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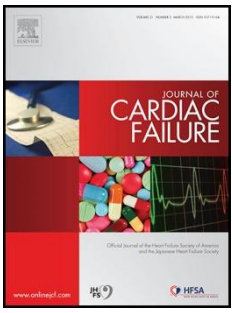

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Cognitive impairment and heart failure: systematic review and meta-analysis

Authors

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Abstract

Background: Cognitive impairment and dementia are associated with a range of cardiovascular conditions including hypertension, coronary artery disease and atrial fibrillation. We aimed to describe the association with heart failure, summarising published data to give estimates around prevalence, incidence and relative risk of cognitive impairment/dementia in heart failure.

Methods: We searched multidisciplinary databases including MEDLINE (OVID), EMBASE (OVID), CINAHL (EBSCO), PsychINFO (EBSCO), Web of Science (Thomson Reuters) and CENTRAL (Cochrane Library) from inception until 31st May 2015. All relevant studies looking at cognitive impairment/dementia in heart failure were included. Studies were selected by two independent reviewers using pre-specified inclusion/exclusion criteria. Where data allowed we performed meta-analysis and pooled results using random effects models.

Results: From 18,000 titles 37 studies were eligible (n=8411 participants). Data from 4 prospective cohorts (n= 2513 participants) suggest greater cognitive decline in heart failure compared to non-heart failure over the longer term. These data were not suitable for meta-analysis. In case-control studies describing those with and without heart failure (n=4 papers, 1414 participants) the odds ratio for cognitive impairment in the heart failure population was 1.67 (95% confidence interval 1.15 -2.42). Prevalence of cognitive impairment in heart failure cohorts (n=26 studies, 4176 participants) was 43% (95% confidence interval 30-55%).

Conclusions: This review suggests a substantial proportion of patients with heart failure have concomitant cognitive problems. This has implications for planning treatment and services. These data do not allow us to comment on causation and further work is needed to describe the underlying pathophysiology.

Keywords: Meta-analysis

Introduction

The clinical syndrome of heart failure (HF) imposes an immense burden of symptoms on patients, reduces quality of life and is one of the leading causes of hospitalisation and mortality, particularly in more developed countries.[1] Due to aging of the population and improved survival from coronary artery disease (CAD) prevalence of HF is expected to double within the next 40 years.[2] These arguments of high symptomatic and economic burden and increasing absolute numbers in the context of an ageing population equally apply to the syndromes of cognitive impairment and in particular, dementia. Cognitive impairment is an umbrella term encompassing everything from mild cognitive impairment at one end of the spectrum to dementia at the other end. Cognitive impairment is usually diagnosed on neuropsychological testing comparing performance across various cognitive domains against age and sex standardised mean scores. Diagnosis of cognitive syndromes, for example dementia, is clinical and usually made according to a recognised classification system.

Cognitive impairment has been reported in a variety of cardiovascular disorders. It is described in patients with hypertension,[3] atrial fibrillation (AF)[4] and CAD, especially after coronary artery bypass grafting (CABG).[5] Many patients with HF, if not most, have a history of one or more of these co-morbidities and these could account for cognitive impairment in patients with HF. On the other hand, HF per se might also lead to cognitive impairment. Putative mechanisms include cerebral hypoperfusion and systemic inflammation.[6,7] Thus, there are several plausible reasons to suspect an association between HF and cognitive decline. Central to the treatment of HF is a relatively complex multi-drug pharmacological treatment which requires careful biochemical surveillance, strict adherence and high level self-management.[8] Successful self-management may be jeopardised by cognitive impairment.

A literature describing cognitive impairment in HF is available but papers are published in disparate specialty medical journals (cardiology, neurology, psychiatry, nursing), sample sizes can be modest and results are inconsistent. In this situation a

comprehensive synthesis of all published literature with summary statistics can give useful information.

We aimed to conduct a systematic review and meta-analysis looking at the association between HF and cognitive impairment.

Methods

Our systematic review was designed, conducted and reported according to the "Preferred Reporting Items for systematic reviews and meta-analyses" (PRISMA) guidelines.[9] We created a search protocol, available on an open access web-based resource (PROSPERO, registration number CRD42014015485).[10]

Our primary aim was to describe an association between HF and cognitive impairment (where cognitive impairment is a syndrome including mild cognitive impairment, multi-domain cognitive impairment and varying severities of dementia). Two independent researchers trained in systematic review, performed all aspects of searching, selection, extraction and assessment (J.A.C & P.M) any disagreements were referred to a third arbitrator (T.J.Q).

Inclusion/exclusion criteria

Our eligibility criteria were defined prior to any literature searches and were outlined as follows:

1. Studies published in English.
2. Studies with at least 50 human participants.
3. Original research published in peer reviewed scientific journals.
4. Studies presenting data on cognitive impairment and HF with the following study designs: prospective cohorts, cross sectional population studies and case-control studies.
5. Studies using at least one validated measure of cognition or clinical diagnosis of a cognitive syndrome made according to recognized criteria.
6. Studies including patients with a formal clinical diagnosis of HF.

We excluded randomized controlled trials that collected cognitive data as primary or secondary outcome as we felt the included participants may not be generalizable to an unselected HF population. Abstracts were included in the search but, for the final selection of studies we only included those that had been fully published in peer reviewed journals. Papers were not excluded on the basis of year of publication.

