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Polycystic ovary syndrome, personality, and depression: A twin study

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ABSTRACT

Background: Women with polycystic ovary syndrome (PCOS) are at elevated risk for suffering from depression. Neuroticism is a personality trait that has been associated with an increased risk for developing major depressive disorder (MDD). The aim of the present study was to quantify and decompose the correlation between neuroticism, PCOS, and MDD into shared and unique genetic and environmental etiologies, by using quantitative genetic methods.

Methods: In a cohort of 12,628 Swedish female twins born from 1959 to 1985, neuroticism, PCOS identified by symptoms of hyperandrogenemia (i.e., hirsutism) and oligo- and/or anovulation, and lifetime MDD status were determined through questionnaire responses. Structural equation modeling was used to study the genetic and environmental sources of the variation within, and covariation between neuroticism, PCOS, and MDD.

Results: Female twins with PCOS (n = 752) had significantly higher levels of neuroticism than women without PCOS, and a 2-fold increase in odds for a lifetime prevalence of MDD. The phenotypic correlation between PCOS and MDD was 0.19, with 63% of the correlation attributable to common genetic factors between the two traits. When taking into account neuroticism, 41% was attributable to common genetic factors and 9% attributable to common environmental factors shared between all three traits, with the remainder attributable to components unique to PCOS and MDD.

Conclusion: There are common genetic factors between neuroticism, PCOS, and MDD; however, neuroticism shares approximately half of the genetic and environmental components behind the phenotypic correlation between PCOS and MDD, providing some etiological evidence behind the comorbidity between PCOS and depression.

1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder which affects 5–15% of reproductive-aged women and is characterized by hyperandrogenism, oligoovulation or anovulation, and polycystic ovaries (Lizneva et al., 2016b). It has been well documented that women with PCOS report a reduced quality of life, score higher on depression symptom scales, and have higher rates of depression diagnoses (Barry et al., 2011b; Cesta et al., 2016; Hart and Doherty, 2014; Hung et al., 2014; Mansson et al., 2008; Weiner et al., 2004). However, causes behind this common comorbidity are currently only speculative. One hypothesis is that elevated levels of androgens in PCOS increase the risk for depression (Cesta et al., 2016). In support of this notion, higher levels of circulating androgens have been related to mood disorders in women (Baischer et al., 1995; Weber et al., 2000; Weiner et al., 2004). Moreover, many of the physical symptoms of PCOS which could have negative psychological consequences are attributable to hyperandrogenemia (e.g., hirsutism, acne, obesity, infertility). However, studies comparing androgen levels in relation to symptoms of depression in PCOS patients are limited and show no association (Hollinrake et al., 2007; Mansson et al., 2008; Rasgon et al., 2003). Additionally, insulin resistance and metabolic syndrome are common in women with PCOS, and these disorders may also have a role in the development of depression (Hollinrake et al., 2007; Marazziti et al., 2014).

Neuroticism is a personality trait defined as the tendency to respond with negative emotions to threat, frustration, or loss. Neuroticism is theorized to be based on activation thresholds of the fight-or-flight response; those with high neuroticism have a lower activation threshold and are therefore less able to control their emotional reaction to minor stressors (Eysenck and Eysenck, 1975). Individuals with high levels of neuroticism are less emotionally stable, more likely to perceive stress (Rietschel et al., 2014), and also more sensitive to the adverse effects of stress (Kendler et al., 2006). As neuroticism is strongly associated with

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lifetime risk for major depression in adults (Lahey, 2009), it may be another possible source for the increased risk for depression in women with PCOS. A small clinical study has reported that women with PCOS score higher on a neuroticism scale (Barry et al., 2011a).

The aim of the present study was to examine the potential role for common genetics behind the comorbidities of neuroticism, PCOS and MDD. By using quantitative genetic methods we aimed to quantify and decompose the correlation between neuroticism, PCOS, and MDD into shared and unique genetic and environmental etiologies.

