Original Article

Association between Coronary Heart Disease, Heart Failure, and Risk of Alzheimer's Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: Cardiovascular diseases such as coronary heart disease (CHD), heart failure (HF), and stroke have been linked to the development of Alzheimer's disease (AD). However, previous studies have reported inconsistent results. The study aimed to investigate the association between CHD, HF, and the risk of AD using a meta-analysis. **Methods:** STATA 12.0 software is used to compute odds ratios (ORs)/relative risks (RRs) and 95% confidence intervals (CIs) for the association between CHD, HF, and the risk of AD. **Results:** A total of 12 studies (including N = 36,913 individuals with AD and N = 1,701,718 participants) investigated the association between CHD and the risk of AD. Meta-analysis indicated that CHD was associated with an increased risk of AD with a random effects model (OR/RR: 1.22, 95% CI: 1.00–1.48, $I^2 = 97.2\%$, $P < 0.001$). Additionally, seven studies (including N = 5,119 individuals with AD and N = 1,231,399 participants) investigated the association between myocardial infarction (MI) and the risk of AD. Our meta-analysis demonstrated no significant association between MI and the risk of AD with a fixed effects model (RR: 1.09, 95% CI: 0.91–1.30, $I^2 = 42.8\%$, $P = 0.105$). Finally, six studies (including N = 83,065 individuals with AD and N = 2,414,963 participants) examined the association between HF and the risk of AD. Our meta-analysis revealed that HF was associated with an increased risk of AD using a random effects model (RR: 1.53, 95% CI: 1.05–2.24, $I^2 = 96.8\%$, $P < 0.001$). **Conclusion:** In conclusion, our meta-analysis suggests that CHD and HF are associated with an increased risk of developing AD. Nonetheless, more large-scale prospective studies are necessary to further investigate the associations between CHD, HF, and the risk of AD.

Keywords: Alzheimer's disease, coronary heart disease, heart failure, meta-analysis

Introduction

Alzheimer's disease (AD), the most common cause of dementia, is a global health problem with great influences on family and society.[1] Alzheimer's disease is an age-related neurodegenerative disease, accounting for 50–75% of dementia.[2] Alzheimer's disease is a multifactorial disease, which is influenced by the interaction of genetic susceptibility and environmental factors throughout the whole life.[3] Identification of and intervention into these potential risk factors become key components of AD prevention.

Cardiovascular diseases (CVD) such as coronary heart disease (CHD), heart failure (HF), and stroke have been linked to the development of AD[4] and vascular dementia (VD).[5] However, previous studies have reported inconsistent results. Some studies[6-8] reported that CHD and HF are associated with the higher risk of AD. However, some studies[6,9] found no significant association between CHD, HF, and the risk of AD. The role of CHD and HF in AD is still unclear. The study aimed to investigate the association between CHD, HF, and the risk of AD using a meta-analysis.

Methods

Search strategy, inclusion criteria, and exclusion criteria

The meta-analysis searched for literature published before March 2023 in these databases (PubMed and Web of Science) by two researchers (Shanshan Zhuo and Hao Wu). The following search terms were used: ("coronary heart disease" OR "angina pectoris" OR "myocardial infarction" OR "heart failure") AND ("Alzheimer's disease" OR "AD").

The study included studies based on these inclusion criteria: 1) studies explored CHD or HF; 2) studies investigated the risk of AD. The following exclusion criteria were used: 1) reviews, case reports, and meta-analysis; 2) studies which did not investigate the association between CHD, HF, and the risk of AD; 3) studies which did not provide sufficient information to obtain odds ratio (OR) or relative risk (RR) and 95% confidence interval (CI) for the association between CHD, HF, and risk of AD. Two researchers (Shanshan Zhuo and Hao

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Submitted: 24-Apr-2023 **Revised:** 02-Jun-2023 **Accepted:** 24-Jun-2023
Published: 25-Aug-2023

DOI: 10.4103/aian.aian_361_23

Wu) independently read all the abstracts and full texts. Articles were discussed and decided by the three authors (Weifeng Sun, Shanshan Zhuo, and Hao Wu) after the appearance of inconsistent selections.

Data extraction and meta-analysis

Shanshan Zhuo and Hao Wu extracted data from included studies. These data included: Author and publication year, study country, study type, population, sample size (AD and total population), mean age of population, gender of population, CHD type or HF, follow-up time, adjustment, and results.

Odds ratios from case-control studies and RRs from cohort studies with their CIs were computed to generate a pooled effect size and 95% CI; first, for all studies together (considering OR from case-control studies to be estimates of RR) to generate a pooled effect size and 95% CI, and second, separately for case-control and cohort studies. All the analyzes were conducted with STATA 12.0 software. For high heterogeneity (P value for Q test ≤ 0.05 and $I^2 \geq 50\%$), a random effects model was adopted to compute these results; for low heterogeneity (P value for Q test > 0.05 and $I^2 < 50\%$), a fixed effects model was adopted to summarize all results. Meta-regression was adopted to investigate the source of heterogeneity. Subgroup studies (for different races and different study types) were applied to investigate the source of heterogeneity. Stabilization of the study was assessed by adopting sensitivity analysis. Finally, funnel plot, Begg's test, and Egger's test were adopted to assess publication bias.

Results

Study characteristics

After inclusion and exclusion, N = 15 studies[6-20] were finally included in the study. Figure 1 shows the inclusion and exclusion process. Table 1 shows study characteristics. A total of 12 studies[6-8,10-18] (including N = 36,913 individuals with AD and N = 1,701,718 participants) investigated the association between CHD and the risk of AD. Among the 12 studies, seven studies[6,7,10,12-14,16] (including N = 5,119 individuals with AD and N = 1,231,399 participants) investigated the association between myocardial infarction (MI) and the risk of AD. Six studies[8,9,15,18-20] (including N = 83,065 individuals with AD and N = 2,414,963 participants) examined the association between HF and the risk of AD.

