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REVIEW ARTICLE

Neuroticism's prospective association with mental disorders halves after adjustment for baseline symptoms and psychiatric history, but the adjusted association hardly decays with time: a meta-analysis on 59 longitudinal/prospective studies with 443 313 participants

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Background. This meta-analysis seeks to quantify the prospective association between neuroticism and the common mental disorders (CMDs, including anxiety, depression, and substance abuse) as well as thought disorders (psychosis/schizophrenia) and non-specific mental distress. Data on the degree of confounding of the prospective association of neuroticism by baseline symptoms and psychiatric history, and the rate of decay of neuroticism's effect over time, can inform theories about the structure of psychopathology and role of neuroticism, in particular the vulnerability theory.

Method. This meta-analysis included 59 longitudinal/prospective studies with 443 313 participants.

Results. The results showed large unadjusted prospective associations between neuroticism and symptoms/diagnosis of anxiety, depression, and non-specific mental distress ($d = 0.50$–0.70). Adjustment for baseline symptoms and psychiatric history reduced the associations by half ($d = 0.10$–0.40). Unadjusted prospective associations for substance abuse and thought disorders/symptoms were considerably weaker ($d = 0.03$–0.20), but were not attenuated by adjustment for baseline problems. *Unadjusted* prospective associations were four times larger over short (<4 year) than long ($\geqslant 4$ years) follow-up intervals, suggesting a substantial decay of the association with increasing time intervals. *Adjusted* effects, however, were only slightly larger over short *v.* long time intervals. This indicates that confounding by baseline symptoms and psychiatric history masks the long-term stability of the neuroticism vulnerability effect.

Conclusion. High neuroticism indexes a risk constellation that exists *prior* to the development and onset of any CMD. The adjusted prospective neuroticism effect remains robust and hardly decays with time. Our results underscore the need to focus on the mechanisms underlying this prospective association.

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Neuroticism

Neuroticism is one of the broad traits at the apex of personality taxonomy. The term neuroticism has its roots in Freudian theory, but the modern concept of neuroticism has been introduced by Hans Eysenck and contemporaries, who used a range of methods from personality psychology, including psychophysiological and lexical studies (Dumont, 2010).

Currently, consensus has developed that, at its core, neuroticism is the propensity to experience negative emotions (Clark & Watson, 1999; John *et al.* 2008; Matthews *et al.* 2009; Widiger, 2009), including anxiety, fear, sadness, anger, guilt, disgust, irritability, loneliness, worry, self-consciousness, dissatisfaction, hostility, embarrassment, reduced self-confidence, and feelings of vulnerability, in reaction to various types of stress, and tend to select themselves into situations that foster negative affect (Lüdtke *et al.* 2009; Specht

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et al. 2011; Jeronimus *et al.* 2014; Riese *et al.* 2014). Importantly, the total 'excess economic costs' associated with the 25% highest neuroticism scores in the Netherlands have been estimated at twice that of all common mental disorders (CMDs) combined, and about two-thirds of the excess costs of somatic problems (Cuijpers *et al.* 2010).

Association with psychopathology

High neuroticism scores are strongly associated with psychopathology, in particular the CMDs, including anxiety, mood, and substance use disorders (Ormel *et al.* 2001; Saulsman & Page, 2004; Malouff *et al.* 2005; Ruiz *et al.* 2008; Kotov *et al.* 2010). An influential meta-analysis quantified neuroticism's cross-sectional association with CMDs, ranging in magnitude from Cohen's *d* of 0.50 for substance disorders, to 2.00 for some anxiety and mood disorders (Kotov *et al.* 2010). Neuroticism is also prospectively associated with CMDs, although the associations are typically smaller (*d* = 0.20–0.60, see Lahey, 2009; Kotov *et al.* 2010; Ormel *et al.* 2013; Hakulinen *et al.* 2015*a*, *b*; Vall *et al.* 2015).

Neuroticism's prospective association with CMDs has fueled the assumption that neuroticism is an independent etiologically informative risk factor. This *vulnerability* model postulates that neuroticism sets in motion processes that lead to developing CMDs. However, five other models seek to explain the association, including the *spectrum* model (extreme neuroticism is called disorder), *common cause* model (distinct constructs that share determinants), *state* and *scar* models (CMD episodes change neuroticism levels temporarily/permanently). Recently we reviewed the validity of these models provided the available literature on confounding of the prospective association by baseline symptoms and psychiatric history, operational overlap, stability and change, determinants, and treatment effects (Ormel *et al.* 2013). We concluded that none of the models can account for (virtually) all findings, viz. the state and scar model cannot explain the prospective association, the spectrum model has some relevance, especially for internalizing disorders, but common causes are important as well.

Some of the reviewed findings, such as the prospective associations and interactions of neuroticism with stress (Kendler *et al.* 2003; Lüdtke *et al.* 2009; Specht *et al.* 2011; Jeronimus *et al.* 2014; Riese *et al.* 2014), are especially consistent with the vulnerability model. Also the higher stability of neuroticism over time than internalizing symptoms supports the vulnerability model (Ormel *et al.* 2013; Nivard *et al.* 2015*a*, *b*). However, firm conclusions regarding the vulnerability model were hampered by limited data on the degree of confounding of the prospective association by baseline symptoms and psychiatric history, and the rate of decay of neuroticism's effect over time. The present meta-analysis aims to ameliorate this lack of insight as much as possible, provided the available data, and included studies of the prospective association between neuroticism and CMDs, to compare the strength of the prospective associations by differencing follow-up period, with and without adjustment for baseline problems. Additionally, the present meta-analytic study included some non-CMDs as well, such as thought disorders.

Thought disorders

The link between neuroticism and CMDs received most attention. Nonetheless, neuroticism also appears to be related to a set of prominent cognitive-perceptual and affect regulation problems, grouped in what has been called the schizo-affective-psychosis continuum of 'thought disorders' (Markon, 2010; Kotov *et al.* 2011; Keyes *et al.* 2013). Thought disorders are marked by idiosyncratic perceptions (or 'positive symptoms') that are quite common in the general population (Hanssen *et al.* 2005; Nuevo *et al.* 2012), including deviant beliefs ('delusions'), feelings, and perceptions ('hallucinations'), which can flair up temporary (i.e. 'schizotypy'), or decompensate into a full-blown disorder (van Os *et al.* 2009; Keyes *et al.* 2013; including schizophrenia, psychotic disorders, obsessive compulsive disorders, and schizotypical personality disorders). Thought disorders are also marked by social deficits ('negative symptoms'), including poor social skills, social anxiety, withdrawal, social disinterests (anhedonia), and impaired perspective-taking ability (Brown *et al.* 2008; Pijnenborg *et al.* 2011). Recently it has been argued that thought disorders represent the most general expression of psychopathology, and may account for the overlap between internalizing and externalizing symptoms/disorders (Lahey *et al.* 2011; Caspi *et al.* 2013; Kotov *et al.* 2015; Laceulle *et al.* 2014). Although thought disorders are less prevalent than the CMDs, they represent an important domain of psychopathology, and therefore it is important to investigate the prospective association between neuroticism and thought disorders.

The present study

The current study seeks to quantify the prospective association between neuroticism on the one hand and CMDs, thought disorders, and non-specific mental distress on the other. Additionally, we seek to quantify the extent of confounding of the prospective association between neuroticism and CMDs by baseline symptoms and/or psychiatric history. To do so, we were particularly

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interested in studies that assessed psychopathology at baseline (i.e. concomitant with neuroticism), and reported on adjusted prospective associations. For example, prospective associations adjusted for baseline symptoms, or studies that excluded subjects with a history of and/or current psychopathology. Finally, the vulnerability model of psychopathology assumes limited decay of the association with increasing time between baseline assessment of neuroticism and outcome assessment. Therefore the temporal persistence of the prospective association between neuroticism and psychopathology was examined as well. Altogether, all studies that report on univariate and multivariate models for baseline neuroticism prospectively predicting psychopathology were identified (with and without adjustment for baseline problems and psychiatric history), and the reported coefficients were transformed, pooled, and compared in the current meta-analysis.

Materials and method

Search strategy

The Web of Knowledge was searched on 1 November 2015 with three search strings; (*a*) neuroticism, trait anxiety, negative affectivity or emotional stability; (*b*) mental disorder, internalizing disorder, externalizing disorder, psychopathology, mental health/illness, anxiety, depression, substance abuse, substance dependence, alcohol dependence, drug dependence, psychosis, psychoses, psychotic, psychotic disorder, schizophrenia, schizoaffective disorder, delusional disorder, paranoid psychosis, schizophreniform disorder, or dissociative disorder, and (*c*) longitudinal, prospective or follow-up. We also searched the references of the included studies for additional studies to overcome search string limitation. From the manuscripts we coded information on sample size, history of psychopathology, comorbidities, the personality measure, and psychopathology measure (e.g. continuous or categorical/binary Sx or Dx). The application of the search strategy is depicted in a flowchart given as Fig. 1 and all included studies can be found in Table 1.

Study selection criteria

Studies were included that comprised (*a*) an adult sample that was aged at least 18 years at follow-up (T_2) from (*b*) the general population with (*c*) at least 200 participants that assessed (*d*) neuroticism at baseline (T_1) and (*e*) psychopathology [symptoms (Sx) or diagnosis (Dx)] at T_2, and (*f*) the follow-up interval (T_1–T_2) had to be at least 1 year. This means that twin studies were included but patient groups (psychiatric/somatic) and prisoners were excluded. The included measures of psychopathology had to fit the five selected categories of interest: (*a*) *Anxiety disorders*, including post-traumatic sreess disorder (PTSD), panic disorder, generalized anxiety disorder (GAD), and phobic disorders; (*b*) *Depression*, including suicide and dysthymia; (*c*) *Substance abuse*, such as illicit drugs, alcohol and tobacco; (*d*) *Thought disorders*, including psychosis and schizophrenia, and (*e*) non-specific mental distress.

