



Variation among human populations in endometriosis and PCOS: A test of the inverse comorbidity model

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Received 19 July 2021; revised version accepted 14 September 2021

ABSTRACT

Evidence linking endometriosis to low prenatal testosterone, and evidence that risk of polycystic ovary syndrome (PCOS) is associated with high prenatal testosterone, have motivated the hypothesis that endometriosis and PCOS exhibit inverse comorbidity. The inverse comorbidity hypothesis predicts that populations exhibiting higher prevalence of one disorder should show lower prevalence of the other. To test this prediction, data were compiled from the literature on the prevalence of endometriosis and PCOS, levels of serum testosterone in women during pregnancy and digit ratios as indicators of prenatal testosterone, in relation to variation in inferred or observed population ancestries. Published studies indicate that rates of endometriosis are highest in women from Asian populations, intermediate in women from European populations and lowest in women from African populations (i.e. with inferred or observed African ancestry); by contrast, rates of PCOS show evidence of being lowest in Asian women, intermediate in Europeans and highest in individuals from African populations. Women from African populations also show higher serum testosterone during pregnancy (which may increase PCOS risk, and decrease endometriosis risk, in daughters), and higher prenatal testosterone (as indicated by digit ratios), than European women. These results are subject to caveats involving ascertainment biases, socioeconomic, cultural and historical effects on diagnoses, data quality, uncertainties regarding the genetic and environmental bases of population differences and population variation in the causes and symptoms of PCOS and endometriosis. Despite such reservations, the findings provide convergent, preliminary support for the inverse comorbidity model, and they should motivate further tests of its predictions.

Lay Summary: Given that endometriosis risk and risk of polycystic ovary syndrome show evidence of having genetically, developmentally, and physiologically opposite causes, they should also show opposite patterns of prevalence within populations: where one is more common, the other should be more rare. This hypothesis is supported by data from studies of variation among populations in rates of endometriosis and PCOS and studies of variation among populations in levels of prenatal testosterone, which mediate risks of both conditions.

KEYWORDS: endometriosis; polycystic ovary syndrome; population variation; testosterone; evolution

INTRODUCTION

Human populations differ in their genetics, environments and risks and symptoms of disease [1, 2]. Such variation involves effects of local selection, adaptation and maladaptation manifest as disease, for populations in their long-term ancestral environments. For populations and individuals that have recently moved from one environment to another, or who are subject to rapid environmental change *in situ*, mismatches of environments to phenotypes and genetics are also expected to increase risks of disease [3, 4]. How and why local selective pressures, and mismatches, affect disease risks is expected to be population-specific, and depend on complex, context-contingent effects and interactions of genes and environments.

Variation in disease risks and symptoms among human populations is important for studying, preventing and treating diseases, and in the empirical framework of understanding the evolutionary processes that give rise to risks and forms of disease. Productive synergism between analyses of the proximate, mechanistic causes of disease and its ultimate, evolutionary bases is pronounced in the study of diseases that vary geographically, where understanding the genetic, selective and evolutionary history of a population has direct impacts on disease etiology and treatments [5]. Geographically variable diseases are especially important because they differentially affect human groups according to their populations of origin, and inferred or documented ancestries, which can contribute to inequalities in health care caused by variation in socioeconomic level, racial and gender biases, and other societal and cultural factors (e.g. [6]).

In this paper, I analyze among-population variation in the prevalence of two of the most common disorders of female reproduction, endometriosis and polycystic ovary syndrome (PCOS). First, I describe the symptoms, diagnoses and current knowledge of disease causation for endometriosis and PCOS, especially in the context of effects from prenatal testosterone. Second, I explain a recently developed model for understanding how and why PCOS and endometriosis are related to one another [7, 8]. Under this model, PCOS and endometriosis are expected to exhibit a pattern of opposite causes and phenotypes, due in large part to high prenatal testosterone increasing risk of PCOS, and low prenatal testosterone increasing risk of

endometriosis. The two disorders are also predicted to show evidence of inverse comorbidity across populations, such that higher rates of one of the disorders in a given population should coincide with lower rates of the other disorder. Third, I test the predictions of the inverse comorbidity model, using data from (i) recent meta-analyses of variation among populations in PCOS and endometriosis prevalence [9, 10], and other relevant studies of among-population variation in these disorders, (ii) studies of among-population variation in women's testosterone levels during pregnancy and (iii) studies of among-population variation in prenatal testosterone exposure (as indicated by digit ratios), that has been implicated in the etiologies of the disorders.

POLYCYSTIC OVARY SYNDROME

PCOS is found in about 5–15% of women of reproductive age and impacts substantially upon health, fertility and well-being [11, 12]. This syndrome is characterized by the presence of three main symptoms: (i) hyper-androgenism (high levels of ovarian and serum testosterone, which can be associated with acne, increased body or facial hair and endocrine dysfunction); (ii) polycystic ovaries, that contain multiple small follicles that have stopped developing at early stages and thus resemble cysts; (iii) anovulation or oligo-ovulation (absent or infrequent ovulation during menstrual cycling). The presence and severity of these symptoms is highly variable among women, and there is no consensus among medical practitioners concerning its specific set of diagnostic criteria; several different diagnostic protocols are in use, especially the 1990 NIH criteria (criteria (i) and (iii) above) and the 2003 Rotterdam criteria (any two of the three criteria above) [12, 13]. The syndrome is also often associated with abdominal obesity and insulin resistance. PCOS is moderately to highly heritable, with heritability estimates of around 70% as estimated from comparisons of monozygotic with dizygotic twins [14].

