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Generalized anxiety disorder and depression: childhood risk factors in a birth cohort followed to age 32

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ABSTRACT

Background. The close association between generalized anxiety disorder (GAD) and major depressive disorder (MDD) prompts questions about how to characterize them in future diagnostic systems. We tested whether risk factors for MDD and GAD are similar or different.

Method. The representative 1972–73 Dunedin birth cohort of 1037 males and females was followed to age 32 with 96% retention. Adult GAD and MDD were diagnosed at ages 18, 21, 26, and 32 years, and juvenile anxiety/depression were also taken into account. Thirteen prospective risk measures indexed domains of family history, adverse family environment, childhood behavior, and adolescent self-esteem and personality traits.

Results. Co-morbid MDD + GAD was antedated by highly elevated risk factors broadly across all domains. MDD + GAD was further characterized by the earliest onset, most recurrence, and greatest use of mental health services and medication. Pure GAD had levels of risk factors similar to the elevated levels for co-morbid MDD + GAD; generally, pure MDD did not. Pure GAD had risks during childhood not shared by pure MDD, in domains of adverse family environment (low SES, somewhat more maltreatment) and childhood behavior (internalizing problems, conduct problems, somewhat more inhibited temperament). Pure MDD had risks not shared by pure GAD, in domains of family history (of depression) and personality (low positive emotionality).

Conclusions. Specific antecedent risk factors for pure adult MDD *versus* GAD may suggest partly different etiological pathways. That GAD and co-morbid MDD + GAD share many risk markers suggests that the presence of GAD may signal a pathway toward relatively more severe internalizing disorder.

INTRODUCTION

This article was prepared in response to a call for research to inform how generalized anxiety disorder should be characterized in relation to depression in forthcoming diagnostic systems (Kendler & Goldberg, 2004). Proposals to

collapse major depressive disorder (MDD) and generalized anxiety disorder (GAD) together in DSM-V would be supported if the two disorders shared common antecedent risk factors. Here we test whether prospectively assessed risk factors for MDD and GAD are similar or different. Prospective longitudinal research of this nature has been called for to help define the boundaries of mental disorders for DSM-V (Widiger & Clark, 2000).

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Six empirical observations point to a close association between MDD and GAD. First, according to epidemiological studies, MDD and GAD co-occur beyond chance expectations (Mineka *et al.* 1998; Angold *et al.* 1999); among all disorders GAD is most co-morbid with MDD (Kessler *et al.* 1996). Second, according to twin studies, MDD and GAD share joint genetic susceptibility (Kendler, 1996); among anxiety disorders GAD is genetically closest to MDD (Kendler *et al.* 1995). Third, according to personality studies, MDD and GAD share a continuously distributed vulnerability trait called neuroticism or negative emotionality (Krueger *et al.* 1996; Barlow & Campbell, 2000; Watson *et al.* 2005). Fourth, according to statistical models of the structure of psychopathology, MDD and GAD converge on the same latent internalizing factor (Krueger *et al.* 1998; Krueger, 1999; Krueger & Finger, 2001; Vollebergh *et al.* 2001). Fifth, anxiety during childhood is a risk predictor for later MDD, according to longitudinal studies (Breslau *et al.* 1995; Parker *et al.* 1999; Lewinsohn *et al.* 2000; Zahn-Waxler *et al.* 2000; Pine *et al.* 2001) and multigeneration family studies (Weissman *et al.* 2005). Sixth, MDD and GAD symptoms often respond to the same drugs (Kuzma & Black, 2004).

These six observations have prompted speculations that MDD and GAD may be two clinical presentations of one disorder process, in which GAD-MDD co-occurrence is a sign of severity (Coryell *et al.* 1992; Sartorius *et al.* 1996; Wittchen, 1996; Mineka *et al.* 1998; Zahn-Waxler *et al.* 2000; Merikangas *et al.* 2003). However, arguments are also put forward that GAD and MDD should remain nosologically separate as independent diagnoses (Kessler, 2005; Kessler *et al.* 2005), albeit grouped together with MDD in a new class to be entitled distress disorders (Watson *et al.* 2005). Thus, the relation between GAD and MDD, and the nosological implications of that relation, remain controversial (Wittchen *et al.* 2000; Kessler & Wittchen, 2002).

