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Research Article

COURSE AND RISK FACTORS OF FUNCTIONAL IMPAIRMENT IN SUBTHRESHOLD DEPRESSION AND ANXIETY

Julie Karsten, Ph.D.,^{1*} Brenda W.J.H. Penninx, Ph.D.,^{1,2,3} Charlotte E Verboom, Ph.D.,¹ Willem A. Nolen, M.D., Ph.D.,¹ and Catharina A. Hartman¹

Background: *Although persons with subthreshold depression or anxiety are known to be at risk for full-syndromal disorders, little is known about their functioning over time. In this study, we investigate the functional impairment of persons with subthreshold depression or anxiety over time, compared to that of controls. Furthermore, we evaluate which illness, personal, and environmental risk factors influence its course. Methods:* Data come from the Netherlands Study of Depression and Anxiety (N = 1,266, aged 18–65). Linear mixed models were used to identify predictors of functional impairment at baseline, 1-, and 2-year follow-up. Risk factors were evaluated in their overall effect on functioning and on change in functioning over time, and whether they differed for respondents with and without subthreshold depression or anxiety. **Results:** *Functional impairment in subthreshold respondents improved over time, but remained much higher than in controls. Prior anxiety disorder, high neuroticism, low conscientiousness, more somatic conditions, and more childhood trauma all predicted greater functional impairment. Older age predicted lower functioning only in subthreshold respondents, while the effect of neuroticism was stronger in subthreshold respondents relative to controls. Conclusions:* Functional impairment in subthreshold respondents improved over time, but remained elevated compared to that of controls. Given continuously elevated levels of impairment, preventive interventions should be focused on persons with subthreshold symptoms; in particular those with prior anxiety disorder, high neuroticism, low conscientiousness, somatic conditions, or childhood trauma. *Depression and Anxiety 30:386–394, 2013.* © 2012 Wiley Periodicals, Inc.

Key words: *depression; anxiety/anxiety disorders; mood disorders; epidemiology; measurement/psychometrics*

INTRODUCTION

Functional impairment is part of the definition of mental disorders, as a benchmark to differentiate mental disorder from “normal problems of living.”^[1] As such,

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functional impairment may contribute to the identification of clinically relevant symptoms, as a description or count of symptoms alone cannot capture the impact of disease at an individual and societal level, much of which is person and context dependent.^[2] This holds true especially for subthreshold disorders, that is, disorders not fulfilling the number of symptoms needed for a specific diagnosis, which are nonetheless associated with considerable functional impairment.^[3,4] It may thus be argued that not a clinical symptom threshold, but rather the associated functional impairment is the critical outcome variable that defines an illness.

Specifically in persons with subthreshold depression and subthreshold anxiety, substantial functional impairment has been reported.^[5–8] However, little is known about the course of functional impairment over time. Many studies have shown the clinical relevance of subthreshold depression and anxiety as risk factors for future full-syndromal depressive and anxiety disorders.^[9–11] But, in order to evaluate the future clinical relevance of subthreshold disorder, it is important to not only focus on the course of symptoms, but also on the course of associated functional impairment.

Beyond symptoms of depression or anxiety, several additional factors may influence the level of functional impairment. The World Health Organization states in its International Classification of Functioning, Disability, and Health (ICF)^[12] that disability, a term closely related to functional impairment as specified in DSM-IV, is the result of an “interaction between an individual (with a health condition) and that individual’s contextual factors (personal and environmental factors).” Personal factors are features of the individual that are not part of a health condition or state—including for example, gender, lifestyle, and psychological characteristics. Environmental factors comprise the physical, social, and attitudinal environment in which people live, and which are external to the individual. They include for example support networks from family and friends.^[12] The combination of illness, personal, and environmental factors will determine who will be most impaired, now, but even more important, in the near future. Identification of these factors may aid in directing selective prevention or intervention to those most at risk.

Based on the ICF model, Verboom et al.^[13] selected several illness, personal, and environmental factors to explain heterogeneity in functioning among persons with full-syndromal major depressive disorder (MDD). They found that although the amount of impairment was best explained by illness factors, personal factors, for example, personality traits, and environmental factors, for example, household income, also explained impairment. However, this study was conducted among persons with full-syndromal depressive disorder. Among persons with subthreshold depression or subthreshold anxiety, when illness severity is milder, personal and environmental factors may play a different part.

In this study, our aim is threefold. First, we will describe the course of functional impairment of persons

with subthreshold depression or subthreshold anxiety, compared to that of controls. Functional impairment in this study is defined as disability conceptualized by the ICF, encompassing body functions and structures, and activities and participation. By comparing persons with subthreshold symptoms to controls without subthreshold symptoms, we will be able to assess whether their differences in levels of functioning coincide over time, or alternatively remain stable or even drift apart.

Second, we aim to identify illness, personal, and environmental factors that predict the course of functional impairment over time. Illness, personal, and environmental factors included in this study are based on factors put forward by Verboom et al.,^[13] based on the ICF.

