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Type D personality as a risk factor for adverse outcome in patients with cardiovascular disease: an individual patient data meta-analysis

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Abstract

Objective: Type D personality, a joint tendency toward negative affectivity (NA) and social inhibition (SI), has been linked to adverse events in patients with heart disease, though with inconsistent findings. Here, we apply an individual patient-data meta-analysis to data from 19 prospective cohort studies (N=11151), to investigate the prediction of adverse outcomes by Type D personality in acquired cardiovascular disease (CVD) patients.

Method: For each outcome (all-cause mortality, cardiac mortality, myocardial infarction (MI), coronary artery bypass grafting, percutaneous coronary intervention, major adverse cardiac event (MACE), any adverse event), we estimated Type D's prognostic influence and the moderation by age, sex, and disease type.

Results: In CVD patients, evidence for a Type D effect in terms of the Bayes factor (BF) was strong for MACE (BF=42.5; OR = 1.14) and any adverse event (BF=129.4; OR = 1.15). Evidence for the null hypothesis was found for all-cause mortality (BF=45.9; OR = 1.03), cardiac mortality (BF=23.7; OR = 0.99) and MI (BF=16.9; OR = 1.12), suggesting Type D had no effect on these outcomes. This evidence was similar in the subset of coronary artery disease (CAD) patients, but inconclusive for heart failure (HF) patients. Positive effects were found for NA on cardiac- and all-cause mortality, the latter being more pronounced in males than females.

Conclusion: Across 19 prospective cohort studies, Type D predicts adverse events in CAD patients, while evidence in HF patients was inconclusive. In both CAD and HF patients, we

found evidence for a null effect of Type D on cardiac- and all-cause mortality.

Key words: Type D personality; Cardiovascular disease; Meta-analysis; Negative affectivity; Cardiac events

Acronyms: BF = Bayes factor; CABG = coronary artery bypass grafting; MACE = major adverse cardiac event; NA = Negative affectivity; OR = Odds ratio; PCI = percutaneous coronary intervention; SI = Social inhibition.

Introduction

Type D ("distressed") personality is defined as the joint tendency toward negative affectivity (NA) and social inhibition (SI). Individuals with high NA have a tendency to experience negative emotions across time and situations, while those with high SI tend to feel inhibited and insecure during social interactions[10]. Both Type D personality traits are associated with other well-known personality traits. For instance, neuroticism correlates positively with both NA (r =. 68) and SI (r = 0.43), while extraversion correlates negatively with SI (r = -0.65) [10]. NA also correlates strongly with trait anxiety (r = .81) [57] and the trait anxiety scale of the HPPQ questionnaire has been used to measure negative affectivity before the existence of dedicated Type D personality scales such as the DS14 [10] and DS16 [58].

Although SI is associated with introversion, it is also a distinct construct because introversion does not necessarily involve a distressed experience, while high social inhibition also implies high emotionality and personal distress [57]. Although individuals with social inhibition and introverted individuals may both be reticent during social contact, those with social inhibition are so because they feel tense with others, while introverted individuals prefer their own company over being with others. SI expresses how people cope with negative emotions, yet it differs from emotional coping styles such as repression and defensiveness as those involve low distress and unconscious exclusion of negative emotions, while SI (as measured by for instance the DS14) is characterized by high interpersonal distress and conscious suppression of emotions [57]. Indeed, the correlation between SI and defensiveness is very small (r = -.06) [58].

Type D personality has been linked to various medical and psychological outcomes [1,2,3]. The cornerstone of Type D research is the prognostic risk this distressed personality type is thought to pose to cardiovascular disease (CVD) patients. Previous research has found that individuals who inhibit emotional states are at increased risk of cardiovascular dysregulation and complications, such as decreased heart rate variability [59] and cardiovascular recovery [60] and atherosclerosis [61]. Moreover, high SI individuals report that they perceive less social support and are less likely to seek help[62]. Individuals with high NA and high SI persistently experience negative emotional states and inhibit the expression of these emotions in social situations, thereby increasing their risk on adverse cardiovascular events for which they are not likely to seek help.

Several meta-analyses have indicated that Type D personality is associated with an increased risk of adverse events in patients with coronary artery disease (CAD), while this has not been found for other types of CVD [1,2]. Some have argued that the effect sizes expressing the prognostic risk posed by Type D personality have declined over the years, based on the observation that the earlier studies with smaller sample sizes showed larger effects than more recent and larger studies [4]. However, others have stated that the difficulty in replicating some of the earlier studies can be explained in terms of differences across studies in endpoints and patient characteristics such as age and cardiac diagnosis [5]. For instance, a meta-analysis concluded an increased mortality risk of Type D patients with CAD, but no increased mortality risk in patients with heart failure [1]. Furthermore, a re-analysis of four earlier published studies indicated that in CAD patients, Type D personality was not predictive of all-cause mortality, but it did show an increased risk on cardiac events, primarily in adult patients younger than 70 years old [6].

Estimating a Type D personality effect

Two constructs synergistically affect another when the conditional effect of each construct on the outcome increases with higher scores on the other construct. Various scholars have argued that a Type D effect involves a synergy between its subcomponents NA and SI [7–9]. For instance, Denollet, Sys and Brutsaert [9] claimed that the interaction of emotional distress and inhibition of one's feelings can be viewed as a form of stress that may create or exacerbate serious health problems'' (p. 583). Most earlier studies aimed to capture this synergistic effect by classifying people in a Type D group when they score high on *both* the NA and SI total scores [10]. Various researchers have criticized this *2-group method*, not only for resulting in less statistical power, but also for risking spurious Type D effects [11,12]. A *4-group method* was commonly applied to solve this issue by also including groups for people with high scores on only one of the two NA or SI traits. However, two recent simulation studies showed that not only the 2-group method may produce false positive Type D effects when in reality only NA *or* SI was driving the effect, but that the 4-group method to a lesser extent suffers from a similar bias due the correlation between NA and SI [13,14]. In some of this simulated data, only one personality trait (e.g., only NA) was causally related to an outcome. However, analyzing such data with the 2-group and 4-group methods often produced statistically significant effects of the Type D group compared to the other groups. This implies that methods that estimate the Type D effect based on two or four personality groups cannot distinguish a causal effect of Type D personality from an effect of only one of the underlying personality traits NA or SI.

In line with earlier recommendations [11,12], these simulation studies concluded that of all commonly used methods, the *continuous method*, which does not analyze personality groups but

rather the NA and SI total scores, is least biased in detecting various ways in which NA and SI synergistically relate to an outcome measure. This method models the effect of both continuous variables NA, SI, as well as their quadratic effects and interaction. A quadratic effect for NA or SI would imply that the risk this personality trait poses on adverse events is not constant but increases with higher trait scores. Detecting that *both* NA and SI independently predict an outcome would point to an *additive Type D effect* because the effect of both NA and SI remains constant across the entire score range of these traits. However, researchers have argued that the Type D effect involves a synergy between NA and SI [7,8,9] and that such synergistic effects can be adequately tested by means of an interaction effect between two continuous variables [12,13,14]. If there is an interaction effect between NA and SI on the outcome, then the effect of these traits is not constant, but the effect of one trait changes across scores on the other trait. If the interaction effect is positive, then the effect of one trait on the outcome increases for higher scores on the other trait. We consider such as interaction to reflect a synergy between NA and SI, because higher scores on both traits result in increasingly higher predicted values on the outcome measure. Negative interaction effects would not represent a synergistic effect, because then the effect of one personality trait on the outcome decreases with higher scores on the other trait.

Reconsidering the published Type D literature

Although earlier simulations have indicated that the 2-group and 4-group methods may lead researchers to erroneously conclude a Type D effect when only NA *or* SI explains variation in the outcome[13,14], the extent of this problem in the Type D literature is still unclear. A recent systematic review of all published studies in the Type D literature included all studies that have estimated a Type D effect according to both the 2-group and continuous method. It turned out

that approximately half of the significant 2-group effects were not Type D effects according to the continuous method, but effects of NA *or* SI only [15]. This suggests a major inconsistency in the conclusions drawn from these two methods, questioning the validity of the conclusions drawn from earlier published studies using only the 2-group method. The conclusions of earlier published meta-analyses are equally affected, as those were invariably based on 2-group method effects [1,2].