Non-specific mental distress

A number of studies examined symptoms and signs that either did not meet diagnostic criteria (NOS or subthreshold) or were not assessed in a way that linked them to a specific disorder (e.g. a total of all symptoms). We cumulated these data under a separate category of non-specific mental distress, which is conceptually close to high neuroticism, but importantly, assessed on a different time-frame ('state' *v.* 'trait', see Ormel *et al.* 2013, 2014). Non-specific mental distress refers to a continuum of disturbing or unpleasant emotional/mental states that interfere with one's ability to cope with daily living. Because this cluster may inform hypotheses about the personality–psychopathology association it has been included in this meta-analysis.

Conversion of outcomes

The heterogeneity of the outcome measures only allowed us to conduct a bare-bones meta-analysis in which effect sizes were converted into standardized mean difference *d* (Hunter & Schmidt, 2004). Conversion formulas were attained from the literature (Rosenthal, 1994; Sanchez-Meca *et al.* 2003; Peterson & Brown, 2005; Borenstein *et al.* 2009), and can be found in Supplementary Table S1. Odds ratios (ORs) that indicated the effect on outcome per scale unit of the raw metric of the predictor were converted to reflect ORs on standardized metric (i.e. per standard deviation of the predictor). In addition, ORs for neuroticism scales that indicated low-neuroticism with high scores were mirrored via 1/ORs to enable comparison. Four included studies reporting hazard ratios were excluded from our meta-analytic estimates, as they cannot be converted to ORs exactly. The relationship index *r* depicts measures of association or variance accounted for effect size. We classified correlations (*r*) and betas as small if between 0.10 and 0.20, moderate between 0.20 and 0.30, and large if >0.30, based on the effect sizes commonly found in social psychology (Richard *et al.* 2003; Peterson & Brown, 2005).

Summary statistics

Summary statistics were calculated for each cluster of disorders separately (anxiety, depression, substance

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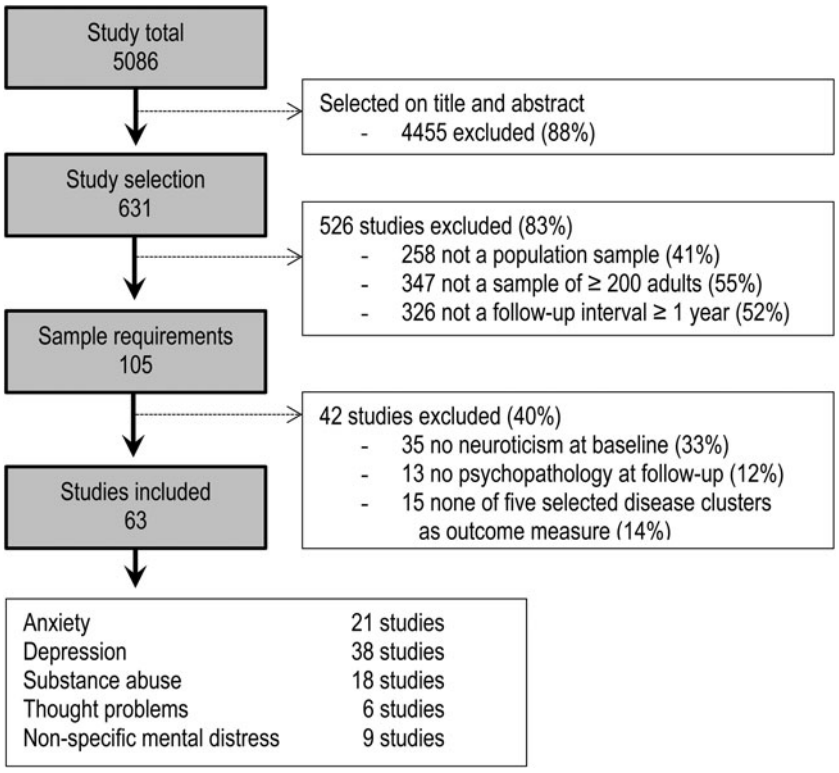

Fig. 1. Flow chart of the search strategy of studies on the prospective association between neuroticism and common mental disorders, thought disorders and, non-specific mental distress. The sum of all disorders exceeds 63 because some studies assessed multiple outcomes. The percentages (%) indicate the proportion for which this requirement was not met.

abuse, thought disorders, non-specific mental distress). If the study reported multiple outcome measures within a given category on a given sample (e.g. multiple depression scales), effect sizes were averaged to ensure that assumption of independence of observations is met, as recommended by Hunter & Schmidt (2004). Summary statistics were sample-size weighted to obtain most accurate estimates. If a study reported data on multiple follow-ups, the longest follow-up interval between personality assessment and psychopathology assessment was chosen. Three detailed selection rules were applied for the summary statistics. (*a*) If manuscripts reported several effect-sizes for the same association (outcome) in the same sample but for different levels of adjustment the best-adjusted effect size was included in the adjusted summary statistic (e.g. exclusion of subjects with a history of psychopathology *and* adjustment for baseline Sx). (*b*) If manuscripts reported several effect sizes for the same association (outcome) in the same sample, but for dichotomous and continuous measures, the latter was chosen for analyses. (*c*) In addition, analyses were stratified by follow-up interval. To do so, we divided our estimates over a short- and long-term follow-up interval, based on the median split; which is an arbitrary decision. This median split was based on the overall median study duration (to increase comparability), but was also calculated for dichotomous and continuous measures separately. In sum, all effect sizes that could be converted into Cohen's *d* values were used to estimate the summary statistics reported in Tables 2–4.

Results

Study selection

A total of 5086 records were screened for inclusion. The selection on title and abstracts reduced the number to 631 papers, which were further scrutinized with the study selection criteria, as outlined above. Eventually 63 studies were included, while the estimates in 59 studies could be converted to Cohen's *d*. This yielded 111 effect estimates. Our meta-analyses were based on 443 313 participants over almost 5 million follow-up years. At baseline the participants ranged in age from 14 to 104 years.

Some studies were performed in the eligible population and administered all variables of interest, but reported on other variables as predictor and/or outcome (e.g. Bak *et al.* 2005). Other studies adjusted the prospective association between neuroticism and outcome for the other four broad personality domains

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Table 1. *Prospective population-based studies (k = 63) linking neuroticism (N) to psychopathology [symptoms (Sx) or diagnoses (Dx)]*

First-named author	Pub. year	Sample	Size	♀ (%)	Age (range and mean (S.D.) at T_1)	T_1/T_2 (yr)		Outcome variable	N scale	Cat.	Comp.	Effect sizes study outcome	*d*'s	Adjustment for baseline (T_1) psychopathology	
Anxiety (including PTSD, panic disorder, GAD, and phobic disorders)															
Newton-Howes	2015	Pop.	903	Nsc	14	10 (10)	Dx	Since previous assessment	EPI	30	S.D.	OR = 1.56[a]	0.12	No	
												OR = 1.25[a]	0.06	Yes	e.g. childhood mental health problems, sexual/physical abuse
Aldinger	2014	Pop.	266	56	M = 25 (2.3)	9	Dx	Past 9 yr	NEO-FFI	48	2 *v.* 1 (8)	OR = 6.84[c]	0.51	No	
												β = 1.92[c]	2.34		
												β = 0.17[a]	0.44	Yes	Adj. for internalizing Sx at T_1
Kendler	2011	Twins	2395	100	29 (8)	8 (1)	Sx	Past mo.	EPQ-R	48	Cont.	SPRC = 0.24[d]	0.60	No	
Calkins	2009	Pop.	643	100	36–45, M = 40	3	Dx	Past 3 yr	NEO-FFI	48	Cont.	HR = 1.08[a]^S.D.		Yes	Ss LT depression at T_1 excl.
							Dx	Past 3 yr			Cont.	HR = 1.02[ns]^S.D.		Yes	Ss LT depression at T_1 excl. adj. for T_1 AnxSx
Vink	2009	CC	1712	49	55–85	9	Dx	Past mo.	DPQ	50	Cont.^S.D.	OR = 1.46[a]	0.23	Yes	Ss with Dx depression/anxiety at T_1 were excl.
							Dx	Past mo.			Cont.^S.D.	OR = 1.26[ns]	0.14	Yes	Ss with Dx depression/anxiety at T_1 were excl., and results adj. for Sx depression/anxiety at T_1
Cox	2008	Pop.	585	49	M = 43 (17)	1	Sx	Past wk	NEO-FFI	20	Cont.	*r* = 0.56[ng]	1.35	No	
							Sx	Past wk			Cont.	β = 0.23[a]	0.57	Yes	Adj. for Sx anxiety at T_1
Beard	2007	Pop.	968	57	18–85	1	Dx	Any, past yr	EPQ	24	*v.* Ctr.	OR = 1.22[a]	0.12	Yes	Ss with mental Dx (ICD-10 criteria) at T_1 excl.
							Dx	GAD, past yr		24	*v.* Ctr.	OR = 1.33[d]	0.17	Yes	Ss with mental Dx (ICD-10 criteria) at T_1 excl.
Moffitt	2007	Pop.	945	48	M = 18	14	Dx	GAD, ⩾1 mo.	MPQ NE,	Z	*v.* Ctr.	*t* = 5.29[a]	0.66	Yes	Adj. for childhood mental disorders Dx
Schmidt	2007	Pop.	405	61	M = 19 (4)	2	Dx	Past 2 yr	STPI-Trait	60	Cont.	OR = 2.20	0.48	Yes	Ss with psychiatric Sx/Dx past 12 mo. excl. at T_1
							Dx	Panic Dx			Cont.	OR = 2.00	0.42	Yes	Ss with psychiatric Sx/Dx past 12 mo. excl. at T_1
							Dx	Panic attack			Cont.	OR = 2.20	0.48	Yes	Ss with psychiatric Sx/Dx past 12 mo. excl. at T_1