Third, we will determine if illness, personal, and environmental factors associated with functional impairment or its course over time are different for persons with subthreshold depression or subthreshold anxiety than for controls. Different factors may be of importance in these groups, as personal and environmental needs for optimal functioning may change after the onset of subthreshold depression or subthreshold anxiety.

MATERIALS AND METHODS

STUDY SAMPLE

Data were derived from an ongoing longitudinal cohort study, the Netherlands Study of Depression and Anxiety (NESDA).^[14] The study examines the etiology, course, and consequences of depressive disorders, that is, MDD and dysthymia, and of anxiety disorders, that is, social phobia, panic disorder, agoraphobia, and generalized anxiety disorder. A total of 2,981 persons were included, aged 18 through 65, consisting of persons with a current depressive or anxiety disorder, persons with subthreshold symptoms, and controls. Recruitment took place in community, primary care, and secondary care. Exclusion criteria were (1) a primary clinical diagnosis of a psychiatric disorder not subject of NESDA: psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder, and (2) not being fluent in Dutch. The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each participating center. After full verbal and written information about the study, written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

The present study on functional impairment in respondents without full-syndromal depressive or anxiety disorder is based on data of baseline, 1-year, and 2-year follow-up assessments. Of the 2,981 respondents, 1,701 (57.1%) had had a full-syndromal depressive and/or anxiety disorder within the last 6 months before baseline, as measured by the Composite Interview Diagnostic Instrument (version 2.1), and were excluded from this study. Of the remaining 1,280 respondents, functional impairment data of at least one assessment (baseline, 1-year follow-up, 2-year follow-up) and data needed to assess baseline subthreshold depression and subthreshold anxiety were available for 1,266 (98.9%). Of the 1,266 eligible respondents without full-syndromal depressive or anxiety disorder, 437 (34.5%) met the cut-off scores for subthreshold depression or subthreshold anxiety (see below) and were included as subthreshold respondents. The remaining 829 (65.5%) respondents did not reach the cut-off scores for subthreshold depression or subthreshold anxiety and were included as controls. Of the subthreshold respondents, 254 (58.1%) had experienced a prior depressive and 183 (41.9) a prior anxiety disorder. Of the controls, 254

(30.6%) had experienced a prior depressive and 161 (19.4%) a prior anxiety disorder. There were no differences between subthreshold respondents and controls in terms of nonresponse or attrition at baseline or 1-year follow-up, but at 2-year follow-up subthreshold respondents were more likely to not complete the requested questionnaires or to have dropped out from the study, compared to controls (respectively, 14.6 and 9.7%; $\chi^2(1) = 7.08, P = .009$).

DEFINITION OF SUBTHRESHOLD DEPRESSION AND SUBTHRESHOLD ANXIETY

As described in a previous paper,^[7] subthreshold depression was defined as a score of at least 14 on the Inventory of Depressive Symptomatology-Self Report (IDS-SR₃₀),^[15] in the absence of full-syndromal depressive disorder. We found that these participants experienced substantially more functional impairment than participants scoring within normal range (0–13). Subthreshold anxiety was defined as a score of at least 11 on the Beck Anxiety Inventory (BAI),^[16] in the absence of full-syndromal anxiety disorder.^[8] These participants experienced more functional impairment than participants with a BAI score within the normal anxiety range (0–9). Applying these criteria resulted in 225 respondents with pure subthreshold depression, 26 respondents with pure subthreshold anxiety, and 186 respondents with both. Due to the large overlap of subthreshold anxiety with subthreshold depression in our data, data were analyzed as a single group with subthreshold depression/anxiety.

OUTCOME MEASURE

Functional Impairment. Functional impairment was assessed using the World Health Organization Disability Assessment Schedule II (WHODAS II).^[17] The WHODAS II is based on the ICF framework and assesses the limitations in activities and restrictions in participation experienced by an individual, independently from a medical diagnosis, either somatic or psychiatric. Specifically, the 36 items of the WHODAS II evaluate the functioning of the individual on six subscales: (1) communication and understanding, (2) getting around, (3) self-care, (4) getting along with people, (5) household or work activities, and (6) participation in society. A 5-point rating scale is used, the respondents rate the level of difficulty experienced within each domain as none, mild, moderate, severe, or extreme. Standardized total scores range from 0 to 100. Higher scores on the standardized WHODAS II indicate higher levels of impairment.

PREDICTORS

Illness Factors. Subthreshold status as defined above was assessed using the IDS-SR₃₀ and the BAI. A history of depressive or anxiety disorder was defined as the occurrence of the disorder at any time during the individual's prior lifespan, but not within the last 6 months before baseline.