Search strategy

We created a sensitive search strategy based around concepts of [heart failure] and [cognition/dementia/cognitive testing]. Where available we used validated search strings and supplemented these with MeSH terms and other controlled vocabulary. (figure 1). We searched multidisciplinary databases from inception until 31st May 2015: MEDLINE (OVID), EMBASE (OVID), CINAHL (EBSCO), PsychINFO (EBSCO), Web of Science (Thomson Reuters) and CENTRAL (Cochrane Library). Where the facility was available, we used the "explode" function in those databases. Bibliographies of included papers and relevant reviews were searched for further possible titles and the process was repeated until no new titles were found. Where the same data were presented in more than one publication we used the primary (first) publication.

After de-duplication, titles generated from the initial database searches were screened and if felt to be relevant, then the full text was reviewed.

Data extraction

For papers eligible for inclusion, we extracted data to a pre-specified and piloted proforma. We collated information regarding diagnosis of HF, with particular focus on subtypes of HF (HF with preserved [HF-PEF] or reduced ejection fraction [HF-REF]); severity of HF (symptomatic or objective marker); sampling frame (outpatient or inpatient/mixed) and cognitive assessment or criteria employed.

Risk of bias and generalizability assessment

We assessed for internal and external validity using the approach outlined in critical appraisal skills (CASP) guidance.[9] We used the CASP checklists for cohort and case-control studies and assessed domains relating to sampling frame, case ascertainment (dementia and HF) and confounding to create a semi-quantitative assessment. We defined a paper as low risk of bias where the following criteria were met: samples recruited had robust diagnosis of HF based on current ESC guidelines; cognitive function was assessed using standardized cognitive assessment tools or diagnosis of a cognitive syndrome made using validated classification system; confounding factors taken into account in the analyses of results. For longitudinal studies we identified a

follow up period of 18 months to be an appropriate timescale for development of cognitive impairment. For each study we considered external validity and whether the results could be applied to a contemporary HF population.

Data analyses

We created summaries of findings into tables to inform a narrative synthesis of the included papers. We performed meta-analyses to give summary estimates in those instances where more than 3 papers used a similar study design and contained similar cognitive assessments. We assessed heterogeneity through visual inspection of forest plots and quantitatively using Higgins I^2 and we assessed for potential publication bias using a funnel plot. All meta-analyses were run with both a fixed and random effects model.

We pre-specified differing statistical approaches depending on the study design. For case-control data we calculated odds ratios comparing proportions with cognitive impairment in the HF population versus the healthy control population. For cross-sectional studies we described point estimates of prevalence of cognitive impairment / dementia. For prospective studies, we planned to assess rates of incident cognitive impairment / dementia and calculate summary hazard ratios.

We pre-specified a sensitivity analysis, restricted to those studies judged as low risk of bias on our validity assessment and we pre-specified subgroup analyses restricted to outpatient populations only.

All analyses were performed using Stata version 14 (Stata Corp, College Station, Texas).

Results

From 18000 titles identified, we selected 350 abstracts for review, we assessed 87 full manuscripts and 37 papers (n=8411 participants) were eligible for inclusion in the final review. Figure 1.

Narrative review of included studies

We included 7 case control studies (representing 1781 participants),[10-17] 4 of which included healthy participants as the control group[13, 15-17] with the other 3 comparing rates of cognitive impairment between HF cohorts i.e. between those with HF-PEF and HF-REF.[10, 12&14] 26 cross-sectional studies were included[18-42] (representing 4177 participants) the majority of which (n=18) recruited patients from the outpatient setting.[18-21, 24-26, 32-34, 36-43] Only 4 studies (with 2513 participants) examined for incident cognitive function / dementia in patients with HF over prospective longitudinal follow up.[44-47] All key study characteristics are summarised in tables 1- 3.

Available longitudinal studies included ambulatory patients with HF followed for between six months and ten years.[45, 47] Within the prospective study rubric, various study designs were employed including comparison of HF-PEF and HF-REF and comparison of HF with healthy controls. The heterogeneity precluded any attempt at meta-analysis. Three studies compared HF and non-HF groups, [44-46] where follow-up was longer than two years the HF group seemed to have greater decline in cognition although a follow up duration of 9-10 years may be too long to look for differences in cognition, given the high 5 year mortality associated with HF. (Table 4).

Quantitative analyses

Of our eligible studies n=20 (n=2290 participants) cross-sectional[20, 24-37, 39-43] and n=5 (n=1414 participants) case-control were suitable for quantitative summary analyses.[13, 15-17] There was substantial heterogeneity across all analyses (I^2: 98.5% for cross-sectional; 71.5% for case-control) and we preferentially report random effects data.

For cross-sectional studies describing prevalence of cognitive impairment there was a spread in reported values from 0.1 (95% CI: 0.07-0.14) to 0.79 (95% CI: 0.75-0.82). Summarising the data, the overall prevalence for cross sectional studies was 0.43 (95% CI: 0.30-0.55). For our subgroup analysis restricted to those studies including only outpatients (n=14 papers; 1620 participants),[20, 24-26, 32-34, 36-37, 39-43] results were similar (0.40, 95% CI: 0.28-0.52) as were summary results in our sensitivity analysis restricted to low risk of bias studies (n=13 papers; 2012 participants) (0.44, 95% CI: 0.29-0.59).[20, 24-27, 32-37, 39, 43] (Figures 2-4). We performed a sub group analysis by age using a cut-off age of 69 years. The mean age for all 20 cross-sectional studies was 68 years with a median of 69 years. These results are presented in figure 5 and show a larger effect size in those studies with a mean age of >69 years (0.39, 95% CI: 0.26-0.53). There were insufficient studies to allow for our proposed subgroup analysis looking at HF-PEF and HF-REF.

