

Associations between heart failure and risk of dementia

A PRISMA-compliant meta-analysis

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Abstract

Background: There are differences among the outcomes regarding cognitive impairment in heart failure (HF) because the evidence is fragmented and sample size is small. Therefore we aimed to systematically review and analyze the available evidence about the association between HF and dementia.

Methods: In the present study, we searched for articles published until August 2019 in the following databases: PubMed, Web of Science, EMBASE, Medline and Google Scholar. The pooled multivariate odds ratio (OR) or relative risk (RR) and 95% confidence intervals (CI) were obtained by the use of STATA 12.0 software.

Results: The meta-analysis showed a positive association between HF and risk of all-cause dementia (OR/RR = 1.28, 95% CI 1.15 to 1.43, $I^2 = 70.0\%$, $P < 0.001$). Additionally, the study showed no significant association between HF and risk of Alzheimer's disease (AD) (OR/RR = 1.38, 95% CI 0.90 to 2.13, $I^2 = 74.8\%$, $P = 0.008$).

Conclusion: In conclusion, HF was associated with an increased risk of developing dementia. In addition, large scale prospective studies are essential to explore the associations between HF and risk of AD.

Abbreviations: AD = Alzheimer's disease, CI = confidence intervals, HF = heart failure, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analysis, RR = relative risk.

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

1. Introduction

Heart failure (HF) is defined as a complex clinical syndrome that the cardinal symptoms are fatigue, dyspnea and/or edema.^[1] HF is a clinical diagnosis based on disease history and physical examination. One in five people >40 years old in America will develop HF.^[2] The risk of developing HF is increasing with age and the HF prognosis is poor with high readmission and mortality rates.

Dementia is identified as a syndrome of cognitive impairment or cognitive decline that result in gradual loss of ability to live independently.^[3] Most of the dementias in aged people are Alzheimer's disease (AD). The prevalence of AD was

approximately 5.05%, and increased with age.^[4] The brain consumes 20% of the body's total oxygen, so it is easy to be injured in blood flow. In the context of an aging population disease of the heart and brain play an important role in the elderly people, and aggravate the economic burden of society.

Several studies revealed that HF increases the risk of dementia.^[5,6] However, there are differences among the outcomes regarding cognitive impairment in HF because the evidence is fragmented and sample size is small. Therefore we aimed to systematically review and analyze the available evidence about the association between HF and dementia.

2. Methods

The study was performed on the basis of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline.^[7] The study is a meta-analysis, an analysis with secondary processing. Thus, ethical approval was not necessary in the study.

2.1. Search strategy and selection criteria

In the present study, we searched for articles published until August 2019 in the following databases: PubMed, Web of Science, EMBASE, Medline and Google Scholar. Search terms were showed as follows: ('heart failure') AND ('dementia' OR 'cognitive deficits' OR 'cognitive dysfunction' OR 'cognitive impairment' OR 'Alzheimer's disease'). After exclusion of duplicates, 2179 studies were included. All included studies should report relative risk (RR) or odds ratio (OR) and 95% confidence intervals (CI) related to heart failure and risks of dementia. Those studies were also included if the RR or OR and

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95%CI could be calculated from the data provided in the studies. In addition, we eliminated secondary processing articles (meta-analyses and reviews) and case-reports from the present study.

2.2. Data extraction

We extracted data as follows: Author, publication year, study design, study location, sample sizes, information of participants (gender and age), explored variables, follow-up years, the RRs or ORs and 95%CIs after multivariate adjustments and adjusted variables.

2.3. Meta-analysis

We computed the results using STATA 13.0 software. We assessed heterogeneities between studies with the Q test and I^2 .

We used random effects models as pooling methods with invariably high heterogeneity (P value for Q test $\leq .05$); we used fixed effects models with invariably low heterogeneity (P value for Q test $> .05$). We performed meta-regression analyses to explore source of the heterogeneity. Additionally, we used sensitivity analysis to evaluate the stabilization of the study. We conducted Begg test, Egger test and funnel plot to evaluate publication bias.