The continuous method, however, is also often not adequately applied. According to earlier simulation studies [13,14], the continuous method should not only include both the NA and SI main effects and their interaction, but also check whether this interaction is confounded by NA and SI *quadratic* effects [16]. Most published studies using a continuous method did not model these quadratic NA and SI effects. To the best of our knowledge only two earlier published studies have done this [17,18]. This suggests that for the remaining literature it stays unclear whether a significant NA*SI interaction indicates a Type D effect, or merely a main- or quadratic effect of NA or SI. This highlights the importance of reconsidering the published Type D literature.

A first reanalysis of Type D's prognostic effect in CAD patients modeled the Type D effect according to both the 2-group and continuous approaches [6]. Both approaches showed that Type D increased the risk on cardiac events in CAD patients. A follow-up analysis revealed that this effect was only found for patients younger than 70 years old and did not apply to older patients. Comparisons between older and younger patients may be threatened by survivorship bias in that the older patients may be more resilient to the potential risk their personality trait represented because they have been able to survive for longer. Furthermore, older patients may

experience less environmental (work) pressure and may therefore be less susceptible to stress related cardiac events [6]. On the other hand, the increased isolation of older patients can increase their social stress levels [84]. It remains unclear why Type D personality does not seem to be a risk factor for cardiac events in older individuals with CAD.

Methodological limitations of this previous reanalysis [6] are that the quadratic NA and SI effects were not included and that only the dichotomous method was used to show that the Type D effect was less pronounced at older ages, making it unclear whether age moderated the Type D effect, or whether it moderated a NA or SI effect only. A second limitation is a possible selection bias because the included data originated from four subsequent cohorts from the same university hospital. Individual patient meta-analysis on data from a diverse set of research groups is essential to achieve a more representative sample of studies.

Here, we present the results of an individual patient meta-analysis focusing on Type D's prognostic effect in cardiovascular disease patients. Individual patient meta-analysis enables an efficient re-analysis of large collections of studies designed to answer a similar research question [19]. This results in high statistical power to detect small effects that are hard to detect in each of the included studies individually. Whereas traditional meta-analyses are only able to estimate moderator effects at the study level, individual patient meta-analyses can test moderator effects at the individual level, resulting in more power to detect moderators of Type D's prognostic influence.

Our first aim is to aggregate the data of earlier published prospective cohort studies and test the association between Type D personality and the occurrence of adverse events during follow-up in patients with cardiovascular disease. Another aim is to determine whether this Type D effect depends on age, sex and cardiac diagnosis. Previous research has found that males with Type D personality show a more elevated heart rate response to social tasks than females with Type D personality [64]. Studies have also shown that Type D is more predictive of MACE in younger ages than older ages [6] and a meta-analysis concluded an increased mortality risk of Type D patients with CAD, but no such risk in patients with heart failure [1]. Although our final conclusions will be based on the continuous method, a secondary aim is to estimate the Type D effect according to the 2-group, 4-group and continuous methods to illustrate the difference in the results they generate. In line with earlier research, we expect (1) that Type D personality is a risk factor for cardiac events but not for all-cause mortality and (2) that the Type D effect is more pronounced in younger than in older individuals [6].

Method

Inclusion criteria

We only included prospective cohort studies involving patients who at baseline were diagnosed with cardiovascular disease, coronary artery disease, heart failure or ventricular arrhythmia, and in which the Type D traits NA and SI were measured using the DS16[58], DS14[10] (or any other validated instrument designed to measure these personality traits), and for whom the occurrence of adverse events was recorded over the study's follow-up time. We excluded case-control, cross-sectional studies, imaging studies, case series and case reports. When several studies had been published on the same cohort, we included the study with the largest sample size and/or longest

follow-up time. Of each included study we contacted the corresponding author (or other authors in case of non-response) and requested the raw data listed below. Included studies at least had to provide data on Type D personality (individual item scores or total scores for NA and SI) and adverse outcomes (at least one of the following: all-cause mortality; cardiac mortality; myocardial infarction (MI); coronary artery bypass grafting (CABG); percutaneous coronary intervention (PCI)). Additionally, we requested data regarding clinical characteristics (type of cardiovascular disease), demographic characteristics (age; sex) and study characteristics (date of baseline measurement; follow-up duration).

Search strategy

We conducted a literature search on January 4th 2020, using the electronic databases PubMed, Web of Science and PsycINFO. We updated this literature search on April 1st 2022. We searched for the terms 'Type D personality' AND ['cardiovascular disease' OR 'coronary artery disease' OR 'coronary heart disease' OR 'heart failure' OR 'ventricular arrhythmia'] AND ['adverse event' OR 'myocardial infarction' OR 'mortality' OR 'cardiac death' OR 'cardiac event' OR 'MACE']. Furthermore, we performed hand searches, selecting articles included in earlier systematic reviews and meta-analyses. We limited our search to a period between 1996 and January 2020, because the first publication on Type D personality was in 1996. Two authors (PL & MA) independently performed the screening process. In the first step, titles and abstracts were screened and studies were included or excluded based on the established criteria. In the second step, inclusion of studies passing the first round was determined by examining the full text. In case of disagreements between the two reviewers (PL & MA), a third reviewer (NK) was consulted. We have used the QUIPS tool to assess the quality of the prospective cohort studies

included in our meta-analysis[30]. During the quality assessment we have not evaluated the statistical analysis and inclusion of confounders, because we are responsible for those analysis choices in our individual patient data meta-analysis. Supplemental Digital Content, Tables S3 and S4, http://links.lww.com/PSYMED/A902 present the results of this quality assessment.

Data extraction

The participating researchers were requested to share their data in either an Excel or SPSS file. Because the shared data already contained all information required to conduct the individual patient data meta-analysis, it was not necessary to further extract data from the included articles. If raw DS-14 item scores were shared, then we checked the calculation of the NA and SI total scores to prevent errors in calculating the total scores (e.g., reverse coding). For each study, the NA and SI scores were standardized within studies to accommodate for the fact that three of the included studies did not use the DS14 questionnaire but other instruments to measure NA and SI that preceded the DS14. Within cluster (i.e., within study) standardization is recommended in multilevel studies when effects of person level predictors (e.g., personality traits) are of primary interest [20].

Operationalizing Type D personality

We operationalized Type D personality according to the continuous interaction method. The Supplemental Digital Content files, http://links.lww.com/PSYMED/A902 contain the methods and results for analyses based on the 2-group and 4-group methods. The continuous method models both the continuous NA and SI main effects, as well as their interaction. The method further investigates whether the interaction is confounded by quadratic NA or SI effects[14]. The

quadratic and interaction effects are calculated by multiplying the mean-centered or standardized NA and SI scores. When no quadratic NA or SI effects are found, the interaction effect in the model without the quadratic effects was used to represent the Type D effect.

Endpoints

As endpoints we investigated five observed endpoints all-cause mortality, cardiac mortality, MI, CABG, and PCI, and two composite endpoints MACE and any adverse event. MACE was defined as the occurrence of cardiac mortality, MI, CABG, or PCI during follow-up. *Any adverse event* was defined as the occurrence of MACE or all-cause mortality during follow-up. If the effect of a composite endpoint is only driven by one of the observed endpoints included in the composite, then a significant composite endpoint could wrongly raise the impression that the other observed endpoints are also affected[75]. Therefore, we did not limit our analyses to these composite endpoints, but also present the findings for each of the directly observed outcomes. The included studies differed in the number of recorded endpoints. When computing the MACE and *any adverse event* endpoints, only studies were included that recorded each of the endpoints included in these composites. For instance, if a study only recorded cardiac mortality, then this study could not be used in analyses of the MACE or any adverse events endpoint because it was unknown whether these patients had an MI or underwent CABG or PCI.

