Effect of Vascular Risk Factors and Diseases on Mortality in Individuals with Dementia: A Systematic Review and Meta-Analysis

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OBJECTIVES: To assess the effect of cardiovascular diseases and risk factors on mortality in individuals with dementia.

DESIGN: Systematic review and meta-analysis. English- and Dutch-language studies in PubMed, EMBASE, and PsycINFO databases were searched in April 2014 with hand-searching of in-text citations and no publication limitations. Inclusion criteria were original studies reporting on cardiovascular risk factors or diseases and their relationship with survival in individuals with dementia. The Quality In Prognosis Studies tool was used to appraise all included articles.

SETTING: Population-, hospital-, and nursing home–based.

PARTICIPANTS: Community-dwelling, hospitalized individuals and nursing home residents with dementia.

MEASUREMENTS: A random-effects meta-analysis was performed to investigate the effect of several cardiovascular diseases and risk factors on overall mortality.

RESULTS: Twelve studies with 235,865 participants were included. In pooled analyses, male sex (hazard ratio (HR) = 1.67, 95% confidence interval (CI) = 1.56–1.78), diabetes mellitus (DM) (HR = 1.49, 95% CI = 1.33–1.68), smoking (ever vs never) (HR = 1.37, 95% CI = 1.17–1.61), coronary heart disease (CHD) (HR = 1.21, 95% CI = 1.02–1.44) and congestive heart failure (CHF) (HR = 1.37, 95% CI = 1.18–1.59) were associated with mortality. Stroke, high blood pressure, being overweight, and hypercholesterolemia were not statistically significantly related to mortality.

CONCLUSION: Individuals with dementia and DM, smoking, CHD, and CHF have a greater risk of death than individuals with dementia without these risk factors or diseases. **J Am Geriatr Soc 64:37–46, 2016.**

Key words: cardiovascular disease; dementia; meta-analysis; prognosis; review

Dementia is a severe disease with an often poor prognosis. The literature suggests that mortality risk of individuals with dementia is at least twice as high as mortality risk of persons without dementia, with even higher risks in younger individuals.[1,2] The burden of dementia is steadily rising, and it is expected that dementia will be the leading cause of death in the near future.[3] Survival time ranges broadly[4] and ultimately depends on underlying risk factors including sex, age, socioeconomic factors, type of dementia, and presence of comorbidity (e.g., cardiovascular disease (CVD)).[5,6]

CVD and dementia are closely related because they share many risk factors (RFs), and vascular diseases are the second most common cause of dementia.[7] Research on the relationship between CVD, RFs, and dementia has focused mainly on the development of dementia in the presence of CVD and RFs. These factors increase the incidence of dementia.[8] In contrast, the effect of these factors on the progression of dementia is less consistent, and the effect on mortality risk in individuals with dementia is not clear at all.[9]

Information on the effect of CVD and RFs on the prognosis of individuals with dementia is valuable for individuals, caregivers, and clinicians because the estimated prognosis inevitably determines decision-making regarding diagnostic and therapeutic interventions. Individual studies have had inconsistent results on the effect of CVD and RFs on the prognosis of individuals with dementia, and systematic reviews on this topic are lacking Therefore, this study aimed to systematically review and meta-analyze the effect of CVD and RFs on mortality risk in individuals diagnosed with dementia.

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METHODS

The systematic review, including a meta-analysis, was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

Search Strategy

A systematic literature search was conducted on April 1, 2014, to identify all relevant publications on the effect of CVD and RFs on mortality in individuals diagnosed with dementia. An electronic search was conducted using PubMed, EMBASE, and PsycINFO without any restriction as to calendar time. The complete search syntax for PubMed can be found in Appendix S1.

Reference lists of all identified studies were also searched for other relevant citations that the search did not obtain.

Inclusion and Exclusion Criteria

Articles were included if the study population included individuals diagnosed with dementia with and without CVD and RFs; they reported on cohort studies reporting on all-cause mortality; the determinants of interest (CVD and RFs) were evaluated (e.g., hypertension, diabetes mellitus (DM); hypercholesterolemia, smoking, overweight or body mass index, myocardial infarction, stroke, congestive heart failure (CHF)); they were original articles; and they were published in English or Dutch.