3. Results

3.1. Study selection and characteristics

Figure 1 showed the selection procedures. Supplementary Table 1, <http://links.lww.com/MD/D598> showed study characteristics and results. In all included studies, 12 studies^[8–19] (including

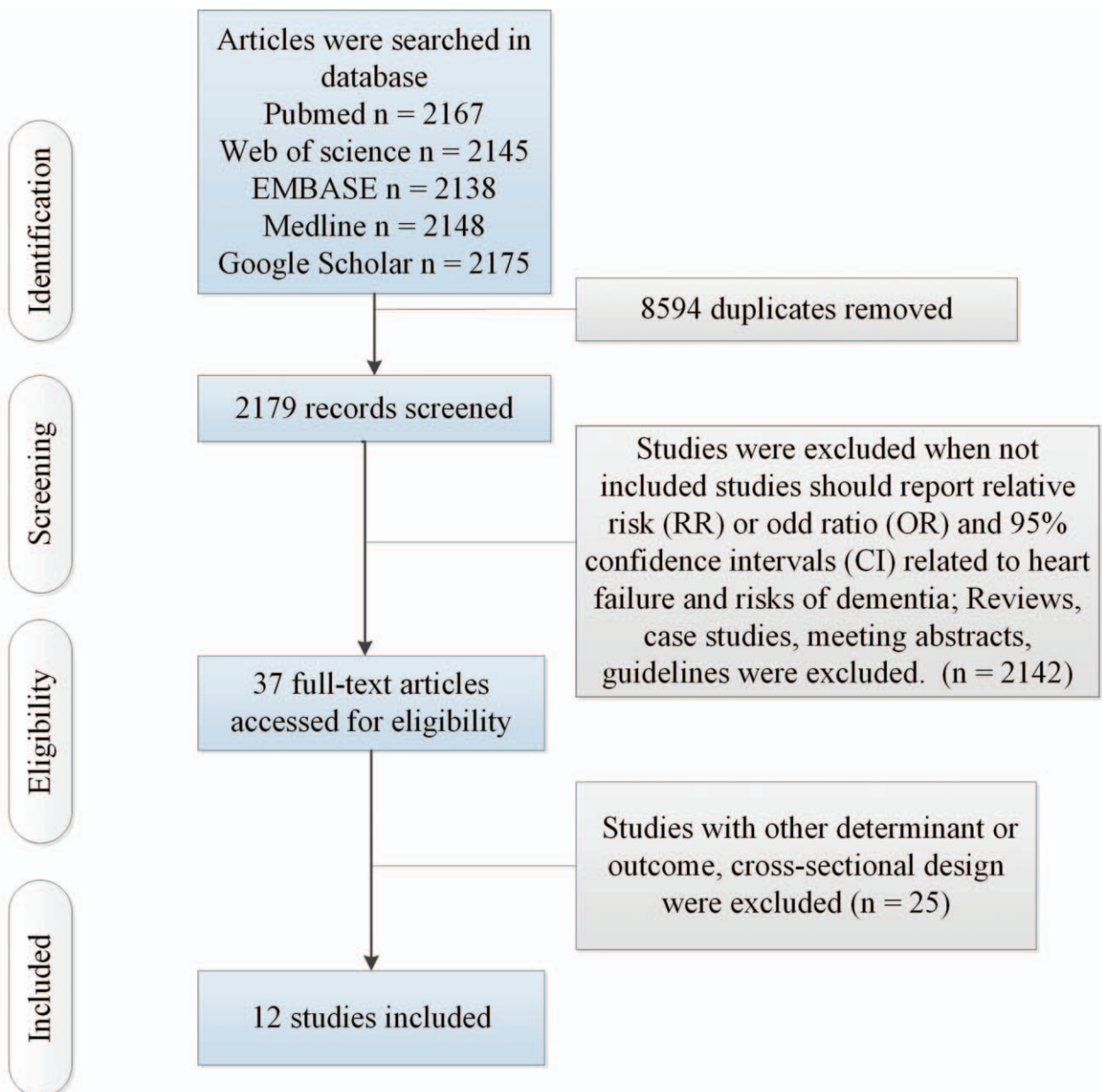


Figure 1. Flow of information through the different phases of a systematic review.