A seventh type of evidence relevant to the classification of GAD and MDD would be information about antecedent risk predictors. Are risk factors for GAD and MDD the same or different? There is no shortage of studies reporting risk factors for anxiety, or for depression. However, such studies constitute

two quite separate literatures, one for each disorder. Findings from these separate literatures could be compared, but such comparison would confound any differences in risk factors with other differences between studies, such as differences in sample characteristics, research design, measurement age, or data collection methods (Phillips *et al.* 2005). What is needed are systematic comparisons carried out within one cohort sample between GAD and MDD risk factors. Such a single-cohort comparison would offer the key additional advantage of being able to take co-morbidity between GAD and MDD into account while making comparisons between them. Finally, such a comparison should ideally draw on risk factors measured prospectively before the onset of GAD and MDD, to document temporal precedence of risk factors. Prospective measurement also avoids relying on retrospective reports of risk factors, which may be biased by recall failure or by study participants' experience of disorder. This article describes child and adolescent risk factors for adult MDD and GAD in the prospective-longitudinal Dunedin birth cohort.

Our choice of risk factors for the present research was guided by Kendler's influential developmental model addressing the etiological complexity of internalizing disorders (Kendler *et al.* 2002). Although Kendler's review focused on pathways to depression, it incorporated all known antecedent risk factors for both depression and anxiety. The child/adolescent risk constructs specified were as follows: predisposing genetic influences (here operationalized as family history of anxiety or depression, and maternal internalizing symptoms), exposure to an adverse family environment including deprivation, abuse or premature parental loss (here operationalized as low childhood socioeconomic status, child maltreatment, and childhood parental absence due to death or marital dissolution), early-onset anxiety and internalizing problems (here operationalized as preschool inhibited temperament, childhood internalizing problems of anxiety and withdrawal, and childhood depression symptoms), conduct disorder (here operationalized as childhood conduct problems), and a dysfunctional self-schema (here operationalized as low adolescent self-esteem). Predisposing personality traits were also specified (Kendler *et al.* 2002). Here

we examine two adolescent personality trait measures that have featured prominently in the literature on depression and anxiety, called negative emotionality and positive emotionality. Prior evidence suggests that high negative emotionality (e.g. neuroticism, alienation, irritability, stress reactivity) poses common risk for depression and anxiety, whereas low positive emotionality (e.g. well-being, social potency, social closeness) poses specific risk differentiating depression from anxiety (Watson, 2005).

Elsewhere we described the longitudinal development of GAD and MDD in the Dunedin cohort from adolescence to adulthood, and the co-morbidity between them (Moffitt *et al.* in press). The odds ratio for cumulative MDD + GAD co-morbidity in the cohort up to age 32 [odds ratio (OR) 5.6, 95% confidence interval (CI) 3.9–7.2] resembled those from the National Co-morbidity Survey (NCS) (OR 6.0) (Kessler *et al.* 1996) and the NCS-Replication (OR 6.4) (Kessler *et al.* 2005). The research question for the current article is whether MDD and GAD have the same or different risk factors. However, because over half of MDD and GAD cases are the same individuals, this co-morbid overlap necessarily must produce virtually identical risk factors for the two disorders. Therefore, tests for differential risk factors reported here isolate risk factors for GAD-only cases having no history of MDD and for MDD-only cases having no history of GAD, while including two further groups for comparison purposes: co-morbid MDD + GAD, and study members with no history of any mental disorder.

METHOD

Sample

Participants are members of the Dunedin Multidisciplinary Health and Development Study (Moffitt *et al.* 2001). Of infants born in Dunedin, New Zealand between April 1972 and March 1973, 1037 children (91% of eligible births; 52% male) participated in the first follow-up assessment at age 3, constituting the base sample for the remainder of the study. Cohort families represent the full range of socioeconomic status in the general population of New Zealand's South Island and are primarily white. Participants attend the Research Unit for a full day of individual data collection. The

Otago Ethics Committee granted ethical approval for each phase of this longitudinal study. Study members gave informed consent before participating. Assessments have been carried out at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26 and most recently at age 32 when we assessed 972 (96%) of the 1015 study members still alive in 2004–2005. Cohort members having missing diagnostic data from two or more of five periods (ages 18, 21, 26, 32 and juvenile) were excluded when we defined diagnostic groups for comparison in this article; 945 individuals were thus studied here, 8.6% with one missing diagnostic data-point and 91.4% with no missing diagnostic data-point.