The primary symptoms of PCOS can be recapitulated in animal models via the administration of testosterone during an early, sensitive period of prenatal development [15–17]. Risk of PCOS is thus associated with two indicators of high prenatal testosterone: long anogenital distances (AGDs) (Table 1) and low 2D : 4D digit ratios (Table 2). Long AGDs [35] and low 2D :



Table 1. All studies that tested for associations of endometriosis and PCOS with anogenital distance, an anatomical correlate of prenatal testosterone. AGD-AF distance is from the posterior fourchette to the anus, and AGD-AC is from the clitoral surface to the anus. See Dinsdale and Crespi [7] for more details

Location [Study]	Participants	Findings
Endometriosis—comparisons between adults		
Italy [18]	114 women with endometriosis and 105 control women	AGD-AF was highly significantly shorter in endometriosis group. Women in the lowest tercile were 7.6 times more likely to have endometriosis, compared to upper tercile. Women below the median were 41.6 times more likely to have deep infiltrating endometriosis. These data were also used in Sánchez-Ferrer <i>et al.</i> [19, 20]. AGD-AC did not show significant differences.
France [21]	98 women with endometriosis and 70 control women	AGD-AF and AGD-AC were highly significantly shorter in the endometriosis group in univariate analyses. AGD-AF had a specificity of 0.98 and positive predictive value of 0.97 with a 20-mm cutoff. AGD-AF difference was significant in a multivariate analysis and AGF-AC was not.
Netherlands [22]	43 women with endometriosis and 43 control women	AGD-AC was highly significantly shorter in women with endometriosis compared to controls and women with PCOS. Differences were not found for AGD-AF.
Polycystic ovary syndrome—comparisons between adults		
China [23]	156 women with PCOS and 180 control women	Both AGD measures were highly significantly longer in the PCOS group. Women with AGD-AF in highest tercile were 18.8 times more likely to have PCOS than women in lowest tercile.
Spain [19]	126 women with PCOS and 159 control women	Both AGD measures were highly significantly longer in the PCOS group in univariate tests, and AGD-AC (but not AGF-AF) was significantly longer in multivariate tests. Women with AGD-AC in the highest tercile were 2.9 times more likely to have PCOS than women in lowest tercile. These data were also reported in Hernández-Peñalver <i>et al.</i> [24]
Turkey [25]	65 women with PCOS and 65 control women	AGF-AF was longer in women with PCOS at the $P=0.08$ level, and AGF-AC at the 0.17 level. The ratio of AC to AF was associated with PCOS at $P=0.003$

(continued)

Table 1. Continued

Location [Study]	Participants	Findings
Netherlands [22]	43 women with PCOS and 43 control women	Neither measure was significantly different in women with PCOS than in control women
Polycystic ovary syndrome—comparing offspring of women with PCOS to those of control women USA [26]	300 mother–daughter dyads, where 23 mothers had PCOS	AGD-AF was longer in daughters of women with PCOS than in daughters of control women, using linear regression models (at $P=0.05$). AGD-AC difference was not significant ($P=0.18$). Results stronger for term births (P values of 0.02 and 0.09, respectively).
Denmark [27]	Daughters of 60 women with PCOS, compared to daughters of 635 control women	No differences were found between groups for either AGD measure.
Israel [28]	12 daughters and 15 sons of women with PCOS, compared to normal reference range (data from same researchers), by gender	AGD was highly significantly longer in fetuses of women with PCOS. AGD was measured in fetuses from the anus to the posterior commissure of the labia in females, using ultrasound.

4D digit ratios [36, 37] are both associated with higher prenatal testosterone during the human week 8–14 ‘masculine programming window’ [38] of fetal development, with AGD apparently being a more accurate metric than digit ratio [39]. Males have longer AGDs and shorter digit ratios than do females, and there is considerable variation within each sex as well.

As a consequence of the prenatal timing of androgenic effects, PCOS risk is strongly trans-generational, such that daughters of women with PCOS are at increased risk (of about 50%) of the disorder due to both substantial heritability and a higher-testosterone prenatal environment [40, 41]. The findings described above, and the established links of high prenatal and postnatal testosterone with the symptoms and physiological causes of PCOS, indicate that risk of this syndrome is strongly mediated by developmental, *in utero* programming of the hypothalamic–pituitary–gonadal (HPG) axis by relatively high testosterone, in association with other environmental and genetic risk factors [12, 15, 16, 42].

ENDOMETRIOSIS

Endometriosis, which is found in at least 5–10% of women of reproductive age, is defined by the presence of endometrial

tissue persisting outside of the uterine cavity, mainly at ‘ectopic’ sites in the peritoneal cavity, ovaries, fallopian tubes or rectovaginal area [43, 44]. Growth, inflammation and degradation of ectopic (extrauterine) and eutopic (uterine) endometrial tissue can cause dysmenorrhea (menstrual pain caused by strong uterine contractions), menorrhagia (heavy menstrual bleeding), chronic pelvic pain and lower fertility in about one-third of patients. Symptoms vary from none (asymptomatic endometriosis), to minor, to severe and debilitating and definitive diagnosis of cases in the literature has usually involved laparoscopic examination.

In contrast to PCOS, endometriosis has been linked with relatively low BMI, low serum testosterone and faster, more-regular menstrual cycling (reviewed in [7]).

The causes of endometriosis are poorly understood [43, 45]. It may be potentiated by retrograde movement of endometrial cells to fallopian, peritoneal and other sites [46], but most women experience retrograde flow while a much smaller percentage develop the disorder [47]. Endometriosis may also be mediated by endometrial or pre-endometrial stem cells or partially differentiated cells that become displaced during development, and are later stimulated to develop into endometrial tissue, although the evidence for these processes is limited [48].



