ann. behav. med. (2012) 43:299–310
DOI 10.1007/s12160-011-9339-0

ORIGINAL ARTICLE

Association Between Type D Personality and Prognosis in Patients with Cardiovascular Diseases: a Systematic Review and Meta-analysis

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Published online: 12 January 2012

Abstract
Background Since 1995, the association of type D personality and mortality in patients with cardiovascular diseases has been increasingly investigated.
Purpose The aim of this meta-analysis was to integrate conflicting results and to examine possible moderators of this association.
Methods Prospective studies assessing type D personality and hard endpoints were selected and pooled in meta-analyses. Cardiovascular diagnosis, type and quality of adjustment, and publication date were examined in moderator analyses.
Results Twelve studies on patients with cardiovascular diseases (N=5,341) were included. Pooled crude and adjusted effects demonstrated a significant association of type D personality and hard endpoints (odds ratio (OR) of 2.28 (95% CI [1.43–3.62]), adjusted hazard ratio (HR) of 2.24 (95% CI [1.37–3.66])). The OR decreased over time (OR 5.02 to OR 1.54). There was no association in congestive heart failure patients.
Conclusions More recent methodologically sound studies suggest that early type D studies had overestimated the prognostic relevance.

Electronic supplementary material The online version of this article (doi:10.1007/s12160-011-9339-0) contains supplementary material, which is available to authorized users.

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Keywords Meta-analysis · Cardiovascular disease · Type D personality · Mortality

Introduction

Sixteen years ago, the first study on the association of type D personality with a higher mortality rate in patients with coronary artery disease (CAD) was published [1], marking a milestone regarding the potential influence of personality characteristics on physical health in behavioral medicine. Type D personality refers to the "distressed" personality type and is characterized by the interaction of two traits: a high level of negative affectivity and a high level of social inhibition [2]. Since that time, this personality trait has been increasingly investigated and discussed as an independent risk factor for the prognosis of patients with heart disease.

Five reviews that included hard endpoints have been published since then; among these are two narrative reviews [2, 3] and three systematic reviews [4–6]. All these reviews consistently concluded that type D personality is associated with an increased risk of adverse cardiac events. However, methodological shortcomings of earlier reviews weaken this conclusion substantially. The first critical point is related to the definition of hard endpoints, which is a core condition for validity. Reich and Schatzberg selected studies with standardized measures of physical illness as endpoints—including health-related quality of life, arrhythmias, success of heart surgery, and cardiac events—for their meta-analysis [4]. Even the most recent meta-analyses [5, 6], which were restricted to prognostic studies with hard endpoints, included composite endpoints of major cardiac events, including revascularization. A second point to consider is that all studies analyzed in earlier reviews were conducted in Denollet's work group and were based exclusively on samples from The

Netherlands and Belgium. In the review by Denollet and colleagues [5], data turned out to be subsamples [7, 8] of a more comprehensive study [9, 10], which were included in duplicate in the meta-analysis. Because the literature search of earlier reviews was limited to February 2009 [6], the most recent studies with very large samples were not considered [11–13]. Since research on type D has become more popular in recent years, other work groups have conducted prognostic studies on type D. Therefore, these more recent results from primary studies should be taken into consideration to strengthen the overall findings and conclusions on the prognostic effect of type D in patients with cardiovascular diseases.

The aims of our systematic review were to examine whether an updated meta-analysis including more recent observational studies and studies with conflicting results would replicate earlier results on the relation of type D personality with hard endpoints in patients with cardiovascular diagnoses. Only mortality and nonfatal cardiac events were considered as endpoints to improve validity. Subgroup analyses were conducted to examine the influence of additional study characteristics on the association of type D and patient prognosis. These study characteristics refer to (a) the type of cardiovascular diagnoses (CAD vs. congestive heart failure (CHF)) as they might be associated with different causal links of type D and pathogenesis, (b) the type and quality of adjustment (i.e., psychological factors, biological factors, social/sociodemographic factors) as there exist large differences with regard to the number and kind of variables included in multivariate models that could be related to effect sizes of type D, and (c) the publication date of the study as later studies are often methodologically more sound.

Materials and Methods

Inclusion Criteria

Our systematic review and meta-analysis included prospective cohort studies with a baseline assessment of type D and adverse outcomes such as mortality (all cause, cardiac) or a combination of mortality and nonfatal cardiac events. The study sample had to consist of patients with any type of cardiovascular disorder (i.e., CAD, CHF, peripheral artery disease, arrhythmias). No restrictions on sample size, length of follow-up, publication date, and language of publication were applied.

Information Sources and Literature Search

The literature search covered PubMed (US National Library of Medicine, 1950–2011/08) (n=117 references), PsycInfo (American Psychological Association, 1966–2011/08) (n=16 references), Embase (Excerpta Medica Database, 1990–2011/08) (n=87 references), and Web of Science (Social Science Citation Index, 1900–2011/08) (n=121 references). Specific search strategies were developed for each database (e.g., for Pubmed: "distressed personality" OR "type d" OR "social inhibition" AND "mortality"). We searched for additional studies by a hand search of reference lists and earlier reviews on type D personality (n=1 reference).

Study Selection and Data Collection

All results were downloaded and stored with the software Reference Manager. From a total of 342 references, 195 unique references remained after deletion of duplicates. These references were screened for eligibility by title and abstract; the resulting papers were retrieved and consulted in full text. Reasons for exclusion were coded. For data extraction, an electronic extraction sheet was used. Descriptive information on setting, type of assessment of type D, sample characteristics, and data on effect measures (odds ratios (OR), hazard ratios (HR)) were extracted. All papers were coded independently by two raters (GG, MR). Disagreements were resolved by consensus with a third reviewer (JB).

Extracted Data

Type D Personality

We accepted all assessment instruments for the classification of type D personality. We needed a dichotomous classification of type D vs. non-type D personality.