Measures of disorder

MDD at ages 18, 21, 26 and 32 years was diagnosed as follows. Structured interviews with study members used the Diagnostic Interview Schedule (DIS) (Robins *et al.* 1989, 1995), administered by health care professionals with tertiary degrees in clinical psychology, medicine, public health, or social work (not lay interviewers). At ages 18 and 21, diagnoses followed DSM-III-R (APA, 1987) and at ages 26 and 32 diagnoses followed DSM-IV (APA, 1994). Variable construction details, reliability and validity, and evidence of impairment for diagnoses in the cohort are reported elsewhere (Feehan *et al.* 1994; Newman *et al.* 1996; Hankin *et al.* 1998). For example, attesting to validity, study members diagnosed with MDD at age 32 self-reported their mean impairment resulting from MDD as 3.57 (s.d. = 0.99) on a scale from 1 (some impairment) to 5 (severe impairment); 62% said they had received mental health services in the past year; and 31% said they took medication for their disorder. The past-year MDD prevalence of 14% averaged across ages 15–32 for the Dunedin cohort is comparable to the past-year prevalence of 12% published for 15- to 34-year-olds in the NCS (Kessler *et al.* 1993).

GAD at ages 18, 21, 26, and 32 years was diagnosed using instruments and procedures parallel to those described above for MDD. To allow study of co-morbidity, GAD was diagnosed if criteria were met regardless of the presence of MDD. Attesting to validity, study members diagnosed with GAD at age 32 self-reported their mean impairment resulting from

GAD as 3.62 (s.d.=0.95) on a scale from 1 (some) to 5 (severe), 49% said they had received mental health services in the past year, and 25% said they took medication for their disorder. The past-year GAD prevalence of 7.0% averaged across ages 18 to 32 for the Dunedin cohort is comparable to the past-year prevalence of 5.5% across all ages in the NCS (Kessler *et al.* 2005) (published NCS data did not allow a comparison matched on age group).

For this article, GAD diagnoses followed the DSM-III 1-month criterion instead of the DSM-IV 6-month duration criterion, because a 6-month criterion is stricter than MDD's 2-week criterion, a difference that would confound our comparisons between the two disorders on risk factors. Thus, all GAD cases in this article met full symptom criteria for GAD, but approximately half of the cases had 6-month duration while the other half met GAD criteria for some shorter period between 1 and 6 months. Twin research shows that the etiology of GAD is the same whether GAD lasts 6 months or 1–6 months (Kendler, 1996). The NCS-R showed that clinical significance and impairment are similar whether GAD lasts 6 months or 1–6 months (Kessler *et al.* 2005). As in the NCS-R, relaxing the duration criterion in the Dunedin Study increased the GAD prevalence rate, for example from 7.7% to 13.5% at age 32. However, as in the NCS-R (Kessler *et al.* 2005), associations between GAD and other study variables were virtually unaffected. Continuity from juvenile anxiety disorder to adult GAD was similar with the 6-month or 1-month duration criterion (OR 2.9 *v.* 2.5), as was the female:male ratio for GAD (1.6:1 *v.* 1.4:1). GAD-diagnosed study members' rating of how much GAD symptoms had impaired their lives in the past year at age 32 was similar with the 6-month or 1-month criterion (mean=3.81, s.d.=0.90 *v.* mean=3.62, s.d.=0.95), as was the percentage who received mental health services (55% *v.* 49%). Most relevant here, longitudinal co-morbidity was similar; with the 6-month or 1-month criterion among MDD+GAD co-morbid cases, anxiety onset before or concurrently with MDD in 68% (6-month GAD criterion) *v.* 66% (1-month GAD criterion) (Moffitt *et al.* in press).

Juvenile depression and anxiety disorder were included because ignoring participants'

pre-adult disorder history would create inaccurate classifications of pure, co-morbid, and healthy groups. Diagnoses followed DSM-III criteria (APA, 1980) based on structured interviews using the Diagnostic Interview Schedule for Children-Child Version (Costello *et al.* 1982). Resulting diagnoses at age 11, 13 and 15 years have been described elsewhere (Anderson *et al.* 1987; Frost *et al.* 1989; McGee *et al.* 1990).

Indicators of mental health service use were assessed using the Life History Calendar. This visual method (columns=time units, rows=events) has been shown to enhance recall reliability (Caspi *et al.* 1996a; Belli *et al.* 2001). As part of the assessment of life events from ages 20–32, participants reported years in which they received mental health services (e.g. from a general practitioner, psychiatrist, psychologist or emergency room), or took psychiatric medications, for anxiety or depression. One-month test-retest reliability of the calendar was evaluated in a sample of 30 psychiatric outpatients; 10-year reports of service use and medication showed >90% test-retest agreement.

