Published as: Crespi B, Dinsdale NL. The sexual selection of endometriosis. Evolutionary Behavioral Sciences. 2023 Apr;17(2):123.

The Sexual Selection of Endometriosis

Bernard Crespi and Natalie Dinsdale

Department of Biological Sciences, Simon Fraser University, 8888 University Drive, Burnaby, British Columbia, Canada V5A1S6

ABSTRACT

Selection can generate risk of maladaptive extremes in sexually dimorphic and sex-limited traits. In humans, such extremes commonly manifest in diseases associated with sex and reproduction. Endometriosis involves endometrial tissue that proliferates at non-uterine sites. The proximate causes of endometriosis remain enigmatic, and its ultimate, evolutionary basis has only recently come under investigation. 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 high female reproductive fitness and low testosterone. The theory is supported by extensive data, from humans and non-human mammals, showing that: (1) endometriosis involves higher expression of major female-biasing genes, and lower expression of major male-biasing genes, that orchestrate prenatal sexual differentiation, including the genes Foxl2, Wnt4, Fst, Ctnnb1, Rspo1, Sox9 and Amh, (2) endometriosis and its correlates are associated with low prenatal and postnatal testosterone, both of which have female-biasing effects on traits, (3) 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, (4) relatively female-biased expression of these traits is commonly associated with higher fertility and fecundity, (5) 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 (6) 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. Such trait expression is mediated by genetic and environmental factors that bias development and physiology towards relatively low-testosterone and high-estradiol (as well as high-oxytocin) states. The hypothesis makes many testable predictions, and has direct implications for understanding the causes and treatment of endometriosis.

1. Introduction

Risks and forms of human disease have evolved (Williams and Nesse 1991). One of the primary evolutionary-medical frameworks for understanding human disease risks is that they can represent maladaptive extremes of adaptations. Under this framework, adaptations evolve along a lineage, and are subject to deleterious genetic and environmental effects leading to losses or gains of function, or under- or over-expression, that can manifest in symptoms of disease (Crespi and Go 2015). Cell replication provides a simple example. Here, cancer involves over-expression, degeneration involves under-expression, and adaptive optima lie in between. Many examples are much more complex. Under this paradigm, the key to understanding the evolution of disease risks and forms becomes determining what adaptive system has become dysregulated, and how its functioning has changed.

The selection and evolution of adaptive traits commonly involves not just optima, but also tradeoffs between opposing selective pressures whose effects are mediated by ineluctable physical and temporal constraints. A prominent form of selective tradeoff, in many animals, is tradeoffs between sexual selection and natural selection (Fisher 1915). By this process, sexual selection favors a trait that 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 comes to be expressed at too extreme a level, then it can become maladaptive and disfavoured by natural selection, in the context of survival or some other component of fitness unrelated to mate choice or mating competition. A balance between sexual and natural selection can ensue.

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 basis of endometriosis risk, symptoms and correlates in humans. We first describe endometriosis, 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. Finally, we describe the implications of results for the diagnosis, prevention, and treatment of endometriosis, and make specific suggestions for future collection of data.

2. Endometriosis

2.1. 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.

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 luterinizing hormone (Dinsdale and

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 (Matalliotakis et al., 2008; Nnoaham et al., 2012; Day et al., 2015; Gupta et al., 2015; Yasui et al., 2015; Wei et al., 2016).

Endometriosis may be potentiated by retrograde movement of endometrial cells from the uterus to fallopian, peritonial, and other sites (Sampson 1925); however, most women experience retrograde flow, while only 5-10% 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 and Taylor 2008; Yovich et al., 2020). Currently, there is no cure for endometriosis, and treatments commonly involve pain medication, surgery, GnRH-based therapies that stop menstruation, or, usually in older women, hysterectomy.

2.2. Ultimate, evolutionary factors

The evolutionary changes that potentiated endometriosis evolved in other selective contexts, and have given rise to the risks and forms of this disorder, which involves reduced fitness, 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 as well (see also Dinsdale et al., 2021). These changes include:

(1) the evolution of more extensive endometrial proliferation and menstruation (Strassmann 1996; Evans et al., 2016; Jarrell 2018), concomitant to more-invasive placentation, which generates higher menstrual activity including retrograde flow (movement of menstrual blood and other tissues into the peritoneal cavity, ovaries, or other sites), and high inflammation during the menstruation process;

(2) deeper implantation and invasion of the embryo and trophoblast into endometrial tissue representing a highly inflammatory process, which may also contribute to inflammation in endometrial tissue (Pijnenborg 2002; Dekel et al., 2010);

(3) more-extensive development of the uterine musculature that facilitates parturition, given the enlarged cranium of human neonates (Rosenberg 1992; Dunsworth and Eccleston 2015), which may potentiate strong and painful uterine contractions during menstruation;

(4) reduced interbirth intervals, from about six years to about three years (Hrdy 2009; Nakahashi et al., 2018), which 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;

(5) 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), and which may also function as indicators of high female reproductive capabilities;

(6) the development of pronounced sexual dimorphism in facial features, vocal pitch, and other steroid hormone related traits (Puts et al., 2012), which may serve as indirect indicators of female reproductive capabilities;

(7) increased paternal care, which is expected to generate selective conditions favoring male choice of relatively fertile and fecund females (Hrdy, 2009);

(8) the evolution of higher levels of monogamy and guarding of females by males (Schacht and Kramer, 2019), which can reinforce male choice and select for male choice of relatively-young females with high nubility and reproductive value (Lassek and Gaulin, 2019) who can be controlled and 'owned' by males for long periods of time (Hrdy, 1997) and

(9) 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 and Chaplin, 2017), and which generates 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 5-10%, is driven by recent secular trends towards earlier menarche and later age of first reproduction, both of which increase numbers of the menstrual cycles that increase the potential for retrograde flow and estrogenic stimulation of endometrial tissue growth. 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). The presence of such mismatch would be expected to exacerbate, rather than generate de novo, the symptoms and severity of endometriosis.

3. Sexual selection of endometriosis

3.1. Hypothesis for the evolution of endometriosis risk

Given what is known about the physiology of endometriosis, and the set of changes in human phenotypes along the human lineage, a simple, testable hypothesis can be developed for how risk of this disorder has evolved. By this hypothesis, females were subject to selection for increased expression of female-limited or sexually-dimorphic phenotypes, such as a low waist-to-hip ratio, that increased their reproductive success. This is just natural selection: the only way to get from the adaptations of a chimp-human ancestor to the adaptations of a modern human female. These phenotypes, and their correlates, 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 mates as well (Puts 2010; DelPriore et al., 2017).

The expected evolutionary response to sexual selection by males for female-biased phenotypes that are 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). Such individuals thus come, after some period of time, to exhibit extremes 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 that is mediated by 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 endometriosis, due to the joint dependence of these two phenomena on sex steroids, was originally suggested by Laura Buggio and colleagues (2012), and is specified, developed, extended, and tested here.

By the hypothesis evaluated here, endometriosis can be conceptualized as the 'extreme female body' with regard to reproductive traits, traits indicative of high reproductive success, and developmentally or functionally associated sex-limited or sexually-dimorphic traits. The hypothesis is conjectural, but makes a large series of explicit predictions for each process involved in the evolution and maintenance of endometriosis risk. The hypothesis is therefore amenable to robust tests, and it provides the first conceptual framework, grounded in human evolutionary biology, for understanding this enigmatic disease.

3.2. 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 and differentiation. This hypothesis is evaluated by determining if 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 binary (barring aneuploidies), the phenotypic expression of sexually dimorphic quantitative traits varies continuously within each sex.

Second, the hypothesis predicts that physiological and morphological traits associated with endometriosis should be sexually dimorphic or female limited, 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 (indicating youthful and recent sexual maturity), or some combination of these components of fitness, as decribed above.

Fourth, the hypothesis predicts that 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.

Fifth, the hypothesis predicts that female traits that are preferred by males should be mediated in their development and expression by relatively low testosterone (prenatal, postnatal or both) and high estradiol. This prediction applies specifically to female-limited or sexually dimorphic traits, such as vocal pitch, facial sexual dimorphism, and relative breast size, that due 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, males of species of non-human 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, including for example low prenatal and postnatal testosterone, higher estradiol, early onset of reproduction, faster cycling, and endometriosis-related ovarian phenotypes. 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.

4. Evaluating the Predictions

4.1. Endometriosis should involve relative female biases to the early *in utero* development of sexually dimorphic and female limited phenotypes

The development of sexual dimorphism in humans begins prenatally, during weeks 6-8 after conception, under the influences of SRY 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 differentiation, 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 low versus high levels of testosterone, guide early sex determination and differentiation, as well as functioning in aspects of adult reproductive physiology including the maintenance of ovarian versus testicular functions (e.g., Murphey 2010 what a difference). We surveyed the literature on the primary genes underlying early prenatal human sex differentiation (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 human sex differentiation (Figure 3). The hypothesis addressed here thus predicts that endometriosis (and the differential expression of genes that characterizes it) should be associated with higher expression, during sex differentiation, 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).

AMH. 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 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., Garg and Tal, 2016; Sahmay et al., 2014; Dumont et al., 2015; Dinsdale and Crespi 2021). 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 (Murphy 2010; Verdin and DeBaere 2012). Knockouts of FOXL2 cause partial (in mice), or complete (in goats) female to male sex reversals (Uhlenhart et al., 2009; Bertho et al., 2019), and reduced expression in humans commonly results in premature ovarian failure (Verdin and DeBaere 2012) and increased levels of androgens (Murphey 2010 what a difference). Compared with controls, expression of FOXL2 is increased about three-fold 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 (Heikkila 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 production of this gene in endometrial tissue (leading to higher local production of estradiol), contribute to the symptoms of endometriosis. Finally, the WNT4 gene also harbours SNPs that are significantly associated with endometriosis, from GWAS results, at the genome-wide significant level (Rahmioglu et al., 2014, 2018), although if 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 (Parma et al., 2006; Biason-Lauber 2012; Clevers and Nusse 2012) 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 (Matsuzaki et al., 2014; Hundt 2016).

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' signalling 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 (Xiong et al., 2016; Pazhohan et al., 2018, 2021), 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 (Torres et al., 2007; Florio et al., 2009).

Taken together, these major mammalian sex-differentiation and sex-development genes, 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 sex differentiation and adult reproductive functions. Future studies might usefully test for pleiotropic effects, of these genes and their major interaction partners, on other sexually dimorphic and endometriosis-associated traits.

4.2. Endometriosis and endometriosis-associated traits should involve relative female biases to sexually dimorphic or female limited 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 to females without endometriosis (Figure 2). We evaluate this prediction here for endocrine, physiological and morphological phenotypes, with the results summarized in Table 1.

4.2.1. 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 and

Sharpe 2013; Liu et al., 2014; Thankamony et al., 2016; Schwartz et al., 2019). Female mammals that develop under relatively low levels of prenatal testosterone, or higher levels of estrogens, thus 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 (Zheng and Cohn 2011; Manning et al., 2014). In female humans and mice, lower prenatal testosterone is associated with higher digit ratios. Digit ratio studies show considerable heterogeneity and lacks of replicability in their findings (e.g., Voracek 2009), and have been subject to limited validation through direct measurements of prenatal steroid concentrations. 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.

Four recent studies, representing three independent data sets, have reported that women with endometriosis exhibit shorter AGDs than do females without endometriosis (Mendiola et al., 2016; Peters et al., 2020; Crestani et al., 2020, 2021). 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 20mm-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 non-significant 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; Matalliotakis et al., 2008; Mendiola et al., 2012; Mira-Escolano et al., 2014a,b; Ono et al., 2014; Gupta et al., 2015). 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 (Shah 2013; Dural et al., 2021). 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 (Barrett et al., 2017; Ottolina et al., 2020).

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

4.2.2. Postnatal testosterone

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

No studies have tested observationally for associations of serum testosterone with 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).

4.2.3. 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 to controls, in endometrial tissue and in menstrual blood, though not in serum (Takahashi et al., 1989; Huhtinen et al., 2012; Stilley et al., 2012). Women with endometriosis thus show increased local estradiol production in eutopic and ectopic endometrium, which stimulates excessive endometrial tissue proliferation.

4.2.4. SHBG

Serum hormone binding globulin (SHBG) regulates the bioavailability of testosterone and estradiol. Serum SHBG is about twice as high in women than in men (Hammond 2017 SHBG metabolic syndrome), 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 to controls (Panidis et al., 1993; Misao et al., 1995), and treatment of endometriosis with danazol leads to reduced SHBG levels (Panidis et al., 1993). 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).

4.2.5. Oxytocin

The peptide hormone oxytocin orchestrates a suite of female reproductive functions including lactation, and uterine contraction during menses and parturition (Kunz and Leyendecker 2002). Serum levels of oxytocin are higher in women than men in some studies (e. g., Carter 2007; Imamura et al., 2017; Marazziti et al., 2019; Kunitake et al., 2020; Orihashi et al., 2020) but other studies show no difference (e.g., Marazziti et al., 2006; Floyd et al., 2010; Koven and Max 2014; 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 (Leyendecker et al., 2004; Liedman et al., 2008; Harada 2013; Huang et al., 2017).

4.2.6. 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 and Fillingim 2013; Hashmi and Davis 2014), with this sex difference is attributable in part to levels of testosterone, because pain sensitivity is inversely related to serum testosterone in both sexes (Cairns and Gazerani 2009; Bartley et al., 2015), and 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 high sensitivity to pain (van Aken et al., 2018), and exhibit low levels of β-endorphin (Vercellini et al., 1992), compared to 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 is programmed during prenatal development (Cicero et al., 2002). These finding 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.

4.2.7. 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 and 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 and Flanagan 2016). Higher levels of inflammation in women then men are caused in part by the pro-inflammatory effects of estrogens and the anti-inflammatory effects of testosterone (Pergola et al., 2011; Klein and Flanagan 2016; Garcia-Gomez et al., 2020). Endometriosis is characterized by elevated systemic and local inflammation (Zhang De et al., 2018 Riccio et al., 2018), with increased rates of autoimmune disorders (Shigesi et al., 2019; Shafrir et al., 2021). Chronic inflammation also appears to mediate infertility in endometriosis by interfering with implantation (Lin et al., 2018).

4.2.8. Waist-hip ratio (WHR)

Females exhibit a lower 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 and lactation (Wells 2007; Wells et al., 2010; Chiappa and Singh 2017). Among reproductive-aged women, lower WHR is associated with lower levels of serum testosterone (Sowers et al., 2001; van Anders and 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 (Mondragon-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 to controls, in association with a more-peripheral, and less male-typical 'android' (central and visceral), distribution of body fat (McCann et al., 1993; Shah et al., 2013; Backonja et al., 2016, 2017; Rossi et al., 2021) and a 'lean' body shape (Aarestrup et al., 2020).

4.2.9. Body mass index (BMI)

Body mass index is a measure, derived from body weight and height, that is designed to provide a relative 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 to less-dense fat, this measure is problematic to compare between the sexes. BMI is positively correlated with serum testosterone in women (Taponen et al., 2003; Sidhu et al., 2017; Stanikova et al., 2019), but it is not associated with digit ratios (Fink et al., 2006; Swami et al., 2019).

BMI is substantially and significantly lower in women with endometriosis compared to controls (Shah et al., 2013; Backonja et al., 2017; Rossi et al., 2021; Aarestrup et al., 2020; Garitazelaia et al., 2021; and by meta-analyses in Yong and Weiyuan (2017) and Jenabi et al. (2019).

4.2.10. Muscularity

Males exhibit substantially higher levels of muscle mass than do females, due primarily to the anabolic effects of higher testosterone (Lassek and Gaulin 2009). Among females, lower digit ratio is associated with enhanced muscularity and athletic performance, but the roles of serum testosterone in these effects remain unclear (Hönekopp and Schuster, 2010; Kim and Kim, 2016; Eklund et al., 2020).

In the single study that quantified muscle tissue among women with endometriosis, affected women exhibited significantly reduced upper arm muscle mass compared to controls (Backonja et al., 2017); for this phenotype, males show about 50% higher muscle mass (Frisancho, 1974).

4.2.11. 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 (Videira et al., 2013; Hernando et al., 2016a). This system is mediated by a suite of genes and alleles, some of which exert large phenotypic effects (Maroñas et al., 2015; Pavan and 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 et al., 2016a,b), 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; Rees and Harding 2012; Martinez-Cadenas et al., 2013; Wilde et al., 2014; Rocha 2020). At the genome-wide level, Stern et al. (2021) found that less pigmented 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.

4.2.11.1. Skin pigmentation

Adult females exhibit less pigmented skin than males across almost all human groups worldwide, that 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 (van den Berghe and Frost 1986; Jablonski and Chaplin 2000; Frost 2007, 2014; Sitek et al., 2018). 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 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 to 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% medium or dark, 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 to women with African ancestry, by meta-analysis (Bougie et al., 2019), and in studies that should, due to their designs, be subject to minimal effects from ascertainment biases related to racial health-care biases and socioeconomic disparities (Missmer et al., 2004; Eggert et al., 2008).

4.2.11.2. Sun sensitivity and melanoma risk

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 et al., 2016b), and the three studies conducted to date demonstrate that women with endometriosis show significantly higher sensitivity of the skin to sun exposure compared to 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 to 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).

4.2.11.3. Eye coloration

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 to 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 to 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 to (pooled) controls and women with milder, ovarian endometriosis (endometriomas).

4.2.11.4. Hair coloration

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 (Woodworth et al., 1995; Wyshak and Frisch 2000; Missmer et al., 2006; 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, $\chi 2=15.3$, $P < 0.0001$), in Kvaskoff et al. (2009) (Table 2 data: red, and blond versus 'chestnut', brown and 'dark', $\chi 2= 5.33$, $P < 0.025$), and in Kvaskoff et al. (2014) (Table 3 data: red and blond versus brown and black, $\chi 2=5.7$, $P < 0.025$).

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 phaeomelanin (yellow and red) pigmentation (Latraeille 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 (Mogil et al., 2003; Raimondi et al., 2008; White and Rabago-Smith 2011; Haddadeen et al., 2015; Frost et al., 2017). 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 and 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 (Mogil et al., 2003; Liem et al., 2005; Delaney et al., 2010; Chen et al., 2013). 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 affected by a SNP at the MC1R locus (Shin et al., 2020).

