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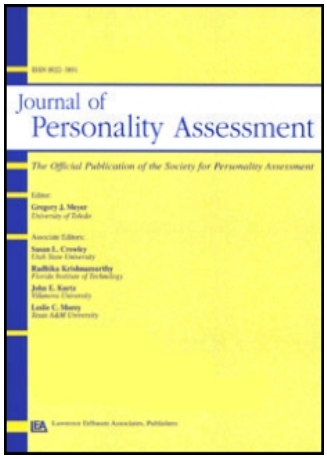

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Type D Personality as a Prognostic Factor in Heart Disease: Assessment and Mediating Mechanisms

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Type D personality, a synergy between negative affectivity and social inhibition, has established itself as a serious risk factor for morbidity and mortality in patients suffering from cardiovascular disease. In this review, we summarize studies on the validity of the assessment methods of Type D, emphasizing its role as an independent vulnerability factor in the progression of cardiovascular disease. We further present evidence on the physiological characteristics that accompany the 2 psychological traits negative affectivity and social inhibition and may mediate the relation between personality and prognosis in heart disease. Further research needs to determine the mechanisms by which Type D affects the course and outcome of cardiovascular disease as well as how Type D patients may benefit from psychosocial intervention.

The etiologies of major chronic cardiovascular diseases such as atherosclerosis, hypertension, coronary heart disease, and heart failure are complex. All these diseases have biological characteristics in common such as an increased blood pressure, increased inflammation, and increased sympathetic cardiac drive (Bautista et al., 2001; Brook & Julius, 2000). Moreover, a wide variety of psychological and psychosocial factors have been identified that are associated with the incidence and progression of heart disease such as depression (Barth, Schumacher, & Herrmann-Lingen, 2004; Musselman, Evans, & Nemeroff, 1998), anxiety (Rozanski, Blumenthal, & Kaplan, 1999; Yu, Lee, Woo, & Thompson, 2004), low social support (Orth-Gomer et al., 1998), chronic life stress (Rozanski et al., 1999), and personality (Denollet et al., 1996; Denollet, Vaes, & Brutsaert, 2000; Lachar, 1993). These psychological factors often cluster together in heart patients, and this clustering elevates the risk for cardiac events even more (Albus, Jordan, & Herrmann-Lingen, 2004; Rozanski et al., 1999).

Personality types can be seen as stable constellations of lower level traits (such as sociability and assertiveness; Eysenck, 1967), which are major determinants of affective states such as anxiety, depression (Watson, Clark, & Harkness, 1994), or psychological distress (Ormel & Wohlfarth, 1991). Nonpsychopathological behavioral characteristics were first associated with somatic disease in the 1950s when M. Friedman and Rosenman (1959) discovered a cluster of symptoms and behavioral signs that put people at risk for heart disease. This type A behavior pattern (TABP) constitutes a global pattern of competitive, hard-driving behavior including a well-rationalized predisposition to interact with others in a hostile or aggressive manner (M. Friedman & Rosenman, 1974). The psychological flip-side of type A is type B, which describes even tempered, patient people that are not at increased risk for heart disease. During the 1970s and 1980s, many clinical trials assessed the role of the TABP as a predictor for coronary artery disease (CAD)-related adverse events, resulting in the final notion that there is some evidence for a small relationship between angiographically determined CAD and the TABP among younger patients (Dembroski & Williams, 1989). Although initially a cluster of symptoms and behavioral signs were involved in portraying TABP, ultimately hostility remained as one of the core characteristics (Dembroski, Macdougall, Costa, & Grandits, 1989). Because of the emergence of these relatively unsatisfactory results in relation to the TABP (Gallacher, Sweetnam, Yarnell, Elwood, & Stansfeld, 2003; Lachar, 1993), personality factors have mostly been neglected in cardiovascular research since. Depression, and to a lesser extent anxiety, became the focus of attention as predictors in cardiovascular research. However, things were not clear cut for depression either. Although depression and depressive symptoms are strong predictors of onset and progression in heart disease (e.g., Bush et al., 2001; Frasure-Smith, Lesperance, & Talajic, 1993), attempts to successfully reduce biomedical risk factors by treating depression (either behaviorally or pharmaceutically) have yielded mixed findings (Carney et al., 2004; Glassman et al., 2002).

During the past 15 years, research has started to regain interest in the role of personality in health and disease

(H. S. Friedman, 1990; Scheier & Bridges, 1995). Renewed attention to the personality approach is warranted because personality traits may have more explanatory power than depression (Pedersen & Denollet, 2003; Rozanski et al., 1999; Schiffer et al., 2005).

There is increasing evidence in support of the notion that global traits such as neuroticism may underlie psychiatric diagnoses such as major depression (Fanous & Kendler, 2004; Solomon, Haaga, & Arnow, 2001). Personality may also have substantial predictive value in terms of prognosis among cardiac patients, and because of the known clustering of unfavorable psychosocial characteristics (Rozanski et al., 1999), it is important that a personality approach is taken in identifying those patients who are at increased risk for emotional stress-related cardiac events.

