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Body symmetry and reproductive hormone levels in women

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Key words: biological condition, fertility, fecundity, AMH, gonadotropins, estradiol.

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Abstract

Fluctuating asymmetry (FA), a morphological marker of developmental stability, may be related to an individual's biological condition, e.g., health or fertility. The aim of this study was to test if the level of a woman's FA was related to her fertility and reproductive potential as measured by reproductive hormone levels. Fifty-three healthy, non-pregnant, naturally cycling women (mean age=23.42, SD=1.85 years), participated in the study, conducted in Wrocław (Poland) in May 2015. Early-follicular phase serum levels of anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) were measured. FA was calculated based on anthropometric measures of six bilateral body traits, and the composite FA index was used in statistical analyses. No relationship was observed between FA and the levels of FSH, LH and AMH ($p>0.05$), controlled for potential confounders. However, the level of E2 was positively correlated with FA ($p<0.05$). Thus, in young women, FA was not related to hormones levels related to ovarian reserve, but more symmetrical women had lower E2 levels. As FA is an index of developmental stability, environmental and genetic stress, the results of the study confirm previous research suggesting that developmental conditions may be related to women's endogenous estrogen levels.

Key words: biological condition, fertility, fecundity, AMH, gonadotropins, estradiol.

Introduction

Developmental instability (DI) refers to an individual's inability to resist the adverse effects of various perturbations during development, which may result in reduced fitness (Van Dongen & Gangestad, 2011). A frequently employed morphological measure of DI in empirical research is fluctuating asymmetry (FA). FA is defined as small, random deviations from the ideal symmetry on bilateral traits that are, on average, symmetrical at the population level. Those asymmetries emerge during development and are considered to reflect an individual's fitness (Van Dongen & Gangestad, 2011).

Prior studies have shown that the level of FA is related to an individual's general health, reproductive fitness and immune system efficacy and thus may be a signal of biological condition both in men and women (Gangestad et al., 2010; Thomas et al., 2015; Van Dongen & Gangestad, 2011). The level of FA has also been reported to be positively related to susceptibility to infectious diseases (Møller, 2006; but see Thomas et al., 2015), serious medical conditions (e.g., anemia, cancer, diabetes, hepatitis, kidney infections) (Van Dongen & Gangestad, 2011), respiratory infections (Thornhill & Gangestad, 2006), weak defenses against parasites, mutations and environmental toxins (Møller, 2006), high levels of oxidative stress (Gangestad et al., 2010), and poor developmental condition (Özener & Fink, 2010).

Evidence also exists for a strong preference toward symmetric partners both in men and women (Van Dongen, 2014; Wade, 2010; Zaidel & Hessamian, 2010). This preference may be adaptive as symmetry seems to be related not only to general health but also to fertility and reproductive success in both sexes (Pflüger et al., 2012). The level of FA has been negatively related to the total number of sperm per ejaculate and to sperm motility (Firman et al., 2003; Jeffery et al., 2016; Manning et al., 1998), to number of lifetime sexual

partners (Van Dongen et al., 2009), and extra-pair copulations in men (Gangestad & Thornhill, 1997). Also, the number of children has been positively correlated with body symmetry in men and women (Manning et al., 1997; Møller et al., 1995; Waynforth, 1998). More symmetrical women have a lower level of oxidative stress in the first trimester of pregnancy, which is related to a lower risk of problems during gestation, preterm delivery, and newborn health problems (Żelaźniewicz et al., 2015). Also, symmetry in women seems to be positively associated with estradiol level (Jasieńska et al., 2006), which may be one important hormonal indicator of a woman's potential to conceive (Lipson & Ellison, 1996).

The research indicating a relationship between FA and women's reproductive physiology are based on measures of symmetry in only one bilateral trait (4^{th} finger - Jasieńska et al., 2006), which may not reliably reflect actual body asymmetry. The reliability of FA as a marker of developmental instability is greater when a composite asymmetry measurement, aggregating FA of multiple developmentally independent traits, is used (e.g., ear and knee asymmetry) (VanDongen, 2012; Van Dongen & Gangestad, 2011). Also, so far, estradiol levels are the only hormones that have been examined in relationship to FA in women (Jasieńska et al., 2006). While estradiol is a primary female sex hormone involved in the processes related to ovulation, fertilization and implantation (Cha et al., 2012; Lipson & Ellison, 1996), the hormonal mechanisms regulating a woman's fertility and her reproductive potential are more complex. Various hormones are related to oocyte maturation, ovulation, fetus implantation, ovarian reserve (a number of antral follicles in ovary), and the level of a woman's fecundity (Pincus, 2013; Unuane et al., 2011).