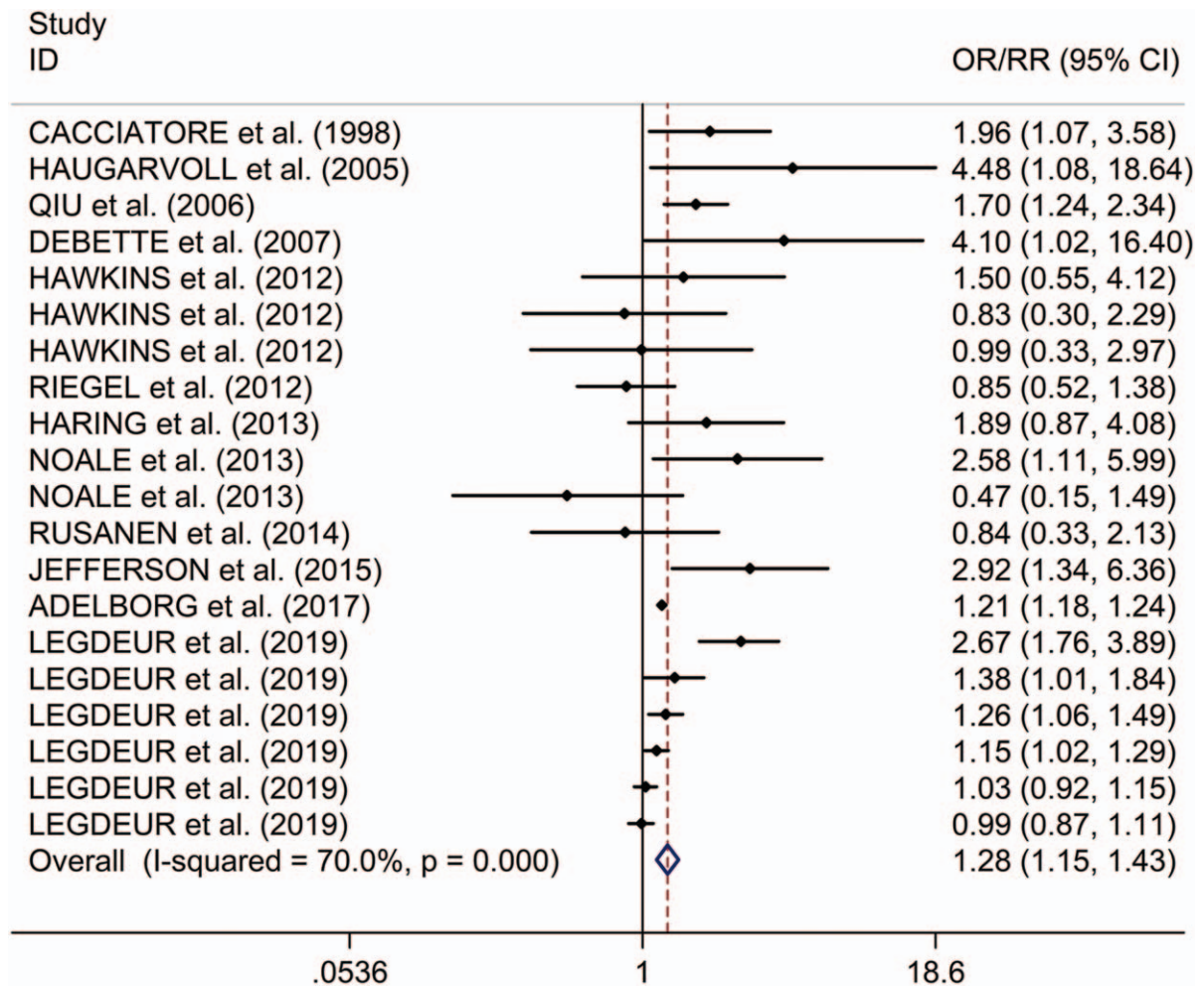


Figure 2. Forest plot regarding associations between HF and risk of all-cause dementia. HF=heart failure, OR=odds ratio, RR=relative risks.

