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No impact of developmental conditions on serum estradiol levels among Bangladeshi women in the UK and Bangladesh

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Introduction: While many aspects of female ovarian function respond to environmental stressors, estradiol (E2) appears less sensitive to stressors than progesterone, except under extreme ecological conditions. However, earlier studies relied on saliva samples, considered less sensitive than blood. Here, we investigated E2 variation among 177 Bangladeshi and UK white women, aged 35-59, using single serum samples. Bangladeshi women either grew up in Sylhet, Bangladesh (exposed to poor sanitation, limited health care, and higher pathogen loads but not poor energy availability), or in the UK.
Methods: We collected samples on days 4-6 of the menstrual cycle in menstruating women and on any day for post-menopausal women. Participants included: i) Bangladeshi sedentees (n=36), ii) Bangladeshis who migrated to the UK as adults (n=52), iii) Bangladeshis who migrated as children (n=40), and iv) UK white women matched for neighborhood residence to the migrants (n=49). Serum was obtained by venipuncture and analyzed using electrochemiluminescence. We collected anthropometrics and supplementary sociodemographic and reproductive data through questionnaires. We analyzed the data using multivariate regression.
Results: E2 levels did not differ between migrant groups after controlling for age, BMI, physical activity, psychosocial stress, parity, and time since last birth (parous women). Paralleling results from salivary E2, serum E2 did not differ among women who experienced varying developmental conditions.
Conclusion: Our results reinforce the hypothesis that E2 levels are stable under challenging environmental conditions. Interpopulation variation may only arise under chronic conditions of extreme nutritional scarcity, energy expenditure, and/or high disease burdens.

Key Words: Serum estradiol, migration, Bangladeshi women, developmental conditions, reproductive function

1. Introduction

Reproductive ecologists have long shown that aspects of female reproductive function respond to environmental stressors, such as energy availability and physical activity (Ellison et al., 1993; Jasienska & Ellison, 2004; Ziomkiewicz et al., 2008). The responsiveness of the female endocrine system to these environmental stressors likely facilitates adjustments in female ovarian function to optimize the probability of a successful reproductive event (Ellison, 1990). While hormonal fluctuations are influenced by acute conditions, the environment during development likely primes an individual's baseline hormone levels in response to overall energy availability (Ellison, 1996). Developmental changes that influence reproductive set points, combined with the sensitivity of reproductive hormones to changes in environmental conditions, help to optimize the timing and frequency of reproduction to maximize fitness in an individual's specific ecological setting. Evidence in support of this strategy has been provided by progesterone's (P4) sensitivity to changes in environmental stressors as well as its variation across different ecologies (Baird et al., 1999; Bentley et al., 1998; Clancy et al., 2013; Ellison et al., 1993; Jasienska & Ellison, 2004; Jasienska & Jasienski, 2008; Núñez-de la Mora et al., 2007; Panter-Brick & Ellison, 1994; Vitzthum et al., 2002; Ziomkiewicz et al., 2008). As estradiol (E2), like P4, is critical for fecundity and fertility, we would expect it to follow a similar pattern of sensitivity to environmental change.

E2 does respond to acute stressors and varies as expected in harsh ecological conditions, such as those characterized by extreme nutritional scarcity and high disease burden. For example, E2 levels vary across menstrual cycles (Chatterton et al., 2005; Jasienska & Jasienski, 2008) and are associated with measures of acute conditions such as physical activity, body composition, and dietary composition (Emaus et al., 2008; Ennour-Idrissi et al., 2015; Williams et al., 2010; Wu et al., 1999; Ziomkiewicz et al., 2008). With regard to harsh ecological conditions, researchers have found that Lese women had lower salivary E2 levels than Boston women (Bentley et al., 1998). Bolivian Aymara women also had significantly lower salivary E2 levels than Chicago women in non-conception, but not conception, cycles (Bentley et al., 2000). Developmental conditions also contribute to variation in adult E2 levels. A study in Polish women found that greater fatness at birth predicted reduced sensitivity to the potentially stressful effects of physical activity on E2 hormone levels in adulthood (Jasienska et al., 2006).