2. Methods

2.1. Data sources

The Study of Twin Adults: Genes and Environment (STAGE) is a web-based survey performed in 2005 among all Swedish twins born between 1959 and 1985 (n = 42,852) that was comprised of approximately 1300 questions about common complex disease and common exposures (Lichtenstein et al., 2006). Zygosity has been determined by the responses to a series of questions regarding intra-pair similarities in childhood, which has been validated against genotypic measures of zygosity (Lichtenstein et al., 2002). The study was approved by the regional ethics committee in Stockholm, Sweden. STAGE female twins (n = 14,180) were of reproductive age (20–46 years) when responding to the survey and 89% (n = 12,628) had data available to determine PCOS status via the responses to the questionnaire.

2.1.1. PCOS

The current clinical diagnostic criteria for PCOS, known as the Rotterdam criteria, require two of the following three conditions to be present: clinical and/or biochemical signs of hyperandrogenism (HA), oligo- and/or anovulation (OA), or polycystic ovarian morphology (PCOM), after the exclusion of secondary causes. (Rotterdam, 2004) Hence, four PCOS phenotypes are possible, where the HA + OA and HA + OA + PCOM phenotypes are considered 'classic' PCOS phenotypes. (Lizneva et al., 2016b)

Validation studies in a large Finnish birth cohort have concluded that the presence of the typical endocrine features of the PCOS phenotype that includes both hyperandrogenemia and oligomenorrhea can reliably be established through self-completed questions concerning hirsutism and oligomenorrhea (Taponen et al., 2004; Taponen et al., 2003).

Therefore, in this study, women with PCOS were identified by their responses to questions addressing menstrual irregularities and hirsutism, which included answering 'yes' to one or both of the following questions: *"Have you, during any period of your life, had irregular menstrual periods − more than 5 weeks between periods?"* or "*Have you ever missed more than three periods without any natural causes such as pregnancy or menopause, etc?*" and answering 'yes' to *"Do you feel that you have abnormal hair growth on parts of the body?"*, to identify with the classic HA + OD phenotype.

2.1.2. Neuroticism

The STAGE questionnaire contained questions from the short form of the Eysenck Personality Inventory (EPI-Q) (Floderus-Myrhed et al., 1980; Floderus, 1974), developed from the Eysenck Personality Inventory (EPI Form B) (Eysenck and Eysenck, 1975). Neuroticism was evaluated with nine yes/no questions from which a score from 0 to 9 was calculated. If the participant answered fewer than 7 questions, the score was set to missing. For 22% of all female twins in STAGE (n = 2794), there was insufficient data to determine a neuroticism score.

2.1.3. Depression

Lifetime prevalence of MDD was measured using a computerized version of the Composite International Diagnostic Interview-Short Form (CIDI-SF)(Kessler et al., 1998) which was adapted from its original version to assess lifetime prevalence of major depression according to criteria A, C and E in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 2000). Criteria A and C had to be fulfilled in order to be classified as having MDD. To meet the A criteria, at least 5 of the following symptoms had to have been present during the same 2 week period at some point in life: depressed mood, sleep disturbance, markedly diminished interest or pleasure from almost every activity, significant weight change or change of appetite, feeling inhibited or agitated, feeling of a lack of energy, feelings of guilt or worthlessness, diminished ability to concentrate, recurrent thoughts about death or suicide. To fulfill criteria C, these symptoms had to cause clinically significant distress or impairment in daily functioning. For 8.7% of all female twins in STAGE (n = 1093), there was insufficient data to determine their lifetime prevalence of MDD.

2.2. Statistical analysis

Initial analyses of the associations in the whole cohort of female twins between neuroticism and PCOS, and PCOS and MDD were conducted by logistic regression, accounting for the twin structure of the data. Descriptive statistics and logistic regression was preformed using Stata statistical software (Stata Corps, Texas, USA). Intra-pair and cross-twin cross-trait correlations were calculated to generate a first impression of the genetic variance and covariance of the three traits: neuroticism, PCOS, and MDD.

