
A Twin Study of Lifetime Generalized Anxiety Disorder (GAD) in Older Adults: Genetic and Environmental Influences Shared by Neuroticism and GAD

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The nature of Generalized Anxiety Disorder (GAD) and worry across the lifespan remains incompletely understood. We investigated genetic and environmental influences on GAD and the proportion of genetic and environmental variation in GAD that is shared with neuroticism in older adult twins. Participants included 1618 monozygotic and 2291 same-sexed dizygotic twin pairs from the Swedish Twin Registry aged 55 to 74. Participants provided personality information in 1973 and also participated in a telephone screening between 1998 and 2002 that included an assessment for lifetime GAD. Univariate biometric models indicated that both GAD and neuroticism were moderately heritable (.27 and .47, respectively), while the balance of variation reflected environmental factors unique to the individual. Bivariate analyses indicated that approximately one third of the genetic influences on GAD were in common with genetic influences on neuroticism, while individual specific environmental influences were virtually unshared between GAD and neuroticism. Analyses of sex effects suggested that men and women differed in the frequency of lifetime GAD and level of neuroticism; however, no sex differences for genetic and environmental influences for either trait were identified.

Generalized Anxiety Disorder (GAD) is a commonly occurring anxiety disorder in the general population, with lifetime rates estimated at 5.7% in the National Comorbidity Survey Replication (Kessler, Chiu, et al., 2005). Since its inception in the 1980s, the definition of GAD has undergone several revisions in both the United States diagnostic classification system (American Psychiatric Association, 1980, 1987, 1994) and in the International Classification of Disease system (World Health Organization, 1973, 1992). GAD in adults currently is defined as excessive, uncontrollable worry, about a number of events, more days than not for at least 6 months, associated with symp-

toms of negative affect or tension, such as restlessness, being easily fatigued, concentration problems, irritability, muscle tension and sleep disturbances, which is associated with significant dysfunction (American Psychiatric Association, 1994).

GAD is a chronic disorder that most often arises in childhood or adolescence and persists until late life (Beck et al., 1996; Blazer et al., 1991; Kessler, Brandenburg, et al., 2005; Le Roux et al., 2005). Remission rates for GAD are relatively low across age groups (Schuurmans et al., 2005; Woodman et al., 1999). Relatively little is known about GAD in older adults compared to younger adults, despite the fact that it is one of the most prevalent psychiatric disorders in later life, with rates estimated as high as 7.3% (Beekman et al., 1998). Even less is known about the course and variations of GAD within the older adult population, though some research is beginning to appear (Beck et al., 1996; Diefenbach et al., 2003; Lenze et al., 2005; Mohlman et al., 2004; Stanley et al., 2001; Wetherell et al., 2003). However, because of its low remission rate, a substantial proportion of older adults reporting a lifetime history of GAD are likely to be experiencing a current episode of GAD as well.

Worry, the hallmark of GAD, seems to be a common behavior among both young adults (Craske et al., 1989) and older adults (Montorio et al., 2003; Wetherell et al., 2003). Worry represents the most frequent mental health topic raised with general practitioners (Goldberg et al., 1987) and anxiety disorders are the most common mental health problems for older adults (Flint, 1994; Kessler, Berglund, et al., 2005). Worry has important consequences and correlates; those older adults

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who report high levels of worry also tend to report higher levels of anxiety symptoms and poorer health compared to older adults who do not worry (Beck et al., 1996; Wetherell et al., 2003, 2004; Wisocki, 1988) as well as possibly an increased risk for Alzheimer's disease in Caucasians (Wilson et al., 2003, 2005).

Research indicates that several factors are related to the occurrence of GAD and chronic worry, such as sociodemographic variables, psychological history, genetic influences, and the personality variable neuroticism. Behavioral genetic studies of GAD have found that 14% to 40% of the variation in GAD is attributed to additive genetic factors with the balance of variation due to individual specific environmental factors, while shared environment has not been found to significantly influence GAD (Kendler et al., 1992; Kendler et al., 1995; Roy et al., 1995; Scherrer et al., 2000; see Hettema, Neale, et al., 2001, for a review). Despite differences between genders in the rate of GAD, genetic and environmental influences appear to be similar across genders (Hettema, Prescott, et al., 2001), suggesting that men and women differ in liability threshold (i.e., prevalence) rather than in underlying causes.

Neuroticism, which influences worry and GAD, is thought to be a basic component of personality (Eysenck & Eysenck, 1985). Neuroticism represents a tendency toward emotional intensity (McFatter, 1998), such that people with higher levels of neuroticism experience more intense and more frequent levels of distress. Recent research in younger adults has found that higher neuroticism scores were significantly related to both a GAD diagnosis and a measure of GAD symptom severity (Gomez & Francis, 2003). Higher levels of neuroticism also have been related to increased levels of worry symptoms on the Penn State Worry Questionnaire in younger adults (Robichaud & Dugas, 2005).