Variables Used in Adjusted Models

We extracted whether the authors used socio-demographic (e.g., age, gender, education level), biological (e.g., cardiovascular risk factors, left ventricular ejection fraction), and psychological variables (e.g., depressive mood, anxiety) in adjusted analyses.

Outcomes

We extracted three different outcomes: (1) all-cause mortality, (2) cardiac death, and (3) a composite measure including nonfatal myocardial infarction and cardiac death. Data on surgical procedures such as angioplasty or bypass surgery were not considered because these procedures rely also on subjective and clinical decisions. In the meta-analysis, we analyzed only one type of outcome according to a pre-specified hierarchy (1 preferred over 2 and 2 preferred over 3).

Data Analysis

The effects of type D personality on the prognosis of cardiac patients were included in the meta-analysis as odds ratios. If adjustments were done, adjusted hazard ratios (HRadj) were used. These HRadj more precisely represent the net effect of type D personality on mortality or morbidity. For both effect measures, corresponding confidence intervals (CI) were used to estimate the precision of the effect. If results were presented by a two-by-two table, we separately calculated OR values. All statistical analyses were done with STATA 11 by the command metan [14]. The reported summary statistics were calculated both as fixed and random effects models. Fixed effects models weigh studies according to their measurement error only, whereas random effects models take into account the heterogeneity between studies and give studies more equal weight. Pooling was done according to the DerSimonian and Laird method [15] using the inverse variances of the primary studies. Cumulative meta-analysis was used to take into account the publication year of the study. The CI represents 95% ranges, which indicate a statistically significant effect when values of 1.0 are excluded from the OR or adjusted HR values. Values of OR or HRadj above 1.0 indicate a negative association between type D personality and prognosis of the cardiovascular disease.

Heterogeneity between studies was assessed by examining forest plots of studies, by calculating a chi-square heterogeneity test, and through I^2 statistics. The chi-square value indicates heterogeneity if statistical significance is found. In addition, higher I^2 values indicate greater variability between studies than would be expected by chance alone (range 0–100%); Higgins and colleagues [16] proposed values of 25%, 50%, and 75% as indicators of low, moderate, and high heterogeneity. Publication bias was explored by funnel plots and the Egger test for small study effects [17].

We limited our analysis to one outcome measure per study. The effect of adjustments was explored by selecting studies that adjusted for socio-demographic, biological, or psychological variables in the analysis. An additional sensitivity analysis was conducted for studies that adjusted for all three dimensions in their analyses. This procedure was intended to achieve more homogeneous results since the same mediating variables were included in the primary study.

Results

Study Selection

Of the 195 publications, 146 were excluded by title and abstract. The resulting 49 papers were retrieved in full text. Another 28 papers were excluded after consultation of the full text. Twenty-one papers were included in the systematic review. For each of the 174 excluded papers, the reasons for exclusion were coded: 88 papers referred to a different, biologically defined "type D," 28 papers were nonempirical, 30 were based on a cross-sectional design, 25 used other endpoints, two papers assessed social inhibition but not type D personality [18, 19], and one paper was based on a sample with a diagnosis other than cardiovascular disease [20].

Of the 21 papers included in the systematic review, two reported secondary analyses on pooled data from studies already published [21, 22]. An additional five papers referred to results from a subsample or pilot study and were excluded, too [1, 7, 8, 23, 24]. This selection procedure resulted in a final number of 14 papers (see Fig. 1).

Twelve studies were published in 14 papers [9–13, 25–33]. Some papers referred to identical patient samples. Thus, two papers [26, 29] were merged and labeled as "Denollet et al., 2006" [26], and two papers [10, 27] were merged into "Pedersen et al., 2004" [10] (due to a more detailed description of results and the earlier publication date, respectively). This resulted in a total number of 12 studies (Table 1). In one study, only univariate statistics were available [26], and therefore the adjusted HR was based on 11 studies. Six studies were carried out in The Netherlands [10, 11, 13, 30–32], four in Belgium [9, 25, 26, 28], one in Switzerland [33], and one in Germany [12]. All papers were published in English. Five studies analyzed a consecutive sample of patients with CAD [9, 10, 25, 26, 31]; one of these was restricted to patients admitted to a hospital due to acute myocardial infarction [31]. In the other four studies, CAD patients were recruited in the rehabilitation center within 2 months after acute myocardial infarction, bypass surgery, or percutaneous transluminal coronary angioplasty. Three studies enrolled patients with chronic heart failure [11, 13, 33]. One study enrolled patients with mixed cardiac diagnoses (CAD, structural heart disease, arrhythmias) [12], and one study included patients with peripheral arterial disease [30]. Two samples were recruited after a medical intervention: heart transplantation [28] and first implantable cardioverter defibrillator [32], respectively. Mean length of follow-up ranged between 9 months and 7.9 years. Sample sizes at enrollment ranged from 51 to 1,040 participants. All studies included participants of both genders; the proportion of women was between 8% and 38%. The mean ages of study samples ranged from 54.1 to 70.7 years. Type D prevalence varied from 13.5% to 35%. Type D personality was assessed by a combined index from the subscale Social Inhibition of the Heart Patient Psychological Questionnaire [7, 9, 34] and the State-Trait Anxiety Inventory [35] in one study [9] and by the DS16 in two studies [25, 26]. All other studies used the DS14 [2]. The outcome most often assessed was all-cause mortality in eight studies [9, 11–13, 28, 30, 32, 33]; three studies used cardiac mortality as the outcome [9, 13, 25], and four studies used a composite index of nonfatal myocardial

