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We propose and evaluate a new theory for helping to explain the evolution of endometriosis risk in humans. By this theory, endometriosis risk evolved in the context of sexual selection by males for high, relatively female-biased expression of sexually dimorphic and female-limited phenotypes associated with low testosterone and high female reproductive fitness. The theory is supported by extensive data, showing that: (a) endometriosis involves higher expression of major female-biasing genes, and lower expression of major male-biasing genes, that orchestrate prenatal sexual differentiation; (b) endometriosis and its correlates are associated with low prenatal and postnatal testosterone, both of which have female-biasing effects on traits; (c) low prenatal and postnatal testosterone, and endometriosis, are associated with relatively female-biased phenotypic expression for a large suite of sexually dimorphic and sex-limited traits; (d) relatively female-biased expression of these traits is commonly associated with higher fertility and fecundity; (e) some traits, including female facial features, vocal pitch, and breast size, fit with all of the predictions of the model, though they have yet to be studied in relation to endometriosis; and (f) traits linked with low prenatal and postnatal testosterone or high estradiol, and traits associated with endometriosis in humans, are preferred by males across multiple species of non-human mammals. Risk and symptoms of endometriosis thus appear to involve and represent, in part, maladaptive extremes of sexually selected female-limited and sexually dimorphic traits.

Public Significance Statement
We describe evidence from genetics, hormones, morphology, behavior, and life history that risk for endometriosis is associated with low testosterone. We also describe how endometriosis involves "relatively female" expression for a large suite of traits and that risk of this disorder appears to have evolved in the context of male choice of females with endometriosis-associated traits that signal relatively high reproductive capabilities. This work shows how human mate choice can lead to maladaptive extremes of reproductive adaptations that manifest in symptoms of disease and provides new insights relevant to the causes of endometriosis.

Keywords: endometriosis, evolution, mate choice, sexual selection, testosterone

The selection and evolution of adaptive traits commonly involves tradeoffs between opposing selective pressures whose effects are mediated by ineluctable physical and temporal constraints (Crespi & Go, 2015; Williams & Nesse, 1991). A prominent form of tradeoffs is those involving sexual selection and natural selection (Fisher, 1915). By this process, sexual selection favors a trait that

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confers advantages with regard to competitive mating and reproduction, via mate choice, intrasexual competition, or both, which leads to increased or enhanced trait expression. If, however, the trait becomes too highly expressed, then it can interfere with survival or other components of fitness, resulting in a balance between sexual and natural selection.

The purpose of this article is to describe and evaluate a new model, based on the interplay of sexual and natural selection, for understanding the evolutionary and behavioral basis of endometriosis. We first describe endometriosis and its symptoms, its proximate causes and correlates, and previous ideas regarding its ultimate, evolutionary causes. Second, we explain the hypothesis proposed here for endometriosis risk, and some of the findings that motivated its development. We then list a series of predictions that follow from the hypothesis and evaluate them with data from the literature.

Endometriosis

Proximate, Physiological Factors

Endometriosis is defined by the presence of endometrial tissue outside of the uterine cavity, usually in the peritoneal cavity, ovaries, fallopian tubes, or rectovaginal area (Bulun et al., 2019; Wang et al., 2020). Growth, inflammation, and degradation of displaced, as well as uterine, endometrial tissue is associated with dysmenorrhea (menstrual pain due to strong uterine contractions), menorrhagia (heavy menstrual bleeding), chronic pelvic pain, and reduced fertility, to a degree that varies from mild to severe. Endometriosis has been reported in all human populations investigated for this disorder, although its prevalence appears to vary across populations, being relatively high in Caucasian populations, subject to caveats associated with ascertainment biases (Bougie et al., 2019; Crespi, 2021).

The causes of endometriosis are enigmatic (Bulun et al., 2019; Chapron et al., 2019). At the physiological level, its effects are driven by excessive local production of estrogen in proliferating endometrosis tissue, at both uterine and extra-uterine, ectopic sites, as well as high levels of inflammation in such tissues. The disorder is also characterized by high levels of oxytocin (that increase uterine contractility), low serum and ovarian testosterone, and high follicle stimulating hormone relative to luteinizing hormone (Dinsdale & Crespi, 2021). Menarche occurs at a younger than average age in typical-weight women who develop endometriosis, menstrual cycles are shorter and more regular, and menopause is earlier (Day et al., 2015; Gupta et al., 2015; Matalliotakis et al., 2008; Nnoaham et al., 2012; Wei et al., 2016; Yasui et al., 2015).

Endometriosis may be potentiated by retrograde movement of endometrial cells from the uterus to fallopian, peritoneal, and other sites (Sampson, 1925); however, most women experience retrograde flow, whereas only 5% to 10% develop the disorder (Halme et al., 1984), so other factors must be involved. Cells that develop into endometriotic tissue may also reach extra-uterine sites via the venous circulation, or though displacement of stem cells during prenatal sexual and genitourinary system development (Sasson & Taylor, 2008; Yovich et al., 2020). Currently, there is no cure for endometriosis, and treatments commonly involve pain medication, surgery, GnRH (Gonadotropin-Releasing Hormone)-based therapies that stop menstruation, or, usually in older women, hysterectomy.

Ultimate, Evolutionary Factors

The evolutionary changes that potentiated endometriosis risk in women evolved in other selective contexts and have given rise to the risks and forms of this disorder, which involves reduced health and fertility as secondary effects. These changes, along the lineage from the chimp-human ancestor to modern humans, involve a suite of traits that are relevant to the development of endometriosis and the selective pressures that, by the hypotheses addressed here, are associated with it (see also Dinsdale et al., 2021). These changes include the following factors:

First, humans have evolved especially invasive hemochorial placentation and deep trophoblast invasion (Brosens et al., 2009; Crosley et al., 2013), through selective processes that may involve maternal-fetal conflicts (Haig, 1993) and selection for large human brain size (Martin, 2003). The evolution of more extensive endometrial proliferation and menstruation (Clancy, 2009; Evans et al., 2016; Jarrell, 2018; Strassmann, 1996), concomitant to more-invasive placentation, has generated higher menstrual activity which causes increased potential for retrograde flow (movement of menstrual blood and other tissues into the peritoneal cavity, ovaries, or other sites), and high levels of

inflammation during menstruation, given that menstruation is inherently highly inflammatory. The selection pressures involved in the evolution of spontaneous decidualization and highly developed, copious menstruation in humans may involve aspects of reproductive energetics and ecology, maternal-fetal conflicts, preconditioning of the uterus in preparation for implantation, or other factors (Brosens et al., 2009; Clancy, 2009; Emera et al., 2012; Jarrell, 2018; Strassmann, 1996), that remain matters of investigation. Whatever its causes, highly developed menstruation represents an important precondition for the evolution of endometriosis, given that it involves greater retrograde flow and strong estrogen-driven stimulation for rapid growth of endometrial tissue.

Second, deeper implantation and invasion of the embryo and trophoblast into endometrial tissue, as found in humans, also represent highly inflammatory processes, that may also have contributed to high inflammation in endometrial tissue (Dekel et al., 2010; Pijnenborg, 2002).

Third, more extensive development of the uterine musculature that facilitates parturition has evolved in humans, in association with the enlarged cranium size of human neonates relative to the size of the birth canal (Dunsworth & Eccleston, 2015; Rosenberg, 1992). This phenotypic change may potentiate strong and painful uterine contractions during menstruation.

Fourth, reduced interbirth intervals, from about six years to about three years, have evolved along the human lineage (Hrdy, 2009; Nakahashi et al., 2018), which have led to higher reproductive rates, and probably also to higher variance in female reproduction, which would increase the opportunity for selection on female reproductive phenotypes.

Fifth, the development with menarche of high levels of gluteofemoral fat, and large permanent breasts that harbor stores of fat, that are utilized for the high energy demands of gestation and lactation (Wells, 2010), have also evolved in humans and may also function as indicators of high female reproductive capabilities.

Sixth, pronounced sexual dimorphism in facial features, vocal pitch, and other steroid hormone related traits have evolved along the human lineage (Puts et al., 2012), and these traits may serve as indirect indicators of female reproductive capabilities.

Seventh, increased paternal care has evolved in humans, which is expected to generate selective conditions favoring male choice of relatively fertile and fecund females (Hrdy, 2009).

Eighth, the evolution of higher levels of monogamy and guarding of females by males has evolved in humans (Schacht & Kramer, 2019); these traits can select for male choice of females with high nubility (youthful and recent sexual maturity), and reproductive value (Lassek & Gaulin, 2019) who can be reproductively "controlled" by males for extended periods of time (Hrdy, 1997).

Ninth, the recent evolution of reduced hair, eye and skin pigmentation in some populations, which influences availability and metabolism of the key reproductive nutrients vitamin D, folate, and calcium (Parra, 2007; Jablonski & Chaplin, 2017), has generated new phenotypic and genetic substrates for sexual selection.

A final factor important to the current prevalence of endometriosis is evolutionary mismatch, between adaptations to past environmental conditions, and environments that have changed too rapidly for selection and response to selection to track them. By this hypothesis, the current notably high prevalence of endometriosis in women, about 5% to 10%, is driven in part by recent secular trends towards earlier menarche and later age of first reproduction, both of which increase numbers of the menstrual cycles that elevate the potential for retrograde flow effects and estrogenic stimulation of endometrial tissue growth (Clancy, 2009; Jarrell and Arendt-Nielsen, 2016; Scioscia et al., 2019). This hypothesis is consistent with epidemiological data linking endometriosis risk with correlates of numbers of menstruations (Scioscia et al., 2019), although directionalities of causality remain unclear because genes underlying endometriosis are also pleiotropically associated with earlier menarche (Ponomarenko et al., 2020). A second environmental factor that likely potentiates endometriosis risk is increased exposure to estrogenic or anti-androgenic chemicals (e.g., Sirohi et al., 2020). The presence of such mismatches would be expected to exacerbate, rather than generate *de novo*, the symptoms and severity of endometriosis. As such, mismatches are relevant to the current prevalence and proximate causes of endometriosis, but not to the evolution of endometriosis risk along the human lineage. Data on endometriosis or its strong correlates are needed from hunter-gatherer or other traditional human populations, to further evaluate hypotheses based on mismatch.

Sexual Selection of Endometriosis

Hypothesis for the Evolution of Endometriosis Risk

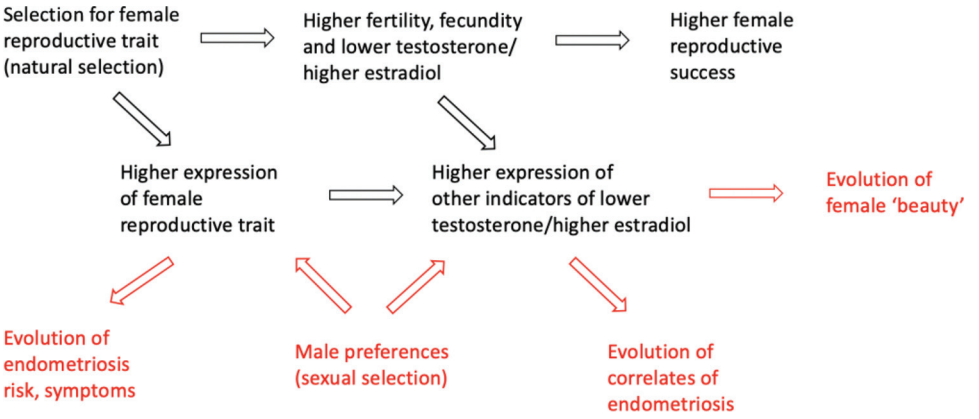
Given what is known about the physiology of endometriosis, and the set of changes in phenotypes along the human lineage, a simple, testable hypothesis can be developed for how risk of this disorder has evolved. We hypothesize that females were subject to selection for increased expression of female-limited and sexually dimorphic phenotypes, such as wider hips with more gluteofemoral fat, that increased their reproductive success. This process represents natural selection on females, in the context of reproductive ecology and physiology. Such phenotypes, and their correlates, subsequently came to serve as indicators of increased reproduction and reproductive potential, in the context of social and sexual interactions among males and females in one's local group. In such situations, males were subject to selection for choice of females, and more investment of resources in females, that exhibited higher levels of these fitness-related traits and their indicators (Figure 1). This is a form of sexual selection because it involves choice of mates. Once males began to compete for females in this manner, females would, in turn, have been subject to within-sex competition for acquiring relatively high-fitness and high-provisioning mates as well (DelPriore et al., 2017; Puts, 2010). By this process, females are subject to selection both in the context of their reproductive ecology as mediated by such factors as energetics, stress, and life history tradeoffs (Clancy, 2009), as well as in the context of mate choice by males.

