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Differential Circadian Catecholamine and Cortisol Responses between Healthy Women with and without a Parental History of Hypertension

Gary D. James^{1,2,3}, Alexandria S. Alfarano¹, and Helene M. van Berge-Landry^{1,2}

¹Department of Anthropology, Binghamton University, Binghamton, NY 13902

²Decker School of Nursing, Binghamton University, Binghamton, NY 13902

³Department of Bioengineering, Binghamton University, Binghamton, NY 13902

Abstract

Objectives—Previous studies suggest that otherwise healthy individuals who have a parental history of hypertension (PH+) have an accentuated reactive rise in catecholamines and cortisol to laboratory stressors as well as elevated plasma levels when compared to those with no parental history (PH−); however, few if any studies have evaluated whether parental history affects the responses of these hormones to changing environmental circumstances in everyday life. The purpose of this study was to compare urinary catecholamine (epinephrine and norepinephrine) and cortisol excretion and ambulatory blood pressures across three daily microenvironments between women with and without a parental history of hypertension.

Methods—The women in the study (PH+, N=62, age=35.2±9.1; PH−, N=72, age=33.8±10.0) worked in clerical, technical or professional positions at a major medical center in NYC. Urinary hormone excretion rates and ambulatory BP were measured across three daily microenvironments: work (11AM–3PM), home (approx. 6PM–10PM) and during sleep (approx. 10PM– 6AM). History group comparisons by microenvironment were made using repeated measures ANCOVA and ANOVA analyses.

Results—The results show that epinephrine excretion among PH+ women was 36% higher than PH− women ($p<.008$) over the entire day, and that nocturnal cortisol excretion was also greater among PH+ women ($p<.045$). PH+ women also had statistically significantly higher systolic (4 mmHg higher; $p<.01$) and diastolic (2 mmHg higher, $p<.03$) BP compared to PH− women across all daily microenvironments.

Conclusion—These findings suggest that there may be genetically-linked mechanisms which elevate tonic epinephrine levels and nocturnal cortisol levels that contribute to elevating circadian blood pressure.

Address Correspondence to: Gary D. James, Ph.D., Department of Anthropology, Binghamton University-SUNY, Binghamton, New York, 13902, Tel: 607-777-6016, Fax: 607-777-6162, gdjames@binghamton.edu.

CONFLICT OF INTEREST: None

Keywords

Parental history of hypertension; Ambulatory blood pressure; Catecholamines; Cortisol

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INTRODUCTION

Numerous studies have found that having a parental history is a risk factor for developing hypertension, but the nature of that association is not well characterized (e.g. Lauer et al., 1991; Williams et al., 1991; Goldstein et al., 2008; Mitsumata et al., 2012). Given the complex nature of blood pressure regulation, genetic variation in a number of regulatory systems could contribute to the association. The levels and reactive dynamics of the sympathetic adrenal medullary system and hypothalamus adrenal pituitary axis have both been studied with regard to their relationship with parental hypertension. Several studies have found that otherwise healthy individuals with a parental history of hypertension exhibit an accentuated acute increase in plasma or urinary catecholamine and cortisol levels with laboratory stress tasks such as mirror image tracing, mental arithmetic, the Stroop color word conflict test, and the cold pressor test (e.g. Falkner et al., 1979; Horikoshi et al., 1985; Fredrickson et al., 1991; Corvelli, 2006; Bennett et al., 2013) and with exercise (Cirolac et al., 2010). Other studies reveal that normotensive adults with a parental history of hypertension may also have higher fasting plasma levels of catecholamines (Goldstein et al., 2008; Rafidah et al., 2008) and cortisol (Matuzek and Boutcher, 2008).

While the acute reactivity of catecholamines and cortisol to laboratory stressors and fasting plasma levels may be accentuated in normotensive adults with a parental history of hypertension, few if any studies have examined whether the response of catecholamines and cortisol to changing daily environments differ by parental history. Specifically, while numerous studies have shown that urinary catecholamine (epinephrine and norepinephrine) and cortisol as well as ambulatory blood pressure responses vary across and within daily microenvironments in a myriad of contexts (e.g. James, 1991a,b; 2013; Light et al., 1995; Luecken et al., 1997; James et al., 1993; 1996; 2004; 2008; Brown and James, 2000; Marco et al., 2000; Steptoe et al., 2000; James and Bovbjerg, 2001; Brown et al., 2006; Dettenborn et al., 2005; Van Berge Landry et al., 2008; 2010; 2013), none have evaluated whether the responses differ by parental history of hypertension. The purpose of this study was to evaluate whether the within-individual variation in urinary catecholamine (epinephrine and norepinephrine) and cortisol excretion, and ambulatory blood pressure (BP) across three daily microenvironments (work home and sleep) differed between healthy, normotensive women with and without a reported parental history of hypertension.