Measures of risk factors

Each risk measure has published descriptions of variable construction and evidence of good construct validity and reliability (test-retest, inter-rater, and/or internal consistency, as appropriate); relevant citations are provided below.

Family history data were collected and cases identified using the interview protocol and case-definition algorithms of the Family History Screen (Thompson *et al.* 1980; Weissman *et al.* 2000). History was ascertained by separately interviewing three respondents per study family in 2003–2006: the 32-year-old study member, his/her mother, and his/her father (or an aunt if a parent was unavailable). Three informants reported for 78% of cohort families, two for 93% and one for 97%. Reported on were the study member's four biological grandparents, two biological parents, and 0–10 biological siblings (range=1–16 members per family, mean=9). We report the proportion of family members identified with symptoms of anxiety, and depression.

Maternal internalizing symptoms were measured with the Malaise Inventory (Rodgers *et al.* 1999), which assesses symptom complaints

associated with anxiety and depression (e.g. insomnia, hopelessness, tension, somatic complaints). It was completed by mothers when the study child was 5, 7, and 9 years old and scores were standardized and averaged (McGee *et al.* 1985*a*).

Low childhood socio-economic status was measured as the highest of father's or mother's occupation using a 6-point scale for New Zealand (Elley & Irving, 1976), and repeated measures over the first 15 years of the study child's life were averaged (Wright *et al.* 1999).

Maltreatment at ages 3–11 years was ascertained using behavioral observations of rejecting mother-child interactions at age 3, parental reports of harsh discipline at ages 7 and 9, two or more changes in primary care-giver before age 11, and retrospective reports by the study members at age 26 of exposure to injurious physical abuse or unwanted sexual contact before age 11. In the full sample, 9% of children experienced at least two indicators of maltreatment (Caspi *et al.* 2002).

Parental loss was recorded from parents' reports at child ages 3, 5, 7, 9, and 11 years of whether a biological parent had become permanently absent from the family due to death, separation or divorce (Jaffee *et al.* 2002).

Inhibited temperament at ages 3–5 years was assessed through ratings made by staff-members after they observed the child in a 90-minute testing session with an unfamiliar examiner at ages 3 and 5 years. Factor and cluster analyses reduced these ratings to three reliable temperament types (Caspi & Silva, 1995; Caspi *et al.* 1996*b*), since replicated in other samples (Robins *et al.* 1996; Asendorpf *et al.* 2001; Hart *et al.* 2003). We report on the inhibited type.

Internalizing problems at ages 5–11 years were reported by parents and teachers on the Rutter Child Scales assessing items such as worrying, unhappiness, misery, and fearfulness (Elander & Rutter, 1996). Ratings made when the study child was 5, 7, 9, and 11 years were standardized and averaged (McGee *et al.* 1985*b*).

Conduct problems at ages 5–11 years were reported by parents and teachers on the Rutter Child Scales assessing items such as fighting, bullying, stealing, tantrums, and lying (Elander & Rutter, 1996). Ratings made when the study child was 5, 7, 9, and 11 years were standardized and averaged (Moffitt *et al.* 2001).

Psychiatrist's count of child's depression symptoms at age 9 years was a measure obtained through an interview of each child by a psychiatrist in 1981–1982. Fewer than 1% of children met full diagnostic criteria for MDD at age 9, but the count of symptoms was archived and is used here as a scale (Kashani *et al.* 1983).

Self-esteem at ages 11, 13, and 15 years was assessed through adolescent self-report using the Rosenberg Self-Esteem Scale (Rosenberg, 1965), standardized and averaged across ages (Trzesniewski *et al.* 2006).

Personality traits at age 18 years were assessed through self-report using the Multidimensional Personality Questionnaire (MPQ; Patrick *et al.* 2002). Items of the Negative Emotionality scale measure interpersonal alienation, irritable-aggressive attitudes, and reactivity to stress. Items of the Positive Emotionality scale measure well-being, social potency, achievement, and social closeness. These two scales are relatively independent, internally consistent, and stable over time (Krueger *et al.* 1996).