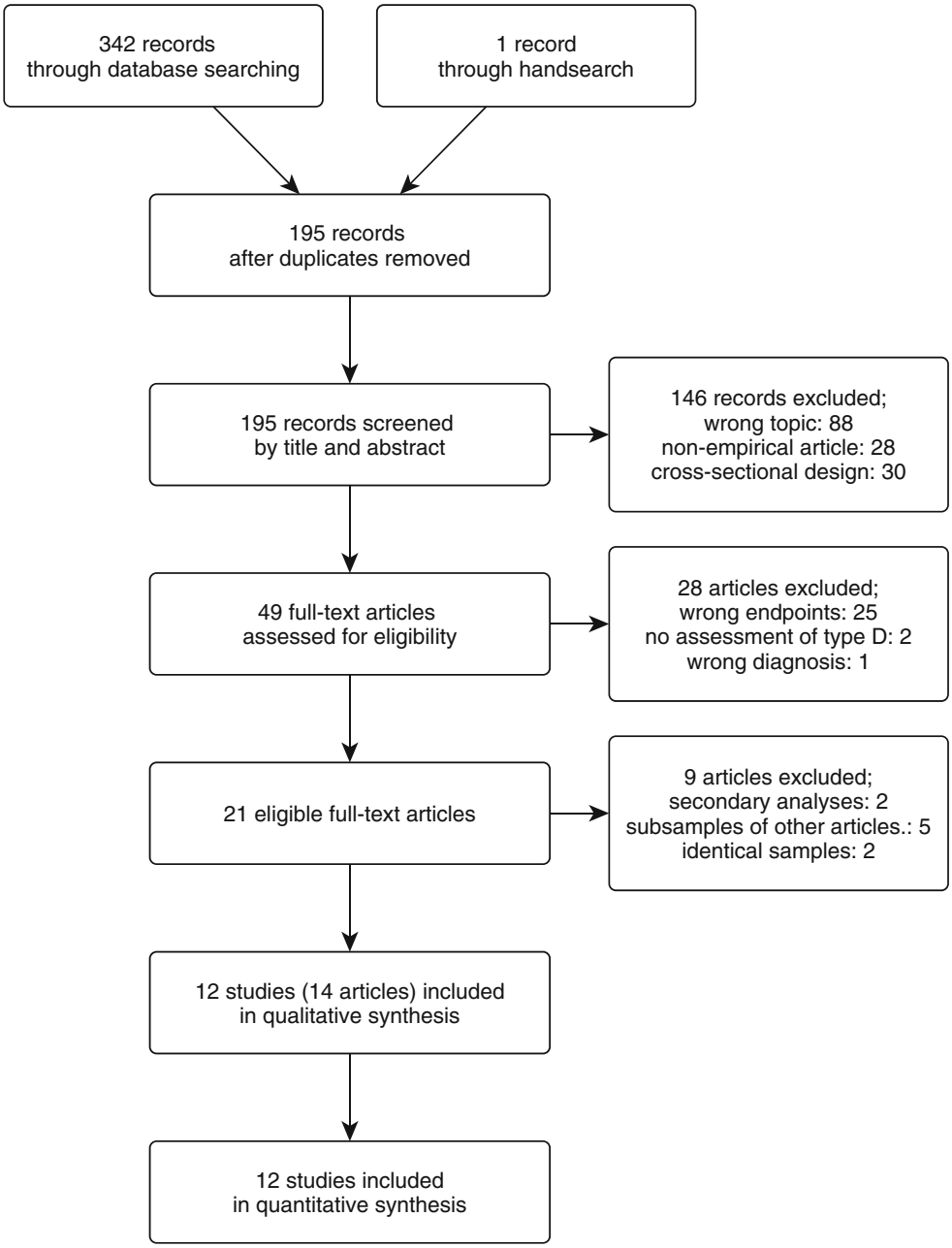

Fig. 1 Flow chart for the selection of studies after initial search

infarction and cardiac death [25, 26, 31, 32]. The number and type of variables used in the multivariate regression models varied considerably (Table 2). All studies except three [9, 11, 33] controlled for age. Only two of 11 studies did not adjust for any biological variables [28, 30]. Six of 11 studies controlled for at least one psychological variable [9, 11–13, 25, 31].

Crude Effects of Type D Personality on Prognosis

Using a fixed effects model, the association between type D personality and hard endpoints (mortality or combined index of cardiac mortality and nonfatal myocardial infarction) was supported with an OR of 1.54 (95% CI [1.26–1.89]) (see Fig. 2). An analysis on the cumulative OR ranked according to the publication date yielded a continuously decreasing relation between type D and prognosis starting at 5.02 (95% CI [2.47–10.21]) and going down to 1.54 (see Fig. 3). Applying a random model resulted in an OR of 2.28 (95% CI [1.43–3.62]) (see Fig. 4). There was marked heterogeneity between studies (χ^2=45.41; df=11; p<0.001; I^2=75.8%). Additional analyses were conducted to examine the results for publication bias. The Egger test for bias indicated a significantly larger effect for small studies (t= 4.02; p=0.002). A visual exploration of the funnel plot showed that eight studies with moderate sample sizes

Table 1 Descriptive information of prognostic studies assessing type D personality and hard endpoints in patients with cardiovascular diseases