Articles were excluded if they did not meet the inclusion criteria, if they compared mortality risk of individuals diagnosed with dementia with that of (healthy) controls without dementia, if comorbid conditions were not subclassified into CVD and RFs, if risk of death in individuals with dementia could not be obtained, and if there was no abstract or full text available.

Selection Process

Search results from the aforementioned syntax were imported to Refworks, and duplicates were removed after screening for being correctly selected as duplicates. The selection process comprised three stages: selection by title, review by abstract, and review by full-text.

Three independent reviewers (IvdV, IV, RV), screened titles for relevance, then two independent reviewers (IvdV and RV) reviewed potentially relevant abstracts and full text. If there was any disagreement between the reviewers, the final decision was reached by consensus. Three of the six articles that were not available online were retrieved from authors, and the other three whose authors did not respond were excluded.

Assessing the Risk of Bias

The Quality In Prognosis Studies tool, developed to support assessment of bias in prognostic studies, was used to assess the risk of bias for all included studies.[11] For each publication, the type of bias according to six domains was assessed (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement, appropriate statistical analyses).

Data Extraction and Analysis

After inclusion of all articles, information on first author, year of publication, study design, year of data collection, characteristics of study population (sample size, mean age, distribution of sex, type of dementia), criteria used to diagnose dementia, the CVD and RFs under investigation and source of information on comorbidities, number of deaths, and duration of follow-up was extracted from the included studies. If studies provided information on multiple factors influencing survival time, only information on CVD and RFs was included in this review. One study provided data for participants with Alzheimer's disease (AD) and vascular dementia separately.[12] To simply compare mortality risks across the different studies, only information on individuals diagnosed with AD was extracted from this study because all other studies reported particularly on individuals with unspecified dementia or AD.

A meta-analysis was conducted to assess the direction and strength of the association between the determinants and outcome of interest. For all analyses, effect estimates per CVD and RF provided in the original publications were used. Most studies provided hazard ratios (HRs) or relative risks (RRs) for mortality per CVD and RFs separately. HRs were assumed to equal RRs. If studies did not provide HRs or RRs, two-by-two tables were reconstructed to calculate RRs by using extracted numbers of participants with dementia who died or not and with or without the determinant. If articles presented data insufficient to reconstruct two-by-two tables, the authors were contacted and asked whether their data could be reanalyzed. If it was not possible to generate the data or if the authors did not respond, articles were excluded (n = 4).[13–16] The log(risk ratio) and standard error per determinant were calculated if not reported.

Results from all studies were combined using random effect models, stratifying the data for each CVD and RF. Random effect models were used because heterogeneity in results across studies was assumed because of differences in how determinants were measured and defined and differences in participant characteristics and selection. Pooled effect estimates were presented as RRs with corresponding 95% confidence intervals (CIs). A univariate pooled and, if available, a multivariate pooled effect estimate per determinant was provided. Data were pooled and graphically displayed using Review Manager 5.3 software from the Cochrane Collaboration (Nordic Cochrane Centre, Copenhagen, Denmark).

The I^2-statistic and prediction intervals were used to quantify heterogeneity. The I^2-statistic is a measure of inconsistency that describes the percentage of observed variability in results, which reflects real differences in effects rather than variation that can be expected because of chance. I^2 values greater than 50% indicate significant heterogeneity.[17] A 95% prediction interval shows the likely range of values for the HR that can be expected if a new and large study would be performed comparable with ones included in this review. The prediction interval provides insight into the variability or consistency between the results of individual studies, whereas a 95% CI around the pooled

estimates provides insight into how certain the value of the pooled estimate is. The amount of between-study variation (also known as the tau-squared value of a random effects model) is the critical factor determining the width of a 95% prediction interval; large values of between-study variation will result in a wide prediction interval, even if a large number of studies are included in a review.[18,19]

RESULTS

Selection and Characteristics of Studies

The initial search returned 15,774 potentially relevant articles (Figure 1). Duplicate studies were deleted (n = 3,071). After assessing abstracts, applying inclusion and exclusion criteria, and assessing risk of bias, 12 articles remained. The rest were excluded mainly because they did not concern the determinants of interest (e.g., comorbidities other than CVD) or the domain of interest (e.g., older adults without distinction between those with and without dementia). No additional articles were found from reference lists. Table 1 summarizes the characteristics of the included articles and outcomes of interest.

