

## Original Article

# Correlation between serum high-density lipoprotein level and senile dementia risk: a meta analysis

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**Abstract:** Senile dementia including Alzheimer's disease (AD) and vascular dementia (VaD), are the major disease for Chinese aged and show the high risk of lethal and mutilation. However, there is not decisional conclusion for the relationships with serum high-density lipoprotein (HDL) and senile dementia. This study aims to explore relationships with serum high-density lipoprotein (HDL) and senile dementia by Meta analysis. We found that there was a significant difference in HDL level for normal people and Alzheimer's disease patients; meanwhile, there was a significant difference in HDL level for Alzheimer's disease risk. However, there is significant correlation between HDL level and vascular dementia.

**Keywords:** Meta analysis, high-density lipoprotein, senile dementia

## Introduction

There are mainly 2 types of dementia, namely Alzheimer's disease (AD) and vascular dementia (VaD). AD is a neurodegenerative disease characterized by its insidious onset, progressive development, frequently occurrence in the elderly and high incidence rate. VaD refers to severe cognitive dysfunction syndrome resulting from ischemic stroke, hemorrhagic stroke and cerebral vascular diseases causing hypoperfusion in memory, cognition, behavior and other brain regions. Some studies suggest that serum high-density lipoprotein (HDL) content and senile dementia onset risk may be correlated, but many study results are controversial.

Therefore, the relevant literatures were retrieved and the studies were quantitative consolidated using meta-analysis method to comprehensively assess the correlation between HDL level and AD or VaD incidence.

## Study methods

### Retrieval strategy

The relevant clinical studies were searched in PubMed, EMBASE, Cochrane and other data-

bases using literature retrieval and related methods. The retrieval ending date was April 2015. The retrieval keywords were Alzheimer's disease, vascular dementia and high density lipoprotein.

The retrieval strategy was: (Alzheimer\* OR (vascular dementia) OR AD OR VaD OR VD) AND (((high density lipoprotein) OR HDL) AND (plasma OR serum OR (plasma lipid))) AND risk.

### Literature screening

The retrieved literatures were screened gradually by the title, abstract and full text. Literature screening was conducted simultaneously by 2 investigators; all disagreements were addressed through discussion with the third investigator.

Inclusion criteria: 1) The studies conducted comparison between normal individuals and patients with AD or VaD; 2) The included studies analyzed the incidence of AD corresponding to serum HDL or different concentrations of HDL; 3) The studies provided the specific diagnostic criteria for patients with AD or VaD; 4) The included studies were observational; 5) The

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literatures were in English and the study subjects were human.

Exclusion criteria: 1) Reviews, meeting excerpts, correspondence, etc. were excluded; 2) Studies involving patients with non-senile dementia (AD/VaD) as the study subjects were excluded; 3) Studies without providing HDL concentration (AD vs. control or VaD vs. control) or relation between HDL and AD/VaD onset risk were excluded; 4) Studies without obtaining serum samples from surviving patients with senile dementia (AD/VaD) were excluded.

## *Data extraction and study quality evaluation*

Data extraction and quality evaluation were also conducted by 2 investigators independently; all disagreements were addressed through discussion with the third investigator. The extracted data included: the first author, publication year, study type, time period covered by the cases, country, follow-up time, included population, diagnostic criteria, grouping results, number of cases included in each group, age, HDL-C concentration, AD/VaD onset risk.

NOS (Newcastle-Ottawa Scale) was used to evaluate cohort studies and case-control studies [1], AHRQ cross-sectional study evaluation criteria were selected to evaluate cross-sectional studies [2].

## *Statistical analysis*

This meta-analysis mainly compared AD group, VaD group and healthy control group. AD or VaD onset risk was consolidated using risk ratio (RR) and its 95% CI as the effect size in order to assess the correlation between HDL concentration and AD/VaD onset risk. HDL-C concentration was consolidated using weight mean difference (WMD) and its 95% CI as the effect size. Cochran Q statistics and  $I^2$ -test [3] were used to examine the heterogeneity between different studies;  $P < 0.05$  or  $I^2 > 50\%$  indicated the presence of heterogeneity between different studies, accordingly, the random effect model was selected; otherwise, the fixed effect model was selected. Sub-group analysis of the included studies was carried out by grouping of different study types. All statistical analysis was completed with RevMan 5.3. The occurrence of publication bias analysis was investigated by Begg test and by visual inspection of funnel plots.

