Published in final edited form as:

J Affect Disord. 2016 January 15; 190: 349–356. doi:10.1016/j.jad.2015.09.038.

The relationship between anxiety disorders and dimensional representations of DSM-IV personality disorders: A co-twin control study

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Abstract

Background—There is substantial comorbidity between personality disorders (PDs) and anxiety disorders (ADs). Sharing of familial risk factors possibly explains the co-occurrence, but direct causal relationships between the disorders may also exist.

Methods—2801 persons from 1391 twin pairs from the Norwegian Institute of Public Health Twin Panel were assessed for all DSM-IV PDs and ADs. Bivariate Poisson-regression analyses were performed to assess whether PDs predicted ADs at three different levels: All PDs combined, PDs combined within DSM-IV-clusters and each individual PD separately. Next, bivariate co-twin control analyses were executed within monozygotic (MZ) and dizygotic (DZ) twin pairs. A similar analytic strategy was employed in multivariate models including PDs as independent variables.

Results—PDs predicted ADs at all levels of analysis in bivariate regression models. Bivariate co-twin control analyses demonstrated an increased risk of ADs in all PDs combined, all PD-clusters and in schizotypal, paranoid, borderline, antisocial, avoidant and dependent PD. In the multivariate regression model, all PD-clusters and schizotypal, borderline, avoidant and obsessive-compulsive PD predicted ADs. Only borderline and avoidant PD predicted ADs in the multivariate co-twin control analysis.

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Conflict of interest

None.

Role of funding source

No commercial interests.

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Limitations—Over-adjustment may explain the results from the multivariate analyses. The cross-sectional study design hampers causal inference.

Conclusions—Comorbidity between ADs and PDs can be largely accounted for by shared familial risk factors. However, the results are also consistent with a direct causal relationship partly explaining the co-occurrence. Our results indicate specific environmental factors for comorbidity of ADs and borderline and avoidant PDs that are not shared with other PDs.

Keywords

Anxiety disorders; Personality Disorders; Comorbidity; Twin study; Co-twin control design; Genetic epidemiology

Introduction

Co-occurrence beyond chance, or comorbidity, between personality disorders (PDs) and anxiety disorders (ADs) is commonly observed in both clinical and population-based studies (Grant et al., 2005; Lenzenweger et al., 2007; Shea et al., 2004). By themselves, both of these groups of disorders represent a major public health challenge as they are prevalent in both the general community setting and in clinical populations, and they are characterized by substantial morbidity and high financial costs for the society (Huang et al., 2009; Whiteford et al., 2013). In addition, results from previous studies indicate that comorbidity of PDs and ADs exerts a negative influence on treatment response and long-term prognosis in affected individuals (Ansell et al., 2011; Crawford et al., 2008; Skodol et al., 2014).

An increased understanding of the association between these disorders may inform the development of preventive, treatment, and classification efforts, and may also contribute to the understanding of etiological mechanisms (Krueger and Markon, 2006). There are several possible reasons why PDs and ADs co-occur. Alternative, but not mutually exclusive, explanations include common genetic and environmental risk factors between PDs and ADs and direct causal relationships between the disorders (Krueger and Markon, 2006; Neale and Kendler, 1995).

It has previously been suggested that the observed co-occurrence between common psychiatric disorders could be accounted for by two broad, underlying dimensions or latent risk factors of psychopathology, usually called ‘internalizing’ and ‘externalizing’ (Kendler et al., 2003; Krueger, 1999). The corresponding groups of comorbid disorders are referred to as the ‘internalizing’ and ‘externalizing’ spectra. The first include ADs and depression, whereas the second include substance abuse and dependence and antisocial PD. Additional dimensions have been identified after inclusion of psychotic disorders and other PDs (Kotov et al., 2011a; Kotov et al., 2011b; Markon, 2010; Roysamb et al., 2011). While the degree of comorbidity appears to be highest among psychiatric disorders within the same psychopathological spectrum, substantial cross-spectral relationships also exist, e.g. as in the case of ADs and PDs (Harford et al., 2013). Current evidence suggests that this underlying structure of psychopathology, and the observed co-occurrence patterns between individual disorders, arise primarily as a result of genetic influences (Kendler et al., 2011a).