Statistical analyses

Findings for categorical measures are reported as group percentages. Findings for continuous measures are reported as group means on *z* scores standardized to a mean of 0 and standard deviation of 1 (the difference between two group means for this representative cohort may be interpreted as an effect size). Comparisons between diagnostic groups were tested using regression analysis; we report odds ratios for dichotomous risk measures, and *t* tests (associated with beta weights) for continuous risk measures. The sexes were combined to augment statistical power but sex was controlled as a covariate. The purpose of this research was to compare risk factors across diagnostic groups, *not* to ascertain whether any associations between a risk factor and a diagnosis were unique or causal. Therefore, bivariate risk-diagnosis associations are presented; multivariate models were not performed.

RESULTS

As an initial screening step, basic analyses tested which risk factors predicted MDD, and which risk factors predicted GAD, by comparing the diagnostic groups against a healthy control

group of study members never diagnosed with any Axis-I mental or substance-abuse disorder. First, study members with GAD differed significantly from healthy controls on all 13 risk factors (all $p < 0.05$, tests not tabled). In a separate parallel analysis, study members with MDD differed from healthy controls on 11 of the 13 risk factors (all $p < 0.05$, tests not tabled); the exceptions were childhood SES and behavioral inhibition at age 3. However, as anticipated, the aforementioned two comparisons were not particularly informative because, given the high rate of co-morbidity, a substantial proportion of GAD- and MDD-diagnosed study members were the same individuals, virtually guaranteeing these similar risk-factor associations. As such, the following analyses set the MDD + GAD group apart, to look specifically at MDD-only and GAD-only groups.

Four mutually exclusive groups were defined on the basis of their adult diagnostic status at ages 18, 21, 26 and 32 years, and their juvenile diagnostic history from ages 11 to 15 years. The MDD-only group was diagnosed with MDD in adulthood, but never with GAD in adulthood or anxiety as a juvenile ($n = 162$ pure cases of MDD). The GAD-only group was diagnosed with GAD in adulthood, but never with MDD in adulthood or as a juvenile ($n = 52$ pure cases of GAD). The MDD + GAD group comprised cohort members diagnosed with both disorders during the adult study period ($n = 189$, 20% of the cohort). No-diagnosis controls were cohort members never diagnosed with any disorder, as described above ($n = 205$ healthy).

Table 1 compares the four groups, first on descriptors, then on risk factors. As a natural consequence of the greater prevalence of MDD among women, the MDD-only and MDD + GAD groups had more women whereas the GAD-only had more men. However, sex was controlled as a covariate in all group comparisons, so differential risk patterns for GAD versus MDD reported below were not an artifact of any sex differences in risk factors.

The MDD-only group's findings are shown in column A of Table 1. First, regarding family history, the MDD-only group was distinguished from healthy controls by a worse family history of depression, as well as more maternal internalizing symptoms. Second, regarding family environment, the MDD-only group differed

from healthy controls only on maltreatment. Third, regarding childhood behavior, the MDD-only group differed from controls only in showing somewhat more conduct problems, although the MDD groups' conduct problems were not above the cohort mean. Fourth, regarding personality, the MDD-only group was distinguished from controls by significantly lower positive emotionality and higher negative emotionality scores (column A). Finally, column B of Table 1 shows the MDD-only group was at markedly *lower* levels of risk than the MDD + GAD co-morbid group, scoring significantly healthier on 9 of 13 risk measures.

The GAD-only group's findings are shown in column C of Table 1. First, regarding family history, the GAD-only group differed from healthy controls on only maternal internalizing symptoms. Second, regarding family adversity, the GAD-only group differed from controls on low socio-economic status and maltreatment. Third, regarding childhood behavior, the GAD-only group differed from controls on both childhood internalizing problems and conduct problems. Additionally, the GAD-only group had elevated risk on inhibited temperament. However, this reached only marginal significance (note: the comparison between the GAD-only group and controls had less statistical power than the comparison between the MDD-only group and controls). Fourth, regarding personality, the GAD-only group was distinguished from healthy controls by worse scores on negative emotionality but not positive emotionality (column C). Finally, column D of Table 1 shows that on the majority of childhood risk factors the GAD-only group was *not* at significantly lower risk than the co-morbid MDD + GAD group; the GAD-only group scored as poorly as the MDD + GAD group on 9 of 13 risk measures. This overall pattern of similar childhood risk for GAD-only and MDD + GAD was not merely an issue of low statistical power; the group-difference effect sizes were small.

