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Original article

Meta-analysis Evaluating the Efficacy of Statins to Prevent Alzheimer's Disease

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ABSTRACT

Background and aims*. Statins are class of drugs that reduce cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase. We carried out this meta-analysis to investigate the correlation between use of statins and the reduction of risk of Alzheimer's disease (AD), focusing on lipophilicity and hydrophilicity of statins as importatnt determinants of the efficacy of the drugs.* ***Methods****. A systemic search was performed of PubMed, Google Scholar databases from their inception to march 2022. Adults with no history of cognitive dysfunction treated with statins were included from high- quality cohort studies.* ***Results****.We included eight cohort studies that reported relative risks with 95% confidence intervals for this correlation. A random effects model was used to calculate the summary risk estimates. Studies eligible for analysis involved 707637 participants. The summary of relative risk of Alzheimer's disease for the statins user was 0.672 (95% CI = 0.479–0.943; P =0.021). In addition, the secondary anaylses showed that both lipophilic and hydrophilic statins induced reduction in the risk of Alzheimer's disease. The summary of relative risk of Alzheimer's disease for both hydrophilic and lipophilic statins user were 0.862 (95% CI= 0.0.75-0.991; p = 0.037),0.836 (95% CI= 0.802- 0.871; P= 0.000) respectively.* ***Conclusions****. Findings of the present meta-analysis show that statin use was associated with a reduced risk of Alzheimer's disease (AD), and both hydrohpilic and lipophilic statins are effective in risk reduction.*

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INTRODUCTION

Alzheimer disease (AD) is a heterogeneous disease with a complex pathobiology. The neuropathological hallmarks of the disease include accumulation of senile plaques, extracellular β-amyloid deposition as neuritic plaques and intracellular accumulation of hyperphosphorylated tau protein as neurofibrillary tangles remains the primary neuropathologic criteria for AD [1]. There is evidence supporting that Aβ initiates the pathogenesis of AD [2,3]. However, the failure of clinical trials of "anti-Aβ" therapies indicates that the intervention should be applied earlier, because Aβ deposition commences decades before the development of clinical symptoms of AD [4,5] .The most proposed protective mechanism of statin therapy is by reducing the microvascular and large blood vessel damage caused by hyperlipidemia, and thus reduces the risk of stroke and vascular dementia and reduce the formation of amyloid- β protein by reducing plasma cholesterol [6]. Also by minimizing the inflammatory response induced by amyloid- β protein. It has been shown that statins can suppress the production of microglial interleukin-1 β, TNF and nitric oxide [7]. Furthermore, reduction in the formation of isoprenoids which are one of the downstream products of cholesterol synthesis. Certain types of these isoprenoids such as farnesylpyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) and they are suggested that statin play a role in the prenylation of some GTPases which are involved in the pathogenesis of Alzheimer's disease [8].

Many clinical studies have been reported that statins could reduce the incidence of Alzheimer's disease [9], and other a prospective cohort studies suggested that use of hydroxyl methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors(statins), which are widely prescribed for the treatment of hypercholesterolemia patients, decreases the incidence of AD by half [10]. The protective effect of statin on Alzheimer disease (AD) is still controversial, probably due to the debate about when to start the use of statins, an early statin use from midlife was significantly associated with risk reduction [11]. However, controversy exists regarding whether statins have therapeutic effects on AD. In this regard we

conducted meta-analysis study to test whether statins are clinically effective in reducing the incidence of AD in human, and which group of these agent will be more effective in terms of their lipid solubility.

METHODS

Study design

This meta-analysis has been performed and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines and recommendations [12,13]. Because all the analyses were performed on the basis of previous published studies. No ethical approval or informed agreement was required.

Search strategy

A systematic and comprehensive literature search was performed on Google Scholar, PubMed, EMBASE databases, recover eligible articles from January 2000 up to March 2022.