Although it is reasonable to assume that underlying dimensions of psychopathology might explain a large part of the observed comorbidity between PDs and ADs, it is also possible that associations can be at least partly explained by direct causal relationships at the level of individual disorders, i.e. that suffering from one psychiatric disorder increases the risk of developing a second one independently of shared liability factors (Heath et al., 1993; Krueger and Markon, 2006; Neale and Kendler, 1995). Both unidirectional and bidirectional relationships may exist. The strain of suffering from a PD may heighten an individual's risk of developing ADs (Links and Eynan, 2013). Vice versa, ADs tend to have both an early age of onset and debilitating consequences (Alonso et al., 2011; Kessler et al., 2005), and these features may contribute to the development of personality pathology.

The extent to which the comorbidity between PDs and ADs is caused by common underlying genetic or environmental risk factors or by direct causal relationships can be explored in twin studies using co-twin control methodology (Carlin et al., 2005; Fagnani et al., 2014; McGue et al., 2010). By using one twin in each twin pair as a matched control for his or her co-twin, it is possible to adjust for the effect of familial risk factors (genetic effects and environmental influences shared between the co-twins) on the association between PDs and ADs. Whether a causal relationship between the disorders is unidirectional or bidirectional, or whether the association is confounded by specific environmental influences that have affected only one of the co-twins, can however not be determined with the application of this non-experimental study design alone.

In the current study, the co-twin control method was employed in a population-based sample of Norwegian twins assessed for both PDs and ADs to investigate whether the comorbidity between these disorders could be fully accounted for by the sharing of familial risk factors. We had four main aims:

1. Estimation of associations between PDs and ADs without adjustment for potential confounding variables.
2. Estimation of associations between PDs and ADs while adjusting for shared genetic and environmental risk factors
3. Estimation of associations between PDs and ADs while adjusting for comorbid PDs.
4. Estimation of associations between PDs and ADs while adjusting for genetic and environmental risk factors and accounting for comorbid PDs.

Material and methods

Sample

This research report is based on analyses of data from the Norwegian Institute of Public Health Twin Panel (NIPHTP) (Nilsen et al., 2013). The twins in this database were identified through information from the National Medical Birth Registry, established January 1, 1967, which receives mandatory notification of all live- and stillbirths of at least 16 weeks gestation. NIPHTP is based on all Norwegian twins born between 1967 and 1979. 15 370 twins were born in Norway during this period. Two questionnaire studies have

previously been conducted in this sample: the first one in 1992 on twins born 1967–1974 and the second one in 1998 on twins born 1967–1979. 12 698 twins (6349 pairs) received the second questionnaire, and with 8045 responders after one reminder (3334 pairs and 1377 single responders), the response rate was 63%.

Data from the current report stem from an interview-based study that was conducted between 1999 and 2004. All complete pairs from the 1998 questionnaire study in which both twins had agreed to further contact (3153 pairs) were invited, as well as 68 pairs unintentionally drawn directly from the NIPHTP. Altogether, 2801 twins (44% of those eligible) from 1391 twin pairs were assessed at personal interview for DSM-IV Axis I and Axis II disorders between 1999 and 2004. The recruitment process is presented in Figure 1.

The twins had a mean age of 28.2 years, their mean number of years of education was 14.9 and 62% of the participants were married or living in cohabitation at the time of data collection. The sample characteristics are reported in Table 1. 2.786 participants had valid data on all phenotypes, and the sample consisted of 1.017 males and 1.769 females, 219 monozygotic male pairs (MZM), 116 dizygotic male pairs (DZM), 446 monozygotic female pairs (MZF), 261 dizygotic female pairs (DZF), 338 dizygotic opposite sex pairs (DZO) and 26 single responders. Zygosity was determined by a combination of questionnaire items and genotyping. The misclassification rate was estimated to be below 1%, and it is unlikely that this introduced any substantial bias on the results (Neale, 2003).

After a complete description of the study, written informed consent was given by all participants, and the study protocol was approved by the Regional Ethic Committee and the Norwegian Data Inspectorate.

Measures

All participants completed structured clinical interviews for DSM-IV Axis I and II disorders. ADs were assessed with a computerized version of the Composite International Diagnostic Interview (CIDI; Wittchen et al., 1997), developed by the World Health Organization and used worldwide in major psychiatric surveys in recent years (Kessler et al., 2011). This instrument has been shown to have good test–retest and interrater reliability (Wittchen et al., 1998). Diagnoses were assigned without hierarchical rules in order to examine co-occurrence without exclusions.