Recently, a novel personality type was introduced that combines the traits negative affectivity (NA) and social inhibition (SI; e.g., Denollet, 2000; Denollet et al., 1996). Both NA and SI are viewed as global traits that are relevant in numerous situations. As in other models of personality, these traits reflect consistencies in the general affective level and behavior of individuals. The combination of these two personality traits, called *Type D* personality, has shown to reliably predict adverse outcome in several groups of patients suffering from cardiovascular disease (e.g., Al-Ruzzeh et al., 2005; Aquarius, Denollet, Hamming, & De Vries, 2005; Denollet & Brutsaert, 1998). In this review, we summarize evidence showing that Type D is a potent risk factor for adverse cardiovascular events. Over the past decade, several assessment methods have been used to identify a Type D individual, which we review following. Although the relationship between Type D personality and cardiac events is becoming more and more established, the mechanisms underlying this relationship remain largely unclear so far. In the end, in this review, we focus on some plausible biological mechanisms underlying the relationship between Type D and heart disease. First, however, we give a brief overview on Type D personality itself.

TYPE D PERSONALITY

In 1995, the concept of Type D, or "Distressed" personality, was first introduced as a vulnerability characteristic of heart patients. The term *distressed* refers to a discrete personality configuration designating individuals who are inclined to experience emotional and interpersonal difficulties, which is likely to affect physical health (Denollet, Sys, & Brutsaert, 1995). The distressed personality construct distinguishes itself from other psychological measures that are currently being examined as predictors of prognosis in heart disease such as social support and major depressive disorder. Although major depression reflects a psychopathologic condition, Type D represents a common personality construct (Denollet, 2005; Denollet et al., 1995), with prevalences in the general population varying between 13% and 25% (Aquarius et al., 2005; Denollet, 2005; Pedersen & Denollet, 2004). Between 26% and 53% of cardiac patients can be classified as Type D (Aquarius et al., 2005; Conraads et al., 2005; Denollet, 2005; Denollet et al., 1995; Pedersen & Denollet, 2004).

Comparison With Type A and B Behavior Patterns

Several behavior patterns have been related to the onset and course of disease over the past 50 years. Type D personality is different from these behavior patterns in several distinct ways. TABP, which we briefly described previously, is a pack of behavioral characteristics that is only fairly related to Type D personality. A recent German study in 90 CAD patients (30% Type D) and 86 healthy participants (21% Type D) showed that the Type D is correlated with hostility. For NA and SI, correlations with hostility were reasonable at .60 and .38, respectively. Type D individuals experienced more anger ($p < .01$); encountered others with more hostility ($p < .001$), cynicism ($p < .001$), and physical aggression ($p < .05$); and showed increased expression of anger toward other persons ($p < .001$) as well as increased expression of inward-directed anger ($p < .001$; Perbandt, Hodapp, Wendt, & Jordan, 2006). It has yet to be determined how TABP assessed by the TABP interview (1978) or the Jenkins Activity Scale (1979) relates to Type D personality.

Concluding, correlational studies show that Type D personality is different from behavior patterns A and B. To date, almost no study has compared TABP directly with Type D in one multivariate prospective analysis to determine which of them proves to be a stronger predictor of prognosis in heart disease.

Defining Type D Personality

The conceptualization of Type D personality has been previously described (Denollet, 2000; Denollet et al., 1995). Briefly, the Type D personality construct was delineated according to the existing personality theory and the notion that the interaction of specific traits may have deleterious effects on health (Rozanski et al., 1999). Using statistical cluster analysis, the amalgamation of the two constructs, NA and SI into the Type D personality was empirically demonstrated in patients with coronary artery disease (Denollet, 1993a; Denollet & De Potter, 1992). A median split of the total score on NA and SI was used as an operational definition of the Type D personality. Type D individuals therefore are characterized by a tendency to experience negative emotions and to inhibit self-expression in a social context (Denollet et al., 1995, 1996).

The tendency seen in Type D individuals to experience negative emotions and to inhibit the expression of these

emotions in a social context represents a synthesis of the traits NA and SI, both familiar constructs in personality research.

NA. NA is a broad personality trait that is defined by the tendency to experience negative emotional states across time and situations and comprises on one hand dysphoria and on the other hand feelings of tension and worry (Watson & Clark, 1984). Individuals scoring high on NA not only experience more feelings of dysphoria and tension but also have a negative view of self, report more somatic symptoms, and have an attention bias toward adverse stimuli (Watson & Pennebaker, 1989). Individuals characterized by high NA (high neuroticism) find themselves more often exposed to stressful events and tend to react more strongly to them (Suls & Martin, 2005). The NA construct is closely related to neuroticism because it correlates highly ($r = .68$) with the neuroticism scale from the NEO–Five Factor Inventory (Hoekstra, Ormel, & de Fruyt, 1996) in healthy participants (de Fruyt & Denollet, 2002) and with the Neuroticism scale ($r = .64$) from the Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1975) in patients with ischemic heart disease (Denollet, 1998a).

The moderating effect of SI. SI represents the stable tendency to inhibit the expression of emotions, thoughts, and behaviors in social interaction. It is defined by the tendency to avoid potential dangers involved in social interaction due to anticipation of negative reactions from others such as disapproval. They may therefore feel inhibited, tense, and insecure when in company of others and thus prefer keeping other people at a distance in social contact situations (Asendorpf, 1993). In concert with these behavioral predispositions, high SI individuals are less likely to seek social support (Eisenberg, Fabes, & Murphy, 1995). Research has shown that there is a negative correlation between SI and extraversion in healthy participants ($r = -.59$) and cardiac patients ($r = -.65$; Denollet, 2005). In addition, avoidance temperament, a concept closely related to SI, has also been associated with neuroticism ($r = .86$), behavioral inhibition ($r = .65$), and negative emotionality ($r = .93$; Elliot & Thrash, 2002). In conclusion, SI is a global trait that has been associated with high negative emotionality and personal distress and refers to pervasive individual differences in reticence, withdrawal, and nonexpression.