The expected evolutionary response to sexual selection by males for increases in female-biased phenotypes associated with higher reproduction is increases and elaboration of these traits. These changes are propelled by both natural selection (for female reproductive traits that increase fitness) and sexual selection (for male choice of females with higher expression of such traits). As the distributions of these traits shift, over evolutionary time, in the "female" direction, the females in the forefront —the female biased tail—of the distribution would exhibit relatively extreme levels of the salient phenotypes (Figure 2).

Some such individuals thus come, after some period of evolutionary time, to exhibit extreme expression of these reproduction-related adaptations that can become maladaptive and manifest as symptoms of disease that reduce fitness. Sexual and natural selection for "more-female" traits, and higher reproduction, may then come to be more or less balanced by natural selection against reproductive problems and disease. This process essentially represents Fisher's (1915) original model for sexual selection, applied to human reproductive development, physiology and behavior. The idea that female "attractiveness" may be associated with

Figure 1

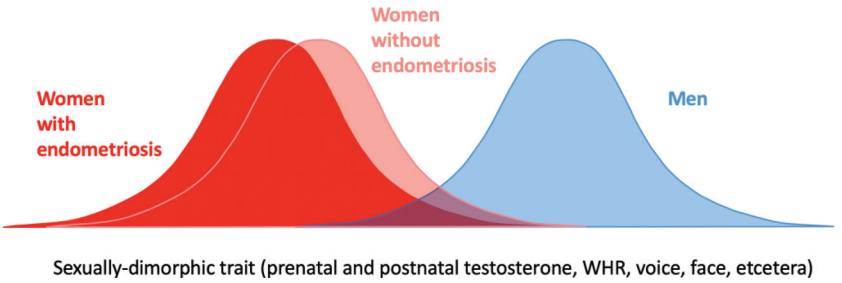
The Set of Processes Involved in the Hypothesis That Sexual Selection Has Mediated the Evolution of Human Risk for Endometriosis



Note. Processes associated with sexual selection are shown in red. See the online article for the color version of this figure.

Figure 2

Endometriosis Is Characterized by Relatively Female Expression for a Wide Range of Sexually Dimorphic Traits



Note. See text and Table 1 for details. See the online article for the color version of this figure.

endometriosis, due to the joint dependence of these two phenomena on sex steroids, was originally suggested by Buggio and colleagues (2012), and is specified, developed, extended, and tested here. This hypothesis provides the first conceptual framework, grounded in human evolutionary biology and behavior, for understanding this enigmatic disease.

Testing the Hypothesis

The predictions of the sexual selection hypothesis for endometriosis fall into six major domains. The predictions involve different sets of links between endometriosis, endometriosis-associated traits, sexual dimorphism, testosterone and estradiol, correlates of fitness, and male mate preferences, among humans and non-human mammals.

First, the hypothesis predicts that endometriosis should be associated with shifts toward "more-female" gene expression during early *in utero* human sexual development. This hypothesis is evaluated by determining whether endometriosis in adult females is associated with higher expression of genes that exhibit "pro-female" and "anti-male" effects in early fetal development, and lower expression of genes that exhibit "anti-female" and "pro-male" effects. This prediction is predicated on the observation that although chromosomal sex (XX and XY) is (aside from aneuploidies) binary, the phenotypic expression of sexually dimorphic quantitative traits varies continuously within each sex.

Second, the hypothesis predicts that endocrinological, physiological and morphological traits associated with endometriosis should be sexually dimorphic (differing in mean between the sexes), or female limited (found only among females), and that women with endometriosis should show relative female biases in the development and expression of these traits. These female biases should, in turn, tend to be associated with relatively low prenatal and postnatal testosterone, relatively high effects from estradiol, or both.

Third, the hypothesis predicts that endometriosis-associated traits and genotypes should be associated with higher reproductive fitness (and correlates thereof), even though endometriosis itself, as a maladaptive condition, tends to reduce fitness overall. This prediction evaluates the idea that endometriosis involves having "too high" expression of traits, and "too many" alleles, for causes of higher reproduction, where reproduction may specifically include fecundity, fertility, reproductive value, nubility or some combination of these correlates of fitness.

Fourth, the hypothesis predicts that many endometriosis-associated traits should tend to be preferred by males, because they are usually linked with higher female reproduction. Such preferences should tend to be expressed cross culturally in humans and should be expressed at higher levels in populations where endometriosis is more prevalent. Some of the traits preferred by males may be directly related to female reproduction and reproductive value (e.g., low waist to hip ratio, WHR), whereas other such traits (such as relatively female facial features or vocal pitch) may represent indirect indicators of reproductive potential due to their developmental and functional links with levels of steroid hormones such as testosterone and estradiol.

Fifth, the hypothesis predicts that female traits that are preferred by males should be mediated in

their development and expression by relatively low testosterone and high estradiol (prenatal, postnatal or both). This prediction applies specifically to female-limited or sexually dimorphic traits, such as vocal pitch, facial sexual dimorphism, and relative breast size, that owing to current lack of available published evidence, are not known to be linked with higher endometriosis risk but are expected to be, according to the hypothesis.

Sixth, non-human male mammals are expected to exhibit mate choice for females expressing relatively "more-female" traits, and indicators of higher reproduction, and these indicators are predicted to be associated with correlates of endometriosis. Such correlates include for example low prenatal and postnatal testosterone, high estradiol, early onset of reproduction, fast cycling, and endometriosis-related reproductive physiology, such as fast ovarian aging. Conversely, males of such species are expected to exhibit preferences against traits that indicate relatively high effects of testosterone in females. As for humans, females of non-human animals who express more endometriosis-associated traits are also predicted to show higher fecundity or other correlates of fitness.

Evaluating the Predictions

Endometriosis Should Involve Relative Female Biases to the Early In Utero Development of Sexually Dimorphic, and Female Limited, Phenotypes

The development of morphological and physiological sex differences between human females and males begins prenatally, during weeks 6–8 after conception, under the influences of SRY (Sex-determining Region Y) gene expression and higher prenatal testosterone in males than in females (Rey et al., 2020). These changes occur in conjunction with differential patterns of gene expression in the two sexes that orchestrate loss of the Müllerian ducts in males, loss of the Wolffian ducts in females, and a large suite of concomitant divergent developmental changes. During early sexual development, some genes thus exert "anti-male" or "pro-female," or oppositely, "anti-female" and "pro-male" effects, in the developing fetus.

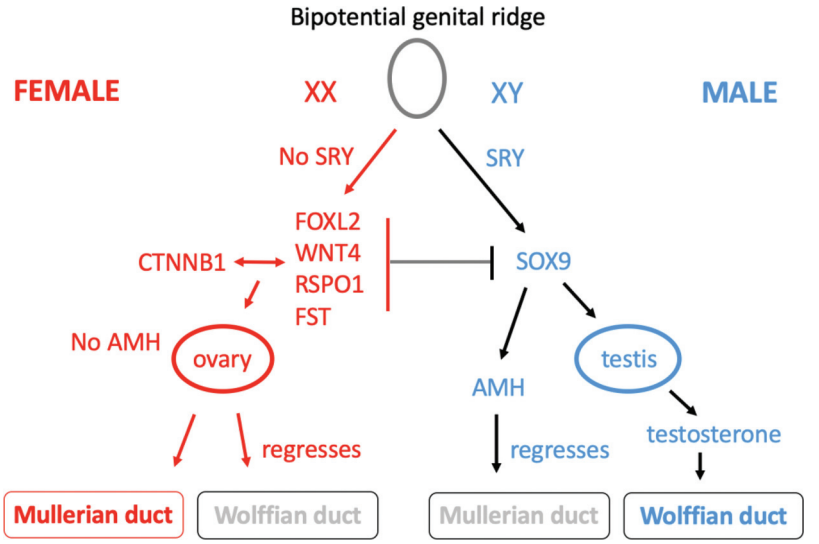
Genes with "pro-" or "anti-" male or female effects, like genes that induce high versus low levels of testosterone, guide the early development of sexually dimorphic traits, as well as functioning in aspects of adult reproductive physiology including the maintenance of ovarian versus testicular functions (e.g., Murphey, 2010). We surveyed the literature on the primary genes underlying early prenatal human sexual development (e.g., Figure 4 in Rey et al., 2020) to ascertain which genes had clear "pro- or anti-male" and "pro or anti-female" effects, as evidenced by data from knockouts, losses of function, duplications, or partial or total XX to XY or XY to XX sex reversals. Data were available on expression in endometriosis versus controls for seven such mammalian genes that are centrally involved in early human sexual development (Figure 3). The hypothesis addressed here thus predicts that endometriosis (and the differential expression of genes that characterize it) should be associated with higher expression, during early sexual development, of genes with "anti-male" or "pro-female" effects and lower expression of genes with "anti-female" or "pro-male" effects.

SOX9 (SRY-Box Transcription Factor 9). Expression of the "anti-female" gene SOX9 is activated by the male-determining factor SRY, and its absence results in XY male to female sex reversal in mammals (Lavery et al., 2011). Expression of this gene also activates expression of AMH (anti-müllerian hormone; De Santa Barbara et al., 1998) and prevents male to female reprogramming of the testis into ovaries. In females, SOX9 expression is repressed, by WNT4 (Wingless-Type MMTV Integration Site Family, Member 4), FOXL2 (Forkhead Box L2) and CTNNB1 (Catenin Beta 1; Maatouk et al., 2008; Suzuki et al., 2015). In women with ovarian endometriosis, expression of SOX9 is substantially reduced in endometriotic tissue (Zhao et al., 2018). The SOX9 gene also regulates expression of the gene TRPS1 (Transcriptional Repressor GATA Binding 1), which is associated with endometriosis risk at the genome-wide significance level (Rahmioglu et al., 2018) and which shows polymorphisms that mediate tanning response (Visconti et al., 2018); SOX9 is also upregulated after UVB exposure, leading to increased production of melanin (Passeron et al., 2007). As described in more detail below, tanning responses are reduced among women with endometriosis (Kvaskoff et al., 2009; Somigliana et al., 2010).

Anti-Müllerian Hormone. Expression of AMH, an "anti-female" gene, drives regression of the Müllerian ducts in early mammalian development, and the ducts are maintained in male knockouts for the gene (Roly et al., 2018). In cycling women, AMH is produced by ovarian granulosa cells and

Figure 3

Endometriosis Involves Higher Expression, During Adulthood, of a Set of Core Early-Developmental "Pro-Female/Anti-Male" Genes (in Red), and Lower Expression of "Anti-Female/Pro-Male" Genes (in Blue); Jointly, These Genes Guide Early Sexual Differentiation and Development



Note. See the online article for the color version of this figure.

regulates the recruitment of follicles. Production of AMH in the ovaries is notably reduced among females with endometriosis (Dong et al., 2019; Kasapoglu et al., 2018; Muzii et al., 2018; Romanski et al., 2019; Sánchez-Ferrer et al., 2019). By contrast, AMH levels are substantially increased among females with PCOS, who also exhibit high levels of ovarian androgens and increased serum testosterone (e.g., Dinsdale & Crespi, 2021; Dumont et al., 2015; Garg & Tal, 2016; Sahmay et al., 2014). AMH has also been suggested as a treatment for endometriosis, given its ability to inhibit the proliferation of endometrial cells *in vitro* (Borahay et al., 2013; Signorile et al., 2014).

FOXL2. The "anti-male" gene FOXL2 antagonizes the effects of "pro-male" gene SOX9, mediates development of the uterus, and positively regulates follicle recruitment and expression of GnRH and FSHB (Follicle Stimulating Hormone Subunit Beta; Murphy, 2010; Verdin & De Baere, 2012). Knockouts of FOXL2 cause partial (in mice), or complete (in goats) female to male sex reversals (Uhlenhaut et al., 2009), and reduced expression in humans commonly results in premature ovarian failure (Verdin & De Baere, 2012) and increased levels of androgens (Murphy, 2010). Compared with controls, expression of FOXL2 is increased about threefold in endometrial tissue of women with endometriosis, where it appears to contribute to tissue proliferation (Governini et al., 2014).