Ovarian reserve is established prenatally and diminishes gradually with age, due to atrophy and ovulation, until the primordial follicle pool is exhausted, resulting in menopause (Wallace & Kelsey, 2010). Anti-müllerian hormone (AMH) is a marker of ovarian reserve, the

quantitative aspect of ovarian aging, allowing assessment of ovarian reserve status and thus the reproductive life-span of women (Loh & Maheshwari, 2011; Shebl et al., 2011; Van Houten et al., 2010; Jeppesen et al., 2013). As prenatal conditions, childhood growth and adult lifestyle affect both ovarian reserve and FA, FA may be related to hormone levels reflective of ovarian reserve (Benderlioglu, 2010; Jasieńska, 2010; King et al., 2009; Weisensee, 2010). AMH level has also been related to some medical conditions, e.g., Fanconi's anemia (Sklavos et al., 2014), pelvic inflammatory disease (Cui et al., 2016), and autoimmune disorders (Lawrenz et al., 2011, Henes et al., 2015). This suggests that an optimal AMH level is related not only to ovarian reserve, but might be also a signal of overall good health status, which should be negatively related to FA levels.

Basal levels (measured in the beginning of the menstrual cycle) of FSH and LH are also useful markers of ovarian reserve and probability of pregnancy (Brodin et al., 2009; Coccia & Rizzello, 2008; Roudebush et al., 2008; Singh et al., 2007) and thus may also be related to women's FA levels. Low cycle day 3 FSH and LH levels are related to high pregnancy rates (Frattarelli et al., 2010; Seckin et al., 2012; van der Steeg et al., 2007; Steiner, 2013). For instance, early follicular LH level is significantly higher in women who exhibit poor response to ovarian stimulation and who have lower antral follicle counts, retrieved numbers of oocytes and mature oocyte counts in IVF procedures (Kunt et al., 2011). Although raised gonadotropin levels is one of the first signs of approaching perimenopause, in young women raised early follicular phase FSH and FSH/LH ratio have been related to diminished ovarian reserve (Barad et al., 2007; El-Toukhy et al., 2002; Shrim et al., 2006; Steiner et al., 2013) and thus may be positively related to FA levels.

The aim of this study was to analyze whether early follicular LH, FSH, E2 and AMH concentration were related to composite FA index levels, estimated with measurements of six bilateral traits, characterized by various developmental trajectories.

Material & Methods

Participants & General Procedure.

Participants were recruited through information posted on social websites, information in the local newspapers, and information posted on bulletin boards at the University of Wrocław. Among 84 women who volunteered to participate in the study, based on information obtained on a preliminary qualifying interview, women were selected for participation if they met following criteria: regular menstrual cycles (cycle length between 21 and 36 days), not smoking, no diagnosed hormonal gynecological/fertility disorders (e.g., Polycystic Ovary Syndrome) or chronic disease (diabetes, hypo/hyperthyroidism), not taking any hormonal medications or using hormonal contraception, and never been pregnant. Fifty-three women (63.1%) from an urban population, aged 20 - 28 years (Mean = 23.42, SD = 1.85 years), mostly students at the University of Wrocław (Poland) took part in the study.

Participants were assessed between the second and fourth days of their menstrual cycles for early-follicular reproductive hormones measurement. Cycle day 3 hormone levels are widely employed in clinical studies as indicative of a woman's fertility and probability of conception within the cycle (Practice Committee of the American Society for Reproductive Medicine 2015; Luna et al., 2007). The study protocol for each participant consisted of a blood sample for hormonal analysis, anthropological measurements and answering the survey questions. A general questionnaire developed for this study was used to collect information on demographic data, health, education, reproductive history, past use of

hormonal medications, age at menarche, level of physical activity, stress level, cigarette smoking and alcohol consumption. All procedures were performed in the same day, before noon.

The study was approved by the Bioethics Commission at the Lower Silesian Chamber of Physicians and Dentists' ethics committee. All participants read and signed the informed consent form.