Table 2. All studies that tested for associations of endometriosis or PCOS with 2D : 4D digit ratio, an anatomical correlate of prenatal testosterone. See Dinsdale and Crespi [7] for more details

Location [Study]	Participants	Findings and comments
Endometriosis and endometriosis-related phenotypes		
Israel [29]	187 healthy women in pregnancy cohort study	Higher digit ratios were associated with more menstrual bleeding and dysmenorrhea (cramping), two strong correlates of endometriosis
Netherlands [22]	43 women with endometriosis and 43 control women	Digit ratios were non-significantly higher in women with endometriosis than in controls. Sample sizes were small for a digit ratio study. Digit ratios would be lower (at $P < 0.05$) in women with endometriosis with sample sizes of ~ 200 per group.
Polycystic ovary syndrome		
Australia [30]	70 women with PCOS compared to 70 control women	Right hand digit ratio was significantly lower in women with PCOS ($P = 0.001$); left hand digit ratio was non-significantly lower ($P = 0.12$)
Canada [31, 32]	96 women with PCOS compared to 48 control women	No significant differences were found between groups
India [33]	200 women with PCOS compared to 200 control women	Right hand and left hand digit ratios were significantly lower in women with PCOS ($P < 0.001$ for each)
India [34]	251 women with PCOS compared to 285 control women	Right hand and left hand digit ratios were significantly lower in women with PCOS ($P < 0.001$ for each)
Netherlands [22]	43 women with PCOS and 43 control women	Digit ratios were not significantly different between women with PCOS compared to controls. Sample sizes were small for a digit ratio study.

Dinsdale and Crespi [7], Crespi and Dinsdale [49] and Dinsdale *et al.* [8] recently proposed and evaluated the hypothesis that an important contributing cause to the etiology of endometriosis is relatively low testosterone, compared to other women, during early *in utero* development. By this hypothesis, low prenatal testosterone programs the female HPG axis, resulting in an increased incidence of the major hallmarks of endometriosis including early menarche, low luteinizing hormone relative to follicle stimulating hormone, low antimüllerian hormone, low ovarian androgen levels, faster folliculogenesis and other alterations [7]. This hypothesis is also supported by recent, well-replicated findings that endometriosis risk is strongly associated with a short AGD compared to controls, which is indicative of low prenatal testosterone among females with this disorder (Table 1). The hypothesis that endometriosis

risk is mediated by low prenatal testosterone, and represents a neuroendocrine disorder with its roots in early development, provides a unifying framework for understanding this disorder, which is compatible with previous hypothesis and empirical evidence on its causes and correlates [7].

PCOS AND ENDOMETRIOSIS AS DIAMETRIC DISORDERS

Data demonstrating that risks of PCOS and endometriosis are associated with higher versus lower prenatal testosterone, respectively, and that the two disorders exhibit opposite phenotypes for a large suite of additional traits that can be causally connected to prenatal testosterone levels, suggest that these disorders are diametric (opposite) to one another in major

features of their causation [7, 8]. Diametric disorders are pairs of diseases that represent effects of opposite, maladaptive extremes of biological axes, with normality at the center. They include, for example, osteoporosis versus osteoarthritis (due to bone undergrowth vs overgrowth), cancer versus degeneration (due to cell overgrowth versus undergrowth), psychosis versus autism (due to overactivity vs underactivity of social brain neural networks), anorexia versus obesity (due to underweight vs overweight and their neuroendocrine bases) and autoimmunity versus infectious disease risk (due to immune system over-activation vs under-activation) [50–52].

Diametric disorders can also be represented as opposite, maladaptive extremes of adaptive variation or tradeoffs which, for prenatal testosterone in humans, appear to involve aspects of sexual dimorphism and sex-limited traits related to reproductive life-histories, survival and other components of fitness [7, 8, 49].

Diametric disorders are important to recognize and analyze because their presence provides for reciprocal illumination of the causes and treatments of a pair of disorders, in highly predictive frameworks [51, 53]. For endometriosis and PCOS, the diametric hypothesis makes a broad suite of predictions, one of which, inverse comorbidity, is tested here. Inverse comorbidity can be considered as the tendency for two disorders to be negatively associated with one another, in their within-population prevalence and in their presence within individuals. In this latter context, Dinsdale and Crespi [7] describe evidence showing that endometriosis and PCOS occur together in women much less often than expected by chance: women with PCOS have about one-half to one-third the prevalence of endometriosis compared to women without PCOS, and virtually all cases are minimal to mild.

The diametric disorders hypothesis for PCOS and endometriosis, applied at the among-population level, predicts that human populations showing higher prevalence of one disorder should show lower prevalence of the other. This prediction is predicated in part on the assumption that human populations differ in their average levels of prenatal testosterone (as assayed in pregnant women), and effects on the developing HPG from such levels (such as differential sensitivity to testosterone in later life), given that these causal factors are considered as important causes of risk for PCOS and endometriosis as described above.