Statistical analysis

We conducted our primary individual patient data meta-analysis according to a one-stage approach [21]. This approach aggregates the data across the included studies and uses a multilevel approach to allow for variation in the estimated regression coefficients across studies. We used a

Bayesian estimation procedure to determine the evidence in favor of both the null and the alternative hypothesis. Bayesian multilevel logistic regression models were fitted using the R-package brms [22]. All regression coefficients (intercept + predictor coefficients) were modeled as random parameters to capture the dependency between scores of participants included in the same study. Parameters were estimated using Markov Chain Monte Carlo (MCMC) sampling with three chains and 3000 iterations, including 1000 warmup iterations. The Type D personality effects on each endpoint were estimated according to each of the 2-group, 4-group, and continuous approaches. Final conclusions were based on the continuous method, because this approach is the least biased according to earlier simulation results [13,14]. Age and sex were both included as covariates and as potential moderators of the Type D effects on each endpoint. Moderation models were estimated separately for age, sex, and disease type, each model including the interaction effect between age/sex/disease on the one hand, and the personality trait variables on the other hand (NA, SI, NA^2, SI^2, NA*SI).

For all models, effects were expressed in terms of odds ratios, including 95% Bayesian credible intervals. In line with earlier research [56], we assumed the priors of the regression coefficients to be normally distributed $N(\mu=0, \sigma=2)$. As a sensitivity analysis we also investigated the same prior but with smaller or larger standard deviation ($\sigma=1$ and $\sigma=4$). For each method, the evidence for a Type D effect in terms of the Bayes factor was quantified as the evidence ratio of the posterior probability of a hypothesis against its alternative. For example, the evidential value for a Type D effect according to the continuous method was determined as the ratio of the posterior probability that the regression coefficient of the NA*SI interaction was larger than 0, against to the posterior probability that this coefficient was 0 or smaller. To

quantify the evidence in favor of the null hypothesis of no Type D effect (regression coefficient of NA*SI interaction = 0), Bayes factors were estimated according to the Savage-Dickey density ratio method [23]. Bayes factors can be used to quantify the support of one model compared to another model. In contrast to frequentist statistics, this allows us to quantify evidence in favor of a hypothesis (e.g., evidence in favor of the null hypothesis of no Type D effect). Bayes factors were interpreted according to guidelines by Kass & Raftery[76] (BFs 1 to 3.2 = "Anecdotal"; BFs 3.2 to 10 = "Substantial"; BFs 10 to 100 = "Strong"; BFs 100 or larger = "Decisive").

As a sensitivity analysis, we also conducted two-step meta-analyses to investigate whether the results of our one-step analysis are robust against the selection of a different meta-analytic approach [24]. In the first step, logistic regression analyses were conducted to estimate for each endpoint the association with Type D personality according to the continuous method. In the second step, a fixed effects meta-analysis [25] was conducted for each endpoint on the log odds ratios and standard errors estimated in step 1. The exponentiated (odds ratio) results of those analyses were visualized in forest plots.

All analyses were conducted using R [26] and the script is available on this project's open science framework page, together with the preregistration of the data collection and analysis plan: https://osf.io/czmhs/.

Results

Our initial literature search resulted in 367 unique studies. The flowchart in Figure 1 shows that after reviewing the titles and abstracts, 330 studies were excluded because they either did not use

a prospective cohort design or did not involve patients with cardiovascular disease. Of the resulting 37 studies, an additional 12 were excluded for similar reasons after examining the full text. We emailed the corresponding authors of the remaining 25 eligible studies. In case of no response, we first sent two reminders before e-mailing other authors. Researchers of 20 studies responded to our emails and 18 were willing to participate in this project by sharing their data. The authors of the remaining studies did either not respond or indicate that the data could not be shared because projects involving that dataset are still in progress. After updating the literature search during the review process, we included one additional study in our analysis, resulting in 19 included prospective cohort studies.

Table 1 shows the characteristics of these 19 studies, comprising a total of 11151 patients with cardiovascular disease who were followed for a average follow-up time of 47.1 months (median = 37, IQR = 15.2 to 63.2). The included studies differed in the cardiac diagnosis, age and sex of patients, but on average the patients were 62.5 years old (SD = 11.3), the majority were male (75.6%) and most were diagnosed with CAD (N_{CAD} = 8096; N_{HF} = 2027; N_{VA} = 638; N_{CVD} = 390). Figure 2 visualizes the bivariate distribution of the NA and SI scores in each study. Across all studies, NA and SI were positively correlated (r = .373). Supplemental Digital Content, Tables S3 and S4, http://links.lww.com/PSYMED/A902 report the quality assessment of each included study. Although some studies were potentially more biased than others, most were at low risk of bias and none of the included studies showed a high risk of bias.

A Bayesian multilevel logistic regression analysis was used to estimate the Type D effects. The number of iterations of the MCMC procedure was sufficient to reach an effective

sample size of at least 500 in the estimation of each model parameter. The R-hat value of each estimated regression coefficient was smaller than 1.05, indicating proper convergence [78]. Table 2 shows for each endpoint the estimated odds ratios (including 95% Bayesian credible interval) of age, sex, the Type D effects according to the three operationalizations. Older age and male sex predicted the occurrence of all-cause mortality and cardiac mortality, but none of the other endpoints. Based on the continuous method, NA and SI showed a synergistic Type D effect on the occurrence of any adverse event during follow-up (OR=1.135, 95%CI=1.029, 1.253). Though the interaction model including quadratic effects also showed a synergistic Type D effect on MACE, when excluding the non-significant quadratic NA and SI effects from the continuous interaction model the 95% Bayesian credible interval contained an odds ratio of one, suggesting no effect (OR=1.126, 95%CI=0.99, 1.286). For all other endpoints, the 95% credible interval of the interaction effect between NA and SI included an odds ratio of one, suggesting Type D did not predict the occurrence of all-cause mortality, cardiac mortality, myocardial infarction, CABG, or PCI. However, an NA main effect was found for both all-cause mortality (OR= 1.156, 95%CI=1.045, 1.296) and cardiac mortality (OR= 1.284, 95%CI=1.088, 1.51). Supplemental Digital Content, Tables S1 and S2, http://links.lww.com/PSYMED/A902 shows for each endpoint, the standard deviation (including 95% Bayesian credible interval) of all random predictor effects according to the continuous method. The fact that many of these credible intervals did not include a standard deviation of zero suggests that these effects differ across studies, supporting our choice to model these parameters as random effects.

Table 3 presents the Bayes factor (BF) estimates according to the continuous method, expressing the evidential value for the presence or absence of a Type D effect on each endpoint

for the complete sample and for CAD and HF patients separately. Evidence for a Type D effect in the complete sample was strong for the endpoint MACE (BF=40.1) and decisive for any adverse event (BF=99.0). Strong evidence for a null effect was found for all-cause mortality (BF=47.18), cardiac mortality (BF=23.34) and myocardial infarction (BF=19.29). The evidence for a Type D effect on CABG and PCI was inconclusive, showing substantial evidential value both in favor and against a Type D effect. When limiting the sample to CAD patients, similar evidential values were found. For patients with HF, however, substantial to strong evidence was found against a Type D effect on all-cause mortality (BF=10.14), while for the other endpoints the evidence was either inconclusive or could not be estimated due to sparse data.

The results in Table 4 indicate that age, sex and type of cardiovascular disease did not moderate the synergistic Type D effects (interaction between NA and SI) on any of the studied endpoints. However, sex turned out to moderate the quadratic NA effect on all-cause mortality, indicating that increasingly higher NA scores were associated with higher odds on all-cause mortality and this effect was more pronounced for male than for female patients (OR=1.184, 95%CI = 1.026, 1.353). A Bayes factor of 89.9 indicated very strong evidence that the population odds ratio of this effect is larger than 1.