Studies selection and the Eligibility criteria

According to PRISMA guidelines, all records retrieved from the search were systematically and sequentially screened, according to titles and abstracts. Each article included after the abstract's screening phase was independently evaluated for full-text eligibility (Fig1). We included studies which met the following criteria: 1) Full text articles of observational studies published in English language. 2) Involved a cohort of cognitively intact participants aged 45 years or older. 3) Statin users compared to non-users with minimum follow up period not less than one year. 4) Reporting an adjusted estimate (RR)/hazard ratio and 95% confidence intervals (CIs) for AD risk as outcome.

Data extraction and quality assessment

Data from the included studies were extracted independently by three authors, were extracted using a standardized electronic form. the collected data were study design and cohort baseline characteristics. An overall, synthetic grade was produced for each study. We accessed the quality of the included studies based on the items of modified Newcastle-Ottawa Scale, including patient selection, study group comparability and outcome assessment [14]. The observational studies scored 0 to 9, studies were categorized as high quality, medium quality or low quality based on the received score of 9, 7-8, ≤6 stars respectively for the inclusion decision, quality assess were reviewed by three authors. Conflicting opinions were discussed among authors and an agreement was reached.

Study characteristics

The characteristics of the selected studies are presented in Table 1. The eight cohort studies [17–24] were published between 2004 and 2020. The number of participants ranged from 2392 to 399979, with a sum of 707637. The length of follow up ranged from 1 to 8 years, with a median of 4.7 years. Adjustment for potential confounding factors differed across studies, and most risk estimates were adjusted for age, sex, education.

Statistical analysis

Our main analyses were focused on the associations between statin use and risk of AD. The RR was used as the common measure of association across studies. In this analysis the outcome of interest was the risk of Alzheimer's disease among participants using statins compared with statins non user. A summary of adjusted hazard ratios with a 95% CI were pooled to reduce the effect of potential confounders. We carried out secondary analyses which include four datasets to assess the impacts of hydrophilicity and lipophilicity of statins on risk reduction.

Meta-analysis has been performed using the comprehensive meta-analysis software were, a trial version 3.3. Heterogeneity of involved studies has been assessed by using Q-statistic and the I^2-statistic, which is a quantitative measure of inconsistency across studies [15]. Potential publication bias was assessed by Egger linear regression test and funnel plot [16]. Overall effect estimate was identified using random effect model to reduce the possibility of heterogeneity among included studies. Subgroup analysis has also been performed to reduce heterogeneity based on statin lipophilicity. All statistical analysis was performed using significance level of p-value ≤ 0.05. The extracted data for each study also included mean age of participants; mean follow up period, percent of males each study group, and study design.