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: (1) compared to men, women are characterized by less

pigmented skin, higher sun sensitivity, higher rates of melanoma, and lighter hair color, and (2) compared to 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.

4.2.12. 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 coloration, 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 to women without endometriosis, thus 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 to women without endometriosis (Bulletti et al., 2002; Nnoaham et al., 2012; Yasui et al., 2015; Wei et al., 2016; Dinsdale and Crespi 2021).

The set of 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 and Crespi 2021; Dinsdale et al., 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.

4.3. 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 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: (1) fertility (level of ability to conceive and bear children), (2) fecundability (conceptions per cycle), (3) fecundity (total numbers of children born), (4) nubility (recent attainment of physical and sexual maturity), (5) residual reproductive value (expected future reproduction downweighted by risk of mortality) (Andrews et al., 2017) and (6) ability to successfully 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 and 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 FSHB (Follicle Stimulating Hormone Subunit Beta), and alleles at the PROGINS locus of the

progesterone receptor gene PR, can also be tested for associations with correlates of reproductive fitness, due to their extensive and well studied pleiotropic effects.

4.3.1. 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 and 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 (1) lower serum testosterone (Mira-Escolano et al., 2014); (2) smaller ovarian follicle number (higher follicle numbers being linked with excess fetal testosterone exposure) (Mendiola et al., 2012); and (3) 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 2014a,b). 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 the 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 (Rosenfield and Ehrmann 2016; Filippou and Homberg 2017; Abbott et al., 2019). 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 (Okon et al., 1997; Cocksedge et al., 2008; 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 Butikofer 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 to 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 (Gleicher et al., 2013; Lu et al., 2014; Shah 2013; Prizant et al., 2014; Dural et al., 2021), and, as discussed above, endometriosis, which causes notable reductions in fertility due to implantation failure 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 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.

4.3.2. Oxytocin and correlates of fitness

Variation in oxytocin may influence female reproductive success especially through effects on fertility and social relationships including parenting. 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). Uterine contraction strength also exhibits an inverse relationship with implantation success (Moraloglu et al., 2010). Overly strong and disorganized uterine contractions, due to high oxytocin and oxytocin receptor levels, appear to mediate reduced fecundability as well as dysmenorrhea in women with endometriosis and adenomyosis (Leyendecker et al., 2004; Kunz et al., 2007; Guo et al., 2013). 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 and 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 (Human et al., 2016; Cardoso et al., 2012) and extraversion also shows strong genetic and phenotypic associations with bipolar disorder (e.g., Quilty et al., 2009; Middeldorp et al., 2011). In turn, bipolar disorder shows notable comorbidity with endometriosis (Dinsdale and Crespi 2017; Chen et al., 2020) 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.

4.3.3. Age at menarche and correlates of fitness

In traditional populations, age at menarche is positively associated with age at first pregnancy (e. g., Udry and Cliquet 1982; Sandler et al., 1984; Hochberg et al., 2011). 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 over 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.

4.3.4. 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 Simmons 2017) and nubility (Lassek and Gaulin, 2019). WHR then tends to increase with numbers of children across the reproductive lifespan (Butovskaya Dronova, 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., Zaadstra et al. 1993; Wass et al., 1997; Singh 2002 mate value; Jasienka et al. 2004; Pawlowski and Dunbar 2005; Cashdan 2008; Singh and Singh 2011; Cloud and Perilloux 2014; Weeden and Sabini 2015; Butovskaya et al., 2017; Bovet 2018).

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., Ramlau-Hansen et al., 2007; Wise et al., 2010; McKinnon et al., 2016; Imterat et al., 2018; Yilmaz et al., 2019). 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 et al. (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 and 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 and 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 confer 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 upon local ecological and social conditions that select for locally optimal life histories, and upon mismatches due to rapid recent environmental change.

4.3.5. Skin pigmentation, associated traits, and correlates of fitness

The strong positive associations of higher latitude and lower UV radiation with reduced pigmentation (Jablonski and Chaplin, 2010, 2017), and the clear links of reduced pigmentation with increased synthesis of vitamin D (Clemens et al., 1982; Åkeson et al., 2016), have motivated the hypothesis that the primary selective pressure favoring the evolution of lighter pigmentation was the more-efficient generation of vitamin D (Chaplin and Jablonski, 2009; Jablonski and 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 and Walther 2013) and very little from plants (Jäpelt and 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 more-equatorial regions (Rees and Harding, 2012; Jablonski and 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), and women's skin lightens at menarche while the skin of men continues to slowly darken (van den Berghe and Frost, 1986).

Second, in contemporary populations of healthy women, lower serum vitamin D concentrations are associated with longer, more-irregular menstrual cycles (Jukic et al., 2019; Jukic et al., 2015), lower serum estradiol (Harmon et al., 2020), and reduced fecundability (conception rate per cycle) (Fung etnal., 2017; Jukic et al., 2019). The effects on fecundability are substantial: for example, Jukic et al. (2019) found that compared to 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 and 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 (Rojansky et al., 1992; Danilenko et al., 2011). Finally, an extensive set of animal-model studies links relatively low vitamin D levels with reduced fertiliy (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 2-3 times higher among pregnant women with more-pigmented compared to 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 to 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; Wimalawansa, 2016; Hoffman et al., 2020; Revez et al., 2020). More generally, lower serum vitamin D is closely associated with high body weight and obesity (Walsh et al., 2017; Hochberg and Hochberg, 2019; Vranić et al., 2019), 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 and 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, although their contributions 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 and Hochberg, 2019; Tiosano et al., 2016).

4.3.6. 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 (Ruth et al., 2015, 2016; Sapkota et al., 2017; Laisk et al., 2018; Rull et al., 2018). 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 fitness, among women who do not have the disease.

4.4. 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.

4.4.1. 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 Jones, 1996; Furnham et a., 2002, 2005; Singh et al., 2010; Singh and Singh, 2011; Cloud and Perilloux, 2014; Grillot et al. 2014; Wang et al., 2015; Andrews et al., 2017; Del Zotto and Pegna, 2017; Bovet, 2018; Lassek and Gaulin, 2019). 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., see Gangestad and 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, that signal high reproductive value (Wang et al. 2015; Lassek and Gaulin 2018).

4.4.2. Skin pigmentation

Males have been reported to prefer females with relatively less pigmented skin (compared to others in the same population) across a large suite of studies conducted within diverse human populations distributed widely across the globe, and including populations without European contact and a population of native South Africans (Coetzee et al., 2012; van den Berghe and Frost, 1986; Feinman and Gill, 1978; Dixon et al., 2007, 2010; Kleisner et al., 2017; reviews in Frost, 2007, 2014; Jones, 2018). 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).

4.5. 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.

4.5.1. Faces

Male preference for morphometrically 'more-female', compared to 'more-male' female faces has been demonstrated in a large suite of studies, including work in traditional and indigenous societies as well as westernized ones (see Lee et al., 2014; Marcinkowska et al., 2014; Scott et al., 2014; Kliesner et al., 2017; Kočnar et al., 2019; 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) Zelazniewicz 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).

4.5.2. Voices

Male preferences for voices of adult females that are relatively high-pitched have been reported consistently across multiple studies (Collins and Missing, 2003; Feinberg et al., 2008; Borkowska and Pawlowski, 2011; 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; Hannoun et al., 2011; Hamdan et al., 2018), 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 (Levrevo et al., 2018). Finally, Atkinson et al. (2012) showed, in an indigenous population in Namibia, that females with higher-pitched voices had more children.

4.5.3. 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; Jemström et al., 1997; Schmidt et al., 2002). As regards prenatal effects, Palmer et al. (2013) showed that 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 (Ford and Beach, 1951; Gitter et al., 1983; Singh and Young, 1995; Furnham et al., 1998, 2006; Gueguen, 2007; Dixson et al., 2011; Zelazniewicz and Pawlowski, 2011; Dixson et al., 2015; Havicek et al., 2017; Koscinski et al., 2020).

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 to 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 and 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 (Pisanski et al., 2016; Mayer et al., 2017).

4.6. 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 between 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) (Mendiola et al., 2016; Peters et al., 2020; Crestani et al., 2020, 2021), earlier first estrus (as in endometriosis, for menarche) (Nnoaham et al., 2012; Day et al., 2015), faster and more-regular cycles (as in endometriosis) (Yasui et al., 2015; Wei et al., 2016), and higher fecundity (as for correlates of endometriosis such as low WHR), 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.

5. Discussion

The general idea that features of higher female-trait expression and female attractiveness may be positively associated with endometriosis risk, due 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, and

morphological 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: (1) endometriosis involves female biases to expression of the major genes that control early *in utero* sexual differentiation; (2) endometriosis involves relatively short anogenital distances in women, which indicate relatively low prenatal testosterone exposure; (3) endometriosis involves relatively female-biased phenotypes, compared to control females, for a wide range of physiological and morphological traits, including effects on postnatal testosterone, oxytocin, β-endorphin, pain perception, inflammation, WHR, BMI, muscularity, and skin, hair and eye pigment-related phenotypes (Table 1), most of which can be linked to low prenatal and/or postnatal testosterone; (4) for several of these traits, including WHR, BMI, and skin phenotypes, males exhibit preferences for the relative female biased traits (e.g., for lower WHR) that are themselves associated with higher female reproductive success; (5) 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 (6) studies of mice, rats, gerbils, hamsters, voles, rabbits, marmots and lemurs provide evidence that, as for endometriosis and its correlates, low testosterone is associated with earlier onset of estrus, shorter and more regular cycles, indicators of higher reproduction, and 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., Prizant et al., 2014; Simitsidellis et al., 2018; Gibson et al., 2020). Little data has 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, animal physiology, genetics, behavior and evolutionary biology.

With regard to preventing and treating endometrosis, a primary insight gained here is that its risk is apparently driven by low testosterone and 'pro-female', '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 and Crespi, 2021). If further supported by targeted work, this paradigm would provide a robust framework for clinical studies 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, driven 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 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., Puts et al., 2012; Marcinkowska et al., 2019). 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 (Muehlenbein and Bribiescas, 2005; Lassek and Gaulin, 2009; Muehlenbein and 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 and Sharpe, 2013; Thankamony et al., 2016; Hua et al., 2018), 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 (Manning et al., 2014; Crewther et al., 2015). 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 (Roland et al., 2010; Rae et al., 2013).

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 (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 Wrangham 2014). However, given the diversity of ecological, reproductive and social selective pressures affecting human populations throughout our history and across the world, recent evolutionary trajectories are expected to be population-specific to a considerable extent, leading, as Darwin (1871) proposed, to sexual selection also generating many of the observed diversity in sexual dimorphism, and female secondary sexual traits, across human populations.

References

Aarestrup, J., Jensen, B.W., Ulrich, L.G., Hartwell, D., Trabert, B., Baker, J.L., 2020. Birth weight, childhood body mass index and height and risks of endometriosis and adenomyosis. Ann. Hum. Biol. 47, 173–180.

Abbott, D.H., Dumesic, D.A., Levine, J.E., 2019. Hyperandrogenic origins of polycystic ovary syndrome–implications for pathophysiology and therapy. Expert Rev. Endocrinol. Metab. 14, 131–143.

Abitbol, J., Abitbol, P., Abitbol, B., 1999. Sex hormones and the female voice. J. Voice 13, 424–446.

Åkeson, P.K., Lind, T., Hernell, O., Silfverdal, S.A., Öhlund, I., 2016. Serum vitamin D depends less on latitude than on skin color and dietary intake during early winter in Northern Europe. J. Pediatr. Gastroenterol. Nutr. 62, 643–649.

Albu, D., Albu, A., 2019. The relationship between anti-Müllerian hormone serum level and body mass index in a large cohort of infertile patients. Endocrine 63, 157–163.

Alebić, M.Š., Stojanović, N., Dewailly, D., 2018. Discordance between serum anti-Müllerian hormone concentrations and antral follicle counts: not only technical issues. Hum. Reprod. 33, 1141–1148.

Anai, T., Miyazaki, F., Tomiyasu, T., Matsuo, T., 2001. Risk of irregular menstrual cycles and low peak bone mass during early adulthood associated with age at menarche. Pediatr. Int. 43, 483–488.

Andrews, T.M., Lukaszewski, A.W., Simmons, Z.L., Bleske-Rechek, A., 2017. Cue-based estimates of reproductive value explain women's body attractiveness. Evol. Hum. Behav. 38, 461–467.

Atkinson, J., Pipitone, R.N., Sorokowska, A., Sorokowski, P., Mberira, M., Bartels, A., Gallup Jr, G.G., 2012. Voice and handgrip strength predict reproductive success in a group of indigenous African females. PLoS One 7, e41811.

Backonja, U., Hediger, M.L., Chen, Z., Lauver, D.R., Sun, L., Peterson, C.M., Buck Louis, G.M., 2017. Beyond body mass index: using anthropometric measures and body composition indicators to assess odds of an endometriosis diagnosis. J. Womens Health 26, 941–950.

Backonja, U., Louis, G.M.B., Lauver, D.R., 2016. Overall adiposity, adipose tissue distribution, and endometriosis: a systematic review. Nurs. Res. 65, 151.

Bánszegi, O., Altbäcker, V., Bilkó, Á., 2009. Intrauterine position influences anatomy and behavior in domestic rabbits. Physiol. Behav. 98, 258–262.

Bánszegi, O., Altbäcker, V., Dúcs, A., Bilkó, Á., 2010. Testosterone treatment of pregnant rabbits affects sexual development of their daughters. Physiol. Behav. 101, 422–427.

Bánszegi, O., Szenczi, P., Dombay, K., Bilkó, Á., Altbäcker, V., 2012. Anogenital distance as a predictor of attractiveness, litter size and sex ratio of rabbit does. Physiol. Behav. 105, 1226–1230.

Barbieri, R.L., Evans, S., Kistner, R.W., 1982. Danazol in the treatment of endometriosis: analysis of 100 cases with a 4-year follow-up. Fertil. Steril. 37, 737–746.

Barbieri, R.L., Sluss, P.M., Powers, R.D., McShane, P.M., Vitonis, A., Ginsburg, E., Cramer, D.C., 2005. Association of body mass index, age, and cigarette smoking with serum testosterone levels in cycling women undergoing in vitro fertilization. Fertil Steril. 83, 302–308.

Barbotin, A.L., Peigné, M., Malone, S.A., Giacobini, P., 2019. Emerging roles of anti-müllerian hormone in hypothalamic-pituitary function. Neuroendocrinology 109, 218–229.

Barkat-Defradas, M., Raymond, M., Suire, A., 2021. Vocal preferences in humans: a systematic review, in: Weiss, B., Trouvain, J., Barkat-Defradas, M., Ohala, J.J. (Eds.), Voice Attractiveness: Studies on Sexy, Likable, and Charismatic Speakers. Springer, Singapore, pp. 55–80.

Barnett, J.B., Woods, M.N., Rosner, B., McCormack, C., Floyd, L., Longcope, C., Gorbach, S.L., 2002. Waist-to-hip ratio, body mass index and sex hormone levels associated with breast cancer risk in premenopausal Caucasian women. J. Med. Sci. 2, 170–176.

Barrett, E.S., Hoeger, K.M., Sathyanarayana, S., Abbott, D.H., Redmon, J.B., Nguyen, R.H., Swan, S.H., 2018. Anogenital distance in newborn daughters of women with polycystic ovary syndrome indicates fetal testosterone exposure. J. Dev. Orig. Health Dis. 9, 307.

Barrett, E.S., Mbowe, O., Thurston, S.W., Butts, S., Wang, C., Nguyen, R., … Sathyanarayana, S., 2019. Predictors of steroid hormone concentrations in early pregnancy: results from a multi-center cohort. Matern. Child Health J. 23, 397–407.

Bartley, E.J., Fillingim, R.B., 2013. Sex differences in pain: a brief review of clinical and experimental findings. Br. J. Anaesth. 111, 52–58.

Bartley, E.J., Palit, S., Kuhn, B.L., Kerr, K.L., Terry, E.L., DelVentura, J.L., Rhudy, J.L., 2015. Natural variation in testosterone is associated with hypoalgesia in healthy women. Clin. J. Pain 31, 730–739.

Biason-Lauber, A., 2012. WNT4, RSPO1, and FOXL2 in sex development. Semin. Reprod. Med. 30, 387–395.

Blouin, K., Boivin, A., Tchernof, A., 2008. Androgens and body fat distribution. J. Steroid Biochem. Mol. Biol. 108, 272–280.

Borahay, M.A., Lu, F., Ozpolat, B., Tekedereli, I., Gurates, B., Karipcin, S., Kilic, G.S., 2013. Mullerian inhibiting substance suppresses proliferation and induces apoptosis and autophagy in endometriosis cells *in vitro*. Int. Sch. Res. Notices 2013, 361489.

Borkowska, B., Pawlowski, B., 2011. Female voice frequency in the context of dominance and attractiveness perception. Anim. Behav. 82, 55–59.

Böttcher, B., Seeber, B., Leyendecker, G., Wildt, L., 2017. Impact of the opioid system on the reproductive axis. Fertil. Steril. 108, 207–213.

Bougie, O., Yap, M.I., Sikora, L., Flaxman, T., Singh, S., 2019. Influence of race/ethnicity on prevalence and presentation of endometriosis: a systematic review and meta-analysis. BJOG 126, 1104–1115.

Bovet, J., 2018. The evolution of feminine beauty, in: Kapoula, Z., Volle, E., Renoult, J., Moreno Andreatta, M. (Eds.), Exploring Transdisciplinarity in Art and Sciences. Springer, pp. 327–357.

Bowyer, L., Catling-Paull, C., Diamond, T., Homer, C., Davis, G., Craig, M.E., 2009. Vitamin D, PTH and calcium levels in pregnant women and their neonates. Clin. Endocrinol. 70, 372–377.

Buggio, L., Roncella, E., Somigliana, E., Vercellini, P., 2016. Vitamin D and benign gynaecological diseases: a critical analysis of the current evidence. Gynecol. Endocrinol. 32, 259–263.

Buggio, L., Vercellini, P., Somigliana, E., Viganò, P., Frattaruolo, M.P., Fedele, L., 2012. "You are so beautiful": behind women's attractiveness towards the biology of reproduction: a narrative review. Gynecol. Endocrinol. 28, 753–757.

Bulletti, C., Coccia, M.E., Battistoni, S., Borini, A., 2010. Endometriosis and infertility. J. Assist. Reprod. Genet. 27, 441–447.