Study	Methods			Sample			Type D assessment			Outcome			Unadjusted effect size with confidence interval	Adjusted effect size with confidence interval
First and last author	Selection of participants	Length of follow-up	Drop-outs	Size and diagnosis	Mean age (SD)	*N* (%) female	Measure	Time assessed	Prevalence	Endpoints (*N*)	Data sources	Number of covariates in multivariate analyses		
Denollet, Brutsaert 1996 [9]	Consecutive rehabilitation participants; 1/1985–12/1988; Antwerp, Belgium	7.9 years (range 6 to 10 years)	No patients lost	303 CAD patients (MI, bypass-surgery, angioplasty within 2 months before enrollment in rehabilitation program)	55.4 (7.9) years	35 (12%)	SI : Heart Patients Psychological Questionnaire; NA: trait STAI; type D by median split (NA≥43, SI≥12	rehabilitation program	28%	Primary endpoint: all-cause mortality (38); secondary endpoint: cardiac death (24)	Hospital records	5	OR 5.02; CI 2.47–10.21	OR 4.1; CI 1.9–8.8
Denollet, Brutsaert 2000 [25]	Consecutive rehabilitation participants; 1/1989–12/1992; Antwerp, Belgium	5 years	Three patients who died of noncardiac causes were excluded	319 CAD patients (MI, bypass-surgery, angioplasty within 2 months before enrollment in rehabilitation program)	56.7 (range 35 to 70) years	27 (8%)	DS16; median split NA≥9, SI≥15	Rehabilitation program	31%	Cardiac death (6); composite cardiac events (cardiac death/ nonfatal MI) (22)	Hospital records	5	OR 11.65 CI 1.34–101.07	OR 8.9 CI 3.2–24.7
Pedersen, van Domburg 2004 [10] Denollet, van Domburg 2006 [27]	Consecutive PCI patients enrolled in RESEARCH registry; 10/2001–10/2002; Rotterdam, Netherlands	9 months	875/1,237 questionnaires returned	875 CAD patients (PCI)	62.2 (10.9) years	246 (28%)	DS14; median split NA/SI≥10	6 months after PCI	29%	Composite cardiac events (cardiac death/MI) (20)	Not reported	5	OR 3.80 CI 1.53–9.41	HR 2.61 CI 1.12–6.09
Denollet, Conraads 2006 [26] Denollet, Pedersen 2008 [29]	Consecutive rehabilitation participants; 1/1993–12/1997; Antwerp, Belgium	5 years	No patients lost	337 CAD patients (MI, bypass-surgery, angioplasty within 2 months before enrollment in rehabilitation program)	57.0 (range 35 to 75) years	40 (12%)	DS16; median split NA≥9, SI≥15)	Rehabilitation program	29%	Composite cardiac events (cardiac death/MI) (n.a.)	Hospital records	n.a.	OR 4.84 CI 1.42–16.48	–
Denollet, Conraads 2007 [28]	Recruitment details not reported; 2/1995–10/2004; Antwerp, Belgium	5.4 years (SD=2.8)	Two in-hospital deaths excluded	51 heart transplant patients	54.1 (9.7) years	13 (25%)	DS14; median split NA/SI≥10	Before transplantation	29%	All-cause mortality (out of hospital) (6)	Not reported	2	OR 16.5 CI 1.72–158.22	HR 11.33 CI 1.24–103.3
Aquarius, Denollet 2009 [30]	Consecutive patients?; 9/2001–3/2004; Tilburg, Netherlands	4.0 years (inter quartile range 3.5 to 4.5 years);	one patient who died of an unnatural cause excluded	184 patients with symptomatic peripheral arterial disease	64.8 (9.8) years	67 (36.4%)	DS14; median split NA/SI≥10	Before PAD diagnosis	35%	All-cause mortality (16)	Ward physician/ medical records	2	OR 2.64 CI 0.93–7.47	HR 3.2 CI 1.2–8.6
Martens, Denollet 2010 [31]	Patients admitted with AMI to one of four hospitals; 5/2003–5/2006; Netherlands	1.8 years (SD=0.8)	No patients lost	466 CAD patients (AMI)	59 (12) years	100 (21%)	DS14; median split NA/SI≥10	Hospital admission due to an AMI	20%	Composite cardiac events (recurrent MI or cardiac death) (44)	Medical records	6	OR 2.32 CI 1.19–4.53	HR 2.34 CI 1.14–4.35
Pedersen, Theuns 2010 [32]	Consecutive patients; 8/2003–12/2008; Rotterdam, Netherlands	1.7 years (SD=0.5)	No patients lost	371 patients with first implanted ICD	57.7 (12) years	76 (20%)	DS14; median split NA/SI≥10	Prior to implantation	22%	All-cause mortality (25)	Medical records	5	OR 2.99 CI 1.30–6.87	HR 2.79 CI 1.25–6.21
Pelle, Denollet 2010 [13]	Consecutive outpatients, multiple hospitals; 1/2003–1/2008; Southern region of The Netherlands	37.6 months (SD=15.6)	No patients lost	641 CHF patients	66.6 (10.0) years	165 (26%)	DS14; median split NA/SI≥10	Within 2 weeks after outpatient visit	20%	Primary outcome: all-cause mortality (123); secondary outcome: cardiac mortality (76)	Medical records or general practitioner	21	OR 1.16 CI 0.72–1.87	HR 1.09 CI 0.67–1.77
Volz, Barth 2011 [33]	Consecutive participants in rehabilitation program; 8/2004–4/2008; Switzerland	2.8 years (SD=1.1)	No patients lost	111 CHF rehabilitation patients	57 (14) years	20 (18%)	DS14; median split NA/SI≥10	At entry of rehabilitation program	30%	All-cause mortality (11)	relatives of deceased patients	2	OR 1.40 CI 0.38–5.14	HR 0.91 CI 0.25–3.32
Grande, Herrmann-Lingen 2011 [12]	Consecutive patients in different settings; 11/2001–2/2003; Germany	71.5 months (SD=3.6)	63 patients (6.1%) lost at follow-up	977 patients with cardiac disease (CAD, structural heart diseases, arrhythmias)	63.3 (10.7) years	220 (22.5%)	DS14; median split NA/SI≥10	Different points of enrollment	25%	All-cause mortality (172)	Regional registration offices	19	OR 0.84 CI 0.57–1.25	HR 0.99 CI 0.61–1.59
Coyne, Sanderman 2011 [11]	Consecutive patients, enrolled in disease management program; 10/2002–2/2005; Netherlands	18 months	252 patients with incomplete data	706 patients with heart failure	70.7 (11.5) years	270 (38.2%)	DS14; median split NA/SI≥10	Hospital admission due to heart failure	13.5%	All cause mortality (192)	Medical records	2	HR 0.89 CI 0.58–1.37	HR 0.78 CI 0.49–1.24

AMI acute myocardial infarction, *CAD* coronary artery disease, *CHF* congestive heart failure, *DS14* type D scale 14-item version, *DS16* type D scale 16-item version, *ICD* implantable cardioverter defibrillator, *MI* myocardial infarction, *NA* negative affectivity, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *SI* social inhibition, *STAI* State–Trait Anxiety Inventory