Association between CHD and the risk of AD

Meta-analysis indicated that CHD was associated with an increased risk of AD with a random effects model [OR/RR: 1.22, 95% CI: 1.00–1.48, I^2 = 97.2%, $P < 0.001$; Figure 2]. Meta-regression study indicated that publication year, age, gender, and follow-up time were not responsible for the heterogeneity between included studies (publication year: $P = 0.337$; age: $P = 0.380$; gender: $P = 0.341$; follow-up time: $P = 0.327$). Subgroup analysis indicated that CHD was associated with an increased risk of AD in the Caucasian population [OR/RR: 1.23, 95% CI: 1.01–1.51; Figure 3]. Subgroup analysis indicated that CHD was associated with an increased risk of AD in cohort studies [OR/RR: 1.27, 95% CI: 1.04–1.55; Figure 4]. Sensitivity analysis indicated no change in the direction of effect while any study was excluded from meta-analysis [Supplementary Figure 1]. Funnel plot, Begg's test, and Egger's test indicated no significant risk of publication bias [Supplementary Figure 2; Begg's test: $P = 0.807$; Egger's test: $P = 0.613$].

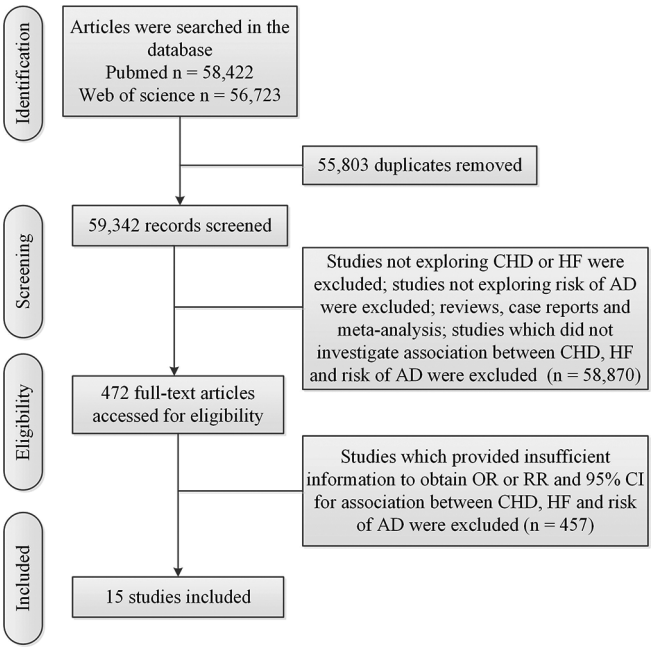


Figure 1: Inclusion and exclusion process. AD, Alzheimer's disease; CHD, coronary heart disease; HF, heart failure

Association between MI and the risk of AD

Our meta-analysis demonstrated no significant association between MI and the risk of AD with a fixed effects model [RR: 1.09, 95% CI: 0.91–1.30, I^2 = 42.8%, $P = 0.105$; Figure 5]. Meta-regression study indicated that publication year, age, gender, and follow-up time were not responsible for the heterogeneity between included studies (publication year: $P = 0.413$; age: $P = 0.632$; gender: $P = 0.351$; follow-up time: $P = 0.231$). Subgroup analysis indicated no significant association between MI and the risk of AD in the Caucasian population [RR: 1.11, 95% CI: 0.90–1.37; Figure 6]. All included studies were designed as cohort studies. Sensitivity analysis indicated a change in the direction of effect while a study published by Sundboll *et al*.[6] was excluded from meta-analysis [Supplementary Figure 3]. Funnel plot, Begg's test, and Egger's test indicated a significant risk of publication bias [Supplementary Figure 4; Begg's test: $P = 0.764$; Egger's test: $P = 0.012$].

Association between HF and the risk of AD

Our meta-analysis revealed that HF was associated with an increased risk of AD with a random effects model [RR: 1.53, 95% CI: 1.05–2.24, I^2 = 96.8%, $P < 0.001$; Figure 7]. Meta-regression study indicated that publication year, age,