Bulletti, C., De Ziegler, D., Polli, V., Del Ferro, E., Palini, S., Flamigni, C., 2002. Characteristics of uterine contractility during menses in women with mild to moderate endometriosis. Fertil. Steril. 77, 1156–1161.

Bulun, S.E., Yilmaz, B.D., Sison, C., Miyazaki, K., Bernardi, L., Liu, S., … Wei, J., 2019. Endometriosis. Endocrine Rev. 40, 1048–1079.

Burriss, R.P., Little, A.C., Nelson, E.C., 2007. 2D:4D and sexually dimorphic facial characteristics. Arch. Sex. Behav. 36, 377–384.

Bütikofer, A., Figlio, D.N., Karbownik, K., Kuzawa, C.W., Salvanes, K.G., 2019. Evidence that prenatal testosterone transfer from male twins reduces the fertility and socioeconomic success of their female co-twins. Proc. Natl. Acad. Sci. U.S.A. 116, 6749–6753.

Butovskaya, M., Sorokowska, A., Karwowski, M., Sabiniewicz, A., Fedenok, J., Dronova, D., … Sorokowski, P., 2017. Waist-to-hip ratio, body-mass index, age and number of children in seven traditional societies. Sci. Rep. 7, 1–9.

Cairns, B.E., Gazerani, P., 2009. Sex-related differences in pain. Maturitas 63, 292–296.

Cardoso, C., Ellenbogen, M.A., Linnen, A.M., 2012. Acute intranasal oxytocin improves positive self-perceptions of personality. Psychopharmacology 220, 741–749.

Carter, C.S., 2007. Sex differences in oxytocin and vasopressin: implications for autism spectrum disorders? Behav. Brain Res. 176, 170–186.

Cashdan, E., 2008. Waist-to-hip ratio across cultures: trade-offs between androgen-and estrogen-dependent traits. Curr. Anthropol. 49, 1099–1107.

Cattrall, F.R., Vollenhoven, B.J., Weston, G.C., 2005. Anatomical evidence for *in utero* androgen exposure in women with polycystic ovary syndrome. Fertil. Steril. 84, 1689–1692.

Chaplin, G., Jablonski, N.G., 2009. Vitamin D and the evolution of human depigmentation. Am. J. Phys. Anthropol. 139, 451–461.

Chapron, C., Marcellin, L., Borghese, B., Santulli, P., 2019. Rethinking mechanisms, diagnosis and management of endometriosis. Nat. Rev. Endocrinol. 15, 666–682.

Chen, S.F., Yang, Y.C., Hsu, C.Y., Shen, Y.C., 2020. Risk of bipolar disorder in patients with endometriosis: a nationwide population-based cohort study. J. Affect. Disord. 270, 36–41.

Chen, W., Li, J., Song, Z., Yang, Z., Huo, J., Jiang, H., Huang, Q., … Zhang, Q., 2013. The melanocortin 1 receptor (MC1R) inhibits the inflammatory response in Raw 264.7 cells and atopic dermatitis (AD) mouse model. Mol. Biol. Rep. 40, 1987–1996.

Chiappa, P., Singh, S., 2017. Sexual dimorphism in waist-to-hip ratio and divorce frequency in human populations. Evol. Behav. Sci. 11, 221.

Chu, J., Gallos, I., Tobias, A., Tan, B., Eapen, A., Coomarasamy, A., 2018. Vitamin D and assisted reproductive treatment outcome: a systematic review and meta-analysis. Hum. Reprod. 33, 65–80.

Cicero, T.J., Nock, B., O'Connor, L., Meyer, E.R., 2002. Role of steroids in sex differences in morphine-induced analgesia: activational and organizational effects. J. Pharmacol. Exp. Ther. 300, 695–701.

Clark, M.M., Crews, D., Galef Jr, B.G., 1991. Concentrations of sex steroid hormones in pregnant and fetal Mongolian gerbils. Physiol. Behav. 49, 239–243.

Clark, M.M., Galef Jr, B.G., 1988. Effects of uterine position on rate of sexual development in female Mongolian gerbils. Physiol. Behav. 42, 15–18.

Clark, M.M., Galef Jr, B.G., 1998. Effects of intrauterine position on the behavior and genital morphology of litter-bearing rodents. Dev. Neuropsychol. 14, 197–211.

Clemens, T.L., Henderson, S.L., Adams, J.S., Holick, M.F., 1982. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. The Lancet 319, 74–76.

Clevers, H., Nusse, R., 2012. Wnt/β-catenin signaling and disease. Cell 149, 1192–1205.

Cloud, J.M., Perilloux, C., 2014. Bodily attractiveness as a window to women's fertility and reproductive value, in Weekes-Shackelford, V.A., Shackelford, T.K. (Eds.), Evolutionary Perspectives on Human Sexual Psychology and Behavior. Springer, pp. 135–152.

Cocksedge, K.A., Saravelos, S.H., Wang, Q., Tuckerman, E., Laird, S.M., Li, T.C., 2008. Does free androgen index predict subsequent pregnancy outcome in women with recurrent miscarriage? Hum. Reprod. 23, 797–802.

Coetzee, V., Faerber, S.J., Greeff, J.M., Lefevre, C.E., Re, D.E., Perrett, D.I., 2012. African perceptions of female attractiveness. PLoS One 7, e48116.

Collins, S.A., Missing, C., 2003. Vocal and visual attractiveness are related in women. Anim. Behav. 65, 997–1004.

Costello, M.F., Misso, M.L., Wong, J., Hart, R., Rombauts, L., Melder, A., … Teede, H.J., 2012. The treatment of infertility in polycystic ovary syndrome: a brief update. Aust. N. Z. J. Obstet. Gynaecol. 52, 400–403.

Crespi, B.J., 2016. Oxytocin, testosterone, and human social cognition. Biol. Rev. 91, 390–408.

Crespi, B.J., Go, M.C., 2015. Diametrical diseases reflect evolutionary-genetic tradeoffs: evidence from psychiatry, neurology, rheumatology, oncology and immunology. Evol. Med. Public Health 2015, 216–253.

Crestani, A., Abdel Wahab, C., Arfi, A., Ploteau, S., Kolanska, K., Breban, M., … Darai, E., 2021. A short anogenital distance on MRI is a marker of endometriosis. Hum. Reprod. Open 2021, hoab003.

Crestani, A., Arfi, A., Ploteau, S., Breban, M., Boudy, A.S., Bendifallah, S., … Darai, E., 2020. Anogenital distance in adult women is a strong marker of endometriosis: results of a prospective study with laparoscopic and histological findings. Hum. Reprod. Open 2020, hoaa023.

Crewther, B., Cook, C., Kilduff, L., Manning, J., 2015. Digit ratio (2D:4D) and salivary testosterone, oestradiol and cortisol levels under challenge: evidence for prenatal effects on adult endocrine responses. Early Hum. Dev. 91, 451–456.

Danilenko, K.V., Sergeeva, O.Y., Verevkin, E.G., 2011. Menstrual cycles are influenced by sunshine. Gynecol. Endocrinol. 27, 711–716.

Darwin, C., 1871. The Descent of Man, and Selection in Relation to Sex. 1981, Princeton University Press.

Day, F.R., Elks, C.E., Murray, A., Ong, K.K., Perry, J.R.B., 2015. Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: the UK Biobank study. Sci. Rep. 5, 1–12. https://doi.org/10.1038/srep11208.

de Mattos, R.M., Pereira, P.R., Barros, E.G., da Silva, J.H., Palmero, C.Y., da Costa, N.M., … Machado, D.E., 2016. Aberrant levels of Wnt/β-catenin pathway components in a rat model of endometriosis. Histol. Histpathol. 31, 933–942.

De Santa Barbara, P., Bonneaud, N., Boizet, B., Desclozeaux, M., Moniot, B., Sudbeck, P., … Berta, P., 1998. Direct interaction of SRY-related protein SOX9 and steroidogenic factor 1 regulates transcription of the human anti-Müllerian hormone gene. Mol. Cell. Biol. 18, 6653–6665.

Dean, A., Sharpe, R.M., 2013. Anogenital distance or digit length ratio as measures of fetal androgen exposure: relationship to male reproductive development and its disorders. J. Clin. Endocrinol. Metab. 98, 2230–2238.

Dekel, N., Gnainsky, Y., Granot, I., Mor, G., 2010. Inflammation and implantation. Am. J. Reprod. Immunol. 63, 17–21.

Dekel, N., Gnainsky, Y., Granot, I., Racicot, K., Mor, G., 2014. The role of inflammation for a successful implantation. Am. J. Reprod. Immunol. 72, 141–147.

Del Zotto, M., Pegna, A.J., 2017. Electrophysiological evidence of perceived sexual attractiveness for human female bodies varying in waist-to-hip ratio. Cogn. Affect. Behav. Neurosci. 17, 577–591.

Delaney, A., Keighren, M., Fleetwood-Walker, S.M., Jackson, I.J., 2010. Involvement of the melanocortin-1 receptor in acute pain and pain of inflammatory but not neuropathic origin. PLoS One 5, e12498.

DelPriore, D.J., Prokosch, M.L., Hill, S.E., 2017. The causes and consequences of women's competitive beautification, in: Fisher, M.L. (Ed.), Oxford Library of Psychology. The Oxford Handbook of Women and Competition. Oxford University Press, UK, pp. 577–595.

Dinsdale, N., Nepomnaschy, P., Crespi, B., 2021. The evolutionary biology of endometriosis. Evol. Med. Public Health eoab008. https://doi.org/10.1093/emph/eoab008.

Dinsdale, N.L., Crespi, B.J., 2017. Revisiting the wandering womb: oxytocin in endometriosis and bipolar disorder. Horm. Behav. 96, 69–83.

Dinsdale, N.L., Crespi, B.J., 2021 Endometriosis and PCOS are diametric disorders. Evol. Appl. (accepted pending minor revisions).

Diogenes, M.E., Bezerra, F.F., Rezende, E.P., Taveira, M.F., Normando, P., Pinhal, I., Donangelo, C., 2013. Infant and maternal bone status are associated in lactating adolescents when calcium intake is low but not following calcium plus vitamin D supplementation. FASEB J. 27, 850.5.

Dixson, B.J., Dixson, A.F., Bishop, P.J., Parish, A., 2010. Human physique and sexual attractiveness in men and women: a New Zealand–US comparative study. Arch. Sex. Behav. 39, 798–806.

Dixson, B.J., Dixson, A.F., Morgan, B., Anderson, M.J., 2007. Human physique and sexual attractiveness: sexual preferences of men and women in Bakossiland, Cameroon. Arch. Sex. Behav. 36, 369–375.

Dixson, B.J., Duncan, M., Dixson, A.F., 2015. The role of breast size and areolar pigmentation in perceptions of women's sexual attractiveness, reproductive health, sexual maturity, maternal nurturing abilities, and age. Arch. Sex. Behav. 44, 1685–1695.

Dixson, B.J., Vasey, P.L., Sagata, K., Sibanda, N., Linklater, W.L., Dixson, A.F., 2011. Men's preferences for women's breast morphology in New Zealand, Samoa, and Papua New Guinea. Arch. Sex. Behav. 40, 1271–1279.

Dong, Z., An, J., Xie, X., Wang, Z., Sun, P., 2019. Preoperative serum anti-Müllerian hormone level is a potential predictor of ovarian endometrioma severity and postoperative fertility. Eur. J. Obstet. Gynecol. Reprod. Biol. 240, 113–120.

Drickamer, L.C., 1996. Intra-uterine position and anogenital distance in house mice: consequences under field conditions. Anim. Behav. 51, 925–934.

Drickamer, L.C., Sessions Robinson, A., Mossman, C.A., 2001. Differential responses to same and opposite sex odors by adult house mice are associated with anogenital distance. Ethology 107, 509–519.

Dumesic, D.A., Goodarzi, M.O., Chazenbalk, G.D., Abbott, D.H., 2014. Intrauterine environment and PCOS. Semin. Reprod. Med. 32, 159.

Dumont, A., Robin, G., Catteau-Jonard, S., Dewailly, D., 2015. Role of Anti-Müllerian Hormone in pathophysiology, diagnosis and treatment of Polycystic Ovary Syndrome: a review. Reprod. Biol. Endocrinol. 13, 1–10.

Dunsworth, H., Eccleston, L., 2015. The evolution of difficult childbirth and helpless hominin infants. Ann. Rev. Anthropol. 44, 55–69.

Dural, O., Kurbanova, T., Yasa, C., Ugurlucan, F.G., Selvi, E., Ozdemir, P.K., Akhan, S.E., 2021. Idiopathic primary ovarian insufficiency is associated with anogenital distance, a marker for prenatal environment. Eur. J. Obstet. Gynecol. Reprod. Biol. 258, 304–308.

Eggert, J., Li, X., Sundquist, K., 2008. Country of birth and hospitalization for pelvic inflammatory disease, ectopic pregnancy, endometriosis, and infertility: a nationwide study of 2 million women in Sweden. Fertil. Steril. 90, 1019–1025.

Eklund, E., Ekström, L., Thörngren, J.O., Ericsson, M., Berglund, B., Hirschberg, A.L., 2020. Digit ratio (2D:4D) and physical performance in female olympic athletes. Front. Endocrinol. 11, 292.

Elias, P.M., Williams, M.L., 2013. Re-appraisal of current theories for the development and loss of epidermal pigmentation in hominins and modern humans. J. Hum. Evol. 64, 687.

Engel, S., Klusmann, H., Ditzen, B., Knaevelsrud, C., Schumacher, S., 2019. Menstrual cycle-related fluctuations in oxytocin concentrations: a systematic review and meta-analysis. Front. Neuroendocrinol. 52, 144–155.

Ertuğrul, B., Özener, B., Pawłowski, B., 2020. Prenatal exposure to oestrogens estimated by digit ratio (2d/4d) and breast size in young nulliparous women. Ann. Hum. Biol. 47, 81–84.

Escobar-Morreale, H.F., Álvarez-Blasco, F., Botella-Carretero, J.I., Luque-Ramírez, M., 2014. The striking similarities in the metabolic associations of female androgen excess and male androgen deficiency. Hum. Reprod. 29, 2083–2091.

Evans, J., Salamonsen, L.A., Winship, A., Menkhorst, E., Nie, G., Gargett, C.E., Dimitriadis, E., 2016. Fertile ground: human endometrial programming and lessons in health and disease. Nat. Rev. Endocrinol. 12, 654–667.

Evans, S.F., Kwok, Y., Solterbeck, A., Pyragius, C., Hull, M.L., Hutchinson, M.R., Rolan, P., 2021. The relationship between androgens and days per month of period pain, pelvic pain, headache, and TLR4 responsiveness of peripheral blood mononuclear cells in young women with dysmenorrhoea. J. Pain Res. 14, 585.

Fabregues, F., Gonzalez-Foruria, I., Peñarrubia, J., Carmona, F., 2018. Ovarian response is associated with anogenital distance in patients undergoing controlled ovarian stimulation for IVF. Hum. Reprod. 33, 1696-1704.

Farland, L.V., Missmer, S.A., Bijon, A., Gusto, G., Gelot, A., Clavel-Chapelon, F., … Kvaskoff, M., 2017. Associations among body size across the life course, adult height and endometriosis. Hum. Reprod. 32, 1732–1742.

Feinberg, D.R., DeBruine, L.M., Jones, B.C., Perrett, D.I., 2008. The role of femininity and averageness of voice pitch in aesthetic judgments of women's voices. Perception 37, 615–623.

Feinman, S., Gill, G.W., 1978. Sex differences in physical attractiveness preferences. J. Soc. Psychol. 105, 43–52.

Feldman, R., Bakermans-Kranenburg, M.J., 2017. Oxytocin: a parenting hormone. Curr. Opin. Psychol. 15, 13–18.

Feldman, R., Gordon, I., Zagoory-Sharon, O., 2011. Maternal and paternal plasma, salivary, and urinary oxytocin and parent–infant synchrony: considering stress and affiliation components of human bonding. Dev. Sci. 14, 752–761.

Filippou, P., Homburg, R., 2017. Is foetal hyperexposure to androgens a cause of PCOS? Hum. Reprod. Update 23, 421–432.

Fink, B., Grammer, K., Mitteroecker, P., Gunz, P., Schaefer, K., Bookstein, F.L., Manning, J.T., 2005. Second to fourth digit ratio and face shape. Proc. R. Soc. Lond. B Biol. Sci. 272, 1995–2001.

Fink, B., Neave, N., Manning, J.T., 2003. Second to fourth digit ratio, body mass index, waist-to-hip ratio, and waist-to-chest ratio: their relationships in heterosexual men and women. Ann. Hum. Biol. 30, 728–738.

Fisher, R.A., 1915. The evolution of sexual preference. Eugen. Rev. 7, 184.

Florio, P., Reis, F.M., Torres, P.B., Calonaci, F., Abrao, M.S., Nascimento, L.L., … Petraglia, F., 2009. High serum follistatin levels in women with ovarian endometriosis. Hum. Reprod. 24, 2600–2606.

Floyd, K., Pauley, P.M., Hesse, C., 2010. State and trait affectionate communication buffer adults' stress reactions. Comm. Monogr. 77, 618–636.

Ford, C.S., Beach, F.A., 1951. *Patterns of sexual behavior.* Harper and Paul B. Hoeber.

Frisancho, A.R., 1974. Triceps skin fold and upper arm muscle size norms for assessment of nutritional status. Am. J. Clin. Nutr. 27, 1052–1058.

Frost, P., 2007. Human skin-color sexual dimorphism: a test of the sexual selection hypothesis. Commentary and Authors' reply. Am. J.Phys. Anthropol. 133, 779–781.

Frost, P., 2014. The puzzle of European hair, eye, and skin color. Adv. Anthropol. 4, 46104.

Frost, P., Kleisner, K., Flegr, J., 2017. Health status by gender, hair color, and eye color: red-haired women are the most divergent. PLoS One 12, e0190238.

Fung, J.L., Hartman, T.J., Schleicher, R.L. and Goldman, M.B., 2017. Association of vitamin D intake and serum levels with fertility: results from the Lifestyle and Fertility Study. Fertility and Sterility, 108, 302-311.

Furnham, A., Dias, M., McClelland, A., 1998. The role of body weight, waist-to-hip ratio, and breast size in judgments of female attractiveness. Sex Roles 39, 311–326.