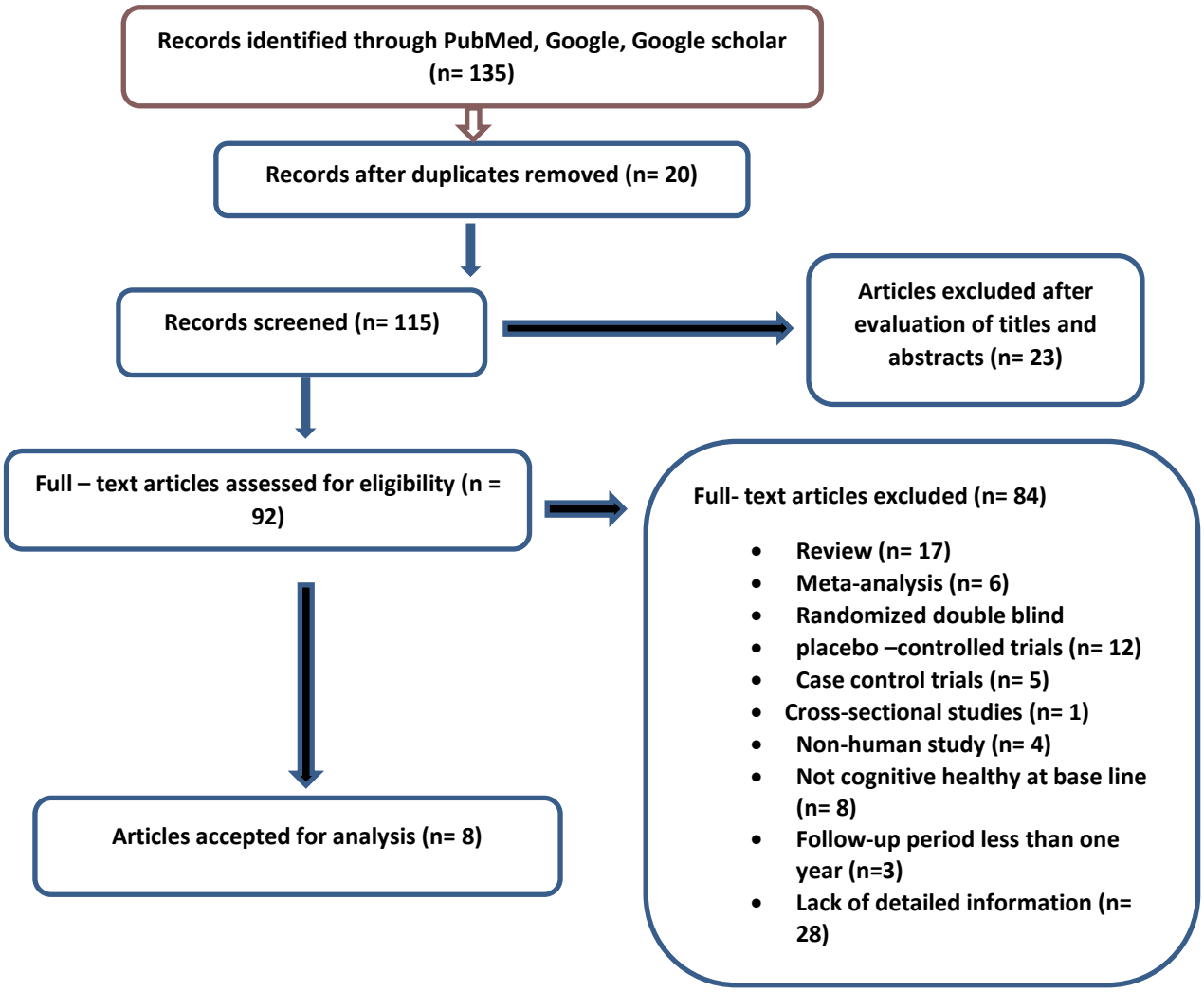

Figure 1. *PRISMA flowchart of study selection for current meta-analysis*

Statistical Methods

The purpose of this study is to identify the statistical tool that used in the meta-analysis to clarify how to measure the heterogeneity. In the statistical methods section, involved on Cochran's Q, τ^2 statistic, I^2statistic, Estimation of confidence intervals and Egger regression.

Cochran's Q

One of the classical methods to estimate the degree of heterogeneity in meta-analysis, also known as Q statistic that follows Chi-square distribution [17].Q statistic can be defined as:

$$Q = \sum_{i=1}^{k} W_i {Y_i}^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i} \quad (1)$$

Where W_i represent is study weight, Y_i denote by the effect size of the study and M is the summary effect size and k is the studies number. Cochran**'s** Q depends on calculating the deviation in each effect size from the square mean, and the weights by variance inverse for studies, the weighted sum squares(WSS) for all studies. To estimate the expected mean of Q where df degrees freedom and k is the studies number by, $df = k - 1$, and the difference between individual study effect and pooled effect across a study which reflects the variation $Q - df$, [18].

T^2 statistic

The τ^2 statistic known as tau squared that depends on measuring the variance of the true effect size in the meta-analysis.

$$T^2 = \frac{Q-df}{C} \qquad (2) \quad , \text{ Where } C \text{ is } \quad C = \sum_{i=1}^{k} W_i - \frac{\sum {W_i}^2}{\sum W_i}$$

Where T is the standard deviation of T^2. $SE(T) = T = \sqrt{T^2}$

I^2-statistic

The I^2 statistic as a method suggested by [19], to measure the proportion in the observed variance that reflects real differences in the effect size and this proportion could assist as a type of noise ratio signal as well as, ranging between (0-100)%, [18]. I^2 It can be calculated by:

$$I^2 = \left(\frac{Q-df}{Q}\right) \times 100\% \implies I^2 = \left(\frac{\tau^2}{\tau^2 + V_Y}\right) \quad (3)$$

The equation (3) is the proportion of real to overall variance in observed effect estimates.