Despite this demonstrated variation, E2 appears to be less sensitive to ecological conditions than P4. For example, while we previously found differences in salivary P4 levels between Bangladeshi sedentees, immigrants from Bangladesh to the UK, second generation British-Bangladeshis, and UK white women who were of prime reproductive age (19-39) (Núñez-de la Mora, et al., 2007), we observed no significant differences in salivary E2 levels by migrant status in this same sample (Núñez-de la Mora et al., 2008). Additionally, a similar migrant study comparing serum E2 levels among Pakistani women in Pakistan, adult Pakistani migrants to the UK, Pakistani women born in the UK, and UK white women also found no significant differences in E2 across these groups (Pollard et al., 2009). While E2 variation among post-reproductive women is not well-studied, serum E2 levels do not appear to vary by

population or ethnicity among women during the peri- or postmenopause (Golden et al., 2007; McTiernan et al., 2008; Randolph et al., 2003; although see Setiawan et al., 2006). The poor characterization of E2 variation among postmenopausal women is likely a combination of several reasons, including the fact that E2 levels are low after menopause relative to levels in women of reproductive age, estrone (E1) becomes the primary estrogen during the postmenopausal period, and postmenopausal E2 concentrations are not a measure of ovarian function. Instead, E2 is largely produced via the conversion of androgens in muscle and adipose tissue (Santen, 2009; Simpson, 2003). This study will examine variation in E2 levels across groups of postmenopausal women who vary by migration status.

Some large epidemiological studies have found variation in E2 levels among groups that do not experience extreme differences in ecological conditions, such as between ethnicities within regions (Ausmanas et al., 2007; Randolph et al., 2004). However, these studies did not control for key biocultural or demographic variables that may have confounded their results, such as parity, physical activity, psychosocial stress, age at last birth, and/or migrant status/country of birth.

This body of research suggests that reproductive hormones are not equally sensitive to environmental stressors, and Núñez-de la Mora et al. (2008) have argued that variation in E2 levels may be observed only in the most challenging environments. Less extreme conditions, such as those of Bangladeshi sedentees and migrants to the UK who did not suffer food insecurity or seasonal variation in food intake, high workloads, or extremely pathogenic environments, may not significantly influence E2 variation, even though their living standards differed from UK white women and their pathogen exposure in Bangladesh was also higher (Núñez-de la Mora et al., 2008). These authors suggested that E2 variation across populations may only arise under conditions of extreme nutritional scarcity, energy expenditure and/or high levels of immune insults.

Studies of E2 variation have largely used salivary hormone measurements to reach these conclusions. However, some researchers have questioned if early salivary assays were sufficiently sensitive for this work. These criticisms were due, in part, to the potential for contamination from blood (Kivlighan et al., 2005; Vining & McGinley, 1987) and the uncertainty surrounding the validity of early assays to analyze E2 (Sufi et al., 1985). Some researchers still question salivary E2 measures given the rapid fluctuations of E2 concentrations in saliva and express doubts about the analytical validity of E2 salivary assays (Read, 2009; Wood, 2009). This skepticism occurs despite robust evidence suggesting their accuracy, including the existence of commercial enzyme immunoassay kits from various companies (e.g., Creative Diagnostics®, IBL International, Salimetrics®, and others), high correlations between salivary and serum assay profiles (Fiers et al., 2017), conformation to expected profiles (Celec et al., 2009; Chearskul & Visutakul, 1994; Gann et al., 2001; Lipson & Ellison, 1996), and early favorable prognoses for E2 assays from the Tenovus group in Wales that pioneered the use of salivary steroids (Riad-Fahmy et al., 1982, 1983). As such, while most studies examining population variation have used saliva samples, results using blood samples remain the gold

standard. Here we address criticisms of the previous work by examining whether we observe the same results using serum as we found with saliva samples.

