrogen level is found between female AD patients and controls. However, more well-designed studies still need to be performed to verify this conclusion in the future.

Keywords: Estrogen level, female, Alzheimer's disease, meta-analysis

Introduction

Alzheimer's disease (AD) is the most common type of dementia and neurodegenerative disease characterized by memory impairments and loss of cognitive functions which leads to a lot of burden on persons and societies [1]. Currently, AD has become one of the leading causes of disability and death among the elderly [2, 3]. In consideration of its worldwide prevalence and that there is no effective cure for this disease, investigating its modifiable risk factors and find out how to efficaciously prevent it have always been essential and necessary in the field.

Some factors such as genetic, metabolic, and environmental have been broadly explored and discussed in the development and progression of AD [4, 5].

According to epidemiological studies, the risk of AD is higher for women than men, especially in elderly people. Some people consider that this has to do with estrogen levels felling sharply after menopause [6, 7]. Estrogen serving as a neuroprotectant and a neurotrophic agent [8], could promote neuronal cell survival, reduce neuronal injury, protect against neurotoxins, facilitate axonal sprouting and neuronal repair, and enhance synaptic transmission and neurogenesis [9]. Hormone-replacement therapy (HRT) has been proposed as a therapeutic approach to reduce the risk of developing AD and help patients with AD maintain their cognitive function [10, 11]. Some amounts of researches with inconsistent conclusions [12-14] have been done to investigate the association between estrogen and AD. Therefore, we carried out this meta-analysis employ a full-scale search of observational studies to calculate integrated effect sizes of estrogen for AD.

Methods

The study was conducted in accordance to Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations [15].

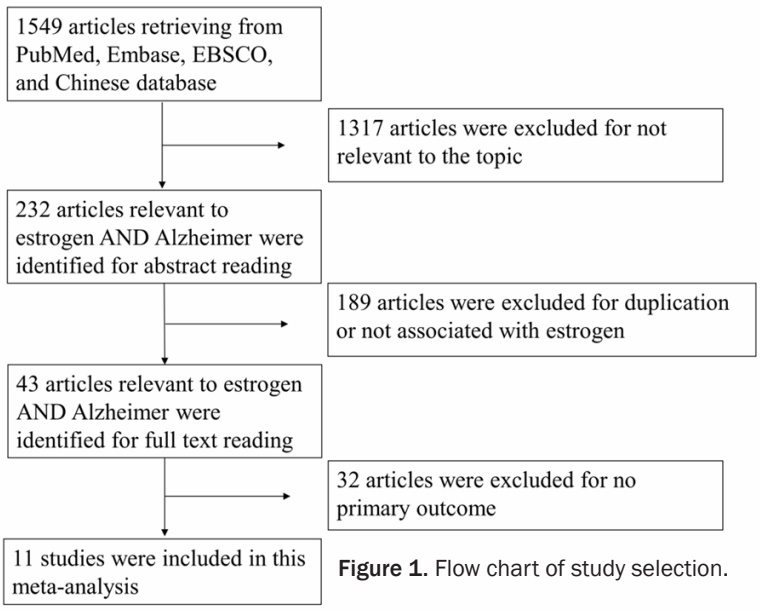

Figure 1. Flow chart of study selection.

Search strategy

Several databases including PubMed, Embase, Web of Science, and Chinese biomedical databases were electronically searched for eligible studies assessing the association of estrogen level and AD risk until May 2016. We used the following search criteria: ("estradiol" OR "estrogen" OR "sex hormone") AND ("Alzheimer" OR "dementia"), There were no restrictions on regions, sample size, or type of report so as to minimize the potential publication bias. In addition, we check the reference lists of retrieved articles to identify more relevant studies.

Inclusion and exclusion criteria

The eligible studies must meet the following criteria: (1) case-control studies or cohort studies; (2) reported estrogen level between two groups; (3) studies were published in English or Chinese language; (4) studies were excluded without primary endpoint. Moreover, meta-analyses, letters, reviews, and editorial articles were excluded. When authors published more than one article using the same sample data, only the most recent paper or paper with the larger sample size was selected.

Data extraction

Two reviewers independently searched and selected literatures and extracted relevant data, and disagreements were solved by the third investigator. The extracted data including: the first author, year of publication, country of origin, sample size, MMSE score, detecting parameters, etc.

Outcomes

The primary clinical endpoint measured was the estrogen level in the AD group and control group. The secondary outcomes were the record of other indicators like testosterone.