Table 1: Characteristics of included studies

Study/ Year	Country	Study type	Population	Sample size (AD/cohort	Mean age (years)	Gender (male%)	CHD type or HF	Median follow-up time	Adjustment	Result
Association between CHD and risk of AD										
Kivipelto *et al.* 2002[13]	Finland	Cohort	Older Population	48/1287	NR	61.8%	MI	21 years	Age, apolipoprotein E genotype, education level, sex, smoking status, alcohol consumption	2.1 (1.1, 4.5)
Kuller *et al.* 2003[14]	USA	Cohort	had an MRI of the brain	330/3608	73	40.9%	MI	Max. 8 years	Age	1.1 (0.70, 1.75)
Newman *et al.* 2005[7]	USA	Cohort	had an MRI of the brain	245/2539	NR	60.1%	MI, AP	5.4 years	Age at baseline, race, education, income, apolipoprotein e-4 allele, Modified Mini-Mental State Examination score at the time of the brain magnetic resonance scan	MI: 1.2 (0.8, 2.0); AP: 1.3 (1.0–1.8)
Qiu *et al.* 2005[17]	Sweden	Cohort	Older Population	260/1301	NR	75.0%	CHD	6 years	Age, education, APOEepsilon4 allele, cognitive impairment, stroke, atrial fibrillation, antihypertensive drug use	1.49 (0.97-2.29)
Hayden *et al.* 2006[10]	USA	Cohort	Older Population	104/3264	73.7	57.7%	MI	3 years	Age, sex, education, hypertension, high cholesterol, diabetes, obesity, stroke, CABG	1.11 (0.49-2.26)
Ikram *et al.* 2008[12]	Netherlands	Cohort	Older Population	479/6347	68.7	41.1%	MI	9.3 years	Age, sex, and additionally adjusted for the presence of APOE 4 allele, systolic blood pressure, diastolic blood pressure, body mass index, atrial fibrillation, diabetes mellitus, current smoking, intima-media thickness, total cholesterol, and high-density lipid cholesterol	1.22 (0.89, 1.67)
Hughes *et al.* 2010[11]	Sweden	Case-control	like-sexed twin pairs	240/3664	48.2	62.0%	AP	31 years	Age, gender, education, smoking, alcohol drinking, BMI, total food compared to others, marital status, exercise	0.80 (0.58-1.11)
Li *et al.* 2011[16]	China	Cohort	Older Population	298/837	NR	41.6%	MI	5 years	Age, sex, education, occupation, depressive symptoms, APOE4, baseline MMSE, and ADL score	1.051 (0.670–1.648)
Rusanen *et al.* 2014[18]	Finland	Cohort	Older Population	102/738	68	37.6%	CAD	7.8 years	Gender, education, midlife systolic blood pressure, cholesterol, body mass index, APOE, midlife smoking, physical activity, diabetes or impaired glucose tolerance, and stroke at late life	1.38 (0.69, 2.77)
Sundbøll *et al.* 2018[6]	Denmark	Cohort	Older Population	3615/1,213,517	67	65.9%	MI	7.7-9.8 years	NR	MI: 0.92, 0.88–0.95;
Kummer *et al.* 2019[15]	USA	Cohort	Older Population	28,610/1,035,53	75.9	40.8%	CHD	5.2 years	Age, sex, race/ethnicity, and baseline Charlson comorbidities	1.44 (1.41–1.47)
Dong *et al.* 2022[8]	UK	Cohort	Older Population	2,582/464,616	56.6 (8.1)	46.0%	CHD	11.2 (1.5) years	Age at baseline, race/ethnicity, educational years, income level, physical activity level, leisure activities, BMI, smoking status, diabetes status, hypertension status, and APOE	1.50 (1.28, 1.75)

Contd...

Table 1: Contd...

Study/ Year	Country	Study type	Population	Sample size (AD/cohort	Mean age (years)	Gender (male%)	CHD type or HF	Median follow-up time	Adjustment	Result
Association between HF and risk of AD										
Qiu *et al.* 2006[20]	Sweden	Cohort	75 years or older Population	333/1301	83.3 (5.4)	80%	HF	5.02	Age, sex, education, follow-up survival status, baseline MMSE score, stroke, diabetes mellitus, pulse rate, body mass index, and if applicable, SBP, DBP, and antihypertensive drug use	1.61 (1.11, 2.34)
Rusanen *et al.* 2014[18]	Finland	Cohort	Older Population	102/1510	50.3 (6.0)	37.6%	CHF	25	Diabetes or impaired glucose tolerance and stroke at late-life.	1.11 (0.43, 2.81)
Jefferson *et al.* 2015[19]	USA	Cohort	participants free from clinical stroke, transient ischemic attack, or dementia	26/1039	69 (6)	47%	Cardiac index (MRI)	7.7	Education, APOE4 status, and FSRP (which assigns points for age, systolic blood pressure, anti-hypertensive medication, diabetes mellitus, cigarette smoking, left ventricular hypertrophy, CVD history, and atrial fibrillation by sex)	2.87 (1.21, 6.80)
Adelborg *et al.* 2017[9]	Denmark	Cohort	patients with a first-time hospitalization for heart failure	51 412/1,946,497	77 (IQR 69–84)	52%	HF	2–6.5	Stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score	1.00 (0.96, 1.04)
Kummer *et al.* 2019[15]	USA	Cohort	Older Population	28,610/1,035,53	75.9	40.8%	HF	5.2 years	Age, sex, race/ethnicity, and baseline Charlson comorbidities	1.90 (1.72–2.10)
Dong *et al.* 2022[8]	UK	Cohort	Older Population	2,582/464,616	56.6 (8.1)	46.0%	HF	11.2 (1.5) years	Age at baseline, race/ethnicity, educational years, income level, physical activity level, leisure activities, BMI, smoking status, diabetes status, hypertension status, and APOE	1.57 (1.28, 1.92) *n*

AD, Alzheimer's disease; ADL, activity of daily living; AP, Angina pectoris; APOE, apolipoprotein E; BMI, Body Mass Index; CABG, coronary artery bypass graft; CHD, coronary heart disease; DBP, diastolic blood pressure; HF, heart failure; MI, myocardial infarction; MMSE, Mini-mental State Examination; MRI, Magnetic Resonance Imaging; NR, not reported; SBP, Systolic Pressure; UK, United Kingdom; USA, United States