WNT4. The gene WNT4 mediates mammalian sex determination and female gonad development. Deletion of the gene causes masculinization of XX female mice, and its deficiency causes increased testosterone production in females (Heikkilä et al., 2005). By contrast, duplication of WNT4 causes sex reversal of XY males (Jordan et al., 2003). WNT4 thus functions as an "anti-male" gene in early development. In women with endometriosis, WNT4 expression is increased in ovarian granulosa cells (Sanchez et al., 2014); it also shows higher expression in a rat model of endometriosis (de Mattos et al., 2016). By contrast, in endometrial tissue, WNT4 expression is lower in women with endometriosis than in controls (Liang et al., 2016; Logan et al., 2018). Lower WNT4 in this tissue is associated with higher testosterone production, which contributes to the proliferation of endometrial cells via its aromatization to estradiol (Huhtinen et al., 2014). As such, both higher production of

WNT4 in ovaries, leading to low ovarian testosterone as found in endometriosis (Ono et al., 2014), and higher expression of this gene in endometrial tissue (leading to higher local production of estradiol), contribute to the symptoms of endometriosis. Finally, the WNT4 gene also harbors SNPs that are significantly associated with endometriosis, from GWAS results, at the genome-wide significant level (Rahmioglu et al., 2014, 2018), although whether and how these SNPs affect WNT4 expression remains unknown.

RSPO1 (R-spondin 1). The gene RSPO1 interacts with WNT4 to antagonize SOX9 in early sexual development. Its loss of function causes XX sex reversal in humans (Biason-Lauber, 2012; Clevers & Nusse, 2012; Parma et al., 2006) and Müllerian duct agenesis in mice (Miyamoto et al., 1997); it thus represents a "pro-female" gene in its developmental effects. RSPO1 also shows increased expression in endometriosis, in association with a general increase in WNT pathway activation in endometrial tissue of affected women (Hundt, 2016; Matsuzaki et al., 2014).

CTNNB1 (Catenin beta 1). This gene codes for β-catenin, a protein that mediates transcription of other genes and cell-cell adhesion. In early fetal development, β-catenin antagonizes the effects of SOX9 and acts as an "anti-testis" and "pro-ovary" signaling molecule; its experimental overexpression causes XY sex reversal with loss of expression of SOX9 and AMH and increased expression of WNT4, FOXL2, and FST (Maatouk et al., 2008). β-catenin expression is increased in ectopic endometrial tissue in women with endometriosis (Pazhohan et al., 2018, 2021; Xiong et al., 2016), where it promotes cell proliferation and migration (Matsuzaki et al., 2014).

FST (Follistatin). Follistatin is an activin-binding protein that is encoded by the FST gene. Its expression in early prenatal development in females inhibits the formation of the coelomic vessel, a male-specific artery that is required for testis development; FST-null XX mice thus undergo a partial sex reversal (Yao et al., 2004). FST also exerts "pro-ovary" effects that enhance oocyte survival, and it is positively regulated by FOXL2 and WNT4 (Kashimada et al., 2011). Levels of follistatin are higher in serum and ectopic endometrium of women with endometriosis (Florio et al., 2009; Torres et al., 2007).

Taken together, these major mammalian genes affecting early sexual development, which also exert important reproductive functions in adult females or males, demonstrate a pattern of "anti-female" and "pro-male" genes being underexpressed in endometriosis (SOX9 and AMH), and "anti-male" and "pro-female" genes (FOXL2, WNT4, RSPO1, CTNNB1 and FST) being overexpressed or, when underexpressed (WNT4 in endometrial tissue) promoting increased endometrial proliferation, a hallmark of endometriosis. These findings thus support the hypothesis that endometriosis is characterized by a female bias to early sexual development and adult reproductive functions.

Endometriosis and Endometriosis-Associated Traits Should Involve Relative Female Biases to Sexually Dimorphic Phenotypes

This hypothesis predicts that for phenotypes present in both sexes, females with endometriosis should exhibit phenotype distributions, for reproduction-related traits, that are shifted in the female direction, away from males, compared with females without endometriosis (Figure 2). We evaluate this prediction here for endocrine, physiological and morphological phenotypes, with the overall results summarized in Table 1.

Prenatal Testosterone. Early prenatal testosterone in the fetus is problematic to measure directly in humans, so two proxies of its levels have been extensively used. First, anogenital distance (AGD), from the anus to landmarks on the genitalia, is substantially longer in males than in females, and it is longer under the influence of higher prenatal testosterone, and lower estrogen, as indicated by extensive experimentation with non-human animals and studies of humans naturally subject to altered levels of the relevant hormones (Dean & Sharpe, 2013; Liu et al., 2014; Schwartz et al., 2019; Thankamony et al., 2016). The use of AGD as an indicator of prenatal testosterone has thus been well validated with hormonal measurements, in both sexes, among humans and animals (e.g., Dean & Sharpe, 2013; Schwartz et al., 2019; Sharpe, 2020; Thankamony et al., 2016). Female mammals that develop under relatively low levels of prenatal testosterone, or higher levels of prenatal estrogens, exhibit relatively short AGDs.

Second, the ratio of the 2nd to 4th digits of the front limbs ("digit ratio") is shorter on average in male than female humans, as well as in mice (Manning et al., 2014; Zheng & Cohn, 2011). In female humans and mice, lower prenatal testosterone is usually associated with higher digit ratios. Digit ratio studies show considerable heterogeneity and

Table 1
Findings Salient to the Hypothesis That Risk of Endometriosis Has Evolved, in Part, as a Result of Sexual Selection by Males for Trait Expression in Females That Indicates Relatively High Reproductive Fitness, and That Is Mediated by Lower Prenatal and Postnatal Testosterone and Higher Estradiol

Trait	Sex difference, female bias?	Greater female bias in women with endometriosis?	Female bias associated with lower prenatal testosterone, higher prenatal estradiol?	Female bias associated with higher fecundity or fertility, or correlates thereof, in healthy women?	Female biased trait expression preferred by males?
Prenatal testosterone	YES, females lower	YES	n/a	YES in some studies	Not directly
Postnatal, adult testosterone	YES, females lower	YES	YES	YES	Not directly
Postnatal, adult oxytocin	YES? Females higher in about half of studies	YES	Predicted	YES?	Unknown
Antimullerian hormone	Yes, females lower	YES	YES	Unknown	Unknown
Waist-hip ratio	YES, females lower	YES	NO	YES	YES
Body mass index	Varies	YES	YES	YES to a point	YES
Breast-under-breast ratio	YES, females higher	Predicted	YES	Predicted	YES
"More female" facial features	YES, by definition	Predicted	YES	Predicted	YES
Vocal pitch	YES, females higher	Predicted	YES	Predicted	YES
Level of skin pigmentation	YES, females lower	YES	YES?	YES? Only in northern regions	YES
Muscularity	YES, females lower	YES	YES	Unknown	Unknown
Pain	YES, females higher	YES	YES	Unknown	n/a
β-endorphin levels	YES, females lower	YES	Unknown	Unknown	Unknown
Inflammation	YES, females higher	YES	YES	Unknown	n/a

lacks of replicability in their findings (e.g., Voracek, 2009), and have been subject to limited validation through direct measurements of prenatal steroid concentrations (de Sanctis et al., 2017; Swift-Gallant et al., 2020). As such, digit ratios provide much less-reliable and less-accurate information about prenatal testosterone, or prenatal testosterone relative to estradiol, than does AGD. Large sample sizes, as well as multiple independent replications, of digit ratio studies are necessary for meaningful interpretation of the results. With regard to tests of the hypotheses addressed here, findings based on digit ratios need to be corroborated across studies, or validated by other independent means, for robust inferences to be drawn.

Four recent studies, representing three independent data sets, have reported that women with endometriosis exhibit shorter AGDs than do females without endometriosis (Crestani et al., 2020, 2021; Mendiola et al., 2016; Peters et al., 2020). These differences are substantial and highly predictive; for example, Mendiola et al. (2016) reported an odds ratio of 41.6 ($p = 0.002$) for AGD in deep infiltrating endometriosis, and Crestani et al. (2020) found a specificity of 0.98 and positive predictive value of 0.97 for a 20-mm-length AGD cutoff value for endometriosis as a whole. The single study that measured digit ratios among women with and without endometriosis (Peters et al., 2020) reported nonsignificant results (in the predicted direction), although its statistical power was low (with $N = 43$ for each group). Higher digit ratio has been associated with heavier menstrual bleeding and dysmenorrhea (painful menstrual periods due

to uterine contractions), both of which are strong correlates of endometriosis (Tabachnik et al., 2020).

In addition to endometriosis, shorter AGDs have been linked with lower serum testosterone, relatively low numbers of follicles per ovary, and more-regular menstrual cycles of mothers before pregnancy, in a non-clinical, university-age population of women; all three of these variables are also associated with endometriosis (Barbieri et al., 2005; Gupta et al., 2015; Matalliotakis et al., 2008; Mendiola et al., 2012; Mira-Escolano, Mendiola, Mínguez-Alarcón, Melgarejo, et al., 2014, Mira-Escolano, Mendiola, Mínguez-Alarcón, Roca, et al., 2014; Ono et al., 2014). Shorter AGDs are also associated with lower AMH levels (a strong correlate of endometriosis), among women without endometriosis or PCOS who were undergoing *in vitro* fertilization (Fabregues et al., 2018), and shorter AGDs are reported in women with premature ovarian insufficiency, which represents a strong correlate of endometriosis (Dural et al., 2021; Shah, 2013). Taken together, these findings convergently support the hypothesis that endometriosis involves relatively low levels of prenatal testosterone. Risk of endometriosis, and correlates of endometriosis, have also been connected in some studies with early to midgestation exposures to pro-estrogenic or anti-androgenic endocrine disrupting chemicals, including for example diethylstilbestrol and bisphenol A (e.g., Barrett et al., 2019; Ottolina et al., 2020).

In contrast to these results, women with polycystic ovary syndrome, which is known to be mediated by high prenatal testosterone (Abbott et al., 2019; Dumesic et al., 2014; Filippou & Homberg, 2017), exhibit evidence of longer AGDs compared with controls in all studies conducted to date (Hernández-Peñalver et al., 2018; Peters et al., 2020; Sánchez-Ferrer et al., 2017a, 2017b; Simsir et al., 2019; Wu et al., 2017; see also Barrett et al., 2018) and significantly shorter digit ratios in three of five studies (Cattrall et al., 2005; Lujan et al., 2010; Pandit et al., 2016; Perlman et al., 2020; Peters et al., 2020; Roy et al., 2018). More generally, PCOS involves a broad suite of phenotypes that are opposite to those found in endometriosis (Dinsdale et al., 2021; Dinsdale & Crespi, 2021).

Postnatal Testosterone. Levels of serum testosterone are substantially lower in females than males both prenatally and during adulthood (Lutchmaya et al., 2004; Reyes et al., 1974). Serum testosterone levels are also lower in females with endometriosis, compared with controls, as well as being lower in ovarian tissue (Barbieri et al., 2005; Ono et al., 2014; Pellicer et al., 1998). Low testosterone levels in ovaries apparently contribute to apoptosis of granulosa cells and accelerated attrition of oocytes, thus contributing to premature ovarian insufficiency and earlier menopause (Dural et al., 2021; Ono et al., 2014; Shah, 2013).

No studies have tested observationally for associations of levels of serum testosterone with expression of sexually dimorphic traits in women with endometriosis, but treatment of women with endometriosis with the synthetic androgen danazol results in a suite of androgenic changes including hirsutism, reduced breast size, weight gain especially for visceral fat, absence of the menstrual cycle, acne, and lowering of vocal pitch (Barbieri et al., 1982).

Estradiol. Serum estradiol levels are higher in females than males during adulthood, and during prenatal development in one study (Reyes et al., 1974) but not in another (Lutchmaya et al., 2004). Levels of estradiol are higher in women with endometriosis, compared with controls, in endometrial tissue and in menstrual blood, though not in serum (Huhtinen et al., 2012; Stilley et al., 2012; Takahashi et al., 1989). Women with endometriosis thus show increased local estradiol production in eutopic and ectopic endometrium, which stimulates excessive endometrial tissue proliferation.

SHBG. Serum hormone binding globulin (SHBG) is a glycoprotein that regulates the bioavailability of androgens and estrogens. It is produced in the liver, endometrium, and several other tissues (Hammond & Bocchinfuso, 1996; Misao et al., 1995, 1997). Levels of serum SHBG are about twice as high in women than in men (Hammond, 2017), and SHBG levels in women show an inverse association with levels of testosterone (Hammond, 2017). Women with endometriosis show elevated levels of SHBG, in endometrium and serum, compared with controls (Misao et al., 1995; Panidis et al., 1993), and treatment of endometriosis with danazol leads to reduced SHBG levels (Panidis et al., 1993). The overexpression of SHBG in ectopic endometrium may also contribute to the high local estradiol levels found in this tissue in women with endometriosis (Misao et al., 1995).