2.2.1. Genetic modelling

For genetic analyses, only female twins from same-sexed pairs were included. Structural equation modeling was used to study the genetic and environmental sources of the variation within, and covariation between neuroticism, PCOS, and MDD. Using this method, (co)variation in the population can be attributed to additive genetic factors (A), dominant genetic factors (D), shared environmental factors (C), and unique environmental factors (E). E also includes measurement error. Monozygotic twins (MZ) are genetically identical and dizygotic (DZ) twins on average share half of their co-segregating alleles and therefore A can be assumed to be 100% shared between MZ twins, and 50% shared in DZ twins. For dominant genetic factors, D is assumed to be 100% shared between MZ twins, and 25% shared for DZ twins. Both MZ and DZ twin pairs are assumed to share 100% of C, and no correlation for E (Rijsdijk and Sham, 2002).

The quantitative genetic models were conducted under the assumptions of the classic twin design: equal environments of the MZ and DZ pairs, no gene-environment interaction, and random mating (Plomin et al., 2013). Violation of the equal environments assumption, where MZ twins share more of their environment than DZ twins, will result in an incorrect inflation of the estimate of A. However, there is little evidence for most traits that controlling for environmental similarity reduces heritability, with the exception of neuroticism. However, is it accepted that the resulting bias is likely to be modest (Felson, 2014). PCOS and MDD were defined as binary traits. Therefore, the liability-threshold method was used in analyzing the data. Each individual is assumed to have an underlying normally distributed liability of having the binary trait, with '0' observed if the liability is lower than an estimated threshold and '1' observed if it is above the threshold, where the thresholds are determined by the prevalence of the traits. The analyzed measure of association is the correlation between the assumed underlying normal distribution of liability, also referred to as the tetrachoric correlation. Twin pairs with missing values for any of the three traits were omitted from analysis.

2.2.2. Model fitting

The intra-pair correlations for neuroticism, PCOS, and MDD separately in the DZ twins was less than half of that in the MZ twins

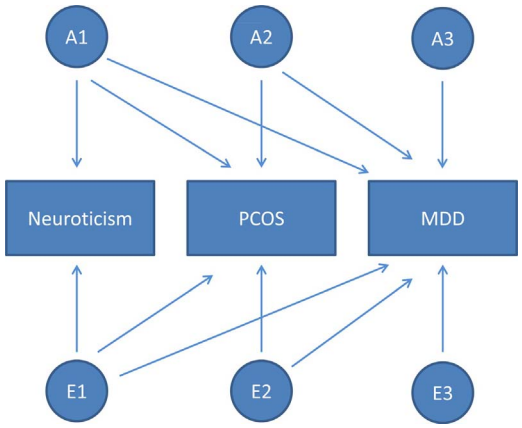

Fig. 1. Illustration of the trivariate Cholesky decomposition model within one twin for the additive genetic and unique environmental influences contributing to the phenotypic correlation between neuroticism, PCOS, and MDD.
Note: A1-A3 = additive genetics components for traits 1–3; E1-E3 = unique environment for traits 1–3; PCOS = polycystic ovary syndrome; MDD = major depression. Variances of latent factors fixed at 1.

(Table 2). This indicates that a dominant genetic component is present in the variation of these traits. Since the models cannot estimate both the dominant genetic and shared environmental component in the same model, it was determined that no C parameter was to be estimated for any of the models. Therefore, only ADE and the reduced AE trivariate models were fit. The goodness-of-fit for the AE model was evaluated compared to the ADE model using the likelihood ratio test, and the lowest Akaike's Information Criteria (AIC) value was used to identify the most parsimonious model.

2.2.3. Trivariate analysis

The A, D, and E sources of variance were modelled in a so-called trivariate Cholesky decomposition model. The factors of the first phenotype (neuroticism) loaded on all three traits, while the factors of the second phenotype (PCOS) only loaded on the second and third (MD) traits. The factors of the third phenotype load on only the third trait (Fig. 1). The univariate heritability and bivariate heritability, which is the fraction of the phenotypic correlation explained by genetic factors, were first calculated. Next, the genetic and environmental correlations between 1) neuroticism and PCOS and 2) PCOS and MDD, were calculated. Lastly, the model assessed the fraction of the phenotypic correlation between PCOS and MDD that is explained by genetic and environmental factors shared across neuroticism, PCOS, and MDD, and factors that are shared by PCOS and MDD, but not neuroticism.