Table 1 (*cont.*)

First-named author	Pub. year	Sample	Size	♀ (%)	Age (range and mean (S.D.) at T_1)	T_1/T_2 (yr)		Outcome variable	N scale	Cat.	Comp.	Effect sizes study outcome	*d′s*	Adjustment for baseline (T_1) psychopathology	
Parslow	2006	Pop.	2085	53	20–24	4	Sx	PTSD, past wk	EPQ-R	2 (3)	*v.* Ctr.	M (S.D.)	0.55	No	
							Sx	PTSD, past wk		24	Cont.	IRR^S.D. = 1.18	0.11	Yes	Adj. for T_1 depression and anxiety Sx.
De Graaf	2004	Pop.	2869	53	M = 42 (12)	3	Dx	Past 3 yr	GNS	14	*v.* Ctr.	OR = 1.12[a]	0.07	Yes	Ss with history of mental Dx excl. at T_1
Goodwin	2003	Pop./CC	961	50	M = 14	7	Dx	GAD, past 3 yr	EPI	2 (3)	2 *v.* 1	Rates (%)[ng]	0.86	No	
							Dx	Panic, past 3 yr			2 *v.* 1	Rates (%)[ng]	1.57	No	
							Dx	Soc.Ph., past 3 yr			2 *v.* 1	Rates (%)[ng]	0.76	No	
De Graaf	2002	Pop.	5618	50	18–64	1	Dx	Past yr	GNS	2 (4)	2 *v.*1	OR = 2.05[d]	0.44	No	
							Dx	Past yr			2 *v.* 1	OR = 1.23[ns]	0.13	Yes	Adj. for Sx depression and substance abuse at T_1
Hagglin	2001	Pop.	310	100	38–54	24	Sx	High dental fear	EPI-B	48	2 *v.* 1	$X^2 = 9.2$[d]	0.37	No	
Wetherell	2001	Twins	1031	57	29–95, M = 61 (13)	6	Sx	Past wk	STPI-Trait	50	Cont.	$r = 0.58$[ng]	1.42	No	
De Beurs	2000	Pop.	1602	84	55–85	3	Sx	Past mo.	DPI	2 (5)	2 *v.* 1	OR = 2.8[d]	0.62	Yes	Ss with anxiety excl. at T_1
Krueger	1999	Pop./CC	961	50	M = 18	3	Dx	Past yr	MPQ NE	Z	Cont.	OR = 1.63[d]	0.30	Yes	Adj. for Anxiety Sx at T_1
							Sx	Past yr			Cont.	$\beta = 0.18$[d]	0.46	Yes	Adj. for Anxiety Sx at T_1
Gershuny	1998	Pop.	466	53	M = 18 (1)	3	Sx	Past wk	EPQ	23	Cont.	$r = 0.30$[a]	0.63	No	
							Sx	Past wk			Cont.	$\beta = 0.067$[ns]	0.23	Yes	Adj. for Sx anxiety at T_1.
Caspi	1996	CC	1037	48	M = 3	18	Sx	Past yr	BRIC	2 (2)	*v.* Ctr.	M(S.D.)[ns]	0.18	No	
Krueger	1996	Pop.	897	48	M = 18	3	Sx	Past yr	MPQ NE	49	Cont.	$r = 0.27$[c]	0.56	No	
Levenson	1988	Pop.	1324	0	40–98	10	Sx	Any, past 3 mo.	EPI	9	Cont.	$r = 0.42$[a]	0.93	No	
							Sx	Phobic, past 3 mo.		9	Cont.	$r = 0.26$[a]	0.54	No	
Depression (including suicide and dysthymia)															
Hakulinen	2015b	Pop.	56 735	54.7	15–104, M = 49.0	5	Sx	Past 5 yr	(*n*=9), various	15	Cont.	$\beta = 0.12$[a]	0.34	No	Adj. for extraversion, conscientiousness, openness and agreeableness (!)
Newton-Howes	2015	Pop.	903		14	10 (10)	Dx	Since previous assessment	EPI	30	S.D.	OR = 1.54[a]	0.11	No	
												OR = 1.39[a]	0.09	Yes	Adj. for childhood mental health problems and sexual/physical abuse, among others
Aldinger	2014	Pop.	266	56	M = 25 (2.3)	9	Dx	Past 9 yr	NEO-FFI	12	2 *v.* 1 (8)	OR = 14.00[a]	0.69	No	
												$\beta = 2.64$[a]	2.16	No	
												$\beta = 0.08$[d]	0.26	Yes	Adj. for internalizing Sx at T_1

Kendler	2011	Twins	2395	100	29 (8)	8 (1)	Sx	Past mo.	EPQ-R	12	Cont.	SPRC = 0.24[d]	0.60	No	
Inoue	2010	Pop.	15 256	0	18–67	5	Dx	Past 5 yr	EPQ-R	3	3 *v.* 1	HR = 3.32[c]		Yes	Ss with LT mental disorder at T_1 excl.
Kendler	2010	Pop.	7733	Mix	>18	2.5	Dx	Past yr	EPQ-S	12	*v.* Ctr.	OR = 1.56[a]	0.27	No	
Sen	2010	Pop.	740	54	26–30 (72%)	1	Sx	Past 2 wk	NEO-FFI	12	Cont.	r = 0.115[a]	0.24	Yes	Adj. for Sx depression at T_1.
							Sx	Past 2 wk			Cont.	β = 0.24[a]	0.60	Yes	Adj. for Sx depression at T_1, personal history of depression, difficult early rearing environment
Vink	2009	CC	1712	49	55–85	9	Dx	Past mo.	DPQ	50	*v.* Ctr.	OR = 1.58[a]	0.28	Yes	Ss with Dx depression/ anxiety at T_1 are excl.
							Dx	Past mo.			*v.* Ctr.	OR = 1.36[a]	0.19	Yes	Ss with Dx depression/ anxiety at T_1 are excl., Adj. for Sx anxiety/ depression at T_1
Weiss	2009	CC	512	76	65–100, M = 79 (7)	1.8	Dx	MD, past mo.	NEO-FFI	2	*v.* Ctr.	M (S.D.)	0.94	Yes	Ss with major/minor depression at T_1 excl.
						Dx	Minor, past mo.				*v.* Ctr.	M (S.D.)	0.49	Yes	Ss with major/minor depression at T_1 excl.
							Dx	MD, past mo.		T	Cont.	OR = 2.28	0.50	Yes	Ss with major/minor depression at T_1 excl.
							Dx	Minor, past mo.			Cont.	OR = 0.50	0.27	Yes	Ss with major/minor depression at T_1 excl.
Duberstein	2008	Pop.	275	55	M = 70	15	Dx	Past 15 yr	MPI	48	Cont.	HR = 1.05[a]^10.1		Yes	Ss with Sx or history of mental Dx excl. at T_1
							Dx	Past 15 yr			Cont.	HR = 1.06[a]^10.1		Yes	Ss with Sx or history of mental Dx excl. at T_1, and adj. for incident dementia $\leqslant T_2$ (n = 51)
Beard	2007	Pop.	968	57	18–85	1	Dx	Past yr	EPQ	24	*v.* Ctr.	OR = 1.27	0.16	Yes	Ss with any mental Dx (ICD-10) at T_1 excl.
Chien	2007	Pop.	1348	63	18–25, M = 20 (1)	1	Sx	Past wk	FFI	48	Cont.	r = 0.49[c]	1.12	No	
Fanous	2007	Twins	3030	0	20–58, M = 37 (9)	1.6	Dx	Past yr	EPQ	12	Cont.	RR = 3.01[a]	0.81	No	
							Dx	Past yr			Cont.	RR = 1.85[a]	0.43	Yes	Ss with episodes of MD prior to or at T_1 excl.
Moffitt	2007	Pop.	945	48	M = 18	14	Dx	MD, past mo.	MPQ NE	Z	*v.* Ctr.	t = 6.18[a]	0.65	Yes	Adj. for childhood mental disorders Dx.
Kendler	2006	Twins	20 692	Mix	14–77, M = 29 (9)	25	Dx	1st onset MD, past LT	EPI	9	*v.* Ctr.	X_1^2 = 199.5[a]	0.21	Yes	Ss with a history of MD at T_1 excl.
							Dx	1st onset MD, past LT			*v.* Ctr.	HR = 1.31[a]		Yes	Ss with a history of MD at T_1 excl.