METHODS

Design

Numerous human biological studies which evaluate stress response differences in everyday life have employed a “natural experimental” approach that features naturally occurring environmental contrasts (e.g. Flinn and England, 1997; Garruto et al., 1999; Decker, 2000; Brown et al., 2006; James, 2007b; Worthman and Panter-Brick, 2008; James and Bovbjerg,

2012; Ice et al., 2012). Some of these designs that compare different daily environments are modeled on laboratory experiments of stress reactivity, where a baseline condition is established and then participants are exposed to stressful stimuli (for example, see James et al., 2004; James, 2007a, James and Ice, 2007, Ice and James, 2012, and James and Bovbjerg, 2012 for discussion). As has been often noted, moving the laboratory experimental paradigm to a “natural experimental” context requires some modification since no true baseline can be established in everyday life (see James et al., 2004; James and Ice, 2007; James and Bovbjerg, 2012 for explanation).

Over the years, many researchers have shown that the urban environment is heterogeneous, with various distinct microenvironments (e.g. Harrison and Jefferies, 1977; Harshfield et al., 1982; James, 1991a; Garruto et al., 1999; James and Bovbjerg, 2012). There are often clear and stark demarcations between these microenvironments that define them as separate conditions. As has been noted in many previous studies, a “natural experiment” can be set up by contrasting biological responses across these urban microenvironments (James, 1991b; Garruto et al., 1999; Dettenborn et al., 2005; James, 2007a; James and Bovbjerg, 2012).

Work (place of employment) and home (place of residence) have been firmly established as microenvironmental conditions that are useful in studying physiological or endocrine changes in everyday life (e.g., Harrison et al., 1981; Harshfield et al., 1982; Frankenhaeuser et al., 1989; James et al., 1993; Luecken et al., 1997; Chandola et al., 2010; James, 2013). The work microenvironment is a setting where social interaction occurs with non-related individuals, where a specific occupational hierarchy dictates social relationships, and where there is a general conformity of behavior (James, 1991b; 2007b; James et al., 2004). The parameters of this microenvironment contrast sharply with the home microenvironment, where domestic tasks and leisure activity occur in a social context where interactions are mostly with relatives and neighbors (James, 1991b; 2007b; James et al., 2004). The changes in physiological or endocrine measures across the work and home microenvironments can be evaluated as a “natural experiment” in which the response to the stressors associated with paid employment and domestic life are compared. A microenvironment that is similar for all subjects (such as overnight sleep, or more specifically, lying quietly in a dark room) can act as a pseudo-baseline in this “natural experiment” for biological responses such as blood pressure and the catecholamines (see James et al., 2004; James, 2007b, Ice and James, 2012; James and Bovbjerg, 2012; James 2013), although with urinary cortisol, the evening home environment is more appropriate for this purpose, given its circadian rhythm (see Dettenborn et al., 2005 for discussion).

As noted in numerous previous reports, in developing our field studies of blood pressure and endocrine variation in women, we took advantage of the naturally occurring and easily differentiable microenvironmental variation inherent in the cosmopolitan New York City area and compared the endocrine and blood pressure responses of employed women across their work, home and sleep microenvironments within this aggregate urban setting (e.g. James, 1991; Kario et al., 2002; James, 2007b, 2013). To add further control to the study, occupational location and type were also limited; thus only women working in technical and

clerical positions who were employed at a major medical center in Manhattan in NYC were examined (see James and Bovbjerg, 2001; Kario et al., 2002).

As we noted in earlier studies, a limitation of this research design is the facts that the “baseline” conditions uniformly follow the experimental conditions, such that data were collected at work first, followed by home and then sleep (see for example, James et al., 2004; James and Bovbjerg, 2012). Studies have found that there can be carry-over effects of stress at work that could elevate subsequent physiologic measures at home and during sleep (e.g., James et al., 1989). However, if the sleep “baseline” before the work condition was used, the possible carry-over effects of work the previous day on that sleep measure would be unknown and thus have an unknown bias.