Statistical analysis

We used SMD and their corresponding 95% CI to assess the association between estrogen level and AD. Heterogeneity among included studies was examined by chi-square-based Q test and I^2 test. If the data showed no heterogeneity ($P>0.10$, $I^2<50\%$), Mantel-Haenszel fix effect model was used, otherwise DerSimonian-Laird random effect model was applied. Data were analyzed using STATA 11.0 SE (Stata Statistical Software, College Station, TX, USA, www.stata.com) software. In addition, sensitivity analysis was performed by omitting each study in order to investigate the influence of every single study on the overall risk estimation. Publication bias was quantitatively assessed by Egger's linear regression test and visual inspection of Begg's funnel plots.

Results

Literature search

1549 relevant studies were obtained by searching electronic databases. Of these, 1317 were excluded due to not relevant to the topic. On the basis of their title and abstract of the remaining 232 articles, 189 were excluded for duplication or not associated with estrogen. The full texts of the rest 43 articles were retrieved and read by two independent investigators. From these 43 articles, 32 articles were excluded because of no primary outcome. The remaining 11 articles [12-14, 16-23] which contained 577 patients with AD and 824 controls met all inclusion criteria and were included in the meta-analysis. The screening process was illustrated in **Figure 1**.

Table 1. Characeristics of included studies in the meta-analysis

Study	Country	Age (A/C) years		MMSE (A/C)		Other detecting parameters	Sample size (A/C)
Zhou 2002	China	82.2 (7.5)	82.0 (7.4)	/	/	FSH, T, BMI etc.	61/61
Yang 2006	China	70.26 (9.48)	70.61 (9.86)	13.12 (5.62)	24.32 (1.98)	FSH, LH, T etc.	23/23
Carlson 2000	Canada	75.9 (8.1)	74.8 (5.0)	19.3 (4.9)	/	Education, GDS Mood Scores, Socioeconomic Status, AD Duration, Age at onset	23/23
Manly 2000	American	78.2 (7.5)	73.9 (5.8)	/	/	education, APOE-[epsilon] 4 allele, estrone level etc.	50/93
SchoÈnknecht 2001	Germany	72.6 (8.8)	69.0 (6.8)	16.3 (6.7)	26.8 (1.9)	BMI, Aβ42, Aβ40, Tau protein	30/11
Cunningham 2001	Ireland	77.1 (6.0)	69.8 (6.3)	20.8 (3.2)	27.8 (1.7)	Education, GDS score, Testosterone, Androstenedione etc.	52/60
Rasmuson 2002	Sweden	76.4 (7.8)	75.4 (7.5)	17.0 (5.1)	29.6 (0.7)	Androstenedione, Testosterone, Cortisol etc.	21/12
Hogervorst 2003	UK	77 (8)	76 (8)	/	/	BMI, SHBG	66/62
Hoskin 2004	USA	80.74 (7.25)	74.88 (5.67)	/	/	DHEA, LH, FSH, SHBG, etc.	179/397
Paoletti 2004	Italy	77.26 (2.1)	76.01 (1.15)	21.48 (4.8)	30	BMI, Testosterone, SHBG, DHEAS etc.	64/72
Smith 2006	USA	76.5 (1.3)	77.0 (1.6)	20.1 (1.3)	29.4 (0.2)	Testosterone, DHT, 3α, 5α-THP etc.	8/10

Note: A: Alzheimer's disease; MMSE: Mini-Mental Status Examination; GDS: Geriatric Depression Scale; LH: Luteinizing hormone; FSH: Follicle Stimulating Hormone; T: testosterone; SHBG: Sex Hormone Binding Globulin; BMI: Body Mass Index; DHT: dihydrotestosterone; THP: Tetrakis Hydroxymethyl Phosphonium Sulfate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; DHEA: dehydroepiandrosterone; Aβ: amyloid-beta protein. Continuous variables were expressed with the mean and standard deviation (SD). Estrogen unit: 1 pg/ml = 3.67*pmol/L.