Even though Type D individuals experience a wide range of negative emotions, Type D personality comprises more than negative emotions alone. Due to the inclusion of the SI component, the Type D construct also indicates that SI moderates the effect of NA on clinical outcome (Denollet et al., 1996). Only those individuals that score high on both subcomponents are at increased risk. The presence of synergistic qualities of the two subscales in Type D is illustrated by three reports that show that Type D remains a significant predictor of adverse clinical outcome when adjusting statistically for measures of negative affect such as anxiety and depression (Denollet, 1998a; Denollet et al., 1996, 2000). Very recently, Denollet, Pedersen, Ong, et al. (2006) examined the interaction of SI and NA directly. In that study, Denollet, Pedersen, Ong, et al. (2006) examined SI and NA as predictors of major adverse cardiac events (MACEs) in CAD patients who had undergone balloon angioplasty treatment. To test this, Denollet, Pedersen, Ong, et al. (2006) created a personality type that differs from Type D on the SI component. Patients were coded as "1" if they scored $\geq$10 on NA and $\leq$9 on SI and "0" if they scored $\leq$9 on both subscales. The predictive qualities of this type were compared to Type D personality in which patients were required to score $\geq$10 on both NA and SI. Results showed that the combined effect of inhibition with NA rather than negative emotions alone was a predictor of poor prognosis (difference in risk was significant at a $p < .05$ level). Depression ($p = .23$) or anxiety ($p = .63$) symptoms did not explain away this moderating effect of SI. It was also shown that patients with high NA but low SI were not at increased risk ($p = .76$) for a MACE (including death, myocardial infarction [MI], coronary artery bypass graft, or percutaneous coronary intervention).

The aforementioned results provide evidence that Type D personality is more than NA or neuroticism alone and that SI is an important moderator of the effects of negative emotions on adverse clinical outcomes. This does not mean, however, that depression and anxiety are of no importance. Future research may benefit from the inclusion of Type D in addition to the well-known traditional psychosocial risk factors because of this distinctive moderating effect of SI.

ASSESSMENT OF TYPE D PERSONALITY

Over the past years, several methods of assessment have been used to determine Type D personality. In the beginning, a combination of scales methods was used to get the appropriate item combination. Then, the Type D Scale–16 (DS16; Denollet, 1998a) was developed based on a large database of items originating from the Minnesota Multiphasic Personality Inventory–2 (MMPI–2; Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989), and self-constructed items (Denollet, 1998a). The DS16 was revised to form the DS14, the most recent and parsimonious version of the Type D questionnaire (Denollet, 2005). In the following, we discuss all three methods and demonstrate Type D personality's discriminative power in the risk assessment for prognosis in cardiovascular disease.

The Combination of Scales Method

The Type D construct was originally developed in Belgian cardiac patients in an attempt to investigate the role of personality traits in prognosis of coronary artery disease. In this early Type D study, patients who had survived a MI were asked to fill out the Heart Patients Psychological

TABLE 1
Items of the DS16 and DS14

DS16		*DS14*
Makes contact easily when meeting people[a]	1	Makes contact easily when meeting people[a]
Finds it hard to express opinions	2	Makes a fuss about details
Often talks to strangers[a]	3	Often talks to strangers[a]
Often feels unhappy[a]	4	Often feels unhappy
Is hopeful about the future[a]	5	Easily irritated
Has little impact on other people	6	Is inhibited in social interactions
Takes a gloomy view of things	7	Takes a gloomy view of things
Like to be in charge of things[a]	8	Has difficulties starting a conversation
Often in a bad mood	9	Often in a bad mood
Is often in charge in groups[a]	10	Is a closed kind of person
Feels at ease most of the time[a]	11	Tends to keep others at a distance
Often worries about something	12	Tends to worry a lot
Often down in the dumps	13	Tends to be down in the dumps
Does not find things to talk about	14	Does not find things to talk about
Finds it hard to make "small talk"	15	—
Feels happy most of the time[a]	16	—

Note. Italic items of the DS16 have been removed or replaced in the DS14. [a]Reversely scored items.

Questionnaire (HPPQ; Erdman, 1982), which assessed the SI component of Type D, and the Trait scale of the Spielberger State–Trait Anxiety Inventory (STAI; Van Der Ploeg, Defares & Spielberger, 1980), which assessed the second dimension (NA) of the distressed personality construct. A median split was used in both questionnaires to categorize patients as Type D (high on both) or not. Of all 105 patients, 26.7% were classified as having a distressed personality. After on average 3.8 years of follow-up period, 15 patients had died. A significant amount ($n = 10$) of these deceased patients were classified as having a distressed (Type D) personality ($p < .01$). A multiple logistic regression showed that depressive symptoms (assessed by Millon Behavioral Health Inventory, which is a psychological symptoms questionnaire especially developed for the medical setting; Millon, Green, & Meagher, 1982) did not add to the variance explained by the presence of a distressed personality (Denollet et al., 1995).