Furnham, A., Moutafi, J., Baguma, P., 2002. A cross-cultural study on the role of weight and waist-to-hip ratio on female attractiveness. Pers. Indiv. Diff. 32, 729–745.

Furnham, A., Petrides, K.V., Constantinides, A., 2005. The effects of body mass index and waist-to-hip ratio on ratings of female attractiveness, fecundity, and health. Pers. Indiv. Diff. 38, 1823–1834.

Furnham, A., Swami, V., Shah, K., 2006. Body weight, waist-to-hip ratio and breast size correlates of ratings of attractiveness and health. Pers. Indiv. Diff. 41, 443–454.

Gangestad, S.W., Scheyd, G.J., 2005. The evolution of human physical attractiveness. Ann. Rev. Anthropol. 34, 523–548.

García-Gómez, E., Vázquez-Martínez, E.R., Reyes-Mayoral, C., Cruz-Orozco, O.P., Camacho-Arroyo, I., Cerbón, M., 2020. Regulation of inflammation pathways and inflammasome by sex steroid hormones in endometriosis. Front. Endocrinol. 10, 935.

Garg, D., Tal, R., 2016. The role of AMH in the pathophysiology of polycystic ovarian syndrome. Reprod. BioMed. Online 33, 15–28.

Garitazelaia, A., Rueda-Martínez, A., Arauzo, R., de Miguel, J., Cilleros-Portet, A., Marí, S., … García-Santisteban, I., 2021. A systematic two-sample mendelian randomization analysis identifies shared genetic origin of endometriosis and associated phenotypes. Life 11, 24.

Gesink Law, D.C., Maclehose, R.F., Longnecker, M.P., 2007. Obesity and time to pregnancy. Hum. Reprod. 22, 414–420.

Gibson, D.A., Simitsidellis, I., Collins, F., Saunders, P.T., 2020. Androgens, oestrogens and endometrium: a fine balance between perfection and pathology. J. Endocrinol. 246, R75–R93.

Gitter, A.G., Lomranz, J., Saxe, L., Bar-Tal, Y., 1983. Perceptions of female physique characteristics by American and Israeli students. J. Soc. Psychol. 121, 7–13.

Gleicher, N., Kim, A., Weghofer, A., Kushnir, V.A., Shohat-Tal, A., Lazzaroni, E., … Barad, D.H., 2013. Hypoandrogenism in association with diminished functional ovarian reserve. Hum. Reprod. 28, 1084–1091.

Gomez, D., Huchard, E., Henry, P.Y., Perret, M., 2012. Mutual mate choice in a female-dominant and sexually monomorphic primate. Am. J. Phys. Anthropol. 147, 370–379.

Governini, L., Carrarelli, P., Rocha, A.L.L., De Leo, V., Luddi, A., Arcuri, F., … Petraglia, F., 2014. FOXL2 in human endometrium: hyperexpressed in endometriosis. Reprod. Sci. 21, 1249–1255.

Grillot, R.L., Simmons, Z.L., Lukaszewski, A.W., Roney, J.R., 2014. Hormonal and morphological predictors of women's body attractiveness. Evol. Hum. Behav. 35, 176–183.

Gueguen, N., 2007. Women's bust size and men's courtship solicitation. Body Image 4, 386–390.

Guldbrandsen, K., Håkonsen, L.B., Ernst, A., Toft, G., Lyngsø, J., Olsen, J., Ramlau-Hansen, C.H., 2014. Age of menarche and time to pregnancy. Hum. Reprod. 29, 2058–2064.

Guo, S.W., Mao, X., Ma, Q., Liu, X., 2013. Dysmenorrhea and its severity are associated with increased uterine contractility and overexpression of oxytocin receptor (OTR) in women with symptomatic adenomyosis. Fertil. Steril. 99, 231–240.

Gupta, S., Harlev, A., Agarwal, A., 2015. Endometriosis: A Comprehensive Update. Springer International Publishing.

Gurven, M., Costa, M., Trumble, B., Stieglitz, J., Beheim, B., Rodriguez, D.E., … Kaplan, H., 2016. Health costs of reproduction are minimal despite high fertility, mortality and subsistence lifestyle. Sci. Rep. 6, 1–10.

Haddadeen, C., Lai, C., Cho, S.Y., Healy, E., 2015. Variants of the melanocortin-1 receptor: do they matter clinically? Exp. Dermatol. 24, 5-9.

Halme, J., Hammond, M.G., Hulka, J.F., Raj, S.G., Talbert, L.M., 1984. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet. Gynecol. 64, 151–154.

Hamdan, A.L., Tabet, G., Fakhri, G., Sarieddine, D., Btaiche, R., Seoud, M., 2018. Effect of hormonal replacement therapy on voice. J. Voice 32, 116–121.

Hammond, G.L., 2017. Sex hormone-binding globulin and the metabolic syndrome, in: Winters S., Huhtaniemi I. (Eds.), Male Hypogonadism. Humana Press, pp. 305–324. https://doi-org.proxy.lib.sfu.ca/10.1007/978-3-319-53298-1_15.

Hannoun, A., Zreik, T., Husseini, S.T., Mahfoud, L., Sibai, A., Hamdan, A.L., 2011. Vocal changes in patients with polycystic ovary syndrome. J. Voice 25, 501–504.

Harada, T., 2013. Dysmenorrhea and endometriosis in young women. Yonago Acta Medica 56, 81–84.

Harmon, Q.E., Kissell, K., Jukic, A.M.Z., Kim, K., Sjaarda, L., Perkins, N.J., … Mumford, S.L., 2020. Vitamin D and reproductive hormones across the menstrual cycle. Hum. Reprod. 35, 413–423.

Hashmi, J.A., Davis, K.D., 2014. Deconstructing sex differences in pain sensitivity. Pain 155, 10–13.

Hassan, M.A., Killick, S.R., 2004. Negative lifestyle is associated with a significant reduction in fecundity. Fertil. Steril. 81, 384–392.

Havlíček, J., Třebický, V., Valentova, J.V., Kleisner, K., Akoko, R.M., Fialová, J., … Varella, M.A.C., 2017. Men's preferences for women's breast size and shape in four cultures. Evol. Hum. Behav. 38, 217–226.

Hayward, A.D., Nenko, I., Lummaa, V., 2015. Early-life reproduction is associated with increased mortality risk but enhanced lifetime fitness in pre-industrial humans. Proc. R. Soc. Lond. B Biol. Sci. 282, 20143053.

Hazell, G.G., Yao, S.T., Roper, J.A., Prossnitz, E.R., O'Carroll, A.M., Lolait, S.J., 2009. Localisation of GPR30, a novel G protein-coupled oestrogen receptor, suggests multiple functions in rodent brain and peripheral tissues. J. Endocrinol. 202, 223.

Heikkilä, M., Prunskaite, R., Naillat, F., Itäranta, P., Vuoristo, J., Leppäluoto, J., … Vainio, S., 2005. The partial female to male sex reversal in Wnt-4-deficient females involves induced expression of testosterone biosynthetic genes and testosterone production, and depends on androgen action. Endocrinology 146, 4016–4023.

Hernández-Peñalver, A.I., Sánchez-Ferrer, M.L., Mendiola, J., Adoamnei, E., Prieto-Sánchez, M.T., Corbalán-Biyang, S., … Torres-Cantero, A.M., 2018. Assessment of anogenital distance as a diagnostic tool in polycystic ovary syndrome. Reprod. BioMed. Online 37, 741–749.

Hernando, B., Ibarrola-Villava, M., Fernandez, L.P., Peña-Chilet, M., Llorca-Cardeñosa, M., Oltra, S.S., … Ribas, G., 2016a. Sex-specific genetic effects associated with pigmentation, sensitivity to sunlight, and melanoma in a population of Spanish origin. Biol. Sex Diff. 7, 1–9.

Hernando, B., Ibarrola-Villava, M., Peña Chilet, M., Alonso, S., Ribas, G., Martinez-Cadenas, C., 2016b. Sex and MC1R variants in human pigmentation: differences in tanning ability and sensitivity to sunlight between sexes. J. Dermatol. Sci. 84, 346–348.

Hochberg, Z.E., Gawlik, A., Walker, R.S., 2011. Evolutionary fitness as a function of pubertal age in 22 subsistence-based traditional societies. Int. J. Pediatr. Endocrinol. 2011, 1–7.

Hochberg, Z.E., Hochberg, I., 2019. Evolutionary perspective in rickets and vitamin D. Front. Endocrinol. 10, 306.

Hönekopp, J., Schuster, M., 2010. A meta-analysis on 2D:4D and athletic prowess: substantial relationships but neither hand out-predicts the other. Pers. Indiv. Diff. 48, 4–10.

Hotchkiss, A.K., Lambright, C.S., Ostby, J.S., Parks-Saldutti, L., Vandenbergh, J.G., Gray Jr, L.E., 2007. Prenatal testosterone exposure permanently masculinizes anogenital distance, nipple development, and reproductive tract morphology in female Sprague-Dawley rats. Toxicol. Sci. 96, 335–345.

Hrdy, S.B., 1997. Raising Darwin's consciousness. Hum. Nat. 8, 1–49.

Hrdy, S.B., 2009. Mothers and Others. Harvard University, Cambridge, MA.

Hu, B., Shen, N., Li, J.J., Kang, H., Hong, J., Fletcher, … Lu, Q., 2019. Genome-wide association study reveals sex-specific genetic architecture of facial attractiveness. PLoS Genet. 15, e1007973.

Hua, X.G., Hu, R., Hu, C.Y., Li, F.L., Jiang, W., Zhang, X.J., 2018. Associations between hypospadias, cryptorchidism and anogenital distance: systematic review and meta-analysis. Andrologia 50, e13152.

Huang, M., Li, X., Guo, P., Yu, Z., Xu, Y., Wei, Z., 2017. The abnormal expression of oxytocin receptors in the uterine junctional zone in women with endometriosis. Reprod. Biol. Endocrinol. 15, 1–10.

Huchard, E., Courtiol, A., Benavides, J.A., Knapp, L.A., Raymond, M., Cowlishaw, G., 2009. Can fertility signals lead to quality signals? Insights from the evolution of primate sexual swellings. Proc. R. Soc. Lond. B Biol. Sci. 276, 1889–1897.

Hughes, S.M., Dispenza, F., Gallup Jr, G.G., 2004. Ratings of voice attractiveness predict sexual behavior and body configuration. Evol. Hum. Behav. 25, 295–304.

Huhtinen, K., Desai, R., Ståhle, M., Salminen, A., Handelsman, D.J., Perheentupa, A., Poutanen, M., 2012. Endometrial and endometriotic concentrations of estrone and estradiol are determined by local metabolism rather than circulating levels. J. Clin. Endocrinol. Metab. 97, 4228–4235.

Huhtinen, K., Saloniemi-Heinonen, T., Keski-Rahkonen, P., Desai, R., Laajala, D., Ståhle, M., … Aittokallio, T., 2014. Intra-tissue steroid profiling indicates differential progesterone and testosterone metabolism in the endometrium and endometriosis lesions. J. Clin. Endocrinol. Metab. 99, E2188–E2197.

Human, L.J., Thorson, K.R., Mendes, W.B., 2016. Interactive effects between extraversion and oxytocin administration: implications for positive social processes. Soc. Psychol. Personal. Sci. 7, 735–744.

Hundt, J., 2016. Involvement of the WNT pathway in endometriosis. Doctoral dissertation, Technischen Universität Dortmund.

Hysi, P.G., Valdes, A.M., Liu, F., Furlotte, N.A., Evans, D.M., Bataille, V., … Smith, G.D., 2018. Genome-wide association meta-analysis of individuals of European ancestry identifies new loci explaining a substantial fraction of hair color variation and heritability. Nat. Genet. 50, 652–656.

Imamura, Y., Mizoguchi, Y., Nabeta, H., Haraguchi, Y., Matsushima, J., Kojima, N., … Monji, A., 2017. An association between belief in life after death and serum oxytocin in older people in rural Japan. Int. J. Geriatr. Psychiatry 32, 102–109.

Imterat, M., Agarwal, A., Esteves, S.C., Meyer, J., Harlev, A., 2019. Impact of Body Mass Index on female fertility and ART outcomes. Panminerva Med. 61, 58–67.

Jablonski, N.G., Chaplin, G., 2000. The evolution of human skin coloration. J. Hum. Evol. 39, 57–106.

Jablonski, N.G., Chaplin, G., 2010. Human skin pigmentation as an adaptation to UV radiation. Proc. Natl. Acad. Sci. U.S.A. 107, 8962–8968.

Jablonski, N.G., Chaplin, G., 2017. The colours of humanity: the evolution of pigmentation in the human lineage. Philos. Trans. R. Soc. Lond. B Biol. Sci. 372, 20160349.

Jackson, L.M., Mytinger, A., Roberts, E.K., Lee, T.M., Foster, D.L., Padmanabhan, V., Jansen, H.T., 2013. Developmental programming: postnatal steroids complete prenatal steroid actions to differentially organize the GnRH surge mechanism and reproductive behavior in female sheep. Endocrinology 154, 1612–1623.

Jäpelt, R.B., Jakobsen, J., 2013. Vitamin D in plants: a review of occurrence, analysis, and biosynthesis. Front. Plant Sci. 4, 136.

Jarrell, J., 2018. The significance and evolution of menstruation. Best Pract. Res. Clin. Obstet. Gynaecol. 50, 18–26.

Jasieńska, G., Ziomkiewicz, A., Ellison, P.T., Lipson, S.F., Thune, I., 2004. Large breasts and narrow waists indicate high reproductive potential in women. Proc. R. Soc. Lond. B Biol. Sci. 271, 1213–1217.

Jemström, H., Olsson, H., 1997. Breast size in relation to endogenous hormone levels, body constitution, and oral contraceptive use in healthy nulligravid women aged 19–25 years. Am. J. Epidemiol. 145, 571–580.

Jenabi, E., Khazaei, S., Veisani, Y., 2019. The association between body mass index and the risk of endometriosis: a meta-analysis. J. Endometr. Pelvic Pain Disord. 11, 55–61.

Jokela, M., 2009. Physical attractiveness and reproductive success in humans: evidence from the late 20th century United States. Evol. Hum. Behav. 30, 342–350.

Jonasson, T.H., Costa, T.M.D.R.L., Petterle, R.R., Moreira, C.A. and Borba, V.Z.C., 2020. Body composition in nonobese individuals according to vitamin D level. Plos ONE, 15, e0241858.

Jones, D., 1996. An evolutionary perspective on physical attractiveness. Evol. Anthropol. 5, 97–109.

Jordan, B.K., Shen, J.H.C., Olaso, R., Ingraham, H.A., Vilain, E., 2003. Wnt4 overexpression disrupts normal testicular vasculature and inhibits testosterone synthesis by repressing steroidogenic factor 1/β-catenin synergy. Proc. Natl. Acad. Sci. U.S.A. 100, 10866–10871.

Jukic, A.M.Z. and Harmon, Q.E., 2020. Accumulating evidence for vitamin D and conception. Fertil. Steril., 113, 330-331.

Jukic, A.M.Z., Baird, D.D., Weinberg, C.R., Wilcox, A.J., McConnaughey, D.R., Steiner, A.Z., 2019. Pre-conception 25-hydroxyvitamin D (25(OH)D) and fecundability. Hum. Reprod. 34, 2163–2172.

Jukic, A.M.Z., Steiner, A.Z., Baird, D.D., 2015. Lower plasma 25-hydroxyvitamin D is associated with irregular menstrual cycles in a cross-sectional study. Reprod. Biol. Endocrinol. 13, 1–6.

Kasapoglu, I., Ata, B., Uyaniklar, O., Seyhan, A., Orhan, A., Oguz, S.Y., Uncu, G., 2018. Endometrioma-related reduction in ovarian reserve (ERROR): a prospective longitudinal study. Fertil. Steril. 110, 122–127.

Kashimada, K., Pelosi, E., Chen, H., Schlessinger, D., Wilhelm, D., Koopman, P., 2011. FOXL2 and BMP2 act cooperatively to regulate follistatin gene expression during ovarian development. Endocrinology 152, 272–280.

Kim, T.B., Kim, K.H., 2016. Why is digit ratio correlated to sports performance? J. Exerc. Rehabil. 12, 515.

Klein, S.L., Flanagan, K.L., 2016. Sex differences in immune responses. Nat. Rev. Immunol. 16, 626.

Kleisner, K., Kočnar, T., Tureček, P., Stella, D., Akoko, R.M., Třebický, V., Havlíček, J., 2017. African and European perception of African female attractiveness. Evol. Hum. Behav. 38, 744–755.

Klimek, M., Galbarczyk, A., Nenko, I., Jasienska, G., 2016. Women with more feminine digit ratio (2D:4D) have higher reproductive success. Am. J. Phys. Anthropol. 160, 549–553.

Kobayashi, M.Y., 2017. Male mate choice among captive long-tailed macaques (*Macaca fascicularis*). Int. J. Comp. Psychol. 30.

Kočnar, T., Saribay, S.A., Kleisner, K., 2019. Perceived attractiveness of Czech faces across 10 cultures: associations with sexual shape dimorphism, averageness, fluctuating asymmetry, and eye color. PLoS One 14, e0225549.

Kościński, K., 2007. Facial attractiveness: general patterns of facial preferences. Anthropol. Rev. 70, 45–79.

Kościński, K., Makarewicz, R., Bartoszewicz, Z., 2020. Stereotypical and actual associations of breast size with mating-relevant traits. Arch. Sex. Behav. 49, 821–836.

Koven, N.S., Max, L.K., 2014. Basal salivary oxytocin level predicts extra- but not intra-personal dimensions of emotional intelligence. Psychoneuroendocrinology 44, 20–29.

Kunitake, Y., Imamura, Y., Mizoguchi, Y., Matsushima, J., Tateishi, H., Murakawa-Hirachi, T., … Monji, A., 2020. Serum oxytocin levels and logical memory in older people in rural Japan. J. Geriatr. Psychiatry Neurol. 0891988720915526.

Kunz, G., Beil, D., Huppert, P., Leyendecker, G., 2007. Oxytocin–a stimulator of directed sperm transport in humans. Reprod. BioMed. Online 14, 32–39.

Kunz, G., Leyendecker, G., 2002. Uterine peristaltic activity during the menstrual cycle: characterization, regulation, function and dysfunction. Reprod. BioMed. Online 4, 5–9.