Therefore, we investigated the hypothesis that E2 levels are relatively insensitive to environmental conditions using serum samples, the gold standard. We replicated the study design of Núñez-de la Mora et al. (2008) with a sample of women from the same population but with an older age range. To achieve our aim of characterizing the sensitivity of E2 in relation to developmental conditions, we analyzed serum E2 levels among Bangladeshi women who differed in migrant status and compared them to the E2 levels of UK white women. This sample allowed us to investigate three distinct aims: 1) to determine whether E2 levels vary by migrant status during the reproductive-aged years, when E2 serves as a proxy for ovarian function; 2) to investigate whether E2 levels differ across the menopausal transition by migration status; and 3) to better characterize variation in E2 levels during the postmenopause. Previous studies working with this population have collected data on pathogen and cyclone exposure during childhood as well as other aspects of the environment that highlight differences in developmental conditions between women growing up in Bangladesh and those in the UK that could influence hormonal set points (Begum et al., 2016; Murphy et al., 2013). Despite these differences in developmental conditions, we predicted that serum E2 would not differ significantly by migration status after controlling for factors that influence E2, such as BMI and physical activity. Our results have implications for understanding the sensitivity of the female endocrine system to environmental conditions during development and throughout the lifespan.

2. Methods

The total sample size included 186 women aged 35-59. Since only 7 individuals were second generation immigrants to the UK, we excluded those women from the analyses. We also excluded one woman who did not report her menopausal status and another with an E2 level > 750 pg/mL, which fell within the sensitivity range of the assay but was > 2SD above the mean, leaving a final sample size of 177 (128 premenopausal women, and 49 postmenopausal women). The full sample also contained four groups that differed by migration status: i) Bangladeshi sedentees (n = 36), ii) adult migrants in the UK (those who migrated after menarche; n = 52), iii) child migrants in the UK (those who migrated before menarche; n = 40), and iv) UK white women living in similar neighborhoods to the British-Bangladeshis (n = 49). Due to the small sample size of postmenopausal women in the child migrant category (n=1), we limited the migrant status variable to three levels for the main analyses: i) Bangladeshi sedentees, ii) adult migrants to the UK, and iii) UK white women (i.e., child migrants were only included in the supplementary analyses). The women represent a subsample of a larger study that investigated reproductive aging at midlife and who were willing to volunteer for venipuncture (Begum et al., 2016; Dhanoya et al., 2016; Murphy et al., 2013; Sharmeen et al., 2013; Sievert et al., 2008, 2016).

Methods for the larger study are described elsewhere (Begum et al., 2016; Murphy et al., 2013). Briefly, we recruited participants through influential community members (Bangladesh),

community centers (London), personal contacts, and snowball techniques (both locations). Among the UK white women, we recruited participants through advertisements in local newspapers and websites. Eligible women were those aged 35 to 59 who had not used any exogenous hormones in the past three months, were not pregnant or lactating, and had not undergone a hysterectomy or oophorectomy. We excluded any individuals with polycystic ovarian syndrome or other endocrine disorder, such as diabetes or a thyroid condition. These exclusion criteria were applied to remove potential confounding effects on hormone levels.

Participants completed a structured questionnaire to collect demographic details and information on reproductive, migration, educational, lifestyle, and employment histories. The questionnaires were first translated into Bengali by native speakers and then back-translated into English to check for inaccuracies. Both versions were piloted prior to use. Trained researchers administered the questionnaire in person, and women could choose to respond in either Bengali or English.

Fourteen percent of Bangladeshi women did not know their exact birth dates because they were born at home before birth records were routinely collected in Bangladesh (50% of Bangladesh sedentees, 2% of the adult migrants, none of the child migrants). To help with age estimations, we constructed an event calendar including memorable occurrences in Bangladesh, such as the War of Independence, Victory Day, and major national disasters, such as cyclones. To assist with recall of the last menstrual period for older women, we asked them to remember the season of the year and any important events that had occurred at that time. Similar event history calendars are commonly used in survey methodologies to help with reconstructing the past (Belli et al., 2008).

