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Comorbid Major Depression and Generalized Anxiety Disorders in the National Comorbidity Survey follow-up

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Abstract

Background—Although generalized anxiety disorder (GAD) and major depressive episode (MDE) are known to be highly comorbid, little prospective research has examined whether these two disorders predict the subsequent first onset or persistence of the other or the extent to which other predictors explain the time-lagged associations between GAD and MDE.

Methods—Data were analyzed from the nationally representative two-wave panel sample of 5001 respondents who participated in the 1990-2 National Comorbidity Survey (NCS) and the 2001-03 NCS follow-up survey. Both surveys assessed GAD and MDE. The baseline NCS also assessed three sets of risk factors that are considered here: childhood adversities, parental history of mental-substance disorders, and respondent personality.

Results—Baseline MDE significantly predicted subsequent GAD onset but not persistence. Baseline GAD significantly predicted subsequent MDE onset and persistence. The associations of each disorder with the subsequent onset of the other attenuated with time since onset of the temporally primary disorder, but remained significant for over a decade after this onset. The risk factors predicted onset more than persistence. Meaningful variation was found in the strength and consistency of associations between risk factors and the two disorders. Controls for risk factors did not substantially reduce the net cross-lagged associations of the disorders with each other

Conclusions—The existence of differences in risk factors for GAD and MDE argues against the view that the two disorders are merely different manifestations of a single underlying internalizing syndrome or that GAD is merely a prodrome, residual, or severity marker of MDE.

Controversy has surrounded the diagnosis of generalized anxiety disorder (GAD) since its introduction into DSM-III (American Psychiatric Association, 1980). Prior to that time, GAD was conceptualized as one of the two core components of Anxiety Neurosis, the other being panic (American Psychiatric Association, 1968). Recognition that GAD and panic, while often cooccurring, are sufficiently distinct to be considered independent disorders led to their separation in DSM-III., where a diagnosis of GAD required uncontrollable and diffuse anxiety or worry that was excessive or unrealistic in relation to objective life circumstances that persisted for one month or longer in addition to a number of psycho-physiological symptoms.

Early clinical studies in clinical samples found that DSM-III GAD seldom occurred in the absence of major depression (MD) (Breslau, 1985, Breslau & Davis, 1985a), leading some to the suggestion that GAD might best be conceptualized as a prodrome, residual, or severity marker of MD (Brown *et al.*, 1998, Cloninger *et al.*, 1990, Offord *et al.*, 1994). However, this

comorbidity weakened as duration of GAD increased (Breslau & Davis, 1985b), leading the GAD duration requirement be increased to six months in DSM-III-R (American Psychiatric Association, 1987) and DSM-IV (American Psychiatric Association, 1994).

The issue of a strong association between GAD and MD was not resolved, though, with this change, as community epidemiological studies using DSM-III-R and DSM-IV criteria continued to find strong comorbidity between GAD and MD (Grant *et al.*, 2005, Kessler *et al.*, 2005, Kessler *et al.*, 1996). Attempts to explore the factor structure of comorbidity among Axis I disorders concluded that GAD and MD are both strongly related to a general "distress" factor (Krueger, 1999, Krueger *et al.*, 1998, Vollebergh *et al.*, 2001) that also includes dysthymia, PTSD, social phobia, and, in at least one analysis (Slade & Watson, 2006), neurasthenia. However, longitudinal analysis showed meaningful divergence between GAD and MD both in risk factors (Moffitt *et al.*, 2007) and in illness course (Fergusson *et al.*, 2006), arguing that more is involved than a single latent factor leading to both disorders.