Behavioral genetic studies have found that neuroticism is moderately heritable, with heritability estimates of 40% to 60% in adults of different ages (Bouchard, 2004; Loehlin, 1992). Additive genetic and individual specific environmental factors explain significant amounts of variation among individuals, while shared environmental factors consistently have been found to account for less than 10% of the variation (Floderus-Myrhed et al., 1980; Lake et al., 2000). The multivariate genetic relationship between personality and mental health outcomes has increasingly been studied over the last decade (Carey & DiLalla, 1994; Kendler et al., 2004), and significant genetic correlations have been found between neuroticism and several mental health conditions, such as depression and anxiety (Fanous et al., 2002; Hettema et al., 2004; Jardine et al., 1984; Jorm et al., 2000; Kendler et al., 1993). However, no studies have investigated the genetic relationship between neuroticism and GAD or anxiety symptoms in older adults. In younger and middle-aged adults, one study investigated the multivariate genetic relationship between neuroticism and

GAD (Hettema et al., 2004) and another investigated neuroticism and anxiety symptoms (Jardine et al., 1984). Hettema and his colleagues (2004) found that the additive genetic factors influencing GAD were almost indistinguishable from those influencing liability to neuroticism, but they found only a modest overlap of individual specific environmental influences. They also found genetic correlations to be the same in women and men. In a study of the bivariate genetic relationship between anxiety symptoms and neuroticism among adults aged 18 to 64 years, Jardine et al. (1984) found a genetic correlation of .8 and an environmental correlation of .4.

The purpose of the current study was to investigate the degree of overlap in genetic and environmental influences shared by lifetime GAD and neuroticism in a population-based sample of older adults. Based on prior research on GAD and neuroticism, it was expected that univariate behavioral genetic models would indicate that both additive genetic and individual specific environmental factors were important sources of variation for both GAD and neuroticism. Previous work with younger adults with GAD and for anxiety symptoms across the adult lifespan suggests that the genetic influences between GAD and neuroticism would be strongly correlated, whereas individual specific environmental influences would be less strongly correlated. In addition, this study measured neuroticism 25 years prior to the GAD assessment whereas previous studies used concurrent measures.

Materials and Methods

Sample

Participants included all members of the Swedish Twin Registry born in 1926 through 1944 who completed a mailed questionnaire in 1973 and were interviewed by telephone between 1998 and 2002 for the Screening Across the Lifespan-Twin Study (SALT; Lichtenstein et al., 2002). The Swedish Twin Registry consists of a nearly complete registration of all twin births in Sweden. In 1973, a questionnaire was sent to all same-sex twin pairs born from 1926 to 1958. The questionnaire collected twin and family information, demographics, physical health data, and psychosocial variables, including personality measures (Lichtenstein et al., 2002). The SALT interview conducted between 1998 and 2002 included physical health, mental health, and lifestyle variables, including a screen for lifetime GAD that contained questions about worry. The present sample includes the cohort who was aged 55 to 74 when contacted for the SALT interview.

There were 13,107 individuals from same-sex twin pairs who provided usable responses to the neuroticism measure in 1973 and who were alive and aged 55 and older in 1998. Of these, 10,566 (80.6%) individuals participated in the SALT study including the GAD screening, 223 (1.7%) were not interviewable due to physical or cognitive impairments, and 2318 (17.7%) either refused to participate or could not be found for

the SALT study. The dataset included 707 male monozygotic (MZ), 911 female MZ, 1010 male dizygotic (DZ), and 1281 female DZ twin pairs as well as 2748 singletons (1384 males and 1364 females; these were individuals whose twins had died or refused to participate). The average age of all participants was 62.2 years ($SD = 5.5$ years). There were 4818 (45.6%) males and 5748 (54.4%) females. For the Swedish Twin Registry study, zygosity was assigned using standard self-report items, which is 98% accurate when validated against biological markers (see Lichtenstein et al., 2002, for details). This project was approved by the Swedish Data Inspection Authority, the Ethics Committee of the Karolinska Institutet, and the Institutional Review Board of the University of Southern California.

Measures

Generalized anxiety disorder. Lifetime GAD was diagnosed from the computerized Composite International Diagnostic Interview — Short Form (CIDI-SF; Kessler et al., 1998). This computer assisted interview results in diagnoses that map onto Diagnostic and Statistical Manual of Mental Disorders (3rd ed., rev.; DSM-III-R; American Psychiatric Association, 1987) diagnostic categories. For the SALT study, the CIDI-SF was modified from the original form, which assessed 12-month prevalence, to assess lifetime prevalence. In addition, for this study, the first GAD screening question was used as a measure of worrying: ‘have you had an episode lasting at least a month in which you felt worried and anxious most of the time?’ Thus the GAD variable used in this study has two thresholds rather than one, corresponding to three levels: (1) reported neither GAD nor significant worry behavior; (2) reported significant worrying behavior; and (3) diagnosed with GAD. Neither GAD nor significant worry was reported by 82.6% of the sample. Significant worrying behavior, but not GAD, was reported by 14.5% of the sample. GAD criteria were met by 2.9%.