Study Quality and Risk of Bias in Included Studies

Overall, the quality of the included study cohorts was moderate to good (see the summary of results of the

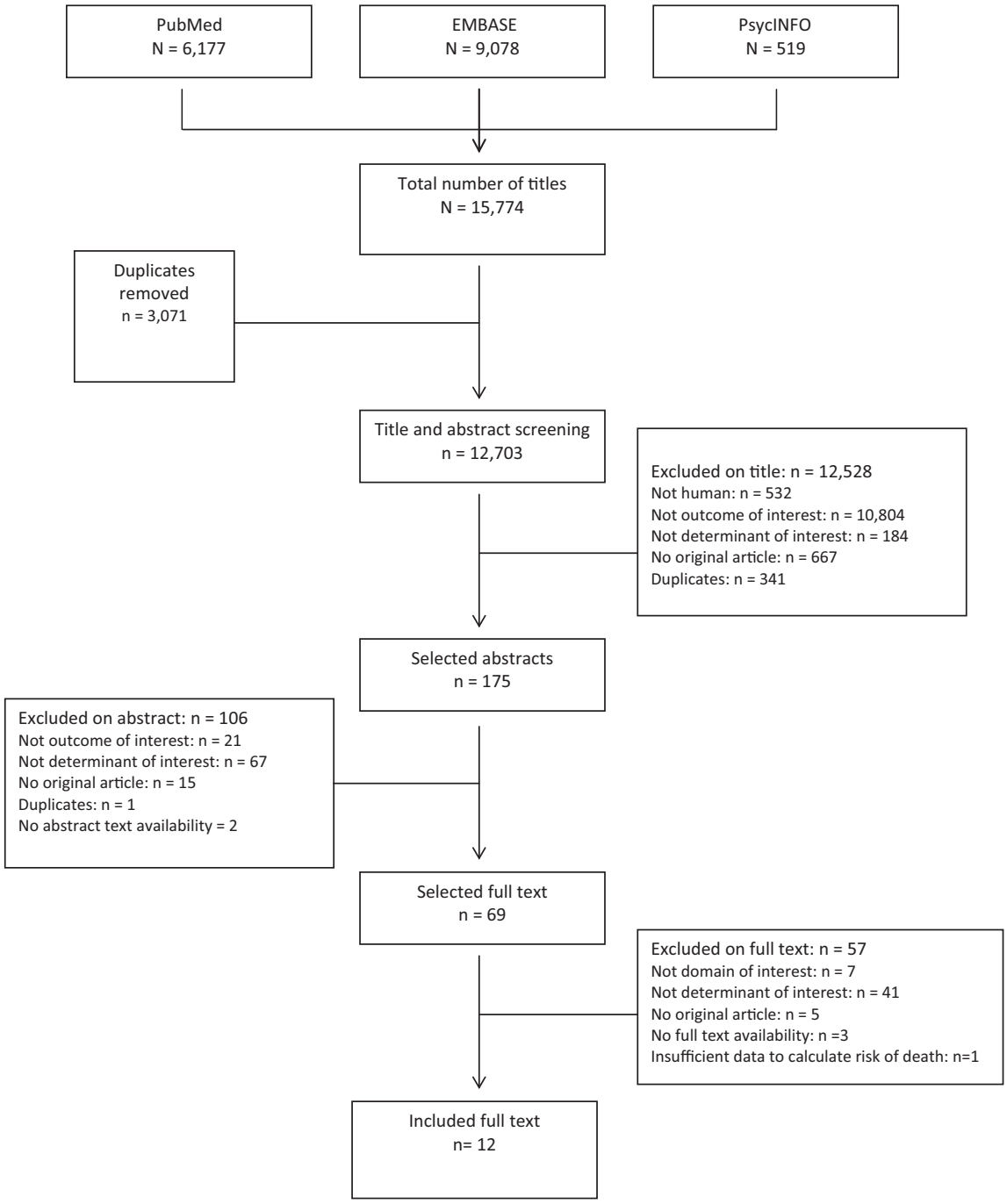

Figure 1. Flowchart of literature search performed on April 1, 2014.