Figure 3 visualizes the Type D effects on each endpoint according to the continuous method estimates for the model including the NA and SI main effects and their interaction. For various standardized NA and SI scores, the figure shows the predicted posterior probability on the occurrence of each endpoint. The colored shades represent the 95% prediction intervals for each level of SI scores. The figure indicates the positive interaction effect between NA and SI on

both MACE and any adverse events. The probability on the occurrence of these events during follow-up increased for higher NA scores and these positive effects became more pronounced for larger scores on SI. Similarly shaped curves, but smaller effects were found for CABG or PCI, though statistical evidence for these Type D effects was inconclusive. To facilitate interpretation of these figures, across the included datasets patients on averaged scored 9.02 on the NA (SD=6.33) and 9.20 on the SI (SD=6.01) measurements of the DS14. Based on these statistics, Figure 3 indicates that the probability on any adverse event during follow-up is 0.14 for patients with average NA and SI scores. For patients scoring two standard deviations above the average on NA (21.7), this risk increases to 0.20. For Type D patients, such as those who score two standard deviations above the average on both NA (21.7) and SI (21.3), the risk of an adverse event increases even further to 0.30. To facilitate the significant interaction effects between NA and SI on any adverse events in cardiovascular disease patients, Supplemental Digital Content, Table S8, http://links.lww.com/PSYMED/A902 reports for both NA and SI the simple slope analysis. The effect of SI on adverse events increases across higher NA scores and the 95%CI of the simple slopes starts to exclude a slope of zero (no effect) at NA scores of 13.8 or higher. The effect of NA on adverse events increases across higher SI scores and the 95%CI of the simple slope starts to exclude a slope of zero at SI scores of 6.2 or higher.

To facilitate interpretation of our model estimates, we have created an online tool (https://anonymousresearcher.shinyapps.io/AdverseEvent_Prediction_TypeD_CVD/) that uses the age, sex, negative affectivity and social inhibition scores and type of cardiovascular disease to calculate according to our model estimates the predicted probability on a particular outcome within the average follow-up time of our meta-analysis. For instance, for a 60-year-old male

cardiovascular disease patient with a high NA score (20), the probability of having an adverse event within 48 months is 40.72% when the SI score is average (10), while the probability increases with 4% to 44.85% when the SI score is high (20).

As a sensitivity analysis, Supplemental Digital Content, Figures S1 to S7, http://links.lww.com/PSYMED/A902 show for each endpoint a forest plot presenting the results of the two-step meta-analyses. These results are like those of the one-step meta-analysis, suggesting that Type D personality (operationalized according to the continuous method) was significantly associated with MACE and any adverse event, but not with any of the other endpoints. Table S5 presents the results of leave-one-out sensitivity analyses, that repeats the meta-analysis multiple times, each time with a different study left out. This sensitivity analysis shows that our findings were generally not driven by a single study, except that excluding one of the studies [28] attenuated the Type D effect on MACE, resulting in a Bayesian 95% credible interval that included the value of no effect (OR=1) and suggesting that the MACE effect is largely driven by that study. Another sensitivity analysis reported in Table S6 estimated the impact of prior distribution specification for the regression coefficients of the Type D effect according to the continuous method. The results show similar conclusions for each endpoint except MACE, with different prior distributions resulting in similarly sized Type D effects, yet slightly wider 95% credible intervals including an odds ratio of no effect, suggesting uncertainty regarding Type D's effect on MACE. Lastly, Table S7 presents for each method to estimate the Type D effect a brier score, expressing the accuracy of predicting the observed endpoint based on the model estimates. For each method and outcome, the brier scores are close to zero, indicating high predictive accuracy.

Discussion

We conducted an individual patient meta-analyses across 19 published prospective cohort studies investigating the prognostic effect of Type D personality in cardiovascular disease patients. We estimated the Type D effect according to the continuous interaction method, which performed best in several simulation studies [13,14]. Bayes factors indicated very strong evidence for the hypothesis that Type D predicts the occurrence of adverse events in patients with coronary artery disease. Simple slope analysis indicated that the influence of both NA and SI on any adverse event increased across higher scores on the other personality trait. Although Bayes factors indicated strong evidence for the Type D effect on MACE, various sensitivity analyses produced 95% credible intervals containing an odds ratio of one, suggesting that we should entertain the possibility of no Type D effect on MACE.

Evidence for a null effect was found for the outcomes all-cause mortality and cardiac mortality. The risk on those mortality endpoints increased with older age, male sex, and higher NA scores. A moderation of sex on a quadratic NA effect suggested that the higher NA scores increasingly resulted in a higher risk of all-cause mortality and this pattern was more pronounced for men in comparison to women. In the subset of patients with HF, there was slightly more evidence against a Type D effect on each studied endpoint, yet generally evidence for Type D's prognostic influence in HF patients remains inconclusive. Future research could investigate potential moderators of Type D's prognostic influence on adverse events in HF patients, for instance by comparing different etiologies (e.g., valvular or ischemic HF) [82].

When interpreting the Type D effect on MACE and any adverse event, it is useful to inspect the effects on each of the MACE components. The Type D effects on CABG, PCI and MI are slightly smaller than the effects on MACE and based on both the Bayes factors and the 95% credible intervals we cannot exclude the possibility of a null effect. Nevertheless, the Type D effects on any of these individual outcomes point in the same direction and they may have become more noticeable when combined in a composite endpoint such as MACE or any adverse event. One could argue that endpoints such as the risk on MACE or any adverse event are more interesting to patients than individual endpoints such as PCI or CABG, as those endpoints reflect a similar disease pathway while their occurrence also depends on more arbitrary factors such as healthcare availability or the location of atherosclerosis.

Our finding that Type D predicts adverse events in patients with CAD is in line with the conclusions drawn from earlier meta-analyses[1,2] and a reanalysis of four of the earlier studies on this topic using the continuous method [6]. However, our multilevel model indicated significant differences between studies in the estimate of this Type D effect. Our two-step meta-analysis reported in the supplement can reveal the studies that primarily drive this effect. The analysis indicated that all but two of the included studies showed positive estimates of the Type D effect on MACE, yet the effect appears to be predominantly driven by three studies [27–29]. Indeed, our leave-one-out meta-analysis reported in Supplemental Digital Content, Table S5, http://links.lww.com/PSYMED/A902 showed that the Type D effect on MACE was no longer statistically significant when excluding one of those studies from the meta-analysis. This study involved a sample of 541 relatively young (M=58.7) and mostly male (87%) patients with CAD [28]. According to the quality assessment there was no reason to exclude this study from our

analysis. Nevertheless, our finding that the Type D effect on MACE depends primarily on this particular study raises doubt on the robustness of this effect. This uncertainty is corroborated by two other observations in our statistical analysis. First, the continuous interaction model excluding the quadratic NA and SI effects did no longer show a significant interaction between NA and SI on MACE. Second, even when including those quadratic effects in the model, the 95% credible interval for the interaction between NA and SI on MACE contained one when using a flat instead of normally distributed prior for the regression coefficients. Altogether, these observations suggest that *there is still uncertainty regarding the effect of Type D on MACE.* Nevertheless, our various sensitivity analyses all suggest an association between Type D personality and adverse events in cardiovascular disease patients.

Our finding that not Type D personality, but only NA was associated with both all-cause and cardiac mortality contrasts with the conclusion of an earlier published meta-analysis [1]. This discrepancy is likely explained by the fact that this previous meta-analysis included Type D effects estimated according to the 2-group method. As this method is not able to distinguish Type D effects from effects of NA or SI only [13,14], meta-analyses including such effects have the same limitation. Previous research estimated that approximately half of all published Type D effects according to the 2-group method were effects of NA or SI only according to the continuous method[15]. Supplemental Digital Content, Figures S1 and S2, http://links.lww.com/PSYMED/A902 show that only one of the currently included studies showed a statistically significant Type D effect on all-cause and cardiac mortality according to the continuous method, while the earlier published meta-analysis included many studies with significant effects according to the 2-group method[1]. The current study suggests that many of

these earlier studies showing a link between Type D personality and mortality endpoints were in fact effects of NA only. Indeed, studies using the continuous method to estimate the Type D effect have shown that only NA was associated with various outcomes, such as in-stent neoatherosclerosis [65], coronary lipid plaque [66], and medication adherence [67]. Future research should use individual patient-data meta-analyses to test whether these findings are confirmed when aggregating across multiple studies.