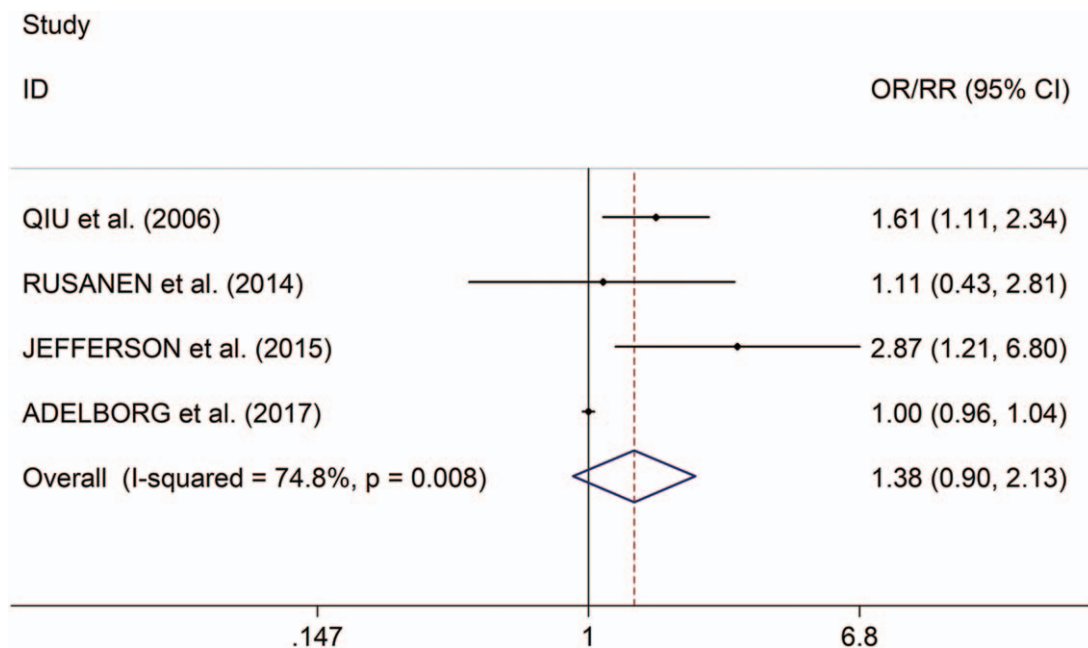


Figure 3. Forest plot regarding associations between HF and risk of AD. AD=Alzheimer's disease, HF=heart failure, OR=odds ratio, RR=relative risks.

2406680 HF patients) explored the association between HF and risk of all-cause dementia. In addition, 4 studies^[10,16,18,19] (including 1950347 HF patients) investigated the association between HF and risk of Alzheimer’s disease (AD).

3.2. Meta-analysis results

The meta-analysis showed a positive association between HF and risk of all-cause dementia (OR/RR=1.28, 95% CI 1.15 to 1.43, $I^2=70.0\%$, $P<.001$, Fig. 2). Meta-regression analysis showed