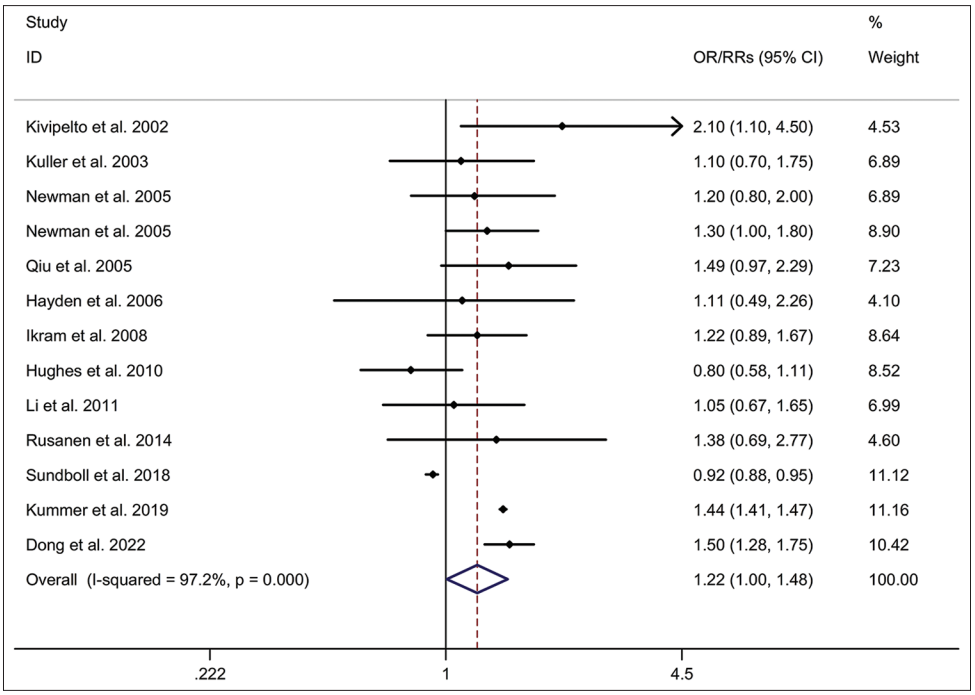


Figure 2: Forest plot for the association between CHD and the risk of AD. AD, Alzheimer's disease; CHD, coronary heart disease; CI, confidence interval; OR, odds ratio; RR, relative risk

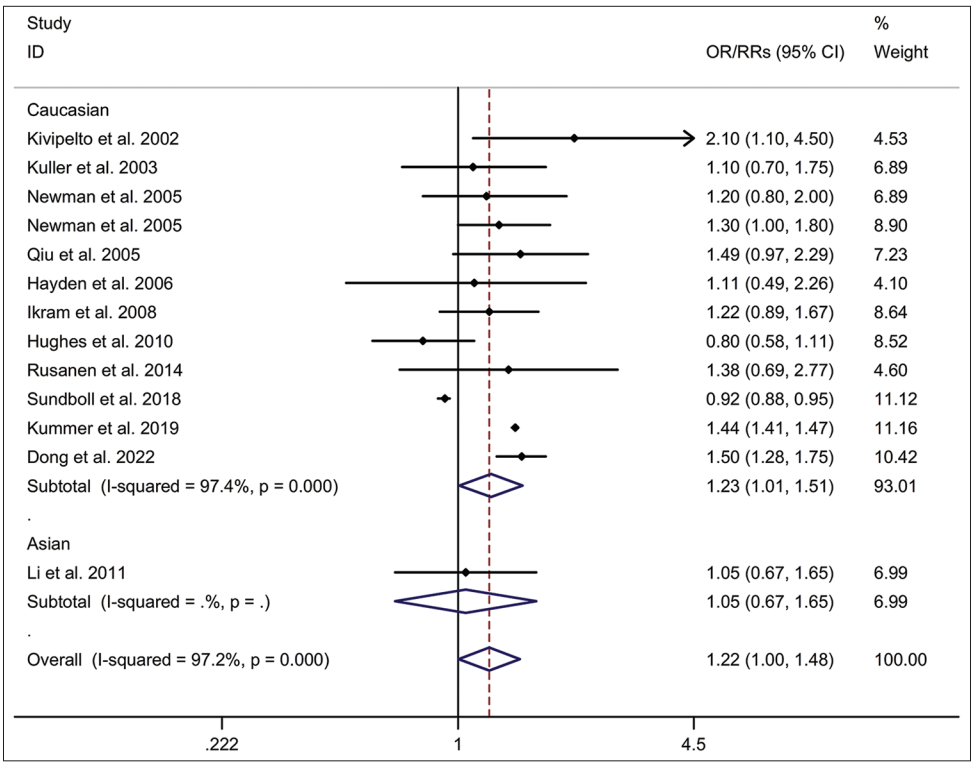


Figure 3: Subgroup analysis for the association between CHD and the risk of AD with different races. AD, Alzheimer's disease; CHD, coronary heart disease; CI, confidence interval; OR, odds ratio; RR, relative risk

gender, and follow-up time were not responsible for the heterogeneity between included studies (publication year: $P = 0.467$; age: $P = 0.475$; gender: $P = 0.493$; follow-up time: $P = 0.453$). All participants were Caucasian. All included studies were designed as cohort studies. Sensitivity analysis indicated no change in the direction of effect, while any study was excluded from meta-analysis [Supplementary Figure 5]. Funnel plot, Begg's test and Egger's test indicated no