Development of Type D Personality Proxies

In addition to using a questionnaire especially developed to assess Type D personality (such as the DS16 or DS14 we describe following), it is also possible to construct Type D personality status from existing questionnaires similar to the combination of scales method Type D assessment started out with. Questions comparable to the items in the DS14 in content and wording should then first be tested together with the DS14 in a separate sample and properly validated. Then it would be possible to classify participants as Type D based on a different but equally valid set of items, originating from, for example, the Spielberger STAI, the Young Adult Self-Report (Achenbach, 1990), the EPQ, and so on. This opens the possibility to include a measure of Type D in already existing research programs. Type D status in these samples would then be determined by taking the median of both subscales as cutoff. However, it should be mentioned that from the onset that SI is not the same as low extraversion or high introversion (Denollet, 1998a, 2000, 2005).

DS16. The DS16 was developed with the purpose to meet with a lack in measurement tools that allow for adequate characterization of individual risk when looking at the impact of psychosocial factors on heart disease. The DS16 was introduced in 1998 as a 16-item questionnaire to assess the distressed personality (see Table 1). Items were selected from a pool of 66 statements derived from an item-level factor analysis of the MMPI–2 and statements that were specifically written for developing a Type D assessment scale (Denollet, 1998a). In the first sample of CAD patients, Type D status was determined using the original strategy of independent measures for the two dimensions. In this study, the determination was based on a combination of the STAI and SI scale of Erdman's HPPQ. Then, we tested the ability of the items to differentiate between Type D and non-Type-D patients (as determined by Type D status based on the original strategy of combining two scales). We then entered the best differentiating items into a principal components analysis that resulted in two sets of eight items that were clearly related to NA and SI (Cronbach's αs were .89 and .82, respectively). In the DS16, all items are answered on a 5-point Likert scale ranging from 0 (*false*) to 4 (*true*). It yields four personality types, but only those who score high on both subcomponents were classified as having a Type D personality. A retest after 3 months in 60 of the 400 initial participants allowed testing–retest reliability, which was high ($r = .78$ and .87 for NA and SI items, respectively). Cross-validation took place

in a second, smaller sample of 100 CAD patients who were not involved in the scale construction study.

The DS16 has been validated in Danish (Pedersen & Denollet, 2004) and has been tested in different contexts. The Danish validation study assessed 149 post-MI patients (33% female) and 115 healthy controls (43% female) for Type D status using the DS16. In addition, neuroticism and extraversion were assessed using the 24-item short version of the EPQ. Results showed that Type D prevalence was 24% in post-MI patients and 25% in the healthy control group. Internal consistency was confirmed for the two subscales (Cronbach's αs were .83 and .76, respectively), and all of the NA items ($p < .001$) and 7 out of the 8 SI items ($p < .001$) differentiated significantly between Type D and non-Type-D individuals. As expected, scores on the NA subcomponent correlated .57 with Eysenck's Neuroticism scores, whereas there was a negative relationship between SI and extraversion ($r = -.52$; Pedersen & Denollet, 2004).

DS14. Nowadays, the presence of Type D personality is determined by means of the new Type D personality scale, DS14 (Denollet, 2005). This questionnaire differs from the earlier DS16 on several points. The DS16 was revised to include the most prominent low-order traits from the NA and SI domains. Four new NA items were added to better reflect feelings of anxiety and irritability. Another 4 new SI items were constructed to enhance the assessment of SI and lack of social poise. DS16 items on dominance were omitted and replaced with 3 new SI items to reflect the tendency to avoid potential dangers involved in social interaction. This strategy resulted in a pool of 24 items (12 for each subcomponent), from which the 14 highest loading items were included in the final DS14: 7 items assessing NA and 7 items assessing SI (see Table 1). Similar to the DS16, all items are answered on a 5-point Likert scale ranging from 0 (*false*) to 4 (*true*). The DS14 yields four personality types, but only those who score above a predetermined, standardized, cut-off score of ≥ 10 on both subcomponents are classified as having a Type D personality. The psychometric properties of the DS14 are good. Factor analysis in 3,678 respondents showed the presence of two personality domains, with all items on NA loading highly (between .69–.82) on one factor, and the items on SI loading highly on the other (.62–.82). The subcomponents of the scale showed high internal consistency, reflected in a Cronbach's α of .88 and .86 for NA and SI, respectively. In a subgroup of 140 healthy participants and 135 cardiac patients, SI and NA correlated highly with Extraversion ($r = -.59, -.65$) and Neuroticism (.68/.68). Temporal stability over a 3-month period was high ($r = .82, .72$ for NA and SI, respectively; Denollet, 2005). In addition, the DS14 has been validated in multiple languages (Grande et al., 2004; Gremigni & Sommaruga, 2005), making it widely applicable. Additionally, the Type D construct was shown to be relatively stable over time. This is illustrated by a recent study (Denollet, 2005) that reported that the individual subscales NA and SI, as measured by the DS14, individually showed high test–retest reliability for NA and SI ($r = .72, .82$) over a 3-month period, indicating that the relative rankings of DS14 scores among patients remain stable over time. Because of its conciseness, the DS14 has shown to be a practical screening instrument for the influence of psychosocial factors in clinical practice (Albus et al., 2004).

The collective findings show that independent of the type of Type D assessment (combination of scales, DS16, DS14), the combination of NA and SI seems to have a pervasive influence on prognosis of a wide range of cardiovascular and other conditions. In addition, the Type D construct is also applicable in other areas of research. When looking closely at the reported prospective studies, one may detect a trend for the more recent studies to report less cardiac or all cause deaths. This observation might be due to advances in treatment over the past decade. Nonetheless, studies until now indicate Type D personality to be an important, easy to assess, predictor of poor prognosis, which should be taken into account in clinical practice.