Neuroticism measure. The neuroticism measure used in this study was a short form of the Eysenck Personality Questionnaire (EPI-Q; Floderus, 1974) used during the 1973 data collection. The measure has nine items, using a dichotomous response scale (yes/no). Scores were prorated for up to two missing items. Cronbach’s alpha for the neuroticism subscale of the EPI-Q was .75 (Floderus-Myrhed et al., 1980). Because GAD was measured on a categorical scale, in order to include neuroticism in the bivariate behavioral genetic models, the neuroticism scale needed to be categorical as well (Neale & Cardon, 1992). Therefore, participants were divided into three groups based on neuroticism scores with those scoring 0 in the low group (20.2%), those scoring 1 to 2 were in the midlevel group (36%) and those scoring 3 and above were in the high group (43.8%).

Statistical Analyses

Descriptive statistics were conducted using SAS 9 (SAS Institute, 2001) and biometric models were computed using the Mx software package (Neale et al., 1999).

Following Neale et al. (1999), we used maximum likelihood estimation with raw data in analyzing associations using ordinal data, which allowed us to include both complete and incomplete twin pairs. Singletons contributed to estimating thresholds, while only complete pairs contributed to twin similarities. Thresholds were tested for equality between sexes. Polychoric correlations were used to describe the degree of covariation or similarity between pairs of twins for the measured constructs.

Univariate models were used to estimate the proportion of variation in each variable attributed to genetic influences (A), shared environmental influences (C), and individual specific environmental influences (E) for men and for women separately (Model 1). Model 2 equated effects of A, C, and E for men and women in order to assess whether quantitative sex differences exist. Subsequent models were tested to investigate the deterioration of model fit if sources of variation were dropped. Model 3 included only C and E, and Model 4 included only A and E. The viability of reduced models compared to the saturated models was assessed using two statistics. First, fit was assessed by taking the difference between -2 times the log likelihood ($-2ll$) for the full model and reduced model. The second statistic used to assess differences between models was Akaike’s Information Criterion (AIC; Akaike, 1987).

To study how genetic and environmental sources of variation on GAD and neuroticism are related, we used a bivariate Cholesky decomposition procedure. For each latent factor, the variance is decomposed into influences of A, C, and E. Finally, the phenotypic correlation between GAD and neuroticism was decomposed into three separate components describing the relationship between the latent traits: additive genetic (r_g), shared environment (r_c), and individual specific environment (r_e) components.

Results

Phenotypic Results

There were sex differences in prevalences for GAD and in means for neuroticism. Whereas the overall lifetime rate of GAD was 2.90%, the rate for women was 3.95% and 1.74% for men. This sex difference was significant, $\chi^2(1) = 44.64$, $p < .0001$. Excluding individuals with GAD, the overall rate of reporting a worry episode was 18.6% among women compared to 10.7% among men, $\chi^2(1) = 125.98$, $p < .0001$. Rates for GAD (as a multiple threshold trait) did not differ by zygosity group for either women, $\chi^2(2) = 3.06$, $p = .217$, or for males $\chi^2(2) = 1.86$, $p = .397$. Average score on neuroticism for women (3.0) was significantly higher than that of men (2.2), $t(10,504) = 18.96$, $p < .0001$. There was a higher proportion of men (25.5%) in the low neuroticism group compared to women (15.9%), whereas a larger proportion of women were in the high neuroticism group (50.9%) compared to men (35.3%), $\chi^2(2) = 293.10$, $p < .0001$. Age was only weakly,

although significantly negatively correlated with both neuroticism ($\rho = -.02$, $p = .02$) and with GAD ($\rho = -.07$, $p < .001$). However, when broken down by gender, age was not significantly correlated with neuroticism in men ($\rho = .001$, $p = .96$), whereas it was in women ($\rho = -.04$, $p = .002$). GAD remained significantly correlated with age in both men and women.

GAD and neuroticism were significantly correlated, polychoric correlation = .29, $p < .001$. The polychoric correlations between worrying and neuroticism were similar for both genders, men = .25, $p < .001$, and women, .28, $p < .001$. Using logistic regression to predict the level of GAD variable, controlling for age and gender, neuroticism was a significant predictor, the odds ratio (with 95% confidence interval) was 1.94 (1.73–2.16).