All structural equation modeling was performed using the package OpenMx version 2.7.4 (Neale et al., 2016). In twin analysis, the precision of estimates were assessed using likelihood-based intervals, referred to as confidence intervals below.

3. Results

PCOS status, lifetime prevalence of MDD, and mean neuroticism score per zygosity are reported in Table 1. Of the 12,628 female twins with data to determine PCOS status, 35% reported having irregular menstruation, 13.2% reported abnormal hair growth, and 6.0%(n = 752) reported both and therefore met the criteria for having PCOS.

Overall, 33.9% of women with PCOS had MDD compared with 20.9% who did not have PCOS. Women with PCOS had a mean (± sd) neuroticism score of 7.90 (± 4.9) compared with a mean of 5.78 (± 4.3) in women without PCOS. The odds ratio (OR) and 95% confidence intervals (CI) measuring the association between PCOS and neuroticism as a continuous variable was 1.11 [95%CI 1.09, 1.13], indicating an 11% increase in the risk for PCOS for each unit increase on the neuroticism scale. Between PCOS and MDD, the OR was 2.01 [95%CI 1.70, 2.36], and when the model was adjusted for neuroticism, the estimate attenuated to OR = 1.37 [95%CI 1.12, 1.68].

Table 1
Characteristics of STAGE 12,628 female twins with known PCOS status.

	PCOS N (%)	Neuroticism Mean (± sd)[a]	MDD N (%)[b]
All female twins	752 (6.0)	5.91 ± 4.4	2739 (21.2)
Monozygotic	290 (6.1)	6.26 ± 4.5	1042 (22.0)
Dizygotic, same sex	202 (5.6)	5.74 ± 4.3	800 (21.6)
Dizygotic, opposite sex	243 (6.2)	5.61 ± 4.2	823 (26.6)
Zygosity unknown	17 (6.1)	6.16 ± 4.4	177 (21.0)
All PCOS cases		7.90 ± 4.9	255 (33.9)

Abbreviations: PCOS = polycystic ovary syndrome; MDD = major depression.
[a] Data were missing to determine a neuroticism score for 2974 twins.
[b] Data were missing to determine lifetime MDD for 1093 twins.

Table 2
Twin and Cross-Twin-Cross-Trait correlations for PCOS, Neuroticism and Major Depression.

	Twin Correlations		
	PCOS	Neuroticism	MDD
Monozygotic	0.61 (0.50, 0.70)	0.54 (0.50, 0.57)	0.49 (0.42, 0.56)
Dizygotic	0.25 (0.05, 0.43)	0.18 (0.12, 0.24)	0.16 (0.06, 0.26)
	CTCT correlations with PCOS		
Monozygotic	–	0.17 (0.10, 0.23)	0.13 (0.05, 0.22)
Dizygotic	–	0.04 (−0.05, 0.12)	0.10 (0.00, 0.21)

Data are given as correlation (95% confidence intervals).
Abbreviations: CTCT = cross-twin-cross-trait; PCOS = polycystic ovary syndrome; MDD = major depression.

3.1. Twin modelling

Both the within-pair correlations and the cross-twin-cross-trait (CTCT) correlations were higher in the MZ twin pairs than the DZ twin pairs, indicating the presence of genetic factors linking PCOS and neuroticism, and as well as PCOS and MDD (Table 2).

For the trivariate model, the most parsimonious fit to the data was provided by the AE model (Supplementary Table 1), and thus results from the AE model are presented.

Univariate and bivariate heritability results, derived from the trivariate model, are presented in Table 3. Heritability estimates − that is the fraction of phenotype variation in the study population that can be attributed to genetic variation − for PCOS, neuroticism, and MDD were 60%, 52% and 46%, respectively. The phenotypic correlation between PCOS and neuroticism was 0.19, and 75% of the correlation was explained by genetic factors, the remainder by unique environmental factors. Similarly for PCOS and MDD, the phenotypic correlation was 0.19, whereof 63% was explained by genetic factors and the remainder by unique environment.