There is also a possibility that women with a parental history could have a general elevation in their endocrine output under all circumstances; that is, a tonic increase in hormonal levels. This kind of difference might be missed if we only examined the within-subject variation across the microenvironments. Therefore, as with our earlier studies of familial breast cancer risk (James et al., 2004; Dettenborn et al., 2005, James et al., 2008; James and Bovbjerg, 2012), this study employed a repeated measures ANOVA/ANCOVA analytic approach (see below) where hormonal output and blood pressure were compared across microenvironments, between parental history groups and across microenvironments within each parental history group so that reactive and tonic differences could be simultaneously evaluated while limiting type 1 error (Salkind and Green, 2008) (see Figure 1).

Subjects

The subjects of this study were 134 normotensive women, 62 with a self-reported parental history of hypertension (maternal and/or paternal) and 72 women without a parental history of hypertension who participated in a larger protocol that was designed to assess the cardiovascular effects of life stress in working women. The women were studied between November and May each year from 1994 to 1998 and were examined on typical mid-week work days (usually Tuesday thru Thursday). They were all volunteers and had to meet several criteria in order to be eligible for study. Specifically, subjects were excluded if they were diagnosed with hypertension, cardiovascular disease, or diabetes, were pregnant, obese (defined as having >40% of body mass as fat as determined from skinfold measurements), on drug therapy (except oral contraceptives) or exhibited significant premenstrual symptoms (defined by clinical treatment for them) (James et al., 1993; Kario et al., 2002). The age range of study subjects was also limited to 18–52 years. The study was approved by the IRB at the Weill College of Medicine of Cornell University and all subjects provided informed consent. Table 1 shows selected biological and demographic characteristics of the study sample.

As indicated, the average age of women in the FH + group was 35.2 ± 9.1 and that in the PH – group was 33.8 ± 10.0 . There were also no statistically significant differences between the parental history groups in any of the biological, behavioral, or demographic variables examined.

Protocol

To be consistent with the research design, the endocrine measurements needed to be integrated so that the assessment reflected the “average” response over the time spent in each microenvironment. Urinary measures provide such an assessment and were thus used in this study as both cortisol and the catecholamines (epinephrine and norepinephrine) can be easily assayed in urine (Pollard and Ice, 2007; Brown, 2007). The procedure used to collect the data was detailed in Kario et al. (2002). Briefly, at the beginning of their workday (between 8 and 9 AM) the women arrived at the Hypertension Center of New York Hospital where they were fitted with the Spacelabs 90207 ambulatory blood pressure monitor. This device has been previously described and validated (e.g. Cates et al., 1990). Just prior to the monitor hook-up, height, weight and a series of anthropometric measurements were taken, and demographic data, medical history and information regarding life stress was also collected at this time. Then, about 1 to 2 hours following the monitor hook-up (11 AM), the women were contacted at their work place and asked to go to the bathroom and empty their bladder, but to not collect that urine specimen. The time of this urination was noted and was the beginning of the work period for the purpose of the study. The subjects were then given a 3-liter polyethylene bottle and instructed to collect all their urine for the next 4 hours. After this period (at 3PM) the subjects were again contacted at their work place and asked to empty their bladder into the polyethylene bottle. The time of this collection was noted. At this time the subjects were then given 2 additional polyethylene bottles for specimen collection at home in the evening and overnight (sleep). They were instructed to empty their bladder upon arriving at home (not collected-at approximately 6 PM) and to note the time. They were then instructed to collect all their urine until bedtime (approximately 10 PM), following the same procedure they did at work. The time of this collection was noted and represented the end of the home period and beginning of the sleep period. Lastly, the subjects were instructed to empty their bladder into the remaining polyethylene bottle upon awakening (at approximately 6 AM), noting the time. This time represented the end of the sleep period. These samples were then returned to the Hypertension center along with the blood pressure monitor the morning following the final urine collection. Thus, the microenvironmental comparisons noted above were made using measurements collected over the following timeframes: work (11 AM–3PM), home (approximately 6 PM to 10 PM) and sleep (approximately 10 PM to 6 AM).