Hormonal analysis.

Venous blood was collected in the early morning hours into serum vacutainers (Beckton Dickinson®). Serum was separated from 10 ml of whole blood sample by centrifugation within two hours of venipuncture. Portioned serum samples were stored at -70^{o}C until analysis. The quantitative determination of AMH levels was performed using enzyme-linked immunosorbent assay (ELISA) and commercial kit (BeckmanCoulter®, catalogue number A79765). The coefficients of inter- and intra-assay variation were less than 5.6% and less than 5.4%, respectively, with an assay sensitivity of 0.08 ng/ml according to the product insert. The serum samples were assayed in duplicate in accordance with manufacturer's instruction. For each serum sample, the AMH concentration was calculated in relation to a standard curve and expressed in ng/ml.

Serum FSH, LH and E2 levels were evaluated by ELISA using appropriate commercial kits (DEMEDITEC®). Participant's serum sample dilution and test procedure were performed according to manufacturer's instructions supplied with the kit. The intra- and inter-assay coefficients of variation and assay sensitivity were respectively: < 7.91% < 7.18% and 0.86ml/IU for FSH; < 7.62%, < 11.02%, and 1.27ml/IU for LH; and < 7.87%, < 8.78%, and < 1.4pg/ml for E2. Hormonal concentrations were calculated in relation to standard curves and expressed in mIU/ml for FSH and LH and pg/ml for E2.

Anthropometry.

Body height was measured with the Martin anthropometer by a trained assistant, with accuracy of 0.1 cm. All measurements were performed by the same person. Body fat percentage (BFP) was measured in the fasting state by bioimpedance using an analyzer (Bodycomp MF, AKERN, Italy) and computer software (BodyGram 1.2, Akern Bioresearch, Italy).

To estimate levels of FA, six bilateral body traits were measured: ear width, ear height, wrist width, elbow width, and length of the second and fourth fingers. The measurements were performed using electronic calipers by a trained assistant with accuracy of 0.01 mm. All measurements were performed by the same person. As asymmetries in metrical characters are small and random, and therefore indistinguishable from measurement error without replicate measurements (Palmer & Strobeck, 1986), all traits were measured twice to establish the repeatability of the FAs. Eight participants reported past fractures or dislocations in the measured traits, such as: broken second left/right finger (N = 2), broken elbow (N = 2), broken right/left wrist (N = 4). For those participants, we excluded those traits from the analyses to avoid asymmetries caused by injuries.

Fluctuating asymmetry calculations and statistical analyses.

Absolute FA was calculated as the difference between the right and left side of the trait (R-L). Repeatability was calculated for signed absolute FAs, and a two-way mixed ANOVA was used to test the ratio between the within-sides variance (measurement error) and the between-sides variance (actual FA). Tests for the significance of the between-sides variance relative to measurement error were conducted following the analysis of variance (ANOVA) procedure outlined in Palmer and Strobeck (1986; 2003) and Palmer (1994).

FA is defined as a normal distribution of R-L differences about a mean of zero. Thus a test for skew and kurtosis of distributions of R-L were conducted. Measurements of all traits met the criterion of FA (Palmer & Strobeck, 1992). The averaged absolute differences between the sides for each measurement were used to calculate the aggregated composite FA index (mean of all six measured traits FAs for each individual).

The values of AMH, LH, FSH and E2 did not demonstrate normal distributions ($p < 0.05$); thus, logarithmic values (ln) for each of these levels were used in the statistical analyses. As body height, adiposity, age and age at menarche have been associated with hormone levels and body FA (Dunson et al., 2002; Emaus et al., 2008; Gangestad et al., 1994; Jasieńska et al., 2006; Manning, 1995; Özener & Ertuğrul, 2011), we controlled for those factors in statistical analyses. Hierarchical multiple regression was used to test for the relationship between FA and hormonal levels. Body height, adiposity, age and age at menarche were entered in the first block and hormone levels were entered in the second block. The factors included in each model were selected based on AIC criterion and differences in the analyses of the relationship between each hormone and FA levels with and without inclusion of those variables. Due to their modest or lack of association, the following variables did not enter the models: 1) participants' age and adiposity did not enter the model analyzing the relationship between FA and AMH level; 2) participants' adiposity and age at menarche did not enter the model analyzing the relationship between FA and E2; 3) participants' age and body height did not enter the model analyzing the relationship between FA and FSH; and 4) participants' age and age at menarche did not enter the model analyzing the relationship between FA and LH. Results were considered significant at the $p < 0.05$ level.