Personal Factors. Age, gender, and years of education were assessed in the baseline interview. Personality was assessed using the NEO-five-factor inventory,^[18] a 60-item personality questionnaire measuring five personality domains: neuroticism, extraversion, agreeableness, conscientiousness, and openness to experience. As a general indicator of somatic health, we used a total sum of 16 somatic conditions commonly assessed in Dutch epidemiological studies (e.g. Netherlands Mental Health Survey and Incidence Study [NEMESIS]^[19]) during the baseline interview, such as heart conditions, diabetes, and cancer. Physical activity was assessed using the International Physical Activity Questionnaire^[20] based on the resting metabolic rate multiplied by minutes of physical activity per week. First degree family history of depressive and anxiety disorders (yes/no) was derived from the family tree inventory.^[21]

Environmental Factors. Childhood trauma was assessed using the childhood trauma interview.^[22] A cumulative index (childhood trauma index) was calculated as the sum of experienced number and frequency of childhood trauma, consisting of emotional neglect, psychological and physical abuse, and sexual abuse in the respondent's first 16 years of life. Adverse life events were assessed as a sum of 12 possible events as measured by the list of threatening experiences.^[23] The presence of a partner and up to two significant friends was assessed using the Close Person Inventory.^[24] Social network size was assessed by the total number of important relatives, friends, and others with whom the respondents had regular contact. Participants with a paid job of eight or more hours per week were considered to be employed, whereas participants with less hours per week or without a job were considered unemployed. Household income was assessed with 24 categories, from less than €500 a month up to €5,000 a month. The respondent was allocated the mean of the applicable income category to create a continuous variable.

STATISTICAL ANALYSES

Linear mixed models (LMM) were used to assess the association of illness, personal, and environmental factors with functional impairment, as it allows for correlated observations over time and missing values on different measurement occasions.^[25,26] All predictors were entered in the models as fixed factors. An unstructured covariance structure was used and estimates were based on maximum likelihood. The dependent variable was the level of functional impairment at baseline, 1-year follow-up, and 2-year follow-up.

First, we assessed the level of functional impairment of subthreshold respondents and its course over 2 years, compared to that of controls. Second, we assessed the influence of illness, personal, and environmental factors on current and future functional impairment. As a first step, we assessed all predictors individually in univariate analyses. To assess the overall effect, the effect on change over time, and a possible differentiation between subthreshold and controls, we started with a full model for each predictor, including three-way interactions (predictor \times time \times group), the three two-way interactions (predictor \times time, predictor \times group, group \times time), and the three main effects (predictor, time, group). If a three-way interaction had no effect on functioning ($P > .10$), it was removed from the model. Next, if no two-way interactions ($P > .10$) had an effect on functioning, they were removed from the model. As a second step, we proceeded to multiple LMM to test whether found univariate associations would hold when corrected for other relevant predictors. We selected all main effects of the predictors, two-way interactions, and three-way interactions with a value of $P \leq .10$ in univariate analyses and examined these simultaneously in multiple LMM analyses.

RESULTS

COURSE OF FUNCTIONAL IMPAIRMENT

Sample characteristics are listed in Table 1. Functional impairment at baseline was significantly correlated with functional impairment at 1-year ($r = .50; P < .001$) and 2-year ($r = .47; P < .001$) follow-up for subthreshold respondents. The same was true for controls at 1-year ($r = .62; P < .001$) and 2-year ($r = .56; P < .001$) follow-up, indicating substantial stability in functioning across time.

As illustrated in Fig. 1, subthreshold respondents were more impaired than controls at baseline ($F(1,1254) = 567.00, P < .001, \eta^2 = .31$), 1-year follow-up ($F(1,1098) = 319.89, P < .001, \eta^2 = .23$), and 2-year follow-up ($F(1,1120) = 279.82, P < .001, \eta^2 = .20$).

TABLE 1. Sample characteristics

Characteristics		Subthreshold (n = 437)	Control (n = 829)
Illness factors baseline			
IDS-SR ₃₀	Mean (SD)	21.0 (7.0)	6.2 (3.7)
BAI	Mean (SD)	10.9 (6.5)	2.7 (2.7)
History of depressive disorder	N (%)	254 (58.1)	254 (30.6)
History of anxiety disorder	N (%)	183 (41.9)	161 (19.4)
Personal factors baseline			
Age	Mean (SD)	44.2 (13.3)	42.0 (14.2)
Female	N (%)	309 (70.7)	522 (63.0)
Years of education	Mean (SD)	11.9 (3.2)	13.1 (3.1)
Personality			
Neuroticism	Mean (SD)	36.3 (6.8)	26.4 (6.3)
Extraversion	Mean (SD)	37.3 (6.1)	42.1 (6.1)
Conscientiousness	Mean (SD)	41.8 (5.5)	45.2 (5.2)
Agreeableness	Mean (SD)	43.3 (4.9)	45.8 (4.6)
Openness	Mean (SD)	38.3 (5.9)	38.5 (5.7)
Number of somatic conditions	N (%)	1.1 (1.2)	0.6 (.9)
Physical activity (× 100 min/week)	Mean (SD)	37.9 (31.2)	38.9 (30.5)
Family history of depressive disorder	N (%)	345 (78.9)	593 (71.5)
Family history of anxiety disorder	N (%)	313 (71.6)	522 (63.0)
Environmental factors baseline			
Childhood Trauma Index	Mean (SD)	0.9 (1.1)	0.5 (.8)
Number of adverse life events	Mean (SD)	0.6 (.9)	0.5 (.8)
Social network size	Mean (SD)	2.7 (1.1)	3.2 (1.2)
Partner present	N (%)	312 (71.4)	620 (74.7)
Friend(s) present	N (%)	328 (75.1)	674 (81.3)
Household income (× 1,000 euro)	Mean (SD)	2.2 (1.1)	2.5 (1.1)
Unemployed	N (%)	120 (27.5)	171 (20.6)