The trivariate model revealed that 41.1% (95%CI 23.3, 73.8%) and 9.2% (95%CI 6.0, 23.6%) of the phenotypic correlation between PCOS and MDD was attributable to genetics and non-shared environment components that are common between neuroticism, PCOS, and MDD, respectively (Fig. 2). The contribution unique to PCOS and MDD was 21.8% (95%CI −32.3, 66.9%) for genetic and 27.9% (95%CI −25.1, 73.1%) for non-shared environmental factors.

4. Discussion

In a cohort of female twins, we found a positive association between PCOS and neuroticism score, and a 2-fold increase in odds for a lifetime prevalence of MDD in women with PCOS. The phenotypic correlation

Table 3
Univariate heritability, bivariate phenotypic and genetic correlations between PCOS, neuroticism, and major depression, and proportion of the phenotypic correlation explained by genetic and unique environmental factors.

	Univariate Heritability, %	Phenotypic Correlation with PCOS	Genetic and environmental correlations		Bivariate heritability [a], %	
	A		*r*A	*r*E	A	E
PCOS	60 (48, 70)					
Neuroticism	52 (48, 55)	0.19 (0.14, 0.25)	0.26 (0.15, 0.38)	0.11 (−0.01, 0.23)	75 (48, 103)	25 (−3, 52)
MDD	46 (38, 54)	0.19 (0.11, 0.26)	0.23 (0.05, 0.40)	0.15 (−0.05, 0.34)	63 (16, 115)	37 (−0.05, 84)

Abbreviations: A, Additive genetic factors; E, non-shared environmental factors; *r*A, genetic correlation; *r*E, non-shared environmental correlation; PCOS = polycystic ovary syndrome; MDD = major depression.

[a] Bivariate heritability is the fraction of the phenotypic correlation explained by genetic and environmental factors.

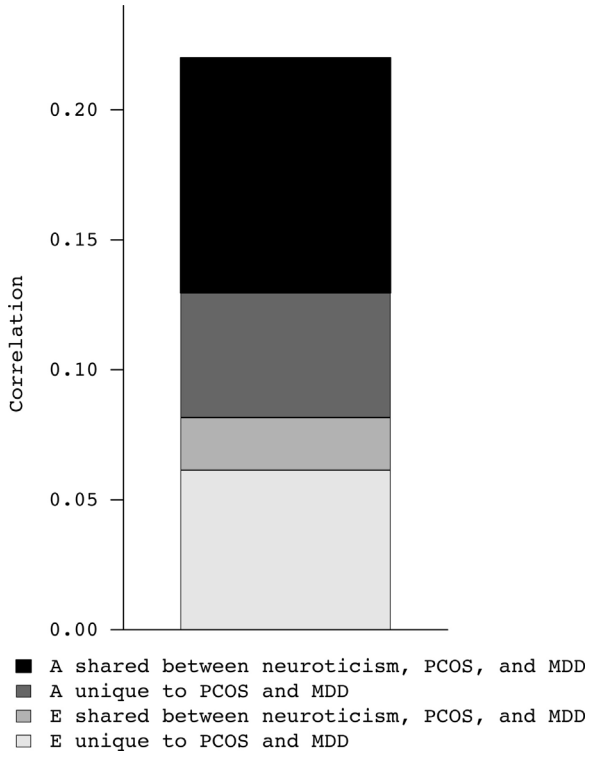

Fig. 2. Estimated Variance of Major Depressive Disorder and Neuroticism in Polycystic Ovary Syndrome.

between PCOS and MDD, while not high (0.19), is largely explained by shared genetic factors. Approximately half of the correlation between PCOS and MDD was attributable to genetic and environmental factors common to neuroticism, PCOS, and MDD indicating that while neuroticism contributes to a large portion of the comorbidity between PCOS and MDD, it does not account for all of it.

Genetic factors are important for all three traits investigated. The univariate heritability estimates for neuroticism, PCOS, and MDD that we report are similar to previously reported estimates (Kendler et al., 2006; Vink et al., 2006). Similar twin modeling studies have indicated that while the correlation between neuroticism and MDD result largely from shared genetic factors, there is a substantial proportion of the genetic vulnerability to MDD that is not reflected in neuroticism (Kendler et al., 2006; Kendler et al., 1993). This is also in line with our findings.