The absence of a moderation of age on the Type D effect on MACE contrasts with a previous analysis of several published studies showing that Type D only predicted MACE in CAD patients if they were younger than 70 years old [16]. Our moderation analysis also found no evidence that the Type D effect on any outcome differs across the type of cardiovascular disease. However, the confidence intervals for these moderations by disease were very wide, suggesting considerable uncertainty in these estimates. Indeed, the subgroup analyses reported in Table 3 show that the Type D effects in CAD patients are similar to those in the full sample, yet much uncertainty remains regarding the effects in HF patients. Sex did not moderate the Type D effect on any outcome, yet moderated a quadratic NA effect on all-cause mortality, suggesting that this quadratic effect differs between the sexes. The prediction model in our shiny app reveals the risk on all-cause mortality increases quadratically with higher NA scores for male CVD patients, whereas females do not show such an NA effect. This finding resonates with earlier research showing that negative mood episodes such as depression increase the mortality risk more in males than females [77].

Our data only allowed adjusting the Type D effects for age and sex. It therefore remains unclear whether the Type D effect on adverse events is confounded by other risk factors, such as lifestyle or depressive symptoms. Alternatively, these risk factors may also signify increased disease progression, and therefore not confound but rather mediate or explain the association between Type D personality and adverse events. Given the high correlation between NA and depressive symptoms, depression may have confounded or mediated the Type D effects found in our study. Indeed, a previous meta-analysis [1] found that the overall association between Type D and CVD prognosis was no longer statistically significant when limiting the analysis to the six studies that had estimated the Type D effect while controlling for related psychological constructs such as symptoms of depression or anxiety. This does not necessarily imply that Type D's prognostic risk is confounded by depression or anxiety symptoms, because an alternative explanation could be that mood symptoms mediate the association between Type D and CAD prognosis.

We were also not able to control for other potential physical or mental morbidities that could produce both an increase in for instance both NA and the risk on adverse events. For these reasons, our findings do not support a *causal* influence of Type D personality on adverse events. On the other hand, the studies included in our analysis that showed the largest effects of Type D on adverse events [27,28] did adjust their analyses for confounders such as decreased systolic function / LVEF, exercise tolerance, and psychological stress. Nevertheless, future research could perform a highly powered preregistered investigation into the added predictive value of Type D personality on adverse events in cardiovascular disease patients above and beyond the effect of depression and other clinical risk factors, while modeling Type D personality according

to the continuous interaction method.

Should such a high-powered preregistered analysis detect a Type D effect on adverse events, then subsequent research could shed more light on the biological pathways underlying this association. Although in earlier work Type D personality has been associated with impaired endothelial function [31], subclinical inflammation [32] and various inflammatory biomarkers [33,34], these analyses were based on the biased personality group methods. Future work should therefore reanalyze these studies using the continuous method to find out whether these effects were truly driven by Type D personality, or by an effect of NA or SI only. Recent work using the continuous method showed that Type D is associated with higher levels of coronary artery calcification, after adjusting for many known CAD risk factors such as depression, smoking, diabetes and hypertension [35]. Coronary artery calcification is itself related to an increased risk of adverse cardiac events, and an unhealthy lifestyle could explain why some individuals develop high coronary artery calcification levels [36]. Type D personality has been associated with less regular physical exercise [37], a less healthy diet [38], and poor self-management [39]. Therefore, future research could focus on testing the role of an unhealthy lifestyle as a possible behavioral pathway mediating Type D's effect on coronary artery calcification and other indicators of heart disease [5].

One clinical implication of our finding is that interventions to reduce *mortality risk* in patients with cardiovascular disease should mainly target NA, because elevated SI does not confer additional risk. Given the close relation between NA and other negative mood episodes such as depression, it may therefore be worthwhile to treat these CVD patients with interventions

that are effective in reducing depressive symptoms. Although a randomized controlled trial found no benefit of stepwise psychotherapy in reducing depressive symptoms in CAD patients, a subgroup analysis revealed the intervention was more effective in those with Type D personality than in those without Type D personality [45]. For preventing *adverse events* in CVD patients, it may be worthwhile to additionally intervene on SI. High SI could be reduced with for instance Cognitive Behavioral Therapy (CBT) [79] or Acceptance and Commitment Therapy (ACT), allowing those with high SI to improve their emotion regulation skills [80], albeit those willing to seek help, because social inhibition may reduce treatment-seeking behavior [81]. Although SI is generally considered a temporally stable personality trait, longitudinal research has estimated that SI is 83% trait and 17% state, while NA is 74% trait and 26% state, suggesting that both constructs are susceptible to change [83]. When individuals show increased SI due to traumatic interpersonal experiences, then targeting such experiences may potentially reduce SI and thereby its increased risk on adverse events in those with high NA.

Strengths and limitations

Strengths of the current research are the large sample size (N=11151), the Bayesian estimation approach (allowing quantification of the evidential value for both the null and alternative hypotheses), the sensitivity analysis (one-step vs. two-step individual patient data meta-analysis), and the various contrasted Type D operationalizations (2-group vs. 4-group vs. continuous method) confirming previous work that the 2-group and 4-group methods cannot distinguish synergistic Type D effects, from main effects of NA or SI only[13,14].

Despite these strengths, our study also has several limitations. First, the cardiac mortality

endpoint may be unreliable because identifying the cause of mortality can be difficult, particularly in elderly multimorbid patients. Second, we did not have sufficient data to adjust our estimate of the Type D effect for earlier received treatments or non-cardiac somatic and psychiatric diagnoses. This raises the question of whether baseline NA or SI measurements were influenced by disease or treatment related factors. Nevertheless, some of the studies included in this meta-analysis found significant Type D effects after controlling for a history of cardiac events such as CABG, PCI, or MI [27,28,29].

Third, 7 of the 25 identified eligible studies could not be included either due to non-response or the reluctance of sharing the raw data. This resulted in excluding the potential data of 1457 patients with HF and 1035 patients with CAD. Although our analyses still involved 2027 patients with HF and 8096 patients with CAD, it was not possible to estimate a Type D effect for some endpoints in patients with HF due to sparse data. As a result, it remains unclear whether Type D is associated with an increased risk on MI, CABG and PCI in patients with HF.

Of the 7 excluded studies, two out of three studies in heart failure patients showed a significant association between Type D personality and mortality using the 2-group method [68,69,70]. The four remaining studies focused on CAD patients, three of which used the 2-group method to show that Type D personality was associated with MACE [71,72,73], while one study indicated that a cluster with CAD patients scoring high on Type D personality had an increased risk of all-cause mortality during follow-up than other patient clusters [74]. None of these seven studies used the continuous method to estimate Type D effects, leaving it unclear whether Type D personality was driving these effects. This is likely only true for some of these studies, given

that approximately half of the studies with significant Type D effects based on the 2-group method are effects of NA or SI only according to the continuous method [15].

Another limitation is that we did not include unpublished studies. Although one earlier meta-analysis did not find evidence of publication bias in the sample of studies investigating the MACE endpoint[2], another indicated that studies with smaller sample sizes showed larger Type D effects than studies with larger sample sizes, possibly hinting at publication bias[1]. Should it be the case that there exist unpublished studies investigating the risk of Type D on adverse events in cardiovascular disease patients, and that those studies differ from published studies in their effect sizes, then publication bias may have affected our conclusions.

Our meta-analysis was applied to total NA and SI scores because individual item scores were no longer available for various studies included in our analysis. Therefore, we were not able to conduct item-level analyses, testing whether specific combinations of NA and SI items interact in predicting adverse events. We recommend researchers in future studies on Type D personality to test item-level interaction effects to investigate which items primarily drive a potential significant interaction effect between NA and SI.