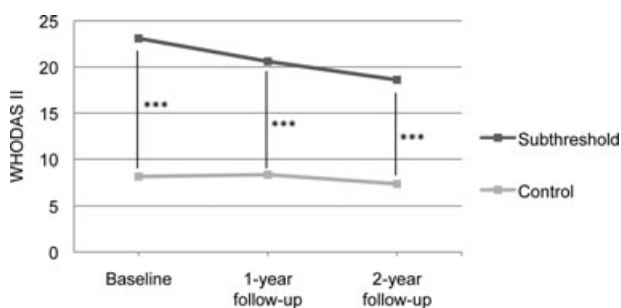


Figure 1. Functional impairment over time in subthreshold respondents and controls.

This finding was consistent for all subscales (Table 2). Subthreshold respondents were most impaired in household or work activities and least impaired in self-care over all three time points. Even when corrected for a history of depressive or anxiety disorder, subthreshold respondents remained more functionally impaired at baseline ($F(1,1253) = 477.65, P < .001, \eta^2 = .28$ and $F(1,1253) = 484.56, P < .001, \eta^2 = .28$, respectively), 1-year follow-up ($F(1,1097) = 255.80, P < .001, \eta^2 = .19$ and $F(1, 1097) = 255.56, P < .001, \eta^2 = .19$, respectively), and 2-year follow-up ($F(1,1119) = 223.18, P < .001, \eta^2 = .19$ and $F(1,1119) = 234.94, P < .001, \eta^2 = .17$, respectively) than controls. The functioning of subthreshold respondents was improved significantly at 2-year follow-up compared to baseline ($t(371) = 6.34, P < .001, \eta^2 = 0.10$), whereas the functioning of controls was not ($t(739) = 1.71, P = .09, \eta^2 = .004$). In summary, functional impairment of subthreshold respondents declined more rapidly over time compared to that of controls ($B = -1.77, SE = 0.32, P < .001$), but remained higher at all three time points.

PREDICTING FUNCTIONAL IMPAIRMENT: UNIVARIATE LMM ANALYSES

The results of univariate LMM analyses (Table 3) indicated a substantial number of factors associated with higher levels of functional impairment overall in both subthreshold respondents and controls. That is, a history of depressive or of anxiety disorder; lower levels of extraversion, conscientiousness, and agreeableness; a higher number of somatic conditions; a family history of depressive or of anxiety disorder; a higher number of traumatic events in childhood; and lower household income were each associated with higher levels of functional impairment, regardless of subthreshold status or time. High levels of neuroticism and a small social network were also associated with higher levels of functional impairment in both subthreshold respondents and controls, with the interactions with subthreshold status showing that these effects were more pronounced in subthreshold respondents. Older age was associated with higher levels of functional impairment only in subthreshold respondents (i.e. no main effect).

In addition to factors associated with severity of functional impairment overall, the following personal and environmental factors were univariately associated with change in functional impairment over the course of 2 years. The interaction of subthreshold disorder and time confirmed our earlier finding that functional impairment in subthreshold respondents decreased at a faster rate than in controls. Although lower levels of conscientiousness at baseline were associated with greater functional impairment overall, functional impairment of both subthreshold respondents and controls with low conscientiousness decreased more rapidly over time. Likewise, higher numbers of adverse life events, not having a partner, and lower household income predicted a more rapid decrease in functional impairment in subthreshold respondents.

TABLE 2. WHODAS II over time for subthreshold ($n = 437$) and controls ($n = 829$)

	Baseline		1-year follow-up		2-year follow-up	
	Subthreshold mean (SD)	Control mean (SD)	Subthreshold mean (SD)	Control mean (SD)	Subthreshold mean (SD)	Control mean (SD)
WHODAS II total score	23.1 (13.3)	8.2 (8.7)*	20.6 (13.5)	8.4 (8.9)*	18.6 (13.7)	7.4 (8.7)*
1. Communication and understanding	18.6 (13.6)	6.5 (9.0)*	18.9 (13.7)	7.4 (9.1)*	15.8 (14.0)	6.0 (9.1)*
2. Getting around	12.6 (15.9)	4.0 (10.0)*	11.4 (15.6)	4.1 (9.4)*	11.2 (15.8)	3.8 (9.1)*
3. Self-care	6.1 (10.1)	1.7 (6.0)*	4.9 (9.1)	1.1 (3.8)*	4.5 (9.3)	1.4 (4.3)*
4. Getting along with people	17.2 (13.1)	7.0 (9.4)*	17.3 (13.4)	8.4 (9.9)*	15.2 (13.5)	6.5 (9.4)*
5a. Household activities	23.0 (16.8)	9.1 (12.6)*	17.7 (17.5)	7.7 (12.1)*	18.2 (17.2)	7.6 (11.5)*
5b. Work activities	23.0 (17.0)	8.6 (12.5)*	18.7 (16.8)	8.8 (12.9)*	17.8 (17.9)	8.2 (12.4)*
6. Participation in society	17.9 (13.1)	5.7 (7.6)*	15.3 (12.8)	5.7 (8.5)*	14.1 (13.2)	5.1 (7.7)*

* $P < .001$ comparison subthreshold and controls.