A Norwegian version of the Structured Interview for DSM–IV Personality Disorders (SIDP–IV; Pfohl et al., 1995) was used to assess the PDs. This instrument is a comprehensive semistructured diagnostic interview for the assessment of DSM–IV Axis II diagnoses. The SIDP–IV has previously been used in a number of studies in several countries, including Norway (Kendler et al., 2008). It includes non-pejorative questions organized into topical sections to produce a natural flow in the interview. The number of criteria for each DSM-IV personality disorder varies from 7 to 9. Each of the specific criteria was rated as follows: 0 = absent; 1 = sub-threshold; 2 = present; and 3 = strongly present. A score of 2 or more on at least 3 to 5 criteria (depending on the PD in question) is required for a diagnosis of PD. The instructions for the SIDP–IV specify a scoring rule which says that behavior typical of the past 5 years represents the basis for the ratings.

The interviewers were trained in the use of SIDP-IV by professionals (one psychiatrist and two psychologists) with extensive experience with the instrument, with close individual follow-up throughout the period of data collection. The interviewers were mainly clinical psychology students in their senior year, or psychiatric nurses with long clinical experience.

Interrater reliability of the measures was assessed by two raters' scoring of 70 audiotaped interviews. The intraclass (and polychoric) correlations for the number of endorsed criteria were as follows: paranoid PD, .92 (.94); schizoid PD, .81 (.86); schizotypal PD, .86 (.90); histrionic PD, .85 (.80); borderline PD, .93 (.94); antisocial PD, .91 (.94); narcissistic PD, .86 (.82); avoidant PD, .96 (.97); dependent PD, .96 (.99); and obsessive-compulsive PD, .92 (.87).

Study design and statistical analyses

ADs have been found to covary and to share underlying risk factors (Blanco et al., 2014). Based on the previous literature, we assumed that one latent factor would account for the observed covariance between individual ADs in our dataset (Roysamb et al., 2011). A confirmatory factor analysis (CFA) demonstrated that a one-factor model had an excellent fit to the data (Comparative Fit Index (CFI) = 1.000). We therefore constructed a unifactorial 'AD'-variable counting the number of lifetime DSM-IV AD-diagnoses for each participant. This ordinal AD-variable had a range of values from 0 to 8, and included the following ADs: generalized anxiety disorder, panic disorder, agoraphobia, social phobia, situational phobia, natural phobias, animal phobia, blood phobia and a low-prevalent group of other, specified phobias. As this AD-variable was a count-variable, Poisson-regression was applied to assess the relationship between ADs and PDs.

In line with a number of previous studies, the PDs were modeled as dimensional traits operationalized as the number of endorsed diagnostic criteria (Kendler et al, 2008; Kendler et al., 2011a). However, in order to aid the interpretation of estimated risk ratios (RR) in Poisson-regression analyses, each dimensional PD-variable was rescaled. Firstly, each criterion-score of 1 (sub-threshold) was given the value of 0.5, and each criterion-score of 2 (symptom present) and 3 (symptom strongly present) were given the value of 1. The sum score of individual criteria was then divided by the number of criteria required to fulfill the diagnostic criteria for each PD (APA, 1994). Estimated RRs in the regression models thereby reflected the change in risk for having a DSM-IV AD when moving from zero PD-criteria present to the number of criteria required for a DSM-IV PD-diagnosis. The PD-variables included symptomatology both above and below the diagnostic threshold, but we use the term "PD" for these variables in the following text to maintain the readability.

To assess the associations between PDs and ADs, bivariate Poisson-regression analyses with PDs as an independent variable and the AD-variable as a dependent variable were performed. As individual PDs covary substantially (Grant et al., 2004) and analyses at the level of individual disorders may suffer from low statistical power, we firstly combined all PDs in one variable in order to address the association between PDs and ADs. Next, we combined individual PDs at the level of the three DSM-IV-clusters: Cluster A (the odd, eccentric cluster), Cluster B (the dramatic, emotional, erratic cluster) and Cluster C (the anxious, fearful cluster). Finally, we assessed associations at the level of the ten individual

PDs. The participants' age and sex were included as independent variables. Information from the 26 single responders in the dataset was included in all these analyses.

Next, co-twin control analyses were performed to address whether, within twin pairs where members differed on PD-symptomatology, the member with more symptoms was more likely to have an AD than his or her co-twin. This analysis allows adjustment for familial confounders on the observed association between PDs and ADs. Members of a twin pair share either 100% (monozygotic (MZ)) or on average 50% (dizygotic (DZ)) of their segregating genes (van Dongen et al., 2012). In addition, environmental factors may either have contributed to similarity (shared environmental effects) or difference (non-shared environmental effects) between members of a pair. By assessing effects within twin pairs, the relationship between PDs and ADs is investigated while controlling for possible effects of shared environmental factors and either all (within MZ-pairs) or half (within DZ-pairs) of the effect of genetic factors (Carlin et al., 2005).