Kvaskoff, M., Han, J., Qureshi, A.A., Missmer, S.A., 2014. Pigmentary traits, family history of melanoma and the risk of endometriosis: a cohort study of US women. Int. J. Epidemiol. 43, 255–263.

Kvaskoff, M., Mesrine, S., Clavel-Chapelon, F., Boutron-Ruault, M.C., 2009. Endometriosis risk in relation to naevi, freckles and skin sensitivity to sun exposure: the French E3N cohort. Int. J. Epidemiol. 38, 1143–1153.

Laisk, T., Kukuškina, V., Palmer, D., Laber, S., Chen, C.Y., Ferreira, T., … Lippincott, M., 2018. Large-scale meta-analysis highlights the hypothalamic–pituitary–gonadal axis in the genetic regulation of menstrual cycle length. Hum. Mol. Genet. 27, 4323–4332.

Landauer, M.R., Attas, A.I., Liu, S., 1981. Effects of prenatal and neonatal androgen on estrous cyclicity and attractiveness of female hamsters. Physiol. Behav. 27, 419–424.

Lao, O., De Gruijter, J.M., van Duijn, K., Navarro, A., Kayser, M., 2007. Signatures of positive selection in genes associated with human skin pigmentation as revealed from analyses of single nucleotide polymorphisms. Ann. Hum. Genet. 71, 354–369.

Lassek, W.D., Gaulin, S.J., 2019. Evidence supporting nubility and reproductive value as the key to human female physical attractiveness. Evol. Hum. Behav. 40, 408–419.

Latreille, J., Ezzedine, K., Elfakir, A., Ambroisine, L., Gardinier, S., Galan, P., … Guinot, C., 2009. MC1R gene polymorphism affects skin color and phenotypic features related to sun sensitivity in a population of French adult women. Photochem. Photobiol. 85, 1451–1458.

Lavery, R., Lardenois, A., Ranc-Jianmotamedi, F., Pauper, E., Gregoire, E.P., Vigier, C., … Chaboissier, M.C., 2011. XY Sox9 embryonic loss-of-function mouse mutants show complete sex reversal and produce partially fertile XY oocytes. Dev. Biol. 354, 111–122.

Law Smith, M.J., Perrett, D.I., Jones, B.C., Cornwell, R.E., Moore, F.R., Feinberg, D.R., … Pitman, R.M., 2006. Facial appearance is a cue to oestrogen levels in women. Proc. R. Soc. Lond. B Biol. Sci. 273, 135–140.

Lebovic, D.I., Mueller, M.D., Taylor, R.N., 2001. Immunobiology of endometriosis. Fertil. Steril. 75, 1–10.

Lee, A.J., Mitchem, D.G., Wright, M.J., Martin, N.G., Keller, M.C., Zietsch, B.P., 2014. Genetic factors that increase male facial masculinity decrease facial attractiveness of female relatives. Psychol. Sci. 25, 476–484.

Levrero, F., Mathevon, N., Pisanski, K., Gustafsson, E., Reby, D., 2018. The pitch of babies' cries predicts their voice pitch at age 5. Biol. Lett. 14, 20180065.

Levy, J.R., Faber, K.A., Ayyash, L., Hughes Jr, C.L., 1995. The effect of prenatal exposure to the phytoestrogen genistein on sexual differentiation in rats. Proc. Soc. Exp. Biol. Med. 208, 60–66.

Leyendecker, G., Kunz, G., Herbertz, M., Beil, D., Huppert, P., Mall, G., … Wildt, L., 2004. Uterine peristaltic activity and the development of endometriosis. Annu. N.Y. Acad. Sci. 1034, 338–355.

Li, E.P., Min, H.J., Belk, R.W., 2008. Skin lightening and beauty in four Asian cultures, in: Lee, A.Y., Soman, D. (Eds.), NA - Advances in Consumer Research Volume 35. Association for Consumer Research, Duluth, MN, pp. 444–449.

Liang, Y., Li, Y., Liu, K., Chen, P., Wang, D., 2016. Expression and significance of WNT4 in ectopic and eutopic endometrium of human endometriosis. Reprod. Sci. 23, 379–385.

Liedman, R., Hansson, S.R., Howe, D., Igidbashian, S., McLeod, A., Russell, R.J., Åkerlund, M., 2008. Reproductive hormones in plasma over the menstrual cycle in primary dysmenorrhea compared with healthy subjects. Gynecol. Endocrinol. 24, 508–513.

Liem, E.B., Joiner, T.V., Tsueda, K., Sessler, D.I., 2005. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. J. Am. Soc. Anesthesiol. 102, 509–514.

Lin, Y.H., Chen, Y.H., Chang, H.Y., Au, H.K., Tzeng, C.R., Huang, Y.H., 2018. Chronic niche inflammation in endometriosis-associated infertility: current understanding and future therapeutic strategies. Int. J. Mol. Sci. 19, 2385.

Little, A.C., Jones, B.C., DeBruine, L.M., 2011. Facial attractiveness: evolutionary based research. Philos. Trans. R. Soc. Lond. B Biol. Sci. 366, 1638–1659.

Liu, C., Xu, X., Huo, X., 2014. Anogenital distance and its application in environmental health research. Environ. Sci. Pollut. Res. 21, 5457–5464.

Liu, F., Bessonova, L., Taylor, T.H., Ziogas, A., Meyskens Jr, F.L., Anton-Culver, H., 2013. A unique gender difference in early onset melanoma implies that in addition to ultraviolet light exposure other causative factors are important. Pigment Cell Melanoma Res. 26, 128–135.

Liu, F., Hamer, M.A., Deelen, J., Lall, J.S., Jacobs, L., van Heemst, D., … Zeng, C., 2016. The MC1R gene and youthful looks. Curr. Biol. 26, 1213–1220.

Logan, P.C., Yango, P., Tran, N.D., 2018. Endometrial stromal and epithelial cells exhibit unique aberrant molecular defects in patients with endometriosis. Reprod. Sci. 25, 140–159.

Lu, Q., Shen, H., Li, Y., Zhang, C., Wang, C., Chen, X., … Wei, L., 2014. Low testosterone levels in women with diminished ovarian reserve impair embryo implantation rate: a retrospective case-control study. J. Assist. Reprod. Genet. 31, 485–491.

Lucas, P.D., Donohoe, S.M., Thody, A.J., 1982. The role of estrogen and progesterone in the control of preputial gland sex attractant odors in the female rat. Physiol. Behav. 28, 601–607.

Lujan, M.E., Bloski, T.G., Chizen, D.R., Lehotay, D.C., Pierson, R.A., 2010. Digit ratios do not serve as anatomical evidence of prenatal androgen exposure in clinical phenotypes of polycystic ovary syndrome. Hum. Reprod. 25, 204–211.

Lummaa, V., Pettay, J.E., Russell, A.F., 2007. Male twins reduce fitness of female co-twins in humans. Proc. Natl. Acad. Sci. U.S.A. 104, 10915–10920.

Lutchmaya, S., Baron-Cohen, S., Raggatt, P., Knickmeyer, R., Manning, J.T., 2004. 2nd to 4th digit ratios, fetal testosterone and estradiol. Early Hum. Dev. 77, 23–28.

Lv, P.P., Jin, M., Rao, J.P., Chen, J., Wang, L.Q., Huang, C.C., … Feng, C., 2020. Role of anti-Müllerian hormone and testosterone in follicular growth: a cross-sectional study. BMC Endocr. Disord. 20, 1–10.

Lycett, J.E., Dunbar, R.I.M., Voland, E., 2000. Longevity and the costs of reproduction in a historical human population. Proc. R. Soc. Lond. B Biol. Sci. 267, 31–35.

Maatouk, D.M., DiNapoli, L., Alvers, A., Parker, K.L., Taketo, M.M., Capel, B., 2008. Stabilization of β-catenin in XY gonads causes male-to-female sex-reversal. Hum. Mol. Genet. 17, 2949–2955.

Manning, J., Kilduff, L., Cook, C., Crewther, B., Fink, B., 2014. Digit ratio (2D:4D): a biomarker for prenatal sex steroids and adult sex steroids in challenge situations. Front. Endocrinol. 5, 9.

Manning, J.T., Barley, L., Walton, J., Lewis-Jones, D.I., Trivers, R.L., Singh, D., … Soler, M., 2000. The 2nd:4th digit ratio, sexual dimorphism, population differences, and reproductive success: evidence for sexually antagonistic genes? Evol. Hum. Behav. 21, 163–183.

Manning, J.T., Bundred, P.E., Mather, F.M., 2004. Second to fourth digit ratio, sexual selection, and skin colour. Evol. Hum. Behav. 25, 38–50.

Manning, J.T., Fink, B., 2008. Digit ratio (2D:4D), dominance, reproductive success, asymmetry, and sociosexuality in the BBC Internet Study. Am. J. Hum. Biol. 20, 451–461.

Marazziti, D., Baroni, S., Mucci, F., Piccinni, A., Moroni, I., Giannaccini, G., … Dell'Osso, L., 2019. Sex-related differences in plasma oxytocin levels in humans. Clin. Pract. Epidemiol. Ment. Health 15, 58.

Marazziti, D., Dell'Osso, B., Baroni, S., Mungai, F., Catena, M., Rucci, P., … Italiani, P., 2006. A relationship between oxytocin and anxiety of romantic attachment. Clin. Pract. Epidemiol. Ment. Health 2, 1–6.

Marcinkowska, U.M., Kozlov, M.V., Cai, H., Contreras-Garduño, J., Dixson, B.J., Oana, G.A., … Prasai, K., 2014. Cross-cultural variation in men's preference for sexual dimorphism in women's faces. Biol. Lett. 10, 20130850.

Marcinkowska, U.M., Rantala, M.J., Lee, A.J., Kozlov, M.V., Aavik, T., Cai, H., … Onyishi, I.E., 2019. Women's preferences for men's facial masculinity are strongest under favorable ecological conditions. Sci. Rep. 9, 1–10.

Maroñas, O., Söchtig, J., Ruiz, Y., Phillips, C., Carracedo, A., Lareu, M.V., 2015. The genetics of skin, hair, and eye color variation and its relevance to forensic pigmentation predictive tests. Forensic Sci. Rev. 27, 13–40.

Martinez-Cadenas, C., Peña-Chilet, M., Ibarrola-Villava, M., Ribas, G., 2013. Gender is a major factor explaining discrepancies in eye colour prediction based on HERC2/OCA2 genotype and the IrisPlex model. Forensic Sci. Int. Genet. 7, 453–460.

Matalliotakis, I.M., Cakmak, H., Fragouli, Y.G., Goumenou, A.G., Mahutte, N.G., Arici, A., 2008. Epidemiological characteristics in women with and without endometriosis in the Yale series. Arch. Gynecol. Obstet. 277, 389–393.

Matsuzaki, S., Botchorishvili, R., Pouly, J.L., Canis, M., 2014. Targeting the Wnt/β-catenin pathway in endometriosis: a potentially effective approach for treatment and prevention. Mol. Cell. Ther. 2, 1–7.

Maybin, J.A., Critchley, H.O., 2015. Menstrual physiology: implications for endometrial pathology and beyond. Hum. Reprod. Update 21, 748–761.

Mayer, C., Windhager, S., Schaefer, K., Mitteroecker, P., 2017. BMI and WHR are reflected in female facial shape and texture: a geometric morphometric image analysis. PLoS One 12, e0169336.

McCann, S.E., Freudenheim, J.L., Darrow, S.L., Batt, R.E., Zielezny, M.A., 1993. Endometriosis and body fat distribution. Obstet. Gynecol. 82, 545–549.

McCoy, S.J., Shirley, B.A., 1992. Effects of prenatal administration of testosterone and cortisone on the reproductive system of the female rat. Life Sci. 50, 621–628.

McDermott, N.J., Gandelman, R., Reinisch, J.M., 1978. Contiguity to male fetuses influences ano-genital distance and time of vaginal opening in mice. Physiol. Behav. 20, 661–663.

McKinnon, C.J., Hatch, E.E., Rothman, K.J., Mikkelsen, E.M., Wesselink, A.K., Hahn, K.A., Wise, L.A., 2016. Body mass index, physical activity and fecundability in a North American preconception cohort study. Fertil. Steril. 106, 451–459.

Medland, S.E., Loehlin, J.C., Willemsen, G., Hatemi, P.K., Keller, M.C., Boomsma, D.I., … Martin, N.G., 2008. Males do not reduce the fitness of their female co-twins in contemporary samples. Twin Res. Hum. Genet. 11, 481–487.

Mendiola, J., Roca, M., Mínguez-Alarcón, L., Mira-Escolano, M.P., López-Espín, J.J., Barrett, E.S., … Torres-Cantero, A.M., 2012. Anogenital distance is related to ovarian follicular number in young Spanish women: a cross-sectional study. Environ. Health, 11, 1–8.

Mendiola, J., Sánchez-Ferrer, M.L., Jiménez-Velázquez, R., Cánovas-López, L., Hernández-Peñalver, A.I., Corbalán-Biyang, S., … Torres-Cantero, A.M., 2016. Endometriomas and deep infiltrating endometriosis in adulthood are strongly associated with anogenital distance, a biomarker for prenatal hormonal environment. Hum. Reprod. 31, 2377–2383.

Middeldorp, C.M., De Moor, M.H.M., McGrath, L.M., Gordon, S.D., Blackwood, D.H., Costa, P.T., … Tanaka, T., 2011. The genetic association between personality and major depression or bipolar disorder. A polygenic score analysis using genome-wide association data. Transl. Psychiatry 1, e50–e50.

Mills, S.C., Koskela, E. and Mappes, T., 2012. Intralocus sexual conflict for fitness: sexually antagonistic alleles for testosterone. Proc. R. Soc. Lond. B Biol. Sci. 279, 1889-1895.

Mira-Escolano, M.P., Mendiola, J., Mínguez-Alarcón, L., Melgarejo, M., Cutillas-Tolín, A., Roca, M., … Torres-Cantero, A.M., 2014a. Longer anogenital distance is associated with higher testosterone levels in women: a cross-sectional study. BJOG 121, 1359–1364.

Mira-Escolano, M.P., Mendiola, J., Mínguez-Alarcón, L., Roca, M., Cutillas-Tolín, A., López-Espín, J.J., Torres-Cantero, A.M., 2014b. Anogenital distance of women in relation to their mother's gynaecological characteristics before or during pregnancy. Reprod. BioMed. Online 28, 209–215.

Misao, R., Hori, M., Ichigo, S., Fujimoto, J., Tamaya, T., 1995. Levels of sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG) messenger ribonucleic acid (mRNAs) in ovarian endometriosis. Reprod. Nutr. Dev. 35, 155–165.

Missmer, S.A., Hankinson, S.E., Spiegelman, D., Barbieri, R.L., Marshall, L.M., Hunter, D.J., 2004. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am. J. Epidemiol. 160, 784–796.

Missmer, S.A., Spiegelman, D., Hankinson, S.E., Malspeis, S., Barbieri, R.L., Hunter, D.J., 2006. Natural hair color and the incidence of endometriosis. Fertil. Steril. 85, 866–870.

Miyamoto, N., Yoshida, M., Kuratani, S., Matsuo, I., Aizawa, S., 1997. Defects of urogenital development in mice lacking Emx2. Development 124, 1653–1664.

Mogil, J.S., Wilson, S.G., Chesler, E.J., Rankin, A.L., Nemmani, K.V., Lariviere, W.R., … Ness, T.J., 2003. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc. Natl. Acad. Sci. U.S.A. 100, 4867–4872.

Mokkonen, M., Kokko, H., Koskela, E., Lehtonen, J., Mappes, T., Martiskainen, H. and Mills, S.C., 2011. Negative frequency-dependent selection of sexually antagonistic alleles in *Myodes glareolus*. Science 334, 972-974.

Monclús, R., Blumstein, D.T., 2012. Litter sex composition affects life-history traits in yellow-bellied marmots. J. Anim. Ecol. 81, 80–86.

Monclús, R., von Holst, D., Blumstein, D.T., Rödel, H.G., 2014. Long-term effects of litter sex ratio on female reproduction in two iteroparous mammals. Funct. Ecol. 28, 954–962.

Mondragón-Ceballos, R., García Granados, M.D., Cerda-Molina, A.L., Chavira-Ramírez, R., Hernández-López, L.E., 2015. Waist-to-hip ratio, but not body mass index, is associated with testosterone and estradiol concentrations in young women. Int. J. Endocrinol. 2015, 654046.

Moraloglu, O., Tonguc, E., Var, T., Zeyrek, T., Batıoglu, S., 2010. Treatment with oxytocin antagonists before embryo transfer may increase implantation rates after IVF. Reprod. BioMed. Online 21, 338–343.

Muehlenbein, M.P., Bribiescas, R.G., 2005. Testosterone-mediated immune functions and male life histories. Am. J. Hum. Biol. 17, 527–558.

Muehlenbein, M.P., Watts, D.P., 2010. The costs of dominance: testosterone, cortisol and intestinal parasites in wild male chimpanzees. BioPsychoSoc. Med. 4, 1–12.

Muller, M.N., Thompson, M.E., Wrangham, R.W., 2006. Male chimpanzees prefer mating with old females. Curr. Biol. 16, 2234–2238.

Mulligan, M.L., Felton, S.K., Riek, A.E., Bernal-Mizrachi, C., 2010. Implications of vitamin D deficiency in pregnancy and lactation. Am. J. Obstet. Gynecol. 202, 429–e1.

Murphy, B.D., 2010. Revisiting reproduction: what a difference a gene makes. Nat. Med. 16, 527–529.

Muzii, L., Di Tucci, C., Di Feliciantonio, M., Galati, G., Di Donato, V., Musella, A., … Panici, P.B., 2018. Antimüllerian hormone is reduced in the presence of ovarian endometriomas: a systematic review and meta-analysis. Fertil. Steril. 110, 932–940.

Nakahashi, W., Horiuchi, S., Ihara, Y., 2018. Estimating hominid life history: the critical interbirth interval. Popul. Ecol. 60, 127–142.

Navarro, G., Allard, C., Xu, W., Mauvais-Jarvis, F., 2015. The role of androgens in metabolism, obesity, and diabetes in males and females. Obesity 23, 713–719.