PREDICTING FUNCTIONAL IMPAIRMENT: MULTIPLE LMM ANALYSES

Predictors with a significance value of $P \leq .10$ in univariate analyses were included in multiple LMM analyses (Table 4). Corrected for other predictors, subthreshold depression/anxiety was no longer associated with functional impairment, indicating that the higher level of functional impairment is explained by personal and environmental factors. A history of anxiety disorder, lower levels of conscientiousness, a higher number of somatic conditions, and a higher number of traumatic events in childhood predicted higher levels of functional impairment overall, regardless of subthreshold status or time since baseline. Higher levels of neuroticism were also associated with higher levels of functional impairment in both subthreshold and controls, with the interaction with subthreshold status showing that this effect was more pronounced in subthreshold respondents. High neuroticism was more strongly associated with greater functional impairment in subthreshold respondents than in controls. Older age was only associated with higher levels of functional impairment overall in subthreshold respondents. The interaction of subthreshold disorder and time was no longer significant, suggesting that the differential course of subthreshold respondents over time was explained by the addition of other illness, personal, and environmental factors in the model. Two factors were associated with change in functional impairment in multiple LMM analyses. In addition to being associated with higher levels of functional impairment overall, lower levels of conscientiousness were also associated with a more rapid decrease in functional impairment over time, in both subthreshold and controls. Not having a partner was also associated with a more rapid decrease in functional impairment over time, but only in subthreshold respondents.

DISCUSSION

Our results show that subthreshold respondents, although their functional impairment declined over time, were more functionally impaired at all three time points

compared to controls. Subthreshold respondents were especially impaired in their work and household roles. Functional impairment of controls did not change significantly over time, indicating a floor effect representing stable, healthy functioning. Illness, personal, and environmental factors predicting functional impairment were similar for subthreshold respondents and controls. Most factors exerted a stable unfavorable effect. A history of anxiety disorder, higher levels of neuroticism, lower levels of conscientiousness, a higher number of traumatic events in childhood, and a higher number of somatic conditions all predicted worse functioning. Older age predicted worse functioning in subthreshold respondents only.

In addition to a stable effect, lower levels of conscientiousness were associated with greater improvement in functioning over time, as was not having a partner in subthreshold respondents. Lower conscientiousness and not having a partner were both associated with higher levels of functional impairment at baseline. It is therefore likely that these effects over time are state effects, with the resulting counterintuitive direction of the time \times predictor effects reflecting the improvement in functioning of our group as a whole, in particular the subthreshold group, resulting from a subsiding in symptoms. Although subthreshold depression is a known risk factor for full-syndromal depressive disorder, the majority of people with subthreshold depression has been found to remit between 1 and 6 years,^[27] 46.0 to 71.4%. Subthreshold respondents were likely at their worst time when recruited at baseline, so it can be expected that their overall functioning improves over time, regressing toward the healthy mean. However, it is noteworthy that after 2 years, their functional impairment compared to that of controls was still considerable.

Our finding that respondents with subthreshold depression/anxiety were most impaired in their household and work roles is in line with earlier work on persons with full-syndromal MDD and anxiety disorders. Both MDD and anxiety disorders are associated with work impairment,^[28–31] even on a subthreshold level.^[32] Possibly household and work activities are the most demanding aspects of daily functioning, requiring

TABLE 3. Univariate predictors of functional impairment over 2 years' time (N = 1,266)