For case-controlled studies, n=5 papers (1414 participants) compared rates of cognitive impairment and dementia in HF versus non-HF controls.[13, 15-17] Overall the random effects model showed a 2.64 odds ratio (95% CI: 1.83 - 3.80) of cognitive impairment in the HF cohort. (Figure 6). There were insufficient data to allow us to compare those case controlled studies comparing HF-PEF and HF-REF.

A funnel plot showing standard error against point estimate for the cross sectional data is shown in figure 7. This shows a relatively symmetrical funnel shape suggesting publication bias was not a major issue.

Discussion

We have demonstrated strong association between HF and cognitive problems. Our summary data suggest that in HF patients recruited into observational studies around 40% will have cognitive impairment. Our subgroup and sensitivity analyses confirm that this high prevalence is robust and not driven by poor quality studies or by inclusion of significant numbers who were unwell with decompensated HF. Case-control data suggest that compared to matched controls with no HF, those with HF have significantly increased risk of cognitive impairment. In fact, as patients with cognitive impairment are frequently excluded from studies (e.g. due to inability to provide informed consent or inability to complete study assessments) the actual prevalence in the clinical setting may be higher than reported here.

Explanation of results

Observational data are susceptible to a variety of biases. The variability of the prevalence rates for cognitive impairment that are reported in the reviewed studies probably results from the differences in the populations studied and the differences in the range and specificity of the instruments used to assess cognition. The heterogeneity of samples including patients and control subjects who had previous neurological injuries poses an additional limitation on the samples in most of the studies included.

We have shown that cognitive impairment is prevalent. To look at causation the ideal study design would involve longitudinal follow up of a group of patients with HF (but free of cognitive impairment at inception) with regular administration of standardised cognitive assessment tools and comparison with a group of age-, sex- and education-matched control cardiac patients as well as healthy control participants. For completion a group of cardiac patients (without HF) should be included to allow us to control for underlying cardiac conditions such as AF and CAD. We found no study that used this specific design.

Data in context of previous research

To put our prevalence estimate of 40% into context, the estimated prevalence of cognitive impairment / dementia in the UK in adults over 65 years old is 7.1% (based on 2013 data). The total number of people with dementia in the UK is forecast to increase to over 1 million by 2025 and over 2 million by 2051 if age-specific prevalence remains stable. This increasing prevalence is driven by ageing of the general population and existence of other co-morbid factors – of which HF could be an important contributor.

We found 15 additional studies that have been conducted since Vogels et al published their systematic review of 22 papers in 2007.[48] These additional papers have been published since 2006 and all describe the prevalence of cognitive impairment in HF. In this review we therefore provide an up to date synthesis of key studies published in this area. Whether the increased risk of cognitive impairment in HF is due to the clinical syndrome of HF itself – or the atherosclerotic risk factors commonly underlying it remains less clear. Other systematic reviews have shown associations between cognitive impairment and other cardiovascular disorders such as AF,[49] stroke[50] and CAD.[51] Many potential confounding variables are relevant to these groups of patients and so although the association with impaired cognition is clear, a causal relationship is harder to prove - or disprove.

Strengths of study approach

The strengths of our review include a comprehensive search strategy based on validated search terms and interrogation of cross-disciplinary electronic databases. All papers were quality assessed using a robust method tailored to our specific study question.

Limitations of study approach

Due to lack of information in some of the manuscripts included, we were not able to include all of the papers in the pre-specified analyses. A further limitation of our summary analyses is the substantial clinical heterogeneity between studies and

participants. Unfortunately patient level data such as ethnicity and sex were not routinely presented in the manuscripts and so further subgroup analyses could not be performed. Excluding 38 studies with fewer than 50 participants and 4 randomised controlled trials from this systematic review may also have influenced the results presented.

Implications for clinical practice/future research

Unfortunately, there are few if any data about the effect of therapeutic interventions specifically for HF on cognitive function and similarly limited information about the efficacy and safety of specific therapies for cognitive impairment in patients with heart failure. Indeed, to our knowledge, no completed large trial to date has measured cognitive function as an outcome (and most excluded patients with significant known cognitive impairment).

The one exception is the new angiotensin receptor neprilysin inhibitor (ARNI), sacubitril/valsartan. Because neprilysin is one of the many mechanisms clearing amyloid-ß peptides from the brain, there is a theoretical concern regarding the long term cognitive effects of neprilysin inhibitors. There was no increase in cognition-related adverse events in the sacubitril/valsartan arm of PARADIGM-HF (compared with the enalapril arm), although cognitive function was not formally assessed during the trial.[52] Two ongoing trials of neprilysin inhibitors are collating serial assessments of cognition. The Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction trial (PARAGON-HF)[53] utilizes MMSE to assess cognition while the Prospective Evaluation of cognitive function in heart failure: A Randomized double-blind Study in Patients with Preserved Ejection fraction Cardiac failure Treated wIth Valsartan or Entresto (PERSPECTIVE), is using a battery of more detailed cognitive tests in addition to cerebral positron emission tomography (PET) imaging for amyloid.[54]

Drugs that are used to treat cognitive impairment include the acetylcholinesterase inhibitors (ACHI) donepezil, rivastigmine and galantamine and the NMDA receptor

antagonist memantine. Adverse cardiovascular events with these drugs are very uncommon. However, there is some evidence that ACHI therapy is associated with increased risk of bradycardia, sick sinus syndrome, heart block and syncope which means caution is necessary when these agents are combined with beta-blockers, ivabradine and digoxin. Rarely, torsades de pointes may occur because of QT prolongation and again caution is needed when ACHIs are combined with other drugs affecting the QT interval such as amiodarone, ivabradine and certain antipsychotics, antidepressants and antimicrobials. Hypokalemia should also be avoided.