Table 1. Characteristics of 12 Studies Describing the Effects of Cardiovascular Disease or Risk Factors on Mortality in Individuals with Dementia

Author	Year	Data Collection	Study Design	Total, n	Female, %	Mean Age	Dementia Subtype	Dementia Criteria	Source of Determinants	Deaths, n	Follow-Up
Bowen[21]	1996	1987–1993	Prospective population based	327	64	79	AD	NINCDS-ADRDA	Clinical examination, records	234	0.1–6.5 years
Freels[12]	2002	1991–1992	Prospective hospital based	113	62	NR[a]	AD	NINCDS-ADRDA	Clinical examination	53	7 years
Larson[1]	2004	1987–1996	Prospective population based	521	66	NR[a]	AD	NINCDS-ADRDA, DSM-III-R	Records, interview, questionnaires	419	Maximum 14 years
Tsai[47]	2007	1996–1998	Prospective hospital based	159	64	74	AD	DSM-III-R	Records	46	Mean 4.3 years
Helzner[39]	2008	1992 and 1999	Prospective population based	323	70	87	AD	NINCDS-ADRDA, DSM-III	Interview, questionnaires	140	Mean 4.0 years
Delva[48]	2013	1994–2007	Prospective population based	454	67	86	NS	NINCDS-ADRDA, Hachinski	Interview, questionnaires	319	5 years
Go[20]	2013	1995–2005	Prospective hospital based	724	71	71	AD	NINCDS-ADRDA	Clinical examination, interview, questionnaires	375	Mean 7.3 years
Koopmans[49]	1994	1980–1989	Prospective nursing home based	767	70	81	NS	DSM-III-R	Clinical examination, records	383	12 years
Van Dijk[50]	1996	1982–1988	Prospective nursing home based	606	72	81	NS	DSM-III-R	Clinical examination, records	278	1–7 years
Gambassi[22]	1999	1992–1995	Prospective nursing home based	9,264	69	82	AD	NINCDS-ADRDA, DSM-IV	Records	4,631	Median 23 months
Hicks[40]	2010	2000–2004	Prospective nursing home based, individuals meeting hospice eligibility criteria	123	55	82	NS	NR	Records, interview, questionnaires	93	Mean 60.8 weeks
Mitchell[24]	2010	2002	Retrospective nursing home based, advanced dementia	222,405	77	85	NS	NR	Records	90,324	12 months

[a]Available only for subgroups.

AD = Alzheimer's disease; VaD = vascular dementia; NS = not specified; NR = not reported; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer's Disease and Related Disorders Association; DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; DSM-IV = *Diagnostic and Statistical Manual, Fourth Edition*.

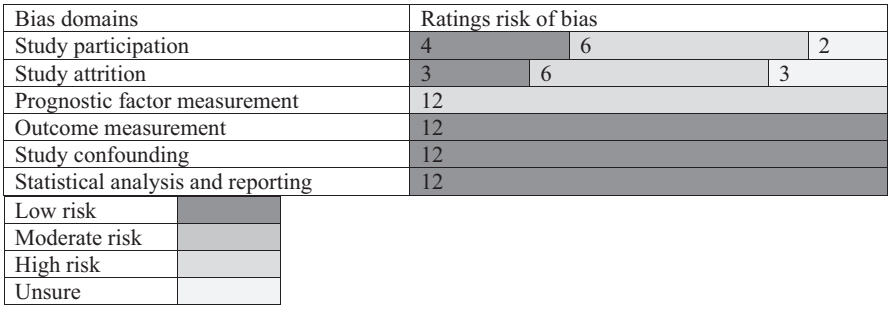

Figure 2. Summary of risk of bias of 12 included studies using the Quality In Prognosis Studies tool.