## *Sensitivity analysis*

To assess the sensitivity of this meta-analysis, we rejected the included literatures one by one to examine the combined results; if the conclusions were consistent before and after the literature was rejected, stable conclusion was indicated; otherwise, unstable conclusion was indicated.

## **Study results**

### *Literature retrieval*

A total of 353 literatures (PubMed: 157, Cochrane library: 4, Embase: 192) were retrieved, 315 literatures remained after removing 38 repeated literatures; 62 studies remained after rejecting 253 by title screening; 30 studies remained and entered into full text review after rejecting 32 studies (4 reviews, 9 meeting excerpts, 5 non-clinical studies, 14 studies unrelated to HDL and AD onset risk). After rejecting 13 studies for lacking HDL-related data, 4 literatures for very low quality, 2 meeting excerpts and 1 study for too few cases from the 30 studies, a total of 10 literatures were finally included [4-13]. The specific literature screening process was shown in **Figure 1**.

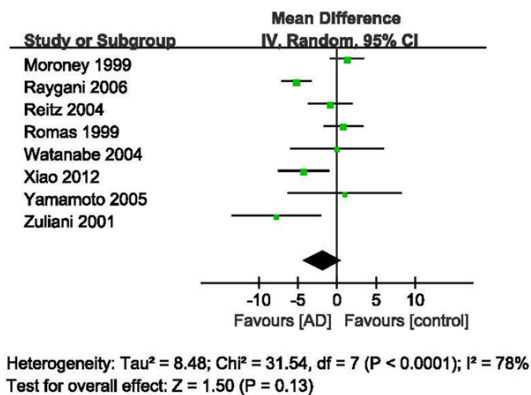
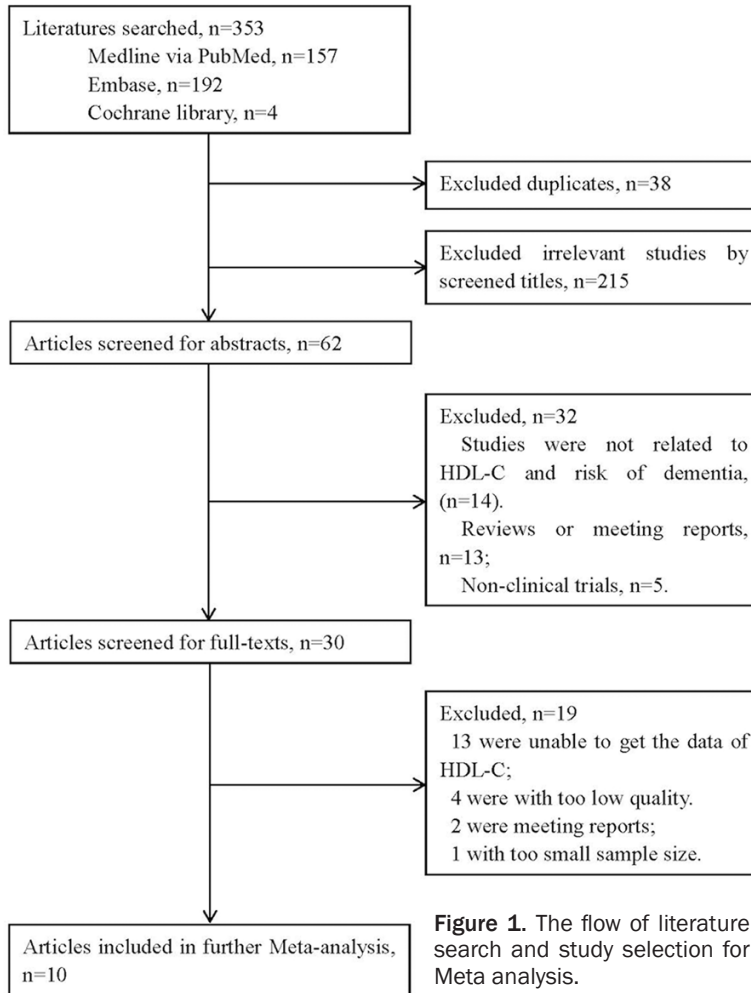
### *Study characteristics*

This meta-analysis included a total of 10 literatures that were all observational studies, among which, 4 were cohort studies [4, 5, 7, 8], 4 were case-control studies [6, 10-12], and 2 were cross-sectional studies [9, 13]. The dementia status of included cases was diagnosed by an overall consideration of the medication history, physical and neurological examinations, and neuropsychological scores. Most studies diagnosed senile dementia with DSM (Diagnostic and Statistical Manual) criteria, AD with NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria), and VaD with NINDS-AIREN (National Institute of Neurological Disorders and Stroke with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences) criteria.