Estimation of upper and lower limits in meta-analysis

The importance of predication of confidence intervals to understand both mean effect size and true effect size to how distributed around mean in random effect analysis, in addition to determine the estimation error in mean, as well as the summary effect in forest plot that represented by diamond through estimation of confidence intervals. The expectation of lower and upper limit supposed the mean of effect size M and the standard deviation of true effect size τ are knew under consideration to follow normal distribution, with 95% confidence intervals that equal to $Z_{0.95} = 1.96$. [18] Then can be calculated by:

$$Lower\ limit_{pre} = M - Z_\alpha \sqrt{\tau^2} \quad and, \quad Upper\ limit_{pre} = M + Z_\alpha \sqrt{\tau^2} \quad (4)$$

Egger regression test

The Egger test is normally used to measure potential publication bias in a meta-analysis through an asymmetry of funnel plot suggested by [16] ,in addition this method depends on a linear regression of the involvement effect estimates on the weight of standard errors via inverse variance. Assume a meta-analysis assembles 1,2,3,…, k of studies, each study indices an effect size Y_i, with S_I^2 is variance within the study, where M is the general mean of effect size under consideration in the random effect model, suppose $Y_I \sim N(M, S_I^2)$ and $M_I \sim N(M, \tau^2)$ where $(\tau^2 = 0)$ is the variance between studies [16]. The standardized effect size of the regression model (Y_i/S_I) on the equivalent precisions $(1/S_I)$ then can be specified by:

$$Y_I/S_I = \beta_0 + M * 1/S_I + \epsilon_I \,, \quad \epsilon_I \sim N(0, \sigma_\epsilon^2) \qquad (5)$$

The Egger regression test of separating by marginal standard deviation division $(S_I^2 + \tau^2)^{1/2}$, the equation (5) changed by :

$$Y_I\,(S_I^2 + \tau^2)^{-1/2} = \beta_0 + M * (S_I^2 + \tau^2)^{-1/2} + \epsilon_I \,, \quad \epsilon_I \sim N(0, \sigma_\epsilon^2) \quad (6)$$

The estimation of regression coefficients by the least square method in equation (6) are $\widehat{\beta_0}$ and $\widehat{M}$ that can be given by:

$T_I = \widehat{\beta_0}$ (7)

Where T_I divided by standard error and follow t distribution with (k-1) degree of freedom, lastly in equation (7) T_I can assist as measure publication bias in meta- analysis [20].

RESULTS

Statins and incident Alzheimer disease

Overall, 8 observational studies were included in the analysis of AD risk (Table 1) [21-28]. We found that participants who received statins were significantly less likely to develop AD compared to those who were not treated with statins (a RR from 8 studies = 0.672 , 95% CI = 0.479 - 0.943, P = 0.021). There was no evidence of publication bias according to Egger test (t- value = 0.349, df = 6, P= 0.738) and the visual inspection of the funnel plot which was used to evaluate the possible publication bias (Figure 3). The Egger's regression test of the funnel asymmetry, showed no observed publication bias (p< 0.021). We used Duval and Tweedies trim and

fill method toward the right of mean to adjust values of the effect size estimates to publication bias and the results tend to be insignificat (aRR= 0.671, 95%, CI= 0.478 - 0.942). Additionally, a significant heterogeneity was found (Q value = 368.299, df= 7 ,I^2=98.09, p= 0.00).

Table 1: Characteristic of included studies.TP= Total participants, RR= Risk ratio, and NOS= Newcastle= Ottawa scale