The polyethylene bottles used to collect the timed urine samples containing .5 grams of sodium metabisulphite (a preservative for the catecholamines). This preservative has been widely used in field studies of urinary catecholamine variation over the last two decades (e.g., Harrison et al., 1981; James et al., 1985; Jenner et al., 1987; Pollard et al., 1996; Brown and James, 2000; Glover and Poland, 2002; James et al., 2004; Brown et al., 2006; Van Berge-Landry et al., 2013). The total volume of each sample was measured to the nearest milliliter and the length of time of the collection to the nearest minute. Epinephrine and norepinephrine were assayed using HPLC with electrochemical detection, and were expressed as a rate of excretion (ng./min.) (Brown and James, 2000). Concentrations of cortisol were determined using a solid phase ¹²⁵I radioimmunoassay (Foster and Dunn, 1974; Dettenborn et al., 2005). The preservative used for the catecholamines has no known effect on the cortisol assay (Glover and Poland, 2002). Cortisol was also expressed as a rate

of excretion ($\mu\text{g}/24$ hrs.). Finally, in order to assess the correspondence between the blood pressures and hormonal excretion rates, the mean pressures over the time frames associated with each microenvironmental urine collection were calculated. On average, there were 15 pressure measurements per urine collection period. Before calculating the means, artifactual readings were removed using previously published criteria (Pickering et al., 1982).

Analysis

Studies have shown that body fat, fat distribution, or body mass is positively associated with urinary catecholamine excretion (Leonetti et al., 1991; James et al., 2004) and ambulatory blood pressures averaged across microenvironments (e.g. Van Berge-Landry et al., 2008; McNamee and James, 2012). Therefore, epinephrine, norepinephrine, and the ambulatory blood pressures were compared across the three daily microenvironments (work, home, and sleep) and between the PH+ and PH- groups using repeated measures ANCOVA, with microenvironment as a repeating factor, parental history as a fixed factor and BMI as a covariate. Urinary cortisol values were examined using repeated-measures ANOVA following Dettenborn et al. (2005). Adjustments for sphericity in the microenvironmental comparisons were made using the Greenhouse-Geisser correction (Green and Salkind, 2008). Prior to the PH+/PH- analysis, comparisons of all hormonal and blood pressure measurements were made between PH+ women who reported a single parent with hypertension (N=42) and women who reported both parents with hypertension (N=20) to determine whether the extent of parental history affected any of the measures. This analysis revealed that there were no differences in any parameter related to the number of parents with reported hypertension; hence, all the PH+ women were pooled into one group for the ANCOVA/ANOVA analyses.

RESULTS

The results of the epinephrine excretion rate repeated measures ANCOVA revealed that there were significant overall microenvironmental differences in the rates of epinephrine excretion with highest values at work and lowest values during sleep ($F=15.849$, $p<.001$; partial $\eta^2=.110$). There was also a significant main effect for parental history group, with the PH+ women having an overall 36% higher excretion rate ($F=7.185$; $p=.008$; partial $\eta^2=.053$); however, the interaction between microenvironment and parental history group was not significant ($F=.686$; $p=.486$; partial $\eta^2=.005$). The epinephrine excretion rate comparisons are illustrated in Figure 2.

The results of the norepinephrine excretion rate repeated-measures ANCOVA revealed that there was an overall microenvironmental difference with highest values at work and lowest values during sleep ($F=5.165$; $p=.007$; partial $\eta^2=.053$). The main effect of parental history group was close to statistical significance ($F=3.467$; $p=.065$; partial $\eta^2=.026$); however the interaction between microenvironment and parental history group was not significant ($F=.652$; $p=.506$; partial $\eta^2=.005$). Figure 3 shows the comparisons for the norepinephrine excretion rates.

The results of the repeated-measures ANOVA for the cortisol excretion rates revealed that there was an overall microenvironmental difference with highest values at work and lowest

values at home in the evening, ($F=24.335$; $p<.001$; partial $\eta^2=.161$). There was no parental history group main effect difference ($F=.231$; $p=.632$; partial $\eta^2=.002$); however, the interaction between microenvironment and parental history group was significant ($F=3.254$; $p=.045$; partial $\eta^2=.025$). Follow-up analysis revealed that the increase in cortisol from home to sleep was significantly greater among the PH+ women ($p<.007$), which was due to a higher cortisol excretion rate during sleep. Figure 4 illustrates the comparison between the parental history groups for the cortisol excretion rates.