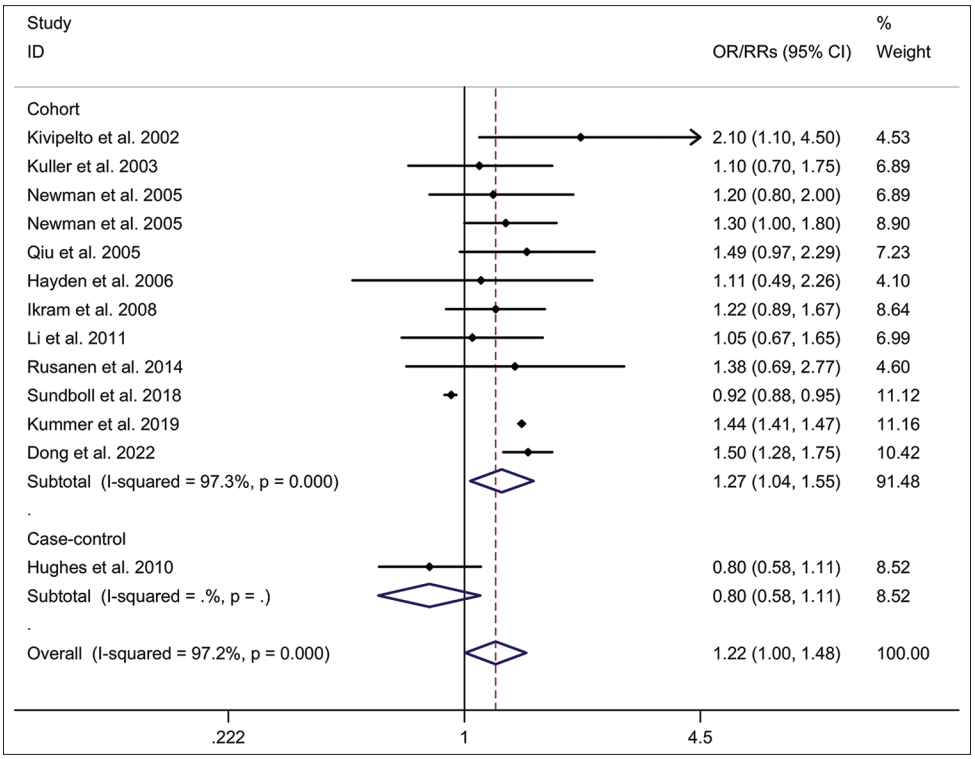


Figure 4: Subgroup analysis for the association between CHD and the risk of AD with different study types. AD, Alzheimer's disease; CHD, coronary heart disease; CI, confidence interval; OR, odds ratio; RR, relative risk

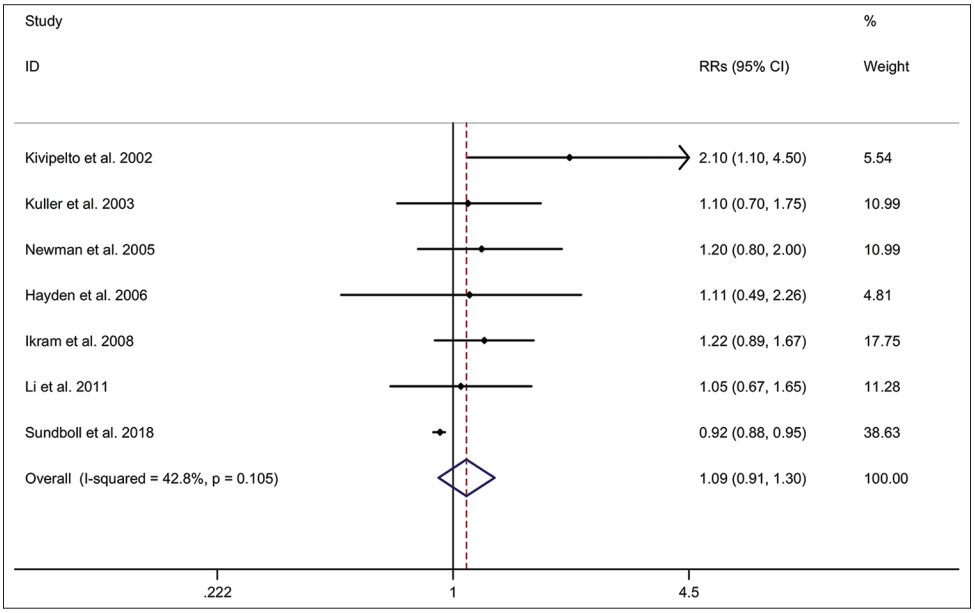


Figure 5: Forest plot for the association between MI and the risk of AD. AD, Alzheimer's disease; CI, confidence interval; MI, myocardial infarction; RR, relative risk

significant risk of publication bias [Supplementary Figure 6; Begg's test: $P = 0.573$; Egger's test: $P = 0.251$].

Discussion

The study reported that CHD was associated with an increased risk of AD. The result was inconsistent with a recent meta-analysis, which showed no significant association between CHD and the risk of AD (RR = 0.99, 95% CI: 0.92–1.07).[21] The present study is an updated study of previous studies. The potential mechanism for the association between CHD and the risk of AD is still unknown. Coronary heart disease has an impact on the heart output, resulting in cerebral hypoperfusion.[22] Cerebral hypoperfusion results

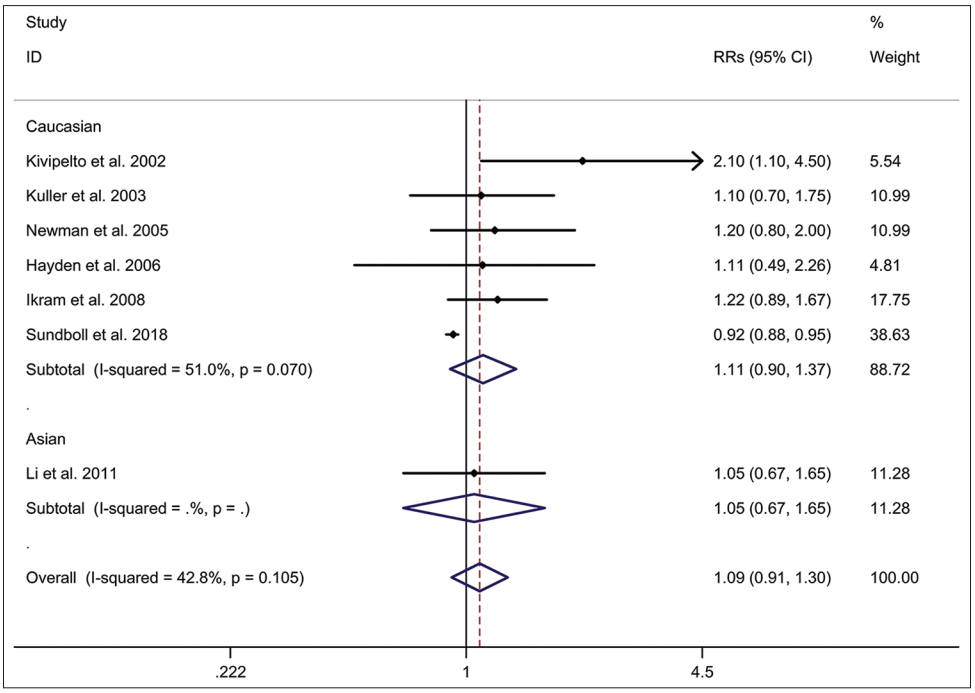


Figure 6: Subgroup analysis for the association between MI and the risk of AD with different races. AD, Alzheimer's disease; CI, confidence interval; MI, myocardial infarction; RR, relative risk