Table 1 (*cont.*)

First-named author	Pub. year	Sample	Size	♀ (%)	Age (range and mean (s.d.) at T_1)	T_1/T_2 (yr)		Outcome variable	N scale	Cat.	Comp.	Effect sizes study outcome	*d*'s	Adjustment for baseline (T_1) psychopathology	
							Dx	1st/rec. MD past LT			*v.* Ctr.	OR = 1.49[a]	0.24	Yes	Ss with a history of MD at T_1 excl.
Kendler	2006	Twins	2935	0	M = ~33 (9)	4	Dx	Past yr	EPI	5	*v.* Ctr.	SPRC = 0.20[a]	0.51	Yes	Adj. for e.g. CD, early onset anxiety
De Beurs	2005	Pop.	1837	56	55–85,M = 71 (8)	6	Sx	Past wk	DPI	30	Cont.	$\beta = 0.09$[a]	0.28	No	
De Graaf	2004	Pop.	2869	53	M = 42 (12)	3	Dx	Mood, past 3 yr	GNS	14	*v.* Ctr.	OR = 1.18[a]	0.10	Yes	Ss with history of mental Dx excl. at T_1
Kendler	2004	Twins	7517	Mix	13–58	9	Dx	MD, past yr	EPI	21	Cont.	$X^2_1 = 109.7$[a]	0.24	No	
Kendler	2004	Twins	1404	100	17–55, M = 30 (8)	2	Dx	Past yr	EPQ-S	Z	Cont.	HR = 1.37		No	
Neeleman	2004	Pop.	3625	53	18–65, M = 42 (12)	3	Dx	Mood, past 2 yr	EPI	28	Cont.	OR = 2.22	0.48	No	
Ormel	2004	CC	4796	Mix	18–64	3	Dx	1st MD, past yr	ABI	14	Cont.	$d = 0.83$[a]	0.83	No	
Goodwin	2003	Pop./CC	961	50	M = 14	7	Dx	Past 3 yr	EPI	2 (3)	2 *v.* 1	Rates (%)[ng]	0.41	No	
Tokuyama	2003	Pop.	1605	53	20–73	1	Dx	Past 2 wk	NEO-FFI	12	Cont.	OR = 3.59[a]	0.77	Yes	Adj. for past history of MD and Dx at T_1
De Graaf	2002	Pop.	5618	50	18–64	1	Dx	Past yr	GNS	2 (4)	2 *v.* 1	OR = 2.45[d]	0.54	No	
							Dx	Past yr			2 *v.* 1	OR = 2.18[d]	0.47	Yes	Adj. for Sx anxiety and substance abuse at T_1
Kendler	2002	Twins	1942	100	M = 29 (8)	7 (1)	Dx	MD, past yr	EPQ-R	5	Cont.	$r = 0.39$[ng]	0.85	No	
							Dx	MD, past yr			Cont.	SPRC = 0.16	0.42	Yes	Adj. for substance abuse and Sx depr/anxiety
Wetherell	2001	Twins	1031	57	29–95, M = 61 (13)	6	Sx	Past wk	STPI-trait	50	Cont.	$r = 0.49$[ng]	1.11	No	
Fergusson	2000	CC	965	50	M = 14	7	Sx	Suicidal id., past 6 yr	EPI	2	*v.* Ctr.	Rates (%)	0.56	No	
							Sx	Suicide att., past 6 yr			*v.* Ctr.	Rates (%)	0.76	No	
							Sx	Suicidal id., past 6 yr		12	Cont.	PHRC = 0.09[a]		No	
							Sx	Suicidal id., past 6 yr			Cont.	PHRC = 0.08[a]		Yes	Adj. Sx depression, anxiety, CD, substance use
							Sx	Suicide att., past 6 y.			Cont.	PHRC = 0.06[d]		No	
							Sx	Suicide att., past 6 yr			Cont.	PHRC = ns		Yes	Adj. Sx depression, anxiety, CD, substance use

Krueger	1999	Pop./CC	961	50	M = 18	3	Dx	Past yr	MPQ NE	Z	Cont.	OR = 1.27[d]	0.14	Yes	Affective disorder Sx at T_1
							Sx	Past yr			Cont.	$\beta = 0.12$	0.34	Yes	Affective disorder Sx at T_1
Gershuny	1998	Pop.	466	53	M = 18 (1)	3	Sx	Past wk	EPQ	23	Cont.	r = 0.26[a]	0.54	No	
							Sx	Past wk			Cont.	$\beta = 0.08^{ns}$	0.27	Yes	Adj. for Sx depression at T_1
Henderson	1997	Pop.	709	52	73–102, M = 80 (5)	4	Sx	Past 2 wk	EPQ-R	24	Cont.	$\beta = 0.08$[d]	0.25	Yes	Adj. for Sx depression at T_1
Caspi	1996	CC	1037	48	M = 3	18	Sx	Past yr	BRIC	2 (2)	2 *v.* 1	OR = 2.2[c]	0.48	No	
							Dx	Suicide att. past yr			2 *v.* 1	OR = 6.5[d]	1.13	No	
Krueger	1996	Pop.	897	48	M = 18	3	Sx	Past yr	MPQ NE	49	Cont.	$r = 0.24$[c]	0.49	No	
Clayton	1994	Pop.	2894	0	19	17	Dx	Unipolar Dep.	FPI	9	*v.* Ctr.	W[a]	0.59	Yes	Ss with depression at baseline were excl.
Kendler	1993	Twins	1733	100	17–55, M = 30 (8)	1.25	Dx	MD, LT		12	S.D.	b = 1.46[a]	0.23	No	
							Dx	MD, past yr			S.D.	b = 2.40[a]	0.53	No	
							Dx	MD, past yr			S.D.	b = 2.33[a]	0.51	Yes	Ss with previous MD episode at T_1 excl.
Fergusson	1989	Pop.	1052	100	20–45	1	Sx	Past yr	EPI	24	Cont.	$r = 0.44^{ng}$	0.98	No	
Levenson	1988	Pop.	1324	0	40–98	10	Sx	Past 3 mo.	EPI	9	Cont.	$r = 0.39$[a]	0.85	No	
Horwood	1986	Pop.	1027	100	20–45	1	Sx	Past yr	EPI	24	Cont.	$r = 0.54^{ng}$	1.28	No	
Substance abuse (Including alcohol, illicit drugs, and tobacco)															
Hakulinen	2015a	Pop.	46 160	54	15–104, M = 50	5.5	Sx	Alcohol, past 5.5 yr	(9)	15	S.D.	OR = 1.07[a]	0.02	No	
Hakulinen	2015c	Pop.	52 684	46	15–104, M = 51	5.5	Sx	Smoking initiation	(9)	20	S.D.	$OR = 1.02^{ns}$	0.00	No	
								Smoking relapse				OR = 1.16	0.04	No	
Newton-Howes	2015	Pop.	903	Nsc.	14	10 (10)	Dx	Alcohol dep.	EPI	30	S.D.	$OR = 1.07^{ns}$	0.02	No	
												$OR = 1.02^{ns}$	0.01	Yes	Adj. for childhood mental health Sx and sexual/ physical abuse, among others
							Dx	Illicit drug dep.				$OR = 1.04^{ns}$	0.01	No	
												$OR = 1.05^{ns}$	0.01	Yes	Adj. for childhood mental health problems and sexual/physical abuse, among others
Lee	2015	Pop.	465	47	M = 21 (0.9)	4	Sx	Problem drinking Alcohol	NEO-FFI	60	Cont.	No effect	0.00	Yes	Adjusted for problem drinking at all waves
						8							0.00	Yes	Adjusted for problem drinking at all waves
						13							0.00	Yes	Adjusted for problem drinking at all waves

Table 1 (*cont.*)

First-named author	Pub. year	Sample	Size	♀ (%)	Age (range and mean (S.D.) at T_1)	T_1/T_2 (yr)		Outcome variable	N scale	Cat.	Comp.	Effect sizes study outcome	*d*'s	Adjustment for baseline (T_1) psychopathology	
Zvolensky	2015	Pop.	2101	Nsc		9	Sx	Smoking	MIDI	16	Cont.	OR = 1.3[a]^S.D.	0.05	No	
												OR = 1.1[a]^S.D.	0.02	Yes	Adj. for depression at T_1
												OR = 1.2[a]^S.D.	0.03	Yes	Adj. for anxiety at T_1
												OR = 1.2[a]^S.D.	0.03	Yes	Adj. for alcohol or drug use problem at T_1
Munafo	2007	Pop.	3562	Nsc	M = 16	37	Sx	Smoking	MPI	12	6 cat.	OR = 1.07[a]	0.02	No	
							Sx	Heavy smoker				OR = 1.14[d]	0.03	No	
Schmidt	2007	Pop.[14]	404	61	M = 19 (4)	2	Dx	Alcohol, past 2 yr	STPI-Trait	60	Cont.	$r = -0.01^{ns}$	−0.02	Yes	Ss with psychiatric Sx/Dx past 12 mo. excl. at T_1
Grekin	2006	Pop.	3720	54	M = 18	2	Sx	Alc., past 3 mo.	NEO-FFI	60	Cont.	$r = 0.07^{c}$	0.14	No	
							Sx	Drug, past 3 mo.			Cont.	$r = 0.06^{c}$	0.12	No	
							Sx	Tobacco, past yr			Cont.	$r = 0.12^{c}$	0.24	No	
Kendler	2006	Twins	2935	0	M = ~33 (9)	4	Dx	Past yr	EPI	5	Cont.	SPRC[ns].	0.00	Yes	Adj. for e.g. CD, early onset anxiety
De Graaf	2004	Pop.	2869	53	M = 42 (12)	3	Dx	Past 3 yr	GNS	14	*v.* Ctr.	OR = 1.09[d]	0.05	Yes	Adj. for Ss with history of mental disorders excl. at T_1
Neeleman	2004	Pop.	3625	53	18–65, M = 42 (12)	3	Dx	Past 2 yr	EPI	28	Cont.	OR = 1.6	0.28	No	
Goodwin	2003	Pop./CC	961	50	M = 14	7	Dx	Past 3 yr	EPI	2 (3)	2 *v.* 1	Rates (%)[ng]	0.07	No	
De Graaf	2002	Pop.	5618	50	18–64	1	Dx	Past yr	GNS	2 (4)	2 *v.* 1	OR = 1.40[d]	0.20	No	
							Dx	Past yr			2 *v.* 1	OR = 1.38[ns]	0.20	Yes	Adj. for Sx mood and anxiety at T_1
Sher	2000	Pop.	457	50	M = 18	1	Dx	Any substance abuse, past yr	EPQ	30		$r = 0.24^{a}$	0.55	No	
						7						$r = 0.17^{d}$	0.35	No	
						1	Dx	Alcohol abuse, past yr				$r = 0.22^{a}$	0.45	No	
						7						$r = 0.13^{d}$	0.26	No	
						1	Dx	Alcohol dependent, past yr				$r = 0.17^{a}$	0.35	No	
						7						$r = 0.12^{d}$	0.24	No	
						1	Dx	Other drugs, past yr				$r = 0.16^{a}$	0.32	No	
						7						$r = 0.10^{d}$	0.20	No	
						1	Dx	Tobacco dependent, past yr				$r = 0.15^{a}$	0.31	No	
						7						$r = 0.14^{d}$	0.28	No	