TESTING THE HYPOTHESIS OF INVERSE COMORBIDITY

Three lines of evidence were used here to test the inverse comorbidity hypothesis. First, evidence on the prevalence of PCOS and endometriosis in different human populations was compiled from the literature. Most of the available publications categorized the populations according to ‘ethnicity’, ‘race’ or

skin color (‘Black’ or ‘White’). As used here, ‘ethnicity’ applies to human groups with shared national or cultural heritage or tradition usually involving some degree of shared ancestry, and ‘race’ refers to human groups with shared physical traits that are indicative in some way of some degree of shared ancestry. Neither of these terms has a clear biological meaning or justification, but they are expected to be indicative of variation, among groups of individuals, that reflects shared ancestry to some extent, even if small in some cases. As such, these categorizations involve both genetic and environmental variation among populations. For the epidemiological data on prevalence of PCOS and endometriosis, and for the data on serum androgen levels in pregnant women, populations were typically grouped by the authors of the relevant articles into ‘White’ or ‘Caucasian’ (typically meaning of European ancestry by the authors, but having no meaningful genetic or geographic specificity) [54], ‘Black’ or of African-American or other African-associated descent or ‘Asian’, referring, often in an unspecified way, to persons from this continent, but sometimes providing information on nationality, or referring to ‘east Asian’ for Chinese, Japanese and/or Korean. ‘Asian’ was not interpretable as a useful population category for any of the analyses unless the geographic location was specified explicitly.

‘African’ and ‘African-American’ are biologically ambiguous in the literature, given the size and diversity of Africa and its populations, and variation among African-Americans in degrees of genetic admixture. For example, in the USA, the average proportion of European admixture for self-described African-Americans is about 15–25% overall, although it varies geographically from very low to over 50% [55–57]. More generally, self-described ethnicities are only moderately to fairly highly associated with genetically defined ethnicities [57, 58]. The primary effect of such variation and uncertainties is to introduce noise or bias (against the predicted results) into the tests of the hypotheses evaluated here, as described in more detail below.

Quotation marks are used for population categories that are not clearly specified as to geographic regions, and terminologies follow those of the authors of the relevant publications except where the unscientific term ‘Caucasian’ clearly refers to ‘White’ or ‘European’.

It is also important to note that some population comparisons, such as ‘Black’ in relation to ‘White’ in the USA, involve genetically heterogeneous groups that have been divided by skin color as a single superficial correlate of inferred large-scale population of ancestry, and that these groups also differ in such factors as socioeconomic level, access to quality health care and, as described above, the degree to which the populations exhibit genetic admixture (e.g. [59, 60]). Ascertainment and other biases that could affect rates of diagnosis for PCOS and endometriosis in such populations are discussed below. Comparisons among human populations for the prevalence of

PCOS and endometriosis focus on the results from recent meta-analyses, and the results from other articles that compare two or more human populations within the same study, using the same criteria (usually 1990 NIH or 2003 Rotterdam) for ascertainment of PCOS.

Second, evidence was compiled from the literature on levels of serum androgens during pregnancy, for studies that included data from two or more populations of pregnant women who were analyzed using the same methods. Most of these studies involved comparisons between 'Black' and 'White' women (and sometimes an additional group) in the same locations. Serum testosterone levels are typically lower among non-pregnant women with shorter AGDs [61], but such analyses have yet to be conducted for pregnant women.

Third, data were compiled from the literature on 2D : 4D digit ratios for individuals of different population ancestries. Comparisons were only made between populations within studies, given differences between studies in methods for digit ratio measurement. Some of the populations involved were located in their long-term ancestral environments, and some were measured in the locations to which they had dispersed, thus representing diverse populations comprised of individuals of different ancestries. Data quality and reproducibility have been questioned for studies of digit ratios, which limits the strength of inferences at least unless the observed patterns are clear and well-replicated.

Serum testosterone levels of pregnant women indicate the potential for relatively high or low levels of testosterone in first-trimester female fetuses, via inheritance of the relevant steroidogenic mechanisms, or through direct transfer of testosterone across placental membranes, as evidenced by the lipophilic nature of steroid hormones and strong positive correlations of maternal with fetal testosterone [62]. Testosterone may also be subject to a variable degree of aromatization in placental tissue, depending for example on the presence of PCOS (e.g. [17, 63]).

In contrast to serum testosterone during pregnancy, digit ratios and AGDs provide measures of the anatomical effects of levels of prenatal exposure to testosterone. AGD represents a notably better and more consistent measure of prenatal testosterone than digit ratio [39], but it has been measured in a much smaller number of studies. The digit ratio of newborn daughters is significantly negatively correlated with levels of testosterone in the mother's amniotic fluid (for the left and right hands), and significantly positively correlated with the mother's digit ratio [64]. These authors also showed that the plasma testosterone concentration of mothers was significantly negatively correlated with the right hand digit ratio of offspring, for daughters and sons pooled. Lower digit ratios are associated with higher adult serum testosterone in some but not all studies of adults, and the presence of such correlations appears to be contingent upon whether or not this hormone is measured in individuals who are engaged in testosterone-relevant activity such as competition or exercise [65, 66].

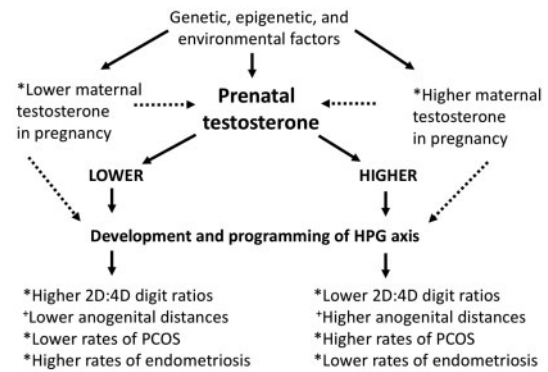


Figure 1. Associations among the variables analyzed in this study. Dotted lines refer to relationships whose mechanisms are less well understood and an * refers to a variable analyzed here. See Dinsdale and Crespi [7] for details regarding links of prenatal testosterone with PCOS and endometriosis

The conceptual framework, and bases in previous work, for this study are depicted in Fig. 1. The primary overall prediction, for the results of the three analyses, is that any population category showing a higher prevalence of PCOS should also demonstrate: (i) a lower prevalence of endometriosis, (ii) higher levels of serum androgens in women during pregnancy, especially during the 'masculine programming' period in the first trimester and (iii) lower digit ratios, which are indicative of higher prenatal testosterone. The converse predictions apply to a higher prevalence of endometriosis.