In addition to the questionnaire, we also collected anthropometric data and single serum samples. We measured height and weight using standardized techniques (Lohman et al., 1988). We calculated the body mass index (BMI) as wt(kg)/ht(m^2). For the serum samples, we collected 5 ml of blood by venipuncture between days 4 to 6 of the menstrual cycle for pre/perimenopausal women and at any time for the post-menopausal women. Days 4 to 6 were chosen to prioritize the time of the cycle when anti-Müllerian hormone, inhibin B, and follicle-stimulating hormone (the primary biomarkers of ovarian reserve) are expected to be highest. Samples were all collected later in the day after the morning peak in E2 levels, after which levels of E2 should be relatively stable (Bao et al., 2003). We analyzed the serum samples to measure both the free and bound E2 (pg/mL) using an electrochemiluminescence immunoassay kit by Roche Molecular, Biochemicals, Mannheim, Germany according to manufacturer instructions. The measuring range of the assay was between 5 and 4,300 pg/mL, and the mean intra- and inter-assay CV was $\leq$10%.

We used R (3.4.1) for statistical analyses of the data. We log-transformed serum E2 levels to normalize the distribution of data and used multivariate regression to predict serum E2 levels while controlling for potential confounders. We determined menopausal status using the World Health Organization guidelines (WHO 1996). Using this system, we classified women as premenopausal if they had menstruated in the previous 2 months, perimenopausal if they last

menstruated between 3 to 12 months ago, and postmenopausal if they had not menstruated in the past 12 months. However, since only 10 women were considered perimenopausal, we included these in the premenopausal sample for most analyses, unless otherwise stated.

We created five models to investigate variation in E2 by migration status followed by robusticity analyses. In exploratory data analysis, we found that E2 levels differed significantly between parous and nulliparous women ($t = 27.63$, p-value < 0.001, 95% CI = 2.42-2.79). Therefore, for each model, we also ran a second analysis including only parous women to ensure that no important differences in the physiology of nulliparous and parous women influenced our results. In Model 1, we analyzed E2 levels among all premenopausal women. Model 2 included the full sample with menopausal status categorized as three levels (pre-, peri- and postmenopausal). In Model 3, we again included all women but categorized menopausal status as binary (pre/perimenopausal and postmenopausal). Model 4 included all women but did not account for menopausal status. Model 5 involved only postmenopausal women.

For each model, we controlled for variables known to affect levels of reproductive steroids from earlier studies (Barrett et al., 2014; Emaus et al., 2008; Ennour-Idrissi et al., 2015; Williams et al., 2010; Ziomkiewicz et al., 2008). For variables suspected to affect E2 levels, such as psychosocial stress (Roney & Simmons, 2015), we included them if they emerged as statistically significant predictors in univariate analyses. The variables included in the main models were age, BMI, parity, frequency of exercise per week (e.g., at a gym), walking more than 20 minutes a day, time spent cleaning (as a measure of physical activity), and self-rated psychosocial stress. To investigate if E2 levels differed across the menopausal transition between women who varied in their migrant status, we included an interaction term between menopausal status and migrant status in Models 2 and 3. However, these models did not include age because it was highly correlated with menopausal status. Exploratory data analysis suggested that age differed between women from the separate migrant groups. Statistical analysis confirmed this difference was statistically significant, so we also used an interaction term between migrant status and age in Model 4 to ensure that sampling issues did not confound the results. Additionally, models including only parous women contained the additional covariate of time since last birth (years), which could not be controlled for in models including nulliparous women. Following the main analyses, we investigated the robusticity of these models by including child migrants (see Supplementary Information). All models in the supplemental analyses contained the same predictors as Models 1-5.

We received ethical permission for the study from the University College London Ethics Committee, UK; the Ethics Committee for the Department of Anthropology, Durham University, UK; the University of Massachusetts Amherst Institutional Review Board, USA; and the Ethics Board, Sylhet MAG Osmani Medical College, Bangladesh.

3. Results

Descriptive statistics for the full sample, by menopausal status, and migrant group are presented in Table 1. Across the migrant groups, women differed significantly for all covariates

($p < 0.05$). Figure 1 compares serum E2 levels across the reproductive lifespan for the four migration groups. Our models are summarized in Table 2.