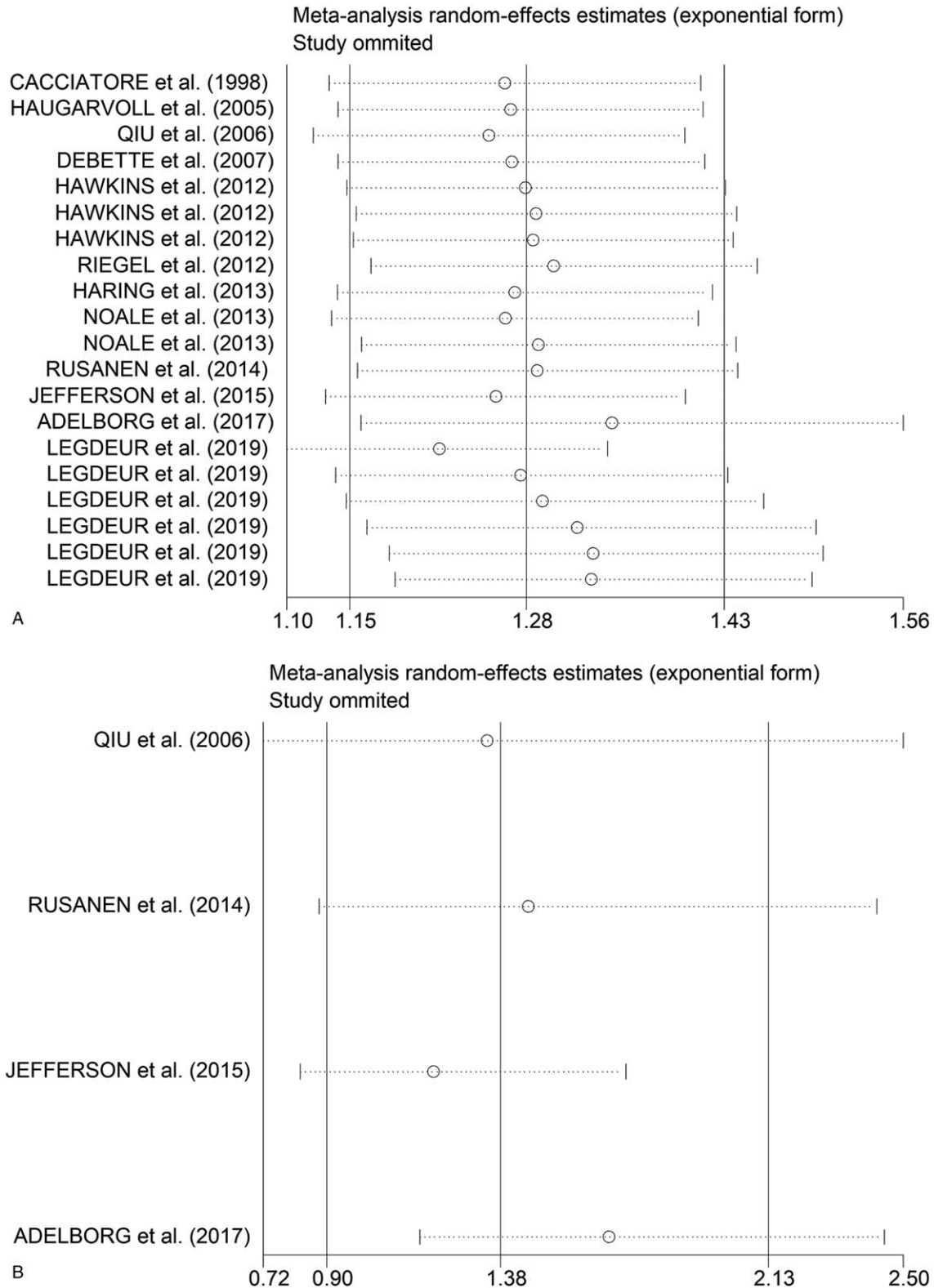


Figure 4. Sensitivity analysis regarding associations between HF and risk of all-cause dementia (A), AD (B). AD=Alzheimer’s disease, HF=heart failure.

that publication years, ages of participants, gender distribution and follow-up years were not responsible for heterogeneity across studies (all $P > .05$, supplementary Table 2, <http://links.lww.com/MD/D599>). Additionally, the study showed no significant association between HF and risk of AD (OR/RR=1.38, 95% CI 0.90 to 2.13, $I^2=74.8\%$, $P=.008$, Fig. 3). Meta-regression analysis showed that publication years, ages of participants,

gender distribution and follow-up years were not responsible for heterogeneity across studies (all $P > .05$, supplementary Table 2, <http://links.lww.com/MD/D599>).