The results of the repeated-measures ANCOVA for systolic pressure revealed that there was an overall microenvironmental difference with highest pressures at work and lowest pressures during sleep ($F=8.946$; $p<.001$; partial $\eta^2=.064$). There was also a significant main effect for parental history group, with the PH+ women having higher pressure (4 mmHg) ($F=6.333$; $p=.013$; partial $\eta^2=.046$); however, the interaction between microenvironment and parental history group was not significant ($F=.307$; $p=.723$; partial $\eta^2=.002$).

Finally, the results of the repeated-measures ANCOVA for diastolic pressure revealed that there was an overall microenvironmental difference with highest pressures at work and lowest pressures during sleep ($F=19.520$; $p<.001$; partial $\eta^2=.130$). There was also a significant main effect for parental history group, with the PH+ women having higher pressure (2 mmHg) ($F=4.492$; $p=.036$; partial $\eta^2=.033$); however, the interaction between microenvironment and parental history group was not significant ($F=.897$; $p=.404$; partial $\eta^2=.007$). Figure 5 shows the differences in average systolic and diastolic pressures across the three daily microenvironments between the parental history groups.

DISCUSSION

Increased catecholamine and cortisol responses to acute laboratory stressors have been reported in otherwise healthy individuals with parental histories of hypertension (e.g. Falkner et al., 1979; Horikoshi et al., 1985; Fredrickson et al., 1991; Covelli, 2006; Bennett et al., 2013). Our findings show that there are clear differences in circadian catecholamine and cortisol urinary excretion between PH+ and PH- women as well, suggesting that the parental history difference in the level and variation of these hormones may be more than just an acute reactive phenomenon. Specifically, the present study shows that women with a reported parental history have a uniform circadian tonic elevation in catecholamines (higher catecholamine output over all the daily microenvironments) and an accentuated nocturnal increase in cortisol relative to women without a parental history, which are further associated with marginally higher ambulatory blood pressures across all the daily microenvironments. Interestingly, PH+ women did not show an increased reactive rise in urinary catecholamines or cortisol to either the work or home microenvironment.

Several recent studies have examined genetic polymorphisms in the catecholamine synthesis pathways in an attempt to identify genetic links to hypertension (e.g. Rao et al., 2007; Nielsen et al., 2010; Currie et al., 2012). They have found that mutations affecting single genes involved with cardiovascular regulation can alter both sympathetic function and blood pressure, supporting what is now being termed the “Neurogenic Hypothesis” (Currie et al.,

2012). Much of the genetic research has been on genome-wide scans and twin studies focusing on specific chromosomal regions. The tyrosine hydroxylase (TH) gene has been of particular interest, since TH catalyzes the conversion of tyrosine to L-dihydroxyphenylalanine, the rate-limiting step in the biosynthesis of catecholamines (Rao et al., 2007). Rao et al. (2007) reported that common single nucleotide polymorphisms (SNPs) in the proximal promoter region of TH are strongly associated with variation in autonomic function, as evidenced by laboratory stress testing of individuals with C-824T and A-581G mutations. They concluded that human catecholamine secretory traits are heritable, displaying joint genetic determination (pleiotropy) with autonomic activity and with blood pressure. Nielsen et al., (2010) later reported that an individual homozygous for the T allele at the position -824 in the TH promoter had a 45% increased relative risk of hypertension, which translated into increases of two to three mmHg in both systolic and diastolic blood pressure. Interestingly, this level of elevation in blood pressure is similar to what we found in the present study.

One might speculate that the difference in the nocturnal urinary cortisol levels between the parental history groups is related to differences in how plasma cortisol increases in the hours prior to wakening, although there is limited information regarding demographic factors that might contribute to the normative inter-individual variation of this phenomenon. Studies show that the nocturnal increase is affected by the balance of REM/non-REM sleep, ACTH sensitivity, and suprachiasmatic nuclei-driven ultradian rhythms (see Born et al., 1999; Wilhelm et al., 2007; Clow et al. 2010 for discussion of nocturnal cortisol variation). Another possibility is that there is some sort of a carryover effect from stressors experienced prior to going to sleep that affected the PH+ women to a much greater extent than the PH- women (e.g. Luecken et al, 1997). Lastly, there may also be some genetic component to the parental history group difference as well, as Watt et al. (1992) found that high blood pressure among subjects with parents that had high blood pressure was associated with specific variants of the glucocorticoid receptor gene, which plays a mediating role in the effects of psychosocial stress on cortisol.