Table 2 Variables in adjusted statistical models of prognostic studies assessing type D personality and hard endpoints in patients with cardiovascular diseases

Study	Sociodemographic variables	Biological variables				Psychological variables
First and last author		Diagnosis/history	Treatment	Disease severity	Comorbidity/medical risk factors	
Denollet, Brutsaert 1996 [9]	–	Three vessel disease	Lack of thrombolysis treatment after MI	LVEF, poor exercise tolerance	Hyperlipidimia	Depression (Pessimism and Future Despair Scale of the Milton Behavioural Health Inventory)
Denollet, Brutsaert 2000 [25]	Age			LVEF, poor exercise tolerance		Symptoms of depression/ anxiety (Zung Depression Scale, State Anxiety of STAI)
Pedersen, van Domburg 2004 [10] Denollet, van Domburg 2006 [27]	Age, gender	Previous CABG	Stent type, stent type×type D			–
Denollet, Conraads 2007 [28]	Age, gender	–				–
Aquarius, Denollet 2009 [30]	Age, gender	–				–
Martens, Denollet, 2010 [31]	Age	Cardiac history	Use of statins	LVEF		Depression (Hamilton Depression Rating Scale), SSRI prescription
Pedersen, Theuns 2010 [32]	Age, gender	CAD, primary prevention indication (primary vs. secondary)		Shock during follow-up		–
Pelle, Denollet 2010 [13]	Age, gender, no partner, educational level, working status	Etiology, cardiac history, time since diagnosis	Prescribed medications, device therapy	Lower LVEF, NYHA functional class	Diabetes, hypercholesterolemia, hypertension, stroke, COPD, peripheral arterial disease, comorbid kidney disease, current smoking	Anxiety/depression (yes or no) (Symptoms of Anxiety/ Depression Index)
Volz, Barth 2011 [33]	–			LVEF, peak oxygen uptake		–
Grande, Herrmann-Lingen 2011 [12]	Age, gender, no partner, educational level	CAD, arrhythmia, other cardiac diagnoses, other cardiac diagnoses×time		CHF stages, CHF stages×time	Charlson index, BMI, BMI squared, total cholesterol, blood pressure, smoking	HADS-depressive mood, HADS-anxiety, SI×time
Coyne, Sanderman 2011 [11]	–			B-type natriureticpeptide		CES-D (depressive symptoms)

BMI body mass index, *CABG* coronary artery bypass graft, *CAD* coronary artery disease, *CES-D* Center for Epidemiologic Studies Depression Scale, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *HADS* Hospital Anxiety and Depression Scale, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *NYHA* New York Heart Association, *SI* social inhibition, *SSRI* selective serotonin reuptake inhibitor, *STAI* State–Trait Anxiety Inventory

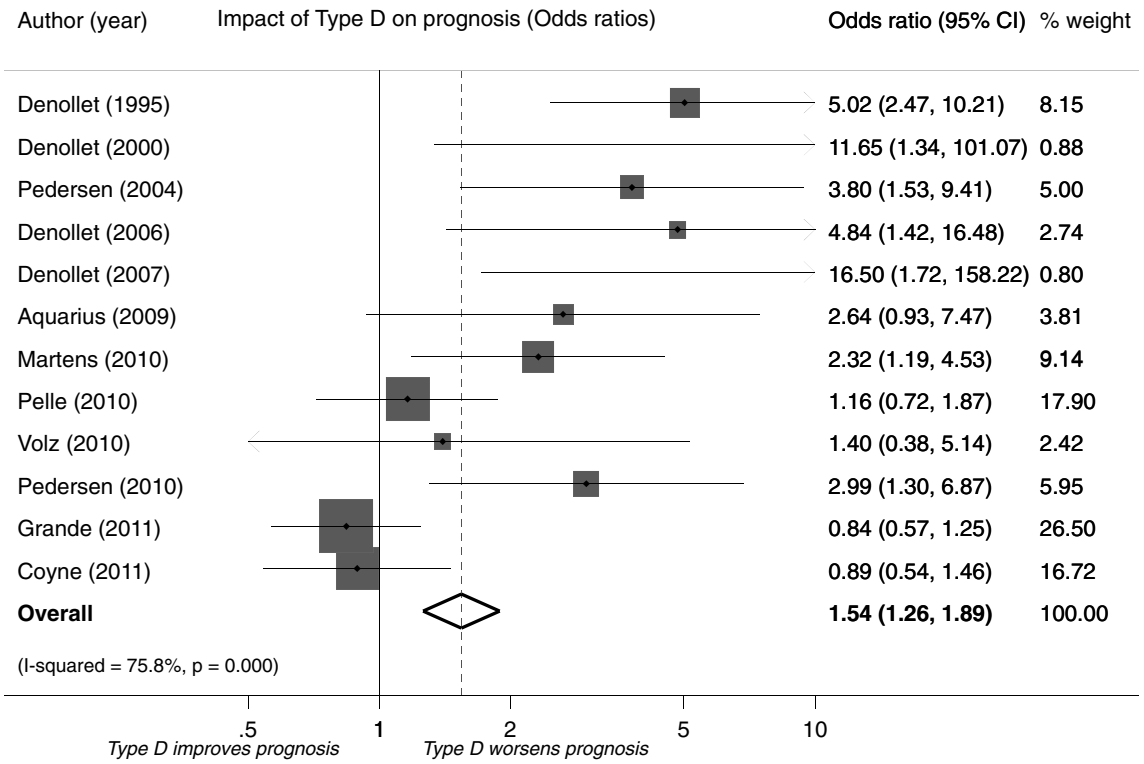

Fig. 2 Forest plot of prognostic studies on assessing the effect of type D personality on mortality/nonfatal myocardial infarction in patients with cardiovascular disorders. Fixed effects model. Odds ratios unadjusted. *N*=12