Twin Pair Polychoric Correlations

Before calculating correlations, assumptions about equality of thresholds across zygosity were tested (Neale & Cardon, 1992). No significant differences in threshold liabilities by zygosity were found for either GAD as a multiple threshold trait ($\Delta\chi^2 = 16.19$, $df = 12$, $AIC = -7.81$) or neuroticism ($\Delta\chi^2 = 11.75$, $df = 12$, $AIC = -12.25$). However, the thresholds could not be equated for men and women for either variable. Therefore, polychoric correlations were calculated for each sex by zygosity separately (MZ-male, MZ-female, DZ-male, and DZ-female twin pairs). See Table 1 for polychoric correlations and 95% confidence intervals for each of the four groups. Polychoric correlations for the GAD trait collapsed across sex were .23 for MZ and .13 DZ twin pairs. There were no differences in the thresholds across zygosity groups within each sex, $\Delta\chi^2 = 7.59$, $df = 4$, $AIC = -.41$. Polychoric correlations were also run with age-adjusted thresholds. While the age beta was significant, the effect was very small ($-.002$). Therefore, age adjustments were not used in subsequent analyses.

Biometric Analyses

Results from univariate analyses (not shown) indicated that the AE model fit the data the best for both GAD and neuroticism. For GAD, 27% of the variance reflected additive genetic factors with the rest attributed to individual specific environmental factors. The results for neuroticism were similar to previous reports (Floderus-Myrhed et al., 1980) with additive genetic factors accounting for 47% of the variance. For both variables, models for males and females could be equated.

For the Cholesky decomposition models, Model 2 served as the saturated model, which included estimates for A, C, and E, but was equated between the sexes based on results from the univariate analyses. Successive model comparisons showed that all three C paths could be dropped without significant loss of fit ($\Delta\chi^2 = -.006$, $df = 3$, $AIC = -6.006$). Using the AE model for comparisons, the common genetic path could not be dropped ($\Delta\chi^2 = 61.61$, $df = 1$, $AIC = 59.61$). It

Table 1

Intra-class and Cross-Twin Cross-Trait Polychoric Correlations (and 95% Confidence Intervals) for GAD and Neuroticism Measures for Male–Male and Female–Female Twin Pairs by Zygosity

	Intra-class correlations		Cross-twin cross-trait correlations
	GAD	Neuroticism	
MZM	.23 (.06, .39)	.42 (.34, .49)	.19 (.06, .31)
MZF	.32 (.20, .46)	.49 (.42, .55)	.24 (.14, .33)
DZM	.11 (-.04, .25)	.17 (.10, .24)	.03 (-.07, .14)
DZF	.08 (-.02, .17)	.23 (.16, .30)	.12 (.03, .220)

Note: Intra-class correlations are correlations on one variable between Twin 1 and Twin 2 of the same pair.

Cross-twin cross-trait correlations are between Twin 1 on one variable and Twin 2 on the other variables.

GAD = three level measure of generalized anxiety disorder, Neuroticism = three level measure of neuroticism.

MZM = male monozygotic, MZF = female monozygotic, DZM = male dizygotic, and DZF = female dizygotic pairs.

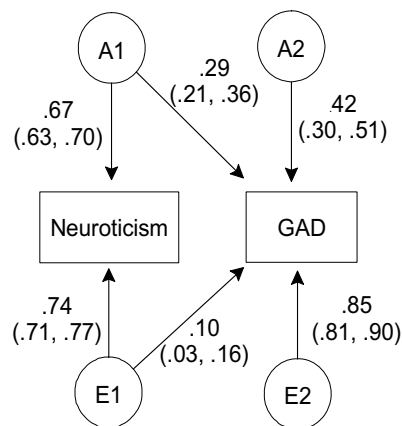
was also necessary to retain the second genetic path ($\Delta\chi^2 = 16.59$, $df = 1$, $AIC = 14.59$), indicating that not all of the genetic variance in GAD was explained by neuroticism. Similarly, the common path for E could not be dropped ($\Delta\chi^2 = 8.47$, $df = 1$, $AIC = 6.47$), although environmental factors influencing GAD were largely individual specific and not those shared with neuroticism. Figure 1 depicts the Cholesky model and the parameter estimates from the final model. The correlation between genetic factors was .57, indicating that about one third of the genetic variation in GAD was shared with neuroticism. The correlation between individual specific environmental factors was much lower, at .11.

Post Hoc Analyses

Post hoc analyses using three alternative definitions of neuroticism thresholds were conducted to assure that results were not dependent on definition. The post hoc tests included an alternative 3-level categorization based on mean scale score + 1 SD, a 4-level categorization, and a 6-level categorization. Polychoric correlations and univariate models showed no loss of information with different number of thresholds or with the particular three categories used in the analyses above.