METHODS

PubMed, Web of Science and Google Scholar were searched exhaustively using search terms appropriate for each of the three domains of data compiled, with inclusion criteria as follows: (i) prevalence of PCOS and endometriosis in relation to specified ethnicity, 'race' or population, (ii) comparisons of serum testosterone levels between pregnant women of different specified ethnicities or populations, in the same study and (iii) comparisons of digit ratios between females (considered separately) of different ethnicities or populations, made in the same study with identical methods. Publication lists of articles meeting the relevant criteria were also scrutinized, as were publications that cited them. Literature searching continued until it became clear that all or virtually all relevant papers had been located, or (for the third domain) until sufficient information had been gathered for clear ascertainment of the major patterns in the data.

RESULTS

Among-population variation in the prevalence of endometriosis and PCOS

Endometriosis. In the only systematic review and meta-analysis of population associations with endometriosis

prevalence to date, Bougie *et al.* [10] stated that ‘compared with White women, Black women were less likely to be diagnosed with endometriosis (OR 0.49, 95% CI 0.29–0.83), whereas Asian women were more likely to have this diagnosis (OR 1.63, 95% CI 1.03–2.58)’. This study also showed no significant difference in odds ratios between Whites and Caucasians. Overall, 16 studies compared Blacks with Whites, 10 studies compared Whites with Asians (from diverse populations including India, Japan and Iran) and 5 compared Whites with Hispanics.

Not included in Bougie *et al.* [10] were several studies [67–69] that, as stated by these authors, did not present or provide data in forms that could be incorporated in their meta-analysis. Zhao *et al.* [67] analyzed rates of endometriosis from a US nationwide inpatient sample database derived from a project analyzing healthcare costs. They reported that ‘rates among

African-American women were significantly lower than those among Caucasians’, but no other comparisons among populations were described as different.

Missmer *et al.* [68] analyzed data on endometriosis from the Nurses Health Study II prospective cohort, which should be subject to low levels of ascertainment or diagnostic bias due to its study design and procedures (including taking account of recent physical exams). In this study, Europeans were reported to exhibit a significantly higher prevalence of endometriosis compared to African-Americans (OR: 0.6, 95% CI: 0.4–0.9) and Hispanics (OR: 0.6, 95% CI: 0.4–1.0), but there was no difference for ‘Asians’ (OR: 0.9, NS).

Eggert *et al.* [69] conducted a study of endometriosis in Sweden using their national health care database, whereby country of birth could be included as a predictor variable. In their analysis, women born in Sweden showed higher risk of endometriosis than did women born in east Africa (Eritrea, Ethiopia and Somalia) (OR: 0.51, 95% CI: 0.33–0.81); this comparison was not significant for ‘other African’ (OR: 0.91, 95% CI: 0.64–1.29), which comprised unspecified additional individuals from this continent. By contrast, women born in Sweden showed lower risk of endometriosis than did women born in either the Middle East (OR: 1.50, 95% CI: 1.33–1.69), or ‘other Asian countries’ (which mainly included east Asian nationalities) (OR: 1.53, 95% CI: 1.32–1.78). The design of this study should have involved relatively low ascertainment bias because health care is nationalized in Sweden, although other social and ethnicity-related factors could have been involved in health care utilization [69].

Finally, Parazzini *et al.* [70] conducted a systematic review and meta-analysis of the prevalence and incidence of endometriosis. For prevalence, they reported that ‘when we considered separately the estimates reported in each study according to geographic area, the pooled estimate was lower in the European studies (1.4%), increased to 5.7% in the US studies and was 15.4% in the Asian ones’. These authors did not

partition the analysis of the ‘Asian’ studies into smaller-scale localities.

PCOS. Ding *et al.* [9] conducted the only systematic review and meta-analysis to date of variation among populations in the prevalence of PCOS. They concluded that their ‘results suggested the lowest prevalence in Chinese women (2003 Rotterdam criterion: 5.6% 95% interval: 4.4–7.3%), and then in an ascending order for Caucasians (1990 NIH criterion: 5.5% 95% interval: 4.8–6.3%), Middle Eastern (1990 NIH 6.1% 95% interval: 5.3–7.1%; 2003 Rotterdam 16.0% 95% interval: 13.8–18.6%; 2006 AES 12.6% 95% interval: 11.3–14.2%), and Black women (1990 NIH: 6.1% 95% interval: 5.3–7.1%)’. By 1990 NIH criteria for diagnosis, the estimated prevalence of PCOS in ‘Black’ women (here, African-American and Afro-Brazilian) was reported as significantly higher (7.4, 95% CI: 6.3–8.7) than that for ‘White’ (here, European) women (5.5, 95% CI: 4.8–6.3); direct statistical comparisons were not possible for the Chinese sample to either ‘Whites’ or ‘Blacks’, due to the use of only the Rotterdam PCOS criteria in the Chinese studies.

In a narrative review of population variation in relation to PCOS, Wolf *et al.* [71] suggested that the available data were not conclusive enough for definitive comparisons. Chen *et al.* [72] (which was not cited in Ding *et al.* [9]) suggested that the prevalence of PCOS was lower in Chinese women (around 2.2–2.4%) than in Europeans (around 6.5–8%), for comparable unselected populations. Huang and Yong [73] likewise suggested that ‘rates of PCOS may be lower in east Asians’ than in other populations, based on rates from Korea, China and Thailand of 4.9, 5.6 and 5.7%, respectively, compared to data from other Asians and Europeans that ranged from 6.3 to 19.9%.