The prospective evidence of somewhat different environmental risk factors for GAD and MD is consistent with the results of genetic epidemiological studies, which suggest that while the genes for GAD and MD are very similar or possibly even identical, the environmental determinants are less strongly related (Kendler, 1996, Kendler *et al.*, 2007, Kendler *et al.*, 1992, Roy *et al.*, 1995). Taken together with the prospective evidence for differential risk factors, these data suggests that, despite strong similarities that might lead them to be placed in the same diagnostic category in the upcoming revisions of the DSM and ICD systems (Watson, 2005), GAD and MD are distinct disorders. This conclusion is consistent with the results of neurobiological studies, which find numerous differences that argue against GAD and MD being the same neurobiological disorder (Martin & Nemeroff, in press). However, the body of prospective epidemiological risk factor evidence that elaborates the implications of this conclusion is thin. The current report presents prospective data that add to this body of evidence by examining patterns and risk factors for onset and persistence of GAD and MD in a nationally representative two-wave panel survey of the household population of the United States.

METHODS

Sample

Data come from the 5001 respondents who participated in the 1990-2 National Comorbidity Survey (NCS) and 2001-03 NCS follow-up survey (NCS-2). The NCS (Kessler *et al.*, 1994) was a nationally representative US survey of 8098 respondents ages 15–54 carried out between in 1990–1992. The response rate was 82.4%. Interviews were conducted by professional survey interviewers and administered in two parts. Part I, which included the core diagnostic interview, was administered to all respondents. Part II, which included additional disorders and risk factors, was administered to a probability sub-sample of 5877 respondents including all respondents ages 15–24, all others with any lifetime DSM-III-R disorder assessed in Part I, and a random sub-sample of remaining Part I respondents. The Part II sample was weighted to adjust for differential probabilities of selection and for non-response bias. Importantly for the purposes of this paper, the non-response adjustment weight was based on the results of a brief screening survey carried out in a representative sub-sample of initial survey non-respondents. Diagnostic stem questions for both MD and GAD were included in that weight, which means that adjustments were made for non-response bias based on MD and GAD. Further details about the NCS design, the non-response survey, and weighting are reported elsewhere (Kessler *et al.*, 1994).

The NCS-2 sought to trace and re-interview the Part II NCS respondents a decade after the NCS. 5463 were successfully traced, of whom 166 were deceased and 5001 re-interviewed,

for a conditional response rate of 87.6%. The unconditional response rate is 72.2% (0.876×0.824). NCS-2 respondents were assessed using an expanded version of the baseline interview that assessed onset and course of disorders between the two surveys. Relative to other baseline NCS respondents, NCS-2 respondents were significantly more likely to be female, well educated, and residents of rural areas. A propensity score adjustment weight (Rosenbaum & Rubin, 1983) corrected for these discrepancies. No difference existed between NCS-2 respondents and nonrespondents in baseline history of either major depressive episodes (MDE) ($\chi^2_1 = 0.8$, p = .39) or GAD ($\chi^2_1 = 2.1$, p = .16), although we have no way to know if subsequent onset-persistence of MDE or GAD differed for follow-up respondents versus non-respondents.

Diagnostic assessment

Lifetime DSM-III-R disorders were assessed in the baseline NCS with the WHO Composite International Diagnostic Interview (CIDI) Version 1.1 (Robins *et al.*, 1988), a fully-structured, lay-administered diagnostic interview. DSM-IV disorders that had first onsets in the decade between the two interviews were assessed in the NCS-2 using CIDI Version 3.0 (Kessler & Ustun, 2004). DSM organic exclusion rules were used in making diagnoses in both surveys. The NCS-2 assessment also considered first onsets of DSM-IV disorders prior to the time of the baseline interview that were not reported at baseline. This inconsistency in reporting was resolved by coding such disorders as having occurred prior to baseline despite not being reported at baseline in order to make lower bound estimates on age of onset. This inconsistency in reporting was uncommon (fewer than 5% of all lifetime cases of MDE and GAD) and equivalent for the two disorders.