	Overall effect predictor		Overall effect time		Predictor × subthreshold		Predictor × time		Subthreshold × time		Predictor × subthreshold × time	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Time (baseline, 1-year, 2-year)												
Time	-0.35†	0.19	N/A	N/A	-1.77***	0.32	N/A	N/A	N/A	N/A	N/A	N/A
Illness factors baseline												
Subthreshold disorder	14.59***	0.61	N/A	N/A	N/A	N/A	-1.77***	0.32	N/A	N/A	N/A	N/A
History of depressive disorder	3.16***	0.54	13.71***	0.62	-0.35†	0.19	-	-	-1.78***	0.32	-	-
History of anxiety disorder	4.09***	0.59	13.65***	0.61	-0.35†	0.19	-	-	-1.77***	0.32	-	-
Personal factors baseline												
Age	-0.01	0.02	9.41***	1.83	-0.35	0.58	0.12**	-	-1.77***	0.32	-	-
Female gender	0.65	0.54	14.54***	0.61	-0.35†	0.19	-	-	-1.77***	0.32	-	-
Years of education	-0.09	0.08	14.48***	0.61	-0.35†	0.19	-	-	-1.77***	0.32	-	-
Personality												
Neuroticism	0.41***	0.05	1.4	2.92	-0.85	0.80	0.25**	0.02	1.32	1.64	-0.09†	0.05
Extraversion	-0.36***	0.04	12.87***	0.63	-0.35†	0.19	-	-	-1.77***	0.32	-	-
Conscientiousness	-0.52***	0.05	12.86***	0.61	-2.99*	1.28	0.06*	0.03	-1.58***	0.33	-	-
Agreeableness	-0.24***	0.05	13.98***	0.62	-0.35†	0.19	-	-	-1.75	0.32	-	-
Openness	0.01	0.04	14.59***	0.61	-0.35†	0.19	-	-	-1.77***	0.32	-	-
Number of somatic conditions	1.81***	0.26	13.71***	0.61	-0.34†	0.19	-	-	-1.77***	0.32	-	-
Physical activity (× 100 min/week)	-0.01	0.01	14.57***	0.61	-0.35†	0.19	-	-	-1.76***	0.32	-	-
Family history of depressive disorder	1.28*	0.59	14.49***	0.61	-0.35†	0.19	-	-	-1.77***	0.32	-	-
Family history of anxiety disorder	1.16*	0.55	14.49***	0.61	-0.35†	0.19	-	-	-1.77***	0.32	-	-
Environmental factors baseline												
Childhood trauma index	1.93***	0.27	13.64***	0.61	-0.34†	0.18	-	-	-1.78***	0.32	-	-
Number of adverse life events	0.54	0.46	14.58***	0.72	-0.40†	0.22	-0.09	0.11	-1.30**	0.38	-0.83*	0.39
Social network size	-0.73**	0.26	17.62***	1.46	-0.34†	0.19	-1.23**	-	-1.76***	0.32	-	-
Partner present	0.05	0.82	14.01***	0.71	-0.49*	0.21	2.03	0.57	-1.05**	0.37	-2.52***	0.71
Friend(s) present	-0.03	0.64	14.59***	0.61	-0.35†	0.19	-	-	-1.77***	0.32	-	-
Household income	-0.73*	0.31	16.38***	1.41	-0.25	0.44	-0.90	-0.04	-3.10***	0.75	0.60*	0.29
Unemployed	0.81	0.61	14.53***	0.61	-0.35†	0.19	-	-	-1.77***	0.32	-	-

N/A, not applicable; -P > .10 and no higher order interaction, therefore not included in the model

† P < .10; * P < .05; ** P < .01; *** P < .001.

TABLE 4. Multivariate predictors of functional impairment over 2 years' time ($N = 1,266$)

	Overall		× Subthreshold		× Time		× Time × subthreshold	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	21.44***	4.48						
Time (baseline, 1-year, 2-year)								
Time	−4.35*	1.89	1.52	1.94				
Illness factors baseline								
Subthreshold disorder	−4.57	4.16			1.52	1.94		
History of depressive disorder	.63	0.52						
History of anxiety disorder	1.85**	0.56						
Personal factors baseline								
Age	−0.03	0.02	0.12**	0.04				
Personality								
Neuroticism	0.22***	0.06	0.31**	0.08	0.04	0.03	−0.08	0.05
Extraversion	−0.06	0.05						
Conscientiousness	−0.30***	0.05			0.06*	0.03		
Agreeableness	−0.05	0.05						
Number of somatic conditions	1.81***	0.25						
Family history of depressive disorder	0.08	0.58						
Family history of anxiety disorder	0.18	0.53						
Environmental factors baseline								
Childhood trauma index	0.91***	0.26						
Number of adverse life events	0.23	0.42	0.05	0.66	0.07	0.24	−0.59	0.39
Social network size	−0.09	0.24	−0.79	0.42				
Partner present	−0.67	0.78	2.18	1.30	0.59	0.46	−2.17**	0.76
Household income	−0.36	0.31	−0.56	0.54	0.05	0.18	0.18	0.32

Only main effects and interactions $P < .10$ in univariate analyses (Table 3) were included in multiple analyses.

* $P < .05$; ** $P < .01$; *** $P < .001$.

multiple hours a day, and are therefore the first to slip when health issues occur. Interventions focusing on work engagement may benefit work functioning, which may in turn even prevent symptoms of depression and anxiety in the future.^[33]

Our study identified two personality traits that predicted a stable course of lower functioning both in subthreshold respondents and controls: high neuroticism and low conscientiousness. Neuroticism has often been found to predict depression and anxiety.^[34,35] Furthermore, neuroticism has been shown to predict the level of functional impairment in a sample with MDD.^[36] Even in the absence of full-syndromal depressive or anxiety disorders, neuroticism in this study seems to reflect a common risk factor for both disorder and functional impairment, particularly visible in individuals that already show symptoms on subthreshold level. In addition, low conscientiousness predicted greater functional impairment over a prolonged period of time in both persons with subthreshold disorder and controls. This finding is in line with Verboom et al.,^[13] who found that low conscientiousness was associated with greater functional impairment in full-syndromal MDD. High levels of conscientiousness have been found to predict active coping strategies,^[37] health-related behavior, and beneficial social environmental factors, such as higher socioeconomic status,^[38] all of which may boost functioning in daily life.