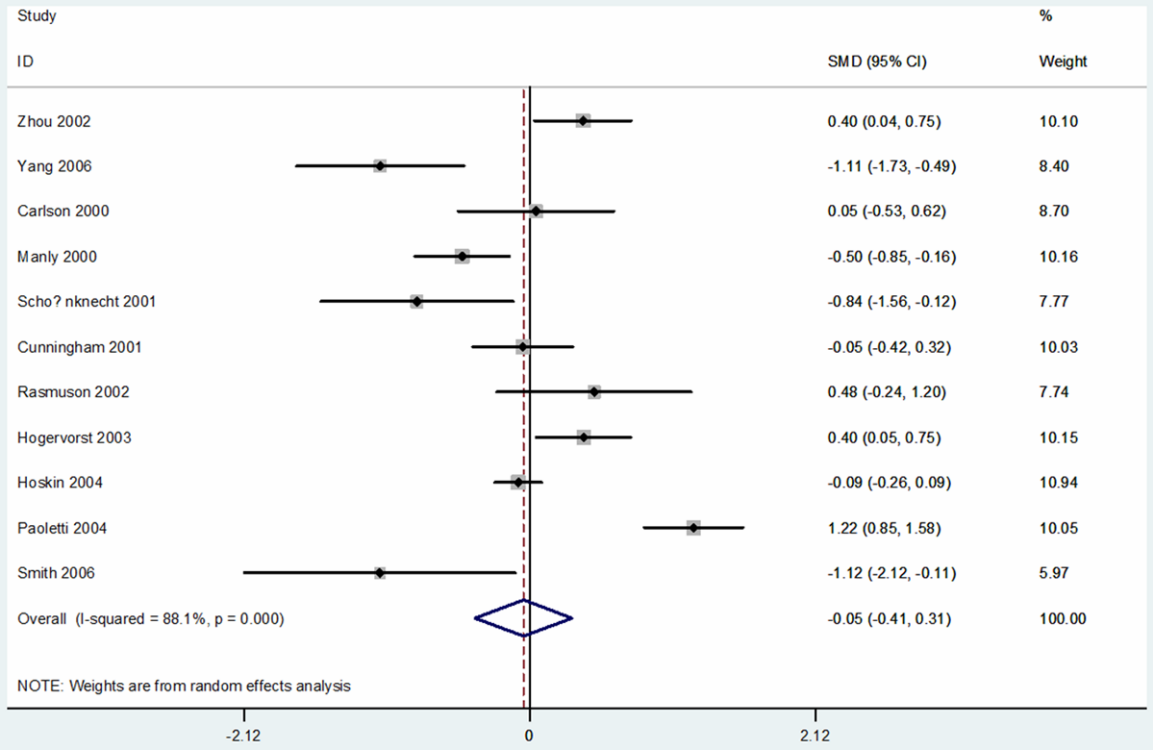

Figure 2. Forest plot with the random effects model between estrogen and female AD Patients. Standard mean difference (SMD) and 95% CI for each study are plotted on the graph. A comparison that does not cross the vertical line at SMD = 0 indicates significance.

Study characteristics

The characteristics of the included studies in this meta-analysis were given in **Table 1**. Among all these studies, 2 of China, 1 of Germany, 3 of American, 1 of Italy, 1 of Canada, 1 of Ireland, 1 of Sweden and 1 of UK. The mean age ranged from 70.26 to 82.2. The mean MMSE score in

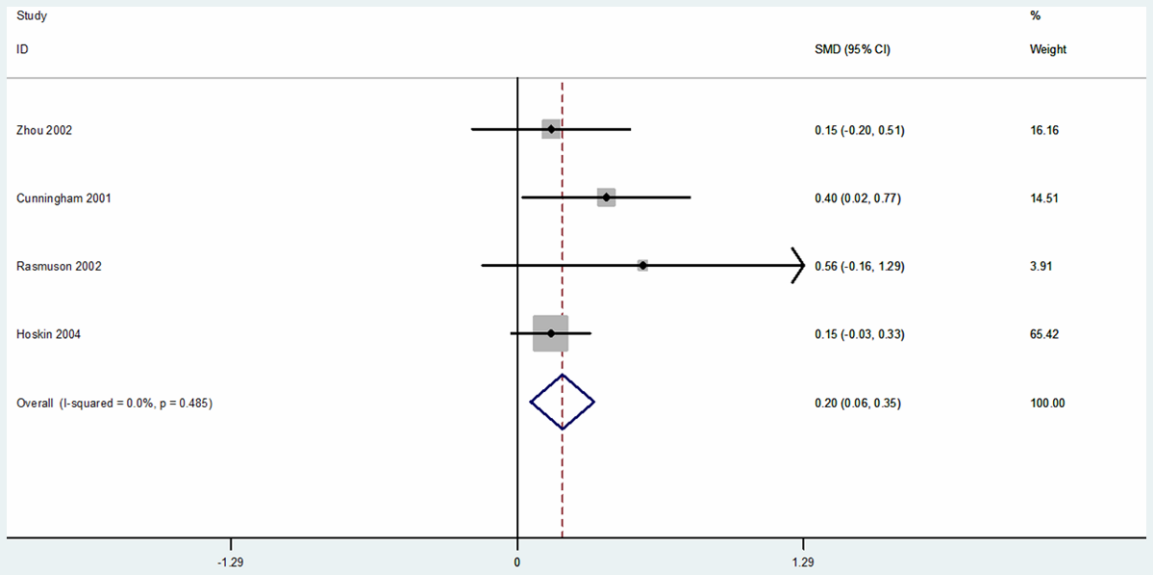

Figure 3. Forest plot with the fixed effects model between testosterone and female AD patients. Standard mean difference (SMD) and 95% CI for each study are plotted on the graph. A comparison that does not cross the vertical line at SMD = 0 indicates significance.

patients with AD ranged from 13.12 to 21.48. Other detecting parameters included follicle stimulating hormone (FSH), testosterone (T), Luteinizing Hormone (LH), Body Mass Index (BMI) etc.