Due to the lack of individual item scores, we were not able to conduct an IRT-based measurement harmonization to link the differently sized DS14 and DS16 scales. As a workaround we standardized the NA and SI total scores to the same z-score metric. We were also not able to determine whether the measurement instruments showed signs of differential item functioning across the included studies. Nevertheless, previous research using item response

theory has shown that the DS14 instrument provides fairly comparable measurements across the general and clinical populations [63]. Future research could investigate this measurement invariance across other factors such as age, sex, or type of cardiovascular disease.

Conclusion

In light of recent findings that a major part of the published Type D effects may be false positives masquerading for effects of NA or SI only [13–15], our study is a first endeavor at a large scale reanalysis of the published Type D literature. Using the continuous method, our reanalysis suggests that some of the earlier published Type D effects on all-cause and cardiac mortality [9,40] are likely effects of NA only. Nevertheless, based on this individual patient data meta-analysis of 19 published prospective cohort studies, Type D personality poses an increased risk on the occurrence of adverse events in patients suffering from coronary artery disease.

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Figure 1: Flow chart of the systematic literature review

Figure 2: For each included study, a scatterplot of the NA and SI sum scores. The dot size represents the frequency of a NA and SI score combination.

Figure 3: Predicted posterior probability on the occurrence of several endpoints during follow-up, given various scores on the standardized NA and SI scores.