Author	Country	Study design	Mean age Male %	TP	Mean Follow up years	Study peroid	Out come	RR	NOS
Ge Li 2010	USA	Prospective	≥65 NA	3392	6.1	NA	AD	0.44(0.249-0.777)	7
Jui-ming 2014	Taiwan	Retrospective	≥50 NA	2400	8	2000-2008	AD	0.480(0.302--0.764)	7
Zandi 2005	USA	Prospective	75.5 ±7.1 NA	5092	5	1995-2000	AD	1.190(0.405-3.490)	8
GL i 2004	USA	Prospective	70.5±6.1 Male 40.2%	2392	3.9		AD	0.820(0.460-1.461)	7
Kerstin 2012	USA	Prospective	78.6±3.3 Male 54%	3069	6	NA	AD	0.570(0.386-0.841)	8
Georgina 2020	USA	Retrospective	45 Male 52.5%	288515	3	NA	AD	0.464(0.440-0.490)	8
Julie-m 2017	USA	Retrospective	≥65 NA	399979	7.2	2006-2013	AD	0.862(0.832-0.893)	8
Thomas D 2005	USA	Prospective	72.3±5.6 Male 33.7%	2798	1	1991-1994	AD	1.210(0.763-1.918)	8

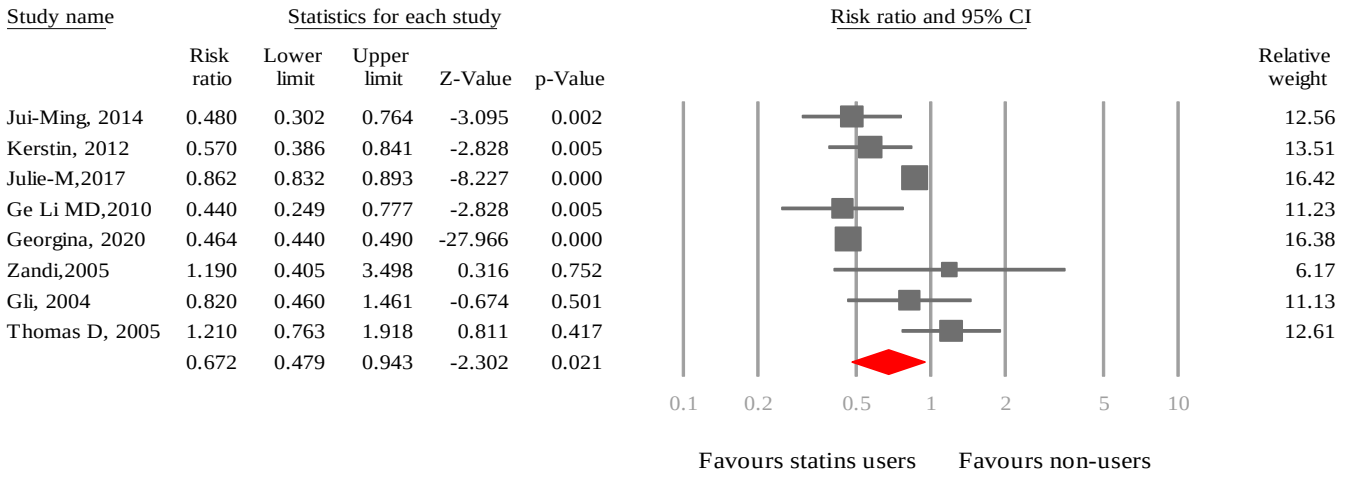

Figure 2. The forest plot of random-effects meta-analyses of the use of statins and incidence of Alzeimers disease