### *Quality evaluation*

This meta-analysis strictly controlled the quality of included literatures; the 4 included cohort

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**Figure 2.** The forest plot for AD-HDL-C for Meta analysis. AD: Alzheimer's disease; SD: standard deviation; IV: Inverse Variance; Random: random effect model; CI: confidence interval.

studies had higher quality and the NOS scores were all  $\geq 7$  points. Three of the 4 case-control studies had higher quality [6, 10, 11]. For the 2 cross-sectional studies, the study by Romas et

al [9] had higher quality and the AHRQ score was 7.

## Outcome comparison

### AD vs. healthy control

**HDL-C concentration:** Eight studies compared the difference in HDL-C concentration between AD group and healthy control group; the heterogeneity test results showed that there was significant heterogeneity among the included studies ( $P < 0.01$ ,  $I^2 = 78\%$ ); after combination using random effect model, the result was  $WMD = -1.86$  (95% CI: -4.29, 0.57) (**Figure 2**); the results showed that HDL-C concentration was lower in AD group than in healthy control group, but the difference was insignificant ( $P = 0.13$ ). The included 8 studies were grouped for sub-group analysis according to study type (cohort study, case-control study and cross-sectional study). The heterogeneity test results showed cohort study ( $P = 0.24$ ,  $I^2 = 29\%$ ) and case-control study ( $P = 0.18$ ,  $I^2 = 38\%$ ); the 2

sub-groups had no significant heterogeneity while the cross-sectional studies still had significant heterogeneity ( $P = 0.007$ ,  $I^2 = 86\%$ ). The combined results showed that HDL-C concentration was lower in AD group than in healthy control group in case-control study sub-group, the difference had significance ( $WMD = -3.64$  (95% CI: -6.06, -1.21),  $P = 0.003$ ) (**Figure 3**).

**HDL-C and AD onset risk:** Four studies reported the correlation between HDL concentration and AD onset risk. A total of 2347 cases (AD group: 408, healthy control group: 1939) were included. In these studies, HDL-C concentration was divided into 4 gradient levels (Q1, Q2, Q3 and Q4 represented the 4 grades of serum HDL-C concentration from the lowest to the highest, respectively); AD onset status corresponding to the highest concentration of HDL-C was used as the reference for comparative analysis. For Q1 vs. Q4 ( $P = 0.38$ ,  $I^2 = 0\%$ ), Q2 vs. Q4 ( $P = 0.60$ ,  $I^2 = 0\%$ ) and Q3 vs. Q4 ( $P = 0.58$ ,  $I^2 = 0\%$ ), there