TABLE 1, TABLE 2, & FIGURE 1 ABOUT HERE

3.1 Premenopausal analysis

In the first set of analyses, we analyzed E2 levels among premenopausal women by migrant group (Table 2). Model 1a was not statistically significant (n = 80, adjusted $r^2 = 0.09$, model $p = 0.07$, $F = 1.89$). We then investigated if the results differed when the sample was limited to parous women (Model 1b). This model was also not statistically significant (n = 60, adjusted $r^2 = 0.09$, model $p = 0.15$, $F = 1.56$). We tested the robusticity of these models by running a supplemental model including the child migrants, which was also not statistically significant (see Supplementary Information).

3.2 Menopausal Transition Analyses

Secondly, we investigated if serum E2 levels differed across the menopausal transition by migration status (Table 2). In Model 2a (n = 120, adjusted $r^2 = 0.21$, $p < 0.001$, $F = 3.23$), we found that postmenopausal women had lower E2 levels than premenopausal women ($B = -1.22$, $SE = 0.33$, $p < 0.001$). We also found that Bangladeshi sedentees had higher E2 levels than UK white women ($B = 0.83$, $SE = 0.32$, $p = 0.009$). In Model 2b (n = 96, adjusted $r^2 = 0.31$, $p < 0.001$, $F = 3.9$), when limiting the sample to parous women only, we found that postmenopausal women had significantly lower E2 levels than premenopausal women ($B = -1.28$, $SE = 0.46$, $p = 0.007$). In neither model was the interaction term statistically significant.

We next reran the menopausal transition analyses classifying menopausal status as a binary variable (premenopausal or postmenopausal) (Table 2). In Model 3a (n =120, adjusted $r^2 = 0.22$, $p < 0.001$, $F = 4.11$), we found that postmenopausal status was a significant negative predictor of E2 concentrations ($B = -1.24$, $SE = 0.32$, $p < 0.001$). We also found that Bangladeshi sedentees showed higher E2 levels than UK white women ($B = 0.78$, $SE = 0.30$, $p = 0.01$). We then limited the analysis to parous women in Model 3b (n = 96, adjusted $r^2 = 0.34$, $p < 0.001$, $F = 5.03$). In this model, postmenopausal status predicted lower E2 levels ($B = -1.28$, $SE = 0.43$, $p = 0.004$) and Bangladeshi sedentees had significantly higher E2 levels than UK white women ($B = 0.58$, $SE = 0.29$, $p = 0.05$). As above, in neither model was the interaction term statistically significant.

Model 4a accounted for age but not menopausal status in the interaction term with migrant status (n = 120, adjusted $r^2 = 0.25$, $p < 0.001$, $F = 4.57$). Age was the only significant predictor in this model ($B = -0.09$, $SE = 0.02$, $p < 0.001$). Model 4b, which included parous women only, produced similar results (n = 96, adjusted $r^2 = 0.30$, $p < 0.001$, $F = 4.42$) with age being the only significant predictor ($B = -0.09$, $SE = 0.03$, $p = 0.006$).

3.3 Postmenopausal Analyses

In our final set of analyses, we investigated E2 differences among postmenopausal women by migrant group (Table 2). In Model 5a (n = 40, adjusted r^2= 0.26, p = 0.03, F = 2.55), we found no differences by migration status. The only statistically significant predictor was age, which negatively predicted E2 levels (B = -0.07, SE = 0.03, p = 0.02). In Model 5b, we limited the sample to parous women. This model was not statistically significant (n = 35, adjusted r^2 = 0.20, model p = 0.11, F = 1.84). To test the robusticity of this analysis, we also investigated if results remained the same when we included the child migrants. In this model, age was the only significant predictor, and it negatively predicted E2 levels (see Supplementary Information).