Under different hypotheses about the relationship between these disorders, we expect different patterns of individual-level effect estimates (obtained from the Poisson-regression analyses in the whole sample) versus within-pair effects (Figure 2) (Ligthart and Boomsma, 2012). Association is a prerequisite for causation, and lack of association within MZ-pairs is inconsistent with causality. If an effect estimate remains substantial both within DZ and MZ pairs after adjustment for familial risk factors, the results are compatible with a hypothesis of direct causal effects. Confounding by familial factors is indicated if the strength of the association is lower within twin pairs than in individual-level analyses, and because all of the genetic effect is controlled for within MZ pairs and only half in DZ pairs, genetic confounding is indicated by lower effects within MZ twin pairs than within DZ twin pairs. These scenarios are not mutually exclusive, and it is possible that both familial confounding and direct causation contribute to an observed association (McGue et al., 2010).

We performed bivariate co-twin control analyses with all PDs combined, PDs combined within clusters and individual PDs as independent variables and ADs as a dependent variable. Because the analyses of individual PDs may suffer from low statistical power, we performed 10 Wald tests to assess whether the effect estimates from the individual-level and the within MZ-pair analyses differed.

We subsequently performed multivariate Poisson-regression analyses including the PD-cluster variables as independent variables (in addition to age and sex). Next, all individual PDs were included as independent variables in an equivalent analysis. Finally, multivariate co-twin control analyses at the level of both the PD-clusters and individual PDs were executed. With this approach, statistically significant associations between ADs and PDs can be assumed to be either directly causal or confounded by non-shared environmental factors that are specific to that pairwise relationship.

CFA was run in Mplus 7.0 by WLSMV estimation. Individual-level regression analyses were performed using random effects for linear models with count data (i.e. the `xtpoisson` command) in the STATA 13.1 software package. Co-twin control analyses were executed

using fixed-effect models among twin pairs. These analyses are based on the following equations representing the association between PDs and ADs for each twin pair:

$$y_{i1} = \beta_{11}x_{i1} + g_{i1} + s_i + \varepsilon_{i1}$$

$$y_{i2} = \beta_{12}x_{i2} + g_{i2} + s_i + \varepsilon_{i2},$$

The subscript i represents the twin pair, the second subscript denotes twin 1 or 2 in the pair. y represents ADs, x represents PDs and g and s denotes the unmeasured genetic and shared environmental factors, respectively. ε is an error term. In the fixed-effect model, the effects of g and s on an association are removed by subtracting y_{i2} from y_{i1} :

$$y_{i1} - y_{i2} = \beta'_{11}(x_{i1} - x_{i2}) + (g_{i1} - g_{i2}) + (s_i - s_i) + (\varepsilon_{i1} - \varepsilon_{i2}).$$

This can be rewritten as

$$y_i^* = \beta'_{11}x_i^* + g_i^* + s_i^* + \varepsilon_i^*,$$

where the asterisk indicates the difference of variables within each twin pair. The confounding effect of familial risk factors is thereby fully controlled for in analyses within MZ-pairs (both genetic and shared environmental effects are equal, hence, both s_i^* and g_i^* are equal to zero), and partly within DZ-pairs (Fujiwara and Kawachi, 2009). The same equations were used in the multivariate co-twin control models, with the additional independent PD-variables added at the right side of the equations.

Results

Sample

The lifetime prevalence for all DSM-IV ADs and the factor-loadings from the CFA for each AD is presented in Table 2. The lifetime prevalence of having at least one AD was 24.1%, ($n = 674$) with the prevalence of individual ADs ranging from 0.6% for other phobias to 9.6% for animal phobia.

The number of lifetime ADs among the individuals in the sample ranged from 0 to 8. Most participants with ADs had either one (15.4%) or two (5.0%) lifetime diagnoses, while only one participant (0.1%) suffered from 8 ADs.

Bivariate analyses

The results from the Poisson-regression models assessing bivariate relationships between ADs and PDs showed a statistically significant elevation of risk for ADs associated with PDs both at the level of all PDs in combination, at the level of DSM-IV clusters and at the level of the individual PDs (See Table 3). The effect estimates were generally substantial, with the highest risk ratio (RR) estimated for schizotypal (12.1) and borderline PD (7.3), and the lowest RR for antisocial and obsessive-compulsive PD (2.8).

The bivariate co-twin control analyses in the DZ pairs showed that both all PDs combined, the DSM-IV clusters and all individual PDs except schizoid and antisocial PD remained significantly associated with ADs in the bivariate models. Among the MZ twin pairs, a significantly increased risk of ADs was found for all PDs combined, each PD-cluster and six individual PDs: schizotypal, paranoid, borderline, antisocial, avoidant and dependent PD.