Sensitivity analysis showed no changes in the direction of effect when any one study was excluded for the studies on associations between HF and all-cause dementia, AD (Fig. 4). In addition, Begg test, Egger tests and funnel plots showed no significant risks

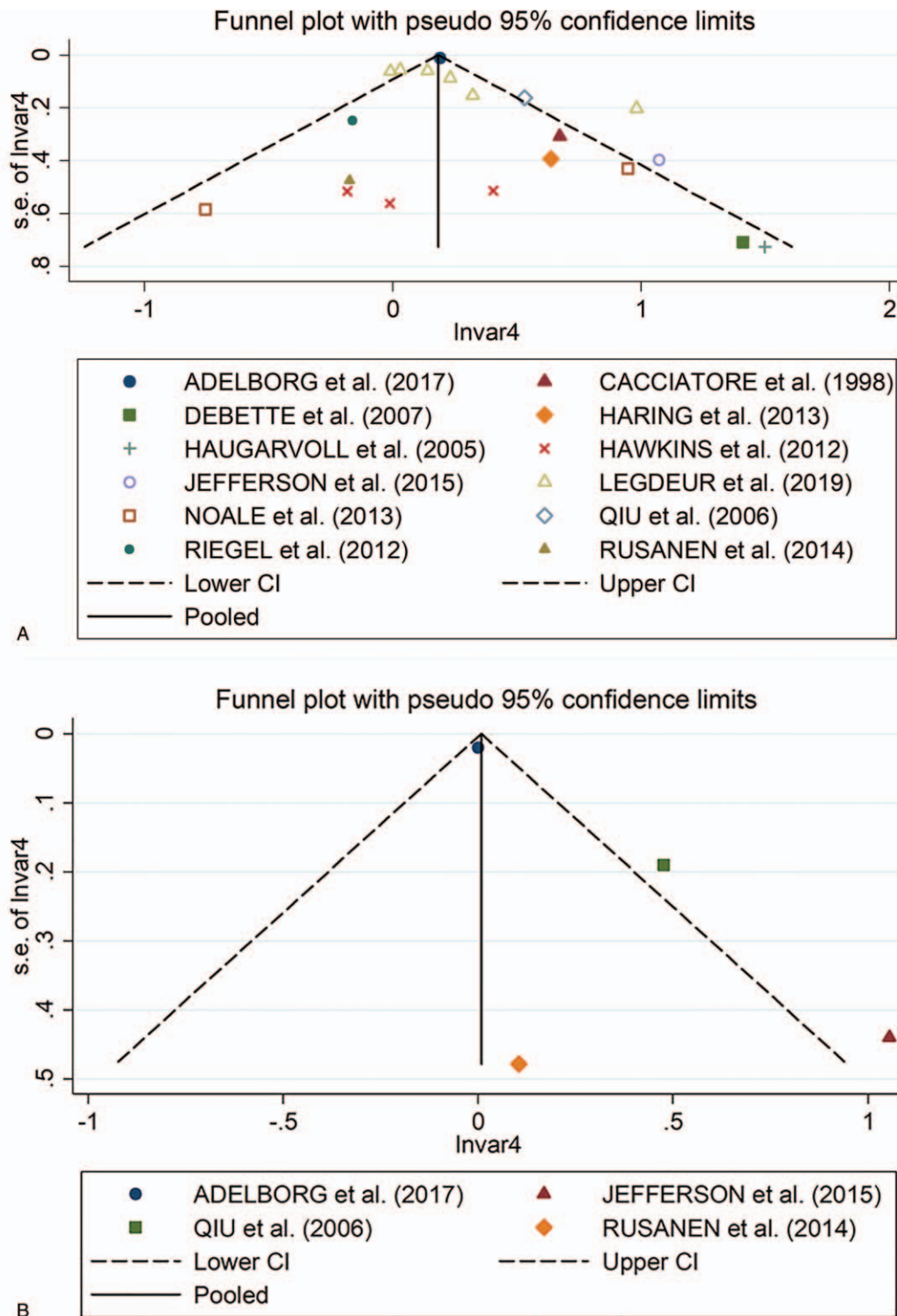


Figure 5. Funnel graph regarding associations between HF and risk of all-cause dementia (A), AD (B). AD=Alzheimer’s disease, HF=heart failure.

of publication bias for studies on associations between HF and all-cause dementia, AD (Fig. 5, supplementary Table 3, <http://links.lww.com/MD/D600>).