Our finding that childhood trauma is associated with functional impairment is in line with previous findings that childhood trauma is associated with poorer functioning in various life domains in patients with social anxiety disorder^[39] and severe mental illness.^[40] The association of somatic illness with functional impairment is also well documented in the general population,^[41–43] and in the presence of depressive or anxiety disorders.^[44] Our results add to the existing literature showing that somatic conditions predict impairment over a prolonged period of time, in both persons with and without subthreshold depression or anxiety. That older age was associated with functional impairment in subthreshold respondents could be due to an additive effect of both age and subthreshold symptoms. As a person gets older, it becomes more difficult to maintain the same level of functioning, such as getting around, self-care, and participation in society. This task may become more difficult when recourses are already taxed by depressive or anxiety symptoms.

This study has several strengths. A particular strength of this study is the prospective design, which enabled us to go beyond retrospective or cross-sectional associations, and predict the course of functional impairment. Also, this study included a large sample of subthreshold respondents and controls, enabling us to study multiple predictors. Furthermore, using LMM analyses, all available information was used, even from

respondents with partly missing data. This study has an important weakness as well. We found little evidence for variables predicting deterioration of functional impairment over 2 years, although our sample was representative and sufficiently large. This finding is likely due to the overall improvement in functioning over time on group level. As argued, the literature suggests that the majority of subthreshold cases tend to develop toward being healthy again.^[27] Still, even if no deterioration is apparent, it would be interesting to observe factors associated with a slower recovery in functioning. For example, although not found in the present sample with subthreshold symptoms, Verboom et al.^[45] found that among persons recovering from full-syndromal MDD, higher age was associated with a slower recovery in functioning over time.

In conclusion, we found that respondents with subthreshold depression or subthreshold anxiety remain functionally impaired over the course of 2 years, compared to controls. Predictors of functional impairment were similar for persons with and without subthreshold depression/anxiety, showing their general relevance. Preventive interventions should be focused on persons with subthreshold symptoms, especially with a history of anxiety disorder, somatic conditions, childhood trauma, older age, high levels of neuroticism, or low levels of conscientiousness, as they are likely to be the most burdened by their symptoms.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
2. Prince M, Glozier N, Sousa R, Dewey M. Measuring disability across physical, mental and cognitive disorders. In: Regier DA, Narrow WE, Kuhl EA, Kupfer DJ, editors. The Conceptual Evolution of DSM-5. Washington, DC: American Psychiatric Publishing; 2011; pp. 189–227.
3. Howland RH, Shettler PJ, Rapaport MH, et al. Clinical features and functioning of patients with minor depression. *Psychother Psychosom* 2008;77:384–389.
4. Baumeister H, Morar V. The impact of clinical significance criteria on subthreshold depression rates. *Acta Psychiatr Scand* 2008;118:443–450.
5. Cuijpers P, De Graaf R, Van Dorsselaer S. Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. *J Affect Disorders* 2004;79:71–79.
6. Batelaan NM, De Graaf R, Van Balkom AJLM, Vollebergh WAM, Beekman ATF. Thresholds for healthy and thresholds for illness: panic disorder versus subthreshold panic disorder. *Psychol Med* 2007;37:247–256.
7. Karsten J, Hartman CA, Ormel J, Nolen WA, Penninx BWJH. Subthreshold depression based on functional impairment better defined by symptom severity than by number of DSM-IV symptoms. *J Affect Disorders* 2010;123:230–237.
8. Karsten J, Penninx BWJH, Nolen WA, Hartman CA. Subthreshold anxiety better defined by symptom self-report than by diagnostic interview. *J Affect Disorders* 2011;129:236–243.
9. Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. *Acta Psychiatr Scand* 2004;109:325–331.
10. Shankman SA, Lewinsohn PM, Klein DN, Small JW, Seeley JR, Altman SE. Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. *J Child Psychol Psych* 2009;50:1485–1494.
11. Karsten J, Hartman CA, Smit JH, et al. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. *Brit J Psychiatr* 2011;198:206–212.
12. World Health Organization. Towards a Common Language for Functioning, Disability and Health: ICF. Geneva: World Health Organization; 2002.
13. Verboom CE, Sentse M, Sijtsema JJ, Nolen WA, Ormel J, Penninx BWJH. Explaining heterogeneity in disability with major depressive disorder: effects of personal and environmental characteristics. *J Affect Dis* 2011;132:71–81.
14. Penninx BWJH, Beekman ATF, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Method Psych Res* 2008;17:121–140.
15. Rush AJ, Giles DE, Schlessler MA, Fulton CL, Weissenburger J, Burns C. The Inventory for Depressive Symptomatology (IDS): preliminary findings. *Psychiatr Res* 1986;18:65–87.
16. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psych* 1988;56:893–897.
17. World Health Organization. World health Organization Disability Assessment Schedule (WHODAS II). Geneva: World Health Organization; 2000.
18. McCrae RR, Costa PT, Jr. Towards a new generation of personality theories: theoretical contexts for the five-factor model. In: Wiggins JS, editor. *The Five-Factor Model of Personality: Theoretical Perspectives*. NY: Guilford Press; 1996; pp. 51–87.
19. Bijl RV, Ravelli A. Current and residual functional disability associated with psychopathology: findings from the Netherlands Mental health Survey and Incidence Study (NEMESIS). *Psychol Med* 2000;30:657–668.
20. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sport Exer* 2003;35:1381–1395.
21. Fyer AJ, Weissman MM. Genetic linkage study on panic: clinical methodology and description of pedigrees. *Am J Med Genet* 1999;88:173–181.
22. De Graaf R, Bijl RV, Smit F, Vollebergh WAM, Spijker J. Risk factors for 12-month comorbidity of mood, anxiety, and substance