Multivariate analyses

Table 3 also includes results from the multivariate regression analyses. All PD-clusters and four individual PDs significantly and independently predicted ADs: schizotypal, borderline, avoidant and obsessive-compulsive PD.

At the level of PD-clusters, the only statistically significant finding in the multivariate co-twin control analyses was for Cluster C disorders among DZ pairs. At the level of individual disorders, only borderline and avoidant PD predicted ADs among MZ twins, with respective RRs of 3.1 and 2.3. Among the DZ pairs OCPD also predicted ADs, while a negative relationship between antisocial PD and ADs was identified.

Discussion

In unadjusted regression models DSM-IV PDs at all three levels of analysis (That is; all PDs combined, PDs combined within DSM-IV clusters and individual PDs analyzed separately) implied a substantially increased risk of concurrent or prior suffering from an AD. The pattern of associations appears to cut across the grouping of specific DSM-IV PDs into three clusters, rather supporting a notion of widespread pairwise associations between ADs and PDs. However, controlling for the high degree of co-occurrence among different PDs in the multivariate Poisson-regression model, the unique and independent increased risk of ADs among schizotypal, borderline, obsessive-compulsive and avoidant PDs is in line with patterns of associations demonstrated in previous studies (Grant et al., 2005; Harford et al., 2013; Pulay et al., 2009). However, despite these reassuringly similar results across epidemiological investigations, cautious interpretation is warranted when comparing the RRs for different PDs. The RR metric depends on the base rate in the population. Therefore, quite different RRs could index the same level of underlying association, or the same RR might index different levels of association.

If shared familial risk factors had fully accounted for the observed co-morbidity, one would have expected the statistically significant pairwise associations between PDs and ADs identified in the bivariate regression models to disappear when we controlled for the possible confounding effects of latent familial risk factors in co-twin control models. However, both for all PDs combined, all DSM-IV clusters, and for six of the individual PDs; schizotypal, paranoid, antisocial, borderline, avoidant and dependent; the bivariate co-twin control results are compatible with a hypothesis of causal pathways through the disorders influencing comorbidity with ADs. Causal mechanisms have previously been argued to be at play between PDs and ADs (Shea et al., 2004). PDs are characterized by subjective psychological distress and challenges in interpersonal relationships, and are associated with reduced quality of life and daily functioning, also at levels below the diagnostic thresholds defined in the DSM-IV (Grant et al., 2009). PDs are also characterized by an increased

likelihood of exposure to various stressful life events. These features associated with PDs may increase the risk of developing an AD over and above familial risk factors shared between the disorders (Links and Eynan, 2013).

In the current study, PDs were modeled as exposure-variables and ADs as the outcome. However, as we did not apply full multivariate biometric models to assess whether alternative explanatory models including reverse or reciprocal causation fit the current data better, we can not draw inferences about the direction of causation between PDs and ADs in this study (Neale et al., 1994). Both kinds of disorders tend to start at an early age, with ADs being relatively prevalent already during childhood and early adolescence, and behavioral patterns consistent with PDs developing during adolescence and early adulthood (de Clercq et al., 2009; Kessler et al., 2005; Shiner, 2009). In the current study, the mean age of onset for ADs was 11.0. Most ADs are characterized by substantial psychological distress with possible detrimental effects on school and work functioning and, also, various problems in social situations and interpersonal relationships. It might be that these aspects of ADs directly influence an affected individual's risk of developing personality pathology (Craske et al., 2009).

However, even though such statistically significant findings in co-twin control studies can be regarded as a prerequisite for causal inference, alternative non-causative explanations are far from eliminated (Carlin et al., 2005; McGue et al., 2010). Importantly, the influence of non-shared environmental risk factors may have led to differences in both PDs and ADs between members of a twin pair. The current findings may therefore be equally well explained by environmental effects unique to one member of a twin pair. Rather than the observed differences in psychopathology within twin pairs per se, the actual causal factors may be the factors that led to those differences. The current study did not include direct measurements of environmental influences, so it was not possible to assess such effects in more detail.