Assessment of Type D Personality in Healthy Individuals Using the DS14

Presently, multiple studies are underway that use the DS14 to assess Type D personality in other than cardiac diseased populations. Previous results (based on DS16 assessment of Type D) already have put forward that Type D personality not only is a prognostic factor in heart disease but also predicts development of cancer in men with established CAD (odds ratio [OR] $= 7.2$, $p = .002$; Denollet, 1998b). Furthermore, DS14-derived Type D was found to be more prevalent in a population of psychosomatic patients compared to the general population (Grande et al., 2004). Preliminary results show that Type D also predicts all-cause mortality in a sample of patients who received a heart transplantation (work in progress).

In addition, the assessment of Type D personality also has been extended to different settings, and the DS14 is used as an instrument of risk stratification in work-related stress research (Hanebuth, Meinel, & Fischer, 2006; Preckel, Känel, Kudielka, & Fischer, 2005). For example, a study of 822 employees in a European aircraft manufacturing plant showed that the NA and SI subcomponents of Type D personality, as assessed by the DS14, are distinct factor units in an exploratory factor analysis including items from the DS14 and items from the Hospital Anxiety and Depression Scale (HADS; Spinhoven et al., 1997) and the Maastricht Vital Exhaustion Questionnaire (Appels & Mulder, 1989). It was shown that NA was significantly associated with both the Anxiety subscale ($r = .54$, $p < .01$) and the Depression subscale ($r = .64$, $p < .01$) of the HADS. SI was also significantly correlated to these subscales but in a more moderate way ($r = .37, .27$, respectively; Kudielka, Von Känel, Gander, & Fischer, 2004). Another study of 634 workers in a European

aircraft manufacturing plant (average age = 39.9 years) examined the role of Type D personality on vital exhaustion, which refers to unusual fatigue, loss ofenergy, increased irritability, and feelings of demoralization. Results showed a correlation of .57 ($p < .001$) between Type D and vital exhaustion. Multivariate regression analysis showed that of the total 52% explained variance, 33% of the variance in vital exhaustion was explained by Type D, whereas 11% was explained by overcommitment to the job, 5% by depression, and 1% by effort–reward imbalance (Preckel et al., 2005).

VALIDITY OF TYPE D PERSONALITY AS A PREDICTOR IN HEART DISEASE

Multiple studies in heart patients testify to the viability of Type D as a psychosocial risk factor for morbidity and mortality in patients suffering from cardiovascular disease. In this section, we summarize these studies.

Denollet et al. (1996), using the combination of scales method, a total of 303 CAD patients were assessed for Type D at baseline, and the amount of cardiac and noncardiac deaths after a 6 to 10 year follow-up period was documented. At the end of the follow-up period, 38 (14%) patients had died, of which 24 were because of cardiac and 14 because of noncardiac causes. In this study, Type D personality was a significant predictor of both cardiac (OR = 3.8, $p = .0067$) and noncardiac death (OR = 6.4, $p = .0054$), independent of other biomedical and psychosocial (depressive symptoms and social alienation) predictors and disease severity. CAD may present itself in various forms of severity, one of the more severe forms being a combination of coronary occlusion with diminished pumping efficiency as indicated by a decreased left ventricular ejection fraction (LVEF). In a study (Denollet & Brutsaert, 1998) of 87 such patients, a similar assessment of SI (using the HPPQ) and NA (using the trait scale of the STAI) took place. Results showed that the event-free survivors differed significantly on several biomedical indicators from the patients who died but also on levels of anxiety ($p = .04$), depression proneness ($p = .01$), Type B behavior ($p = .04$), and Type D personality ($p = .0003$). In a multivariate analysis, both Type D (OR = 4.7, $p = .001$) and LVEF < 30% ($p = .006$) were retained as independent predictors of cardiac death over a follow-up period of on average 8 years. Because of the relatively small number of actual deaths in this study (13 out of 87) and in the previous one (15/105 in Denollet et al., 1995), these results should be interpreted with caution.

Using the DS16 as assessment method for Type D personality, Denollet et al. (2000) followed 319 CAD patients who received optimal treatment in terms of medication, surgery, and rehabilitation over 5 years and confirmed the predictive qualities of Type D (OR = 8.9, $p = 0.0001$), independent of biomedical factors, such as LVEF and age, and despite the appropriate treatment in a multivariate analysis. Co-occurrence of these risk factors increased the risk of poor outcome even more. A more recent study (Denollet, Pedersen, Vrints, & Conraads, 2006) examined the influences of current stress levels (assessed by the General Health Questionnaire; Goldberg & Williams, 1988) and of Type D personality (DS16) on 5-year prognosis in CAD patients. Results showed that both increased levels of baseline stress (OR = 2.01, $p = .054$) and presence of Type D personality (OR = 2.90, $p = .003$) independently predicted cardiac events over a 5-year period in addition to biomedical risk factors. This result is important because it shows that Type D personality reflects more than transient changes in stress level and thus strengthens the notion that Type D is a stable personality trait that aids in risk stratification above and beyond more temporary states, such as in this case, current stress levels.