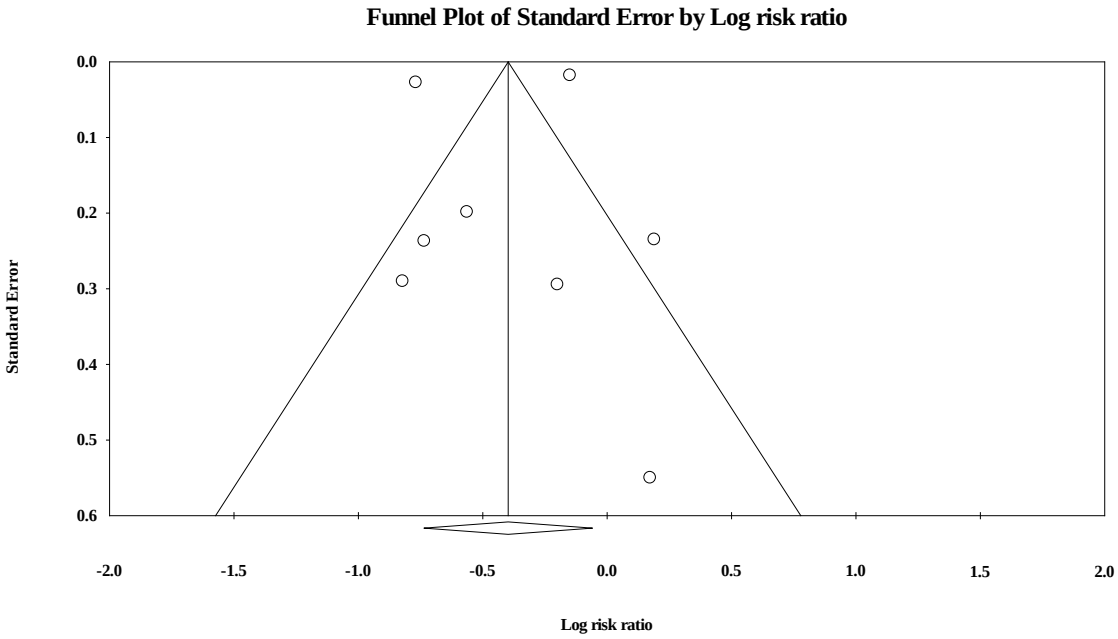

Figure 3. Funnel plot. (RR, risk ratio).

Secondary analysis

Across three studies (*Figure 4*),the secondary analysis showed that the use of of hydrophilic statins reduced the risk of incident AD the statistical trend level (a RR= 0.862; CI= 0.750 – 0.991 ; P= 0.037). There was no evidence of publication bias according to Egger test (t- value = 0.365 , df = 5 , P= 0.252). we used Duval and Tweedies trim and fill method toward the right of mean to adjust values of the effect size estimates to publication bias and the results tend to insignificant (aRR= 0.862, 95%, CI= 0.749 - 0.99, Q-value= 4.0928). Additionally ,no significant heterogeneity was found (Q value = 4.093, df= 5 ,I^2=26.702, p-value= 0.252).

While the use of lipophilic statins was associated with reduced risk of AD (a RR =0.836 ; CI= 0.802- 0.871; P= 0.000) (*Figure 5*) . There was no evidence of publication bias according to Egger test (t- value = 0.311 , df = 2 , P= 0.785). we used Duval and Tweedies trim and fill method toward the right of mean to adjust values of the effect size estimates to publication bias and the results tend to insignificant (aRR= 0.835, 95%, CI= 0.802 - 0.87, Q-value= 1.314). Additionally , no significant heterogeneity was found (Q value = 1.315, df= 3 ,I^2=0.00, p-value= 0.726).