The prevalence data described above is affected not just by ascertainment and diagnostic biases and variation, but also by variation among populations in the phenotypic expression of the different symptoms and correlates of PCOS. For example, hyper-androgenism appears to be less common and severe in some east Asian populations than in other populations while polycystic ovaries are more common (e.g. [73–75]). Rates of obesity and insulin resistance, which can impact the expression of PCOS phenotypes and diagnoses, can also vary among populations (e. g. [76–78]). These considerations suggest that ‘ethnicity-specific’ diagnostic criteria [79] would be useful for more accurate PCOS diagnosis, to help prevent its under-diagnosis in some populations [9].

Among-population variation in serum testosterone among pregnant women

Five studies were ascertained that compared levels of serum testosterone between pregnant women of different populations,



Table 3. Comparisons of serum testosterone levels between pregnant women of different populations

Location [study] and serum testosterone collection period(s)	Participants	Main findings
USA [80] During first trimester	20 'Black' and 20 'White' women, matched by age, weight and length of gestation	Higher serum testosterone was reported in 'Black' women (mean 114.4 ng/dl) than in 'White' women (77.3 ng/dl, $P=0.0009$)
USA [81] 'Typically' at 10–12 weeks	56 African-American, 225 'Caucasian', and 109 Hispanic women	Higher serum testosterone was reported in African-American women (mean 70.9 ng/dl) than in 'Caucasian' women (42.0 ng/dl) and Hispanic women (49.1 ng/dl), all $P<0.01$. Adjustment were made for age, education and gestation age at blood draw
USA [82] During first and third trimesters	150 'Black' and 150 'White' women	Higher serum total testosterone was reported in 'Black' women (mean 1.4 ng/dl) than in 'White' women (1.0 ng/dl, $P<0.01$), in first trimester. The significance level was the same for free testosterone, and for third trimester data. Adjustments were made for gestational age, mother's age, weight, smoking and socioeconomic index
USA [83] Upon admission to hospital for delivery	34 'Black' and '50' White women	Higher serum testosterone was reported in 'Black' women (mean 215 ng/dl) than in 'White' women (117 ng/dl, $P<0.05$). The difference was highly significant ($P<0.0001$) in multiple regression analysis controlling for age, weight and height
USA [84] During first or second trimester	62 'African-American'/'Black' and 368 'White' women	Lower serum total testosterone (by 29.5%) was reported in 'White' than 'Black' women, and free testosterone 29.4% lower, both $P<0.001$ (mean values not given). Adjustments were made for age, parity, BMI, gestational age, fetal sex and study center

in the same study. In all cases 'Black' women were compared to 'White' women in the USA, and one study also included Hispanic women (Table 3). Four of the five studies included testosterone measurements from the first trimester of pregnancy, which is the period most directly relevant to the 'programming window' for prenatal androgen effects on HPG axis development and functioning, and risk for PCOS or endometriosis.

All five studies reported that serum testosterone levels were substantially and significantly higher in 'Black' women than in 'White' women (and, in one study, Hispanic women), during all stages of pregnancy considered (Table 3). Significantly higher serum levels were also found for the androgen androstenedione in 'Black' than 'White' women, for the two studies that measured this metabolite [81, 83], and for free and total testosterone,

for the two studies that measured both [82, 84]. For estradiol, which may interact with testosterone in early HPG axis programming, three of the five studies showed no significant difference between groups, one showed significantly lower levels in 'White' than 'Black' women [84], and one showed levels in 'White' women lower at $P=0.05$ [82].

Absolute values for concentrations of serum testosterone cannot be compared across studies that used different methods for hormone quantification. However, the magnitude of the percentage differences, between 'Black' and 'White' women, in testosterone during pregnancy were comparable (30–46%, mean 34%) to the differences in serum testosterone levels between pregnant women with and without PCOS (27–56%, mean 39%) [85–88]; two studies of Europeans, one study in London and one in Chile (with the latter two lacking ethnicity information). Studies are needed that compare 'Black' and 'White' pregnant women, either with or without PCOS, for levels of testosterone in the first to early second trimester of pregnancy. For interpretation of these data, it is also necessary to note that levels of maternal serum testosterone in pregnancy have not, as yet, been linked directly with either PCOS or endometriosis in daughters [89], although other connections have been demonstrated between maternal PCOS, high prenatal testosterone and PCOS or PCOS-related phenotypes in daughters (e.g. [26, 28, 41, 90]).

Among-population variation in digit ratios

Nine studies were ascertained that met the search criteria for this analysis (Table 4). Five of these studies included direct comparisons between groups within single geographic populations (i.e. 'Black' or African populations compared to 'White' or European populations), and four studies compared across geographic populations. Where statistical comparisons of relevant pairs of populations were not provided, t-tests for differences were computed from means, standard deviations and sample sizes.

'Black' or African-American females (women or children, depending on the study) showed significantly lower digit ratios than did 'White' women, across all five studies that made these within-locality comparisons (Table 4). These differences were found for both the right and left hands in all but one study [97] that showed a P -value of 0.066 for the left hand. African-American female children also demonstrated significantly lower digit ratios compared to Chinese and Japanese children in McIntyre *et al.* [99], and Chinese women showed significantly lower digit ratios than 'White' women in Brañas-Garza *et al.* [97]. In the large (>100 000 people) BBC Internet study [94], 'Black' and Chinese women showed significantly lower digit ratios than 'White' women.