4. Discussion

The results duplicate findings from our earlier study (Núñez-de la Mora et al., 2008) and support our hypothesis that E2 levels are relatively stable across moderately challenging environments during development and later adult life. With regard to Aim 1 (to determine whether E2 levels vary by migrant status during the reproductive-aged years), we have again shown that E2 levels do not vary by migration status during the reproductive years. With regard to Aim 2 (to investigate whether E2 levels differ across the menopausal transition by migration status), our results suggest that E2 levels do not vary by migration status across the menopausal transition. With regard to Aim 3 (to better characterize variation in E2 levels during the postmenopause), again, we were able to show that there were no differences by migrant group.

The conserved nature of E2 reflected in our findings may be a result of its critical role in fecundity, specifically for conception, or a function of the physiology of the menstrual cycle, although these explanations are not mutually exclusive. Even though both P4 and E2 influence fecundity, population variation in E2 is not evident in conception cycles while differences in P4 persist (Bentley et al., 2000; Lipson and Ellison, 1996; Vitzthum et al., 2004). P4 has a greater role in the maintenance of pregnancy – low P4 levels are associated with greater odds of miscarriage (Arck et al., 2008). Additionally, the quality and selection of ovarian follicles relies on a long process of development spanning almost a calendar year during which the granulosa cells surrounding antral follicles that produce E2 are steadily maturing and contribute to the ovarian steroidogenic milieu (Gougeon, 1986). In contrast, the corpus luteum that produces P4 is specific to one cycle and it may be possible to modify its function more quickly in response to environmental signals (Hannon & Curry, 2018).

E2 variation may also be more conserved because of its critical role in other functions beyond reproduction. For example, estrogens are necessary for bone growth and maintenance, brain function, skin physiology, cardiovascular health, and the immune system (Cutler, 1997; Hall & Phillips, 2005; Khosla et al., 2012; Klein & Flanagan, 2016; Mcewen, 2002; Moulton, 2018; Murphy & Kelly, 2011; Robinson et al., 2014; Shu & Maibach, 2011). While P4 also has many functions in the body, the widespread physiological effects of E2 may constrain its variability in response to changes in environmental conditions.

Despite many studies showing similar E2 levels among populations from different countries or immigrant groups, some previous literature suggests E2 may differ by ethnicity

(Ausmanas et al., 2007; Randolph et al., 2004). However, because many medical studies of hormonal differences by ethnicity assume these differences are due to genetic variation, they often fail to collect relevant biocultural and demographic variables that may explain their results. For example, serum E2 levels significantly differed among 9 ethnic groups in the Pan-Asia Menopause study (Ausmanas et al., 2007). However, they only controlled for age and BMI in their analyses and did not include other important covariates in their models that were significantly different between groups in this study, such as parity. They also failed to collect data on other relevant variables, such as physical activity, psychosocial stress, diet, and age at last birth. In the US, a study using data from the Study of Women's Health Across the Nation found that E2 levels were similar among white, African American, and Hispanic women but were significantly lower among Japanese and Chinese women (Randolph et al., 2004). However, the effect sizes were small, and they did not control for the many of the same relevant covariates discussed above (parity, physical activity, psychosocial stress, age at last birth, and more comprehensive measures of diet composition beyond dietary estrogens).

The limited research among postmenopausal women or those experiencing the menopausal transition suggests that E2 levels do not differ by ethnicity (Golden et al., 2007; McTiernan et al., 2008; Randolph et al., 2003), although the Multiethnic Cohort Study found that Native Hawaiians, Japanese Americans, and African Americans had significantly higher plasma E2 levels than white women (Setiawan et al., 2006). However, they only observed a difference of 2.7 pg/mL between the most extreme groups. Considering the range of expected E2 levels in the US among menstruating women is 15 to 350 pg/mL (Mayo Clinic Laboratories), it is not likely that a difference of 2.7 pg/mL is biologically meaningful. These examples highlight the need to examine results of large epidemiological studies critically to ensure that important biocultural variables are controlled for and that small differences between groups are interpreted with an understanding of the underlying biology.