The co-morbid MDD + GAD group also provided notable findings (Table 1). As a group, co-morbid study members scored significantly worse than the GAD-only group on 3 of 13 risk factors (column D), worse than the MDD-only group on 9 of 13 risk factors (column B), and worse than healthy controls on all 13 risk factors (all $p < 0.01$, tests not tabled). This

Table 1. *Prospective risk factors: comparing co-morbid versus non-co-morbid cases of major depressive disorder and generalized anxiety disorder defined cumulatively from age 18 to 32, while taking childhood disorder history into account*

	Diagnostic groups, ages 18–32 years				Planned group comparisons			
	Healthy controls (<i>n</i> = 205)	MDD only (<i>n</i> = 162)	GAD only (<i>n</i> = 52)	MDD + GAD (<i>n</i> = 189)	A. MDD-only v. healthy controls	B. MDD-only v. co-morbid	C. GAD-only v. healthy controls	D. GAD-only v. co-morbid
Group descriptors								
Percentage of birth cohort, <i>n</i> = 945	22%	17%	6%	20%				
Female ^a	42%	62%	40%	63%	OR 2.30 (1.5–3.6)	OR 1.03 (0.7–1.6)	OR 0.96 (0.5–1.8)	OR 2.5 (1.3–4.7)
First MDD diagnosis by age 15		2%		14%		OR 8.67 (2.6–29.2)		
First anxiety diagnosis by age 15			12%	37%				OR 4.51 (1.8–11.3)
Recurrent MDD (2+ episodes)		27%		61%		OR 4.26 (2.7–6.7)		
Recurrent GAD (2+ episodes)			14%	50%				OR 6.70 (2.8–15.8)
Received mental health services, age 20–32	9%	41%	35%	57%	OR 6.78 (3.8–12.2)	OR 1.89 (1.2–2.9)	OR 6.16 (2.8–13.5)	OR 2.09 (1.1–4.1)
Psychiatric medication, age 20–32	5%	22%	19%	39%	OR 5.10 (2.4–10.8)	OR 2.30 (1.4–3.7)	OR 5.05 (1.9–13.3)	OR 2.25 (1.0–4.9)
Risk factors								
Proportion of family members with a history of depression (mean % of pedigree members)	21%	29%	25%	33%	<i>t</i> = 3.70, <i>p</i> < 0.001	<i>t</i> = 1.69, <i>p</i> = 0.09	<i>t</i> = 1.26, <i>p</i> = 0.20	<i>t</i> = 2.64, <i>p</i> = 0.009
Proportion of family members with a history of anxiety disorder (mean % of pedigree members)	15%	18%	19%	26%	<i>t</i> = 1.85, <i>p</i> = 0.07	<i>t</i> = 3.92, <i>p</i> < 0.001	<i>t</i> = 1.19, <i>p</i> = 0.23	<i>t</i> = 2.86, <i>p</i> = 0.005
Maternal internalizing symptoms (mean <i>z</i> score)	−0.24	−0.05	0.16	0.27	<i>t</i> = 2.12, <i>p</i> = 0.035	<i>t</i> = 2.76, <i>p</i> = 0.006	<i>t</i> = 2.70, <i>p</i> = 0.007	<i>t</i> = 0.75, <i>p</i> = 0.46
Childhood SES (mean <i>z</i> score)	0.13	0.20	−0.19	−0.09	<i>t</i> = 0.61, <i>p</i> = 0.54	<i>t</i> = 2.72, <i>p</i> = 0.007	<i>t</i> = 2.16, <i>p</i> = 0.032	<i>t</i> = 0.43, <i>p</i> = 0.67
Child maltreatment before age 11	3%	9%	14%	14%	OR 2.60 (1.0–6.6)	OR 1.56 (0.8–3.1)	OR 4.49 (1.5–13.5)	OR 1.00 (0.4–2.5)
Lost a parent before age 11	9%	12%	14%	19%	OR 1.50 (0.8–3.0)	OR 1.61 (0.9–2.9)	OR 1.62 (0.6–4.1)	OR 1.30 (0.5–3.3)
Inhibited temperament ages 3–5	5%	4%	12%	12%	OR 0.75 (0.3–2.0)	OR 2.93 (1.2–7.1)	OR 2.31 (0.8–6.6)	OR 0.83 (0.3–2.2)
Internalizing problems ages 5–11 (mean <i>z</i> score)	−0.23	−0.18	0.07	0.29	<i>t</i> = 0.32, <i>p</i> = 0.74	<i>t</i> = 4.40, <i>p</i> < 0.001	<i>t</i> = 2.07, <i>p</i> = 0.04	<i>t</i> = 1.15, <i>p</i> = 0.25
Conduct problems ages 5–11 (mean <i>z</i> score)	−0.30	−0.17	0.06	0.09	<i>t</i> = 2.50, <i>p</i> = 0.013	<i>t</i> = 2.93, <i>p</i> = 0.004	<i>t</i> = 2.70, <i>p</i> = 0.007	<i>t</i> = 0.67, <i>p</i> = 0.50
Depression symptom count age 9 (mean <i>z</i> score)	−0.15	−0.20	0.10	0.19	<i>t</i> = 0.33, <i>p</i> = 0.74	<i>t</i> = 3.62, <i>p</i> < 0.001	<i>t</i> = 1.44, <i>p</i> = 0.15	<i>t</i> = 1.30, <i>p</i> = 0.19
Self-esteem, ages 11–15 (mean <i>z</i> score)	0.30	0.19	0.08	−0.34	<i>t</i> = 0.67, <i>p</i> = 0.50	<i>t</i> = 5.07, <i>p</i> < 0.001	<i>t</i> = 1.65, <i>p</i> = 0.10	<i>t</i> = 2.50, <i>p</i> = 0.013
Negative emotionality age 18 (mean <i>z</i> score)	−0.56	−0.04	0.09	0.48	<i>t</i> = 6.18, <i>p</i> < 0.001	<i>t</i> = 4.97, <i>p</i> < 0.001	<i>t</i> = 5.29, <i>p</i> < 0.001	<i>t</i> = 3.27, <i>p</i> = 0.001
Positive emotionality age 18 (mean <i>z</i> score)	0.26	−0.15	0.06	−0.10	<i>t</i> = 3.88, <i>p</i> < 0.001	<i>t</i> = 0.44, <i>p</i> = 0.66	<i>t</i> = 1.35, <i>p</i> = 0.18	<i>t</i> = 0.83, <i>p</i> = 0.40