All of the studies that compared digit ratios among geographically separated populations showed that the women in populations with African ancestry (Jamaican, Afro-Caribbean

or from indigenous African populations (Zulu, Datoga or Meru)) showed lower digit ratios than the women in 'White' or 'Caucasian' (as stated by the authors) groups (Berber from north Africa, Uygur, Russian, Tartar and various European nationalities), within each study (Table 4), with two exceptions: digit ratios in Finns being comparable to those in Jamaicans and Zulu, and Zulu being comparable to Hungarian gypsies [91].

Additional findings for these comparisons include digit ratios in women of two indigenous groups from India being statistically intermediate between English (higher) and Zulu (lower, $P<0.01$ for both pairwise comparisons) [92], and Han Chinese women showing significantly higher digit ratios than Uygur and Jamaican ('Black') women, but not differing from Berbers [93].

For robust analysis of digit ratios in relation to human population variation, larger samples from more populations, collected using standardized methods, are required. However, taken together, the among-geographic population comparison studies, and the studies conducted within single diverse populations, both provide evidence consistent with the hypothesis that women in or from African populations demonstrate lower digit ratios than women from other populations.

The comparisons for women from east Asian populations (Chinese and Japanese), by contrast, are scant and ambiguous. Thus, the results of these findings suggest that prenatal testosterone levels are higher among females of or from African populations than among female Europeans, subject to the assumption that the developmental connections of prenatal testosterone with digit ratios are the same in these two groups.

DISCUSSION

The primary prediction of this study, that population categories showing a higher prevalence of PCOS should also demonstrate: (i) lower prevalence of endometriosis, (ii) higher levels of serum androgens in women during pregnancy, particularly during the first trimester and (iii) lower digit ratio, are supported, at least on a preliminary basis, by the comparisons of women from African populations with women from European populations. Thus, compared to women from African populations, European women show evidence of higher rates of endometriosis, lower rates of PCOS, lower serum testosterone in pregnancy and higher digit ratios, which are indicative of lower exposure to testosterone during early *in utero* development. These results show a convergence of diverse and independent lines of evidence, in that all four variables, prevalence of PCOS, prevalence of endometriosis, pregnancy androgen levels and digit ratios, demonstrate links with prenatal testosterone (e.g. [36, 61, 62, 64]; Tables 1 and 2).



Table 4. Comparisons of 2D : 4D digit ratios between females of different populations

Populations and sample sizes [Study]	Main findings for women of or from African, European and Asian populations, and comments
<p>Women, children from South Africa and Jamaica (African populations), and women of six European or 'Caucasian' populations; highly variable sample sizes [91]</p> <p>Women from UK (European, $n=214$), India ($n=80$) and South Africa ($n=72$) [92]</p>	<p>Digit ratios of women of the two African populations were significantly lower than those of women of 4/6 European or 'Caucasian' populations, not different from two others</p> <p>Digit ratios of women of African populations were significantly lower than those of women of Indian and European populations, and significantly lower in Indian women than Europeans. Only the right hand was measured. South African population data may overlap with data in Manning <i>et al.</i> [91]</p>
<p>Women, children including Berber from Morocco, Uygur from northwest China (both referred to as 'Caucasian'), Han Chinese and African population from Jamaica; highly variable sample sizes ($n=36-229$) [93]</p>	<p>Digit ratios of women of African populations were significantly lower than those of each other population, by pairwise tests. Han Chinese women also showed digit ratios significantly higher than Uygur women. Only the right hand was measured. Jamaican population data appears to overlap with data in Manning <i>et al.</i> [91]</p>
<p>BBC internet study of digit ratios data; 'White' ($n=172$ 298), 'Asian', Middle Eastern, 'Black' ($n=2683$) and Chinese ($n=4357$) populations, residing in Europe or USA [94]</p>	<p>Digit ratios of women of African and Han Chinese populations were highly significantly lower than those of European women, in pairwise tests, for both hands. Digit ratios of women of a Han Chinese population were significantly lower than those of women of 'Black' populations, in pairwise tests, for right hand but not left hand. Other groups were too unspecified for analysis here.</p>
<p>246 'White' women and 46 'Black' women in Manchester, UK, referred for HPV testing [95]</p>	<p>Digit ratios were highly significantly lower among 'Black' women than 'White' women</p>
<p>20 'Black' women and 590 'White' women, in Canada; study of times to pregnancy [96]</p>	<p>Digit ratios were significantly lower among 'Black' women than 'White' women</p>
<p>478 women of Chinese, 'White', South Asian and 'Black' populations, in UK; study of risk-taking [97]</p>	<p>Digits ratios were significantly lower in 'Black' women compared to 'White' women, and in Chinese women compared to 'White' women</p>
<p>1296 women and children from populations in traditional locations (except Russians in Moscow): Datoga and Meru (Africa) and Russians and Tartars ('Caucasians') [98]</p>	<p>Digit ratios of African women were significantly lower than those of European or 'Caucasian' women for all four comparisons for right hand, and for 2/4 comparisons for left hand. Sample sizes were very low for some groups (25 and 31 for Datoga and Tartar women).</p>

The evidence regarding the third main population group considered, Asian (comprising both east Asian and other groups), broadly but weakly supports the predictions for PCOS and endometriosis. Thus, PCOS prevalence is lower among Chinese women compared to African and European women (by meta-analysis, Ding *et al.* [9]) (with inadequate data on women of other Asian populations), and endometriosis prevalence is higher in Asian women (of several pooled ethnicities) than among women of or from African or European populations (also by meta-analysis, Bougie *et al.* [10]). The strength of these

findings is limited mainly by the paucity of information on the prevalence of PCOS among women from Asian populations other than Chinese. There is also insufficient data at present from Asian women (compared to other women) for tests of the predictions regarding testosterone in pregnancy, and digit ratios.