One recent study showed donepezil to be safe in patients without symptomatic heart disease and actually reduced levels of plasma BNP in patients with subclinical HF.[55] Further research is needed to fully understand the effects of these drugs in patients with heart failure. Little is known about the cardiovascular effects of memantine but there have been reports of bradycardia and reduced cardiovascular survival associated with its use.[56]

Although the idea of concomitant cognitive impairment and HF will be familiar to most clinicians it is not routinely screened for in the cardiology outpatient setting. Cognitive screening is not currently recommended in the European Society of Cardiology heart failure guidelines and this is in part due to the lack of standardised screening tools that are accessible, easy to administer in a timely fashion and that have clear clinical cut-off scores. Although this systematic review clearly shows a high prevalence of cognitive impairment in the HF population recent observational data suggest that informal assessment of cognition by a cardiologist is insufficiently sensitive with 3 in 4 patients with cognitive impairment not recognised as such in routine consultations. Cognitive assessment tools may have a role in research and practice, although first we should reach a consensus on appropriate assessment score cut-offs in this population and outline specific cognitive profiles in these patients. Although clearly important, systematic data on cognitive impairment in HF does not remove the need for prospective studies and experimental models to clarify the pathogenesis of this condition.

To progress our understanding we recommend increasing use of cognitive assessment using standardised screening tools in future HF studies. Although we found numerous studies assessing prevalence, there is a dearth of studies investigating the incidence of CI in HF. Once the incidence and prevalence of CI in HF are better defined we need to evaluate the consequences of CI in HF. Identifying underlying mechanisms for CI in HF may present targets for intervention, the 'holy grail' of cognitive research. A number of processes have been postulated, and we now need confirmatory studies using new developments in neuroimaging and biomarkers in representative populations of HF patients. All of this will require a multidisciplinary approach between HF and dementia research teams.

In conclusion, much of the heterogeneity in the prevalence of cognitive impairment / dementia seen in the HF population can be explained by differences in study methodology and case mix. Although we found numerous studies assessing prevalence, there is a dearth of studies investigating the incidence of cognitive impairment in HF which should be addressed in future research. Once the incidence and prevalence of cognitive impairment in HF are better defined we then need to evaluate the consequences of cognitive impairment in HF and identify its underlying mechanisms.

Disclosures

None

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Figure 1. Search strategy and review profile for the systematic review of cognitive impairment and heart failure