4. Discussion

In this study, we showed that there is a strong association between HF and all-cause dementia, but no association between HF and AD.

Two studies have recently involved the risk dementia in HF patients.^[18,20] The Danish nationwide cohort study revealed that there is an association between HF and all-cause dementia [1–35 year HRs=1.21 (95%CI, 1.18–1.24)], but no association between HF and AD [1–35 year HRs=1.00 (95%CI, 0.96–1.04)].^[18] This study also showed that HF patients under age 70 have a higher probability to be with all-cause dementia than patients above 70 years old [<60 years old: 1–35 year HRs=1.93 (95%CI, 1.68–2.23); 60–69 years old: 1–35 year HRs=1.56 (95%CI, 1.46–1.66); 70–79 years old: 1–35 year HRs=1.22 (95%CI, 1.18–1.27); >80 years old: 1–35 year HRs=1.06 (95%CI, 1.02–1.10)]. And men [1–35 year HRs=1.31 (95%CI, 1.26–1.36)] are easier to get all-cause dementia than women [1–35 year HRs=1.15 (95%CI, 1.11–1.18)] in HF patients.^[18] The Dutch cohort study showed that the risk of dementia decreases with age for HF patients [65–70 years old: RR=2.67 (95%CI, 1.76–3.89); 70–75 years old: RR=1.38 (95%CI, 1.01–1.84); 75–80 years old: RR=1.26 (95%CI, 1.06–1.49); 80–85 years old: RR=1.15 (95%CI, 1.02–1.29); 85–90 years old: RR=1.03 (95%CI, 0.92–1.15); >90 years old: RR=0.99 (95%CI, 0.87–1.11)].^[20] The results of these studies are consistent with ours.

HF may directly reduce brain blood flow, which contributes to cerebral hypoperfusion and brain tissue injury. Decreased cardiac output is linked to cognitive decline in HF patients.^[21] The Framingham Heart Study demonstrated that cardiac index reduction and left ventricular ejection fraction relate to cognition impairment.^[22] In addition, HF activates neurohormonal, which may cause inflammation and brain microvascular dysfunction.^[23] These mechanisms may contribute to chronic cerebral hypoxia and lead directly to dementia pathogenesis. The Danish nationwide cohort study showed a significant association between HF and the risk of vascular dementia [1–35 year HRs=1.49 (95%CI, 1.40–1.59)].^[18] Several cardiovascular and endocrine diseases are risk factors of vascular dementia, such as hypertension, dyslipidemia, atrial fibrillation and diabetes mellitus.^[24,25] Some studies showed that HF is a risk factor of AD.^[26] However, our study revealed that there is no association between HF and the risk of AD, which is similar to the Danish study [1–35 year HRs=1.00 (95%CI, 0.94–1.04)].^[18] It is noteworthy that the different results of the association between HF and AD because of gender difference [male: 1–35 year HRs=1.09 (95%CI, 1.02–1.16); female: 1–35 year HRs=0.94 (95%CI, 0.89–0.99)] in the Danish study.^[18] Therefore we cannot completely exclude the association between HF and AD, additional work is required to prove the outcome.

In this study, we analysed and showed the association between HF and dementia. Both HF and dementia are strongly associated with old people, and it should be noted that cardiovascular diseases play an important role for cognitive impairment in the aged people. However, there were several limitations in our study. First, we lacked the information regarding disease-associated covariates such as sex, age, data on drug treatment, socioeconomic status, HF severity and so on. So we cannot

distinguish the effect of these covariates on the association between HF and dementia. Second, the included studies were performed in North America and Europe, thus most population is Caucasians. So it is uncertain that whether the result can be applied to other populations.

5. Conclusions

In conclusion, HF was associated with an increased risk of developing dementia. In addition, large scale prospective studies are essential to explore the associations between HF and risk of AD Supplementary references, <http://links.lww.com/MD/D601>

Author contributions

Data curation: Yujing Wu, Jing Nie.

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Supervision: Juan Li.

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