Results

Descriptive characteristics

All participants were students or had a higher education degree. Women who practiced sports regularly (N = 32) did not differ from women who declared that they participated in no regular physical activity (N = 21) in terms of hormone levels (AMH: t(51) = -0.29, p = 0.77; E2: t(51) = 0.59, p = 0.56; LH: t(51) = 0.28, p = 0.78; FSH: t(51) = 0.26, p = 0.79) or FA levels (t(51) = -1.45, p = 0.15). None of the participants suffered from chronic or acute diseases and none declared past use of hormonal medications.

None of the controlled variables (body height, weight, BMI, adiposity) was related to FA (p > 0.05 for each variable) (Table 1). Among these variables, only age at menarche was negatively related to AMH levels (r = -0.30, p = 0.03) but not to other studied hormones. Also, body height was negatively related to LH level (r = -0.31, p = 0.03).

Correctness of composite FA index measurement

For each individual, the between-sides variance (Mean squares of the sides x individuals interaction) was significantly larger than measurement error for each trait measured; thus, all traits showed significantly higher between-sides variance than measurement error (Table 2). None of the mean sided right-minus-left differences were significantly different from zero (Table 3), indicating no evidence for directional asymmetry. In addition, frequency distributions of right-minus-left differences exhibited no significant skew (Table 3). No antisymmetry or other peculiar departures from ideal FA (Palmer & Strobeck, 1992) were observed. Also, the difference between sides (R-L) did not depend on trait size, (R+L)/2 (Table 3); thus, the values of FA were not standardized for the trait size.

Thus, body FA measurements were conducted correctly and calculated composite FA index reliably reflects participants' fluctuating asymmetry level.

Fluctuating asymmetry and AMH levels

Correlation analysis showed no relationship between AMH and FA level (Table 1). Hierarchical linear regression analysis was performed to evaluate whether FA was related to AMH levels. In the first block, we entered covariates (height, menarche age). In the second block, we entered FA level. We found no relationship between AMH and FA levels (Table 4 – Model 1).

Fluctuating asymmetry and E2 level

Correlation analysis showed positive relationship between E2 and FA level (Table 1). Also, hierarchical linear regression analysis was performed to assess whether FA was related to E2 levels. In the first block, we entered covariates (height, age). In the second block, we entered FA level in the model and found that it explained an additional 13% of variance, and this change in R^2 was statistically significant ($F(1, 49) = 3.99$, $p = 0.04$ (Table 4 – Model 2).

Fluctuating asymmetry and FSH, LH levels

FA was not significantly related to LH ($\beta = 0.02$, $p = 0.89$) or FSH ($\beta = -0.05$, $p = 0.70$) levels (Table 1). Hierarchical linear regression analyses were performed to determine the relation of FA to LH and FSH levels. In the first block, we entered covariates (adiposity and age at menarche for FSH level and adiposity and height for LH level). In both models, in the second block, we entered FA level and found no relationship to FSH or LH (Table 4 – Models 3 & 4).

Discussion

Face and body symmetry is perceived as a physically attractive trait, and as FA has been shown to be negatively related to many biologic markers, mate preferences for more symmetrical individuals may have evolved to facilitate choosing partners in better biologic condition (Jasieńska et al., 2006; Manning et al., 1998). As both ovarian hormones levels and FA level may result from the influences of environmental stressors affecting fetal development (King et al., 2009; Singh & Rosen, 2001), one may expect a positive relationship between the optimal fertility hormone profiles and body symmetry. The results of this study, however, did not unequivocally confirm this presumption. We found no relationship between the level of fluctuating asymmetry and early-follicular AMH, FSH and LH levels. However, we found that more symmetrical women had lower early-follicular estradiol concentration.