Persistence of baseline disorders in the decade between interviews was assessed in NCS-2 with a life history calendar (Belli, 1998) that charted prevalence for each year in the decade between the interviews. The life history calendar method has been shown experimentally to produce significantly more accurate retrospective recall than more conventional survey methods (Belli *et al.*, 2001). Blinded clinical re-interviews assessed concordance of CIDI diagnoses with clinical diagnoses using the Structured Clinical Interview for DSM-III-R (Spitzer *et al.*, 1992) in the NCS and the Structured Clinical Interview for DSM-IV (First *et al.*, 2002) in the NCS-2. Good CIDI-SCID concordance was found for MDE and for GAD in both surveys, with AUC of .78 for MDE and .71 for GAD in the NCS (Kessler *et al.*, 1998) and .75 for MDE and .83 for GAD in the NCS-R (Haro *et al.*, 2006).

Prospective risk factors

Three risk factor sets were examined: childhood adversities, parental history of common mental-substance disorders, and respondent personality. All three have been found to predict both MDE and GAD in previous studies (Hettema *et al.*, 2006, Kendler *et al.*, 1997, Moffitt *et al.*, 2007). The childhood adversities included three dimensions of maltreatment (neglect, physical abuse, sexual abuse) and three dimensions of loss (parental death, parental divorce, other long-term separation). The parent disorders included MDE, GAD, panic disorder, antisocial personality disorder, and alcohol-drug dependence. The personality dimensions included neuroticism, extroversion, and openness to experience. Detailed discussions of measurement have been presented elsewhere (Kendler *et al.*, 1997, Kessler *et al.*, 1997, Mickelson *et al.*, 1997) and will not be repeated here other than to note that childhood adversities were assessed with questions developed specifically for the NCS, parental psychopathology with the Family-History Research Diagnostic Criteria (FHRDC) interview (Endicott *et al.*, 1978), and personality with a modified version of the Goldberg (1992) personality scales. Childhood adversities and parental history were defined dichotomously. Personality was defined continuously using standardized scales with a mean of zero and variance of one.

Statistical analyses

Cross-tabulations were used to estimate lifetime prevalence and persistence. Discrete-time survival analysis with person-year as the unit of analysis (Efron, 1988) was used to study prospective predictors of first onset and persistence. A logistic link function was used in the survival models. Survival analysis was used instead of logistic regression to consider information in the life history calendar about speed of onset and the number of years of persistence in the decade between interviews. Prior lifetime history of MDE was studied as a time-varying predictor on GAD and vice versa. MDE was "time-varying" in the sense that we took into consideration retrospectively reported information about age-of-onset (AOO) of MDE in predicting later GAD and vice versa. Standard errors and confidence intervals were estimated using the Taylor series method (Wolter, 1985) implemented in the SUDAAN software system (Research Triangle Institute, 2002) to adjust for the weighting and clustering of the data. Multivariate significance was evaluated using Wald χ^2 tests based on design-corrected coefficient variance-covariance matrices. Statistical significance was evaluated consistently using two-tailed .05-level tests.

RESULTS

Prevalence And Lifetime Comorbidity Between Mde And Gad

As of the time of the baseline NCS, 21.2% (0.8% standard error) of NCS-2 respondents met lifetime criteria for DSM-III-R MDE. 9.6% (0.8) of respondents without baseline lifetime MDE had an onset by NCS-2, resulting in a 28.8% (0.9) lifetime prevalence at NCS-2. GAD was much less prevalent, with 8.6% (0.5) lifetime prevalence at baseline, 3.6% (0.4) onset between waves, and 11.9% (0.6) lifetime prevalence at NCS-2. Lifetime MDE and GAD were strongly comorbid at baseline, with odds-ratio (OR) (95% Confidence Interval in parentheses) of 7.5 (5.5– 10.3). The association at NCS-2 was 6.6 (3.3–13.3).