The limitations of our study highlight areas for future research on this subject. While our study has a relatively large sample size and our findings advance previous work by using serum samples, we only collected a single sample from each woman. As female reproductive hormones may exhibit large fluctuations between cycles (Chatterton et al., 2005; Jasienska & Jasienski, 2008), future work should collect serum samples from multiple menstrual cycles to account for changes in hormone concentrations between cycles and in aspects of the acute environment that may influence E2 levels. Additionally, future work should investigate the degree to which the sensitivity of E2 to acute conditions, such as body composition or physical activity, changes during the reproductive lifespan, which could affect quantification of E2 variation in studies with dramatically different sample characteristics.

In addition, the Bangladeshi sedentees in this study are from Sylhet, a relatively wealthy area of Bangladesh, and Bangladeshi migrants are not necessarily representative of the larger population, since only those with relatively greater financial resources could afford to emigrate to the UK. More research is needed with migrant groups in this population to verify whether the difference in E2 levels between Bangladeshi sedentees and UK white women in some of our

models was due to sampling issues. In summary, future work should build upon previous studies of E2 variation by investigating levels in a range of ecological conditions to better characterize the degree and type of environmental stressors that most strongly contribute to variation in this hormone and more thoroughly disentangle the effects of acute and developmental conditions on E2 levels across different ecologies.

5. Conclusion

In this study, we investigated E2 levels among women who varied in their developmental and current environmental conditions due to migration to the UK. Using serum samples, we found no differences in E2 levels among Bangladeshi women living in Bangladesh, Bangladeshi immigrants to the UK, and UK white women after adjusting for age and aspects of the current environment that may influence E2 levels. These results confirm earlier results using salivary samples and suggest that E2 set points may be relatively insensitive to variation in environmental conditions during development. In conclusion, our findings provide support for the hypothesis that E2 levels are more robust under challenging environmental conditions than progesterone, with variation across populations likely only occurring under long-term, extreme environmental conditions.

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Data Availability Statement

The data that support the findings of this study are openly available in Durham University Collections (DOI: 10.15128/r2jh343s330).

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Table 1: Descriptive statistics for the full sample, by menopausal status, and by group. Mean (standard deviation). (*) indicates a statistically significant difference among the groups ($p < 0.05$). For the comparisons between migrant groups, UK white women were used as the reference group.

	Premenopausal Women					**Postmenopausal Women**					**Full sample**
	Bangladesh Sedentees	**Adult Migrants**	**Child Migrants**	**UK White Women**	**All**	**Bangladesh Sedentees**	**Adult Migrants**	**Child Migrants**	**UK White Women**	**All**	
N	18	36	39	35	128	18	16	1	14	49	177
Age (years)	40.69 (4.63)*	42.39 (4.95)	39.34 (3.43)*	43.67 (5.01)	41.60 (4.81)	52.51 (4.13)*	52.77 (3.73)	48.8	55.60 (3.70)	53.40 (4.05)	45.94 (7.03)
BMI (kg/m2)	25.90 (3.11)	27.69* (3.47)	27.72 (4.20)*	25.14 (5.27)	26.78 (4.31)	24.40 (6.01)	26.20 (3.05)	25.79	25.63 (4.30)	25.37 (4.62)	26.38 (4.43)
Serum Estradiol	80.20 (70.70)*	44.63 (23.61)	46.38 (37.39)	58.87 (68.19)	54.31 (51.68)	22.50 (7.59)*	28.52 (40.48)*	19.54	10.42 (8.70)	20.97 (24.60)	44.87 (48.01)
Parity	2.89 (1.45)*	3.61 (1.79)*	3.26 (1.43)*	0.91 (1.29)	2.65 (1.87)	3.06 (1.59)*	3.25 (1.39)*	3	1.14 (1.23)	2.57 (1.66)	2.62 (1.81)
Times exercised per week	1.25 (2.43)*	1.35 (1.96)*	1.14 (1.78)*	2.57 (2.43)	1.66 (2.19)	1.06 (2.46)	1.56 (2.33)	0	1.39 (1.82)	1.30 (2.20)	1.55 (2.19)
Walk more than 20 minutes a day (% yes)	61.11%	72.22%	69.23%	70.73%	71.09%	43.75%	75%	100%	69.23%	63.04%	68.8%
Time spent cleaning (min/wk)	1345.63 (705.89)*	1136.12 (509.08)*	1092.59 (630.41)	787.59 (867.85)	1055.71 (707.73)	1336.24 (1150.24)	815.94 (622.16)	690	656.73 (1104.83)	959.01 (1004.23)	1028.32 (800.96)
Self-rated stress (0-6)	4.15 (1.41)	4.97 (1.31)*	3.98 (1.41)	3.93 (1.64)	4.33 (1.48)	4.22 (1.11)	4.43 (1.79)	4	3.73 (1.42)	4.16 (1.41)	4.28 (1.46)
Years since last birth (parous women only)	11.55 (7.12)	10.62 (4.53)	8.37 (4.36)	11.23 (6.65)	10.14 (5.49)	21.48 (6.54)	21.99 (3.96)	15.8	25.35 (5.80)	22.26 (5.62)	13.76 (7.83)