Multiple studies have employed the DS14 to investigate its influence on prognosis in heart disease, for example, in heart failure. Chronic heart failure is a progressive disease in which the heart muscle weakens and gradually looses the ability to pump blood efficiently. Often, heart failure develops following chronic hypertension, cardiomyopathy, or MI. Several studies show that psychological factors, such as depression (Jiang et al., 2004; Konstam, Moser, & De Jong, 2005) but also personality, may influence the progression of chronic heart failure.

Both Denollet et al. (2003) and Conraads et al. (2006) investigated the role of Type D personality in chronic heart failure (CHF). Because proinflammatory cytokines play an important role in the pathogenesis of CHF (Aukrust, Gullestad, Ueland, Damas, & Yndestad, 2005), both studies sought to elucidate whether proinflammatory cytokines may be involved in the link between Type D personality and adverse clinical outcomes in heart failure. Denollet et al. (2003) determined plasma levels of the proinflammatory cytokine tumor necrosis factor alpha (TNF-α), including its soluble TNF-α receptors 1 and 2, in a sample of 42 men with stable CHF. Type D prevalence was 38% in this group of patients. Results showed that Type D patients had higher levels of circulating TNF-α ($p = .003$) and soluble TNF-α receptors (TNF-αr1: $p = .014$; TNF-αr2: $p = .019$). After controlling for ischemic etiology and disease severity, Type D remained an independent predictor of circulating TNF-α (OR = 9.5, $p = .004$) and soluble TNF-α receptor (1 and 2) levels (OR = 6.1, $p = .014$). Conraads et al. included 91 stable CHF patients (both male and female). Patients filled out the DS14, and 33% of them were classified as having a Type D personality. Factor analysis confirmed the two-factor structure in the DS14, and Cronbach's alpha was high for both subscales (NA $\alpha = .84$, SI $\alpha = .88$). There were no sex differences in Type D classification. There was a difference in severity, with Type Ds doing worse than non-Type Ds ($p = .021$; disease severity was determined by NYHA class). It was reported that CHF patients with a Type D personality had higher plasma levels of TNF-α ($p = .066$) and the soluble TNF-α receptors 1 ($p = .009$) and 2 ($p = .006$), whereas interleukin 6 levels

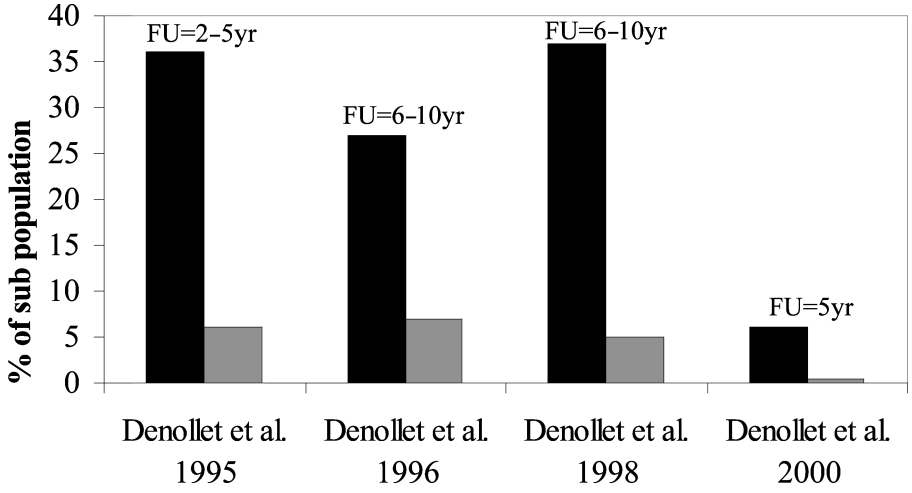

FIGURE 1. Summary of incidence of all-cause deaths in patients with coronary artery disease stratified for Type D personality. Black bars represent the percentage of all-cause (cardiac and noncardiac) deaths in the Type D subpopulation. Gray bars represent the percentage of all-cause (cardiac and noncardiac) deaths in the non-type-D subpopulation. FU = follow-up period; yr = years.

did not differ. After controlling for sex, age, ischemic etiology, and disease severity, Type D remained an independent predictor of increased levels of TNF-α (OR = 2.9, $p = .048$) and the receptor TNF-αr2 (OR = 3.9, $p = .018$). Because the study had a cross-sectional design, no conclusions can be drawn on causality. Future studies should encompass a design that allows testing for causality.

In the context of a large cardiological clinical research project (RESEARCH; Pedersen, Lemos, et al., 2004), CAD patients were treated invasively with percutaneous coronary intervention (PCI). The PCI treatment procedure unblocks narrowed coronary arteries by placing a small, hollow metal tube (stent) in the narrowed artery to keep it open after a balloon angioplasty has been carried out. In a subsample of the RESEARCH registry, Pedersen, Lemos, et al. (2004) sought to determine the impact of Type D personality on the prognosis of patients treated with PCI. It was reported that Type D personality independently predicted the incidence of death or MI 9 months later while adjusting for biomedical confounders.