Krueger	1999	Pop./CC	961	50	M = 18	3	Dx	Past yr	MPQ NE	Z	Cont.	OR = 1.58[c]	0.28	Yes	Adj. for Sx Substance dependence disorder at T_1
							Sx	Past yr			Cont.	$\beta = 0.09$	0.28	Yes	Adj. for Sx Substance dependence disorder at T_1
Heath	1997	Twins	4974	63	27–90, M = 44	10	Dx	Alcohol ♀, LT	EPQ	2 (6)	2 *v.* 1	OR = 1.55[d]	0.27	Yes	Adj. for LT Dx axis 1 at T_1
							Dx	Alcohol ♂, LT			2 *v.* 1	OR = 1.87[d]	0.38	Yes	Adj. for LT Dx axis 1 at T_1
Caspi	1996	CC	1037	48	M = 3	18	Sx	Alcohol, past yr	BRIC	2 (2)	*v.* Ctr.	OR = 1.8[ns]	0.36	No	
Krueger	1996	Pop.	897	48	M = 18	3	Sx	Past yr	MPQ NE	49	Cont.	$r = 0.36$[c]	0.77	No	
Thought disorders (Including psychosis, bipolar disorder, and schizophrenia)															
Bogren	2010	Pop.	3215	49	$M_d = 33$	40	Dx	Psychosis (non-affective and affective)	(7)	52	Cont.	HR = 2.84[a]		No	Adj. for age and sex
												HR = 2.38[c]		Yes	Adj. for T_1 paranoid-schizotypal and tired-distracted Sx
			2503	48	$M_d = 34$	50	Dx		(7)	52	Cont.	HR = 2.27[c]		No	Adj. for age and sex
												HR = 2.31[c]		Yes	Adj. for T_1 paranoid-schizotypal and tired-distracted Sx
Lönnqvist	2009	Pop.	213 443	0	M = 20 (1.3)	14.1	Dx	Schizophrenia, LT	MMPI	Nsc.	Cont.	OR = 1.40	0.09	No	
												OR = 1.26	0.06	No	Adj. for intellectual performance, age at testing
							Dx	Bipolar, LT				OR = 1.19	0.05	No	
												OR = 1.15	0.04	No	Adj. for intellectual performance, age at testing
							Dx	Other psychoses				OR = 1.32	0.07	No	
												OR = 1.19	0.05	No	Adj. for intellectual performance, age at testing
Krabbendam	2005	Pop.	4848	Nsc	18–64	3	Sx	Psychotic-like	GNS	14	Cont.	OR = 1.16[a]	0.04	No	
											Cont.	OR = 1.20[a]	0.05	Yes	Adj. for gender, education, any psychiatric Dx lifetime
											3 *v.* 1	OR = 3.89[a]	0.36	No	
Goodwin	2003	Pop./CC	961	50	M = 14	4	Sx	Psychotic-like	EPI	4	4 *v.* 1	IRR = 2.9[a]		No	
												IRR = 1.8[a]		Yes	Adj. for childhood factors and mental disorders
						7						IRR = 2.4[a]		No	
												IRR = 1.5[a]		Yes	Adj. for childhood factors and mental disorders

Table 1 (*cont.*)

First-named author	Pub. year	Sample	Size	♀ (%)	Age (range and mean (s.d.) at T_1)	T_1/T_2 (yr)		Outcome variable	N scale	Cat.	Comp.	Effect sizes study outcome	*d's*	Adjustment for baseline (T_1) psychopathology	
Krabbendam	2002	Pop.	3929	53	18–64, M = 42 (12)	3	Dx	Psychosis (na.def.)	GNS	28	Cont.	OR = 1.20[a]	0.05	No	
								Psychosis (br.def.)				OR = 1.16[a]	0.04	No	
												OR = 1.16[a]	0.04	Yes	Adj. for T_1 level of anxiety and depression and self-esteem
												OR = 1.20[a]	0.05	Yes	Adj. for T_1 lifetime Dx, marital and employment status, age, sex, education, urbanicity, minority status.
Van Os	2001	Pop.	5362	48	M = 16	27	Dx	Schizophrenia	MPI	12	Cont.	OR = 1.93	0.17	No	
												OR = 1.83	0.16	Yes	Adj. for PSE neurotic/ affective Sx, PSF Anx./ Dep. Sx at age 36 (after 20 years, but 16 years before outcome).
												OR = 1.41	0.09	No	After adj. for selective attrition for Neuroticism and Ext.
Non-specific mental distress															
Mezquita	2015	Pop.	241	66	18–29, M = 21	5	Sx	Internalizing	NEO-FFI	60	Cont.	$\beta = 0.58$[a]	1.57	No2	Adj. for externalizing spectrum at T_2
								Externalizing				$\beta = 0.00$[ns]	0.00	No	Adj. for internalizing spectrum at T_2
Johansson	2014	Pop.	800	Nsc.	38–54	6	Sx	LT	EPI	24	Cont.	OR = 1.19	0.05	No	
						12						OR = 1.20	0.05	No	
						32						OR = 1.21	0.05	No	
						38						OR = 1.13	0.03	No	
Beard	2007	Pop.	968	57	18–85	1	Dx	Any Dx, past yr	EPQ	24	*v.* Ctr.	OR = 1.21[a]	0.12	Yes	Ss with any mental Dx (ICD-10) at T_1 excl.
Neeleman	2004	Pop.	3625	53	18–65, M = 42 (12)	3	Dx	Any psychiatric, past 2 yr	EPI	Z	Cont.	OR = 2.2[a]	0.48	No	
Kuh	2002	Pop.	1086	100	M = 15	32	Sx	Past yr	MPI	12	Cont.	$\beta = 0.27$[a]	0.66	Yes	Adj. for adolescent antisocial and anxious Sx

Tyssen	2001	Pop.	396	57	24–49, M = 28 (3)	3.6	Sx	Past yr	BCI-TV	9	Cont.	OR = 1.3[a]	0.16	No	
							Sx	Past yr				OR = 1.0[ns]	0.00	Yes	Adj. for previous mental health problems
Wetherell	2001	Pop.	1031	57	29–95, M = 61 (13)	6	Sx	Psych.som. past wk	STPI-Trait	50	Cont.	r = 0.42[ng]	1.01	No	
Van Os	1999	Pop.	2415	50	M = 16	27	Sx	Past yr	MPI	12	Cont.	β = 3.8[c]	2.07	Yes	Adj. for mental health at T_1 and Ss with schizophrenia were excluded (n = 30)
Ormel	1991	Pop.	296	47	M = 39 (12)	7	Sx	Psych.dis. past mo.	ABV	8	Cont.	r = 0.55[d]	1.32	No	

ABI, Amsterdam Biographic Inventory; ABV, Amsterdam Biographic Questionnaire; Adj, adjusted; Anx, Anxiety; BCI-TV, Basic Character Inventory's trait-vulnerability scale; BFI, Big Five Inventory; BIS, behavioral inhibition system; br.def, broadly defined; BRIC, Behavioral Ratings Inhibited child; cat., categories (i.e. range of the neuroticism scale, e.g. 4 items with a 5-point likert scale is 20 categories); CC, case control; CD, conduct disorder; Comp., comparison (the number of neuroticism levels that were distinguished in the statistical test, e.g. high *v.* low); Cont, continuous; Dep., Depression; DPI, Dutch Personality Inventory; DPQ, Dutch Personality Questionnaire; DS14, Type D-personality questionnaire; Dx, diagnosis; EPI, Eysenck Personality Inventory; EPI-N, Neuroticism scale of the EPI; EPQ, Eysenck Personality Questionnaire; EPQ-R, Revised EPQ; ES, Emotional Stability; excl, excluded; Ext., Extraversion; FFI, Five Factor Inventory; FPI, Freiburg Personality Inventory; GNS, Groningen Neuroticism Scale; HR, hazard ratio; IR, interquartile range; IRR, incident rate ratio; LT, life time; M, mean; M_d, median; MD, major depression; mo., month; Mix, mixed; MPI, Maudsley Personality Inventory; MPQ, Multidimensional Personality Questionnaire; na, not available; N, Neuroticism; na.def., narrowly defined; NE, Negative Emotionality; NEO-FFI, NEO-Five Factor Inventory; Nsc, Nescio (I do not know); OR, odds ratio; PHRC, proportional hazards regression coefficients; Pop., population cohort; Psych.dis, psychological distress; Psych.som, psychological somatization; PSE, Present State Examination; PSF, Psychiatric Symptom Frequency; PTSD, Post-traumatic stress disorder; *r*, correlation coefficient; rec., recurrent; RR, relative risk; S.D., standard deviation; Soc.ph, social phobia; SPRC, standardized partial regression coefficients or path coefficients; ss, subjects; STPI-Trait, State Trait Personality Inventory's Trait-Anxiety measure; Suicidal id., suicidal ideation; Suicidal att., suicidal attempt; Sx, symptoms; T, *t* score (mean=50, S.D.=10) or *t* test; *v.* Ctr, *v.* controls (without Dx); W, Wilcoxon test; wk, weeks; yr, year; Z, *z* score (mean=0, S.D.=1).