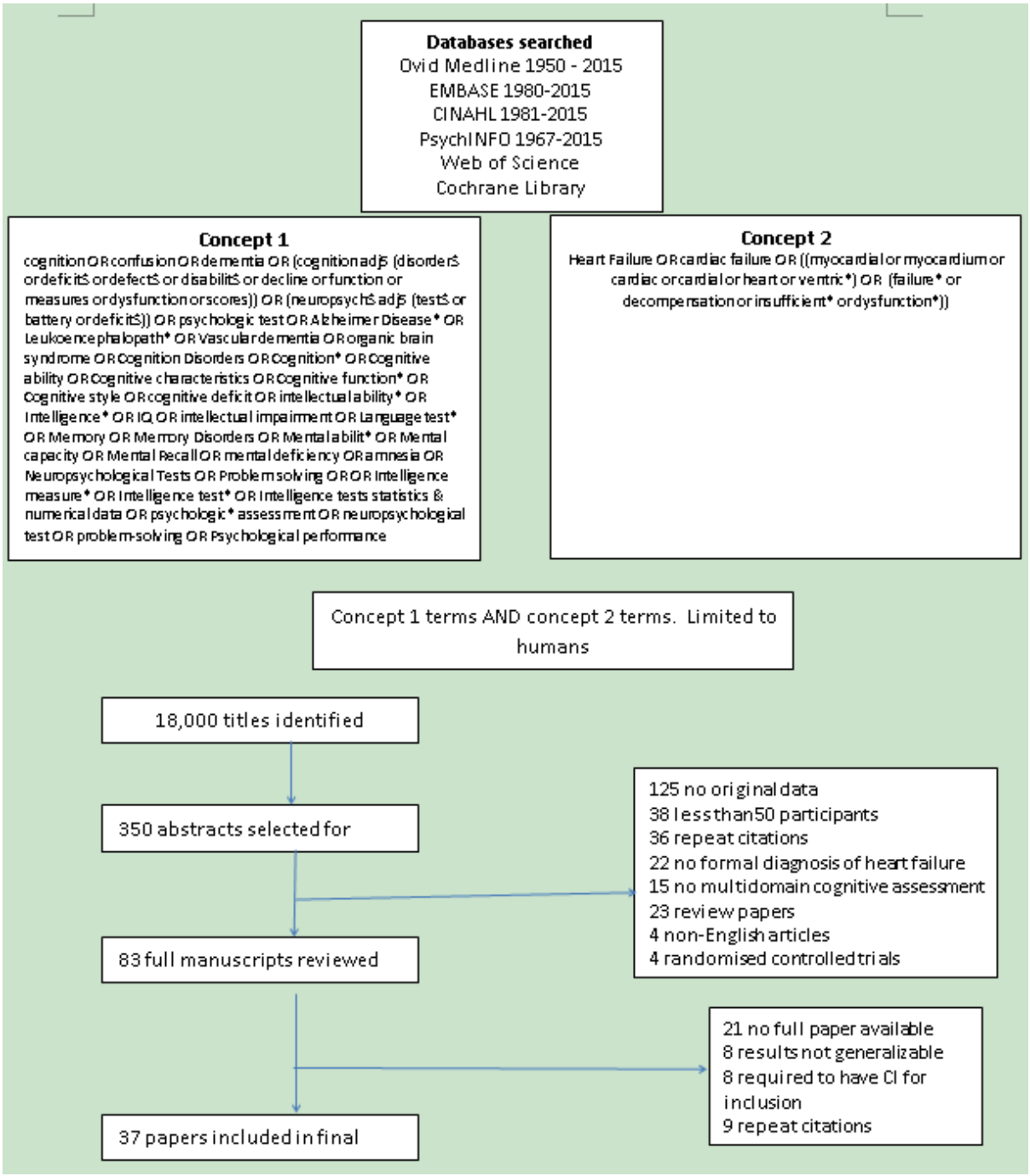


Figure 2. Forest plot showing fixed and random effects for all cross sectional studies

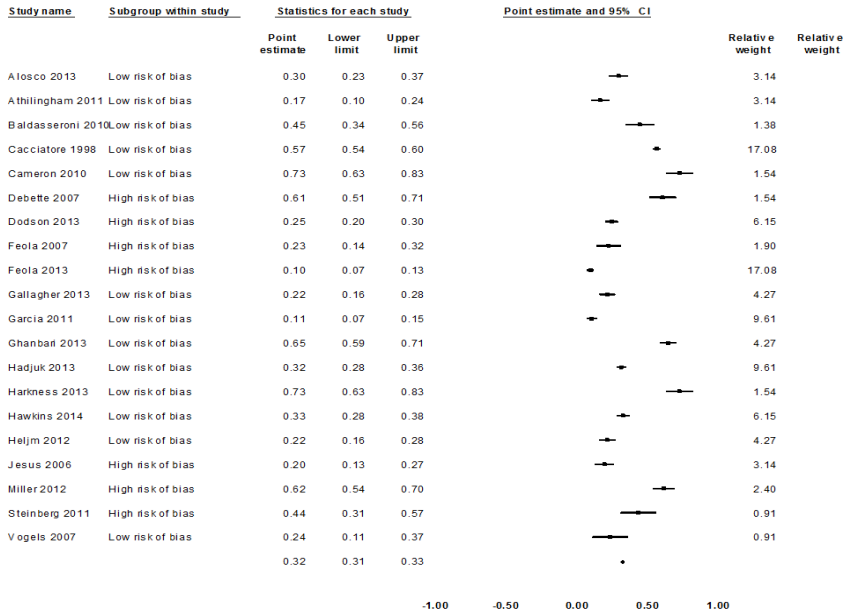


Figure 3. Forest plot showing fixed and random effects for all cross sectional studies with outpatient sampling

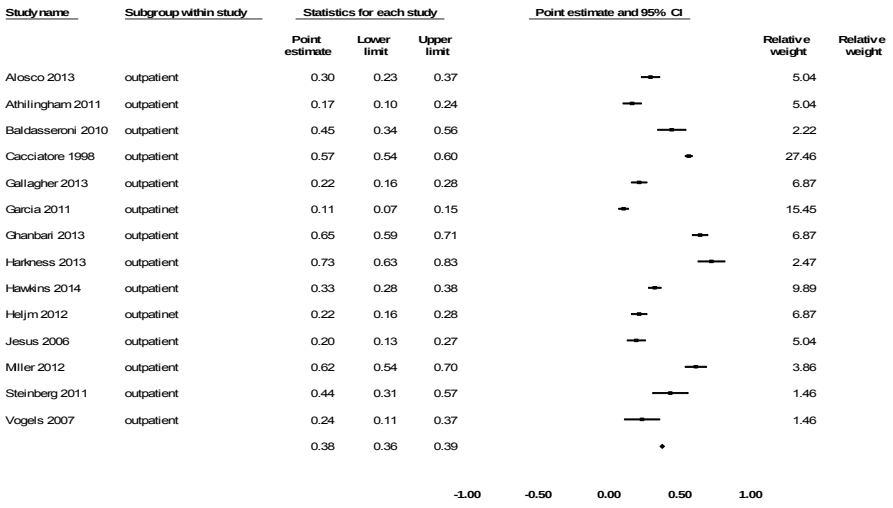


Figure 4. Forest plot showing fixed and random effects for cross sectional studies with low risk of bias

