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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Review question

The aims of our meta-analysis are threefold:

1. We aim to determine the risk of having a Type D personality on adverse events (including (all-cause) mortality as well as cardiac events) in the population of people suffering from either coronary artery disease, heart failure or ventricular arrhythmia.
2. Kupper & Denollet (2016) showed that the heterogeneity in the results of Type D studies can partly be explained by moderators. Therefore, our second aim is to determine whether age, sex, cardiac diagnosis (e.g. coronary artery disease vs. heart failure), and event type (e.g. all-cause mortality vs. major cardiac event) moderate the association between Type D and adverse events.
3. In the literature, several psychometric methods have been used to operationalize Type D personality. Recent research indicated these methods differ not only conceptually, but also in terms of bias and false positives. Our third aim is to analyze our individual patient data meta-analysis according to each of these psychometric methods and compare the results they generate.

Searches

We plan to conduct a systematic literature search using the following electronic databases: PubMed, EMBASE and PsycINFO. We will search 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 'cardiac event' OR 'MACE' OR 'myocardial infarction' OR 'all-cause mortality' OR 'mortality' OR 'cardiac mortality' OR 'cardiac death']. Furthermore, we will perform hand searches, selecting articles included in earlier systematic reviews and meta-analyses. We will limit our searches to a publication period between 1996 and 2019, because the first publication on Type D personality was in 1996. Lastly, we will additionally perform a cited reference search in Web of Science for the two seminal papers on Type D personality and cardiac events (Denollet et al., 1996; 2000).

Types of study to be included

We will include prospective cohort studies investigating the association between Type D personality and adverse events (including all-cause mortality, cardiac mortality, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention). We will include studies involving healthy samples as well as patient samples with any kind of diagnosis. We will exclude case-control, cross-sectional studies, imaging studies, case series and case reports. Studies that did not measure Type D personality using psychological questionnaires designed to assess the two traits negative affectivity and social inhibition (e.g. the DS-14 or DS-16). If several studies have been published on the same sample of participants, we will include the study with (1) the largest sample size, (2) the longest follow-up time. Of each included study we will contact the corresponding author (or other authors in case of non-response) and request the raw data listed below. Though researchers are encouraged to share all the listed information, studies will be excluded if researchers are not able to at least share the bold faced information.

- **Type D personality** (Raw item scores of DS-14 or DS-16 questionnaire, or any of its translations)
- **Adverse outcome** (as many of the following: all-cause mortality; cardiac mortality; myocardial infarction; coronary artery bypass grafting; percutaneous coronary intervention)
- Longest follow-up time
- Cause of death (If applicable)

- Clinical characteristics (Type of cardiovascular disease)
- Demographic characteristics (Age, Sex)
- Study characteristics (date of baseline measurement; follow-up duration)

Condition or domain being studied
Cardiovascular disease; Type D personality; Adverse outcome; Cardiac events; Myocardial infarction; Mortality.

Participants/population
Population of people who at baseline were diagnosed with coronary artery disease, heart failure or ventricular arrhythmia, who filled out the DS-14 questionnaire assessing Type D personality, and for whom the occurrence of adverse events was recorded over the study's follow-up time.

Main outcome(s)

Adverse outcome, including:
- All-cause mortality
- Cardiac mortality
- Major adverse cardiac events (MACE), including but not limited to myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery.

Additional outcome(s)
The primary outcome will consist of any adverse outcome. Sensitivity analyses will be performed investigating Type D's effects on the specific outcome measures all-cause mortality, cardiac mortality and MACE.

Moderators
We will assess the moderating influence on the association between Type D and adverse events of the variables age (continuous), sex (dichotomous), and cardiac diagnosis (nominal with coronary artery disease as reference category).

Data extraction (selection and coding)
Two reviewers will independently perform the screening process. In the first step, titles and abstracts will be screened and studies will be included or excluded based on the established criteria. In the second step, studies which pass the first round will be included or excluded based on full-text screening. In case of disagreements between the two reviewers, a third reviewer will be consulted.