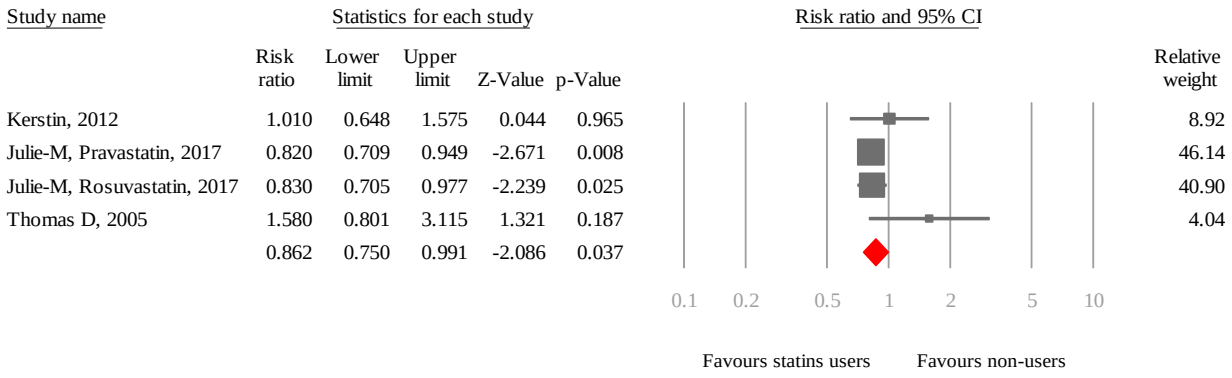

Figure 4. Effect of Hydrophilic statin use on incidence of AD

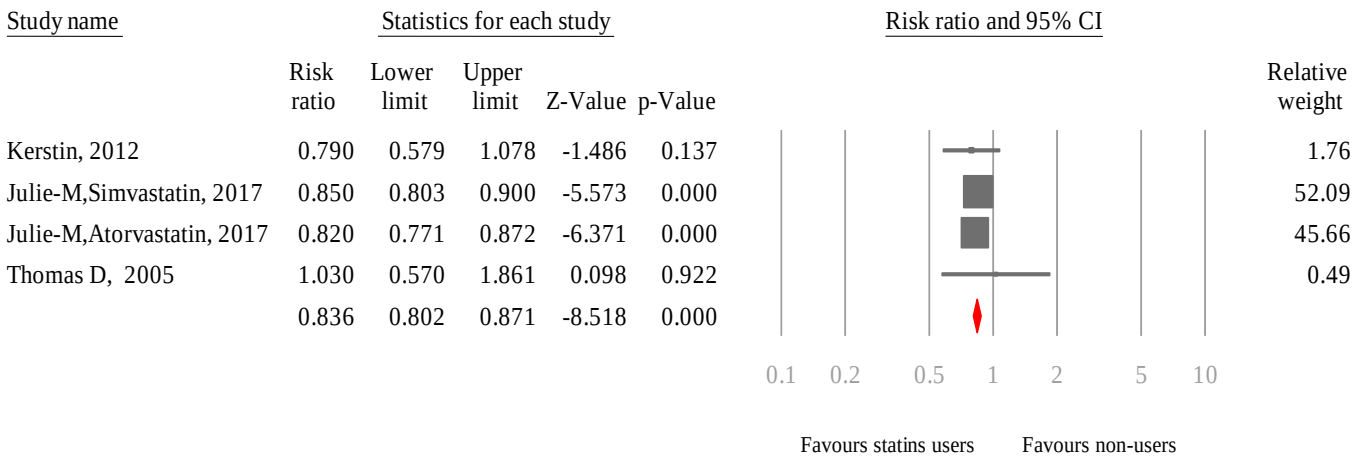

Figure 5. Effect of lipophilic statin use on incidence of AD

DISCUSSION

With the help of data base information, we present our meta-analysis of 8 observational studies estimating the value of statins in reduction the incidence of Alzheimer's disease (AD). This study include 707637 individuals without impairment of cognitive function ,and mean age ≥ 65year. It is noteworthy that statins associated with remarkable risk reduction of 62.5% of AD, these data support many previous published meta-analyses that suggest the use of statins have a protective effect against AD [29-31]. As well as our results are compatible with the results of some observational and randomized-controlled studies [32-37]. Additionally analyses of AD incidence among diabetic patients showed that a regular statin use was associated with a 13% risk reduction [22]. In a Multi-Institutional Research in Alzheimer's Genetic Epidemiology study, other study provided evidence that statins were associated with lowered risk of AD in the elderly population [37]. It has been concluded that statin therapy exerts a beneficial effect on profound dementia of AD,which are consistent with our results [38].

The quality of the evidence was high because of the current study was designed by including studies with higher methodological quality and lower bias ,and the findings of our study are fully adjusted in age, gender, and different types of covariates and morbidities.

On the contrary, there are meta-analysis showed that statin medications might not be useful in Alzheimer's disease. Furtheremore, a systematic review about the efficacy of statins for the treatment of Alzheimer's disease, they conclude that statins don't appear to produce significant aids to patients with AD [39,40].

Compared to above ,we note that most of studies including our analysis suggest that statins may be protect selected patients from the incidence of Alzheimer's disease.

As the pathophysiology of AD still not be fully clarified, sorts of biological mechanisms that might explain the correlation between statins use and Alzheimer's disease (AD). It has been proven that increased serum total cholesterol level in midlife is associated with higher risk of developing dementia later in life including AD and VAD [41]. Since increased cholesterol level in brain was shown to be associated with an elevated level of beta-amyloid protein (β-AP) production, which is a known pathological biomarker for AD [6]. As that high levels of serum cholesterol may promote the pathological processes that lead to AD [42]. Statins are effective treatments for hypercholesterolemia, a possible risk factor for both dementia and AD [32]. Statins lower the level of 24S-hydroxycholesterol, a major product of brain cholesterol metabolism, in patients with AD [43,44].