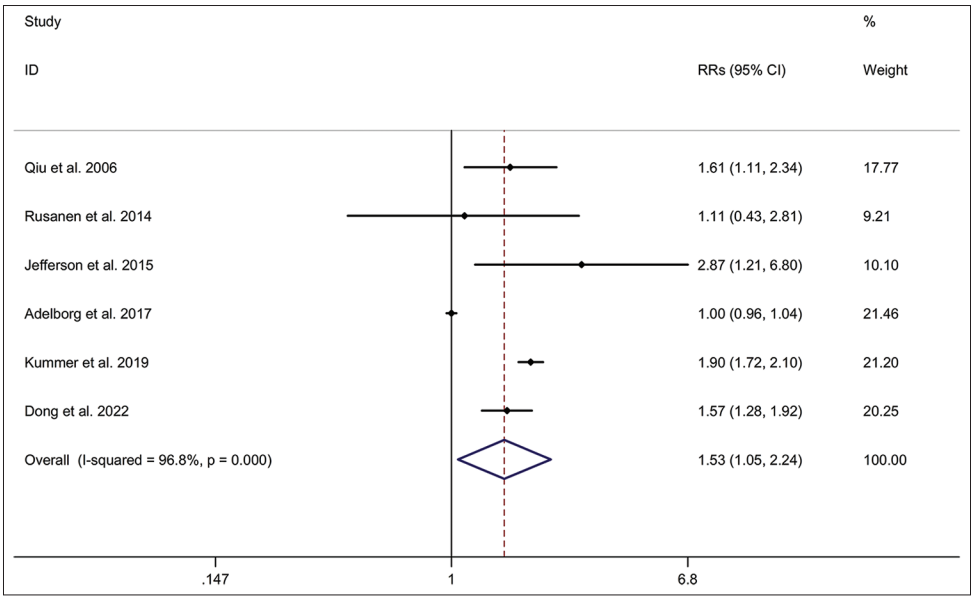


Figure 7: Forest plot for the association between HF and the risk of AD. AD, Alzheimer's disease; CI, confidence interval; HF, heart failure; RR, relative risk

in the formation of amyloid β plaques and neurofibrillary tangles, which are important characteristics of AD.[23] In addition, apolipoprotein E (APOE) might be a confounder in the association between CHD and AD. Moreover, the release of inflammatory cytokines might also play an important role in the cognitive impairment.[24,25] However, the study showed no significant association between MI and the risk of AD. Available studies exploring the association between MI and the risk of AD are few, and results were equivocal with either a slightly increased risk or no association. More studies were needed to investigate the association between CHD and the risk of AD.

Meta-analysis indicated that HF was associated with an increased risk of AD. The result was not corresponding to a recent meta-analysis, which showed no significant association between HF and the risk of AD (OR/RR = 1.38, 95% CI 0.90–2.13).[26] A previous study reported that the association between HF and the risk of AD differed in different gender (male:

RR = 1.09 (95%CI, 1.02–1.16); female: RR = 0.94 (95%CI, 0.89–0.99)).[9] However, the meta-regression analysis showed that gender was not responsible for the heterogeneity between included studies. Heart failure is associated with atrial fibrillation, hypertension, and diabetes, which are strongly associated with AD.[27] More studies were essential to explore the association between HF and the risk of AD.

Our results computed previous findings and indicated that CHD was associated with 22% elevated risk of AD. In addition, HF was associated with 53% elevated risk of AD. These findings have important implications for the prevention of AD and the management of patients with CHD or HF.

There are some limitations in the study. Firstly, the high heterogeneity limited the promotion of the present study. In the study, meta-regression and subgroup analyzes were used to detect the source of heterogeneity. However, the source of heterogeneity is still unclear. Secondly, regarding the association between MI and the risk of AD, the study showed a significant risk of publication bias; these results might be distorted.

Conclusions

In conclusion, our meta-analysis suggests that CHD and HF are associated with an increased risk of developing AD. Nonetheless, more large-scale prospective studies are necessary to further investigate the associations between CHD, HF and the risk of AD.

Financial support and sponsorship

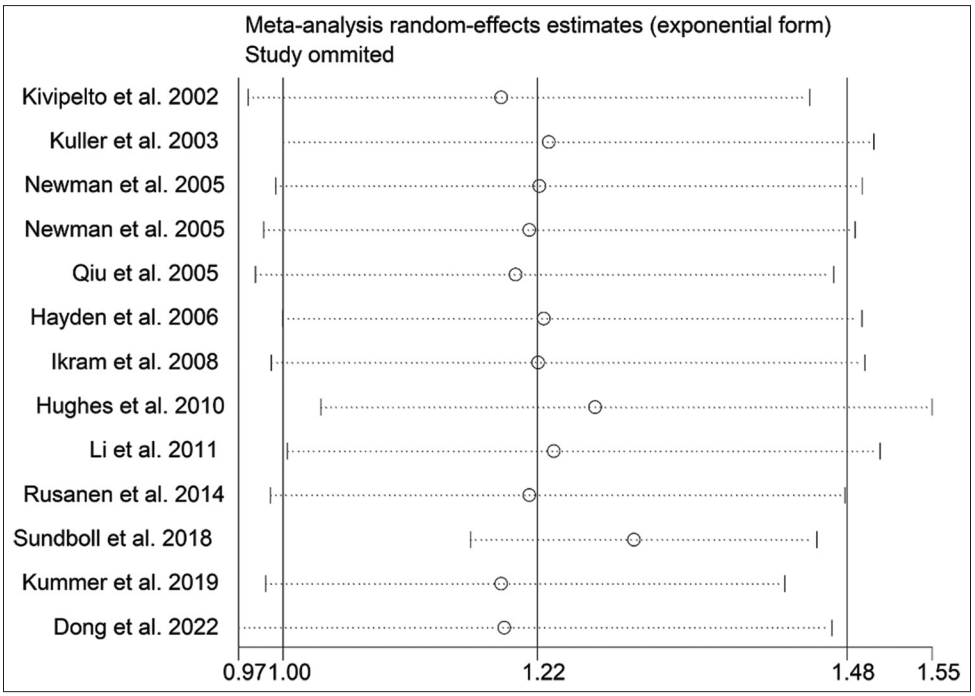
The study was supported by the Ningbo Health Branding Subject Fund (No. PPXK2018-01).