Significant comparisons at an alpha criterion of 0.05 are presented in bold type.

^a Gender was controlled in group comparisons.

MDD+GAD group was also characterized by younger onset, greater recurrence, and more use of mental-health services and medications, as compared with the pure MDD and GAD groups (columns B and D).

DISCUSSION

This article reports new information about risk factors for MDD and GAD from a prospective longitudinal study. Findings indicate that MDD and GAD share some, but not all, antecedent risk factors. Findings for each group are discussed in turn below.

First, adults who were diagnosed with both MDD and GAD had the most pronounced risk histories, as indicated by family psychiatric history, childhood adversity and behavior, and predisposing personality traits. This high-risk history is consistent with clinical outcomes, in which individuals with co-morbid MDD+GAD were set apart by having a recurrent course of both disorders, and by elevated health burden as indicated by service use and medication. Prior studies have shown that co-morbidity is common, and that co-morbid cases are more severe and persistent than pure cases (Hagnell & Gräsbeck, 1990; Murphy, 1990; Lewinsohn *et al.* 1997; Pine *et al.* 1998; Wittchen *et al.* 2000; Merikangas *et al.* 2003; Moffitt *et al.* in press). This article adds that co-morbid cases have more marked antecedent risk histories than pure cases.

Second, MDD in the absence of co-morbid GAD was not strongly associated with risk factors during childhood. Indeed, pure MDD was predicted most strongly by family history of depression and adolescent personality traits (negative and positive emotionality). As anticipated from prior research, low positive emotionality predicted pure MDD but not pure GAD, suggesting that individuals with a high threshold for experiencing positive emotion are at specific risk for MDD (Watson, 2005). This differential risk also seemed to apply to family history. A family history of depression predicted the MDD-only group more than the GAD-only group, a pattern reported previously (Wickramaratne & Weissman, 1993; Klein *et al.* 2004). A related finding about MDD was that non-co-morbid MDD involved markedly lower levels of risk than co-morbid MDD+GAD, as

indicated by milder risk factors and less extreme personality traits. This pattern suggests that adult MDD occurring in the absence of any lifetime history of juvenile anxiety or GAD might warrant special research focus to ascertain whether it has a unique etiology. Findings here suggest the hypothesis that pure adult MDD does not involve risk during childhood, but instead could arise from genetic and personality predispositions that are only manifested as depression when predisposed individuals encounter stressful life events as adults. Previously we reported fewer childhood risks for adult-onset than juvenile-onset MDD (Jaffee *et al.* 2002).