Figure 1

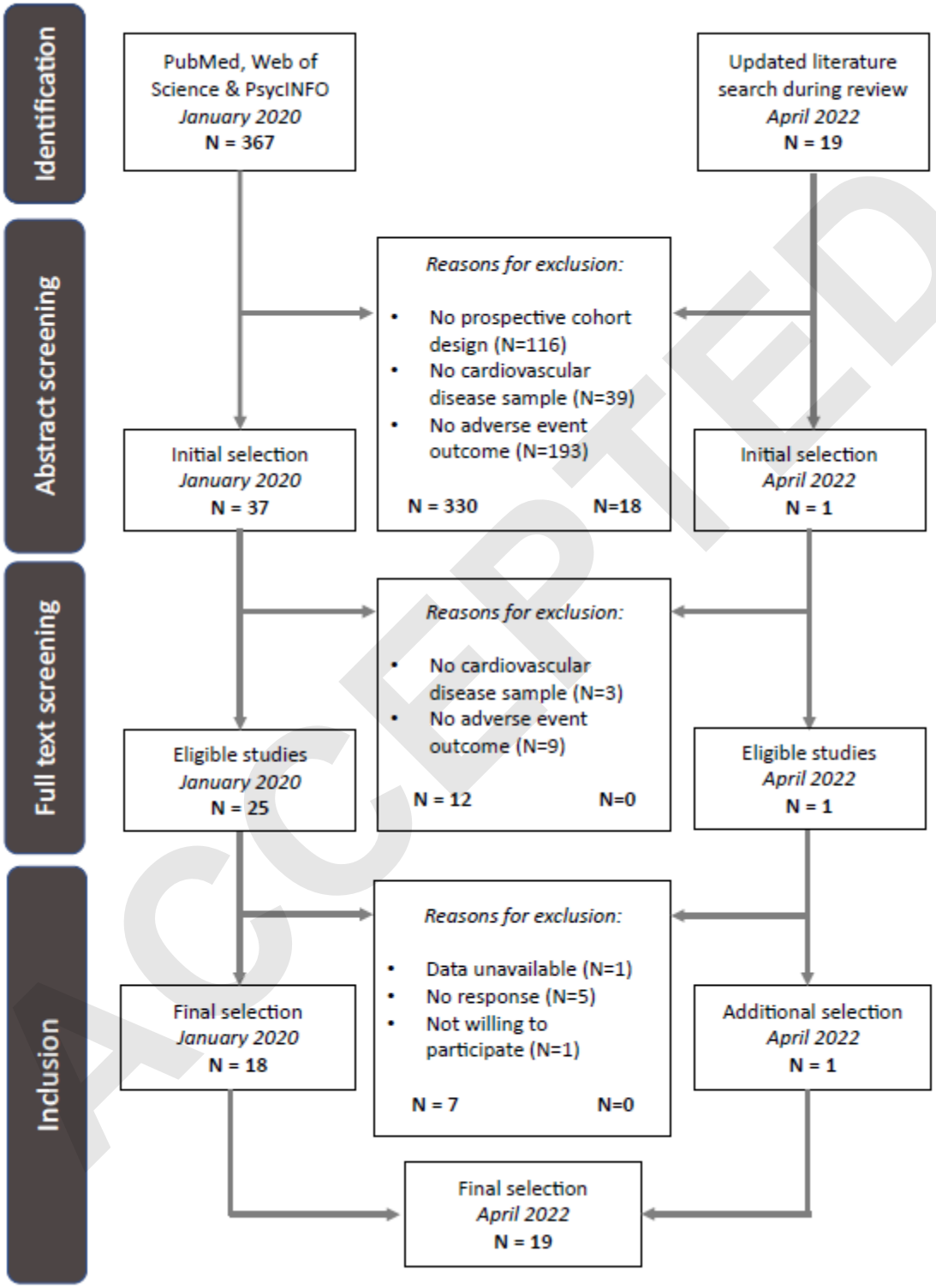

Figure 2

Figure 3

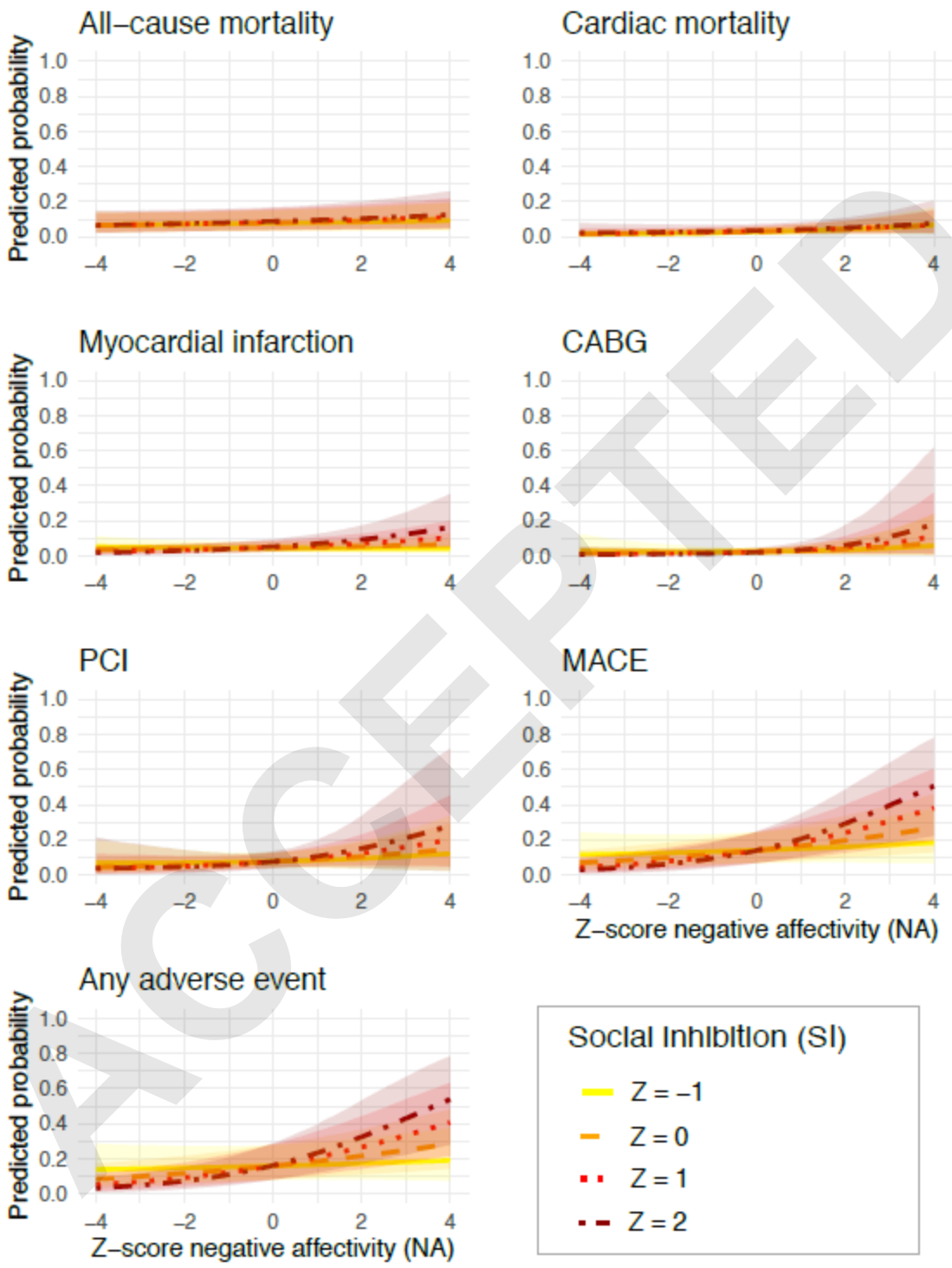

Table 1: Characteristics of studies included in the individual patient-data meta-analysis

Study	N	Diagnosis	Country	Follow-up (months)	Age (M)	Men (%)	Type D personality measure	Negative affectivity (M, SD)	Social inhibition (M, SD)
Denollet et al. (1996) [40]	378	CAD	Belgium	95	55.6	88.6%	STAI & HPPQ	9.8 (6.7)	10.5 (6.6)
Denollet et al. (2000) [41]	364	CAD	Belgium	60	56.5	91.8%	DS16	9.7 (6.6)	14 (6.6)
Denollet et al. (2006) [27]	326	CAD	Netherlands	20	56.8	87.1%	DS16	9.2 (6.6)	13.3 (6.3)
Martens et al. (2010) [29]	466	CAD	Netherlands	22	59.3	78.5%	DS14	7.3 (6.2)	9.1 (6.5)
Pelle et al. (2010) [42]	641	HF	Netherlands	37	66.4	74.3%	DS14	7.1 (6.4)	9.1 (6.5)
Schmidt et al. (2011) [43]	137	CAD	Brazil	12	60.2	63.5%	DS14	10.6 (6.7)	10.3 (7.4)
Coyne et al. (2011) [44]	1047	HF	Netherlands	18	70.9	62.6%	DS14	6.3 (6.0)	7.8 (6.9)
Herrmann-Lingen et al. (2016) [45]	569	CAD	Germany	18	59.2	78.9%	DS14	15.8 (4.8)	11.8 (5.9)
Grande et al. (2011) [46]	1091	MIX	Germany	71	62.7	74.8%	DS14	10.1 (5.7)	8.3 (5.2)
Denollet et al. (2013a) [47]	638	VA	Netherlands	38	62.9	80.6%	DS14	7.5 (6.4)	9.0 (6.3)
Denollet et al. (2013b) [28]	541	CAD	Belgium	60	58.7	87.4%	DS14	9.0 (6.3)	9.8 (6.3)
Meyer et al. (2014) [48]	470	CAD	Germany	60	63.7	76.8%	DS14	10.6 (5.7)	9.2 (5.7)
Sumin et al. (2015) [49]	682	CAD	Russia	12	58.5	81.8%	DS14	9.1 (4.1)	9.3 (3.5)
Dulfer et al. (2015) [50]	1190	CAD	Netherlands	120	62.3	72.6%	DS14	9.4 (6.8)	9.1 (6.5)
Gostoli et al. (2016) [51]	117	VA	Italy	24	63.1	74.4%	DS14	8.1 (6.7)	7.4 (6.5)
Pushkarev et al. (2017) [52]	939	CAD	Russia	12	58.7	75.3%	DS14	10.4 (5.8)	9.7 (5.5)
Conden et al. (2017) [53]	941	CAD	Sweden	76	70.5	66.7%	DS14	6.6 (5.6)	7.9 (5.8)
Lin et al. (2019) [54]	222	HF	Taiwan	18	60.4	66.2%	DS14	6.5 (5.1)	6.0 (5.7)
Lv et al. (2020) [55]	392	CAD	China	12	61.6	68.9%	DS14	11.4 (4.7)	10.9 (4.9)

CAD = coronary artery disease; HF = heart failure; VA = ventricular arrythmia; MIX = mix of various cardiovascular disease diagnoses.

HPPQ = heart patients psychological questionnaire; STAI = state trait anxiety inventory

Table 2: For each endpoint, the estimated odds ratios [95% Bayesian credible interval] of demographic predictors, the Type D effects according to the continuous method. The 95%CI of bold cells does not include an odds ratio of one.

Outcome	All-cause mortality	Cardiac mortality	Myocardial infarction	CABG	PCI	MACE	Any adverse event
Sample size	N = 10647	N = 6166	N = 6269	N = 2832	N = 2840	N = 4315	N = 6013
Predictor	OR [95%CI}	OR [95%CI}	OR [95%CI}	OR [95%CI}	OR [95%CI}	OR [95%CI}	OR [95%CI}
Demographics [m3]							
Age (standardized)	**1.933 [1.559, 2.355]**	**1.56 [1.238, 1.991]**	1.107 [0.785, 1.615]	0.945 [0.561, 1.65]	0.835 [0.674, 1.032]	1.087 [0.833, 1.436]	1.14 [0.918, 1.456]
Men	**1.27 [1.012, 1.597]**	**1.681 [1.096, 2.648]**	1.089 [0.735, 1.676]	0.832 [0.299, 2.224]	0.725 [0.406, 1.212]	1.069 [0.762, 1.461]	1.021 [0.748, 1.369]
Continuous method							
NA [m1]	**1.156 [1.045, 1.296]**	**1.284 [1.088, 1.51]**	1.118 [0.96, 1.325]	1.296 [0.829, 1.861]	**1.205 [1.002, 1.435]**	**1.283 [1.146, 1.44]**	**1.269 [1.139, 1.425]**
SI [m1]	1.011 [0.922, 1.136]	1.061 [0.873, 1.341]	1.09 [0.947, 1.277]	0.977 [0.69, 1.384]	1.045 [0.874, 1.247]	1.049 [0.945, 1.166]	1.05 [0.952, 1.165]
NA2 [m2]	1.038 [0.975, 1.107]	1.054 [0.918, 1.179]	1.074 [0.977, 1.181]	1.026 [0.757, 1.298]	1.004 [0.842, 1.144]	1.023 [0.948, 1.101]	1.019 [0.952, 1.09]
SI2 [m2]	1.005 [0.916, 1.084]	0.927 [0.809, 1.059]	1.076 [0.946, 1.26]	1.088 [0.82, 1.422]	1.041 [0.9, 1.194]	1.058 [0.967, 1.157]	1.041 [0.962, 1.126]
NA * SI [m3]	0.996 [0.918, 1.092]	0.996 [0.851, 1.191]	1.069 [0.937, 1.232]	1.171 [0.844, 1.666]	1.112 [0.896, 1.351]	**1.14 [1.001, 1.286]**	**1.167 [1.033, 1.313]**
NA * SI [m5]	1.02 [0.953, 1.116]	0.994 [0.870, 1.142]	1.120 [0.995, 1.282]	1.165 [0.891, 1.507]	1.099 [0.884, 1.308]	1.126 [0.99, 1.268]	**1.135 [1.029, 1.253]**

CABG = coronary artery bypass grafting; MACE = major adverse cardiac event; OR = Odds ratio; PCI = percutaneous coronary intervention

m1: Model = Age + Men + NA + SI
m2: Model = Age + Men + NA + SI + NA2 + SI2
m3: Model = Age + Men + NA + SI + NA2 + SI2 + NA*SI (normally distributed priors (mean)
m4: Model = Age + Men + NA + SI + NA2 + SI2 + NA*SI (flat prior)
m5: Model = Age + Men + NA + SI + NA*SI

Table 3: For each endpoint, Bayes factor (BF) estimates and evidential value for the presence (main hypothesis) or absence (null hypothesis) of a Type D effect according to the continuous methods. Bold faced cells indicate strong or decisive evidential value.