Conflicts of interest

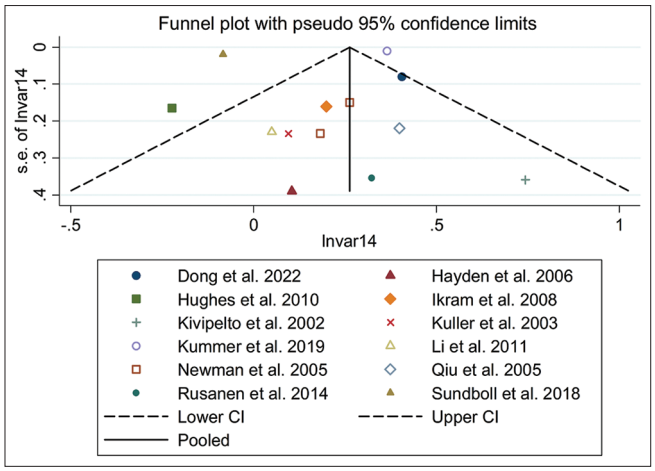
There are no conflicts of interest.

References

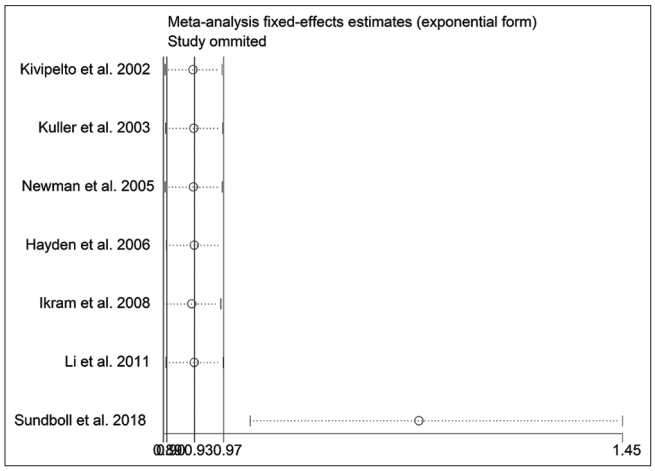
1. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, *et al*. Alzheimer's disease. Lancet (London, England) 2021;397:1577-90.
2. Wortmann M. World Alzheimer report 2014: Dementia and risk reduction. Alzheimer's Dementia 2015;11:P837.
3. Zhang XX, Tian Y, Wang ZT, Ma YH, Tan L, Yu JT. The epidemiology of Alzheimer's disease modifiable risk factors and prevention. J Prev Alzheimers Dis 2021;8:313-21.
4. de Bruijn RF, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. BMC Med 2014;12:130.
5. Gustavsson AM, van Westen D, Stomrud E, Engström G, Nägga K, Hansson O. Midlife atherosclerosis and development of Alzheimer or vascular dementia. Ann Neurol 2020;87:52-62.
6. Sundbøll J, Horváth-Puhó E, Adelborg K, Schmidt M, Pedersen L, Bøtker HE, *et al*. Higher risk of vascular dementia in myocardial infarction survivors. Circulation 2018;137:567-77.
7. Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W, *et al*. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. J Am Geriatr Soc 2005;53:1101-7.
8. Dong C, Zhou C, Fu C, Hao W, Ozaki A, Shrestha N, *et al*. Sex differences in the association between cardiovascular diseases and dementia subtypes: A prospective analysis of 464,616 UK Biobank participants. Biol Sex Differ 2022;13:21.
9. Adelborg K, Horvath-Puho E, Ording A, Pedersen L, Sorensen HT, Henderson VW. Heart failure and risk of dementia: A Danish nationwide population-based cohort study. Eur J Heart Fail 2017;19:253-60.
10. Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, *et al*. Vascular risk factors for incident Alzheimer disease and vascular dementia: The cache county study. Alzheimer Dis Assoc Disord 2006;20:93-100.
11. Hughes TF, Andel R, Small BJ, Borenstein AR, Mortimer JA, Wolk A, *et al*. Midlife fruit and vegetable consumption and risk of dementia in later life in Swedish twins. Am J Geriatr Psychiatry 2010;18:413-20.
12. Ikram MA, van Oijen M, de Jong FJ, Kors JA, Koudstaal PJ, Hofman A, *et al*. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. Stroke 2008;39:1421-6.
13. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, *et al.* Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med 2002;137:149-55.
14. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, *et al*. Risk factors for dementia in the cardiovascular health cognition study. Neuroepidemiology. 2003;22:13-22.
15. Kummer BR, Diaz I, Wu X, Aaroe AE, Navi BB. Associations between cerebrovascular risk factors and parkinson disease. Ann Neurol 2019;86:572-81.
16. Li J, Wang YJ, Zhang M, Xu ZQ, Gao CY, Fang CQ, *et al*. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. Neurology 2011;76:1485-91.
17. Qiu CX, Winblad B, Fratiglioni L. [Risk factors for dementia and Alzheimer' s disease-findings from a community-based cohort study in Stockholm, Sweden]. Zhonghua Liu Xing Bing Xue Za Zhi 2005;26:882-7.
18. Rusanen M, Kivipelto M, Levälahti E, Laatikainen T, Tuomilehto J, Soininen H, *et al.* Heart diseases and long-term risk of dementia and Alzheimer's disease: A population-based CAIDE study. J Alzheimers Dis 2014;42:183-91.
19. Jefferson AL, Beiser AS, Himali JJ, Seshadri S, O'Donnell CJ, Manning WJ, *et al*. Low cardiac index is associated with incident dementia and Alzheimer disease: The Framingham Heart Study. Circulation 2015;131:1333-9.
20. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: A population-based cohort study. Arch Intern Med 2006;166:1003-8.
21. Liang X, Huang Y, Han X. Associations between coronary heart disease and risk of cognitive impairment: A meta-analysis. Brain Behav 2021;11:e02108.
22. Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac output and cerebral blood flow: The integrated regulation of brain perfusion in adult humans. Anesthesiology 2015;123:1198-208.
23. Salvadores N, Searcy JL, Holland PR, Horsburgh K. Chronic cerebral hypoperfusion alters amyloid-β peptide pools leading to cerebral amyloid angiopathy, microinfarcts and haemorrhages in Tg-SwDI mice. Clin Sci (Lond) 2017;131:2109-23.
24. Corona AW, Fenn AM, Godbout JP. Cognitive and behavioral consequences of impaired immunoregulation in aging. J Neuroimmune Pharmacol 2012;7:7-23.
25. Abete P, Della-Morte D, Gargiulo G, Basile C, Langellotto A, Galizia G, *et al*. Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. Ageing Res Rev 2014;18:41-52.
26. Li J, Wu Y, Zhang D, Nie J. Associations between heart failure and risk of dementia: A PRISMA-compliant meta-analysis. Medicine (Baltimore) 2020;99:e18492.
27. Stampfer MJ. Cardiovascular disease and Alzheimer's disease: Common links. J Intern Med 2006;260:211-23.