Importantly, there is also a tendency towards lower effect estimates in the bivariate co-twin control analyses compared to the individual-level regression models. These results indicate confounding effects of familial risk factors on the association between PDs and ADs. When studying all PDs combined and PD-clusters, the non-overlapping confidence intervals between effect estimates at the individual level and within MZ twin pairs indicate partial confounding by familial risk factors of the relationship between ADs and PDs. A similar pattern is evident for the individual PDs, but the broader confidence intervals around the effect estimates at this level of analysis hampers firm conclusions about familial confounding. However, the results from the Wald tests indicate that confounding by familial risk factors is present for schizotypal, paranoid, borderline, obsessive-compulsive and dependent PD, while cautious interpretation of the observed trends are warranted with respect to the 5 remaining PDs.

A comparison of the results from the co-twin control analyses within MZ and DZ pairs also render clues as to whether familial confounding is due to genetic pleiotropic effects or shared environmental factors. The general pattern of lower effect estimates within the genetically identical MZ pairs compared to the DZ pairs sharing half of their segregating

genes implies that common genetic factors contribute substantially to the co-occurrence between ADs and PDs (McGue et al., 2010).

The results from the multivariate analyses shed further light on the structure of the risk factors influencing comorbidity between PDs and ADs. As expected the effect estimates in the multivariate regression model are consistently considerably lower than in the bivariate regression models. In fact, the results more closely resemble the effect estimates in the co-twin control models within MZ-pairs. Results from previous studies indicate that comorbidity among various PDs can be largely explained by shared, primarily genetic, risk factors (Kendler et al., 2008). In the light of the current research literature, one may therefore expect that the inclusion of all PDs as independent variables in a multivariate regression model produces results similar to co-twin control analyses. The current results lend support to an explanatory model of a limited number of etiological pathways underlying PDs and ADs, with shared risk factors at the level of broad dimensions of psychopathology partly accounting for the observed diagnostic co-occurrence between ADs and PDs (Krueger and Markon, 2006).

However, the findings from the multivariate co-twin control model also indicate that direct causal influences, or non-shared environmental effects, partly explain the comorbidity of lifetime ADs and borderline and avoidant PD. In addition, these findings are compatible with the existence of specific influences on the relationship between ADs and borderline and avoidant PDs that are not shared with the other DSM-IV PDs. For illustrative purposes, the reader can imagine a MZ twin pair where one member suffers from borderline PD symptomatology at the level of the diagnostic threshold, while the other member has no such symptoms. Besides the differences concerning borderline PD, both twins have identical levels of PD-symptomatology. According to the current results, the twin suffering from borderline PD will have a tripled risk of suffering from an additional AD compared to his or her co-twin. In the multivariate co-twin control analyses at the level PD-clusters we were unable to identify the potentially important specific relationship between ADs and borderline and avoidant PD. The mapping of such specificity versus generality of risk factors for comorbidity of psychiatric disorders is of considerable research interest, both with regard to future revisions of the classification systems and explanatory models of comorbid psychopathology (Kessler et al., 2011).

In accordance with these results, Borderline PD has previously been shown to share liability factors with internalizing psychiatric disorders to a larger extent than other PDs (Blanco et al., 2013; Eaton et al., 2011; Reichborn-Kjennerud et al., 2010; Roysamb et al., 2011). In addition, emotional dysregulation, including heightened anxiety, has been described as a core aspect of this disorder by several authors (Crowell et al., 2009; Reichborn-Kjennerud et al., 2013). Avoidant PD is largely defined by symptoms of anxiety, especially social fears, and has been conceptualized by many authors as a severe variant of the AD generalized social phobia (Reich, 2009)

This leads us to an important question regarding the validity of the DSM-IV diagnostic categories that has been the focus of this study. These are clinical-historical constructs, and the boundaries between these categories are both fuzzy and in many cases arbitrarily placed

(Kendler et al., 2011b). It is possible that overlap of diagnostic content between ADs and these two PDs create artificially high estimates of co-occurrence, and that the high levels of AD-symptoms associated with these PDs may be better conceptualized as a part of these disorders rather than as a simultaneously occurring separate form of psychopathology.

The current findings may be of interest from a clinical perspective. The demonstration of strong pairwise relationships between PDs and ADs, which are presumed to be distinct psychiatric disorders, reinforces the importance of assessing the presence of ADs in any patient with symptoms of PDs. The co-twin control results may further inform the development of preventive and therapeutic interventions targeting modifiable risk factors. The possibility of direct causal effects between disorders suggests that early interventions can be useful to prevent the development of psychiatric comorbidity. Both PDs and ADs are characterized by yearlong delays from the age of onset until clinical care is provided, and the development of comorbidity during this treatment gap may have an unfavorable effect on long-term prognosis and make optimal clinical management more challenging to achieve (Skodol et al., 2014). Direct causal effects aside, the specific environmental risk factors for comorbid ADs and borderline and avoidant PDs that may alternatively be assumed from the multivariate co-twin control analyses, might be important intervention targets (Haggerty and Mrazek, 1994).