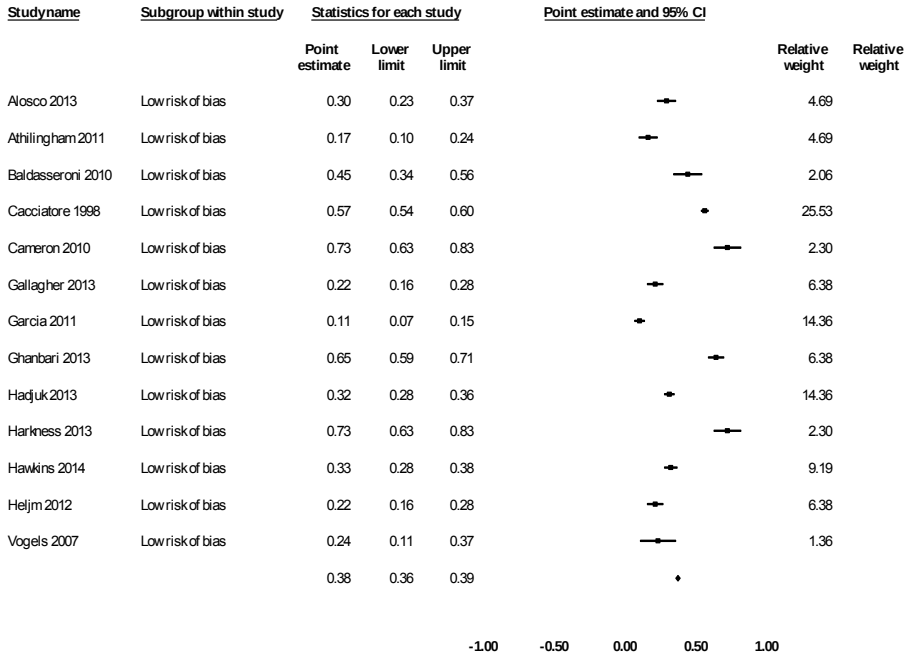


Figure 5. Forest plots showing fixed and random effects for cross sectional studies with median age <69 years compared to cross sectional studies with median age >69 years.

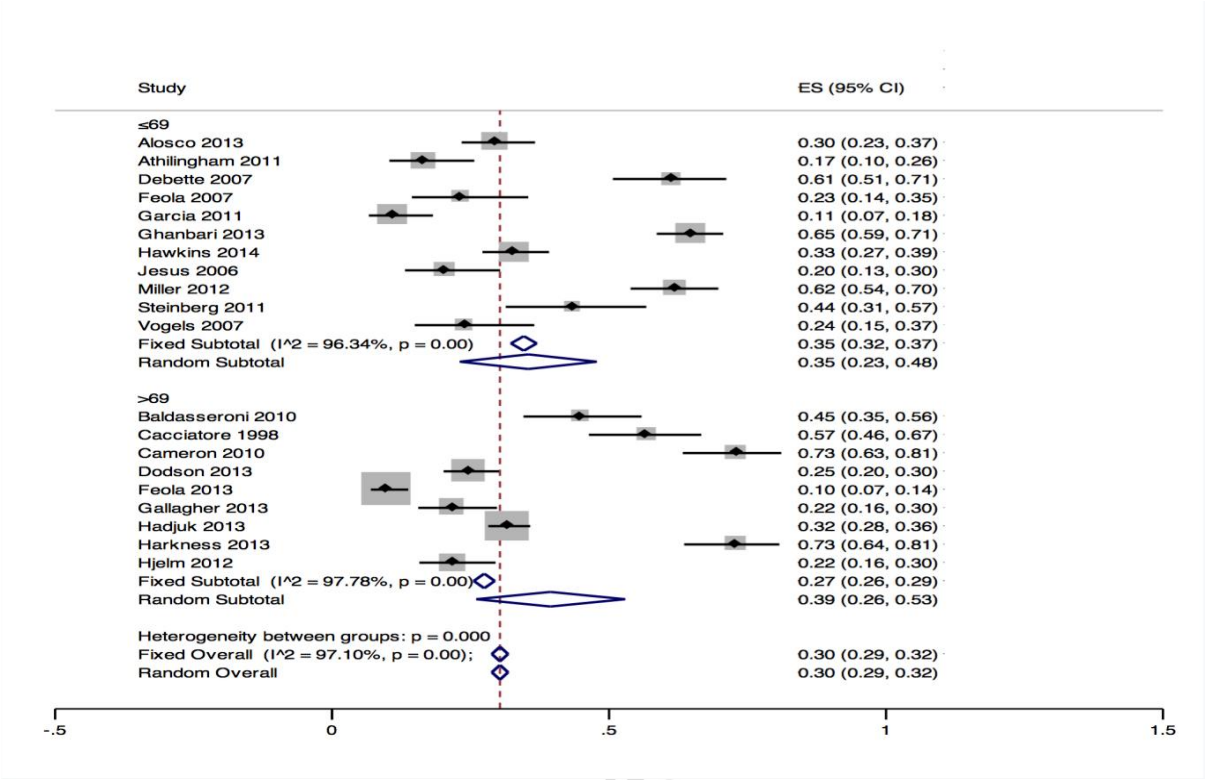


Figure 6. Forest plot showing fixed and random effects for case controlled studies (heart failure vs. no heart failure)