Finally, the results may also have implications for the study of allostatic load. Specifically, metabolic failure over time including cardiovascular pathology has been hypothesized to stem from the wear and tear that results from inappropriate up-regulation of the sympathetic adrenal medullary system and hypothalamus pituitary adrenal axis that occurs with the stresses of life (e.g. McEwen and Wingfield, 2010; Del Giudice et al., 2011). Thus, while it is possible that there is an emergent up-regulation of catecholamines and cortisol that developed during adolescence in what might be termed a shared hypertension-promoting familial environment among individuals who are PH+, it is also possible that there is an inherited up-regulation of the circadian dynamics of catecholamines and cortisol in the PH+ subjects that could predispose them to allostatic load. Indeed, this latter possibility is supported by a recent study which found that differences in allostatic load appear to be influenced by inherent genetic variation (see Smith et al., 2009). Specifically, Smith et al. (2009) found that genetic polymorphisms in angiotensin-1 converting enzyme (ACE), corticotrophin-releasing hormone receptor 1 (CRHR1), and serotonin receptors (HTR3A and HTR4) were associated with allostatic load.

Caution should be used in extrapolating these results to the general population. The present study included only women in a specific set of occupations, and it is quite possible that results among men or mixed gender samples evaluated under different environmental circumstances may be different. Because women were the focus of this study, one might also presume that the menstrual cycle could influence the results. However, earlier studies have shown that the circadian microenvironmental levels of urinary catecholamines and cortisol and average ambulatory blood pressures do not significantly differ between the follicular and luteal phases of the cycle (see James and Marion, 1994; James et al, 1996) and thus menstrual effects are unlikely. Finally, it should be noted that only a single day was investigated in this study, so whether parental history group differences are persistent is unknown.

In sum, the results of this study show that women with a reported parental history of hypertension have both elevated circadian catecholamine levels and greater nocturnal cortisol when compared to those with no parental history. Further longitudinal studies that explicitly tie the hormone differences to gene markers are needed to verify these findings.

Acknowledgments

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Figure 1.

Natural experimental design highlighting both within-subject stress response changes across different daily microenvironments and differences in those responses between parental history of hypertension groups (PH+ and PH-).

Figure 2.

Epinephrine excretion rates (ng/min) in women with (PH +) and without (PH –) parental hypertension over a 24hr period, across three contrasting daily microenvironments (work, home and sleep). Values calculated at a BMI of 24.9.

Figure 3.

Norepinephrine excretion rates (ng/min) in women with (PH +) and without (PH –) parental hypertension over a 24hr period, across three contrasting daily microenvironments (work, home and sleep). Values calculated at a BMI of 24.9.

Figure 4. Cortisol excretion rates (ug/24 hrs) in women with (PH +) and without (PH –) parental hypertension over a 24hr period, across three contrasting daily microenvironments (work, home and sleep).

Figure 5.

Ambulatory blood pressure measurements (mmHg) in women with (PH+) and without (PH-) parental hypertension over a 24hr period, across three contrasting daily microenvironments (work, home and sleep). Values calculated at a BMI of 24.9.

Table 1 Selected Characteristics of the Study Sample (N=134)^a.

Characteristic	PH + (n=62)	PH - (n=72)
N	62	72
Age(Yrs.)	35.2±9.1	33.8±10.0
Height (M)	1.62±.73	1.63±.67
Weight (Kg)	66.2±12.6	65.7±11.8
BMI (Kg/M ²)	25.1±4.2	24.8±4.2
Education (yrs.)	16±2	16±2
Perceived work stress ^b	3.6±2.2	3.6±2.3
Perceived home stress ^b	3.1±2.5	3.4±2.4
Ethnicity (%)		
European-American	36	47
African-American	34	22
Other	30	31
Currently Married (%)	50	32
w/Children (%)	43	48
On Oral Contraceptives (%)	24	21
Consume alcohol (%)	98	98
Drink Coffee (%)	37	49
Smoke Cigarettes (%)	16	18
Commute to Manhattan (%)	31	40
Studied in luteal phase (%)	36	38

^aMean ±Standard Deviation or percentage. All characteristics were compared between the groups using either unpaired t-tests (continuous variables) or χ^2 analysis (categorical variables). There were no statistically significant differences between the parental history groups for any of the variables.

^bOn a scale of 0 to 10 where 0 is no stress.