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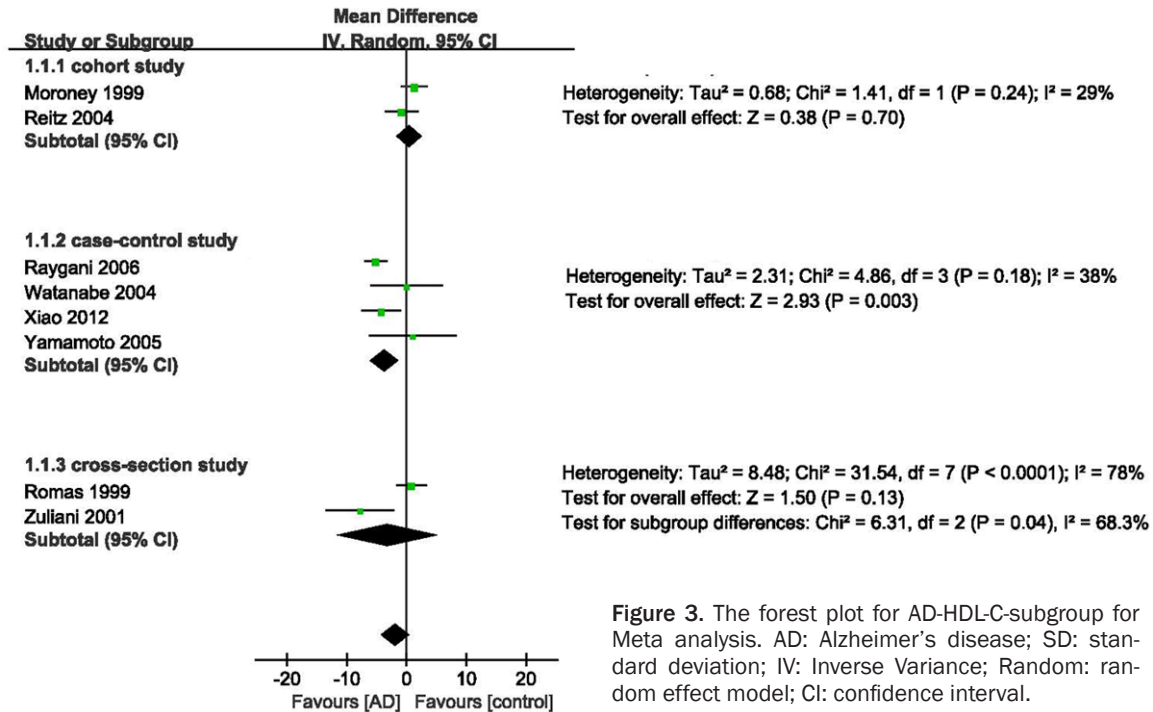


Figure 3. The forest plot for AD-HDL-C-subgroup for Meta analysis. AD: Alzheimer's disease; SD: standard deviation; IV: Inverse Variance; Random: random effect model; CI: confidence interval.

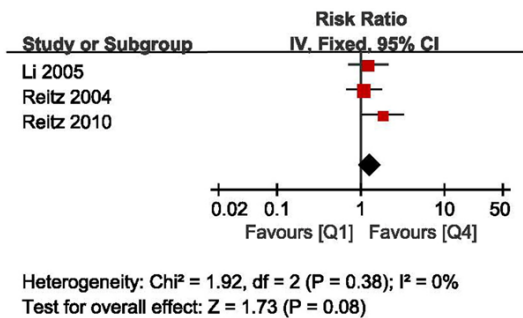


Figure 4. The forest plot for AD-Q1-Q4 for Meta analysis. Q1: the lowest concentration of HDL-C; Q4: the highest concentration of HDL-C; SE: standard error; IV: Inverse Variance; Fixed: fixed effect model; CI: confidence interval.

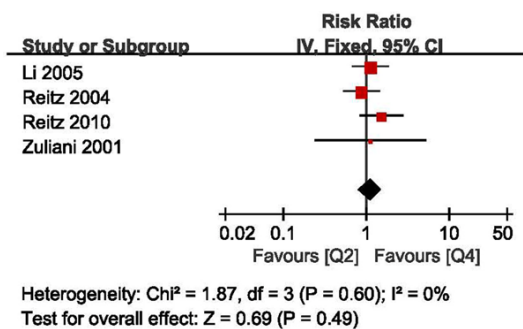


Figure 5. The forest plot for AD-Q2-Q4 for Meta analysis. Q2: the second concentration gradient of HDL-C; Q4: the highest concentration of HDL-C; SE: standard error; IV: Inverse Variance; Fixed: fixed effect model; CI: confidence interval.

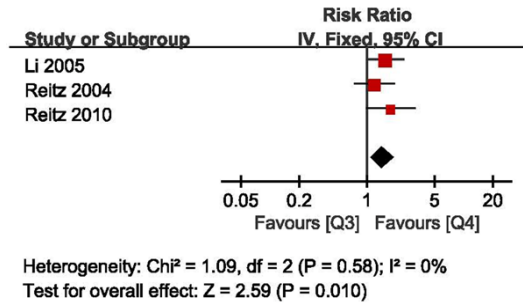
was no significant heterogeneity among the included literatures; the fixed effect model was used for consolidation. The combined results showed that AD onset risk had no significant difference (Figures 4, 5) between Q1 and Q4 (RR=1.31 (95% CI: 0.96, 1.79), P=0.08) or between Q2 and Q4 (RR=1.11 (95% CI: 0.82), 1.51, P=0.49). However, the difference in AD onset risk between Q3 and Q4 had significance (RR=1.46 (95% CI: 1.10, 1.95), P=0.01) (Figure 6). The results suggested that high concentration of HDL-C was correlated with AD onset risk.