Time-lagged associations involving first onset of the MDE and GAD

We examined time-lagged associations of first onset using retrospective age-of-onset (AOO) reports. The OR of temporally primary MDE predicting subsequent first onset of GAD is 2.7 (Table 1, Part I). The OR of temporally primary GAD predicting subsequent first onset of MDE is 3.2 (Table 1, Part II). Both associations are somewhat stronger among respondents who were adolescents (15–24 years of age) than adults (25–54 years of age) at baseline (3.7 vs. 1.7–2.4 for MDE predicting GAD; 3.6 vs. 3.0–3.1 for GAD predicting GAD).

The time-lagged ORs decrease dramatically with time since onset of the temporally primary disorder, although the elevated ORs remain statistically significant more than a decade after onset. All these ORs are somewhat more pronounced among respondents in the younger than older cohorts. Strikingly, the ORs associated with GAD and MDE starting in the very same year are much higher than any of the time-lagged ORs (54.1–54.9 vs. 2.7–8.9). We cannot distinguish temporal priority between MDE and GAD within a year, though, so we have no way to know if same-year onsets involve MDE starting before, after, or simultaneous with GAD.

Time-lagged associations involving persistence of MDE and GAD

Some 46.2% (with a standard error of 1.8%) of respondents with lifetime MDE at baseline had recurrences of MDE in the intervening decade. On average, baseline cases reported having recurrent MDE in 19.8% (1.0) of the years between the two interviews, again with an inverse relationship with age and a relatively narrow range from the youngest to oldest age groups (21.9-16.4%). Inter-temporal persistence of GAD was slightly higher, with 49.7% (2.4) of

baseline lifetime cases having episodes in at least one inter-current year and a mean of 27.4% (1.7) of years in episode.

We examined time-lagged association between baseline MDE and persistence of GAD and vice versa. An important asymmetry was found: that prior GAD significantly predicted persistence of MDE (1.8), while prior MDE did not significantly predict persistence of GAD (1.2). (Table2) These prediction equations controlled for AOO of the outcome disorder, which was consistently associated with significantly decreased risk of recurrence. The association between comorbid GAD and persistence of MDE was unrelated to temporal priority in first onset of MDE and GAD.

Prospective risk factors for first onset of MDE and GAD

When considered one at a time, most of the childhood adversities considered here were associated with significantly elevated risk of subsequent GAD, with ORs in the range 1.4–1.8. (Table 3) More detailed analysis (results available on request) showed that these effects are largely confined to childhood-adolescent onsets. Associations of childhood adversity with subsequent onset of MDE were more complex. As with GAD, most childhood adversities were associated with significantly elevated risk of MDE in the total sample (1.4–2.2). However, unlike GAD, where significant ORs were largely confined to childhood-adolescent onsets, more detailed analysis (results available on request) showed that childhood adversities also predict first onset of MDE into early adulthood (ages 25–39). Furthermore, parental death significantly predicts adolescent onsets of MDE (1.6) but not GAD (0.8).

Parent history of MDE, GAD, substance disorder and panic disorder all predicted GAD (1.5–1.6). More detailed analyses (results available on request) showed little evidence of variation based on number of parents with the disorder, sex of the parent with the disorder in cases where only one had it, or match between sex of disordered parent and respondent. As with childhood adversities, more detailed analyses (results available on request) showed effects confined to childhood-adolescent onsets. The effects of parental disorders on MDE were somewhat more consistent and stronger. As with GAD, more detailed analyses (results available on request) showed little evidence of variation in effects based on number of parents with the disorder, sex of parent with the disorder in cases where only one had it, or match between sex of disordered parent and respondent. However, unlike GAD, effects of parent disorders on MDE also were significant in adulthood.