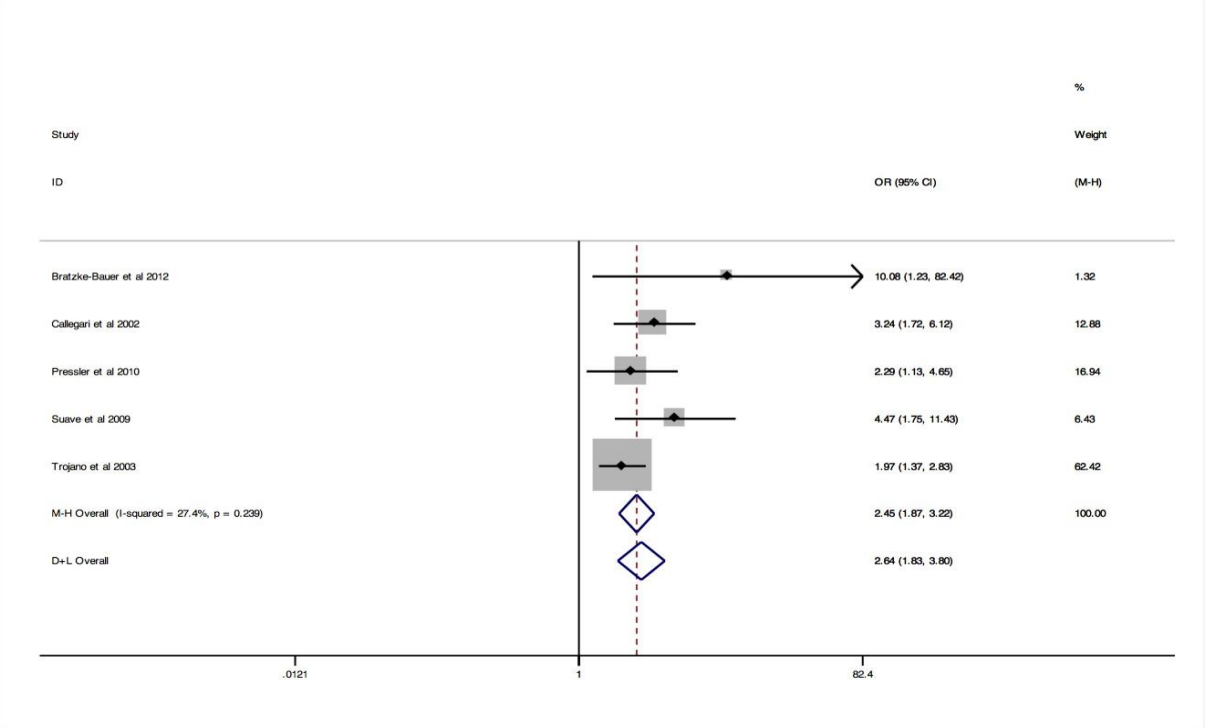
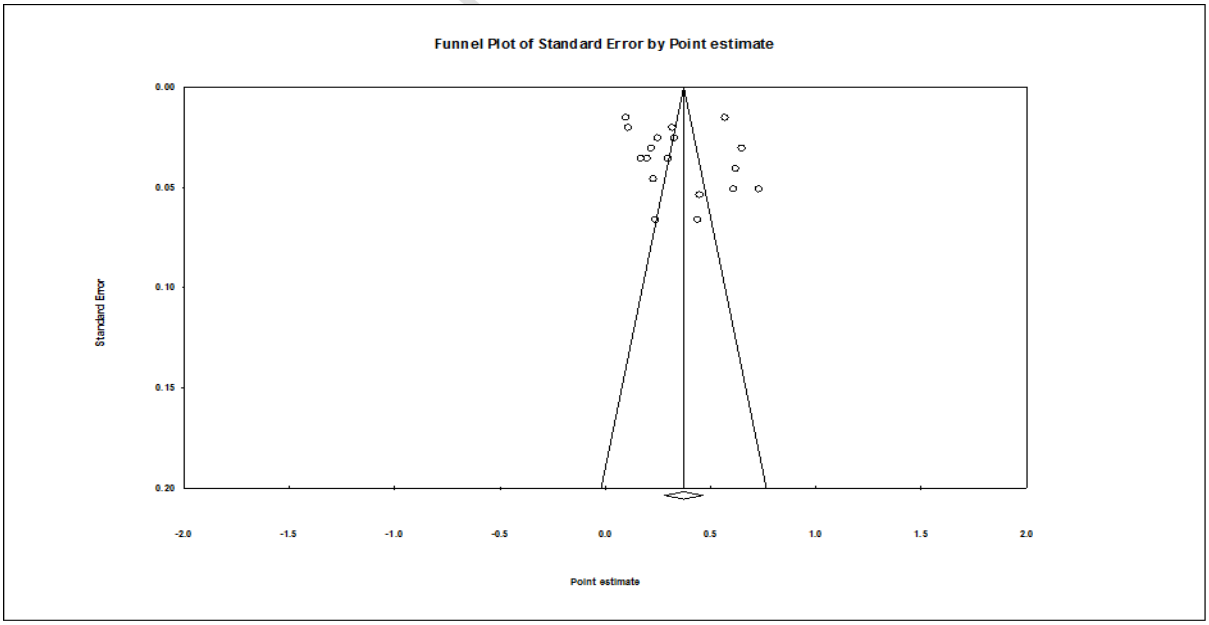


Figure 7. Funnel plot of standard error by point estimate



Tables 1 -3: Study design

Table 1. Design of case-controlled studies

Study	Sample	Population	CV Measures/Criteria	Cognitive assessment tool used
Bauer et al 2011[11]	51 HF-REF patients 29 HF-PEF patients	Outpatients only	LVEF NYHA	RBANS Neuropsychological battery
Bratzke-Bauer et al 2013[12]	47 HF-REF patients 33 HF-PEF patients	Outpatients only	LVEF NYHA	MMSE RBANS Neuropsychological battery
Callegari et al 2002[13]	64 HF patients 321 healthy control participants	Consecutive admissions	LVEF<50% NYHA I-III CPET Right heart catheterisation	Neuropsychological battery
Festa et al 2011[14]	169 HF-REF patients 38 HF-PEF patients	Outpatients only	LVEF	Neuropsychological battery
Pressler et al 2010[15]	249 HF patients 63 healthy control participants 102 general medical patients	Outpatients only	NYHA LVEF	MMSE Neuropsychological battery
Sauvé et al 2009[16]	50 HF patients 50 healthy control participants	Outpatients only	LVEF≤40% NYHA II-IV	Neuropsychological battery
Trojano et al 2003[17]	149 HF NYHA II patients 159 HF NYHA III/IV patients 207 non HF control patients	Consecutive admissions	No measure of LV function NYHA II-IV	MMSE Neuropsychological battery