Oxytocin. The peptide hormone oxytocin orchestrates a suite of female reproductive functions including lactation, uterine contraction during menses and parturition (Kunz & Leyendecker, 2002). Serum levels of oxytocin are higher in women than men in some studies (e.g., Carter,

2007; Imamura et al., 2017; Kunitake et al., 2020; Marazziti et al., 2019; Orihashi et al., 2020), but other studies show no difference (e.g., Floyd et al., 2010; Koven & Max, 2014; Marazziti et al., 2006; Nishizato et al., 2017). These differences may be associated with such factors as conditions of measurement, age, stress, and reproductive status. Within each sex, levels and effects of oxytocin are inversely related to levels and effects of testosterone, in mice (Okabe et al., 2013) and humans (Crespi, 2016), and in women, oxytocin production is positively regulated by estradiol (Hazell et al., 2009). Levels of serum oxytocin, oxytocin receptor expression, and strength of uterine contractions, are higher in women with endometriosis than in controls, and higher plasma and receptor expression levels are associated with dysmenorrhea (Harada, 2013; Huang et al., 2017; Leyendecker et al., 2004; Liedman et al., 2008).

***β*-Endorphin and Pain.** Pain, a core symptom of endometriosis, shows clear sex differences in its levels and endocrine mediation. Women thus show higher pain sensitivity than men (Bartley & Fillingim, 2013; Hashmi & Davis, 2014), with this sex difference attributable in part to levels of testosterone, because pain sensitivity is inversely related to serum testosterone in both sexes (Bartley et al., 2015; Cairns & Gazerani, 2009); it is also attributable in part to levels of the endogenous opioid β-endorphin, which are lower in women than in men of typical weights (Ritter et al., 1991).

Women with endometriosis experience higher sensitivity to pain (van Aken et al., 2018), and exhibit lower levels of β-endorphin (Vercellini et al., 1992), compared with controls, and treatment with the androgen danazol alleviates pain symptoms, as well as causing atrophy of ectopic endometrial tissue (Selak et al., 2001). Lower levels of androgens are also associated with higher levels of pain in young women with dysmenorrhea (Evans et al., 2021), a major feature of endometriosis. Female rats treated prenatally with testosterone show pain responses similar to those of males, which indicates that pain sensitivity can be programmed during prenatal development (Cicero et al., 2002). These findings demonstrate that women with endometriosis exhibit evidence of a female-biased extreme for pain and its causes, with clear roles for testosterone in its effects.

Inflammation. Inflammation, which involves adaptive immunological responses to cellular injury, is centrally involved in embryo implantation (Dekel et al., 2014) and degradation of endometrial tissue during menstruation (Maybin & Critchley, 2015). High inflammation of endometrial tissue also characterizes endometriosis (Lebovic et al., 2001), where this tissue implants at ectopic sites. Females in general exhibit higher levels of inflammation than males, as evidenced, for example, by their stronger immune responses and their fourfold higher rates of autoimmune disorders (Klein & Flanagan, 2016). Higher levels of inflammation in women than men are caused in part by pro-inflammatory effects of estrogens and the anti-inflammatory effects of testosterone (García-Gómez et al., 2020; Klein & Flanagan, 2016; Pergola et al., 2011). Endometriosis is characterized by elevated systemic and local inflammation (Riccio et al., 2018; Zhang et al., 2018) and with increased rates of autoimmune disorders (Shafrir et al., 2021; Shigesi et al., 2019). Chronic inflammation also appears to mediate infertility in endometriosis by interfering with implantation (Lin et al., 2018).

Waist-Hip Ratio. Females exhibit a lower waist-hip ratio (WHR) than do males, in the context of high levels of gluteofemoral, "gynoid" fat deposition serving as stores to support the high energetic costs of gestation, lactation, and offspring early brain development (Chiappa & Singh, 2017; Lassek & Gaulin, 2008; Wells, 2007; Wells et al., 2010). Among reproductive-aged women, lower WHR is associated with lower levels of serum testosterone (Sowers et al., 2001; van Anders & Hampson, 2005); low WHR (with large breast size) is also associated with high salivary estradiol (Jasieńska et al., 2004), and a combination of high testosterone with low estrogen characterizes women with the highest WHR values (Mondragón-Ceballos et al., 2015). WHR is not, however, consistently associated with digit ratio as a measure of prenatal testosterone, with two studies showing lacks of association (Fink et al., 2003; Swami et al., 2019), one study showing higher digit ratio associated with lower WHR in an English and in a Jamaican population (Manning et al., 2000), and one study showing higher (left hand only) digit ratio associated with lower WHR, in a population of Polish college students (Zurawiecka et al., 2019). WHR is lower in women with endometriosis compared with controls, in association with a more-peripheral (below the waist), and less male-typical "android" (central and visceral), distribution of body fat (Backonja et al., 2016, 2017; McCann et al., 1993; Rossi et al., 2021; Shah et al., 2013) and a "lean" body shape (Aarestrup et al., 2020).

Body Mass Index. Body mass index (BMI) is a measure, derived from body weight and height, that

is designed to provide a relative overall measure of thinness and obesity. Because women are shorter on average than men, as well as exhibiting a lower body percentage of more-dense muscle compared with less-dense fat, this measure is problematic to compare between the sexes. BMI is positively correlated with serum testosterone in women (Sidhu et al., 2017; Stanikova et al., 2019; Taponen et al., 2003), but it is not associated with digit ratios (Fink et al., 2005; Swami et al., 2019).

BMI is substantially and significantly lower in women with endometriosis compared with controls (Aarestrup et al., 2020; Backonja et al., 2017; Garitazelaia et al., 2021; Rossi et al., 2021; Shah et al., 2013); and by meta-analyses in Liu and Zhang (2017), Yong and Weiyuan (2017) and Jenabi et al. (2019). For example, one study found that women with the most severe stage of endometriosis had the lowest BMI, although the overall relationship between disease severity and BMI was non-linear (Byun et al., 2020).

Muscularity. Males exhibit substantially higher levels of muscle mass than do females, due primarily to the anabolic effects of higher testosterone (Lassek & Gaulin, 2008). Among females, lower digit ratio is associated with enhanced muscularity and athletic performance, but the roles of serum testosterone in these effects remain unclear (Eklund et al., 2020; Hönekopp & Schuster, 2010; Kim & Kim, 2016). In the single study that quantified muscle tissue among women with endometriosis, affected women exhibited significantly reduced upper arm muscle mass compared with controls (Backonja et al., 2017); for this phenotype, males show about 50% higher muscle mass (Frisancho, 1974).

Skin Pigmentation, Sun Sensitivity, Melanoma Risk, Hair Color, and Eye Color. These five traits are associated with one another because they are all functionally linked with the human developmental and physiological system for the production of melanins (Hernando, Ibarrola-Villava, et al., 2016; Videira et al., 2013). This system is mediated by a suite of genes and alleles, some of which exert large phenotypic effects (Maroñas et al., 2015; Pavan & Sturm, 2019), with variation in a given gene affecting from one to all of the five pigment-related phenotypes. Many of the effects of allelic variation on skin, hair and eye color phenotypes, and melanoma risk, are sex-specific (e.g., Hernando, Ibarrola-Villava, et al., 2016; Hernando, Ibarrola-Villava, et al., 2016), implicating sex steroid hormones in their physiological effects.

Phenotypic variation in skin pigmentation, sun sensitivity, hair and eye color is especially pronounced in European populations, though it is also notable in east Asia, among some African populations, and in admixed populations in South America (e.g., Frost, 2014; Rocha, 2020; Vicuña et al., 2020). Much of this variation has evolved within the past few tens of thousands of years (see Yang et al., 2018), with substantial evidence for positive selection of allelic variation that mediates reduced pigmentation levels at higher latitudes (e.g., Lao et al., 2007; Martinez-Cadenas et al., 2013; Rees & Harding, 2012; Rocha, 2020; Wilde et al., 2014). At the genome-wide level, Stern et al. (2021) found that skin pigmentation and hair coloration, and tanning and skin sensitivity, were among the top eight phenotypes that showed evidence of polygenic adaptation by positive selection in humans.

Adult females exhibit less pigmented skin than males across almost all human groups worldwide, which follows in part from skin lightening at menarche; female skin also becomes more pigmented during pregnancy and in non-fertile periods of the menstrual cycle (Frost, 2007, 2014; Jablonski & Chaplin, 2000; Sitek et al., 2018; van den Berghe & Frost, 1986). Among females, but not males, less pigmented skin has also been associated with higher digit ratios, in a population of Causcasians (Manning et al., 2004). These findings implicate steroid hormones in human skin pigmentation, although they require further replication and the mechanistic basis of any such links remains largely unknown.

Two studies have tested for differences in skin pigmentation in women with endometriosis compared with controls (see Viganò et al., 2012). Kvaskoff et al. (2009) reported that endometriosis was associated with less pigmented skin in unadjusted analyses, and in analyses that adjusted for age, BMI, age at menarche, menstrual cycle length and menopause age, but not in analyses that additionally adjusted for "hair color, skin complexion, skin sensitivity to the sun, and number of naevi and freckles." Somigliana et al. (2010) found a non-significant difference in skin color between women with endometriosis (28% fair or pale, $N = 98$) versus controls (18% fair or pale, $N = 94$), with an adjusted OR of 1.85 and 95% CI from 0.91-3.75. Kvaskoff et al. (2014) also reported that the risks of endometriosis were significantly lower in women of Asian or African-American ancestry than among women of Caucasian ancestry, and that risk of melanoma was also significantly lower in the former two groups; they suggested that these differences

were associated with pigmentation-related effects. Endometriosis risk has also been reported to be higher among Caucasian women, compared with women with African ancestry, by meta-analysis (Bougie et al., 2019), and in studies that should, by their designs, be subject to minimal effects from ascertainment biases related to racial health-care inequalities and socioeconomic disparities (Crespi, 2021; Eggert et al., 2008; Missmer et al., 2004).

Less pigmented human skin coloration is associated with higher sensitivity to the sun and reduced ability to tan, although these variables are also partially independent because tanning ability depends on conditional physiological responses to UV exposure. Females exhibit higher sun sensitivity than males (Hernando, Ibarrola-Villava, et al., 2016), and the three studies conducted to date demonstrate that women with endometriosis show significantly higher sensitivity of the skin to sun exposure compared with controls (Kvaskoff et al., 2009, 2014; Somigliana et al., 2010). In turn, higher sun sensitivity is strongly linked with increased risk of cutaneous melanoma, the most-deadly form of skin cancer (Newton-Bishop et al., 2011). Melanoma risk is higher among females than males for individuals under age 45, with a peak sex difference during the female reproductive period suggesting a role for steroid hormones in the differences (Liu et al., 2013). Melanoma risk is also significantly higher among women with endometriosis compared with controls (Farland et al., 2017; Saraswat et al., 2021), and endometriosis risk is higher among women with a family history of melanoma (Kvaskoff et al., 2014).

Across Caucasian populations, blue and green eye coloration are associated with relatively reduced skin pigmentation, via a suite of genes and alleles affecting one or both traits (Maroñas et al., 2015). In addition to a higher prevalence of red hair, females also show a higher prevalence of green eyes and a lower prevalence of blue or grey eyes, compared with males (Frost et al., 2017; Martinez-Cadenas et al., 2013). Somigliana et al. (2010) reported that rates of endometriosis were higher among females with (pooled) green and blue eyes, compared with controls, and Vercellini et al. (2014) found an excess of blue eyes, and a lower proportion of brown eyes, among women with deep infiltrating (severe) endometriosis, compared with (pooled) controls and women with milder, ovarian endometriosis (endometriomas).

Red hair, blond hair, and light brown hair are more common among females than males (Frost et al., 2017; Hysi et al., 2018), and red hair has been associated with higher risk of endometriosis across a suite of studies (Missmer et al., 2006; Woodworth et al., 1995; Wyshak & Frisch, 2000; see also Kvaskoff et al., 2009, 2014). Frost et al. (2017) suggested that this higher female than male prevalence of red hair is associated with higher prenatal estrogen, but there is no direct evidence to this effect. Relatively light-colored hair is also associated with higher rates of endometriosis by contingency table analyses of data in Vercellini et al. (2014; Table 1 data: red, blond and light brown versus dark brown and black, $\chi^2 = 15.3, p < .0001$), in Kvaskoff et al. (2009; Table 2 data: red, and blond versus "chestnut," brown and "dark," $\chi^2 = 5.33, p < .025$), and in Kvaskoff et al. (2014; Table 3 data: red and blond versus brown and black, $\chi^2 = 5.7, p < .025$).