Quality In Prognosis Studies checklist in Figure 2 and a comprehensive overview in Appendix S2). In eight studies, the source population was not comprehensively described, or the authors referred to previously published articles, some of which were unavailable in full text. Not providing reasons for loss to follow-up caused risk of bias due to study attrition in three studies. The majority of studies collected information on determinants from questionnaires or participant records without a clear definition (e.g., cutoff levels), which might lead to differences in classification of CVD and RFs. The method of data collection in each study was similar for all individuals under investigation in that particular study. All studies provided a clear definition of outcome, adjusted for all important confounders, and used adequate statistical models.

Determinants

Most studies showed an overview of a broad range of factors related to survival time in individuals with dementia. The majority provided solely the statistically significant multivariate HRs or RRs. Univariate and multivariate pooled effect estimates per determinant were therefore calculated only when they were investigated in three or more articles (Table 2). Multivariate effect estimates were graphically presented in forest plots (Figure 3).

Cardiovascular Risk Factors

Sex

All included studies provided univariate HRs or RRs for the effect of sex on risk of mortality in individuals with dementia, and six presented multivariate HRs. More than 200,000 individuals were involved in both analyses. The majority of studies showed a better prognosis for women than men. In the univariate (RR = 1.32, 95% CI = 1.17–1.49) and multivariate (RR = 1.67, 95% CI = 1.56–1.78) pooled analysis, greater mortality risk was observed for men than women. Heterogeneity across studies was nonsignificant according to the multivariate pooled random effect analysis (I^2 = 44%, P = .12). The 95% prediction interval (range of likely values of a new and larger study) for sex ranged from 1.36 to 2.06.

Diabetes Mellitus

The relation between DM and mortality risk was well described in univariate (n = 12) and multivariate analyses (n = 9). Approximately 13,000 individuals were involved in the multivariate meta-analysis. The pooled analysis showed a statistically significantly greater mortality risk in participants with DM (multivariate RR = 1.49, 95% CI = 1.33–1.68), with acceptable heterogeneity across studies (I^2 = 35%, P = .14). The prediction interval for DM ranged from 1.19 to 1.87.

Hypertension

Nine studies reported univariate estimates, and three reported multivariate estimates of the effect of hypertension on mortality risk. The multivariate pooled analysis showed no statistically significant effect of hypertension on mortality risk in individuals with dementia (multivariate RR = 1.25, 95% CI = 0.81–1.93). There was a considerable amount of heterogeneity in results between the studies (I^2 = 61%, P = .08). The prediction interval for hypertension ranged from 0.60 to 2.60.

Smoking

Smoking, defined as ever versus never smoker, was described only in univariate analyses (n = 3). All studies showed a statistically significant higher mortality risk in smokers (RR = 1.37, 95% CI = 1.17–1.61). Evaluation of heterogeneity is difficult with only three studies, but differences between the three studies were small (I^2 = 0%). The prediction interval for smoking ranged from 1.17 to 1.60.

Hypercholesterolemia

Only two studies described the effect of hypercholesterolemia on risk of death,[12,20] so the data were not pooled. Both studies showed that a history of hypercholesterolemia did not increase risk of death in individuals with dementia.

Body Mass Index

Three studies evaluated the effect of weight on mortality risk,[21–23] but body mass index (BMI) was used as a marker of poor nutritional status in two of the three studies and hence was not considered as a risk factor for CVD. Only one study described lower mortality risk in individuals with a BMI of 25.0 kg/m^2 or greater (BMI 25.0–29.9 kg/m^2: RR = 0.76, 95% CI = 0.74–0.77; BMI 30.0–34.9 kg/m^2: RR = 0.66, 95% CI = 0.64–0.68; BMI ≥ 35.0 kg/m^2: RR = 0.66, 95% CI = 0.62–0.71).[24]

Table 2. Overview of Determinants Included in Most Comprehensive Prognostic Model Considered in 12 Studies