Due to the nature of the individual patient data meta-analysis, it is not necessary to extract data from the included articles. If the authors of the included studies are willing to share the requested data, then the shared dataset will contain all the information we need to appropriate conduct our IPD meta-analysis.

Strategy for data synthesis
In this study we will compare the effects of Type D personality on adverse events according to four models used to operationalize Type D personality:

1. **Dichotomized 2-group model.** The most commonly used (and most criticized) method first computes aggregate scores for Type D's subcomponents NA and SI by summing the scores of the items assessing each construct. Subsequently these two sum scores are dichotomized into a high vs. low score using a predetermined cut-off score of 10. These dichotomized NA and SI variables are transformed in a dichotomous Type D variable by assigning a value of 1 to people who score high on

both constructs and otherwise assigning a value of 0. The dichotomous Type D variable will be used as a predictor in a multilevel logistic regression analysis, where the random effect component allows for variation in effects across studies. According to this method the Type D effect is represented by the regression coefficient of the dichotomous Type D variable.

2. **Dichotomized 4-group model.** Another common method uses the dichotomized NA and SI scores to classify people in four rather than two different groups: (1) High NA & High SI (Type D personality); (2) High NA & Low SI; (3) Low NA & High SI; (4) Low NA & Low SI. These four groups are recoded into three dummy variables indicating whether people are classified in group 1, 2, or 3. The fourth group then serves as a reference category. The three dummy variables are entered in a multilevel logistic regression analysis. According to this method the Type D effect is represented by the regression coefficient of the Type D personality group dummy variable.
3. **Interaction model.** Some scholars (e.g. Smith, 2011) have argued that the Type D effect can be seen as a synergy between its subcomponents NA and SI. A significant Type D effect would then correspond to a significant interaction effect between NA and SI in the expected direction (the effect of one trait enhances the effect of the other trait on the outcome). This second model therefore includes as predictors in a multilevel logistic regression analysis the two continuous and mean-centered NA and SI variables, as well as their multiplication (constituting the interaction effect). According to this method the Type D effect is represented by the regression coefficient of the interaction term.
4. **Threshold model.** Other scholars have argued (e.g. Lodder, in preparation) that the Type D effect may not be synergistic, but can better be modeled as a combined threshold effect, where main effects for both NA and SI are required for concluding a Type D effect. Both these main effects are modeled by including the continuous NA and SI variables as predictors in a multilevel logistic regression analysis and using a threshold model (or linear spline model with one knot) instead of a regular linear regression to model Type D's association with adverse events. Recently developed threshold regression models (Muggeo, 2008; Fong et al., 2017) estimate the optimal threshold location for a particular predictor, as well as its linear effects below- and above the threshold location. According to this method the Type D effect is represented by the presence of a significant regression coefficients for both NA and SI above the threshold location. The regression coefficients below the threshold location are expected to be either zero or at least smaller than their counterparts above the threshold.

For each of these four models, the statistical significance (given an alpha of 0.05) and effect size of the Type D effect will be evaluated. Additionally, the fit of the four models will be compared using the AIC and BIC fit measures. The best fitting models will show the lowest AIC and BIC values.

In order to evaluate whether Type D's effect on adverse events depends on demographic or clinical characteristics, we will include the variables age, sex, and cardiac diagnosis as moderators in the abovementioned multilevel logistic regression analyses.

Analysis of subgroups or subsets

The moderator variables will indicate whether the relation between Type D personality and adverse events depends on other factors. Regarding these moderating effects we have formulated three expectations:

1. We expect the Type D effect to be stronger for the cardiac diagnosis 'coronary artery disease' than for other diagnoses.
2. We expect the Type D effect to decline for higher ages.

3. We expect the Type D effect to be stronger for males than for females.

In case of a significant moderator effect, subgroup analyses will be performed, using the moderator as a grouping variable, to shed more light on the nature of this moderating effect.

Our final analysis plan will be officially preregistered after knowing the number and kind of datasets that will be included in our analysis. This preregistration will happen before the aggregation and analysis of these datasets.

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