Skin pigmentation, sensitivity to sun exposure, melanoma risk, hair color, and eye color are controlled in part by genetic variation in the gene MC1R (Melanocortin 1 Receptor), which regulates the production of eumelanin (brown) pigmentation relative to pheomelanin (yellow and red) pigmentation (Latreille et al., 2009). In humans, loss of MC1R expression (due to loss-of-function mutations) results in red hair, fair and highly photosensitive skin, green eyes, and higher risk of melanoma (Frost et al., 2017; Haddadeen et al., 2015; Mogil et al., 2003; Raimondi et al., 2008; White & Rabago-Smith, 2011). MC1R allelic variation also influences variation in blonde and brown hair coloration in human, via a complex system of over 100 alleles (Palmer et al., 2000; Pavan & Sturm, 2019), and has also been demonstrated to affect perceived facial age and "youthful looks" (Liu et al., 2016).

The associations of red or light-colored hair with the MC1R gene, and with endometriosis, may be functionally linked to well-replicated female-specific associations of MC1R loss of function genotypes with a higher intensity of pain perception, and higher levels of inflammation (Chen et al., 2013; Delaney et al., 2010; Liem et al., 2005; Mogil et al., 2003). The MC1R gene has also been associated with endometriosis risk in the most recent GWAS study, in gene-wise analysis, although with a nominal (not statistically adjusted) level of significance (Rahmioglu et al., 2018). By contrast, the gene CDKN2B-AS1, which harbors a SNP that is genome-wide significant for endometriosis risk (Rahmioglu et al., 2018), also mediates hair color (Hysi et al., 2018), risk of melanoma (Read et al., 2016), and risk of facial pigmentary spots, which are also

Table 2

Data From the Non-Human Mammal Literature on Correlates of Endometriosis Related to Aspects of HPO Axis Functioning (Earlier Onset of Reproduction and Faster, More-Regular Cycles), Correlates of Fitness, and Attractiveness of Females to Males, in Relation to Indicators of Female Prenatal Testosterone Exposure Levels (Presence of Males in Litter; Shorter Anogenital Distance; Development Flanked by No Males (0M), Rather Than One Male (1M) or Two Males (2M); Experimental Treatment) and/or Levels of Estradiol

Species	Male choice experiments or other data relevant to choice	Main findings with regard to hormonal effects	References
Lab mice (*Mus musculus*)	Males preferred 0M over 2M females, and 0M females inseminated first in choice experiments	0M females had lower testosterone and higher estradiol at day 18 in utero, compared with 2M females; 0M females had shorter AGDs, earlier vaginal opening and shorter, more regular estrus cycles compared with 2M females; 0M and 2M females did not differ in fecundity	McDermott et al., 1978; vom Saal & Bronson, 1978, 1980a, 1980b; Rines & vom Saal, 1984; vom Saal, 1981, 1989; vom Saal et al., 1990
House mice (*Mus musculus*, wild type)	Males preferred females with shorter AGDs	Females with shorter AGDs had higher reproductive success (more likely to reproduce, higher pregnancy rate, more pregnancies) in field enclosures	Drickamer, 1996; Drickamer et al., 2001
Mongolian gerbils (*Meriones unguiculatus*)	Males preferred 0M and 1M females, compared with 2M females	2M females had later estrus, longer menstrual cycles, fewer litters, and showed higher testosterone than 0M and 1M females	Clark & Galef, 1988, 1998; Clark et al., 1991
Laboratory rats (*Rattus norvegicus*)	Adult treatment with E2 increased attractiveness of females to males; no studies of male choice in relation to prenatal steroids in females found	Females exposed to lower (vs higher) testosterone levels in utero had shorter AGDs; females treated with high testosterone in utero had longer AGDs, later vaginal opening, prolonged and/or irregular estrus cycle, and more preantral and antral follicles; females treated with E2 in utero had shorter AGDs; females with shorter AGDs had earlier vaginal opening and first estrus, and shorter estrus cycles	Lucas et al., 1982; McCoy & Shirley, 1992; Levy et al., 1995; Rhees et al., 1997; Zehr et al., 2001; Hotchkiss et al., 2007; Wu et al., 2010
Golden hamsters (*Mesocricetus auratus*)	Males preferred control females over females treated prenatally with testosterone	Females treated with prenatal testosterone had longer AGDs and less-regular estrus cycles	Landauer et al., 1981
Bank voles (*Myodes glareolus*)	Males and females mated at higher rates in trials with females from low-testosterone lines than in trials with females from high testosterone lines, with one male and one female together	Females tested were offspring of sires and dams selected for high vs low plasma testosterone levels. Daughters from low-testosterone lines had higher fecundity (litter sizes) than daughters from high-testosterone lines. No data on prenatal testosterone effects or AGD.	Mökkonen et al., 2011; Mills et al., 2012
Domestic rabbits (*Oryctolagus cuniculus*)	Males preferred females with shorter AGDs	AGDs were shorter in 0M females (versus 1M and 2M females); females with shorter AGDs had higher fecundity	Bánszegi et al., 2009, 2010, 2012
Yellow-bellied marmots (*Marmota flaviventris*)	Likelihood of getting pregnant and rearing young was lower in young females with longer vs shorter AGDs; no data on male choice	More males in litter leads to longer AGD in females, and delayed onset of breeding, in field	Monclús & Blumstein, 2012; Monclús et al., 2014

(*table continues*)

Table 2 (*continued*)

Species	Male choice experiments or other data relevant to choice	Main findings with regard to hormonal effects	References
Mouse lemurs (*Microcebus murinus*)	Males prefer females with higher serum E2 levels; no data on prenatal effects	Presence of a male in natal litter reduces female pregnancy success, and reduces their serum E2 levels at estrus by ~30%	Gomez et al., 2012; Perret, 2019

Note. See references for details of the choice experiments. Males also preferred control females, compared with females that were experimentally treated *in utero* with testosterone, from studies of sheep (Jackson et al., 2013; Roberts et al., 2008).

affected by a SNP at the MC1R locus (Shin et al., 2021).

The connections of skin color, sun sensitivity, melanoma risk, hair color, and eye color with correlates and causes of endometriosis, other than pain and inflammation linked to MC1R, remain largely unexplored. However, taken together, the data tend to fit with the hypothesis that women with endometriosis exhibit relative extremes of female-biased traits, in that: (a) compared with men, women are characterized by less pigmented skin, higher sun sensitivity, higher rates of melanoma, and lighter hair color, and (b) compared with control women, women with endometriosis also show some evidence of all four differences of these difference in the same, "female," direction. The data for skin pigmentation itself is, however, highly limited, and the data for eye color are insufficient to draw clear conclusions.

Synopsis of Results. Taken together, the findings described above for prenatal and postnatal testosterone, estradiol, SHBG, oxytocin, β-endorphin, pain sensitivity, inflammation, waist hip ratio, BMI, muscularity, and skin pigmentation, sensitivity, and melanoma risk, support the hypothesis that, for traits exhibiting sex differences, women with endometriosis show evidence of exhibiting relative female extremes of trait expression (Table 1). Women with endometriosis, compared with women without endometriosis, thus tend to exhibit phenotype distributions that are further from those of males (Figure 2). These relative "extreme female" phenotypes are also expressed for female-limited reproduction-related traits, in that women with endometriosis exhibit earlier menarche and menopause, shorter faster menstrual cycles, higher rates of dysmenorrhea (pain during menstruation due to uterine contraction), and more-substantial menstrual bleeding, compared with women without endometriosis (Bulletti et al., 2002; Dinsdale & Crespi, 2021; Nnoaham et al., 2012; Wei et al., 2016; Yasui et al., 2015). These findings, from evidence concerning many diverse traits, convergently support the hypothesis that women with endometriosis exhibit relative female extremes of expression of sexually dimorphic, and female limited, traits.

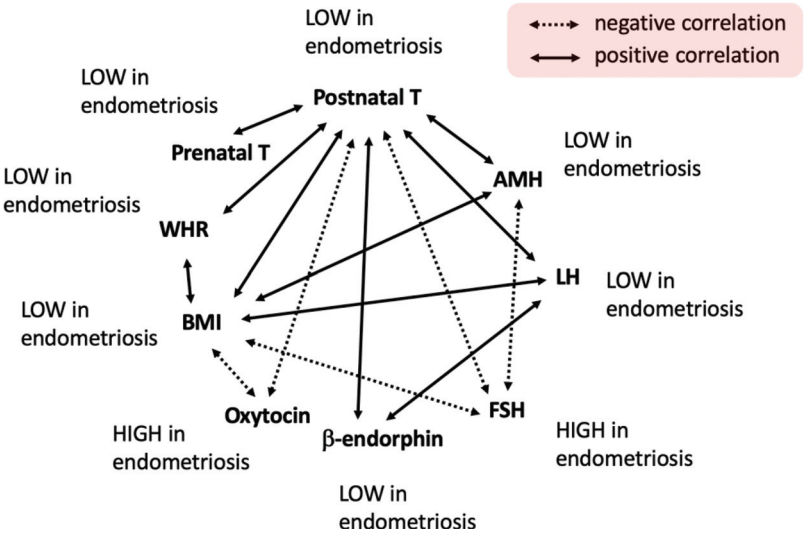
The traits analyzed above do not vary in isolation from one another, in their patterns of differences between the sexes, and between women with and without endometriosis: most of the traits show strong functional connections, especially with levels of testosterone (e.g., Figure 4; Dinsdale et al., 2021; Dinsdale & Crespi, 2021). These associations derive from the highly integrated functioning of the HPO (Hypothalamic-Pituitary-Ovarian) axis in women, such that lower prenatal and postnatal testosterone are physiologically and developmentally linked with lower AMH, higher FSH relative to LH, higher OT, and lower WHR and BMI.

Relationships of Endometriosis-Associated Phenotypes and Genotypes With Correlates of Reproductive Fitness

The next major prediction in the hypothesis evaluated here is that phenotypes and genotypes associated with endometriosis should be linked with correlates of higher reproductive fitness. In testing this prediction, it is essential to bear in mind that endometriosis itself is not expected to be associated with higher reproductive fitness, because it is conceptualized as reflecting a maladaptive extreme of relatively highly female biased traits related to reproduction. Correlates and indicators of female reproductive fitness include: (a) fertility (level of ability to conceive and bear children), (b) fecundability (conceptions per cycle), (c) fecundity (total numbers of children born), (d) nubility (recent attainment of physical and sexual maturity), (e) residual reproductive value (expected future reproduction downweighted by risk of mortality; Andrews et al., 2017), and (f) ability to successfully

Figure 4

The Key Endocrine Phenotypes Associated With Endometriosis That Are Causally Linked With One Another, Whose Covariation Can Be Traced to Relatively Low Prenatal and Postnatal Testosterone That Cause Expression of the Relatively Female Phenotypes Found in Endometriosis



Note. For details regarding the causal associations, see Barnett et al. (2002), van Anders and Hampson (2005), Cashdan (2008), Blouin et al. (2008), Mira-Escolano, Mendiola, Mínguez-Alarcón, Melgarejo, et al. (2014), Mira-Escolano, Mendiola, Mínguez-Alarcón, Roca, et al. (2014), Qian et al. (2014), Sun et al. (2014), Mondragón-Ceballos et al. (2015), Böttcher et al. (2017), Alebić et al. (2018), Fabregues et al. (2018), Albu & Albu (2019), Barbotin et al. (2019), Lv et al. (2020), Stanikova et al. (2019). See the online article for the color version of this figure.

rear the children produced. The values of at least the first five of these variables are expected to be moderately to highly positive correlated, subject mainly to the caveat that fertility and fecundability reach their peaks after the highest levels of nubility and reproductive value (Lassek & Gaulin, 2019).

Data are available for five phenotypic correlates of endometriosis to test for associations with female correlates of reproductive fitness: prenatal and postnatal testosterone, serum oxytocin, age at menarche, WHR and BMI, and pigmentation-related traits. Two genetic factors associated with endometriosis risk, haplotypes of the FSHB gene, and alleles at the PROGINS locus of the progesterone receptor gene PR, can also be tested for associations with correlates of reproductive fitness, because of their well-studied pleiotropic effects.