Association between estrogen level and female AD patients

11 studies with a total of 577AD patients and 824 controls were included in this meta-analysis. As the **Figure 2** demonstrated, the result showed that there was no difference between female AD patients and controls. The SMD was -0.05 (95% CI: -0.41-0.31, random effect model, I^2>50%).

Association between testosterone and female AD patients

In addition, among these studies, 4 studies evaluated the correlation between testosterone and female AD patients, and the result demonstrated that lower level was found in the female AD patients, the SMD was 0.20 (95% CI: 0.06-0.35, fixed effect model), as indicated in **Figure 3**.

Sensitivity analysis

Sensitivity analyses were conducted by omitting individual studies sequentially. The results did not change under some conditions, the indicators for heterogeneity were reduced. Sensitivity study suggested that the results were stable and statistically robust.

Publication bias

Visual inspection of Begg's funnel plot showed substantial asymmetry (**Figure 4**). The Begg's rank correlation test indicated no evidence of publication bias among studies (P=0.64). Moreover, Egger's linear regression test also find no evidence of publication bias (P=0.67).

Discussion

The current meta-analysis was performed to investigate the association of estrogen level and AD. 11 clinical studies were identified, and the data was pooled and analyzed. Overall, we did not observed the differences between of the estrogen lever in both groups. Among the included studies, 4 articles concluded with no differences in estrogen level, whereas 7 articles with significance compared to control group and 4 papers with lower estrogen level in AD group. To our knowledge, this is the first meta-analysis examining the relationship between estrogen level and AD including all case control or cohort studies.

Since there is no reduction in female AD patients, estrogen, which may have the func-

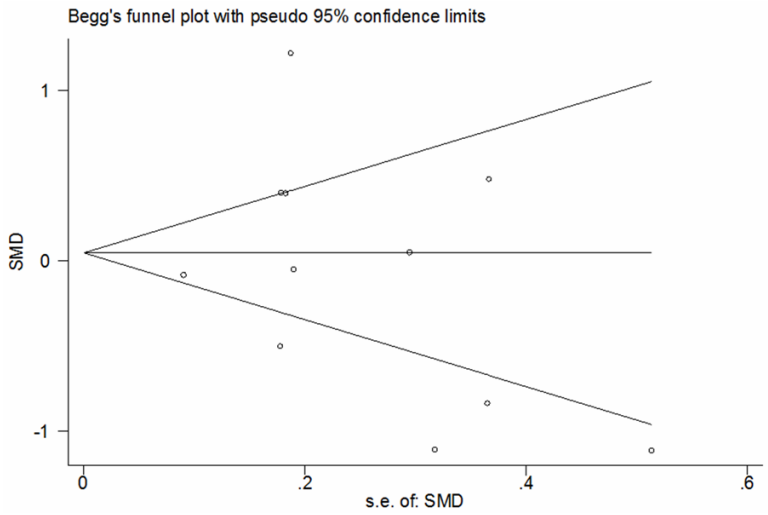

Figure 4. Begg's funnel plot testing potential publication bias among included studies.

tions of promoting the growth of nerve and nerve repair [8, 9], but not the key factor of the AD generated and developed. Therefore, hormone replacement therapy should have certain limitations itself for treatment of AD, which has been demonstrated by several studies [24-26].

A great many observational studies, most of which are retrospective, suggest protective connections between hormone replacement therapy and risk of all-cause dementia and Alzheimer's disease dementia [27]. Substantial body of animal or in vitro research essustained the idea that replacement estrogen might reduce dementia-related neurodegeneration through the following steps: accelerating cholinergic activity, protecting from toxic insult, stimulation of neuron formation, and reducing formation and enhanced clearance of β-amyloid [28, 29]. Yet, it was also acknowledged that hormonetherapy could increase inflammatory markers and hazard of stroke [30, 31], which approximately are associated with increased dementia risk. Thus, it is difficult to say estrogen is definitely associated with the initiation and development of AD.

The reasons of heterogeneity in this meta-analysis may come from the following points: the cognitive function level in each study varies differently, which we could see in the MMSE score; age differences in some articles might contribute to the heterogeneity; in addition, detection method of estrogen could also give rise to some heterogeneity.

In conclusion, based on our results of pooled analysis, the estrogen level in female AD patients is not dropping significantly compared that in the control group. However, due to the limitations of methodology, more well-designed clinical studies are still needed to test the results.

Disclosure of conflict of interest

None.

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