Newton-Bishop, J.A., Chang, Y.M., Elliott, F., Chan, M., Leake, S., Karpavicius, B., … Elder, D.E., 2011. Relationship between sun exposure and melanoma risk for tumours in different body sites in a large case-control study in a temperate climate. Eur. J. Cancer 47, 732–741.

Nishizato, M., Fujisawa, T.X., Kosaka, H., Tomoda, A., 2017. Developmental changes in social attention and oxytocin levels in infants and children. Sci. Rep. 7, 1–10.

Nnoaham, K.E., Webster, P., Kumbang, J., Kennedy, S.H., Zondervan, K.T., 2012. Is early age at menarche a risk factor for endometriosis? A systematic review and meta-analysis of case-control studies. Fertil. Steril. 98, 702–712.

Nunn, C.L., 1999. The evolution of exaggerated sexual swellings in primates and the graded-signal hypothesis. Anim. Behav. 58, 229–246.

Okabe, S., Kitano, K., Nagasawa, M., Mogi, K., Kikusui, T., 2013. Testosterone inhibits facilitating effects of parenting experience on parental behavior and the oxytocin neural system in mice. Physiol. Behav. 118, 159–164.

Okon, M.A., Laird, S.M., Tuckerman, E.M., Li, T.C., 1998. Serum androgen levels in women who have recurrent miscarriages and their correlation with markers of endometrial function. Fertil. Steril. 69, 682–690.

Ono, Y.J., Tanabe, A., Nakamura, Y., Yamamoto, H., Hayashi, A., Tanaka, T., … Ohmichi, M., 2014. A low-testosterone state associated with endometrioma leads to the apoptosis of granulosa cells. PLoS One 9, e115618.

Orihashi, R., Mizoguchi, Y., Imamura, Y., Yamada, S., Ueno, T., Monji, A., 2020. Oxytocin and elderly MRI-based hippocampus and amygdala volume: a 7-year follow-up study. Brain Comm. 2, fcaa081.

Ottolina, J., Schimberni, M., Makieva, S., Bartiromo, L., Fazia, T., Bernardinelli, L., … Gentilini, D., 2020. Early-life factors, *in-utero* exposures and endometriosis risk: a meta-analysis. Reprod. BioMed. Online 41, 279–289.

Pabalan, N., Salvador, A., Jarjanazi, H., Christofolini, D.M., Barbosa, C.P., Bianco, B., 2014. Association of the progesterone receptor gene polymorphism (PROGINS) with endometriosis: a meta-analysis. Arch. Gynecol. Obstet. 290, 1015–1022.

Palmer, J.R., Boggs, D.A., Hatch, E.E., Troisi, R., Titus-Ernstoff, L., Strohsnitter, W.C., … Hoover, R.N., 2013. Prenatal DES exposure in relation to breast size. Cancer Causes Control 24, 1757–1761.

Palmer, J.S., Duffy, D.L., Box, N.F., Aitken, J.F., O'Gorman, L.E., Green, A.C., … Sturm, R.A., 2000. Melanocortin-1 receptor polymorphisms and risk of melanoma: is the association explained solely by pigmentation phenotype? Am. J. Hum. Genet. 66, 176–186.

Pandit, V.K., Setiya, M., Yadav, S., Jehan, M., 2016. Digit ratio (2D:4D): a potential anatomical biomarker for predicting the risk of development of polycystic ovarian syndrome. IOSR J. Dent. Med. Sci. 15, 58–64.

Panidis, D., Kokkinos, T., Vavilis, D., Rousso, D., Tantanassis, T., Kalogeropoulos, A., 1993. SHBG serum level in women with endometriosis before, during and after long-term danazol therapy. Geburtshilfe und Frauenheilkunde 53, 121–124.

Parma, P., Radi, O., Vidal, V., Chaboissier, M.C., Dellambra, E., Valentini, S., … Camerino, G., 2006. R-spondin1 is essential in sex determination, skin differentiation and malignancy. Nat. Genet. 38, 1304–1309.

Parra, E.J., 2007. Human pigmentation variation: evolution, genetic basis, and implications for public health. Am. J. Phys. Anthropol. 134, 85–105.

Pasco, J.A., Henry, M.J., Nicholson, G.C., Brennan, S.L., Kotowicz, M.A., 2009. Behavioural and physical characteristics associated with vitamin D status in women. Bone 44, 1085–1091.

Passeron, T., Valencia, J.C., Bertolotto, C., Hoashi, T., Le Pape, E., Takahashi, K., … Hearing, V.J., 2007. SOX9 is a key player in ultraviolet B-induced melanocyte differentiation and pigmentation. Proc. Natl. Acad. Sci. U.S.A. 104, 13984–13989.

Pattie, M.A., Murdoch, B.E., Theodoros, D., Forbes, K., 1998. Voice changes in women treated for endometriosis and related conditions: the need for comprehensive vocal assessment. J. Voice 12, 366–371.

Pavan, W.J., Sturm, R.A., 2019. The genetics of human skin and hair pigmentation. Annu. Rev. Genomics Hum. Genet. 20, 41–72.

Pawłowski B., G Boothroyd, L., I Perrett, D. and Kluska, S., 2008. Is female attractiveness related to final reproductive success?. Collegium antropologicum 32, 457-460.

Pawłowski, B., Dunbar, R.I., 2005. Waist-to-hip ratio versus body mass index as predictors of fitness in women. Hum. Nat. 16, 164–177.

Pazhohan, A., Amidi, F., Akbari-Asbagh, F., Seyedrezazadeh, E., Farzadi, L., Khodarahmin, M., … Sobhani, A., 2018. The Wnt/β-catenin signaling in endometriosis, the expression of total and active forms of β-catenin, total and inactive forms of glycogen synthase kinase-3β, WNT7a and DICKKOPF-1. Eur. J. Obstet. Gynecol. Reprod. Biol. 220, 1–5.

Pazhohan, A., Danaei-Mehrabad, S., Mohamad-Rezaeii, Z., Amidi, F., Khodarahmian, M., Shabani Nashtaei, M., … Farajzadeh, M.A., 2021. The modulating effects of vitamin D on the activity of β-catenin in the endometrium of women with endometriosis: a randomized exploratory trial. Gynecol. Endocrinol. 37, 278–282.

Pellicer, A., Valbuena, D., Bauset, C., Albert, C., Bonilla-Musoles, F., Remohí, J., Simón, C., 1998. The follicular endocrine environment in stimulated cycles of women with endometriosis: steroid levels and embryo quality. Fertil. Steril. 69, 1135–1141.

Pergola, C., Rogge, A., Dodt, G., Northoff, H., Weinigel, C., Barz, D., … Werz, O., 2011. Testosterone suppresses phospholipase D, causing sex differences in leukotriene biosynthesis in human monocytes. FASEB J. 25, 3377–3387.

Perlman, S., Toledano, Y., Kivilevitch, Z., Halevy, N., Rubin, E., Gilboa, Y., 2020. Foetal sonographic anogenital distance is longer in polycystic ovary syndrome mothers. J. Clin. Med. 9, 2863.

Perret, M., 2019. Litter sex composition affects first reproduction in female grey mouse lemurs (*Microcebus murinus*). Physiol. Behav. 208, 112575.

Peters, H.E., Laeven, C.H., Trimbos, C.J., van de Ven, P.M., Verhoeven, M.O., Schats, R., … Lambalk, C.B., 2020. Anthropometric biomarkers for abnormal prenatal reproductive hormone exposure in women with Mayer-Rokitanksy-Küster-Hauser syndrome, polycystic ovary syndrome, and endometriosis. Fertil. Steril. 114, 1297–1305.

Pflüger, L.S., Oberzaucher, E., Katina, S., Holzleitner, I.J., Grammer, K., 2012. Cues to fertility: perceived attractiveness and facial shape predict reproductive success. Evol. Hum. Behav. 33, 708–714.

Pijnenborg, R., 2002. Implantation and immunology: maternal inflammatory and immune cellular responses to implantation and trophoblast invasion. Reprod. BioMed. Online 4, 14–17.

Pisanski, K., Jones, B.C., Fink, B., O'Connor, J.J., DeBruine, L.M., Röder, S., Feinberg, D.R., 2016. Voice parameters predict sex-specific body morphology in men and women. Anim. Behav. 112, 13–22.

Ponomarenko, I., Reshetnikov, E., Polonikov, A., Verzilina, I., Sorokina, I., Elgaeva, E.E., … Churnosov, M., 2020. Candidate genes for age at menarche are associated with endometriosis. Reprod. BioMed. Online 41, 943–956.

Prizant, H., Gleicher, N., Sen, A., 2014. Androgen actions in the ovary: balance is key. J. Endocrinol. 222, R141–R151.

Probst, F., Bobst, C., Lobmaier, J.S., 2016. Testosterone-to-oestradiol ratio is associated with female facial attractiveness. Q. J. Exp. Psychol. 69, 89–99.

Puts, D.A., 2010. Beauty and the beast: mechanisms of sexual selection in humans. Evol. Hum. Behav. 31, 157–175.

Puts, D.A., Jones, B.C., DeBruine, L.M., 2012. Sexual selection on human faces and voices. J. Sex Res. 49, 227–243.

Qian, W., Zhu, T., Tang, B., Yu, S., Hu, H., Sun, W., … Mao, C., 2014. Decreased circulating levels of oxytocin in obesity and newly diagnosed type 2 diabetic patients. J. Clin. Endocrinol. Metab. 99, 4683–4689.

Quilty, L.C., Sellbom, M., Tackett, J.L., Bagby, R.M., 2009. Personality trait predictors of bipolar disorder symptoms. Psychiatry Res. 169, 159–163.

Rae, M., Grace, C., Hogg, K., Wilson, L.M., McHaffie, S.L., Ramaswamy, S., … Duncan, C., 2013. The pancreas is altered by *in utero* androgen exposure: implications for clinical conditions such as polycystic ovary syndrome (PCOS). PLoS One 8, e56263.

Rahmioglu, N., Nyholt, D.R., Morris, A.P., Missmer, S.A., Montgomery, G.W., Zondervan, K.T., 2014. Genetic variants underlying risk of endometriosis: insights from meta-analysis of eight genome-wide association and replication datasets. Hum. Reprod. Update 20, 702–716.

Rahmioglu, N., Banasik, K., Christofidou, P., Danning, R., Galarneau, G., Ayush, G., … Zondervan, K.T., 2018. Large-scale genome-wide association meta-analysis of endometriosis reveals 13 novel loci and genetically-associated comorbidity with other pain conditions. BioRxiv 406967. https://doi.org/10.1101/406967.

Rahmioglu, N., Banasik, K., Christofidou, P., Danning, R., Galarneau, G., Giri, A., ... Zondervan, T.K. 2018. Large-scale genome-wide association meta-analysis of endometriosis reveals 13 novel loci and genetically-associated comorbidity with other pain conditions. BioRxiv, 406967.

Raimondi, S., Sera, F., Gandini, S., Iodice, S., Caini, S., Maisonneuve, P., Fargnoli, M.C., 2008. MC1R variants, melanoma and red hair color phenotype: a meta-analysis. Int. J. Cancer 122, 2753–2760.

Ramlau-Hansen, C.H., Thulstrup, A.M., Nohr, E.A., Bonde, J.P., Sørensen, T.I.A., Olsen, J., 2007. Subfecundity in overweight and obese couples. Hum. Reprod. 22, 1634–1637.

Read, J., Wadt, K.A., Hayward, N.K., 2016. Melanoma genetics. J. Med. Genet. 53, 1–14.

Rees, J.L., Harding, R.M., 2012. Understanding the evolution of human pigmentation: recent contributions from population genetics. J. Invest. Dermatol. 132, 846–853.

Revez, J.A., Lin, T., Qiao, Z., Xue, A., Holtz, Y., Zhu, Z., … Vinkhuyzen, A.A., 2020. Genome-wide association study identifies 143 loci associated with 25 hydroxyvitamin D concentration. Nat. Comm. 11, 1–12.

Rey, R., Josso, N., Racine, C., 2020. Sexual differentiation, in: Feingold, K.R., Anawalt, B., Boyce, A., et al., (Eds.), Endotext [Internet]. South Dartmouth, MA: MDText.com, Inc.

Reyes, F.I., Boroditsky, R.S., Winter, J.S.D., Faiman, C., 1974. Studies on human sexual development. II. Fetal and maternal serum gonadotropin and sex steroid concentrations. J. Clin. Endocrinol. Metab. 38, 612–617.

Rhees, R.W., Kirk, B.A., Sephton, S., Lephart, E.D., 1997. Effects of prenatal testosterone on sexual behavior, reproductive morphology and LH secretion in the female rat. Dev. Neurosci. 19, 430–437.

Riccio, L.D.G.C., Santulli, P., Marcellin, L., Abrão, M.S., Batteux, F., Chapron, C., 2018. Immunology of endometriosis. Best Pract. Res. Clin. Obstet. Gynaecol. 50, 39–49.

Richard, A., Rohrmann, S., Quack Lötscher, K.C., 2017. Prevalence of vitamin D deficiency and its associations with skin color in pregnant women in the first trimester in a sample from Switzerland. Nutrients 9, 260.

Rilling, J.K., Kaufman, T.L., Smith, E.O., Patel, R., Worthman, C.M., 2009. Abdominal depth and waist circumference as influential determinants of human female attractiveness. Evol. Hum. Behav. 30, 21–31.

Rines, J.P., vom Saal, F.S., 1984. Fetal effects on sexual behavior and aggression in young and old female mice treated with estrogen and testosterone. Horm. Behav. 18, 117–129.

Ritter, M.M., Sönnichsen, A.C., Möhrle, W., Richter, W.O., Schwandt, P., 1991. Beta-endorphin plasma levels and their dependence on gender during an enteral glucose load in lean subjects as well as in obese patients before and after weight reduction. Int. J. Obesity 15, 421–427.

Roberts, E.K., Padmanabhan, V., Lee, T.M., 2008. Differential effects of prenatal testosterone timing and duration on phenotypic and behavioral masculinization and defeminization of female sheep. Biol. Reprod. 79, 43–50.

Rocha, J., 2020. The evolutionary history of human skin pigmentation. J. Mol. Evol. 88, 77–87.

Rojansky, N., Brzezinski, A., Schenker, J.G., 1992. Seasonality in human reproduction: an update. Hum. Reprod. 7, 735–745.

Roland, A.V., Nunemaker, C.S., Keller, S.R., Moenter, S.M., 2010. Prenatal androgen exposure programs metabolic dysfunction in female mice. J. Endocrinol. 207, 213–223.

Roly, Z.Y., Backhouse, B., Cutting, A., Tan, T.Y., Sinclair, A.H., Ayers, K.L., … Smith, C.A., 2018. The cell biology and molecular genetics of Müllerian duct development. Wiley Interdiscip. Rev. Dev. Biol. 7, e310.

Romanski, P.A., Brady, P.C., Farland, L.V., Thomas, A.M., Hornstein, M.D., 2019. The effect of endometriosis on the antimüllerian hormone level in the infertile population. J. Assist. Reprod. Genet. 36, 1179–1184.

Rosenberg, K.R., 1992. The evolution of modern human childbirth. Am. J. Phys. Anthropol. 35, 89–124.

Rosenfield, R.L., Ehrmann, D.A., 2016. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr. Rev. 37, 467–520.

Rossi, H.R., Nedelec, R., Jarvelin, M.R., Sebert, S., Uimari, O., Piltonen, T.T., 2021. Body size during adulthood, but not in childhood associates with endometriosis, specifically in the peritoneal subtype–population-based life-course data from birth to late fertile age. Acta Obstet. Gynecol. Scand. https://doi.org/10.1111/aogs.14090.

Roy, R., Kundu, R., Sengupta, M., Som, P., 2018. Association between digit length ratio (2D:4D) and polycystic ovarian syndrome (PCOS)—A study among eastern Indian population. J. Anat. Soc. India 67, S14–S19. https://doi.org/10.1016/j.jasi.2017.12.006.

Rull, K., Grigorova, M., Ehrenberg, A., Vaas, P., Sekavin, A., Nõmmemees, D., … Laan, M., 2018. FSHB− 211 G>T is a major genetic modulator of reproductive physiology and health in childbearing age women. Hum. Reprod. 33, 954–966.

Ruth, K.S., Beaumont, R.N., Tyrrell, J., Jones, S.E., Tuke, M.A., Yaghootkar, H., … Murray, A., 2015. Genetic evidence that lower circulating FSH levels lengthen menstrual cycle, increase age at menopause, and impact reproductive health: a UK Biobank study. bioRxiv 028001.

Ruth, K.S., Beaumont, R.N., Tyrrell, J., Jones, S.E., Tuke, M.A., Yaghootkar, H., … Murray, A., 2016. Genetic evidence that lower circulating FSH levels lengthen menstrual cycle, increase age at menopause and impact female reproductive health. Hum. Reprod. 31, 473–481.

Sahmay, S., Aydin, Y., Oncul, M., Senturk, L.M., 2014. Diagnosis of polycystic ovary syndrome: AMH in combination with clinical symptoms. J. Assist. Reprod. Genet. 31, 213–220.

Sampson, J.A., 1925. Heterotopic or misplaced endometrial tissue. Am. J. Obstet. Gynecol. 10, 649–664.

Sanchez, A.M., Viganò, P., Quattrone, F., Pagliardini, L., Papaleo, E., Candiani, M., Panina-Bordignon, P., 2014. The WNT/β-catenin signaling pathway and expression of survival promoting genes in luteinized granulosa cells: endometriosis as a paradigm for a dysregulated apoptosis pathway. Fertil. Steril. 101, 1688–1696.

Sánchez-Ferrer, M.L., Jiménez-Velázquez, R., Mendiola, J., Prieto-Sánchez, M.T., Cánovas-López, L., Carmona-Barnosi, A., … Torres-Cantero, A.M., 2019. Accuracy of anogenital distance and anti-Müllerian hormone in the diagnosis of endometriosis without surgery. Int. J. Gynecol. Obstet. 144, 90–96.

Sánchez-Ferrer, M.L., Mendiola, J., Hernández-Peñalver, A.I., Corbalán-Biyang, S., Carmona-Barnosi, A., Prieto-Sánchez, M.T., … Torres-Cantero, A.M., 2017a. Presence of polycystic ovary syndrome is associated with longer anogenital distance in adult Mediterranean women. Hum. Reprod. 32, 2315–2323.