Third, GAD, whether co-morbid or pure, was associated with several risk factors across multiple domains of risk during childhood: maternal internalizing symptoms, low SES, maltreatment, inhibited temperament, internalizing and conduct problems, and high scores on negative emotionality. Moreover, GAD-only cases were similar to co-morbid MDD+GAD on the level of many risks. This pattern for the GAD-only group (broad risks, levels similar to the co-morbid group) contrasted against the pattern for the MDD-only group (somewhat narrower risks, lower levels than the co-morbid group). These patterns find support in previous studies (Ormel *et al.* 1994; Kessler *et al.* 1996, 1999, 2002; Judd *et al.* 1998; Wittchen *et al.* 2000; Phillips *et al.* 2005). That GAD (with or without MDD) has its own set of risk factors not shared with pure MDD is consistent with the view that the presence of GAD may signal a distinct developmental pathway to more serious distress disorder (Kessler, 2005).

This study's findings should be considered in light of its potential limitations. First, although past Dunedin Study findings have generally mirrored those from other countries, research must check whether findings here transcend local conditions and ethnic variation. Second, although we focused on GAD because its relation to MDD is the subject of nosological debate, research should examine other anxiety disorders co-morbid with MDD (Roy-Byrne *et al.* 2000; Stein *et al.* 2001). Third, the gaps between Dunedin assessment windows may have led us to undercount cases. However, we suspect undercounting is trivial because only 4% of cohort members who reported on the life-history

calendar that they received mental-health services in gaps between assessment years had escaped the study's diagnostic net (Moffitt *et al.* 2006). The gaps probably led us to undercount episodes, and consequently to under-identify recurrence, but there is no reason to expect that missed episodes between assessments would be less, or more, co-morbid. Any misassignment of cases having disorder in gaps between assessments to the healthy control group would have made group differences harder to detect. Fourth, our data are right-hand censored at age 32. There is no prospective study yet that can report whether co-morbidity rates or risk predictors change across midlife; continued follow-ups are needed. Fifth, although we were able to examine prospective measures operationalizing the domains of risk specified by leading theorists (Kendler *et al.* 2002; Watson, 2005), we were not able to include biological markers of the activity of the autonomic nervous system, stress hormones, or neurotransmitter systems. Such biomarkers may in future prove essential for resolving nosological questions.

Some readers may find the cumulative prevalence rates of MDD and GAD in the Dunedin cohort unexpectedly high. Several factors may contribute to the Dunedin Study's high prevalence. We diagnose GAD and MDD regardless of the presence of other disorders, eschewing exclusionary criteria followed in most studies (and GAD was diagnosed with a 1-month minimum duration). Also, the cohort's 96% participation rate let us count disordered individuals overlooked by most studies. Moreover, after more than 30 years of participation with no confidentiality violation, longitudinal study members are more forthcoming about psychiatric symptoms than participants in single-wave surveys. Dunedin diagnoses are based on concurrent symptom reports; lifetime cases are not under-counted due to failure to recall criterion symptoms from years past, as occurs in retrospective surveys. The prospective cumulative prevalence reported here comprises a sum of cases ascertained in a series of successive prospective past-year assessments, each of which diagnosed a percentage of the cohort very similar to the percentage diagnosed in the past-year assessments of surveys such as the NCS and NCS-R (Kessler *et al.* 1993, 1999, 2005). Finally, expectations for lower cumulative prevalence

come from retrospective surveys, which are known to underestimate lifetime disorder (Simon & VonKorff, 1995; Kessler *et al.* 2002; Andrews *et al.* 2005). However, cumulative prevalence rates now emerging from prospective longitudinal studies in NC, NY, and Oregon (Lewinsohn *et al.* 1993; Costello *et al.* 2003; Jaffee *et al.* 2005) are elevated like the Dunedin Study's. We suspect that cumulative prevalence rates of GAD and MDD are in reality higher than previously estimated from one-wave retrospective surveys.

This article reports that of the several risk factors studied, relatively few were clearly shared by MDD and GAD. GAD had specific risk factors not shared by MDD (childhood adversity and behavior) and MDD had specific risk factors not shared by GAD (predisposing family history and personality). These findings of differential risk factors point to partly different etiologies, which would not be consistent with collapsing the two into one disorder in future nosological systems. However, the clearest finding here was the similar broad, serious risk history among individuals who develop either pure GAD or co-morbid MDD+GAD as adults. The co-morbid group is common in the population and particularly constitutes a substantial mental health burden (Moffitt *et al.* in press). Antecedent risk factors confirmed here suggest prevention targets to reduce this burden.

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DECLARATION OF INTEREST

None.

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