Table 2: Models predicting E2. Predictors followed by a (*) indicate statistically significant values. Refer to text for the B, SE, and p-value.

Model Number	**Sample (n)**	**Predictors**	**Adjusted R^2**	**P-value**	**F Statistic**
1a	Premenopausal (80)	Migration status, age, BMI, parity, frequency of exercise per week, walking more than 20 minutes per day, time spent cleaning per week, and self-rated stress*	0.09	0.07	1.89
1b	Parous premenopausal (60)	Migration status*, age, BMI, frequency of exercise per week, walking more than 20 minutes per day, time spent cleaning per week, self-rated stress*, and time since last birth	0.09	0.15	1.56
2a	Full sample: pre/peri/post (120)	Menopausal status by migration status interaction, parity, frequency of exercise per week, walking more than 20 minutes per day, time spent cleaning per week, self-rated stress, menopausal status*, and migration status*	0.21	<0.001	3.23

2b	Parous full sample: pre/peri/post (96)	Menopausal status and migration status interaction, parity, frequency of exercise per week, walking more than 20 minutes per day, time spent cleaning per week, self-rated stress, time since last birth, menopausal status*, and migration status	0.31	<0.001	3.9
3a	Full sample: pre / post (120)	Menopausal status and migration status interaction, parity, frequency of exercise per week, walking more than 20 minutes per day, time spent cleaning per week, self-rated stress, menopausal status*, and migration status*	0.22	<0.001	4.11
3b	Full parous sample: pre / post (96)	Migration status and menopausal status interaction, parity, frequency of exercise per week, walking more than 20 minutes per day, time spent cleaning per week, self-rated stress, time since last birth, menopausal status*, and migration status*	0.34	<0.001	5.03

4a	Full sample: (120)	Menopausal status and age interaction, parity, frequency of exercise per week, walking more than 20 minutes per day, time spent cleaning per week, self-rated stress, age*, and migration status	0.25	<0.001	4.57
4b	Full sample: parous (96)	Migration status and age interaction, parity, frequency of exercise per week, walking more than 20 minutes per day, time spent cleaning per week, self-rated stress, time since last birth, age*, and migration status	0.30	<0.001	4.42
5a	Postmenopausal (40)	Migration status, BMI, frequency of exercise per week, time spent cleaning, walk 20 minutes per week, self-rated stress, parity, and age*	0.26	0.03	2.55
5b	Parous Postmenopausal (35)	Migration status, BMI, frequency of exercise per week, time spent cleaning, walk 20 minutes per week, self-rated stress, parity, and age	0.20	0.11	1.84

Figure 1: Serum estradiol (E2) levels (pg/mL) across the reproductive lifespan. Error bars represent the standard deviation. Age categories: 1 = 35-39 (n = 55); 2 = 40-44 (n = 40); 3 = 45-49 (n = 33); 4 = 50-54 (n = 26); 5 = 55-59 (n = 24).