### VaD vs. healthy control

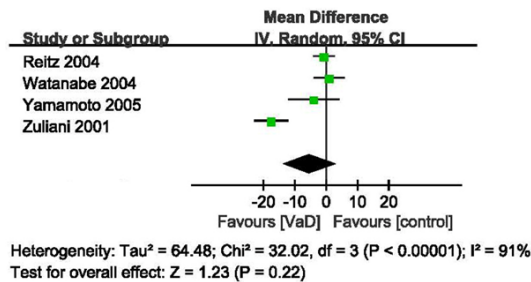
For studies (1 cohort study, 2 case-control studies and 1 cross-sectional study) compared the difference in HDL-C concentration between VaD group and healthy control group. A total of 1187 cases (VaD group: 182, control group: 1005) were included. There were significant heterogeneity among the 4 studies (P<0.01, I<sup>2</sup>=91%). When the fixed effect model was used for consolidation, the combined result was WMD=-5.26 (95% CI: -13.61, 3.10); the difference between the 2 groups had no significance (P=0.22) (Figure 7).

Only Reitz et al reported the correlation between HDL-C and VaD onset risk [7]. The results of this study showed that HDL-C concen-

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**Figure 6.** The forest plot for AD-Q3-Q4 for Meta analysis. Q3: the third concentration gradient of HDL-C; Q4: the highest concentration of HDL-C; SE: standard error; IV: Inverse Variance; Fixed: fixed effect model; CI: confidence interval.



**Figure 7.** The forest plot for VaD-HDL-C for Meta analysis. VaD: vascular dementia; SD: standard deviation; IV: Inverse Variance; Random: random effect model; CI: confidence interval.

tration and VaD onset risk had low level of correlation, the difference in VaD onset risk was insignificant between different concentration gradients of HDL-C.

### Sensitivity analysis

When the included literatures were rejected one by one, in AD group vs. healthy control group, the difference in AD onset risk between Q3 and Q4 was insignificant after Li et al. ( $\text{RR}=1.40$  (95% CI: 0.97, 2.03),  $P=0.08$ ) or Reitz et al. ( $\text{RR}=1.38$  (95% CI: 0.99, 1.91),  $P=0.06$ ) was rejected, leading to reversal of the conclusion; the results suggested that this combination result was unstable. For other outcome indexes, the conclusion was consistent before and after the study was rejected, and the results were stable.

### Publication bias analysis

The Begg's funnel plot for amputation showed that there was an equally distributed around

the overall estimate in this study and the Egger's test showed no publication bias.

### Discussion

Senile dementia including Alzheimer's disease (AD) and vascular dementia (VaD) show the high risk of lethal and mutilation and are the major disease for Chinese aged [14]. However, there is not decisional conclusion for the relationships with serum high-density lipoprotein (HDL) and senile dementia.

The results of this meta-analysis showed that, for the included case-control studies, the difference in HDL-C concentration between AD group and healthy population control group had significance; the healthy population had higher HDL-C concentration. On the other hand, when different concentration gradients of HDL-C were compared with AD onset risk, the difference in AD onset risk between the lower concentration of HDL-C (Q3) and the highest concentration of HDL-C (Q4) had significance. The results suggested that high concentration of HDL-C was correlated with AD onset risk. However, the sensitivity analysis results showed that the conclusion on HDL-C concentration and AD onset risk was unstable. In the future, high-quality clinical studies on HDL-C and AD onset are needed to further determine the correlation.

In this meta-analysis, the comparison of HDL-C concentration between AD/VaD group and normal control group showed higher heterogeneity. The sources of heterogeneity may be as follows: different clinicians may have given distinct neuropsychological scores for patients with senile dementia, causing difference in the disease grade of included cases; the included patients with certain other diseases may cause variations in HDL-C concentration level. The recommendation is to strictly control the included cases in subsequent clinical studies or to conduct correction analysis of factors that may affect the results during analysis. HDL-C concentration is higher in healthy population than in AD/VaD group. High concentration HDL-C and AD onset risk are correlated.

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### Disclosure of conflict of interest

None.

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