Sánchez-Ferrer, M.L., Mendiola, J., Jiménez-Velázquez, R., Cánovas-López, L., Corbalán-Biyang, S., Hernández-Peñalver, A.I., … Nieto, A., 2017b. Investigation of anogenital distance as a diagnostic tool in endometriosis. Reprod. BioMed. Online 34, 375–382.

Sandler, D.P., Wilcox, A.J., Horney, L.F., 1984. Age at menarche and subsequent reproductive events. Am. J. Epidemiol. 119, 765–774.

Sapkota, Y., Steinthorsdottir, V., Morris, A.P., Fassbender, A., Rahmioglu, N., De Vivo, I., … Dorien, O., 2017. Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism. Nat. Comm. 8, 1–12.

Saraswat, L., Ayansina, D., Cooper, K.G., Bhattacharya, S., 2021. Risk of melanoma in women with endometriosis: a Scottish national cohort study. Eur. J. Obstet. Gynecol. Reprod. Biol. 257, 144–148.

Sasson, I.E., Taylor, H.S., 2008. Stem cells and the pathogenesis of endometriosis. Annu. N.Y. Acad. Sci. 1127, 106.

Schacht, R., Kramer, K.L., 2019. Are we monogamous? A review of the evolution of pair-bonding in humans and its contemporary variation cross-culturally. Front. Ecol. Evol. 7, 230.

Schmid, A. and Walther, B., 2013. Natural vitamin D content in animal products. Adv. Nutr. 4, 453-462.

Schmidt, I.M., Chellakooty, M., Haavisto, A.M., Boisen, K.A., Damgaard, I.N., Steendahl, U., … Main, K.M., 2002. Gender difference in breast tissue size in infancy: correlation with serum estradiol. Pediatr. Res. 52, 682–686.

Schwartz, C.L., Christiansen, S., Vinggaard, A.M., Axelstad, M., Hass, U., Svingen, T., 2019. Anogenital distance as a toxicological or clinical marker for fetal androgen action and risk for reproductive disorders. Arch. Toxicol. 93, 253–272.

Scioscia, M., Roman, H., Somigliana, E., Robillard, P.Y., 2019. Increasing number of menstruations in recent generations may contribute to the development of endometriosis: an evolutionary view from a critical analysis of National Health data. Hum. Reprod. 34, 2549–2550.

Scott, I.M., Clark, A.P., Josephson, S.C., Boyette, A.H., Cuthill, I.C., Fried, R.L., … Honey, P.L., 2014. Human preferences for sexually dimorphic faces may be evolutionarily novel. Proc. Natl. Acad. Sci. U.S.A. 111, 14388–14393.

Selak, V., Farquhar, C.M., Prentice, A., Singla, A.A., 2001. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD000068.

Shafrir, A.L., Palmor, M.C., Fourquet, J., DiVasta, A.D., Farland, L.V., Vitonis, A.F., … Missmer, S.A., 2021. Co-occurrence of immune-mediated conditions and endometriosis among adolescents and adult women. Am. J. Reprod. Immunol. e13404.

Shah, D.K., 2013. Diminished ovarian reserve and endometriosis: insult upon injury. Semin. Reprod. Med. 31, 144–149.

Shah, D.K., Correia, K.F., Vitonis, A.F., Missmer, S.A., 2013. Body size and endometriosis: results from 20 years of follow-up within the Nurses' Health Study II prospective cohort. Hum. Reprod. 28, 1783–1792.

Shigesi, N., Kvaskoff, M., Kirtley, S., Feng, Q., Fang, H., Knight, J.C., … Becker, C.M., 2019. The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. Hum. Reprod. Update 25, 486–503.

Shin, J.G., Leem, S., Kim, B., Kim, Y., Lee, S.G., Song, H.J., … Kang, N.G., 2020. GWAS Analysis of 17,019 Korean women identifies the variants associated with facial pigmented spots. J. Invest. Dermatol. 141, 555–562

Sidhu, S., Parikh, T., Burman, K.D., 2017. Endocrine changes in obesity, in: Feingold, K.R., Anawalt, B., Boyce, A., Chrousos, G., de Herder, W.W., Dungan, K., … Wilson, D.P., (Eds.), Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.

Signorile, P.G., Petraglia, F., Baldi, A., 2014. Anti-mullerian hormone is expressed by endometriosis tissues and induces cell cycle arrest and apoptosis in endometriosis cells. J. Exp. Clin. Cancer Res. 33, 1–9.

Simitsidellis, I., Saunders, P.T., Gibson, D.A., 2018. Androgens and endometrium: new insights and new targets. Mol. Cell. Endocrinol. 465, 48–60.

Simsir, C., Pekcan, M.K., Aksoy, R.T., Ecemis, T., Coskun, B., Kilic, S.H., Tokmak, A., 2019. The ratio of anterior anogenital distance to posterior anogenital distance: a novel-biomarker for polycystic ovary syndrome. J. Chin. Med. Assoc. 82, 782–786.

Singh, D., 2002. Female mate value at a glance: relationship of waist-to-hip ratio to health, fecundity and attractiveness. Neuroendocrinol. Lett. 23, 81–91.

Singh, D., Dixson, B.J., Jessop, T.S., Morgan, B., Dixson, A.F., 2010. Cross-cultural consensus for waist–hip ratio and women's attractiveness. Evol. Hum. Behav. 31, 176–181.

Singh, D., Singh, D., 2011. Shape and significance of feminine beauty: an evolutionary perspective. Sex Roles 64, 723–731.

Singh, D., Young, R.K., 1995. Body weight, waist-to-hip ratio, breasts, and hips: role in judgments of female attractiveness and desirability for relationships. Ethol. Sociobiol. 16, 483–507.

Sitek, A., Kozieł, S., Kasielska-Trojan, A., Antoszewski, B., 2018. Do skin and hair pigmentation in prepubertal and early pubertal stages correlate with 2D:4D? Am. J. Hum. Biol. 30, e12631.

Sjaarda, L.A., Mumford, S.L., Kuhr, D.L., Holland, T.L., Silver, R.M., Plowden, T.C., … Schisterman, E.F., 2018. Association of testosterone and antimüllerian hormone with time to pregnancy and pregnancy loss in fecund women attempting pregnancy. Fertil. Steril. 109, 540–548.

Somigliana, E., Vigano, P., Abbiati, A., Gentilini, D., Parazzini, F., Benaglia, L., … Fedele, L., 2010. 'Here comes the sun': pigmentary traits and sun habits in women with endometriosis. Hum. Reprod. 25, 728–733.

Sowers, M.F., Beebe, J.L., McConnell, D., Randolph, J., Jannausch, M., 2001. Testosterone concentrations in women aged 25–50 years: associations with lifestyle, body composition, and ovarian status. Am. J. Epidemiol. 153, 256–264.

Stanikova, D., Zsido, R.G., Luck, T., Pabst, A., Enzenbach, C., Bae, Y.J., … Stanik, J., 2019. Testosterone imbalance may link depression and increased body weight in premenopausal women. Transl. Psychiatry 9, 1–12.

Stern, A.J., Speidel, L., Zaitlen, N.A., Nielsen, R., 2021. Disentangling selection on genetically correlated polygenic traits via whole-genome genealogies. Am. J. Hum. Genet. 108, 219–239.

Stilley, J.A., Birt, J.A., Sharpe-Timms, K.L., 2012. Cellular and molecular basis for endometriosis-associated infertility. Cell Tissue Res. 349, 849–862.

Strassmann, B.I., 1996. The evolution of endometrial cycles and menstruation. Q. Rev. Biol. 71, 181–220.

Street, S.E., Cross, C.P., Brown, G.R., 2016. Exaggerated sexual swellings in female nonhuman primates are reliable signals of female fertility and body condition. Anim. Behav. 112, 203–212.

Suire, A., Raymond, M., Barkat-Defradas, M., 2021. Voice, sexual selection, and reproductive success, in: Weiss, B., Trouvain, J., Barkat-Defradas, M., Ohala, J.J. (Eds.), Voice Attractiveness: Studies on Sexy, Likable, and Charismatic Speakers. Springer, Singapore, pp. 125–138.

Sun, B., Wang, F., Sun, J., Yu, W., Sun, Y., 2014. Basal serum testosterone levels correlate with ovarian response but do not predict pregnancy outcome in non-PCOS women undergoing IVF. J. Assist. Reprod. Genet. 31, 829–835.

Suzuki, H., Kanai-Azuma, M., Kanai, Y., 2015. From sex determination to initial folliculogenesis in mammalian ovaries: morphogenetic waves along the anteroposterior and dorsoventral axes. Sex. Dev. 9, 190–204.

Swami, S., Buddhiraja, V., Gupta, R., Bansal, S., Gaur, N., Sharma, D., 2019. Correlation between second to fourth digit ratio and anthropometric variables indicative of cardiovascular disease. J. Morphol. Sci. 36, 028–032.

Swami, V., Rozmus-Wrzesinska, M., Voracek, M., Haubner, T., Danel, D., Pawłowski, B., … Shostak, A., 2008. The influence of skin tone, body weight, and hair colour on perceptions of women's attractiveness and health: a cross-cultural investigation. J. Evol. Psychol. 6, 321–341.

Tabachnik, M., Sheiner, E., Wainstock, T., 2020. The association between second to fourth digit ratio, reproductive and general health among women: findings from an Israeli pregnancy cohort. Sci. Rep. 10, 1–7.

Takahashi, K., Nagata, H., Kitao, M., 1989. Clinical usefulness of determination of estradiol level in the menstrual blood for patients with endometriosis. Nihon Sanka Fujinka Gakkai Zasshi 41, 1849–1850.

Taponen, S., Martikainen, H., Järvelin, M.R., Laitinen, J., Pouta, A., Hartikainen, A.L., … Ruokonen, A., 2003. Hormonal profile of women with self-reported symptoms of oligomenorrhea and/or hirsutism: Northern Finland birth cohort 1966 study. J. Clin. Endocrinol. Metab. 88, 141–147.

Thankamony, A., Pasterski, V., Ong, K.K., Acerini, C.L., Hughes, I.A., 2016. Anogenital distance as a marker of androgen exposure in humans. Andrology 4, 616–625.

Theodoridou, A., Rowe, A.C., Penton-Voak, I.S. and Rogers, P.J., 2009. Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm. Behav. 56, 128-132.

Tiosano, D., Audi, L., Climer, S., Zhang, W., Templeton, A.R., Fernández-Cancio, M., … Hochberg, Z., 2016. Latitudinal clines of the human vitamin D receptor and skin color genes. G3 6, 1251–1266.

Trumble, B.C., Blackwell, A.D., Stieglitz, J., Thompson, M.E., Suarez, I.M., Kaplan, H., Gurven, M., 2016. Associations between male testosterone and immune function in a pathogenically stressed forager-horticultural population. Am. J. Phys. Anthropol. 161, 494–505.

Turan, T., Uysal, C., Asdemir, A., Kılıç, E., 2013. May oxytocin be a trait marker for bipolar disorder? Psychoneuroendocrinology 38, 2890–2896.

Udry, J.R., Cliquet, R.L., 1982. A cross-cultural examination of the relationship between ages at menarche, marriage, and first birth. Demography 19, 53–63.

Valentova, J.V., Tureček, P., Varella, M.A.C., Šebesta, P., Mendes, F.D.C., Pereira, K.J., … Havlíček, J., 2019. Vocal parameters of speech and singing covary and are related to vocal attractiveness, body measures, and sociosexuality: a cross-cultural study. Front. Psychol. 10, 2029.

van Aken, M., Oosterman, J., van Rijn, T., Woudsma, K., Ferdek, M., Ruigt, G., … Nap, A., 2018. Experimental pain tolerance is decreased and independent of clinical pain intensity in patients with endometriosis. Fertil. Steril. 110, 1118–1128.

van Anders, S.M., Hampson, E., 2005. Waist-to-hip ratio is positively associated with bioavailable testosterone but negatively associated with sexual desire in healthy premenopausal women. Psychosom. Med. 67, 246–250.

van den Berghe, P.L., Frost, P., 1986. Skin color preference, sexual dimorphism and sexual selection: a case of gene culture co-evolution? Ethn. Racial Stud. 9, 87–113.

van Schaik, C.P., van Noordwijk, M.A., Nunn, C.L., 1999. Sex and social evolution in primates. Comp. Primate Socioecol. 204–240.

Vercellini, P., Buggio, L., Somigliana, E., Dridi, D., Marchese, M.A., Viganò, P., 2014. 'Behind blue eyes': the association between eye colour and deep infiltrating endometriosis. Hum. Reprod. 29, 2171–2175.

Vercellini, P., Sacerdote, P., Panerai, A.E., Manfredi, B., Bocciolone, L., Crosignani, G., 1992. Mononuclear cell beta-endorphin concentration in women with and without endometriosis. Obstet. Gynecol. 79, 743–746.

Verdin, H., De Baere, E., 2012. FOXL2 impairment in human disease. Horm. Res. Paediatr. 77, 2–11.

Vicuña, L., Klimenkova, O., Norambuena, T., Martinez, F.I., Fernandez, M.I., Shchur, V., Eyheramendy, S., 2020. Postadmixture selection on Chileans targets haplotype involved in pigmentation, thermogenesis and immune defense against pathogens. Genome Biol. Evol. 12, 1459–1470.

Videira, I.F.D.S., Moura, D.F.L., Magina, S., 2013. Mechanisms regulating melanogenesis. Anais Brasileiros de Dermatologia 88, 76–83.

Viganò, P., Somigliana, E., Panina, P., Rabellotti, E., Vercellini, P., Candiani, M., 2012. Principles of phenomics in endometriosis. Hum. Reprod. Update 18, 248–259.

Visconti, A., Duffy, D.L., Liu, F., Zhu, G., Wu, W., Chen, Y., … Kanetsky, P.A., 2018. Genome-wide association study in 176,678 Europeans reveals genetic loci for tanning response to sun exposure. Nat. Comm. 9, 1–7.

Vom Saal, F.S., 1989. The production of and sensitivity to cues that delay puberty and prolong subsequent oestrous cycles in female mice are influenced by prior intrauterine position. Reproduction 86, 457-471.

Vom Saal, F.S., Quadagno, D.M., Even, M.D., Keisler, L.W., Keisler, D.H. and Khan, S., 1990. Paradoxical effects of maternal stress on fetal steroids and postnatal reproductive traits in female mice from different intrauterine positions. Biol. Reprod. 43, 751-761.

vom Saal, F.S., 1981. Variation in phenotype due to random intrauterine positioning of male and female fetuses in rodents. Reproduction 62, 633–650.

vom Saal, F.S., Bronson, F. H., 1978. *In utero* proximity of female mouse fetuses to males: effect on reproductive performance during later life. Biol. Reprod. 19, 842–853.

vom Saal, F.S., Bronson, F.H., 1980a. Sexual characteristics of adult female mice are correlated with their blood testosterone levels during prenatal development. Science 208, 597–599.

vom Saal, F.S., Bronson, F.H., 1980b. Variation in length of the estrous cycle in mice due to former intrauterine proximity to male fetuses. Biol. Reprod. 22, 777–780.

Voracek, M., 2009. Comparative study of digit ratios (2D:4D and other) and novel measures of relative finger length: testing magnitude and consistency of sex differences across samples. Percept. Mot. Skills 108, 83–93.

Vranić, L., Mikolašević, I., Milić, S., 2019. Vitamin D deficiency: consequence or cause of obesity? Medicina 55, 541.

Wainstock, T., Shoham-Vardi, I., Sheiner, E., Walfisch, A., 2017. Fertility and anogenital distance in women. Reprod. Toxicol. 73, 345–349.

Walsh, J.S., Bowles, S., Evans, A.L., 2017. Vitamin D in obesity. Curr. Opin. Endocrinol. Diabetes Obes. 24, 389–394.

Wang, G., Djafarian, K., Egedigwe, C.A., El Hamdouchi, A., Ojiambo, R., Ramuth, H., … Hambly, C., 2015. The relationship of female physical attractiveness to body fatness. PeerJ 3, e1155.

Wang, Y., Nicholes, K., Shih, I.M., 2020. The origin and pathogenesis of endometriosis. Annu. Rev. Pathol. 15, 71–95.

Wass, P., Waldenström, U., Rössner, S., Hellberg, D., 1997. An android body fat distribution in females impairs the pregnancy rate of *in-vitro* fertilization-embryo transfer. Hum. Reprod. 12, 2057–2060.

Weeden, J., Sabini, J., 2005. Physical attractiveness and health in Western societies: a review. Psychol. Bull. 131, 635–653. https://doi.org/10.1037/0033-2909.131.5.635.

Wei, M., Cheng, Y., Bu, H., Zhao, Y., Zhao, W., 2016. Length of menstrual cycle and risk of endometriosis: a meta-analysis of 11 case–control studies. Medicine 95, e2922.

Wells, J.C., 2007. Sexual dimorphism of body composition. Best Pract. Res. Clin. Obstet. Gynaecol. 21, 415–430.

Wells, J.C., 2010. The Evolutionary Biology of Human Body Fatness: Thrift and Control, Volume 58. Cambridge University Press, UK.

Wells, J.C., Griffin, L., Treleaven, P., 2010. Independent changes in female body shape with parity and age: a life-history approach to female adiposity. Am. J. Hum. Biol. 22, 456–462.

Wheatley, J.R., Apicella, C.A., Burriss, R.P., Cárdenas, R.A., Bailey, D.H., Welling, L.L., Puts, D.A., 2014. Women's faces and voices are cues to reproductive potential in industrial and forager societies. Evol. Hum. Behav. 35, 264–271.

White, D., Rabago-Smith, M., 2011. Genotype–phenotype associations and human eye color. J. Hum. Genet. 56, 5–7.

Whitehouse, A.J., Gilani, S.Z., Shafait, F., Mian, A., Tan, D.W., Maybery, M.T., … Eastwood, P., 2015. Prenatal testosterone exposure is related to sexually dimorphic facial morphology in adulthood. Proc. R. Soc. Lond. B Biol. Sci. 282, 20151351.

Wilde, S., Timpson, A., Kirsanow, K., Kaiser, E., Kayser, M., Unterländer, M., … Burger, J., 2014. Direct evidence for positive selection of skin, hair, and eye pigmentation in Europeans during the last 5,000 y. Proc. Natl. Acad. Sci. U.S.A. 111, 4832–4837.