Discussion

This study investigated the genetic and environmental sources of variation for lifetime GAD and neuroticism in a population-based sample of older twins. About one quarter of the variation in GAD was attributed to genetic factors, which is similar to estimates of genetic

**Figure 1**

Cholesky decomposition parameter estimates (and 95% confidence intervals) for additive genetic and individual specific environmental influences on lifetime GAD and neuroticism measured in 1973.

influences on GAD among younger and middle-aged adults (Kendler et al., 1992, 1995; Roy et al., 1995; Scherrer et al., 2000). In bivariate analyses, we found that the genetic correlation between neuroticism and GAD was .57. This suggests that GAD and neuroticism share many of the same genes influencing liability. This is especially notable since neuroticism was measured in 1973 and lifetime GAD was assessed in 1998. This estimate can be compared to the genetic correlation of .80 between GAD and neuroticism reported for young and middle-aged adults (Hettema et al., 2004) and the genetic correlation of .80 reported by Jardine et al. (1984) between anxiety symptoms and neuroticism, which in both cases were measured concurrently. The lower correlation estimate in the present study may be due to a number of factors. The strength of the genetic correlation could be constrained by the strength of the phenotypic correlation between GAD and neuroticism. In this study, the polychoric correlation was .29 compared to polychoric correlations of .32 for male twin pairs, .52 for female twin pairs, and .28 for opposite-sexed twin pairs in Hettema et al. (2004) and a Pearson correlation of .58 between neuroticism and GAD severity ratings in phenotypic study by Gomez and Francis (2003). In addition, the older age of the sample, the use of a short form of the Eysenck personality inventory, or the time lag in measurement between the two variables, could influence the strength of the genetic correlation.

Similar to previous studies, we found that in addition to genetic factors, only individual specific environmental factors, not shared environment, influenced GAD (Kendler et al., 1992; Roy et al., 1995). The environmental correlation found in this study was .11, suggesting that the types of individual-specific events that influence GAD are not strongly related to those that affect neuroticism scores. So, while there was significant overlap in the genes affecting liability for GAD and neuroticism, the environmental factors

influencing GAD are largely not the same as those of neuroticism. The magnitude of the correlation is similar to the correlation of .19 found by Hettema et al. (2004) between GAD and neuroticism but smaller than the .40 found by Jardine et al. (1984) between anxiety symptoms and neuroticism.

The results of this study further support those of other behavioral genetic studies that suggest that sex differences in GAD reflect differences in prevalence rather than sex differences in contributions of genetic and environmental factors to liability for the trait (Hettema, Prescott et al., 2001; Kendler et al., 2003; Roy et al., 1995). Future studies can focus on possible factors underlying susceptibility to GAD that are more likely to occur in women or place them at increased risk of developing GAD. In addition, because we found that the majority (72%) of the variance in GAD was related to individual specific environment factors independent of neuroticism, future studies need to focus on factors related to personal life experiences not shared among family members. Recent work on cognitive models of GAD and worry (Borkovec et al., 1999; Wells, 2004) which focus on an individual's cognitive distortions related to the values of their worrying behavior, are possible individualistic processes, which may influence the development of GAD.

Future studies need to address the possibility of gene-environment correlation in which high levels of neuroticism are more likely to lead to exposure to stressful experiences, which in turn leads to GAD or worry. Research has shown that people with affective illness, women who have suffered trauma, and those who experience negative life events are more likely to be re-exposed to stressful environments (Brostedt & Pedersen 2003; Dansky et al., 1998; Heady & Wearing; 1989). Possibly those who are neurotic are more likely to seek out worry initiating situations than those with lower levels of neuroticism. Recent research on pathological worrying and GAD seems to support this in that individuals with pathological worry are not only more likely to worry about minor matters (Craske et al., 1989; Wetherell et al., 2003) and to worry about their worrying (metaworry; Wells, 2004), they also are more likely to report distortions about the value of worrying that lead to increased worrying (Borkovec et al., 1999; Davey & Levey, 1999).

Several strengths of this research can be identified. First, this was the first study to measure lifetime GAD in later life. Second, the use of a population-based sample allows for greater generalizability of findings. In addition, the large sample size allows for parameter estimates with smaller standard errors. Another advantage is that neuroticism was measured 25 years prior to the screening for lifetime GAD; this should provide a more reliable estimate of the correlation between individual specific environmental factors influencing the two measures, under the assumption that measurement error is not correlated over time. Finally, the diagnoses of lifetime GAD required a 6-month minimum

symptom duration, as specified in the DSM-IV (American Psychiatric Association, 1994), in contrast to the 1 month minimum duration used in other behavioral genetic studies of GAD (Hettema et al., 2004).

Several limitations in this study can be identified. First, the neuroticism instrument used in this study included a question about worry. However, when the question was dropped from the neuroticism scale and the data reanalyzed, the pattern of results was unchanged. Second, the measure of GAD used in this study did not identify the onset of either the disorder or the worrying episode. This study used a measure of neuroticism taken 25 or more years prior to the assessment of worrying behavior. However, because the version of the CIDI-SF used in this study measured lifetime occurrence of GAD, it cannot be assumed that higher neuroticism scores necessarily preceded GAD or worrying.