Table 2. Design of cross-sectional studies

Study	Sample	Population	Age (years)	CV Measures /Criteria	Cognitive assessment tool used
Alosco et al 2014[18]	110 CHF pts	Outpatients	70 (9)	LVEF NYHA II-IV	3MS
Alosco et al 2012[19]	157 CHF pts	Outpatients	69 (10)	2 minute step test NYHA	Neuropsychological battery
Alosco et al 2013[20]	52 CHF pts	Outpatients	66 (9)	Cardiac Index	MMSE RBANS
Alosco et al 2014[21]	179 CHF pts	Outpatients	68 (10)	LVEF NYHA II-IV	Neuropsychological battery
Antonelli et al 2003[22]	369 CHF pts	Consecutive admissions	77 (7)	NYHA	MMSE Neuropsychological battery
Arslanian- Engoren et al 2014[23]	53 CHF pts	Inpatients	72 (5)	NYHA	Cogstate battery
Athilingam et al 2011[24]	90 CHF pts	Outpatients	62 (9)	NYHA LVEF Cardiac index & 6 minute walk test	MMSE MoCA
Baldasseroni et al 2010[25]	80 CHF pts	Outpatients	72 (6)	NYHA 6 minute walk test LVEF MLHFQ	MMSE
Cacciatore et al 1998[26]	92 CHF participants	Outpatients	74 (6)	NYHA	MMSE
Cameron et al 2010[27]	93 CHF pts	Consecutive admissions	73 (11)	LVEF NYHA Self-care HF index	MMSE MoCA
Debette et al 2007[28]	83 HF pts	Consecutive admissions	62	LVEF<45% NYHA I-IV	MMSE
Dodson et al 2013[29]	282 Decompensated HF pts	Non-consecutive admissions	80 (8)	HF diagnosis based on documentation in medical records	MMSE
Feola et al 2007[30]	60 CHF pts	Inpatients	66	LVEF NYHA II-IV BNP	Neuropsychological battery
Feola et al 2013[31]	303 CHF pts	Consecutive	72 (10)	LVEF NYHA	MMSE

		admissions		BNP 6 minute walk test Non-invasive CO	
Gallagher et al 2013[32]	128 CHF pts	Outpatients	81	NYHA MLHFQ	MoCA
Garcia et al 2011[33]	116 CHF	Outpatients	69 (9)	NYHA 2 minute step test	3MS Neuropsychological battery
Ghanbari et al 2013[34]	239 CHF pts	Outpatients	59 (10)	NYHA LVEF	MMSE
Hajduk et al 2013[35]	577 CHF pts	Inpatients	71	Not specified	MoCA Neuropsychological battery
Harkness et al 2013[36]	100 CHF pts	Outpatients	72 (10)	LVEF ≤45% NYHA I-III Self-care in HF index	MMSE MoCA
Hawkins et al 2014[37]	231 CHF pts	Outpatients	69 (7)	NYHA	Neuropsychological battery
Hawkins et al 2012[38]	250 CHF pts	Outpatients	66 (10)	LVEF	RBANS Neuropsychological battery
Hjelm et al 2013[39]	137 CHF pts	Outpatients	72	NYHA LVEF BNP	MMSE Neuropsychological battery
Jesus et al 2006[40]	83 CHF pts	Outpatients	55 (12)	LVEF	MMSE
Miller et al 2012[41]	140 HF pts	Outpatients only	69 (9)	No measure of LV function No NYHA classification 2 minute step test	Neuropsychological battery
Steinberg et al 2011[42]	55 HF pts	Outpatients only	55 (8)	LVEF≤45% NYHA I-III 6 Minute Walk Test	MMSE Neuropsychological battery
Vogels et al 2007[43]	58 CHF pts	Outpatients	69 (9)	LVEF NYHA	MMSE Neuropsychological battery

Table 3. Design of longitudinal studies

Study	Sample	Population	CV Measures /Criteria	Cognitive assessment tool used	Follow up period
Almeida et al 2012[44]	77 CHF pts with LVEF <40% 73 CAD pts with LVEF >60% 81 controls with no CAD/CHF	Outpatients	LVEF 6 minute walk test	MMSE Neuropsychological battery	24 months
Hjelm et al 2012[45]	95 HF pts 607 non-CHF controls	Outpatients	HF diagnosis based on documentation in medical records	Neuropsychological battery	10 years
Qiu et al 2006[46]	205 CHF pts 1096 controls	Outpatients	Not specified	MMSE	9 years
Riegel et al 2012[47]	279 consecutive HF pts (HF-REF & HF-PEF)	Outpatients	NYHA I-IV LVEF	Neuropsychological battery	6 months

Table 4: Results from longitudinal studies

Study	Sample	Age (Years)	Relative Risk	95% CI	Follow up period	Change over time
Almeida et al 2012[44]	77 CHF pts with LVEF <40% 73 CAD pts with LVEF >60% 81 controls with no CAD/CHF	68 (10) 68 (10) 69 (11)	N/A	N/A	24 months	CAMCOG scores in CHF group declined by 0.9 points over 2 years No other differences between groups
Hjelm et al 2012[45]	95 HF pts 607 non-CHF controls	84(3)	1.258	0.952 – 1.661	10 years	HF patients: Significant decline in episodic memory & spatial performance compared with controls.
Qiu et al 2006[46]	205 CHF pts 1096 Controls	83 (5) 81 (5)	0.878	0.765 – 1.007	9 years	Over 9 years 53% CHF patients developed CI & 61% of controls developed CI
Riegel et al 2012[47]	279 consecutive HF pts (HF-REF & HF-PEF)	62 (12)	N/A	N/A	6 months	No significant change in cognition over 6 months (HF-REF and HF-PEF) Minimal improvement in DSST (53 (18)- 58 (18)) in both groups likely due to learned effect