Furthermore, several recent studies investigated the prevalence of anxiety and depression symptoms (assessed with the HADS) in cardiac patients, while examining the role of Type D personality (assessed with the DS14). A second study by Pedersen, Van Domburg, et al. (2004) included 184 patients with an implantable cardioverter defibrillator. Anxiety symptoms (score $\geq$8) were prevalent in 31% of the sample, whereas depression symptoms (score $\geq$8) were present in 28% of the sample. It was reported that patients with a Type D personality were more likely to suffer from anxiety and depression symptoms. In multivariate logistic regression, it was shown that Type D personality (OR = 7.03), use of psychotropic medication (OR = 8.16) and lack of social support (OR = 0.97) were independent determinants ($p < .05$) of symptoms of anxiety in these patients. Likewise, in the multivariate logistic regression, Type D personality (OR = 7.40) remained a significant determinant of symptoms of depression next to several other contributors. In a sample of 84 patients with systolic heart failure (Schiffer et al., 2005), Type D (DS14) was assessed together with depressive symptoms (Center for Epidemiological Studies Depression scale; Beekman et al., 1997) and mood status Global Mood Scale (Denollet, 1993b); Results showed that Type D individuals were more likely to report symptoms of depression (47% of Type Ds vs. 13% of non-Type Ds; $p = .001$). Most recently (Pedersen et al., 2006), 542 CAD patients who received PCI treatment were assessed for Type D (DS14) depressive and anxiety symptoms (HADS) at 6 and 12 months posttreatment. Results showed that Type D personality independently predicted the onset of depressive symptoms (OR = 3.04, $p = .002$) measured at 12 months posttreatment. At 6 months posttreatment, depressive patients were more likely to classify as having a Type D personality (36% vs. 16%; $p = .003$). The two older studies were cross-sectional, leaving potential causal relationships unknown (Pedersen, Van Domburg, et al., 2004; Schiffer et al., 2005). The latter study, though, had a longitudinal design, resulting in the observation that Type D personality predicts the onset of depressive symptoms in CAD patients. This result supports the idea that personality factors may underlie the presence of depressive disorder (Fanous & Kendler, 2004; Solomon et al., 2001). Figure 1 shows a summary of the most important results for the studies reporting on hard endpoints (all-cause death).

BIOLOGICAL CHARACTERISTICS OF TYPE D

Many studies have shown that NA and related personality traits such as neuroticism have a profound biological basis, just like depression. Moreover, behavioral inhibition is

a temperamental construct that for the most part reflects biologically based, relatively stable individual differences in behavioral style (Marshall & Stevenson-Hinde, 1998). The observed, sturdy association between Type D personality and prognosis in cardiovascular disease implies that pathophysiological markers might be identified that mediate this phenomenon. The disadvantage that Type D patients seem to have might on the other hand also be due to behavioral factors such as worse adherence to treatment or the reticence to disclose symptoms to the physician.

Not much is presently known about biological mechanisms that may explain the observed association between Type D and poor prognosis in heart disease. There are several possibilities. It may be that Type D personality and the physiological alterations seen in cardiovascular disease reflect the same biological susceptibility, in part conveyed by the same genetic factors or by environmental factors. There is evidence that this is, for example, the case for depression and heart disease (McCaffery et al., 2006). It may also be that the physiological dysfunction causes the personality characteristics of Type D patients to be more prominent, possibly by causing overreactivity to stress that evokes long-lasting adaptations in neurotransmission in emotion-related brain circuitry (Habib, Gold, & Chrousos, 2001). A third possibility is that the physiological dysfunction arises as a consequence of how Type D people experience their life. In the following, we highlight several potential biological mechanisms.

Physiological Mechanisms

A substantial number of physiological risk factors for cardiovascular disease have been identified over the past decades. All of these can be examined as potential mediators of the relation between psychological factors, such as depression, anxiety, or Type D personality and the onset and progression of cardiovascular disease. Potential physiological risk factors include among others increased blood pressure (Pickering & Devereux, 1987; Verdecchia, Schillaci, Reboldi, Franklin, & Porcellati, 2001) and heart rate (HR; Palatini, Casiglia, Julius, & Pessina, 1999), reduced heart rate variability (HRV; Dekker et al., 2000), a dysfunctional hypothalamic-pituitary-adrenal axis (Rosmond & Bjorntorp, 2000), and altered immune function (Kop & Gottdiener, 2005; Pucak & Kaplin, 2005). Several studies have examined the correlation between personality traits and physiological features, and up until the present day, mixed results have been found.

Cortisol. Cortisol is an important steroid hormone in the regulation of normal physiology and plays a pivotal role in the body's stress response. As a consequence of continued or frequently repeated stress challenges, basal cortisol may be chronically secreted in excess, with potentially harmful effects. Prolonged glucocorticoid exposure may, among others, lead to hypertension and cardiovascular disease (Girod & Brotman, 2004; Mantero & Boscaro, 1992).

Several papers have shown neuroticism or NA to be related to higher levels of cortisol during the day. Miller, Cohen, Rabin, Skoner, and Doyle (1999) assessed the relationship between major dimensions of personality and basal cardiovascular, neuroendocrine (24-hr urine samples), and immunologic parameters (in serum) in 276 healthy adults. Miller et al. found that participants who reported high levels of neuroticism tended to have higher plasma cortisol levels. In a study of 87 participants that measured the effects of mood and stressors on daytime cortisol, it was shown that distress (negative affect + agitation) was associated with higher daytime cortisol levels (Van Eck, Berkhof, Nicolson, & Sulon, 1996). These results were replicated in a larger ($N = 120$) sample that only assessed negative affect in relation to perceived stress and cortisol levels (Smyth et al., 1998). Contrarily to these studies, however, neuroticism scores have been negatively correlated to basal afternoon levels of cortisol (Leblanc & Ducharme, 2005). It is of note that there were only 20 participants in this latter study. Potential differences between the studies might be explained by the use of different psychological instruments to assess NA or neuroticism.