Study Determinants	Total	Bowen	Freels	Larson	Tsai	Helzner	Delva	Go	Koopmans	Van Dijk	Gambassi	Hicks	Mitchell
Univariate analysis													
Sex	12	x	x	x	x	x	x	x	x	x	x	x	x
Cardiovascular risk factors													
Diabetes mellitus	12	x	x	x	x	x	x	x	x	x	x	x	x
Hypercholesterolemia	2		x					x					
Hypertension	9	x	x	x	x	x		x	x	x			x
Smoking	3	x	x					x					x
Body mass index	3	x						x					
Cardiovascular diseases													
Coronary heart disease	8	x	x	x	x		x		x	x			x
Congestive heart failure	4			x					x	x			x
Stroke	8			x		x	x	x	x	x	x		x
Transient ischemic attack	2					x			x	x			
Heart disease	5	x				x		x			x	x	
Multivariate analysis													
Sex	9					x	x	x	x	x	x	x	x
Cardiovascular risk factors													
Diabetes mellitus	9	x		x		x	x	x	x	x	x	x	x
Hypercholesterolemia	0												
Hypertension	3	x		x		x							
Smoking	0												
Body mass index	2	x											
Cardiovascular diseases													
Coronary heart disease	3	x		x			x						
Congestive heart failure	3			x						x			x
Stroke	3			x			x				x		
Transient ischemic attack	1					x							
Heart disease	3	x									x	x	