Finally, our estimate of lifetime GAD may be viewed as low (2.9%) in comparison to the recent estimate of 5.7% in the National Comorbidity Survey Replication (Kessler, Chiu, et al., 2005), which used DSM-IV (American Psychiatric Association, 1994) criteria. However, prevalence estimates for GAD in adult populations have varied since its introduction in DSM-III (American Psychiatric Association, 1980), probably due to both changes in diagnostic definitions and assessment procedures (see Carter et al., 2001, for a review). The CIDI-SF used in this study is most similar to DSM-III-R (American Psychiatric Association, 1987) criteria, and our rate of lifetime GAD is similar to those found in other studies using DSM-III-R (American Psychiatric Association, 1987) criteria (1.2% – 5.1%; Hettema, Prescott, et al., 2001; Scherrer et al., 2000; Stein & Heimberg, 2004; Wittchen et al., 1994). These studies are based on younger samples, for which one would expect lower rates than those we see in adults over the age of 40. Thus, the lower lifetime prevalence may be due to recall bias. In long-term follow-up studies ranging from 13 to 25 years after index diagnosis, Cohen's kappa coefficients for replicating lifetime diagnoses based on retrospective recall have been low, .32–.35 (Andrews et al., 1999; Mannuzza et al., 2002; Thompson et al., 2004) with the absence of a diagnosis being better recalled than the presence of one (Thompson et al., 2004).

In summary, this was the first study to investigate the genetic and environmental influences shared between lifetime GAD and neuroticism in older adults. Using a population-based sample from the Swedish Twin Registry, we found 2.9% of the population had GAD at some point during their lifetime, while 14.5% of older adults reported a significant worry episode during their lifetime. In addition, while there was a significant overlap of genetic effects between GAD and neuroticism, there appears to be little commonality in environmental influences with individual specific environmental factors accounting for the vast majority of the variation in GAD.

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References

- Akaike, H. (1987). Factor analysis and AIC. *Psychometrics*, 7, 317–333.
- American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.
- American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Andrews, G., Anstey, K., Brodaty, H., Issakidis, C., & Luscombe, G. (1999). Recall of depressive episode 25 years previously. *Psychological Medicine*, 29, 787–791.
- Beck, J. G., Stanley, M. A., & Zebb, B. A. (1996). Characteristics of generalized anxiety disorder in older adults: A descriptive study. *Behaviour Research and Therapy*, 34, 225–234.
- Beekman, A. T., Bremmer, M. A., Deeg, D. J., van Balkom, A. J., Smit, J. H., de Beurs, E., van Dyck, R., & van Tilburg, W. (1998). Anxiety disorders in later life: A report from the Longitudinal Aging Study Amsterdam. *International Journal of Geriatric Psychiatry*, 13, 717–726.
- Blazer, D., George, L. K., & Hughes, D. (1991). The epidemiology of anxiety disorders: An age comparison. In C. Salzman & B. D. Liebowitz (Eds.), *Anxiety in the elderly: Treatment and research* (pp. 17–30). New York: Springer.
- Borkovec, T. D., Hazlett-Stevens, H., & Diaz, M. L. (1999). The role of positive beliefs about worry in generalized anxiety disorder and its treatment. *Clinical Psychology and Psychotherapy*, 6, 126–138.
- Bouchard, T. J. (2004). Genetic influence on human psychological traits. *Current Directions in Psychological Science*, 13, 148–151.
- Brostedt, E. M., & Pedersen, N. L. (2003). Stressful life events and affective illness. *Acta Psychiatrica Scandinavica*, 107, 208–215.
- Carey, G., & DiLalla, D. L. (1994). Personality and psychopathology: Genetic perspectives. *Journal of Abnormal Psychology*, 103, 32–43.
- Carter, R. M., Wittchen, H. U., Pfister, H., & Kessler, R. C. (2001). One-year prevalence of subthreshold and threshold DSM-IV generalized anxiety disorder in a nationally representative sample. *Depression and Anxiety*, 13, 78–88.
- Craske, M., Rapee, R., Jackel, L., & Barlow, D. (1989). Qualitative dimensions of worry in DSM-III-R general-