Previous studies have shown that asymmetry (estimated only on one bilateral trait measurement) in women was negatively related to the mean mid- menstrual cycle E2 levels, which suggests greater fecundity in more symmetrical women (Jasieńska et al., 2006). E2 levels fluctuate significantly within the menstrual cycle, influencing the sequential changes in the female reproductive system that make pregnancy possible. Although women are more likely to become pregnant in menstrual cycles with higher levels of E2 in the follicular phase (Gorkemli et al., 2004; Lipson & Ellison, 1996; Venners et al., 2006), it is the lower E2 concentration on cycle day 3 that is related to higher conception rates within the cycle (Leach et al., 1997; Regan et al., 1990; Smotrich et al., 1995). Thus, the results of both the studies by Jasieńska et al. (2006) and ours are coherent and indicate that symmetrical women have more “profecund” E2 levels in the entire cycle than less symmetrical women. Previous studies also showed that asymmetry varies within the cycle, according to the

fertility level within the cycle and is the lowest in the mid-cycle, when a woman is fertile (Manning et al., 1996).

Our results showed no relationship between the FA levels AMH or cycle day 3 FSH and LH concentrations. E2, AMH and gonadotropins are components of different hormonal mechanisms regulating a woman's fertility. E2 is related to the hypothalamic-pituitary-gonadal axis activity, and its level fluctuates within and between the menstrual cycles, and those fluctuations correspond with changes in the probability of successful conception (Lipson & Ellison, 1996). AMH level, however, does not depend on the activity of hypothalamic-pituitary-gonadal axis, remains stable within and between the cycles, slowly decreasing with age and reflecting ovarian reserve and thus residual reproductive potential (Anderson et al., 2012; Dewailly et al., 2014; Kunt et al., 2011; Streuli et al., 2008). Also, although LH and FSH are strongly related to fertility (Kunt et al., 2011; Singer et al., 2009; Van Loendersloot et al., 2010), their levels are regulated by many factors, and it might be more difficult to detect the relationship between LH, FSH concentration and morphological markers of biological conditions. E2 at normal physiological levels not only influences fertility but also acts as immunostimulant, influencing a woman's health (Barrett-Connor, 2007; Jasieńska et al., 2010; Robinson et al., 2011; Wira et al., 2015) and possibly developmental stability and FA. Thus, the relationship between E2 and FA may be easier to detect. Although AMH level is also related to women's health (Cui et al. 2016; Henes et al. 2015; Lawrenz et al. 2011; Sklavos et al. 2014), it does not have immunostimulant properties comparable to those of E2.

It is also possible that E2, AMH and gonadotropins are different components of female fertility, which may be related differently to such markers of the biological condition as FA levels. Female fertility is determined by two main factors: 1) fecundity within the cycle,

relatively quickly adjusted to current environmental conditions and current energetic status (Jasieńska, 2010); and 2) the length of the reproductive life-span, starting with menarche and ending with menopause. The former can be relatively accurately estimated by measurement of the levels of reproductive hormones (estradiol or progesterone) within the menstrual cycle (Lipson & Ellison, 1996; Jasieńska & Jasieński, 2008). The latter can be estimated with measuring levels of hormones related to ovarian reserve, such as AMH or basal FSH and LH. The results of the present study showed that lower FA was related to E2 levels, indicating potentially higher fertility within the cycle, and seemed not to be related to AMH, FSH or LH, hormones related to a woman's residual reproductive potential. This may suggest that accurate information on a woman's current fertility may be more important for a potential mate than information on the putative age of her menopause. This might be especially true in young women, as the age at menopause may be influenced by many factors, such as a woman's reproductive history and lifestyle factors (Gold, 2011), which may untangle potential relationship between FA and AMH. Some previous research suggests that FA may change even within the menstrual cycle, decreasing in mid-cycle when ovulation occurs (Manning et al., 1996; Scutt & Manning, 1996).

This study had some limitations. First, it is possible that the hypothesized relationship between FA and AMH or gonadotropins levels may be only detected in women of older age. The relatively young age and the narrow age range of participating women (20-28 years) might explain the lack of observation of a relationship between a participants' age and AMH level. Women within age range 23-25 years comprised 88.7% of the studied sample. Although many studies have shown that non-growing follicle recruitment, and thus AMH level, peaks during adolescence or early 20s (Dewailly et al., 2014; Hagen et al., 2010; Kelsey et al., 2011; Wallace & Kelsey, 2010) and then declines gradually with age, some studies