Prenatal and Postnatal Testosterone and Correlates of Fitness. A higher, more female-biased digit ratio, indicative of lower prenatal testosterone, has been associated with higher female fecundity in three populations from England, Germany, and Hungary, and in the English population, married women had higher digit ratios than did unmarried women (Manning et al., 2000). Similarly, in a population from rural Poland, women with higher digit ratios had more children and longer reproductive lifespans (Klimek et al., 2016). In a BBC Internet study with very large sample sizes (>100,000), higher digit ratio in white heterosexual women was correlated with higher numbers of children and an earlier age at birth of their first child (Manning & Fink, 2008). In no studies has lower digit ratio in women been associated with higher fecundity.

Shorter, more female-biased AGDs in non-clinical, college-aged women have been linked with (a) lower serum testosterone (Mira-Escolano et al., 2014); (b) smaller ovarian follicle number (higher follicle numbers being linked with excess fetal

testosterone exposure; Mendiola et al., 2012); and (c) a reduced number of menstrual cycle irregularities in their mothers prior to pregnancy (higher numbers also being linked with excess fetal testosterone exposure, and endometriosis being linked with cycles that are shorter and more regular that in controls; Mira-Escolano, Mendiola, Mínguez-Alarcón, Melgarejo, et al. (2014); Mira-Escolano, Mendiola, Mínguez-Alarcón, Roca, et al. (2014). Shorter AGDs (or other strong correlates of low prenatal testosterone) are also positively associated with correlates of higher fitness, mainly fecundity, in studies of mice, gerbils, rabbits, and lemurs, as described below.

As noted above, significantly longer AGDs than in controls have consistently been reported among women with polycystic ovary syndrome (PCOS), which is a primary cause of anovulatory infertility (Costello et al., 2012); shorter 2D4D digit ratios have also found among women with PCOS in some studies with no difference in others. Most women with PCOS also exhibit substantially elevated levels of ovarian and serum testosterone (Abbott et al., 2019; Filippou & Homburg, 2017; Rosenfield & Ehrmann, 2016). These results are relevant to fitness variation in that relatively high serum testosterone is associated with reduced fertility and fecundity among females due to anovulation or oligo-ovulation, higher rates of miscarriage, and other causes (Cocksedge et al., 2008; Okon et al., 1998; Sjaarda et al., 2018).

Evidence relevant to negative effects of relatively high prenatal testosterone on female reproductive fitness also comes from two studies that compared the fitness of females from same-sex twins versus opposite-sex twins, who are subject to transfer of testosterone *in utero*. Thus, both Bütikofer et al. (2019) and Lummaa et al. (2007) found that females with a male co-twin had significantly lower probabilities of being married as well as significantly lower numbers of children, compared with females with a female co-twin, though another study did not find this effect (Medland et al., 2008).

The primary fitness-related correlates of relatively low prenatal and postnatal testosterone in women include diminished ovarian reserve (Dural et al., 2021; Gleicher et al., 2013; Lu et al., 2014; Prizant et al., 2014; Shah, 2013), and, as discussed above, endometriosis, which causes notable reductions in fertility due to implantation failure, anatomical obstructions, and other factors. Wainstock et al. (2017) reported that AGD was lower among women who had undergone fertility treatment, based on data from five women (in their sample of 300) who underwent such procedures; the causes of these infertility treatments (e.g., endometriosis or some other cause) was not described, and up to 50% of women with infertility have endometriosis (Bulletti et al., 2010).

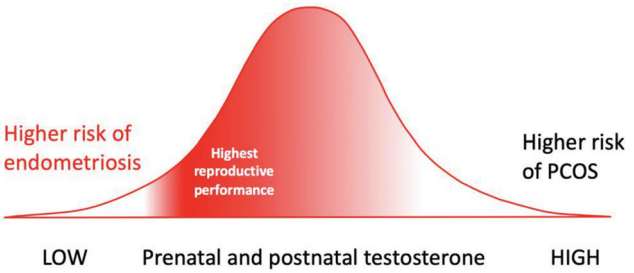
Considered together, these findings provide evidence that relatively low, but not extremely low, levels of prenatal and postnatal testosterone may confer relatively high reproductive fitness among women (Figure 5). The primary limitation of this inference is that much of the evidence comes from lower reproduction in women with relatively high testosterone, so the functional form of the fitness-testosterone association across the full spectrum of female testosterone levels remains unclear. The hypothesis could be tested more directly and precisely using data on AGD, and serum testosterone, in relation to correlates of female reproductive success, especially in traditional societies.

Oxytocin and Correlates of Fitness. As described above, levels of oxytocin are elevated in women with endometriosis. Variation in serum and brain oxytocin levels may influence female reproductive success especially through effects on fertility, maternal behavior, mating, and other social relationships. Serum oxytocin levels are highest around ovulation (Engel et al., 2019), and through its interactions with gonadal steroids this hormone controls the uterine peristalsis that transports sperm up the fallopian tubes (Kunz et al., 2007) and pushes menstrual material out of the body. Uterine contraction strength also exhibits an inverse relationship with implantation success (Moraloglu et al., 2010). Overly strong and disorganized uterine contractions, owing to high oxytocin and oxytocin receptor levels, appear to mediate reduced fecundability as well as dysmenorrhea in women with endometriosis and adenomyosis, a condition closely related to endometriosis (Guo et al., 2013; Kunz et al., 2007; Leyendecker et al., 2004). As such, especially elevated oxytocin levels and high uterine contractility in women with endometriosis may contribute to reduced fertility and fecundity.

Oxytocin also coordinates female behaviors associated with maternal care, including attentiveness, bonding and breast-feeding (Feldman et al., 2011; Feldman & Bakermans-Kranenburg, 2017); however, effects of elevated oxytocin on human maternal care have yet to be studied. More generally, high oxytocin levels are linked to the personality trait of extraversion (Cardoso et al., 2012;

Figure 5

By the Hypothesis Evaluated Here, Endometriosis Risk Engenders Maladaptive Extremes of Effects From Low Prenatal and Postnatal Testosterone; the Highest Female Reproductive Performance Involves Below-Average Testosterone in Women (the Brightest Red), and Reproductive Performance Is Also Reduced When Testosterone Levels Are Relatively High



Note. See the online article for the color version of this figure.

Human et al., 2016) and extraversion also shows strong genetic and phenotypic associations with bipolar disorder (e.g., Middeldorp et al., 2011; Quilty et al., 2009). In turn, bipolar disorder shows notable comorbidity with endometriosis (Chen et al., 2020; Dinsdale & Crespi, 2017) and levels of oxytocin are higher in individuals with bipolar mania (Turan et al., 2013). These findings are concordant with the hypothesis that endometriosis involves extremes of oxytocin-related psychological traits, although links to components of fitness for these phenotypes remain unclear. Oxytocin administration also increases perception of physical attractiveness in others (Theodoridou et al., 2009), raising the hypothesis that women with higher levels of oxytocin, or higher oxytocin reactivity, may also be perceived as more attractive, for reasons related to higher levels of extraversion and positively social interactive behavior. Overall, oxytocin reduces thresholds for positive social engagement in diverse contexts, including parenting, sexuality, and extraversion. As such, relatively high (though not too high) oxytocinergic activity levels are expected to be positively associated with correlates of fitness (e.g., Carter, 2018; Goodson, 2008), including male preference, although this hypothesis has yet to be subjected to direct tests.

Age at Menarche and Correlates of Fitness. In traditional populations, age at menarche is positively associated with age at first pregnancy (e.g., Hochberg et al., 2011; Sandler et al., 1984; Udry & Cliquet, 1982). Younger age at menarche has been linked with higher fecundability in Danish women (Guldbrandsen et al., 2014), and late ages at menarche have been linked with reduced fecundability in the Danish study and in a population in rural China (Guldbrandsen et al., 2014; Zhang et al., 2017). Age at menarche also shows a strong positive association with risk of irregular cycles, from 0, 6, 5, 24 and 45 to 80% irregularity at menarche ages 10, 11, 12, 13, and 14 to more than 14 respectively, in a Japanese population (Anai et al., 2001).

The earlier reproduction, shorter time to pregnancy, and more-regular cycles of women who have earlier ages of menarche may or may not translate into higher fecundity or lifetime reproduction, depending on the presence and strength of tradeoffs between early, fast reproduction and other components of fitness. Four studies of traditional or agricultural populations demonstrate this diversity in outcomes. Hochberg et al. (2011) showed that earlier age at menarche did not confer higher fecundity because it led to smaller body size, which reduced reproductive success. Hayward et al. (2015) reported that higher early life fecundity (number of children birthed under age 25), which is expected to be correlated with early menarche, was associated with higher late-life mortality; however, this tradeoff did not obviate a positive association of higher early life fecundity with higher lifetime fitness overall. Gurven et al. (2016) demonstrated that higher parity and a faster pace of reproduction were associated with lower nutritional condition and higher mortality in the short term, but that such

costs were alleviated when evaluated over longer periods of time. Finally, Lycett et al. (2000) demonstrated a negative association of fecundity with longevity for women with low levels of resources, while the opposite was true for high-resource women. The presence and nature of phenotypic tradeoffs between early, fast reproduction and other female fitness components are thus likely to vary among populations.

WHR, BMI, and Correlates of Fitness. WHR is typically lowest in the first few years after menarche in nulligravid women, who, at this stage in the reproductive lifespan, exhibit their highest reproductive value (Andrews et al., 2017) and nubility (Lassek & Gaulin, 2019). WHR then tends to increase with numbers of children across the reproductive lifespan (Butovskaya et al., 2017).

WHR and BMI may be associated with female reproductive fitness through some combination of direct, naturally selected effects on reproduction, and effects via sexual selection by male mate choice and male contributions to female fitness. Relatively low (below average) WHR may confer benefits to females with regards to higher fecundability (time to pregnancy), higher birth weights of offspring, more-regular menstrual cycles, more-frequent ovulation, higher success with artificial insemination or *in vitro* embryo transfer, higher estradiol and higher estradiol relative to testosterone, and higher levels of serum DHA fatty acid that are crucial for early brain development (e.g., Bovet, 2018; Butovskaya et al., 2017; Cashdan, 2008; Cloud & Perilloux, 2014; Jasieńska et al., 2004; Pawłowski & Dunbar, 2005; Singh, 2002; Singh & Singh, 2011; Wass et al., 1997; Weeden & Sabini, 2005; Zaadstra et al., 1993).

Relatively low BMI (between about 19 and 25) appears to confer similar reproductive benefits as low WHR to women in terms of fecundability (e.g., Imterat et al., 2019; McKinnon et al., 2016; Ramlau-Hansen et al., 2007; Wise et al., 2010; Yilmaz et al., 2009). For example, Wise et al. (2010) and McKinnon et al. (2016) showed evidence of linear decreases in fecundability with BMI, across virtually the full range of values, and Hassan and Killick (2004) and Gesink Law et al. (2007) showed intermediate optima of fecundability for BMI of about 20, with slightly lower values under 19, and substantial reductions over about 25.

These results are subject to the observation and caveat that especially low WHR or BMI are expected to involve reduced fecundability and fecundity (especially in low-resource ecologies), such that these traits may be subject to stabilizing selection overall (Gesink Law et al., 2007; Lassek & Gaulin, 2018), and that male-preferred notably low values for WHR and BMI may signal nubility and high expected reproductive value rather than current high fecundability and fecundity (Lassek & Gaulin, 2019). Thus, although both high BMI and high WHR can impose considerable reproductive costs associated with high testosterone and other factors, they appear to involve higher reproductive costs than do relatively low BMI and WHR. Relatively low WHR and BMI, considered in the context of age and life history, thus appear to provide reproductive value and reproductive fitness benefits, to both females and the males who choose them. As for age at menarche, the degree to which the higher fecundability or fecundity associated with lower WHR or BMI translate into higher lifetime fitness depends on tradeoffs with other components of fitness, such as survival. As for any other mammal, these fitness-related considerations depend strongly on local ecological and social conditions that select for locally optimal life histories, and upon mismatches due to rapid recent environmental change.