Notes: (1) Three waves of neuroticism form one latent variable thus the time-span between neuroticism and mental health reflects does not reflect the given follow-up time; (2) The regression equation contained a dummy variable representing inhibited children (*v.* controls); (3) Neuroticism dichotomized at mean score; (4) Neuroticism dichotomized so that ⅓ received an unfavorable rating; (5) Neuroticism dichotomized at its median score [e.g. De Graaf *et al.* 2004, ⩾5 with scale maximum of 15 (n= 800, or 58%)]; (6) Neuroticism dichotomized above 75th percentile; (7) The Lundby 'nervouse-tense' cluster resulted from a mix of observable behaviors rated by psychiatrists (tense, restless, insecure, strained, vegetative, lachrymose, see Hagnell, 1966) and structured questions (worried, nervous, tense, susceptible to adversity, cries easily, difficult to collect one's thought); (8) Two groups were derived with latent growth analysis and growth mixture modeling, a moderate class (77%, mean intercept= 2.1) and a high class (23%, mean intercept= 2.8), see Aldinger *et al.* (2014); (9) In these analyses ten studies were pooled, and each sample used different instruments, but with a minimum of 15 items each (Hakulinen *et al.* 2015*a*–*c*); (10) The outcomes were measured at age 21, 25, and 30 years, or 4–16 years after baseline, and summarized, with 10 years follow-up as the mean span.

[a]$p < 0.001$, [b]$p < 0.005$, [c]$p < 0.01$, [d]$p < 0.05$, [ns], non-significant, [ng], significance not given.

Table 2. *A summary of predictive effects of neuroticism as sample-size weighted effect-sizes d over K studies and N participants*

		Symptoms				Diagnosis			
Disorder		*K*	*N*	*d*	s.d.*d*	*K*	*N*	*d*	s.d.*d*
Anxiety	Unadjusted	9	10 130	0.68	0.46	4	7748	0.48	0.57
	Adjusted	6	6104	0.38	0.32	9	14 646	0.18	0.14
Depression	Unadjusted	11	13 379	0.74	0.37	12	39 161	0.50	0.36
	Adjusted	4	2 876	0.33	0.14	16	49 585	0.33	0.39
Substance abuse	Unadjusted	7	110 161	0.03	0.02	5	11 564	0.20	0.24
	Adjusted	3	3527	0.09	0.12	8	19 068	0.17	0.26
Thought disorders	Unadjusted	1	4848	0.04	0.00	3	222 734	0.07	0.11
	Adjusted	1	4848	0.05	0.00	2	9291	0.11	0.11
Non-specific mental distress	Unadjusted	5	2764	0.69	0.74	1	3625	0.48	0.00
	Adjusted	3	4804	0.27	0.24	1	968	0.12	0.00

K, Number of studies; *N*, pooled sample size; *d*, sample size-weighted average effect size; s.d.*d*, sample size-weighted standard deviation of effect sizes. Details can be found in the Method section.

Table 3. *A summary of the prospective associations between neuroticism and symptoms/diagnosis as sample-size weighted effect sizes d over K studies and N participants, for short v. long time intervals*

		Symptoms				Diagnosis			
	Years	*K*	*N*	*d*	s.d.d	*K*	*N*	*d*	s.d.*d*
Unadjusted		33	141 282	0.15	0.11	25	284 832	0.15	0.26
Short interval	<4	13	18 684	0.47	0.32	12	49 407	0.42	0.28
Long interval	⩾4	20	122 598	0.11	0.08	14	235 882	0.10	0.23
Adjusted		17	22 159	0.23	0.20	36	93 559	0.25	0.35
Short interval	<4	13	15 185	0.25	0.21	22	49 140	0.24	0.30
Long interval	⩾4	4	6974	0.20	0.21	14	44 419	0.27	0.39

K, Number of studies; *N*, pooled sample size; *d*, sample size-weighted average effect size; s.d.*d*, sample size-weighted standard deviation of effect sizes. The division of studies over short interval (<4 years) and long interval (⩾4 years) was based on the median follow-up time, which was three years for dichotomous measures, four years for continuous measures, and four years overall (i.e. across all 111 estimates). When studies reported estimates for both short and long intervals both were included in the short *v.* long interval estimations, but only one was included in the summary estimates. Unadjusted estimates are the direct associations between neuroticism and outcome. Adjusted estimates provide the prospective associations adjusted for symptoms/diagnosis at baseline (see Method section).

(extraversion/conscientiousness/agreeableness/openness), and although reported in Table 1 (e.g. Hakulinen *et al.* 2015*b*), these estimates were excluded from the meta-analytic estimates. Furthermore, our study included two meta-analysis of prospective cohort studies of the association between neuroticism and depressive symptoms and substance abuse (Hakulinen *et al.* 2015*a*, *b*).

Measurement of personality

Neuroticism was assessed with a variety of standardized questionnaire instruments, including the NEO Five-Factor Inventory (12 items), the revised Eysenck Personality Questionnaire (12 items), the Amsterdam Biographic Interview (14 items), Basic Character Inventory's trait-vulnerability scale (9 items), the Dutch Personality Inventory (15 items), Dutch Personality Questionnaire (25 items), Groningen Neuroticism Scales (14 items), Maudsley Personality Inventory (12 items), the Freiburg Personality Inventory (9 items), and the State Trait Personality Inventory trait-anxiety measure (10 items). These were all developed to measure negative emotionality, neuroticism, emotional stability, trait-anxiety, and/or trait-vulnerability.

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Table 4. *A summary of the standardized drop in Cohen d per year follow-up interval between neuroticism and symptoms/diagnosis as sample-sized weighted effect sizes d over K studies and N participants*

	Symptoms							Diagnosis						
	Unadjusted				Adjusted			Unadjusted				Adjusted		
Cluster	*K*	*N*	*d*	S.D.*d*	*K*	*N*	*d*	S.D.*d*	*K*	*N*	*d*	S.D.*d*	*K*	*N*	*d*	S.D.*d*
Total	33	141 282	0.002	0.003	17	22 159	0.005	0.005	25	284 832	0.002	0.003	36	93 559	0.003	0.006
Anxiety	9	10 130	0.021	0.023	6	6104	0.027	0.022	4	7748	0.095	0.156	9	14 646	0.009	0.016
Depression	11	13 379	0.032	0.042	4	2876	0.044	0.043	12	39 161	0.018	0.023	16	49 585	0.008	0.014
Substance abuse	7	110 161	0.001	0.001	3	3527	0.009	0.014	5	11 564	0.026	0.042	8	19 068	0.009	0.020
Thought disorders	1	4848	0.017	0.000	1	4848	0.017	0.000	3	222 734	0.002	0.003	2	9291	0.005	0.002
Non-specific distress	5	2764	0.023	0.025	3	4804	0.003	0.003	1	3625	0.160	0.000	1	968	0.120	0.000

K, Number of studies; *N*, pooled sample size; *d*, sample size-weighted average effect size; S.D.*d*, sample size-weighted standard deviation of effect sizes.

Prospective associations

The large S.D.s around the averages shown in Table 2, indicate that the pool of studies is quite heterogeneous. Nonetheless, the data clearly support the ability of neuroticism to predict all symptoms and diagnoses under study. The estimated unadjusted prospective associations between neuroticism and symptom measures were comparable for anxiety, depression, and non-specific mental distress, and all quite large (about $d = 0.70$). When these estimates were adjusted for baseline symptoms, the effect size reduced most for non-specific mental distress (−60%), followed by depression (−55%), and anxiety (−45%). The unadjusted prospective associations between neuroticism and diagnosis for anxiety or depressive disorder were slightly lower (about $d = 0.50$), but the trends were similar to the effects seen for symptom scores, as well as the reduction of the association after adjustment for baseline measures. Hence, regarding internalizing symptoms and diagnosed disorders, and non-specific mental distress, unadjusted associations were about twice the size of the adjusted effects, but adjusted effects remained significant.

The estimated unadjusted prospective association between neuroticism and substance use symptoms was considerably weaker (below $d = 0.10$), even though estimates for diagnosis had a moderate effect size ($d = 0.20$). Notably, the latter effect became only little attenuated after adjustment for baseline symptoms (−15%). Although some adjusted estimates appear to be *larger* than the unadjusted estimates, these differences were small ($d \leqslant 0.04$), and are probably insignificant. In sum, adjusted effects were reduced by half for internalizing problems, but not for substance abuse and thought disorders.