have suggested that peak AMH levels may not occur until 24.5 years of age (Kelsey et al., 2011), which could obscure the relationship between AMH level and morphological markers of women's biological condition in this sample. Furthermore, high early-follicular FSH in young women is less strictly related to infertility, compared to older women (Barad et al., 2007). Although research reported reliable relationships between those hormones and other indicators of a woman's life history or biological condition in young women (e.g., Bragg et al., 2012), it is likely that women in this sample were too young to assess correctly the ovarian reserve using AMH level as a measure of a woman's residual reproductive potential. It would be interesting to verify the results obtained in our study on a group of women older than 25 years. A further limitation of our study was the small sample size, which may have resulted in a Type II error and thus provided inadequate statistical power to detect modest but meaningful associations as statistically significant, which may account for the lack of observation of a relation of FA with AMH, LH and FSH. Future follow-up research employing a larger sample size would help to address this shortcoming in our work. Additionally, the multiple comparisons conducted may have resulted in a Type I error.

Another limitations was that the cross-sectional study design allowed us only to observe the presence or absence of the relationship but did not permit assessment of the temporal and thus potentially causal relation of the variables, which can be only detected in longitudinal studies. However, as FA is a morphological marker of developmental instability (Van Dongen & Gangestad, 2011), we would not expect that FA directly affects fecundity in women, but rather a negative and possibly indirect relationship exists between these two variables, which also could best be detected in a longitudinal study. This is due to the fact that asymmetry and unfavorable hormone profiles should both be results of some perturbations during an individual's development.

It is also worthwhile adding that, as pointed out by Ellison (2003), hormone levels in Western women actually appear to be abnormally high. Abundant availability of energy during fetal and childhood development and during adult life contributes to the high levels of ovarian hormones. Such energetic conditions were unlikely features throughout the majority of human evolution (Jasieńska, 2010). Thus, it is possible that the relationship between the level of FA and reproductive hormones would be easier to detect in traditional populations. Also, it is possible that women could not reliably recall their age at menarche, which might have affected the results of the study. To avoid this effect, participants were asked to answer the question only if they remembered their age at menarche well, but it is not possible to determine if it was true.

Despite some limitations, our study results are consistent with the results of the previous study by Jasieńska et al. (2006), showing that symmetrical women have more favorable E2 levels, not only in the mid-cycle but also at the 3rd menstrual cycle day, which should be related to the greater fecundity.

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Table 1. Means (M), standard deviations (SD) and correlations of the examined variables.

		M±SD	Range	Correlation Coefficients r (r^2) [95% CI]				
				5	**6**	**7**	**8**	**9**
1	Age [years]	23.42±1.85	18-28	0.07 (<0.01) [-0.20;0.33]	-0.03 (<0.01) [-0.29-;0.23]	0.18 (0.03) [-0.09;0.42]	0.07 (<0.01) [-0.20;0.33]	-0.05 (<0.01) [-0.31;0.22]
2	Menarche age [years]	12.94±1.45	10-17	-0.02 (<0.01) [-0.28;0.25]	**-0.30*** (0.09) [-0.52;0.03]	0.01 (<0.01) [-0.23;0.28]	-0.11 (0.01) [-0.37;0.16]	0.04 (<0.01) [-0.23;0.30]
3	Body height [cm]	164.53±6.67	150-179	0.10 (0.01) [-0.18;0.36]	-0.20 (0.04) [-0.44;0.07]	0.21 (0.04) [-0.06;0.45]	**-0.31*** (0.10) [-0.53;-0.04]	-0.08 (<0.01) [-0.33-0.19]
4	Body fat mass [%]	26.91±5.70	17-40	0.03 (<0.01) [-0.24;0.29]	0.09 (<0.01) [-0.18;0.35]	-0.11 (0.01) [-0.37;0.16]	-0.05 (<0.01) [-0.31;0.22]	-0.18 (0.03) [-0.43;0.09]
5	Composite	1.17±0.29	0.55-		0.17 (0.03)	**0.28***	-0.22	-0.20

	FA[1]		1.84		[-0.10;0.42)	(0.08) [-0.14;0.38]	(0.05) [-0.46;0.05]	(0.04) [-0.44;0.07]
6	AMH [ng/ml]	4.88±2.51	0.97-11.43			0.11 (0.01) [-0.16;0.37]	0.24 (0.06) [-0.03;0.47]	**-0.30*** (0.09) [-0.52;-0.03]
7	Estradiol [pg/ml]	26.22±18.07	0.55-40.10				-0.15 (0.02) [-0.40;0.12]	-0.18 (0.03) [-0.43;0.09]
8	LH [mIU/ml]	6.36±2.90	1.76-15.04					**0.44** (0.19) [0.19-0.63]
9	FSH [mIU/ml]	8.36±2.49	3.98-17.52					

Note: N = 53; * $p < 0.05$

Table 2. Two-way mixed ANOVA results for testing the relative magnitudes of measurement error and between-sides variation for six bilateral traits measured in the study (N=53).