In laboratory stress tests, it has been shown that participants scoring high on NA react more strongly to stress, evident in a larger cortisol response (Sher, 2005). A recent study in healthy men, however, found no significant associations between NA and cortisol reactivity to social stress (Von Känel et al., 2005). Behavioral inhibition has also been associated with higher cortisol levels, reflected in both the larger awakening response and a larger cortisol response to stress (Kagan, Reznick, & Snidman, 1987).

HR and HRV. Both HR and HRV have shown to be strong predictors of cardiovascular morbidity and mortality (Dekker et al., 2000; Palatini et al., 1999; Singer et al., 1988). Therefore, they seem good candidates to mediate the relationship between Type D personality and poor outcome in heart disease. Until now, HR, related catecholamine levels, and other markers of autonomic activity have been examined mostly for the two subcomponents. No significant relations have been found yet for Type D status in relation to HR and HRV (Habra, Linden, Anderson, & Weinberg, 2003).

Most of the studies on behaviorally inhibited participants, or participants that inhibit the expression of emotions, have reported an increased sympathetic nervous system activity manifest in an increased basal HR, decreased HRV (Horsten et al., 1999; Marshall & Stevenson-Hinde, 1998), and increased reactivity to stress (Gross & Levenson, 1997) and prolonged recovery time (Brosschot & Thayer, 1998) after stress exposure, which is consistent with altered autonomic nervous system function at the heart.

Many studies in depressed participants report similar increases in baseline levels of HR and increased cardiovascular reactivity to both physical and psychological stressors. How-

ever, studies on the proposed underlying personality trait neuroticism/NA are limited and have shown mixed results. In a sample of 20 young adults (11 male), exposure to an extreme physical stressor (cold face test), high neuroticism (assessed by the Big Five Inventory) was associated with a decrease in HR (Leblanc, Ducharme, & Thompson, 2004). A study in 173 healthy undergraduates also showed NA (assessed by the Type D–NA subscale) to be related to a dampened change in HR in reaction to mental stress but only in males (Habra et al., 2003). On the contrary, another recent study in 27 healthy men found no significant associations between NA (assessed by the Type D–NA subscale) and HR reactivity to social stress (Von Känel et al., 2005). Reason for this discrepancy may be the small sample sizes in two of the three studies or the differences between the studies in the type of stressor that was used. Clearly, more and larger studies need to be carried out to investigate the role of HR and HRV as mediators of the relation between Type D personality and cardiac health.

Immune function. Relations between personality characteristics and immunity have received relatively little attention. Several more recent laboratory studies on the relationship between neuroticism and basal immune function have found inconsistent results. Shea, Burton, and Girgis (1993) examined the immune response in participants that score high on neuroticism compared to groups with other personality types and found a lower T-cell level in the high-neuroticism group. In the study by Miller et al. (1999), on the other hand, which was introduced in the cortisol section previously, neuroticism scores were not related to circulating leukocyte levels (total white blood cells, total T lymphocytes, CD41 T lymphocytes, CD81 T lymphocytes, natural killer cells, or B cells) or with natural killer cell cytotoxicity. Behavioral inhibition was never examined in the context of immune function. An indication of relatedness between the immune system and SI was given by the two articles (Conraads et al., 2005; Denollet et al., 2003) on Type D personality and TNF-α in heart failure patients, which showed that Type D personality associates with increased levels of TNF-α and TNF-α receptors, implying a relationship between the functioning of the immune system and both NA and SI.

Further research is needed to examine the influence of personality on levels of immunological markers that are the outcomes of recent advances in immunology such as cytokines, adhesion molecules, and macrophage factors (Avanzas, Arroyo-Espliguero, Garcia-Moll, & Kaski, 2005; Torre-Amione, 2005).

SUMMARY AND CONCLUSIONS

In summary, Type D personality, portrayed by the stable tendency to experience negative emotions and to inhibit these emotions in social interaction, has established itself as a serious risk factor for morbidity and mortality in cardiovascular disease. Several methods of assessment exist. Presently, the DS14 is the method of choice to assess Type D. The brevity of the scale makes it a practical screening instrument in clinical practice and clinical research because of the minimal burden to patients.

Although studies have shown that the subcomponents of Type D personality, NA and SI, have profound biological underpinnings, little is known yet about the biological mechanisms that cause Type Ds to be at increased risk of poor prognosis in cardiovascular disease, although differences in cytokine levels seem to play a significant role in mediating poor outcome in Type D heart failure patients. Many unanswered questions remain, the major questions being the following: "Does Type D personality also predict onset of heart disease?"; "Can the negative effect of having a Type D personality on prognosis be generalized to other diseases than heart disease?"; and "By what physiological mechanisms does Type D personality affect the risk on poor outcome in patients suffering from cardiovascular disease, and how might intervention reduce this risk?"

Investigative strategies to address this latter question would include the identification of biological markers for Type D personality in cardiovascular patients. Screening for Type D personality in an early stage using the DS14 or a proxy measure seems advantageous because then clinical, psychosocial interventions may be launched, directed toward, for example, a better social functioning that might affect the progression of heart disease in this high-risk population positively. Further research would need to determine whether such psychosocial interventions would be able to decrease cardiovascular risk, the amount of depressive symptoms after a cardiac event, and general psychological distress.

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