As personality was assessed only in the baseline NCS, the associations of personality with onset of GAD were examined only in the person-years subsequent to the baseline interview. Neuroticism is the only dimension of personality significantly associated with elevated odds of GAD. Unlike childhood adversity, more detailed analyses (results available on request) found a significantly elevated OR of neuroticism with subsequent GAD in early adulthood (25–39 years of age; OR 1.4). In addition, extroversion is associated with significantly reduced odds of GAD onset in early adulthood (OR=0.7), but not in the total sample or at other parts of the life course examined here. The ORs of neuroticism predicting subsequent onset of MDE are similar in magnitude to those predicting onset of GAD, although not significant. While the association between extroversion and MDE is significant in two of the cohorts it is not consistently correlated (positive during childhood or adolescence, negative in middle age). Openness to experience, finally, is more consistently correlated (positively) with MDE than GAD.

When controls were introduced for all the above risk factors, the significant time-lagged associations (ORs) of temporally primary MDE with subsequent first onset of GAD attenuated somewhat, but remained statistically significant in the total sample (1.8), increased among respondents who were adolescents at baseline (5.0), and became insignificant in older cohorts

(1.4–1.8). The introduction of controls led to more modest attenuation of the OR between GAD and subsequent MDE, which remained statistically significant in the total sample (2.8) as well as in the early adulthood and middle age sub-samples (2.7–3.3).

Prospective risk factors for persistence of MDE and GAD

Persistence of GAD in the total sample was significantly predicted by several childhood adversities (1.4–1.8) and by neuroticism (1.1), but not by any of the measures of parental history of mental or substance disorders. (Results not presented, but available on request.) We were unable to study the stability of these associations across cohorts due to sparse data. Persistence of MDE in the total sample was significantly predicted by a somewhat different set of childhood adversities (1.3–1.5), by parental panic disorder (1.3), and by two personality dimensions: neuroticism (1.1) and openness to experience (1.1). As with GAD, sub-sample associations in cohorts could not be examined because of sparse data. When controls were introduced for childhood adversities, parental history of mental and substance disorders, and personality, the significant time-lagged associations (ORs) of baseline history of MDE with the subsequent persistence of GAD remained insignificant (1.1). In the case of GAD predicting persistence of MDE, the introduction of controls led to modest attenuation of the association, but the association remained statistically significant (1.7).

DISCUSSION

The results reported here are limited in four ways. First, the assessments of MDE and GAD were based on fully-structured diagnostic interviews that are likely to be less accurate than clinician-administered diagnostic interviews. Second, AOO and persistence were assessed retrospectively. Third, although the risk factor data were gathered prospectively, they were based on retrospective reports. Fourth, although analyses were carried out in parallel to predict MDE and GAD, formal modelling procedures were not used to adjust for the influence of a latent “internalizing” variable so as to determine the extent to which the effects of predictors on MDE and GAD are mediated through such a construct.

The impact of the first of these limitations is reduced somewhat by evidence of good concordance between diagnoses based on the CIDI and those based on blinded clinical reappraisal interviews. The second and third limitations are inherent in the design, but are to some extent counterbalanced by the fact that we worked with prospective data. The fourth limitation needs to be addressed in future investigations, but should ideally be studied using a larger set of internalizing disorders (e.g., social phobia, panic disorder, PTSD). It is noteworthy, though, that the possibility of a latent factor completely explaining inter-temporal associations between two variables is inconsistent both with the magnitude of the cross-lagged associations between those two variables (i.e., the association between MDE at time 1 and GAD at time 2 and the association between GAD at time 1 and MDE at time 2) differing significantly from each other and with there being significant interactions involving differential associations of either time 1 variable with onset versus persistence of the other variable (Kessler, 1977, Lazarsfeld, 1973). Both these patterns are observed in our data. Specifically, the cross-lagged associations involving persistence are asymmetric, with GAD predicting MDE more strongly than MDE predicting GAD, and the time-lagged associations are stronger in predicting onset than persistence of both MDE and GAD. Both of these patterns argue against a latent variable explaining the associations, although formal evaluation of this possibility awaits future investigation.