Wilkins, A.S., Wrangham, R.W. and Fitch, W.T., 2014. The "domestication syndrome" in mammals: a unified explanation based on neural crest cell behavior and genetics genetics. Genetics, 197, 795-808.

Williams, G.C., Nesse, R.M., 1991. The dawn of Darwinian medicine. Q. Rev. Biol. 66, 1–22.

Wimalawansa, S.J., 2018. Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. J Steroid Biochem Mol Biol 175, 177-189.
Wise, L.A., Rothman, K.J., Mikkelsen, E.M., Sørensen, H.T., Riis, A., Hatch, E.E., 2010. An internet-based prospective study of body size and time-to-pregnancy. Hum. Reprod. 25, 253–264.

Woodworth, S.H., Singh, M., Yussman, M.A., Sanfilippo, J.S., Cook, C.L., Lincoln, S.R., 1995. A prospective study on the association between red hair color and endometriosis in infertile patients. Fertil. Steril. 64, 651–652.

Wu, X.Y., Li, Z.L., Wu, C.Y., Li, Y.M., Lin, H., Wang, S.H., Xiao, W.F., 2010. Endocrine traits of polycystic ovary syndrome in prenatally androgenized female Sprague-Dawley rats. Endocr. J. 1001060376-1001060376.

Wu, Y., Zhong, G., Chen, S., Zheng, C., Liao, D., Xie, M., 2017. Polycystic ovary syndrome is associated with anogenital distance, a marker of prenatal androgen exposure. Hum. Reprod. 32, 937–943.

Wyshak, G., Frisch, R.E., 2000. Red hair color, melanoma, and endometriosis: suggestive associations. Int. J. Dermatol. 39, 798.

Xiong, W., Zhang, L., Xiong, Y., Liu, H., Liu, Y., 2016. Hypoxia promotes invasion of endometrial stromal cells via hypoxia-inducible factor 1α upregulation-mediated β-catenin activation in endometriosis. Reprod. Sci. 23, 531–541.

Yang, Z., Shi, H., Ma, P., Zhao, S., Kong, Q., Bian, T., … Zhang, X., 2018. Darwinian positive selection on the pleiotropic effects of KITLG explain skin pigmentation and winter temperature adaptation in Eurasians. Mol. Biol. Evol. 35, 2272–2283.

Yao, H.H., Matzuk, M.M., Jorgez, C.J., Menke, D.B., Page, D.C., Swain, A., Capel, B., 2004. Follistatin operates downstream of Wnt4 in mammalian ovary organogenesis. Dev. Dyn. 230, 210–215.

Yasui, T., Hayashi, K., Nagai, K., Mizunuma, H., Kubota, T., Lee, J.S., Suzuki, S., 2015. Risk profiles for endometriosis in Japanese women: results from a repeated survey of self-reports. J. Epidemiol. 25, 194–203.

Yilmaz, N., Kilic, S., Kanat-Pektas, M., Gulerman, C., Mollamahmutoglu, L., 2009. The relationship between obesity and fecundity. J. Womens Health 18, 633–636.

Yong, L., Weiyuan, Z., 2017. Association between body mass index and endometriosis risk: a meta-analysis. Oncotarget 8, 46928.

Yovich, J.L., Rowlands, P.K., Lingham, S., Sillender, M., Srinivasan, S., 2020. Pathogenesis of endometriosis: look no further than John Sampson. Reprod. BioMed. Online 40, 7–11.

Zaadstra, B.M., Seidell, J.C., Van Noord, P., te Velde, E.R., Habbema, J.D., Vrieswijk, B., Karbaat, J., 1993. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ 306, 484–487.

Zeberg, H., Kelso, J., Pääbo, S., 2020. The Neandertal progesterone receptor. Mol. Biol. Evol. 37, 2655–2660.

Zehr, J.L., Gans, S.E., McClintock, M.K., 2001. Variation in reproductive traits is associated with short anogenital distance in female rats. Dev. Psychobiol. 38, 229–238.

Zelazniewicz, A.M., Pawlowski, B., 2011. Female breast size attractiveness for men as a function of sociosexual orientation (restricted vs. unrestricted). Arch. Sex. Behav. 40, 1129–1135.

Żelaźniewicz, A., Nowak-Kornicka, J., Zbyrowska, K. and Pawłowski, B., 2021. Predicted reproductive longevity and women's facial attractiveness. Plos ONE 16, e0248344.

Zhang, Q., Wang, Y.Y., Zhang, Y., Zhang, H.G., Yang, Y., He, Y., … Ma, X., 2017. The influence of age at menarche, menstrual cycle length and bleeding duration on time to pregnancy: a large prospective cohort study among rural Chinese women. BJOG 124, 1654–1662.

Zhang, T., De Carolis, C., Man, G.C.W., Wang, C.C., 2018. The link between immunity, autoimmunity and endometriosis: a literature update. Autoimmun. Rev. 17, 945–955.

Zhao, L., Gu, C., Ye, M., Zhang, Z., Fan, W., Meng, Y., 2018. Integration analysis of microRNA and mRNA paired expression profiling identifies deregulated microRNA-transcription factor-gene regulatory networks in ovarian endometriosis. Reprod. Biol. Endocrinol. 16, 1–13.

Zheng, Z., Cohn, M.J., 2011. Developmental basis of sexually dimorphic digit ratios. Proc. Natl. Acad. Sci. U.S.A. 108, 16289–16294.

Zurawiecka, M., Suder, A., Stangret, A., Teul, I., Wronka, I., 2019. Differences in body fat distribution in women depending on the second to fourth digit ratio value. Anthropologischer Anzeiger 95–100.

Table 1

Findings salient to the hypothesis that risk of endometriosis has evolved, in part, due to 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?**	**Geater female bias in women with endomet-riosis?**	**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	Unknown	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-underbreast 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

Table 2.

Data from the non-human mammal literature on correlates of endometriosis related to 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 2 males (2M); experimental treatment) and/or levels of estradiol. See papers for details of the choice experiments. Males also preferred control females, compared to females that were experimentally treated *in utero* with testosterone, from studies of sheep (Roberts et al., 2008; Jackson et al., 2013).

Species	**Male choice experiments or other data relevant to choice**	**Main findings with regard to hormonal effects**	**References**
Lab mice (*Mus musculatus*)	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 to 2M females; 0M females had shorter AGDs, earlier vaginal opening and shorter, more regular estrus cycles compared to 2M females; 0M and 2M females did not differ in fecundity	McDermott et al., 1978; vom Saal and Bronson, 1978, 1980a,b; Rines and vom Saal, 1984; vom Saal, 1981, 1989 The production; vom Saal Even 1990
House mice (*Mus musculatus*, 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 to 2M females	2M females had later estrus, longer menstrual cycles, fewer litters, and showed higher T than 0M and 1M females	Clark and Galef 1988, 1998; Clark et al., 1991
Laboratory rats (*Rattus norvegicus*)	Adult treatment with E2 increased attractiveness of	Females exposed to lower (vs higher) testosterone levels *in utero* had shorter AGDs; females treated with high	Lucas et al., 1982; McCoy and Shirley, 1992; Levy et al., 1995;

	females to males; no studies of male choice in relation to prenatal steroids in females found	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	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	Landaer 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.	Mokkonen Koskela 2011; Mills Koskela Mappes 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	Banszegi et al., 2009, 2010, 2012
Yellow-bellied marmots	Likelihood of getting pregnant and rearing young	More males in litter leads to longer AGD in females, and delayed onset of breeding, in field	Monclús and Blumstein, 2012; Monclús et al., 2014

(*Marmota flaviventris*)	was lower in young females with longer vs shorter AGDs; no data on male choice		
Mouse lemurs (*Microcebus murinus)*	Males prefer females with higher serum estrogen 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

Figure legends

Fig. 1. The set of processes involved in the hypothesis that sexual selection has mediated the evolution of human risk for endometriosis. Processes associated with sexual selection are shown in red.

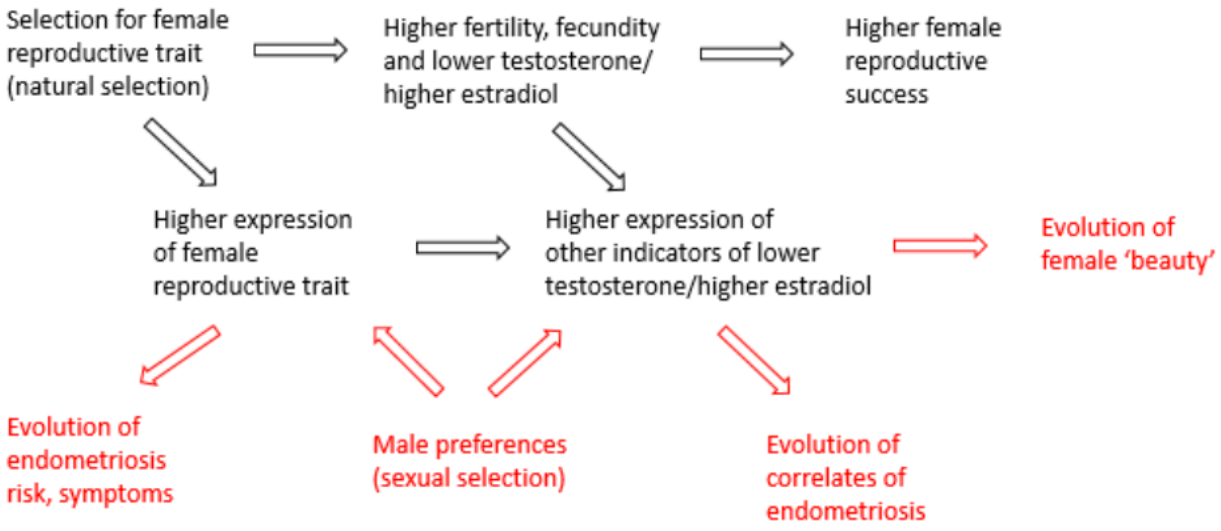

Fig. 2. Endometriosis is characterized by relatively-female expression for a wide range of sexually dimorphic traits. See text and Table 1 for details.

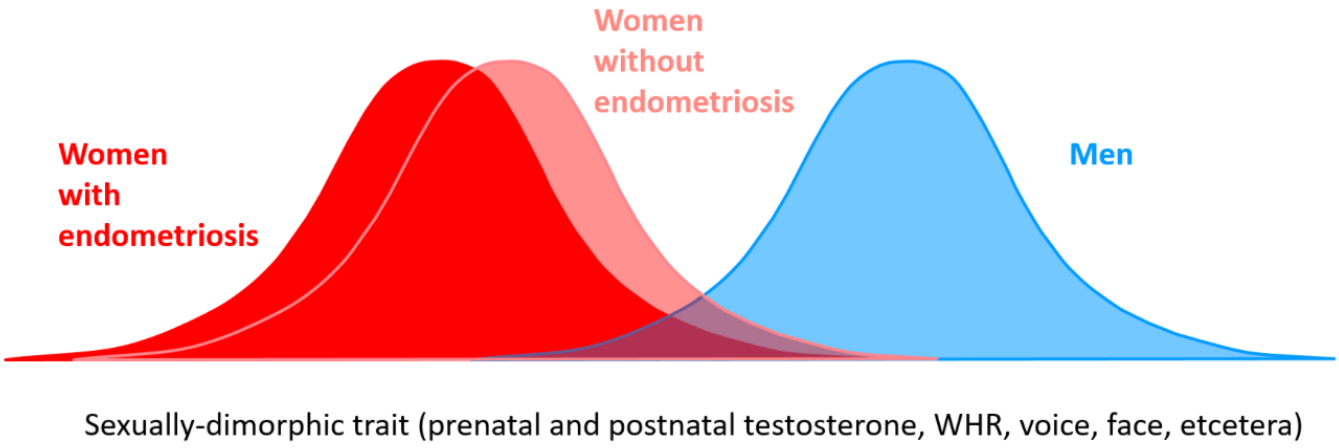

Fig. 3. Endometriosis involves higher expression, during adulthood, of a set of core early-developmental 'pro-female/anti-male' genes (in red), and lower expression of 'anti-female/pro-male' genes (in blue); jointly, these genes guide early sexual differentiation and development.

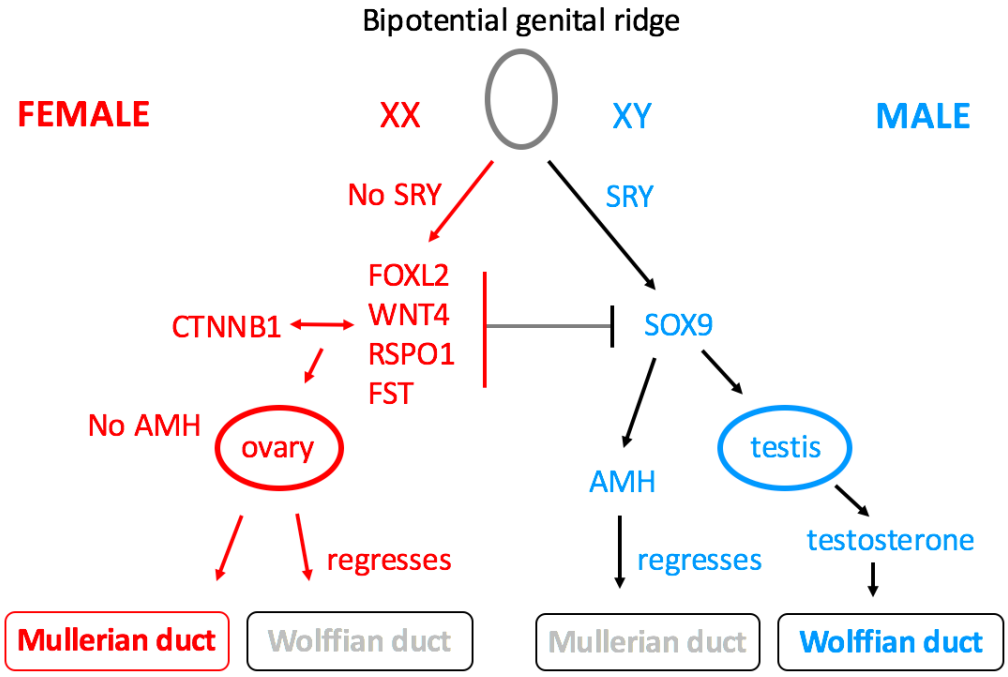

Fig. 4. The key endocrine phenotypes associated with endometriosis that are causally linked with one another, whose covariation can be traced to relatively low prenatal and postnatal testosterone that cause expression of the relatively-female phenotypes found in endometriosis. For details regarding the causal associations, see Qian et al., 2014; Sun et al., 2014; Mondragón-Ceballos et al., 2015; Böttcher et al., 2017; Alebic et al., 2018; Fabregues et al., 2018; Albu and Albu, 2019; Barbotin et al., 2019; Mira-Escolano Mendiola 2014a,b; Lv et al., 2020; van Anders and Hampson 2005; Cashdan, 2008; Blouin et al., 2008; Barnett et al., 2002; Stanikova et al., 2019.

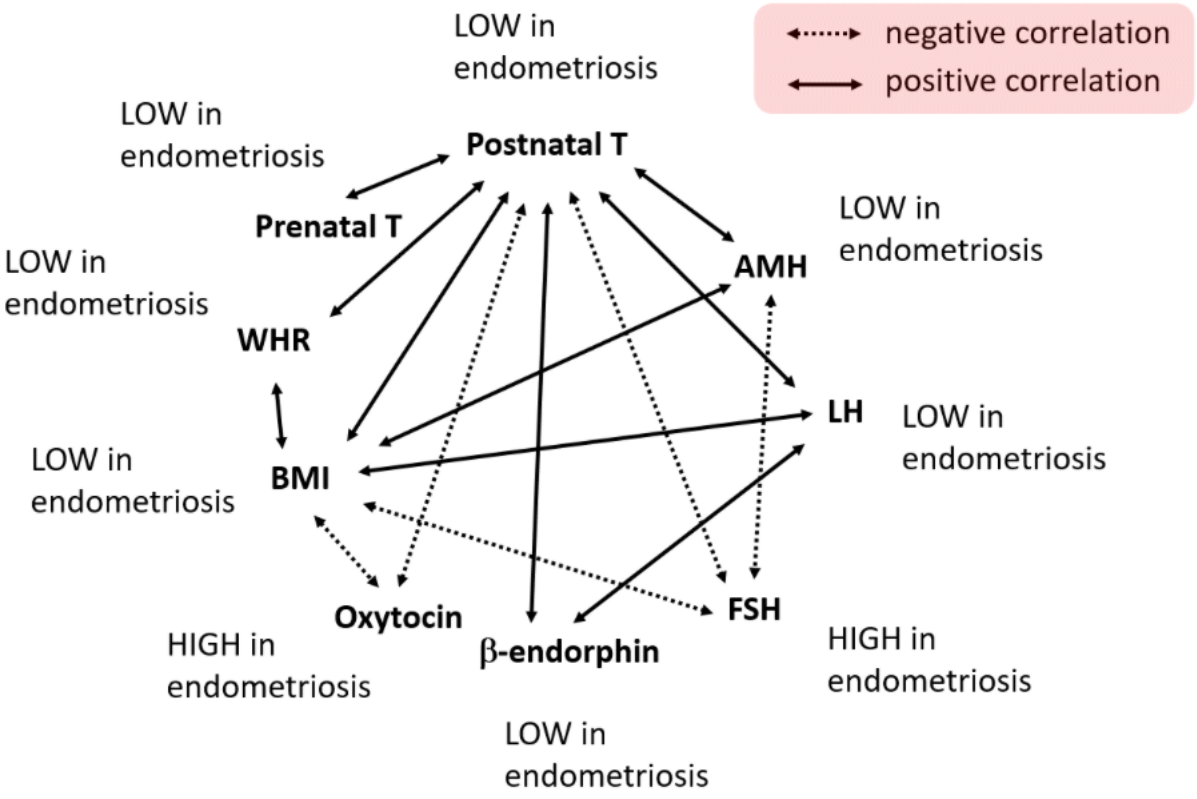

Fig. 5. By the hypothesis evaluated here, endometriosis risk engenders maladaptive extremes of effects from low prenatal and postnatal testosterone; the highest female reproductive performance involves below-average testosterone in women (the brightest red), and reproductive performance is also reduced when testosterone levels are relatively high.