Skin Pigmentation, Associated Traits, and Correlates of Fitness. The strong positive associations of higher latitude and lower UV radiation with reduced pigmentation (Jablonski & Chaplin, 2010, 2017), and the clear links of reduced pigmentation with increased synthesis of vitamin D (Åkeson et al., 2016; Clemens et al., 1982), have motivated the hypothesis that the primary selective pressure favoring the evolution of lighter pigmentation was the more-efficient generation of vitamin D (Chaplin & Jablonski, 2009; Jablonski & Chaplin, 2010). In humans about 90% of vitamin D is obtained from sun exposure, and about 10% comes from the diet, especially from fish, eggs and dairy (Bowyer et al., 2009), with smaller amounts from meat (Schmid & Walther, 2013) and very little from plants (Jäpelt & Jakobsen, 2013). The migration of humans to more-northern latitudes within the past 50,000-60,000 years, and the more-recent advent of agriculture and high-cereal diets, would both have led to greatly reduced vitamin D availability if humans had retained the more-pigmented skin typical of lower latitudes (Rees & Harding, 2012; Jablonski & Chaplin, 2017).

Four convergent lines of evidence suggests that reproductive fitness benefits of reduced skin pigmentation at higher latitudes accrued disproportionately to women. First, women exhibit higher

levels of vitamin D than do men (Jonasson et al., 2020), as well as less pigmented skin overall, as noted above. Vitamin D requirements are especially high during pregnancy (Bowyer et al., 2009; Richard et al., 2017).

Second, in contemporary populations of healthy women, lower serum vitamin D concentrations are associated with longer, more-irregular menstrual cycles (Jukic et al., 2015, 2019), lower serum estradiol (Harmon et al., 2020), and reduced fecundability (conception rate per cycle; Fung et al., 2017; Jukic et al., 2019). The effects on fecundability are substantial: for example, Jukic et al. (2019) found that compared with women with average levels of vitamin D (30-40 ng/ul), women with low levels (<20 ug/ng) showed a 45% reduction in fecundability, and women with high levels (>50 ng/ul) showed a 35% increase. Such effects appear to be mediated by differences associated with ovulation and implantation (Jukic & Harmon, 2020), as evidenced in part by higher *in vitro* fertilization success for women with higher serum levels of vitamin D (Chu et al., 2018). Conception rates are also higher, and menstrual cycles are shorter, in summer than in winter in northern Europe (Danilenko et al., 2011; Rojansky et al., 1992). Finally, an extensive set of animal-model studies links relatively low vitamin D levels with reduced fertility (see Jukic et al., 2019).

Third, skin pigmentation and tanning ability have substantial effects on vitamin D levels at any given locality. In Switzerland, for example, rates of vitamin D deficiency are two to three times higher among pregnant women with more-pigmented compared with less-pigmented skin (and deficiencies are higher in pregnant than non-pregnant women overall; Richard et al., 2017). Similarly, in Australia, vitamin D levels in pregnant women, and in neonate cord blood, show strong effects from both skin pigmentation and tanning ability: women with less pigmented skin who burn and never tan showed rates of vitamin D deficiency or insufficiency that are about half those of women with either low-pigmentation skin who tan, or women with more-pigmented skin (Bowyer et al., 2009). Vitamin D deficiency in pregnancy increases the risk of pre-eclampsia, low birth weight, and poor postnatal growth, among other negative effects on health (Bowyer et al., 2009; Mulligan et al., 2010).

Fourth, if less pigmented and sun-sensitive skin are associated with higher levels of vitamin D, and with endometriosis, then women with endometriosis, and phenotypes associated with it, should tend to exhibit relatively high levels of vitamin D. Four studies have measured vitamin D levels in women with endometriosis compared with controls (reviewed in Buggio et al., 2016); two reported higher levels in endometriosis (for one of the two vitamin D metabolites analyzed), one found no differences, and one reported lower levels. Higher serum levels of vitamin D have also been linked with two strong correlates of endometriosis, lower WHR and lower BMI (Pasco et al., 2009; Revez et al., 2020; Wimalawansa, 2018). More generally, lower serum vitamin D is closely associated with high body weight and obesity (Hochberg & Hochberg, 2019; Vranić et al., 2019; Walsh et al., 2017), in contrast to the leanness associated with risk of endometriosis (Aarestrup et al., 2020). The primary limitations involved in interpreting these data on vitamin D levels, and their effects, is the complexity of the genetic and environmental factors involved, especially in contemporary environments in which sun exposure is generally reduced, and where individuals no longer live in the general locations and environments to which their ancestors were adapted.

Finally, other variables, including the breakdown of folate by UV exposure (Elias & Williams, 2013), effects of vitamin D on calcium metabolism especially in pregnancy and lactation (Diogenes et al., 2013), and the potential effects of mortality from melanoma, may also be involved in the selective pressures affecting skin coloration and tanning. The contributions of these factors to fitness variation among females are relatively difficult to quantify.

The findings described above provide convergent evidence that less pigmented skin coloration provides reproductive fitness benefits to females who live at relatively high latitudes, most likely via effects on the generation of sufficient vitamin D for successful reproduction. Among the clearest support for such fitness benefits comes from the suite of studies, discussed above, that have quantified strong positive selection for alleles associated with lighter skin coloration, in recent human evolution, in some European and east Asian populations. There is also evidence of positive selection in Europe on alleles of the vitamin D receptor gene VDR, and evidence for coadaptation of this gene with the genes for skin pigmentation (Hochberg & Hochberg, 2019; Tiosano et al., 2016).

FSHB Haplotypes, PROGINS Locus Alleles, and Correlates of Fitness. A large haplotype of the gene FSHB is genome-wide significant for risk

of endometriosis in GWAS (Rahmioglu et al., 2018), and the high risk haplotype is associated with earlier age of first birth, higher number of lifetime live births, and lower risk of nulliparity, as well as with lower serum testosterone, earlier menarche and menopause, shorter menstrual cycles and lower risk of PCOS (Laisk et al., 2018; Rull et al., 2018; Ruth et al., 2015, 2016; Sapkota et al., 2017). Similarly, a haplotype of the progesterone receptor gene, which is significantly associated with endometriosis by meta-analysis, is pleiotropically associated with a reduced rate of early miscarriage and having more sisters (Pabalan et al., 2014; Zeberg et al., 2020). These findings suggest that some genetic factors that increase risk of endometriosis may also increase reproductive fitness among women who do not develop endometriosis, as postulated here. This hypothesis predicts that polygenic risk scores for endometriosis should be positively correlated with metrics of reproductive fitness, among women who do not have the disease.

Relationships of Endometriosis-Associated Morphological Phenotypes With Male Preference

By the hypothesis tested here, endometriosis-associated phenotypes should be preferred by males because, as described above, they are indicators of higher female reproductive fitness. This prediction can be evaluated for three traits, WHR, BMI, and skin pigmentation.

WHR and BMI. There is a substantial literature demonstrating evidence for male preference of females with relatively low WHR and BMI, which includes work in pre-industrial and traditional societies (reviews in Andrews et al., 2017; Bovet, 2018; Cloud & Perilloux, 2014; Del Zotto & Pegna, 2017; Furnham et al., 2002, 2005; Grillot et al., 2014; Jones, 1996; Lassek & Gaulin, 2019; Singh et al., 2010; Singh and Singh, 2011; Wang et al., 2015). This body of work shows a high level of consistency in findings across populations and cultures, although with some variation in results that may be related to local ecology (e.g., Gangestad & Scheyd, 2005). The degree to which WHR and BMI represent specific morphological traits that show male preference remains somewhat of an open question; for example, Rilling et al. (2009) showed that low abdominal depth, and a small waist circumference, were stronger predictors of attraction. Low WHR and BMI may also serve as good indicators of other traits, especially young age and nulliparity, that signal high reproductive value (Lassek & Gaulin, 2018; Wang et al., 2015).

Skin Pigmentation. Males have been reported to prefer females with relatively less pigmented skin (compared with others in the same population) across a suite of studies conducted within diverse human populations distributed across the globe, and including populations without European contact and a population of native South Africans (Coetzee et al., 2012; van den Berghe & Frost, 1986; Feinman & Gill, 1978; Dixson et al., 2007, 2010; Kleisner et al., 2017; reviews in Frost, 2007, 2014; Jones, 1996). There are exceptions to this pattern (Dixson et al., 2007; Swami et al., 2008), and such variation may be related to biological and cultural processes whose causes remain unexplored (Li et al., 2008; Swami et al., 2008).

Male Preferences for Other Female Traits Linked With Relatively Low Testosterone

A necessary condition for the sexual selection hypothesis addressed here is that males prefer female sexually selected traits that represent indicators or correlates of relatively low testosterone and/or high estradiol (Figure 1). This prediction applies to any sexually dimorphic or female-limited trait, including those that have not yet been tested for associations with endometriosis. For three traits, sexually dimorphic facial features, voice auditory characteristics, and breast size, sufficient data are available on sexual dimorphism, hormonal determinants, male choice, and fitness-related effects, to evaluate this prediction. These traits can also usefully be used to test the corollary prediction that different indicators of lower testosterone and high estradiol in women, each of which is associated with male preference, should be positively correlated with one another.

Faces. Male preference for morphometrically "more-female," compared with "more-male" female faces has been demonstrated in a large set of studies, including work in traditional and indigenous societies as well as westernized ones (see Kleisner et al., 2017; Kočnar et al., 2019; Lee et al., 2014; Marcinkowska et al., 2014; Scott et al., 2014; reviews in Kościński, 2007; Little et al., 2011). Several studies have linked steroid hormones to female facial features: (a) Whitehouse et al. (2015) reported higher testosterone in umbilical cord blood, and lower left-hand (but not right hand) digit ratios, among women with "more-male" faces; (b) Probst et al. (2016) showed associations of higher

female facial attractiveness with lower serum testosterone and lower testosterone/estradiol ratio; (c) Burriss et al. (2007) showed an association between higher digit ratio and "more-female" facial form (see also Fink et al., 2005); (d) Law Smith et al. (2006) showed that higher late-follicular state estrogen levels were associated with "more-female" faces and higher attractiveness; and (e) Żelaźniewicz et al. (2021) reported that higher female facial attractiveness was linked with lower serum testosterone, higher estradiol, and lower levels of AMH; as described above, AMH is reduced in women with endometriosis. Finally, two studies have linked higher fecundity (numbers of children) with greater facial attractiveness (Jokela, 2009) or both facial attractivess and a "more-female" face (Pflüger et al., 2012); by contrast, one study found no association of facial attractiveness with numbers of children or grandchildren (Pawłowski et al., 2008).

Voices. Male preferences for voices of adult females that are relatively high-pitched have been reported consistently across multiple studies (Borkowska & Pawlowski, 2011; Collins & Missing, 2003; Feinberg et al., 2008; Valentova et al., 2019; reviews in Barkat-Defradas et al., 2021; Suire et al., 2021). Several studies link higher pitch of women's voices with steroid hormone effects: pitch has been associated with lower testosterone and with higher estradiol (Abitbol et al., 1999; Hamdan et al., 2018; Hannoun et al., 2011), administration of a synthetic androgen, danazol, to women with endometriosis causes changes (deepening) of pitch in about 5-10% of cases (Pattie et al., 1998), and vocal pitch is positively correlated with digit ratio among 5-year old children (Levrero et al., 2018). Finally, Atkinson et al. (2012) showed, in an indigenous population in Namibia, that females with higher-pitched voices had more children.

Breast Size. Breast size is notably sexually dimorphic in humans, and larger breast size has been linked with lower levels of testosterone or other androgens, and higher levels of estrogens (e.g., Barbieri et al., 1982; Jernström & Olsson, 1997; Schmidt et al., 2002). As regards prenatal effects, Palmer et al. (2013) showed that prenatal exposure to the potent synthetic estrogen diethystilbestrol was associated with larger breast size at age 20, and Ertuğrul et al. (2020) reported that higher digit ratios were linked with larger breast-to-underbreast ratios in university-aged women. Males tend to express preferences for relatively large breasts in women (or preference for large plus medium over small breasts), in both western and traditional societies, although there is cross-cultural variation in the presence of strength of such preferences, and in some studies larger breast size is only preferred in association with low WHR (Dixson et al., 2011, 2015; Ford & Beach, 1951; Furnham et al., 1998, 2006; Gitter et al., 1983; Gueguen, 2007; Havlíček et al., 2017; Kościński et al., 2020; Singh & Young, 1995; Zelazniewicz & Pawlowski, 2011).