The findings described here are also concordant with variation among human populations in length of the CAG microsatellite in the androgen receptor gene *AR*, the gene through which androgens exert their developmental and functional effects [36].

Fewer CAG repeats has been associated with higher transcriptional activity of the *AR*, and thus stronger effects from a given level of testosterone or other androgen [100]. CAG repeat number has been reported as lowest among individuals from African populations, intermediate in individuals from European populations and highest among individuals from Asian populations (Thai in one study and pooled 'Asians' in another) [101–104], thus coinciding in rank order with the patterns for PCOS and endometriosis described above. The number of CAG repeats in the *AR* is known to impact ovarian functions including folliculogenesis [105, 106], and to mediate the effects of testosterone on insulin resistance in PCOS [107], but its functional roles in endometriosis and PCOS, and their associated phenotypes, otherwise remain largely unknown.

The findings described here have several implications for women's health, and for evolutionary studies of major disorders affecting female reproduction. First, the main results suggest that population variation may influence the prevalence of PCOS and endometriosis, in a manner predicted by the inverse comorbidity model. These findings provide initial evidence that women differ in their overall risks for PCOS and endometriosis as functions of prenatal testosterone levels, which are associated with their population designation. The magnitudes of any such effects remain to be discerned, and the contributions to disease risks of variation in prenatal testosterone levels among individuals, compared to among populations, remain unclear. These results should motivate data collection that targets the predictions of the inverse comorbidity hypothesis in more detail. Determining the presence and degree of such among-population variation in risks for PCOS and endometriosis has important implications for population screening and differential diagnoses of these disorders in comparison to related conditions.

Second, support for the inverse comorbidity hypothesis for PCOS and endometriosis, as demonstrated here, indicates that it has the potential to provide a predictive and explanatory framework for understanding the etiologies of both disorders, and developing new treatments. For example, Dinsdale *et al.* [8] show that some risk factors for PCOS represent treatments for endometriosis, and *vice versa*; examples include androgens, valproic acid, aromatase inhibitors and antagonists versus agonists of the oxytocinergic and endogenous opioid systems. A contribution to endometriosis etiology of relatively low prenatal testosterone is especially important in this general regard, given that the causes of this disorder have been enigmatic since it was first described. Studies that directly compare PCOS and endometriosis, for factors including AGD, and other correlates, mediators, causes and effects of prenatal testosterone on female HPG development and function, should provide further robust tests of the inverse comorbidity model and generate new insights into preventatives and treatments for both disorders. Such studies should also clearly take account of human population variation.

A number of caveats and limitations must be considered, with regard to interpreting the results of this study. A primary limitation of the data used to test the inverse comorbidity model is that the three lines of evidence come from different specific populations, mainly African, European, and Asian, each of which is itself quite diverse. More exacting tests of the model would compare specific pairs or sets of populations for: (i) prevalence of PCOS and endometriosis, (ii) levels of androgens in early pregnancy, in controls and in women with PCOS or endometriosis and (iii) indicators of prenatal testosterone including digit ratios and especially AGD. Ideally, such tests would be conducted in non-admixed populations, in their geographic locations of long-term residence. By contrast, for health-care purposes and more-personalized medical applications, it becomes important to determine the genetic and physiological bases of among-population variation in risks and symptoms of endometriosis and PCOS, in the contexts of admixture, geography and local environmental effects.

An additional caveat, as regards interpretation of the results, is that the observed differences among populations in PCOS and endometriosis prevalence, testosterone levels in pregnancy and digit ratios may be attributable, to some unknown degree, to phenotypic responses to different environments that are associated with population variation. This hypothesis could be evaluated through studies of environmental, and gene by environment, influences on prenatal testosterone levels and their correlates, and additional environmental causal factors, that may affect risks of these two disorders. In this context, it is also important to note that the inverse comorbidity hypothesis is agnostic to the roles of genetic compared to environmental or gene by environment effects on prenatal and postnatal testosterone and other factors that differentially program the developing HPG axis.

The data on endometriosis and PCOS are also subject to variable degrees of ascertainment biases, mainly as a function of women of lower socioeconomic status having reduced access to high-quality health care [6]. Such inequalities may, in particular, reduce the estimated prevalence of endometriosis in some groups, which, historically, can take longer to diagnose than PCOS [108–110]. Ascertainment may also be affected by the historically-based opinions of medical practitioners regarding the prevalence of disease in different groups (see Bougie *et al.* [10]), differences in cultural traits related to medical help-seeking that involves female reproduction and by differences among population groups in the levels of symptoms that motivate help-seeking in the first place, such as pain in endometriosis (e.g. [111]).

Finally, the prevalence, symptom profiles and severities of endometriosis and PCOS are, in developed and developing countries, affected by a wide range of factors including for example Westernization of diets, obesity, type 2 diabetes and endocrine disrupting chemicals, all of which should cause

deviations from evolved, population-specific adaptations and disease risks [3]. The observation that the predictions of the inverse comorbidity model are generally met, despite these limitations and sources of variation, suggests that the model has potential for contributing to our understanding of endometriosis and PCOS across diverse human populations.

ACKNOWLEDGMENTS

The author is grateful to the members of the Crawford Laboratory of Human Evolutionary Studies for comments.

Conflict of interest: None declared.

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