- ized anxiety subjects and nonanxious controls. *Behaviour Research and Therapy*, 27, 397–402.
- Dansky, B. S., Brady, K. T., & Saladin, M. E. (1998). Untreated symptoms of PTSD among cocaine-dependent individuals: Changes over time. *Journal of Substance Abuse Treatment*, 15, 499–504.
- Davey, G. C. L., & Levy, S. (1999). Internal statements associated with catastrophic worrying. *Personality and Individual Differences*, 26, 21–32.
- Diefenbach, G. J., Hopko, D. R., Feigon, S., Stanley, M. A., Beck, J. G., & Averill, P. M. (2003). 'Minor GAD': Characteristics of subsyndromal GAD in older adults. *Behaviour Research and Therapy*, 41, 481–487.
- Eysenck, H. J., & Eysenck, M. W. (1985). *Personality and individual differences*. New York: Plenum Press.
- Fanou, A., Gardner, C. O., Prescott, C. A., Cancro, R., & Kendler, K. S. (2002). Neuroticism, major depression and gender: A population-based twin study. *Psychological Medicine*, 32, 719–728.
- Flint, A. J. (1994). Epidemiology and comorbidity of anxiety disorders in the elderly. *American Journal of Psychiatry*, 151, 640–649.
- Floderus, B. (1974). Psycho-social factors in relation to coronary heart disease and associated risk factors. *Nordisk Hygienisk Tidskrift* [Monograph, Suppl. 6], 1–148.
- Floderus-Myrhed, B., Pedersen, N. L., & Rasmuson, I. (1980). Assessment of heritability for personality based on a short-form of the Eysenck Personality Inventory: A study of 12,898 twin pairs. *Behavior Genetics*, 10, 153–162.
- Goldberg, D. P., Bridges, K., Duncan-Jones, P., & Grayson, D. (1987). Dimensions of neurosis seen in primary care settings. *Psychological Medicine*, 17, 461–470.
- Gomez, R., & Francis, L. M. (2003). Generalized anxiety disorder: Relationships with Eysenck's, Gray's and Newman's theories. *Personality and Individual Differences*, 34, 3–17.
- Heady, B., & Wearing, A. (1989). Personality, life events, and subjective well-being: Toward a dynamic equilibrium model. *Journal of Personality and Social Psychology*, 57, 731–739.
- Hettema, J., Neale, M. C., & Kendler, K. S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *American Journal of Psychiatry*, 158, 1568–1578.
- Hettema, J., Prescott, C., & Kendler, K. (2001). A population-based twin study of generalized anxiety disorder in men and women. *Journal of Nervous and Mental Disease*, 189, 413–420.
- Hettema, J., Prescott, C., & Kendler, K. (2004). Genetic and environmental sources of covariation between generalized anxiety disorder and neuroticism. *American Journal of Psychiatry*, 161, 1581–1587.
- Jardine, R., Martin, N. G., & Henderson, A. S. (1984). Genetic covariation between neuroticism and the symptoms of anxiety and depression. *Genetic Epidemiology*, 1, 89–107.
- Jorm, A. F., Christensen, H., Henderson, A. S., Jacomb, P. A., Korten, A. E., & Rodgers, B. (2000). Predicting anxiety and depression from personality: Is there a synergistic effect of neuroticism and extraversion? *Journal of Abnormal Psychology*, 109, 145–149.
- Kendler, K. S., Kuhn, J., & Prescott, C. A. (2004). The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry*, 161, 631–636.
- Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992). Major depression and generalized anxiety disorder: Same genes, (partly) different environments? *Archives of General Psychiatry*, 49, 716–722.
- Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). A longitudinal twin study of personality and major depression in women. *Archives of General Psychiatry*, 50, 853–862.
- Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry*, 60, 929–937.
- Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry*, 52, 374–383.
- Kessler, R. C., Andrews, G., Mroczek, D., Ustun, B., & Wittchen, U.-L. (1998). The World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF). *International Journal of Methods in Psychiatric Research*, 7, 171–185.
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62, 593–602.
- Kessler, R. C., Brandenburg, N., Lane, M., Roy-Byrne, P., Stang, P. D., Stein, D. J., & Wittchen, H. (2005). Rethinking the duration requirement for generalized anxiety disorder: Evidence from the National Comorbidity Survey Replication. *Psychological Medicine*, 35, 1073–1082.
- Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62, 617–627.
- Lake, R. I. E., Eaves, L. J., Maes, H. H. M., Heath, A. C., & Martin, N. G. (2000). Further evidence against the environmental transmission of individual differences in neuroticism from a collaborative study of 45,850 twins and relatives on two continents. *Behavioral Genetics*, 30, 223–233.