Jasieńska et al. (2004) showed that levels of estradiol were significantly higher among reproductive aged women with the combination of large breasts and low WHRs, in comparison to women with small breasts and low or high WHRs. They inferred a higher reproductive capacity for such women from data on estradiol levels; however, there appear to be no data available on fertility or fecundity of women in relation to breast size. There are also no data in the currently available literature on breast size in relation to endometriosis.

Taken together, these studies on facial form, vocal pitch, and breast size provide evidence for male preference of "more-female" traits whose expression is mediated by low testosterone and/or high estrogen, and that may contribute to female reproductive success. Clear predictions that follow are that women with endometriosis should exhibit relatively "more-female" facial morphology, higher-pitched voices, and larger breast size, compared with controls.

To the extent that female overall "attractiveness" is mediated through the integration of multiple traits, all of which develop in part under the effects of relatively low testosterone and relatively high estradiol, attractiveness-related phenotypes should tend to be positively associated with one another. Such positive associations have been reported for facial with vocal attractiveness (Collins & Missing, 2003; Wheatley et al., 2014), higher vocal attractiveness with lower WHR (Hughes et al., 2004), higher facial attractiveness with lower BMI (Hu et al., 2019; for a genetic correlation), and facial shape with WHR and BMI (Mayer et al., 2017; Pisanski et al., 2016).

Sexual Selection for Correlates of Endometriosis in Non-Human Mammals

The sexual selection hypothesis can also be tested using data from non-human species, given the fundamental similarities in the HPO axes across diverse species of mammals. Because all such non-

human species, except some primates, some bats and spiny mice, do not exhibit menstruation, the predictions involve correlates of endometriosis, including testosterone and estradiol levels, AGD lengths, timing of first estrus, menstrual cycle timing and regularity, correlates of fitness (especially fecundity), and preference by males. Thus the specific predictions are that females who develop under relatively low prenatal testosterone levels (and/or high estradiol) show lower AGDs (as in endometriosis; Crestani et al., 2020, 2021; Mendiola et al., 2016; Peters et al., 2020), earlier first estrus (as in endometriosis, for menarche; Day et al., 2015; Nnoaham et al., 2012), faster and more-regular cycles (as in endometriosis; Wei et al., 2016; Yasui et al., 2015), and higher fecundity (as for correlates of endometriosis), and are preferred by males for mating (as for the correlates of endometriosis discussed above). Converse predictions apply for females who developed under relatively high prenatal testosterone.

From studies of seven species of rodents and primates, female development under conditions of relatively low prenatal testosterone (or high estradiol) is associated with (a) earlier vaginal opening or estrus, in mice, gerbils and rats; (b) shorter or more regular menstrual cycles, or both, in mice, gerbils, rats and hamsters; (c) relatively high fertility or fecundity, in mice, gerbils, rabbits, marmots, and lemurs; and (d) mate preference by males, in mice, gerbils, hamsters and rabbits (Table 2). These findings strongly support the hypothesis that low prenatal testosterone mediates the development of endometriosis-associated phenotypes that are linked with increased female reproductive fitness and preference by males.

Discussion

The general idea that features of higher female-trait expression and female attractiveness may be positively associated with endometriosis risk, owing to the joint effects of sex steroids on both phenomena, was first suggested by Buggio et al. (2012). In this article, we have extended and evaluated their insight and drawn together extensive bodies of literature that provide convergent support for the specific hypothesis that endometriosis risk is linked with female biases in developmental, endocrine, morphological and life history phenotypes that are associated with low testosterone, high estradiol, high reproductive fitness, and preference by males. These findings implicate sexual selection in the evolution and maintenance of risk for endometriosis, and suggest that this disorder represents, in part, a manifestation of maladaptive extremes in female biases to human sexually dimorphic and sex-limited traits (Figures 2 and 5).

The hypothesis that sexual selection for "more-female" trait expression has mediated the evolution and maintenance of endometriosis is supported by six independent lines of evidence: (a) endometriosis involves female biases to expression of the major genes that control early *in utero* sexual development; (b) endometriosis involves relatively short anogenital distances in women, which indicate relatively low prenatal testosterone exposure; (c) endometriosis involves relatively female-biased phenotypes, compared with control females, for a wide range of endocrinological, physiological and morphological traits, including effects on postnatal testosterone, oxytocin, β-endorphin, pain perception, inflammation, WHR, muscularity, and skin, hair and eye pigment-related phenotypes (Table 1), most of which can be linked to low prenatal and/or postnatal testosterone; (d) for several of these traits, including WHR, BMI, and skin phenotypes, males exhibit preferences for the relative female biased traits that are themselves associated with higher female reproductive success; (e) for some additional traits, including female-biased facial morphology, a higher-pitched voice, and larger breasts, relative female biased trait expression shows evidence of being preferred by males, and trait expression is mediated by prenatal and postnatal testosterone and estrogens, although links to endometriosis have yet to be tested; and (f) studies of mice, rats, gerbils, hamsters, voles, rabbits, marmots, and lemurs provide evidence that, as for endometriosis and its correlates in humans, low testosterone and/or high estradiol is associated with earlier onset of estrus, shorter and more regular cycles, indicators of higher reproduction, and/or preference by males for mating. These results are not dependent in any way on inferences from data on digit ratios (which is inconsistent and controversial), although the available, relevant digit ratio data tends to support the predictions.

An important limitation to the sets of data relevant to testing the hypothesis evaluated here is the general paucity of data on AGD in women, such that our knowledge of the links of prenatal testosterone with adult female reproductive and secondary sexual traits remains restricted and indirect. Moreover, there is a notable lack of data on effects of

variation in testosterone on female reproductive development and HPO function, which may be caused by the misconception that androgens are only or mainly salient to the reproductive physiology of males (e.g., Gibson et al., 2020; Prizant et al., 2014; Simitsidellis et al., 2018). Little data have also been collected on phenotypes associated with endometriosis that do not have relatively direct medical impacts, and research on this disease has not been guided by hypotheses informed by evolutionary biology.

The hypothesis proposed and evaluated here makes a large number of testable predictions, that should help to spur progress in understanding the etiology of endometriosis, the roles of recent human evolution in risks of common reproductive diseases, and the ultimate and proximate causes of variation in female primary and secondary sexual traits. Doing so effectively, however, will require integration of approaches and data from gynaecology, endocrinology, physiology, genetics, behavior, and evolutionary biology. The most direct tests of the hypothesis will come from studies of male preference for higher expression of heritable traits in females whose development and expression are associated with relatively low testosterone (or indicators thereof, such as AGD), correlates of higher endometriosis risk (though not endometriosis itself), and higher female fecundity. Additional robust tests will come from evaluating associations of AGD, or serum testosterone, with sexually dimorphic human traits including facial features, body shape, muscularity, and vocal pitch. As described above and shown in Figure 1, the traits preferred by males will include some that are directly related to higher female reproduction and reproductive value (owing to strong functional links with steroid hormone levels in development and adulthood), and some (e.g., facial shape or vocal pitch) that are related to higher female reproduction and reproductive value only indirectly, due to their dependence on levels of the same steroids that directly affect reproduction.

With regard to preventing and treating endometriosis, a primary insight gained here is that its risk is apparently driven by low testosterone and "profemale," "anti-male" gene expression during early *in utero* development, that program the HPO axis and the expression of female primary and secondary sexual traits, leading to highly female-biased, maladaptive physiological extremes. As such, endometriosis should be considered as a developmental-physiological disorder affecting all major bodily systems, with pervasive effects from relatively low prenatal and postnatal testosterone that differentially program and orchestrate the HPO axis (Dinsdale & Crespi, 2021). If further supported by targeted work, this paradigm would provide a robust framework for clinical studies, prevention, and treatment of endometriosis (Dinsdale et al., 2021).

The model for the evolution of endometriosis risk proposed and evaluated here fits closely with Fisher's (1915) scenario for the roles of natural and sexual selection in the evolution of sexual preference. As noted above, Fisher described three phases in the history of secondary sexual traits: an initial phase where the trait expression is favored by natural selection, a second phase driven by sexual selection, by mate choice, for higher levels of the trait, and a third phase where the sexual selection advantages of the trait expression become balanced by natural selection against it, leading to equilibrium.

For endometriosis, the initial, natural selection phase would involve fertility and fecundity advantages associated with the evolution of lower prenatal and postnatal testosterone (and higher estradiol), or other factors that push development and function in a "more female" direction. During the second phase, sexual selection (male preference) for phenotypes directly and indirectly associated with these fitness advantages would drive trait evolution in the same direction as natural selection. And in the third phase, trait expression would become sufficiently extreme to incur naturally selected costs, here, the fecundity-reducing impacts of endometriosis itself, as well as premature ovarian failure.

Humans are highly unusual among primates in the nature of the male mate preferences that have, by the model described here, mediated the evolution of female secondary sexual traits and risk of endometriosis. Among common chimpanzees, for example, males prefer to mate with older females, who are demonstrably better at successfully raising offspring (Muller et al., 2006). In many other primates, males prefer to mate, if they are able, with high-status, more-dominant females, who tend to have higher reproductive success (see Kobayashi, 2017). The closest non-human analog to human female secondary sexual traits appears to be the sexual swellings of some primates that indicate, to some degree, the timing of ovulation; such swellings are found especially among species that live in large multi-male, multi-female groups with non-seasonal reproduction (Nunn, 1999; van Schaik et al., 1999), as do humans. Female sexual swellings signal good physiological condition and high

fitness as a mate as well as high fecundability (Huchard et al., 2009; Street et al., 2016), and they may thus resemble secondary sexual traits in humans to some extent.

The finding that extremes of sexually dimorphic reproductive development appear to increase risk of disease in females raises the question of whether this type of effect also manifests in males. By the results discussed above, reproductive performance appears to be maximized in females under conditions of relatively low (below average, but not extremely low) prenatal and postnatal testosterone: especially low testosterone is linked with endometriosis, and relatively high testosterone is associated with lower fertility, lower fecundity, and reduced preference by males, as well as with symptoms of PCOS (Figure 5). By contrast, for males, reproductive performance may be maximized under conditions of relatively high (above average) prenatal and postnatal testosterone, given, for example, extensive evidence for female choice, and male-male competition threat value, of relatively highly developed male traits such as low vocal pitch, more-male facial features, and high muscularity (e.g., Marcinkowska et al., 2019; Puts et al., 2012). The costs of especially high postnatal testosterone in men have yet to be analyzed in detail, but, from studies of humans and non-human primates, they may include increased metabolic rates, higher food requirements, immunosuppression, and higher risks of some cancers (Lassek & Gaulin, 2009; Muehlenbein & Bribiescas, 2005; Muehlenbein & Watts, 2010; Trumble et al., 2016).

Lower prenatal testosterone in males, as evidenced by shorter AGDs, has been consistently associated with reduced testis and phallus size, lower sperm counts and fertility, lower postnatal serum testosterone, and a higher risk of hypospadias (the urethra opening on the underside the penis rather than the tip) and cryptorchidism (failure of one or both testis to descend; reviews in Dean & Sharpe, 2013; Hua et al., 2018; Thankamony et al., 2016), all or most of which are probably related to lower male fitness. Lower prenatal testosterone as indexed by higher digit ratios in males has also been linked with reduced muscular and athletic performance across a large set of studies (Crewther et al., 2015; Manning et al., 2014). In turn, especially low postnatal testosterone is strongly associated with visceral obesity and type 2 diabetes in males, in striking contrast to the associations of high postnatal testosterone with these traits in females (Escobar-Morreale et al., 2014; Navarro et al., 2015), which appear to be mediated by prenatal high-testosterone effects on development (Rae et al., 2013; Roland et al., 2010).

The recent evolutionary trajectory of secondary sexual traits in women was characterized by Fisher (1915, p. 189) as involving "canons of beauty," whereby a set of correlated female traits has evolved that are preferred by males due to both their direct developmental and physiological linkages with reproductive success and reproductive value (such as for low WHR) and their indirect links with fitness via mate choice (such as for facial and vocal features indicative of low testosterone; Figure 1). The nature of this evolutionary trajectory in females dovetails in an intriguing way with theory and data for the evolution of human self-domestication, which also involves effects from lower testosterone, higher oxytocin, reduced pigmentation, neotenic "more-female" facial features, and more-frequent estrus cycles (Wilkins et al., 2014). Given the diversity of ecological, reproductive and social selective pressures affecting human populations throughout our history and across the world, recent evolutionary trajectories are, however, expected to be population-specific to a considerable extent, leading, as Darwin (1871/1981) proposed, to sexual selection also generating much of the observed diversity in sexual dimorphism, and female secondary sexual traits, across human populations.

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