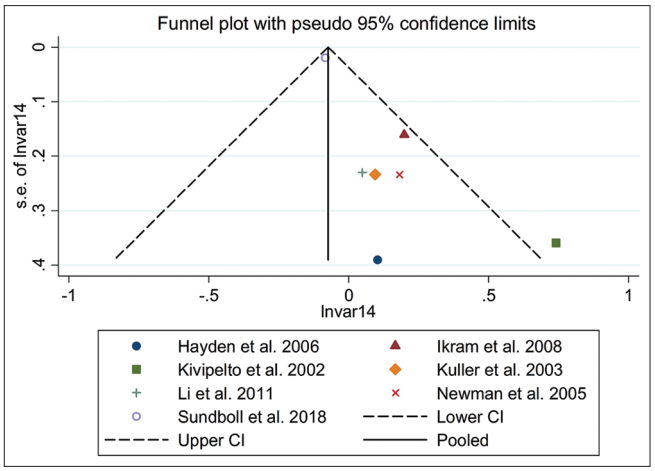
Supplementary Figure 1: Sensitivity analysis for association between CHD and risk of AD. AD, Alzheimer's disease; CHD, coronary heart disease



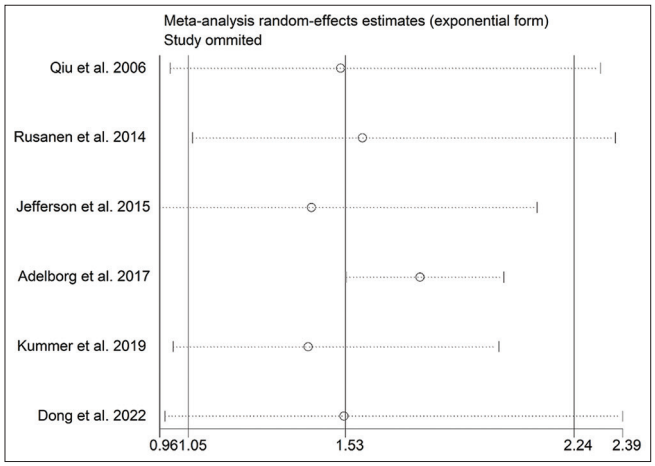
Supplementary Figure 2: Funnel plot for association between CHD and risk of AD. AD, Alzheimer's disease; CHD, coronary heart disease



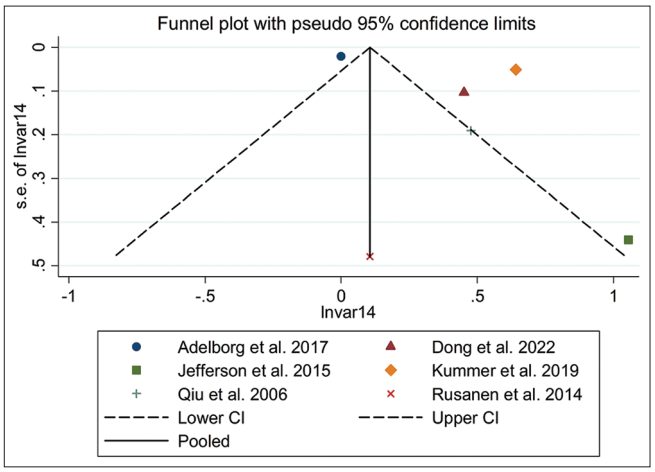
Supplementary Figure 3: Sensitivity analysis for association between MI and risk of AD. AD, Alzheimer's disease; MI, myocardial infarction



Supplementary Figure 4: Funnel plot for association between MI and risk of AD. AD, Alzheimer's disease; MI, myocardial infarction



Supplementary Figure 5: Sensitivity analysis for association between HF and risk of AD. AD, Alzheimer's disease; HF, heart failure



Supplementary Figure 6: Funnel plot for association between HF and risk of AD. AD, Alzheimer's disease; HF, heart failure