These limitations notwithstanding, the study provides useful new information about MDE-GAD comorbidity and prospective predictors of MDE and GAD onset and persistence. The strong MDE-GAD comorbidity found here is consistent with much previous research (Belzer & Schneier, 2004, Gorwood, 2004, Kessler, 2000, Noyes, 2001), although our prospective data

allowed us to decompose this cross-sectional association to document significant reciprocal cross-lagged relationships that vary with amount of time since the onset of the temporally primary disorder in predicting first onset. The most striking aspect of this time decay is the enormous same-year ORs. These same-year associations are so strong that more than one-third of all lifetime co-occurring MDE-GAD above that expected by chance occurs among cases in which both disorders started in the same year. We have no way to know what the strong association between time since onset and risk of comorbidity might mean, but it clearly implies that the temporally primary disorder is more than a mere marker of stable constitutional risk, as the latter would not be expected to produce an association between time since first onset of the temporally primary disorder and risk of the secondary disorder. The time decay also has implications for the argument in the literature that GAD might be nothing more than a prodrome or severity marker of MDE rather than an independent disorder (Brown *et al.*, 1998, Cloninger *et al.*, 1990, Offord *et al.*, 1994). If this argument were correct, the window of risk for secondary depression would be fairly short, which we find that it is not.

An alternative view of the causal processes linking temporally primary GAD with secondary MDE argues that secondary depression is an exhaustion response to unremitting anxiety (Akiskal, 1985). Primary anxiety, in this view, can be conceptualized as a stressor that promotes secondary depression (Akiskal, 1990, Durham *et al.*, 1997). If this were the case, though, we would expect that the OR for GAD predicting secondary MDE would become higher with the passage of time since onset of GAD. The fact that the opposite is the case argues against this interpretation. A more likely scenario is that the cross-lagged associations are due either to unmeasured common causes, to the effects of one disorder on the other, or to some combination of these two effects. We know that stable effects of the former sort exist. Indeed, as noted in the introduction, a number of population twin studies suggest that genetic influences are important common causes of MDE and GAD (Gorwood, 2004, Kendler *et al.*, 2007). However, we can think of no biologically plausible mechanism whereby a genetic common cause would lead to a time decay of the sort seen in the NCS-2 data in the ORs linking onset of temporally primary disorders with subsequent onset of secondary disorders. Nor could common genetic causes account for all the observed comorbidity between MDE and GAD, as the latter is higher than would be predicted based solely on the heritability of MDE and GAD and the strength of the association between the genes for the MDE and GAD. This means that there must also be common environmental causes of MDE and GAD. The estimates in population twin studies suggest that the latter explain between one-third and two-thirds of the significant comorbidity between MDE and GAD, assuming that the joint effects of genetic and environmental causes are additive.

We investigated a number of potentially important prospective risk factors for MDE and GAD that might be considered common causes. Most of these were found to predict the first onset of both MDE and GAD, but fewer were significant prospective predictors of persistence. Statistical control for these common predictors only explained a small proportion of the observed cross-lagged associations between MDE and GAD involving either onset of persistence. This could mean that we simply failed to measure the common environmental causes that are important for explaining the cross-lagged associations between MDE and GAD. Another possibility is that the occurrence of one of these two disorders in itself might increase risk of the subsequent onset of the second disorder, possibly through some type of sensitization or kindling phenomenon (Post & Weiss, 1998). An important implication of the possibility that temporally primary MDE or GAD might itself increase risk of the subsequent first onset of the other disorder is that successful treatment of the temporally primary disorder might be expected in such a case to reduce risk of onset of comorbidity. We are aware of no empirical research on this possibility. Given the high ORs associated with one of the two temporally primary disorders predicting the subsequent first onset of the other in the first few years after first onset, though, the sample size required to detect a preventive effect of this sort in an

effectiveness trial framework with long-term (five-year) follow-up would not be prohibitive. It might be that this kind of experimental investigation is the only way to resolve the uncertainly regarding whether temporally primary MDE and GAD are causal risk factors for each other or only risk markers.