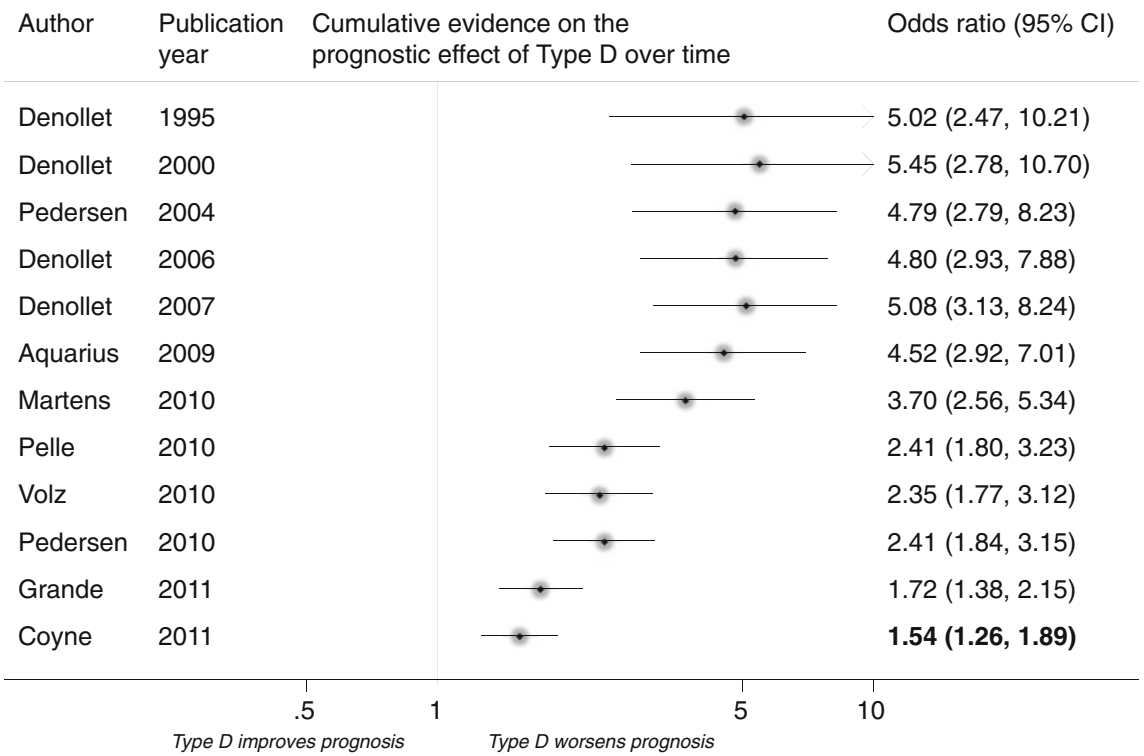

Fig. 3 Cumulative meta-analysis according to publication year of prognostic studies on assessing the effect of type D personality on mortality/nonfatal myocardial infarction in patients with cardiovascular disorders. Fixed effects model. Odds ratios unadjusted. *N*=12

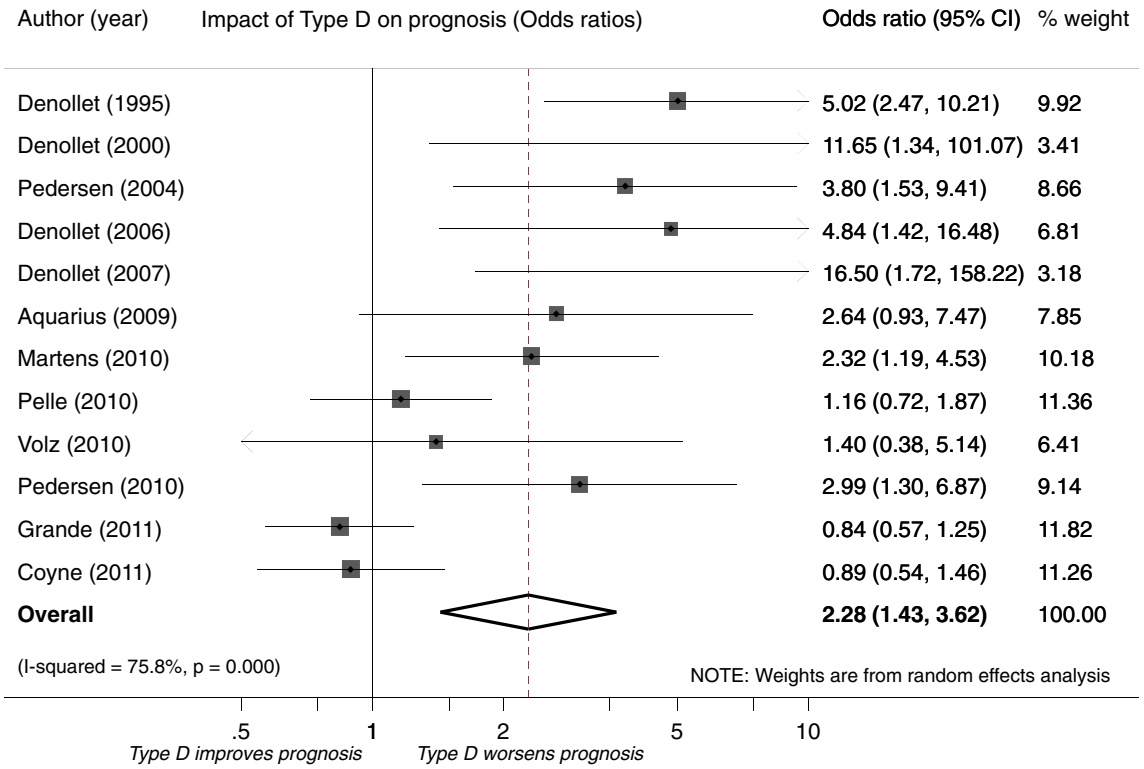

Fig. 4 Forest plot of prognostic studies on assessing the effect of type D personality on mortality/nonfatal myocardial infarction in patients with cardiovascular disorders. Random effects model. Odds ratios unadjusted. $N=12$

showed large effects, whereas three studies with large sample sizes showed effects close to a null finding, which is visualized by the regression line in "Electronic Supplementary Material"—Fig. a1.