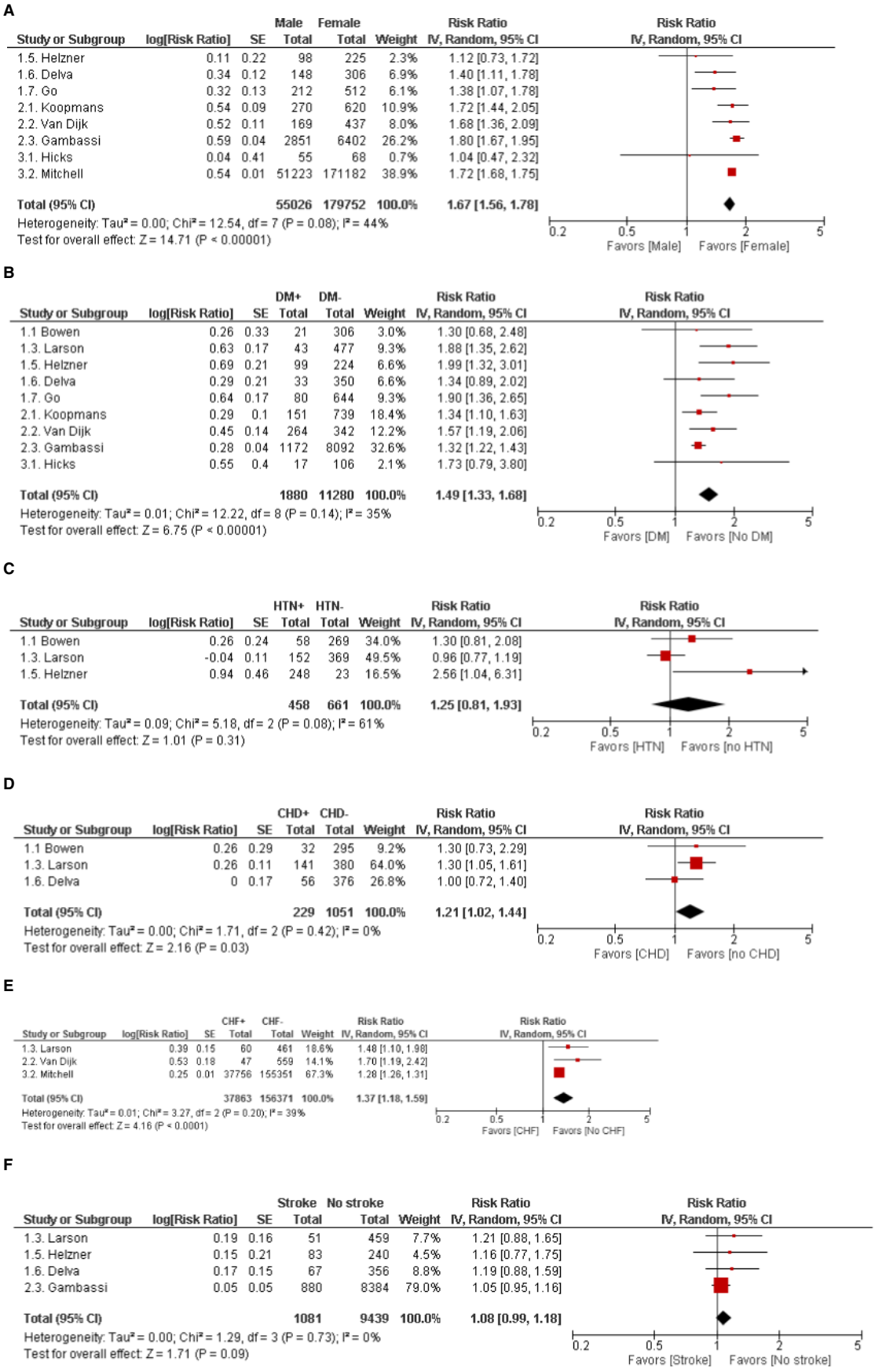

Figure 3. Forrest plots of relative risk for associations between cardiovascular diseases or risk factors and mortality in individuals with dementia. Effect of (A) sex, (B) diabetes mellitus (DM), (C) hypertension (HTN), (D) coronary heart disease (CHD), (E) congestive heart failure (CHF), (F) stroke. SE = standard error; CI = confidence interval; *df* = degrees of freedom.

Cardiovascular Diseases

Coronary Heart Disease

Studies describing the relationship between myocardial infarction, ischemic heart disease, or coronary heart disease (CHD) and all-cause mortality were combined. Three studies provided multivariate HRs for a total of 1,051 participants. A greater mortality risk was observed in participants with CHD, although the effect was marginally significant (multivariate RR = 1.21, 95% CI = 1.02–1.44). Differences between the three studies were small (I^2 = 0%). The prediction interval for CHD ranged from 1.02 to 1.44.

Congestive Heart Failure

Four studies provided univariate HRs, and three provided multivariate HRs. The pooled analysis showed greater mortality risk in individuals with CHF in both analyses (multivariate RR = 1.37, 95% CI = 1.18–1.59). The prediction interval ranged from 1.07 to 1.75.

Stroke

Eight reported univariate effect estimates of stroke on mortality risk, and four studies reported multivariate effect estimates. Whereas the univariate pooled analysis, including 235,145 participants, found a statistically significant effect of stroke on mortality risk in favor of participants without stroke (RR = 1.16, 95% CI = 1.10–1.23), the multivariate meta-analysis, including 10,520 participants, did not (RR = 1.08, 95% CI = 0.99–1.18). Heterogeneity was negligible (I^2 = 0%). The prediction interval ranged from 0.99 to 1.18.

DISCUSSION

The main finding was that several cardiovascular RFs (male sex, DM, smoking) and several CVDs (CHD and CHF) are associated with mortality risk in individuals with dementia. Information on prognosis in individuals with dementia concerning the presence of CVD and RFs is limited in contrast to the wealth of data on the incidence of dementia with respect to CVD and RFs.

The results regarding the cardiovascular RFs that appeared to be associated with greater mortality risk in individuals with dementia are consistent with previously performed studies focusing on older adults but not necessarily individuals with dementia. The negative effect of DM and smoking on life expectancy in general is well known and is primarily based on the greater risk of CVD.[25,26]

It was also found that male sex was associated with poorer prognosis. Although there is some inconsistency in the literature regarding the effect of sex, there is a general tendency toward greater mortality risk in men than in women with dementia.[4,27,28] However, these studies were not included in this review because they did not investigate other RFs or CVD.