Temporal stability

A summary of the prospective associations between neuroticism and CMDs is presented in Table 3. Categorization of the follow-up interval over short and long intervals was based on the median study length (short was ⩽4 years, long was >4 years). Overall the unadjusted prospective associations were identical for studies of symptoms and diagnoses (both $d = 0.15$). However, the unadjusted short-term association was about four times larger than the long-term association, for both symptoms and diagnoses. This indicates a substantial decay of the association with increasing time intervals.

The adjusted effects, on the other hand, were comparable for symptoms and diagnoses (both about $d = 0.25$). The adjusted prospective associations for symptoms were only slightly larger over the short follow-up interval than over the long follow-up interval, while

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for diagnosis the long-term estimate was even slightly stronger than the short term effect (yet with $d = 0.03$ the difference was negligible). Note that all adjusted effects were of moderate effect size, also the long-term associations. So, after adjustment for concomitant problems at baseline and/or psychiatric history, there was little difference between the short and long follow-up interval. This result can be interpreted as concomitant problems at baseline masking the long-term stability of the neuroticism effect on the internalizing CMDs.

Disorder types

The scarcity of studies did not allow for a systematic comparison of prospective associations between neuroticism and each disorder separately. However, the studies given in Table 1 indicate that among the anxiety disorders, large prospective associations were observed for panic disorder, GAD, social phobia, and PTSD, respectively. For depressive disorders the prospective associations were observed for major depressive disorder, minor depressive disorder, and suicidal ideation. Prospective associations between neuroticism and substance use disorders, although small, were observed for smoking and alcohol or illicit drug abuse. Regarding the thought disorders, small prospective associations were observed for schizophrenia and psychosis, but no effect for bipolar disorders.

Post-hoc

The prospective association between neuroticism and the onset of CMDs differs across disorders (e.g. internalizing *v.* externalizing). Because so little data was available for each specific disorder cluster we combined all disorders when calculating the short-term *v.* long-term effects, to focus on broad and general conclusions. *Post-hoc* we also calculated the standardized drop in *d* values per year for each specific cluster, dividing the effect sizes by the number of years between assessments, as reported in Table 4. This dimensional reduction in *d* per follow-up year was rather small, and largely comparable across the disorders, in support of neuroticism as a robust prospective marker for the development of psychopathology.

Discussion

In this paper precise estimates are given of the predictive power of neuroticism for the development of psychopathology, as well as effects for individual disorders. Three key observations were found. First, the unadjusted prospective associations between neuroticism and internalizing symptom measures or diagnosis were quite large ($d = 0.48$ to 0.74, i.e. anxiety, depression, non-specific distress). An adjustment of these estimates for baseline symptoms reduced the effect size by half, but the residual associations remained substantial ($d = 0.12$–0.38). Second, the unadjusted prospective associations between neuroticism and substance use symptoms and thought disorder symptoms were considerably weaker ($d = 0.03$–0.20), but importantly, adjustment for baseline problems did not attenuate these effects ($d = 0.05$–0.17). Third, the adjusted prospective associations between neuroticism and psychopathology remained stable over long follow-up intervals (on average $d = 0.25$, with little decay per year), bolstering our understanding of neuroticism as an independent and robust vulnerability marker for later developing psychopathology.

Over the past three decades theorists proposed a set of theoretical models to explain the complex longitudinal interrelations between personality and psychopathology and to utilize their conceptual differences to infer hypotheses about mechanisms that can account for their (co-)development (e.g. Tackett, 2006; Ormel *et al.* 2013; Durbin & Hicks, 2014). The present study was designed to test inferences from the vulnerability model, which holds that neuroticism sets in motion processes that lead to CMDs. Next to the vulnerability and common cause models (same processes), also the spectrum model (CMDs are extreme levels of neuroticism) and pathoplasty/exacerbation models (independent etiology and onset, but neuroticism influences the course, severity, presentation, or prognosis of CMDs) can account for different aspects of the prospective neuroticism-CMD association, or for different symptom clusters. Different people may even achieve the same end (function) by different means (mechanisms). Next we discuss implications of present findings for each model.

Vulnerability perspective

The vulnerability model postulates that high neuroticism causes the development of CMDs, either 'directly', or by eliciting other risk factors. Examples of direct processes are the cognitive vulnerabilities that are associated with neuroticism, including a pessimistic inferential style (negative attention bias and information recall), rumination, increased reactivity (psychological/physiological), ineffective coping/dysfunctional attitudes, intolerance of uncertainty/anxiety sensitivity, and fear of negative evaluation (Chan *et al.* 2007; Servaas *et al.* 2013; Barlow *et al.* 2014; Hong & Cheung, 2014; Laceulle *et al.* 2015). Examples of indirect vulnerabilities is high neuroticism increasing exposure to stressful life events (Kendler *et al.* 2003; Jeronimus *et al.* 2014; Riese *et al.* 2014), and experiencing three times more interpersonal stressful events (Fergusson & Horwood, 1987; Poulton & Andrews, 1992; van Os & Jones, 1999; Specht *et al.* 2011).

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In our test of the vulnerability model we evaluated the ability of neuroticism to predict the onset of a given disorder after adjusting for the symptoms present at baseline and psychiatric history. This was done to adjust (*a*) for state effects in neuroticism (Ormel *et al.* 2012; Jeronimus *et al.* 2013), which are evidenced by our results, and (*b*) scars that earlier episodes may have left in terms of heightened neuroticism levels (Wichers *et al.* 2010; Klein *et al.* 2011; Ormel *et al.* 2013). Our unadjusted estimate of the prospective association between neuroticism and internalizing disorders ($d = 0.60$) was substantially lower than the meta-analytic estimate of the cross-sectional association by Kotov *et al.* (2010, $d = 1.65$). The cross-sectional estimate was adjusted for unreliability of the included neuroticism scales (as indexed by Cronbach's $\alpha = 0.82$), which amplified this difference.

The current paper showed that half of the prospective association between neuroticism and internalizing problems was due to relationships with mental state (baseline problems and psychiatric history). These state effects, in which neuroticism levels are temporarily heightened by acute internalizing problems, are temporary, and generally disappear after the episode has remitted (Ormel *et al.* 2004, 2013; Jeronimus *et al.* 2013). A moderate but robust residual prospective association with internalizing problems remained ($d = 0.30$ to 0.40), in line with the vulnerability model. But not inconsistent with most other models, including common causes, provided that personality develops earlier than a disorder, even without any direct causal connections. Importantly, this control for baseline problems is a conservative test that takes legitimate variance out of neuroticism, especially from the facet traits anxiety and depression (Riese *et al.* 2016).

For substance abuse and thought disorders the differences between the cross-sectional estimates by Kotov *et al.* ($d = 0.97$) and our unadjusted prospective associations ($d = 0.20$) were even slightly larger. Because baseline problems and psychiatric history did not attenuate the prospective association between neuroticism and substance abuse and thought disorders, neuroticism proves a robust vulnerability factor for their development without much conceptual overlap. Note that the small effect sizes indicate that high neuroticism only plays a modest role in their – undoubtedly multifactorial – etiology, or only for some people.

All adjusted prospective associations between neuroticism and the CMDs were moderate in magnitude and virtually equivalent for the short and long follow-up interval, which indicates that the risk effect of neuroticism did not weaken over time, which is strong support for the vulnerability model. Our results align with previously articulated differences between internalizing (anxiety, depression, non-specific mental distress) and externalizing spectra (substance abuse) of psychopathology and thought disorders (Krueger *et al.* 1996; Krueger & Tackett, 2003; Kotov *et al.* 2010), and indicate that neuroticism is close to the origins of their causal pathways, via vulnerability and common causes. These observations support the argument that neuroticism forms the core of a 'general factor of psychopathology' characterized by negative-emotional dysregulation (distress) and thought disorders (Lahey *et al.* 2011; Caspi *et al.* 2013; Barlow *et al.* 2014; Kotov *et al.* 2015; Laceulle *et al.* 2014; Pettersson *et al.* 2016).

Common causes

Although our results can be interpreted as evidence for the vulnerability model, they do not falsify alternative models, including the common cause model. The common cause model assumes that neuroticism and mental disorder are dynamic phenomena that can change together in response to external forces and developmental pressures such that both become causally intertwined (Ormel *et al.* 2013; Durbin & Hicks, 2014). Only mediation data can disentangle the vulnerability model from common causes, and this was outside the scope of our study. The common cause model is supported by the substantial genetic overlap between neuroticism and CMDs (e.g. Hettema *et al.* 2006), although this does not falsify the spectrum model.

Spectrum perspective

The spectrum perspective holds that neuroticism shades continuously into manifestations of psychopathology at the high end of the distribution, and both share their etiological core (e.g. Krueger & Tackett, 2003; Ormel *et al.* 2013). Importantly, the spectrum model eliminates all conceptual distinctions between neuroticism and CMDs as they tap into the same construct. It follows that (*a*) the correlation between the measures should approach the reliabilities of the measures and (*b*) the measures should show comparable patterns of external correlates (Durbin & Hicks, 2014); which does not hold for neuroticism (Ormel *et al.* 2013). Moreover, the spectrum model implies that psychopathology is simply a label given to extreme scores on a trait, and thus no cases of a disorder will be found below the threshold while all people above the threshold will be cases. The evidence that most people with high neuroticism scores do not experience psychopathology, whereas some people with low neuroticism scores do, contradicts this implication. Further difficulty for the spectrum account is that scoring high on neuroticism prospectively predicts lower romantic and occupational success, subjective wellbeing, longevity, and higher frequency of mental

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and general health service use (Hills & Argyle, 2001; Ozer & Benet-Martínez, 2006; Roberts *et al.* 2007; Steel *et al.* 2008; Lahey, 2009), among others. The spectrum model cannot account for individual differences in personal resources and contextual factors that may result in the eventual non-expression of mental health problems (Duckworth *et al.* 2005; van der Krieke *et al.* 2015), or the natural course and dynamics of personality development – among which a normative decrease in neuroticism of $d = 0.77$ towards middle age (see Roberts *et al.* 2006), nor the bidirectional relationships between neuroticism and symptoms (Ormel *et al.* 2013, 2014).