Even though the prospective risk factors considered here did not explain the time-lagged associations between MDE and GAD, they are important in documenting several differences in the environmental determinants of the two disorders. Most notable in this regard are associations of parental death, extroversion (negative), and openness to experiences on first onset of MDE but not GAD, and generally somewhat stronger and temporally more persistent associations of the majority of risk factors with MDE than GAD. Many of these differences, though, are small. We also found that MDE was not a significant predictor of persistence of GAD, while GAD was a significant predictor of persistence of MDE. This difference is consistent with an earlier finding based on the analysis of retrospective reports in the baseline NCS. This earlier finding was associated with an investigation of whether comorbidity is related more strongly to the persistence and severity of GAD than other anxiety or mood disorders (Kessler *et al.*, 1994). The rationale of this analysis was that if GAD was a prodrome, residual, or severity marker of MDE, as early commentators suggested (Brown *et al.*, 1998, Cloninger *et al.*, 1990, Offord *et al.*, 1994), the persistence-severity of GAD would be more strongly affected by comorbidity than would persistence-severity of depression. Yonkers et al. (1996) reported a similar result in the prospective HARP study. These results provide concrete substantiation that MDE and GAD have partially distinct environmental determinants and add to the evidence from previous prospective studies of differences in the risk factors for MDE and GAD (Moffitt *et al.*, 2007) and differences in inter-temporal stability of these disorders that cannot be explained by a common underlying internalizing factor (Fergusson *et al.*, 2006). Future research needs to search for evidence of additional differences of this sort in an effort to expand our understanding of the distinction between common and distinct risk factors for MDE, GAD, and other internalizing disorder.

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Table 1

Cross-sectional and time-lagged associations of one disorder, either MDE or GAD, predicting the first onset of the other disorder as a function of time since onset of the primary disorder and cohort in the NCS-2 panel sample (n=5001)

	Total		Cohorts (Age at baseline)					
			15–24		25–39		40–54	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
I. Temporally primary MDE predicting subsequent GAD								
Total	2.7*	(2.1–3.5)	3.7*	(2.6–5.2)	2.4*	(1.6–3.7)	1.7*	(1.0–2.9)
0 Years since onset of MDE	54.4*	(37.3–79.3)	51.9*	(36.1–74.5)	50.0*	(28.7–87.3)	40.7*	(12.1–137.4)
1–2 Years since onset of MDE	7.9*	(4.7–13.3)	9.3*	5.5–15.8	5.7*	(2.1–15.7)	4.7*	(2.0–10.8)
3–5 Years since onset of MDE	4.7*	(3.3–6.5)	6.6*	(3.7–11.5)	2.5*	(1.2–5.1)	2.4	(0.8–7.1)
6–10 Years since onset of MDE	2.8*	(1.8–4.3)	4.0*	(1.9–8.4)	2.3*	(1.3–3.9)	0.2	(0.0–1.2)
11+ Years since onset of MDE	3.5*	(2.4–5.0)	2.8*	(1.0–8.0)	4.1*	(2.5–6.5)	2.5*	(1.3–4.8)
II. Temporally primary GAD predicting subsequent MDE								
Total	3.2*	(2.3–4.3)	3.6*	(2.2–6.0)	3.0*	(2.0–4.6)	3.1*	(1.7–5.6)
0 Years since onset of GAD	54.1*	(37.0–79.1)	51.9*	(35.9–74.9)	49.0*	(27.9–86.1)	42.2*	(12.0–148.1)
1–2 Years since onset of GAD	8.9*	(5.5–14.4)	7.5*	(3.5–16.2)	5.2*	(2.2–12.5)	23.0*	(7.7–68.7)
3–5 Years since onset of GAD	3.9*	(2.4–6.4)	4.3*	(2.2–8.2)	4.2*	(1.9–9.6)	0.4	(0.1–2.2)
6–10 Years since onset of GAD	2.0*	(1.2–3.3)	3.1*	(1.2–8.3)	1.8*	(1.0–3.4)	0.6	(0.1–3.3)
11+ Years since onset of GAD	2.8*	(1.9–4.2)	1.6	(0.4–6.3)	3.4*	(2.0–5.6)	3.0*	(1.4–6.7)

*Significant at the .05 level, two-sided test

[1]Based on a discrete-time survival model with person-year as the unit of analysis, controlling for cohort (age at interview), gender, race-ethnicity, and person-year.