Limitations

The CIDI and SIPD-IV interviews represented the third wave of contact with the twins after they had been identified in the Norwegian birth registry. Substantial attrition was observed through 3 waves of contact. However, detailed analyses of the predictors of nonresponse across waves show that cooperation was strongly and consistently predicted by female sex, monozygosity, older age, and higher educational status, but not by psychiatric symptoms or alcohol abuse (Tambs et al., 2009).

The study sample was confined to young adult Norwegians. Extrapolation to other ethnic or age groups may not be warranted. Replication studies in other samples are needed.

The twins were only interviewed once, and although the inter-rater reliability was satisfactory, test-retest reliability might be low. There is a need for prospective studies to account for the effects of measurement error. Analyses of longitudinal data sets may also strengthen causal inferences through assessment of the temporal relationships between assumed exposures and outcomes.

Over-adjustment may partly explain the results from the multivariate co-twin control model (Schisterman et al., 2009). Cautious interpretation is warranted, as the attempt to partial out the effects of such a wide range of possible confounding variables may have led to over-adjustment in the model.

Because the PDs have different base rates in the population, the RRs are not comparable between them. That is, the degree of association (correlation) between disorders A and B might be the same as that between disorders A and C, but the RRs could differ substantially. As a result, inferring whether a greater amount of genetic or common environmental

covariance exists between disorders cannot be readily achieved by, e.g., comparing the rows of Table 2. A structural equation modeling approach would overcome this limitation, and provide opportunities to compare alternative causal and correlational hypotheses about comorbidity (Heath et al., 1993; Neale and Kendler 1995; Neale et al., 1994).

Conclusion

In conclusion, the current study contributes to the existing research literature by describing patterns of comorbidity of lifetime ADs and PDs in a large, population-based sample of young adults. While shared underlying risk factors accounted for a large part of the observed comorbidity, the findings were also compatible with a hypothesis of direct causal mechanisms contributing to the co-occurrence. These findings are in need of replication, and the relationship between ADs and PDs should be investigated further, preferably in longitudinal, genetically informative, population based studies.

Acknowledgments

The work was supported by grant MH-068643 (PI Kendler) and MH-65322 (PI Neale) from the National Institutes of Health. The twin program of research at the Norwegian Institute of Public Health is supported by grants from The Norwegian Research Council, The Norwegian Foundation for Health and Rehabilitation and by the European Commission under the program 'Quality of Life and Management of the Living Resources' of 5th Framework Program (no. QLG2-CT-2002-01254). Genotyping on the twins was performed at the Starr Genotyping Resource Centre at the Rockefeller University. The authors are grateful to the twins for their participation.

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Highlights

- Anxiety disorders are highly comorbid with personality disorders.
- Sharing of familial risk factors does not fully explain the observed comorbidity.
- Anxiety disorders and several personality disorders may have a causal relationship.

Figure 1. The recruitment process

The recruitment process into the 1999–2004 interview study of 2801 Norwegian twins is illustrated above.

Figure 2. Patterns of results under different scenarios

In the above figure, we illustrate the expected pattern of effects of PDs on ADs assessed at the individual level, within DZ pairs and within MZ pairs under different hypotheses about the relationship between the disorders. The pattern in the charts on the left lends support to a hypothesis of direct causal effects and no familial confounding. The middle charts illustrate the expected results under complete confounding, while the pattern of results in the right charts is consistent with a relationship between PDs and ADs that is partly accounted for by sharing of genetic and environmental risk factors and partly explained by direct causal effects between the disorders.

Table 1

Sample characteristics

No. participants	2786
Gender (No. females (percent))	1769 (63%)
Age (mean)	28.2
Education (mean no. years)	14.9
Marital status	
<i>Married (No. (percent))</i>	776 (28%)
<i>Living in cohabitation (No. (percent))</i>	935 (34%)
Zygosity (No. complete pairs)	
<i>MZM</i>	219
<i>DZM</i>	116
<i>MZF</i>	446
<i>DZF</i>	261
<i>DZO</i>	338
No. single responders	26

MZM = Monozygotic male pairs, DZM = Dizygotic male pairs, MZF = Monozygotic female pairs, DZF = Dizygotic female pairs, DZO = Dizygotic opposite-sex pairs