- Le Roux, H., Gatz, M., & Wetherell, J. L. (2005). Age at onset of generalized anxiety disorder in older adults. *American Journal of Geriatric Psychiatry, 13*, 23–30.
- Lenze, E. J., Mulsant, B. H., Mohlman, J., Shear, M. K., Dew, M. A., Schulz, R., Miller, M. D., Tracey, B., & Reynolds, C. F., III. (2005). Generalized anxiety disorder in late life: Lifetime course and comorbidity with major depressive disorder. *American Journal of Geriatric Psychiatry, 13*, 77–80.
- Lichtenstein, P., De Paire, U., Floderus, B., Svartengren, M., Svedberg, P., & Pedersen, N. L. (2002). The Swedish Twin Registry: A unique resource for clinical, epidemiological and genetic studies. *Journal of Internal Medicine, 252*, 184–205.
- Loehlin, J. C. (1992). *Genes and environment in personality development*. Newbury Park, CA: Sage.
- Mannuzza, S., Klein, R. G., Klein, D. F., Bessler, A., & ShROUT, P. (2002). Accuracy of adult recall of childhood Attention Deficit Hyperactivity Disorder. *American Journal of Psychiatry, 159*, 1882–1888.
- McFatter, R. M. (1998). Emotional intensity: Some components and their relations to extraversion and neuroticism. *Personality and Individual Differences, 24*, 747–758.
- Mohlman, J., de Jesus, M., Gorenstein, E. E., Kleber, M., Gorman, J. M., & Papp, L. A. (2004). Distinguishing generalized anxiety disorder, panic disorder, and mixed anxiety states in older treatment-seeking adults. *Anxiety Disorders, 18*, 275–290.
- Montorio, I., Nuevo, R., Marquez, M., Izal, M., & Losada, A. (2003). Characterization of worry according to severity of anxiety in elderly living in the community. *Aging and Mental Health, 7*, 334–341.
- Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (1999). *Mx: Statistical modeling* (5th ed.). Richmond, VI: Department of Psychiatry, Medical College of Virginia of Virginia Commonwealth University.
- Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht, the Netherlands: Kluwer Academic.
- Robichaud, M., & Dugas, M. J. (2005). Negative problem orientation (Part II): Construct validity and specificity to worry. *Behaviour Research and Therapy, 43*, 403–412.
- Roy, M.-A., Neale, M. C., Pedersen, N. L., Mathe, A. A., & Kendler, K. S. (1995). A twin study of generalized anxiety disorder and major depression. *Psychological Medicine, 25*, 1037–1050.
- SAS Institute. (2001). SAS program, version 9. Cary, NC: Author.
- Scherrer, J. F., True, W. R., Xian, H., Lyons, M. J., Eisen, S. A., Goldberg, J., Lin, N., & Tsuang, M. T. (2000). Evidence for genetic influences common and specific to symptoms of generalized anxiety and panic. *Journal of Affective Disorders, 57*, 25–35.
- Schuurmans, J., Comijs, H. C., Beekman, A. T. F., de Beurs, E., Deeg, D. J. H., Emmelkamp, P. M. G., & van Dyck, R. (2005). The outcome of anxiety disorders in older people at 6-year follow-up: Results from the Longitudinal Aging Study Amsterdam. *Acta Psychiatrica Scandinavica, 111*, 420–428.
- Stanley, M. A., Novy, D. M., Bourland, S. L., Beck, J. G., & Averill, P. M. (2001). Assessing older adults with generalized anxiety: A replication and extension. *Behaviour Research and Therapy, 39*, 221–235.
- Stein, M. B., & Heimberg, R. G. (2004). Well-being and life satisfaction in generalized anxiety disorder: Comparison to major depression disorder in a community sample. *Journal of Affective Disorders, 79*, 161–166.
- Thompson, R., Bogner, H. R., Coyne, J. C., Gallo, J. J., & Eaton, W. W. (2004). Personal characteristics associated with consistency of recall of depressed or anhedonic mood in the 13-year follow-up of the Baltimore Epidemiologic Catchment Area Survey. *Acta Psychiatrica Scandinavica, 109*, 345–354.
- Wells, A. (2004). A cognitive model of GAD. In R. G. Heimberg, C. L. Turk, & D. S. Mennin (Eds.), *Generalized anxiety disorder: Advances in research and practice* (pp. 164–186). New York: Guilford.
- Wetherell, J. L., Le Roux, H., & Gatz, M. (2003). DSM-IV criteria for generalized anxiety disorder in older adults: Distinguishing the worried from the well. *Psychology and Aging, 18*, 622–627.
- Wetherell, J. L., Thorp, S. R., Patterson, T. L., Golshan, S., Jeste, D. V., & Gatz, M. (2004). Quality of life in geriatric generalized anxiety disorder: A preliminary investigation. *Journal of Psychiatric Research, 38*, 305–312.
- Wilson, R. S., Barnes, L. L., Bennett, D. A., Li, Y., Bienias, J. L., Mendes de Leon, C. F., & Evans, D. A. (2005). Proneness to psychological distress and risk of Alzheimer disease in a biracial community. *Neurology, 64*, 380–382.
- Wilson, R. S., Evans, D. A., Bienias, J. L., Mendes de Leon, C. F., Schneider, J. A., & Bennett, D. A. (2003). Proneness to psychological distress is associated with risk of Alzheimer's disease. *Neurology, 61*, 1479–1485.
- Wisocki, P. A. (1988). Worry as a phenomenon relevant to the elderly. *Behavior Therapy, 19*, 369–379.
- Wittchen, H.-U., Zhao, S., Kessler, R. C., & Eaton, W. W. (1994). DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Archives of General Psychiatry, 51*, 355–364.
- Woodman, C. L., Noyes, R., Black, D. W., Schlosser, S., & Yagla, S. J. (1999). A 5-year follow-up study of generalized anxiety disorder and panic disorder. *Journal of Nervous and Mental Disease, 187*, 3–9.
- World Health Organization. (1973). *The ICD-9 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines* (9th rev.). Geneva, Switzerland: Author.
- World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines* (10th rev.). Geneva, Switzerland: Author.