	All-cause mortality		Cardiac mortality		Myocardial infarction		CABG		PCI		MACE		Any adverse event	
Type D effect	BF	Evidence	BF	Evidence	BF	Evidence	BF	Evidence	BF	Evidence	BF	Evidence	BF	Evidence
Complete sample (N=11151)														
Main hypothesis: NA*SI > 0	0.82	Anecdotal	0.86	Anecdotal	5.45	Substantial	4.87	Substantial	6.37	Substantial	**40.1**	**Strong**	**99.0**	**Decisive**
Null hypothesis: NA*SI = 0	**47.18**	**Strong**	**23.34**	**Strong**	**19.29**	**Strong**	8.05	Substantial	9.87	Substantial	3.83	Substantial	1.57	Anecdotal
CAD patients (N=8096)														
Main hypothesis: NA*SI > 0	4.96	Anecdotal	4.04	Anecdotal	3.89	Substantial	5.24	Substantial	6.65	Substantial	**39.0**	**Strong**	**175.47**	**Decisive**
Null hypothesis: NA*SI = 0	**17.38**	**Strong**	**10.98**	**Strong**	**22.35**	**Strong**	8.19	Substantial	9.57	Substantial	3.54	Substantial	1.04	Anecdotal
HF patients (N=2027) *														
Main hypothesis: NA*SI > 0	0.55	Anecdotal	0.81	Anecdotal		-		-		-	1.15	Anecdotal	1.24	Anecdotal
Null hypothesis: NA*SI = 0	**10.14**	**Strong**	4.90	Substantial		-		-		-	2.52	Anecdotal	2.88	Anecdotal

BF = Bayes factor; CABG = coronary artery bypass grafting; CAD = coronary artery disease; HF = heart failure; MACE = major adverse cardiac event; PCI = percutaneous coronary intervention

** Empty cells indicate that insufficient data was available to estimate the Type D effect on a particular endpoint for this patient sample*

Table 4: For each endpoint, the estimated odds ratios [95% Bayesian credibility interval] of the moderating influence of age, sex, and disease on the Type D effects according to the continuous method. The 95%CI of bold cells does not include an odds ratio of one.

Outcome	*All-cause mortality*	*Cardiac mortality*	*Myocardial infarction*	*CABG*	*PCI*	*MACE*	*Any adverse event*
Predictor	*OR [95%CI}*	*OR [95%CI}*	*OR [95%CI}*	*OR [95%CI}*	*OR [95%CI}*	*OR [95%CI}*	*OR [95%CI}*
Moderating effect of sex^{m1}							
Men * NA	1.05 [0.861, 1.269]	0.943 [0.571, 1.518]	0.969 [0.696, 1.338]	1.301 [0.502, 3.174]	0.968 [0.622, 1.466]	1.008 [0.755, 1.344]	0.964 [0.727, 1.257]
Men * SI	0.948 [0.78, 1.155]	1.025 [0.66, 1.613]	1.006 [0.727, 1.395]	0.755 [0.298, 1.87]	1.165 [0.782, 1.753]	1.088 [0.839, 1.427]	1.023 [0.787, 1.326]
Men * NA2	**1.184 [1.026, 1.353]**	1.115 [0.842, 1.525]	1.109 [0.875, 1.39]	0.596 [0.289, 1.091]	0.857 [0.63, 1.144]	0.971 [0.801, 1.179]	0.985 [0.825, 1.188]
Men * SI^2	1.005 [0.852, 1.179]	0.811 [0.599, 1.099]	1.075 [0.826, 1.396]	0.673 [0.31, 1.453]	0.852 [0.619, 1.185]	0.925 [0.758, 1.138]	0.962 [0.787, 1.186]
Men * NA * SI	0.987 [0.837, 1.156]	0.984 [0.666, 1.426]	1.008 [0.756, 1.338]	1.707 [0.825, 3.538]	0.864 [0.578, 1.272]	0.923 [0.706, 1.191]	0.916 [0.702, 1.177]
Moderating effect of age^{m2}							
Age * NA	1.02 [0.902, 1.15]	0.977 [0.772, 1.243]	0.873 [0.747, 1.027]	1.088 [0.702, 1.649]	0.944 [0.705, 1.334]	0.97 [0.833, 1.13]	0.993 [0.839, 1.175]
Age * SI	0.955 [0.849, 1.059]	0.991 [0.799, 1.233]	0.997 [0.848, 1.196]	0.964 [0.637, 1.46]	1.077 [0.87, 1.342]	0.968 [0.852, 1.115]	0.913 [0.799, 1.041]
Age * NA^2	1.028 [0.953, 1.112]	1.113 [0.97, 1.278]	1.077 [0.943, 1.234]	0.99 [0.729, 1.37]	1.052 [0.896, 1.241]	1.053 [0.946, 1.173]	1.039 [0.936, 1.151]
Age * SI^2	1.011 [0.935, 1.099]	1.105 [0.919, 1.336]	0.988 [0.864, 1.141]	1.063 [0.712, 1.605]	0.984 [0.811, 1.205]	1.035 [0.927, 1.164]	1.053 [0.937, 1.188]
Age * NA * SI	0.967 [0.878, 1.056]	0.952 [0.785, 1.171]	1.007 [0.86, 1.181]	1.001 [0.663, 1.532]	0.841 [0.679, 1.042]	0.96 [0.833, 1.112]	0.953 [0.812, 1.099]
Moderating effect of disease^{m3}							
Disease * NA	1.001 [0.769, 1.319]	0.97 [0.605, 1.568]	1.036 [0.066, 15.269]	1.085 [0.059, 19.496]	1.105 [0.075, 18.703]	0.937 [0.575, 1.599]	0.959 [0.584, 1.522]
Disease * SI	1.127 [0.852, 1.534]	1.492 [0.82, 2.46]	1.062 [0.077, 16.481]	0.995 [0.064, 16.002]	1.002 [0.064, 15.805]	0.751 [0.449, 1.271]	0.759 [0.462, 1.213]
Disease * NA^2	0.916 [0.774, 1.075]	0.908 [0.6, 1.363]	1.037 [0.07, 15.358]	0.979 [0.052, 15.393]	0.959 [0.065, 13.495]	0.94 [0.671, 1.323]	0.912 [0.644, 1.259]
Disease * SI^2	0.924 [0.707, 1.132]	0.791 [0.532, 1.162]	1.039 [0.066, 15.071]	1.003 [0.062, 15.562]	1.028 [0.064, 16.064]	1.353 [0.952, 1.946]	1.278 [0.949, 1.739]
Disease * NA * SI	1.145 [0.909, 1.408]	1.18 [0.737, 1.873]	1.018 [0.061, 16.898]	1.005 [0.061, 16.547]	1.07 [0.07, 18.78]	1.079 [0.62, 1.825]	1.152 [0.724, 1.851]

CABG = coronary artery bypass grafting; MACE = major adverse cardiac event; OR = Odds ratio; PCI = percutaneous coronary intervention

m1 = Age + Men + NA + SI + NA2 + SI2 + NA*SI + Men*NA + Men*SI + Men*NA2 + Men*SI2 + Men*NA*SI
m2 = Age + Men + NA + SI + NA2 + SI2 + NA*SI + Age*NA + Age*SI + Age*NA2 + Age*SI2 + Age*NA*SI
m3 = Age + Men + Disease + NA + SI + NA2 + SI2 + NA*SI + Disease*NA + Disease *SI + Disease*NA2 + Disease*SI2 + Disease*NA*SI