Table 2

Lifetime prevalences of anxiety disorders

Anxiety disorder diagnosis	No. participants	Lifetime prevalence	Factor-loading
Any anxiety disorder	674	24.1	
Agoraphobia	134	4.8	0.86
GAD	55	2.0	0.72
Social phobia	112	4.0	0.76
Panic disorder	87	2.9	0.83
Blood phobia	107	3.8	0.51
Animal phobia	269	9.6	0.41
Situational phobia	113	4.0	0.71
Natural phobia	153	5.5	0.51
Other phobias	16	0.6	0.64

Table 3

Poisson-regression and co-twin control models

Bivariate models			
	Poisson-regression	Co-twin control	
PD	RR (95% CI)	DZ - RR (95% CI)	MZ - RR (95% CI)
Any PD	1.47 (1.40–1.54) *	1.37 (1.24–1.52) *	1.21 (1.11–1.33) *
Cluster A	2.56 (2.20–2.98) *	2.06 (1.52–2.78) *	1.59 (1.21–2.10) *
Cluster B	2.00 (1.80–2.23) *	1.70 (1.38–2.10) *	1.50 (1.21–1.85) *
Cluster C	2.24 (2.01–2.50) *	2.03 (1.62–2.56)	1.46 (1.18–1.80) *
Schizoid	3.78 (2.43–5.86) *	1.67 (0.74 – 3.76)	2.13 (0.86– 5.27)
Schizotypal	12.13 (7.66–19.23) *	11.49 (3.81 – 34.70) *	3.01 (1.46 – 6.21) * ^φ
Paranoid	4.68 (3.59–6.10) *	2.90 (1.84–4.59) *	2.41 (1.44–4.04) * ^φ
Borderline	7.30 (5.65–9.43) *	5.68 (3.26–9.91) *	2.87 (1.79–4.62) * ^φ
Antisocial	2.81 (2.10–3.75) *	1.42 (0.89–2.28)	2.27 (1.15–4.45) *
Histrionic	3.65 (2.54–5.26) *	3.96 (1.90–8.27) *	1.92 (0.98–3.75)
Narcissistic	4.11 (2.75–6.12) *	3.16 (1.56–6.41) *	2.14 (0.94–4.89)
OCPD	2.75 (2.22–3.41) *	2.55 (1.73 – 3.74) *	1.47 (0.94–2.30) ^φ
Avoidant	3.56 (2.87–4.41) *	2.91 (1.87–4.54) *	2.24 (1.45–3.47) *
Dependent	5.61 (4.04–7.78) *	3.73 (1.83 – 7.61) *	2.05 (1.19–3.55) * ^φ

Multivariate models			
	Poisson-regression	Co-twin control	
PD	RR (95% CI)	DZ - RR (95% CI)	MZ - RR (95% CI)
Cluster A	1.31 (1.08–1.60) *	1.18 (0.79–1.75)	1.20 (0.85–1.71)
Cluster B	1.39 (1.22–1.58) *	1.26 (0.96–1.65)	1.25 (0.94–1.65)
Cluster C	1.69 (1.47–1.94) *	1.71 (1.31–2.23) *	1.19 (0.90–1.56)
Schizoid	0.61 (0.36–1.04)	0.42 (0.16–1.10)	0.71 (0.22–2.29)
Schizotypal	2.04 (1.13–3.67) *	2.85 (0.61–13.20)	1.38 (0.49–3.89)
Paranoid	1.24 (0.87–1.78)	1.02 (0.54–1.90)	1.24 (0.57–2.69)
Borderline	3.53 (2.44–5.10) *	5.28 (2.30–12.08) *	3.14 (1.58–6.23) *
Antisocial	1.11 (0.79–1.55)	0.46 (0.24–0.89) *	1.15 (0.50–2.63)
Histrionic	0.92 (0.59–1.45)	0.91 (0.35–2.39)	0.99 (0.39–2.47)
Narcissistic	0.76 (0.46–1.25)	1.45 (0.57–3.68)	0.44 (0.14–1.40)
OCPD	1.60 (1.26–2.04) *	1.68 (1.07–2.63) *	0.98 (0.56–1.70)
Avoidant	1.98 (1.51–2.61) *	1.93 (1.09–3.40) *	2.33 (1.28–4.22) *
Dependent	1.11 (0.72–1.70)	0.57 (0.20–1.58)	0.55 (0.25–1.22)

PD = Personality disorder, DZ= Dizygotic twin pairs, MZ = Monozygotic twin pairs, RR = Risk ratio, CI = Confidence interval,

* statistically significant effect estimate ($p < 0.05$),

ϕ statistically significant Wald test ($p < 0.05$)

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