Adjusted Effects of Type D Personality on Prognosis

In studies assessing the association of type D personality and prognosis with adjustment for other risk factors, there was a significant adjusted HRadj of 2.24 (95% CI [1.37–3.66]) in a random effects model (see Fig. 5). Heterogeneity between studies was considerably high ($\chi^2=46.51$; $df=10$; $p=0.001$; $I^2=78.5\%$). Similar to the unadjusted odds ratios, results of a fixed model meta-analysis confirmed a smaller effect of HRadj 1.60 (95% CI [1.29–1.97]). Analyses for publication bias again demonstrated a significant small study effect in the Egger test ($t=3.34$; $p=0.009$) for adjusted studies (see "Electronic Supplementary Material"—Fig. a2).

Subgroup Analyses

We performed additional random effects subgroup analyses to examine whether quality of adjustment and the main diagnosis of the study sample altered the results. For studies adjusting for socio-demographic variables, HRadj was 2.65 (95% CI [1.49–4.69]; $I^2=77.7\%$) [10, 12, 13, 25, 28, 30–32]. In studies controlling for biological variables, HRadj was 2.02 (95% CI [1.20–3.41]; $I^2=80.6\%$) [9–13, 25, 31–33]. The pooled effect for the six studies that controlled for psychological symptoms no longer showed an independent effect of type D with an HRadj of 1.83 (95% CI [0.99–3.37]; $I^2=83.8\%$) [9, 11–13, 25, 31]. Also, if we included only those studies that adjusted for all three dimensions of control variables, a nonsignificant effect resulted (HRadj 1.92 (95% CI [0.91–4.05]); $I^2=82.7\%$) [12, 13, 25, 31].

The diagnosis of CAD turned out to be a potential moderator of the association of type D personality and prognosis. In samples of CAD patients [9, 10, 25, 31], we found a larger prognostic effect ($p<0.0006$) of type D personality (HRadj 3.88 (95% CI [2.58–5.85]); $I^2=46.3\%$) compared to studies with CHF patients [11, 13, 33] (HRadj 0.91 (95% [CI 0.66–1.27]); $I^2=0\%$).

Discussion

Our study confirmed a significant association between type D personality and mortality and nonfatal myocardial infarction. However, the initially published odds ratios decreased over time, and heterogeneity between studies was very large, which raises concerns about the robustness of the

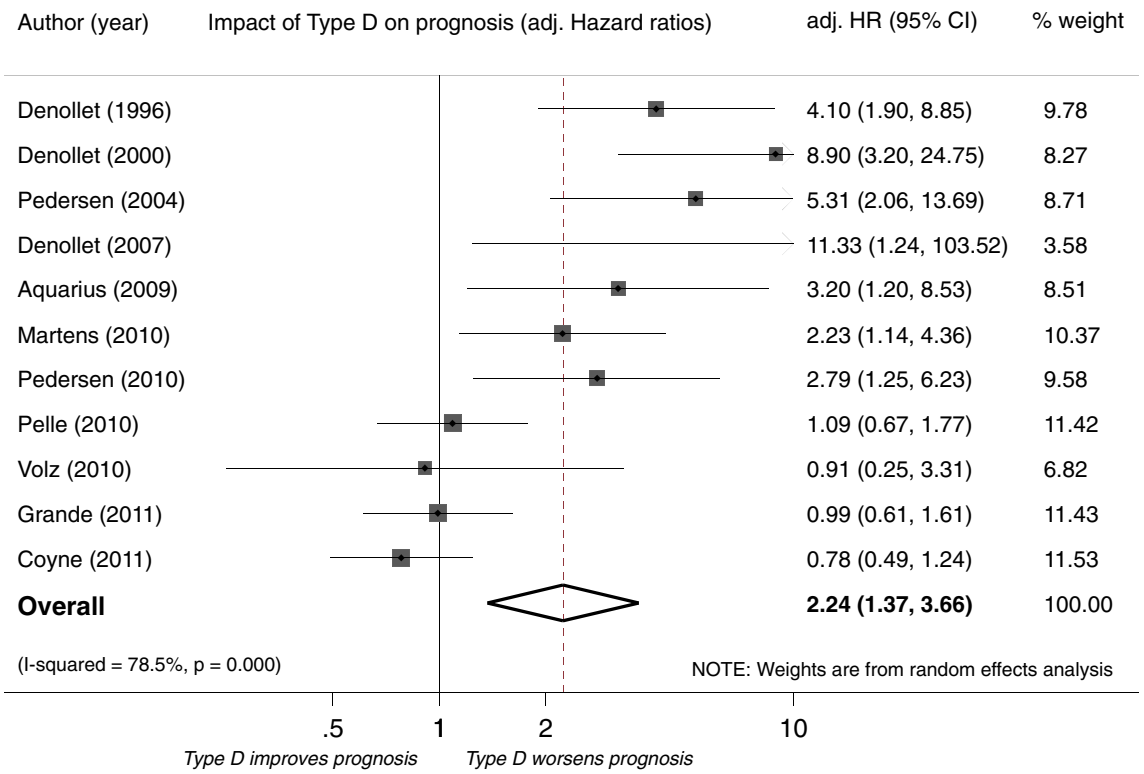

Fig. 5 Forest plot of prognostic studies on assessing the effect of type D personality on mortality/nonfatal myocardial infarction in patients with cardiovascular disorders. Random effects model. Hazard ratios adjusted for other risk factors. $N=11$

effect. The problem of heterogeneity between studies was not reported in earlier meta-analyses [4–6] and partly caused by the integration of the most recent studies with large samples and null findings. These most recent studies included patients with CHF. This raises the questions on whether type D personality does not affect prognosis in CHF or whether larger studies give more precise estimates. A publication bias was found with very large effects in small studies and lower or null effects in the largest studies. The publication bias still holds if studies on CHF patients are excluded. This has important consequences for the interpretation of the results from the two statistical models we used (fixed effects vs. random effects). In fixed effects models, the sample size is represented in the weight of the study, whereas in the random effects meta-analyses, small studies receive more weight. When assessing very large effects of small studies, the mean pooled effect may be overestimated in random effects models, and a fixed effect model may lead to a more appropriate effect size estimate because the study size is better represented. Both analyses arrived at about the same results regarding the lower confidence interval, which were 1.3 and 1.4, and showed significant effects in both models. The size of the effect may be between an OR of 1.5 and 2.3 depending on the statistical procedure used, but for a conservative interpretation, the lower number would be more appropriate.