- use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *Am J Psychiat* 2002;159:620–629.
23. Brugha T, Bebbington P, Tennant C, Hurry J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med* 1985;15:189–194.
 24. Stansfeld S, Marmot M. Deriving a survey measure of social support: the reliability and validity of the Close Persons Questionnaire. *Soc Sci Med* 1992;35:1027–1035.
 25. West BT. Analyzing longitudinal data with the linear mixed models procedure in SPSS. *Eval Health Profes* 2009;32:207–228.
 26. Shek DT, Ma CM. Longitudinal data analyses using linear mixed models in SPSS: concepts, procedures and illustrations. *Scient World J* 2011;11:42–76.
 27. Hermens MLM, Van Hout HPJ, Terluin B, et al. The prognosis of minor depression in the general population: a systematic review. *Gen Hosp Psychiat* 2004;26:453–462.
 28. Kessler RC, Frank RG. The impact of psychiatric disorders on work loss days. *Psychol Med* 1997;27:861–873.
 29. Kessler RC, DuPont RL, Berglund P, Wittchen H-U. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. *Am J Psychiatry* 1999;156:1915–1923.
 30. Kessler RC, Greenberg PE, Mickelson KD, Meneandes LM, Philip S. The effects of medical conditions on work loss and work cutback. *J Occup Organ Psych* 2001;43:218–225.
 31. Wittchen H-U. Generalized anxiety disorder: prevalence burden and cost to society. *Dep Anx* 2002;16:162–171.
 32. Rai D, Skapinakis P, Wiles N, Lewis G, Araya R. Common mental disorders, subthreshold symptoms and disability: longitudinal study. *Br J Psychiat* 2010;197:411–412.
 33. Innstrand ST, Langballe WM, Falkum E. A longitudinal study of the relationship between work engagement and symptoms of anxiety and depression. *Stress Health* 2012;28:1–10.
 34. Krueger RF. Personality traits in late adolescence predict mental disorders in early adulthood: a prospective-epidemiological study. *J Pers* 1999;67:39–65.
 35. Ormel J, Oldehinkel AJ, Vollebergh W. Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Arch Gen Psychiat* 2004;61:990–996.
 36. Rhebergen D, Beekman ATF, De Graaf R, et al. Trajectories of recovery of social and physical functioning in major depression, dysthymic disorder and double depression: a 3-year follow-up. *J Affect Disorders* 2009;124:148–156.
 37. Conor-Smith JK, Flachsbarth C. Relations between personality and coping: a meta-analysis. *J Pers Soc Psychol* 2007;93:1080–1107.
 38. Roberts BW, Walton KE, Bogg T. Conscientiousness and health across the life course. *Rev Gen Psychol* 2005;9:156–168.
 39. Simon NM, Herlands, NN, Marks EH, et al. Childhood maltreatment linked to greater severity and poorer quality of life and function in social anxiety disorder. *Depress Anxiety* 2009;26:1027–1032.
 40. Davidson G, Shannon C, Mulholland C, Campbell J. A longitudinal study of the effects of childhood trauma on symptoms and functioning of people with severe mental health problems. *J Trauma Dissociation* 2009;10:57–68.
 41. Murray CJL. Quantifying the burden of disease: the technical basis for disability-adjusted life years. *B World Health Organ* 1994;72:429–445.
 42. Sprangers MAG, De Regt EB, Andries F, et al. Which chronic conditions are associated with better or poorer quality of life? *J Clin Epidemiol* 2000;53:895–907.
 43. Kessler RC, Greenberg PE, Mickelson KD, Meneades LM, Wang PS. The effects of chronic medical conditions on work loss and work cutback. *J Occup Environ Med* 2001;43:218–225.
 44. Buist-Bouwman MA, De Graaf R, Vollebergh WAM, Ormel J. Comorbidity of physical and mental disorders and the effect on work loss days. *Acta Psychiat Scand* 2005;111:436–443.
 45. Verboom CE, Ormel J, Nolen WA, Penninx BWJH, Sijtsma JJ. Moderators of the synchrony of change between decreasing depression severity and disability. *Acta Psychiat Scand* 2012;126:1–11.