Table 2

Time-lagged associations of baseline MDE predicting the persistence of GAD and of baseline GAD predicting the persistence of MDE by cohort in the NCS-2 panel sample

	Total		Cohorts (Age at baseline)					
			15–24		25–39		40–54	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
I. Baseline MDE predicting the persistence of GAD								
MDE	1.2	(0.9–1.7)	1.2	(0.5–2.6)	1.1	(0.7–1.8)	1.3	(0.8–2.1)
AOO of GAD	0.9*	(0.7–1.0)	0.9	(0.4–1.9)	0.8	(0.7–1.0)	0.8*	(0.6–1.0)
(n)[2]		(531)		(74)		(258)		(199)
II. Baseline GAD predicting the persistence of MDE								
GAD	1.8*	(1.4–2.4)	2.6*	(1.4–4.6)	1.5*	(1.1–2.2)	1.9*	(1.3–2.7)
AOO of MDE	0.8*	(0.7–0.9)	0.4*	(0.2–0.8)	0.7*	(0.6–0.9)	0.9	(0.8–1.1)
(n)[2]		(1442)		(313)		(698)		(431)

*Significant at the .05 level, two-sided test

[1]Based on a discrete-time survival model with person-year as the unit of analysis, controlling for cohort (age at interview), gender, race-ethnicity, and person-year.

[2]Unweighted sample sizes

Table 3

Time-lagged associations of childhood adversities, parental history of mental disorders, and respondent personality with the subsequent first onset of GAD and MDE in the NCS-2 panel sample (n=5001)[1]

	GAD		MDE	
	OR	(95% CI)	OR	(95% CI)
I. Childhood adversities				
Neglect	1.7*	(1.3–2.0)	1.8*	(1.5–2.1)
Physical abuse	1.8*	(1.4–2.4)	2.2*	(1.8–2.7)
Sexual abuse	1.6*	(1.1–2.2)	1.8*	(1.3–2.5)
Death of parent	1.1	(0.7–1.8)	1.1	(0.7–1.6)
Divorce of parents	1.4*	(1.1–1.8)	1.4*	(1.2–1.7)
Other long-term separation	1.3	(0.7–2.1)	1.1	(0.8–1.6)
II. Parental history of mental disorders				
MDE	1.5*	(1.2–2.0)	1.8*	(1.6–2.1)
GAD	1.6*	(1.2–2.1)	1.8*	(1.5–2.1)
Panic disorder	1.5*	(1.1–2.0)	1.9*	(1.5–2.4)
ASPD	1.5	(0.6–3.6)	2.1*	(1.3–3.3)
Substance disorder	1.5*	(1.1–2.0)	1.7*	(1.4–2.0)
III. Respondent personality[2]				
Neuroticism	1.3*	(1.1–1.5)	1.2	(1.0–1.4)
Extroversion	0.9	(0.7–1.1)	0.9	(0.8–1.1)
Openness to experience	1.0	(0.8–1.2)	1.3*	(1.1–1.5)

*Significant at the .05 level, two-sided test

[1]Based on a discrete-time survival model with person-year as the unit of analysis, controlling for cohort (age at interview), gender, race-ethnicity, and person-year.

[2]Estimated only in person-years subsequent to the baseline interview and among those without an onset of the outcome disorder prior to the baseline interview due to the fact that personality was only assessed as of the time of the baseline interview (n=4470).