The association between PCOS and depression has been robustly shown in a number of studies (Barry et al., 2011b; Cesta et al., 2016; Hart and Doherty, 2014; Hung et al., 2014; Mansson et al., 2008; Weiner et al., 2004), while this is only the second study to investigate neuroticism in women with PCOS. Barry et al. (2011a) assessed personality traits using the Eysenck Personality Inventory in a sample of 76 women with PCOS and 49 sub-fertile control women, and reported that women with PCOS had higher scores of neuroticism, more difficulty coping with stress, and more symptoms of anger, when controlling for age and BMI. However, total circulating serum testosterone levels were not correlated with personality traits. Similarly, other studies measuring androgen levels in relation to symptoms of depression in women with PCOS have found no association (Hollinrake et al., 2007; Mansson et al., 2008; Rasgon et al., 2003). Therefore, investigating other sources of liability to depression in women with PCOS is warranted. This study is the first to provide evidence that neuroticism underlies part of the comorbidity between PCOS and depression by sharing genetic and environmental factors common to PCOS and MDD.

4.1. Strengths and limitations

Strength in this study lies in its unique setting of a nation-wide cohort in which all Swedish twins born between 1959 and 1985 were invited to participate (Lichtenstein et al., 2006). PCOS was identified using a validated method based on self-reported symptoms and not on self-reported diagnosis or medical record data, which relies on treatment seeking behavior. Up to 68–69% of women with PCOS experience symptoms yet remain undiagnosed (March et al., 2010). Based on the current diagnostic guidelines, there are four possible phenotypes of PCOS with varying risk for comorbidities (Lizneva et al., 2016b). To be identified as having PCOS, women in this present study must have reported evidence of hyperandrogenism (i.e., hirsutism) and irregular menstruation, thereby creating a homogenous sample of women withone of the four possible PCOS phenotypes. The prevalence of PCOS in our study is comparable to the prevalence of this particular PCOS phenotype in an unselected group of women in Denmark (Lauritsen et al., 2014). However, in the event of misclassification where women without PCOS are classified as women with PCOS in our study, the potential consequence is a dilution of the heritability estimate. Further, while our results may be only generalizable to women with this specific phenotype, it is this particular PCOS phenotype that has been shown to have the highest risk for pathophysiology and is most likely to be referred to health care (Lizneva et al., 2016a,b).

We have analyzed data from a relatively young cohort of women who were between the ages of 20 and 41 when responding to the questionnaire. Approximately half of the women were aged 35 and older, and therefore many may be peri-menopausal which may result in misclassification of their menstrual irregularities. Conversely, the younger women in the cohort may have yet to develop MDD. We do not have information on when the depression occurred or the severity of depression. Current depression or severe past depression may increase levels of neuroticism and therefore inflate the neuroticism scores (Kendler et al., 2006). Studies with a longitudinal design would help to improve the understanding of the causal relationships between these three traits and could assess whether neuroticism could predict which women with PCOS are most likely to develop MDD. Additionally, the

analysis did not take into account antidepressant use, diabetes, or other disorders that may be associated with PCOS and depression. Further, data on oral contraceptive use was not available. Oral contraceptive medication is commonly prescribed to women with PCOS to reduce their symptoms. While oral contraceptives have been linked to depression (Skovlund et al., 2016), they may or may not be associated with reduced depressive symptoms specifically in women with PCOS (Cinar et al., 2012; Dokras et al., 2016).

5. Conclusion

In conclusion, our nationwide population-based twin study showed there are common genetic and environmental factors between PCOS and MDD, and that neuroticism shares approximately half of these factors. These findings contribute to the understanding of the magnitude of the variation and covariation between neuroticism, depression and PCOS, and provide some etiological evidence behind the comorbidity between PCOS and depression.

Conflicts of interest

The authors have no conflicts of interest to disclose. The authors have no financial relationships relevant to this article to disclose.

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Contributors

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Interpretation of results: All authors.
Drafting of the manuscript: Cesta.
Critical revision of the manuscript for important intellectual content: All authors.
Final approval of the version of manuscript for submission: All authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2017.08.007.

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