Co-development model

Recent reviews of etiological models of personality-psychopathology associations concluded that (*a*) the vulnerability, common-cause, and spectrum models are imprecise, which impedes the formulation of critical tests to distinguish them, (*b*) the processes are not mutually exclusive and could co-occur within the same individual or be more relevant for some people than others (Tackett *et al.* 2006; Ormel *et al.* 2013; Durbin & Hicks, 2014), and (*c*) the models lack a dynamic lifespan perspective in which psychopathology can be conceived of as deviation from normative developmental trends (see Cicchetti, 1993). Additionally, processes that link traits and disorders may also vary across developmental periods (Tackett, 2006; Durbin & Hicks, 2014), if only due to different developmental tasks, goals, needs, relationships, developmental contexts, and lifespan personality development (e.g. Roberts *et al.* 2006; John *et al.* 2008).

Durbin & Hicks (2014) therefore proposed a personality-psychopathology co-development model that incorporates the vulnerability, common causes, pathoplasticity, and exacerbation mechanisms, and accounts for lifespan personality development and dynamic processes via which high neuroticism shapes the ways in which people structure and interact with the world around them to explain individual differences in life experiences and transitions and their impact (e.g. Kendler *et al.* 2003; Jeronimus *et al.* 2014). In line with the co-development perspective the adjusted prospective association between high neuroticism and internalizing problems can be interpreted as an independent vulnerability effect for the development of psychopathology (neuroticism→Sx/Dx) while the overlap at baseline may reflect state effects, common causes, or symptoms intervening between neuroticism and diagnosis (neuroticism→Sx→Dx). Recall that our adjusted estimate, controlling for baseline symptoms, also removes true predictive variance from neuroticism. Finally, a transition to and from a psychiatric disorder may proceed as a categorical sudden transition for some people but in terms of a smooth process of change in others (Borsboom *et al.* 2016). Nonetheless, a salient difference between the co-development and spectrum models remains that the former retains conceptual distinctions between neuroticism and disorder.

Future studies

Our understanding of the etiology of psychopathology and early detection and intervention of CMD is unlikely to expand via additional studies of cross-sectional neuroticism–CMD correlations. To further clarify different perspectives we need a deeper understanding of the boundaries between neuroticism and psychopathology, such as function *v.* dysfunction (DSM-5), or trait descriptors as self-identity in semantic memory and mental symptoms as episodic memories (Ormel *et al.* 2014). Also questionnaires without item overlap are needed (Ormel *et al.* 2013). And the inclusion of potential common causes and external correlates of neuroticism and CMDs in longitudinal designs.

At least as important may be the study of individual differences in their individual developmental context and developmentally informed mechanisms underlying the independent prospective association between neuroticism and CMDs. For example, mediation of the vulnerability effect by cognitive biases inherent to neuroticism (e.g. Laceulle *et al.* 2015), or moderation of effects by contextual and sociodemographic factors, ethnicity, or other personality traits. Evidence suggests that CMDs share a pleiotropic genetic susceptibility that is manifest via dysfunction in neurobiological systems, while different interactions with one's environment somehow differentiate between specific disorder outcomes (e.g. Lahey *et al.* 2011). This underscores the need for research designs that can account for both inter-individual and intra-individual variance, such as experience sampling, which may help answer questions about processes that underlie the neuroticism-psychopathology link (Molenaar, 2008; van der Krieke *et al.* 2015).

Finally, studies could improve by accounting for more hierarchical aspects of the personality and psychopathology, which may also increase our understanding of causal processes. Neuroticism comprises multiple lower-order facet traits, including anxiety, depression, angry-hostility, self-consciousness, impulsiveness and vulnerability (Costa & McCrae, 2006). The facets of neuroticism differ in their underlying biology, developmental trends, impact on impairment, and risk factors (Jeronimus, 2015). But also specific CMD symptoms including sadness, insomnia, concentration problems, or suicidal ideation, associate with differences in external outcomes, including social

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relationships, work, and subjective wellbeing (e.g. Fried *et al.* 2014; Fried & Nesse, 2015). Research at this level of granularity may therefore also advance the development of personalized prevention and treatment strategies (Borsboom & Cramer, 2013; van der Krieke *et al.* 2015), which can impact both high neuroticism and CMD episodes (Barlow & Nock, 2009; Lahey, 2009; Ormel *et al.* 2013).

Implications

Our results clearly show independent prospective associations between high neuroticism and manifestations of psychopathology and mental distress. Extant work indicated that neuroticism levels are more malleable than researchers long believed, including the potential of a benign transactional cycle between positive contextual changes and decreases in neuroticism (Lüdtke *et al.* 2011; Kuepper *et al.* 2012; Jeronimus *et al.* 2013, 2014). Multiple studies showed the feasibility of 'treating' high neuroticism or specific neuroticism facets (Jorm, 1989; Zinbarg *et al.* 2008; Glinski & Page, 2010; Martin *et al.* 2014; Hudson & Fraley, 2015), both via psychological and pharmacological interventions ($d = 0.40$–1.25). Therapists could thus focus on prevention strategies that target the vulnerability for mental disorders inherent in neuroticism, rather than only treating the subsequent manifestations of those disorders (Lahey, 2009; Cuijpers *et al.* 2010; Ormel *et al.* 2013; Barlow *et al.* 2014). This could be implemented as aftercare of psychological counseling. From a dynamic system perspective the most promising and rigorous measure to improve future mental health might be to target the developing personality structure from primary school age onwards to smoothen the mental biases and developing belief systems that otherwise could develop into high neuroticism throughout adolescence, to alleviate the observed vulnerability for the co-development of mental disorders associated with high neuroticism.

Limitations

The present work extends earlier work on neuroticism-psychopathology associations to a critical evaluation of the prospective associations to shed light on the vulnerability hypothesis of psychopathology. Other broad personality traits have often been linked to CMDs as well, namely, low Conscientiousness, and to a lesser extent, Extraversion, although their association with CMDs is not as strong and pervasive as that of neuroticism (e.g. Clark, 2005; Khan *et al.* 2005; Malouff *et al.* 2005; Fanous *et al.* 2007; Kotov *et al.* 2010; Klein *et al.* 2011; Hakulinen *et al.* 2015*a*, *b*, *c*). Analyses of these traits are outside the scope of this meta-analysis, but we believe that the implications of our findings on neuroticism are relevant for understanding the relationship between other personality traits and CMDs as well. In this meta-analysis studies that adjusted their neuroticism effects for the other personality traits were excluded. Our aim was to control for baseline symptoms and psychiatric history to establish the likely direction of causality, and adjustment for other traits does not help with that, while it changes the nature of the effect (i.e. it is not whole neuroticism that now predicts). Nonetheless, studies that included all traits supported the primacy of neuroticism (e.g. Hakulinen *et al.* 2015*a*–*c*). Finally, in this paper studies with widely different instruments were compared, and as in previous comparisons, these instruments yield different effects. For example, neuroticism as measured by instruments derived from Eysenck's tripartite taxonomy (MPI, EPI, EPQ, EPQ-R) appeared less predictive for psychopathology than the NEO scales (cf. Kotov *et al.* 2010).

In some categories in Table 3 the S.D. is larger than the mean, which reflects the substantial variability between the estimates. Arguably this is due to the different study groups, from different countries, administered with different instruments and methods. Although large S.D.s may suggest unprecise estimations (due to dispersion), this does not imply that the mean point estimate is not a good parameter. Furthermore, neuroticism's associations with symptom measures based on self-ratings are typically stronger than for diagnoses (Table 2). Diagnoses are typically based on diagnostic interviews. These differences were largest for the internalizing problems (i.e. anxiety, depression, and non-specific mental distress), but reversed for substance abuse and thought disorders. This suggests the existence of method variance, as both neuroticism and symptom measures are typically assessed with self-ratings, whereas diagnostic interviews are based on self-report in response to interviewer questions. Unfortunately, our estimation method impedes an estimate of method variance in the observed prospective associations with diagnoses. Note that in our overall effect estimates, these differences between symptoms and diagnoses disappeared (Table 3).

Conclusion

Our results indicate that high neuroticism and psychopathology are not only closely interwoven but that neuroticism is also an important prospective indicator of risk for the development of psychological disorders in the internalizing domain, especially anxiety, depression, and non-specific mental distress. Neuroticism is also a vulnerability factor for the development of substance abuse and thought disorders, although these effects are much weaker. Half of the prospective effect remained after adjustment for baseline psychopathology and psychiatric history. Particularly relevant is

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the long-term stability of the residual vulnerability effect of high neuroticism. Whereas the unadjusted short-term effect estimates were four times larger than the long-term effects (suggesting a substantial decay of the association with increasing time intervals), the adjusted short-term effect was only slightly larger than the long-term effect. Collectively, our results identify high neuroticism as a stable and significant vulnerability factor for the development of CMDs.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291716001653.

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