Trait	Sides	Individuals	Individuals x Sides	Measurement Error (σ2)	Mixed-Model Significance levels [FA>Measurement error]	
	MS[1] (df = 1)	MS[2] (df = 52)	MS[3] (df = 52)	MS[4] (df = 106)	F	p
Ear Length [mm]	7.15	68.35	2.54	0.20	12.71	*< 0.01*
Ear Width [mm]	6.67	20.67	1.64	0.18	9.03	*< 0.01*
Elbow Width [mm]	5.67	211.16	2.52	0.32	7.86	*< 0.01*
Wrist Width [mm]	2.82	75.17	1.15	0.16	7.07	*< 0.01*
4th Digit [mm]	1.98	100.79	1.02	0.15	6.87	*< 0.01*
2nd Digit [mm]	0.06	93.07	3.15	2.02	1.56	*0.028*

[1] Mean square of the sides
[2] Mean square of the individuals
[3] Mean squares of the sides x individuals interaction
[4] Mean squares of the variance of the repeated measurements [error]

Table 3. Frequency distribution of the difference between sides of six bilateral traits (N=53).

Statistic	Trait [mm]					
	Ear Length	Ear Width	Wrist Width	Elbow Width	2nd Digit Length	4th Digit Length
(R+L)/2 Mean (SE)	55.78 (4.05)	26.22 (2.27)	50.13 (4.35)	77.31 (7.30)	67.72 (4.88)	67.58 (5.02)
R-L Mean (SE)	-0.37 (1.6)	-0.36 (1.28)	0.36 (1.61)	-0.33 (1.80)	0.21 (1.20)	0.19 (1.03)
P*	0.10	0.10	0.11	0.19	0.20	0.18
Kurtosis (p)	-0.78 (0.10)	-0.16 (0.94)	-0.68 (0.19)	0.14 (0.65)	-0.64 (0.24)	-0.34 (0.66)
Skew (p)	0.00 (0.99)	0.31 (0.32)	0.00 (0.99)	0.25 (0.42)	-0.19 (0.53)	-0.42 (0.19)
IR-LI Mean (SE)	1.35 (0.90)	1.05 (0.79)	1.36 (0.93)	1.41 (1.15)	1.01 (0.66)	0.86 (0.57)
Size dependence of FA** Slope (SE,p)	0.09 (0.14, 0.52)	-0.17 (0.14, 0.20)	-0.03 (0.14, 0.85)	0.23 (0.14, 0.10)	-0.14 (0.14, 0.30)	-0.11 (0.14, 0.41)

* Probability that R-L differs from 0.

** Regression analysis of the dependence of character asymmetry IR-LI, on character size, (R+L)/2

Table 4. Summary of hierarchical regression analysis for the relationship between FA and AMH, E2, FSH and LH levels.

Model	Dependent variable	Covariates	Block 1 β	Block 2 β
1	AMH	Height	-0.10	-0.13
		Menarche age	-0.32**	-0.30*
		Composite FA		0.20
		R^2	0.13*	0.17*
		ΔR^2	0.13*	0.04
2	E2	Height	0.20	0.18
		Age	0.15	0.13
		Composite FA		0.28*
		R^2	0.04	0.13*
		ΔR^2	0.06	0.07*
3	FSH	Adiposity	-0.09	-0.09
		Menarche age	0.06	-0.05
		Composite FA		-0.19
		R^2	0.01	0.05
		ΔR^2	0.01	0.04

4	LH	Adiposity	-0.05	-0.06
		Height	-.31*	-0.29*
		Composite FA		-0.19
		R^2	0.10	0.13
		ΔR^2	0.10	0.04

Note: N = 53; * p < 0.05; **p < 0.01