The effectiveness of statins in AD may be attributed to the reduction of athermanous plaque formation and prevention of cognitive impairment, potent anti-inflammatory properties of statins induce the endothelial nitric oxide synthesis, which is vital for vascular function [45], as it regulates cerebral blood flow and increases cerebral vasomotor reactivity [46].

Furthermore, the regulation of low density lipoprotein (LDL) oxidation by statins play a significant role in dementia prevention by the reduction of atherosclerosis [47]. In 2001, it was detected a decrease in serum Aβ levels which is

considered a neuro-pathological hallmark of the disease after treatment with various doses of lovastatin in patients with elevated LDL cholesterol levels ,but not diagnosed with AD [48]. Statins significantly suppress tumor necrosis factor-alpha synthesis in microglia and reduce neuronal damage [49]. Many studies have discovered a relationship between TNF-alpha and the causation of AD, The first indication which identified the presence of TNF at amyloidogenic plaques in post-mortem analysis of AD brains and this provoked investigations about the association between AD and TNF and its receptors [50]. The genetic association between the TNF receptors TNFR1 and TNFR2 reside on chromosome 1p and chromosome 12p, respectively, and these regions show a genetic linkage to late-onset AD.The discovery of up-regulation of TNF-α in the brain and plasma of AD patients and up-regulation of TNFR1 in the AD brain further consolidated the relationship among them [51-53]. These various possible mechanisms suggest that statins have defensive properties against AD.

When we studied the preference of using lipophilic statins over hydrophilic ones , no difference was observed between the two groups in the prevention of AD. Both hydrophilic and lipophilic statins appear to produce similar and significant reductions in the risk of AD. Our results are in line with Previously published meta-analysis [54]. In contrast with previous studies reporting a protective effect limited to lipophilic statins [55].

Worthy to mention that, this meta-analysis has been run on a small number of publications, so the aforementioned point may be required further investigations.

There is a study showed the pharmacogenecity have a crucial role in detremintion of therapeutic response to statins and antihypertensive drugs in AD patients [56]. Apo lipoprotein E(APOE) is a glycoprotein has an important role in lipid metabolism in the brain and other tissues and it has different isoforms according to different distribution of APOE gene alleles among the individuals [57]. Furthermore, persons have APOE4 polymorphism their lipid profile showing low HDLC , high LDLC, and TG levels [58]. All previous lipoproteins levels can be controlled by using statins. It thought that APOE4 gene alleles are responsible for AD pathogenesis and formation of amyloid plagues [59]. Seemingly, APOE4 might be the meeting point between using of statins and decreasing risk of AD.A novel strategy in treatment of AD by targeting APOE4 gene by employing different strategies for instance, anti APOE4 immunotherapy , and structural modification of APOE4 , and others but not yet established [60]. Focusing on preventive measures by using statins for highly suspected population to reduce AD risk appears cost effective ,and accessible way at the present time ,until new therapeutic methods are proving their worth.

Finaly, the current meta-analysis support the evidence of using of statins can reduce the incidence of Alzheimer's disease, regardless of lipophilicity or hydophilcity of these drugs.

CONCLUSION

Results of this meta-analysis of observational studies suggest that statins are unlikely to cause AD or dementia and has no undesirable effect on cognitive function, and can be considered as a safe drug class to treat elderly patients with cardiovascular disease. Our results showed that statin use is significantly associated with a decreased risk of AD. Considering the suggestion presented in our meta-analysis, it is reasonable that statins can contribute to prevent dementia risk because of their role in high total cholesterol and beta-amyloid protein (β-AP) reduction. Furthermore statins reduce AD risk irrespective to their lipophilicty. Our findings highlight that population-based data on the association of statin use and AD risk reduction remain limited, and that further studies should be done to precise the role of statins in the AD risk reduction.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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