Furthermore, some cardiovascular RFs known to be associated with a poor prognosis in middle-aged individuals (hypertension, hypercholesterolemia, overweight) were not associated with greater mortality risk in participants with dementia. Paradoxically, these risk factors have less of an effect on mortality in older adults than in younger individuals, as has been described in previous studies. Although hypertension in midlife is associated with greater risk of dementia, some studies suggest that hypertension in late life is associated with lower risk of death. Moreover, this inverse relationship between blood pressure and mortality risk is most striking in people who are frail, such as individuals with dementia.[29] Hypercholesterolemia has been implicated in the pathogenesis of dementia, but pathophysiological mechanisms have not yet been completely determined.[30] Although high lipid levels are generally associated with greater risk of CVD and death, some observational studies in older adults have demonstrated protective effect of high cholesterol levels with respect to life expectancy.[31] No relationship was found between overweight and mortality risk, and BMI was used as a marker of nutritional status instead of a RF for CVD in two of the three studies. Although high midlife BMI has been associated with brain atrophy, white matter changes, and greater risk of dementia,[32] obesity in elderly adults is associated with better survival outcomes, a phenomenon known as the obesity paradox.[33]

With respect to CVD, a history of CHF was found to be associated with greater mortality risk in individuals with dementia. The unfavorable effect of the combination of CHF and cognitive impairment on prognosis is in line with findings of previous studies that investigated mortality risk in individuals with CHF.[34,35] These studies demonstrated greater mortality risk in individuals with CHF and cognitive impairment than in individuals with CHF without cognitive impairment (HR range 1.9–4.9). A marginally greater risk of mortality was found in individuals with dementia and CHD than those with dementia without CHD. Previous studies have shown that, in general, mortality risk after CHD increases considerably with increasing age, being up to 10 times as great in individuals aged 85 and older with respect to short-term prognosis.[36–38] Furthermore, no differences were found in mortality risk between individuals with and without a history of stroke. This might be a result of survival bias if only participants who survived a certain period of greater risk after their event, thus those with a good prognosis, were included in the studies.

Limitations

Some limitations need to be addressed. Four studies included in this review investigated the effect of "heart disease," including a broad range of CVD and RFs.[20,22,39,40] A clear, standardized definition was lacking, and therefore this determinant could not be taken into account in the analyses. The study was limited in that there were no individual participant data available to study prognosis in more depth and to estimate the prognosis for individual participants.

Strengths and Clinical Implications

This is among the first systematic reviews and meta-analyses focusing on the effect of CVD and RFs in individuals with dementia. Twelve cohorts with 235,865 participants

were included, and the strength and direction of the relationship between several CVDs and RFs and mortality risk were assessed. The findings might be supportive for clinicians, individuals and caregivers concerning advance care planning as this is inevitably associated with expected prognosis.

Furthermore, the question arises how and whether hypercholesterolemia and hypertension should be treated in elderly adults with dementia because these risk factors were not associated with greater mortality risk, although evidence from randomized controlled trials on the effect of treatment of these RFs in vulnerable elderly adults is scarce. In these trials, elderly adults are often defined as persons aged 60 to 80. There is evidence, derived from these trials, that treatment of hypertension reduces the risk of cardiovascular morbidity and mortality and all-cause mortality, although the evidence was not overwhelming, and the effect of the latter was limited to individuals aged 60 to 85.[41–45] Evidence of lower cardiovascular morbidity and mortality in elderly adults undergoing statin therapy is limited to secondary prevention.[46] Because evidence-based guidelines for appropriate care in vulnerable elderly adults, including those with dementia, are limited, initiation or continuation of therapy should be based on individual preferences and improvement of quality of life after careful evaluation of the probable benefits and potential risks of the treatment. Given the limited amount of available data from trials, there is an urgent need for randomized controlled trials representing frail elderly adults, especially individuals with dementia, given the high incidence of this disease in elderly adults, to support management in daily practice in these individuals.

CONCLUSION

Male sex, DM, smoking, CHD, and CHF had an unfavorable effect on mortality in individuals with dementia.

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Author Contributions: All authors: study concept and design, critical review and approval of final manuscript. van de Vorst, de Vries, Vaartjes, Koek: data acquisition. van de Vorst, Vaartjes, Koek, Bots, Reitsma: analysis and writing of manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search Strategy.

Appendix S2. Assessing Risk of Bias of 12 Included Studies.

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