Whereas earlier reviews [5, 6] yielded a pooled effect of 3.72 and 3.16, respectively, our study provided a much more conservative estimate of the adverse effects of type D, which is comparable to other psychosocial variables such as depression, anxiety, and social support, which are about 1.5 to 2.4 [36–42]. In the fully adjusted model, an HR of 1.92 was found, which is in the expected direction of a higher risk for type D patients, but it failed to reach the level of significance. Similarly, studies controlling for psychological variables demonstrated a nonsignificant pooled effect size. Here, some confounding and multicollinearity in the multivariate analyses must be assumed [43] as negative affectivity as a primary emotional factor is very closely associated with subordinate emotional constructs such as anxiety and depression [44, 45]. Differentiating specific negative emotions as well as distinguishing states from traits regarding negative affect is seen as important for improving the understanding of the mechanisms that link emotions with cardiopathogenetic processes [46]. Significant overlaps of measurements and constructs make it difficult to identify whether specific emotions are independently associated with CAD risk or whether additive or interactive effects are more adequate model assumptions [46]. The statistical control for symptoms of anxiety and depression in multivariate models may lead to an attenuation of social inhibition, which does not correspond with the original conceptual idea of type D personality.

The diagnosis of the sample was important for the association between type D and prognosis. In CAD patients, a large effect was demonstrated, whereas null effects were found in

studies with CHF [11–13, 33]. The latter finding is contrary to findings using other psychological characteristics such as depression, which was found to be predictive of mortality and secondary events in CHF patients in a meta-analysis [47]. Our results probably suggest that type D patients with different cardiac diseases carry a different risk for their prognosis. This is clinically relevant as prevalence estimates of type D personality across CAD and CHF subsamples are quite similar (15–29% and 14–33%, respectively) [48].

Pathogenetical mechanisms that link type D to adverse outcomes in cardiovascular diseases are still unclear. Cross-sectional studies provide some evidence for inflammation and dysfunctions in stress regulation via the hypothalamic–pituitary–adrenal axis as mechanisms involved in the pathway from type D to unfavorable medical outcomes [6]. However, the cross-sectional design and the overall small number of studies limit the available evidence substantially.

The prognostic effects of type D studies have decreased considerably across time. It seems that the concept is losing power comparable to the concept of the type A pattern (characterized by hard driving and competitive behavior) decades before [49–52]. Recently, Ioannidis and Panagiotou demonstrated patterns of diminishing relations for most of 35 biomarkers after a prominent highly cited early publication. The editor's motivation to be the first to report on a specific association might neglect problems with small sample sizes [53]. In type D research, a comparable situation may have led to an initial overestimation of the association between type D and prognosis. Our study is another example of an effect that has declined over time.

Our review cannot overcome some serious methodological shortcomings in type D research [43]. The first issue is related to the practice of dichotomization of the interaction of negative affectivity and social inhibition that is seen as the core concept of the type D personality. Evidence is lacking with regard to the validity of the type D vs. non-type D construct and the merging of the three non-type D groups into one [54, 55]. Furthermore, our meta-analysis is based on effect sizes reported for a dichotomous operationalization of the type D personality. Dichotomization may be inadequate for translating the specific interactional character of the type D construct [43]. The general limitations of dichotomizing continuous variables are well known: It may reduce the sensitivity of statistical tests and produce spurious associations [56–58]. Even for the type D measurement, a dimensional operationalization rather than a categorical structure is supported [59]. Because a "natural" category of type D personality cannot be demonstrated empirically, type D research should incorporate continuous scores of negative affectivity and social inhibition and their interaction into statistical analyses instead of the dichotomous construct [43]. At any rate, three of the inclusive studies [11–13] also tested the interaction between continuous negative affectivity and social inhibition dimensions and found no evidence for the predicted association. Lastly, in the smaller studies, the number of events observed is often small, especially relative to the number of covariates included in the multivariate models, which can result in over-fitting and insufficient parameter estimation [60].

Limitations

Our study has several limitations that should be mentioned. First, the included studies were only observational and causal conclusions might be inadequate [61]. Recruitment strategies or data on drop-outs were often not described in detail. In some of the subgroup analyses, the number of remaining studies was very small. We found large heterogeneity between studies, which means that the pooled estimate must be interpreted with caution. Unfortunately, heterogeneity could not be reduced by limiting the study pool to studies with the same variables used for adjustment. However, we found a homogeneous null effect in patients with CHF. A publication bias was present, and smaller studies reported a considerably larger effect of type D on prognosis. The number of published studies is still limited and there are limitations in the methodological quality of the type D operationalization in previous research.

To conclude, our meta-analysis supports the overall finding of an association between the type D personality and prognosis with data from 12 independent samples with a total of 5,341 cardiovascular patients. However, the strength of this association has been declining over the years and studies with high methodological rigor failed to confirm this association. The review suggests that type D personality affects prognosis only in CAD patients but not in patients with CHF. Pre-registered observational studies [62] with an adjustment of biological, social, and psychological characteristics on patients with CAD are urgently required to give clear clinical guidance regarding whether these patients are really at risk.

Conflicts of Interest The authors have no conflicts of interest to disclose.

Sources of Funding No external funding was received for this work.

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