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Journal

Nursing research, 64(3)

ISSN

0029-6562

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Publication Date

2015-05-01

DOI

10.1097/nnr.0000000000000096

Peer reviewed

HHS Public Access

Author manuscript

Nurs Res. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Nurs Res. 2015 ; 64(3): 211–220. doi:10.1097/NNR.0000000000000096.

Neighborhood Socioeconomic Status During Childhood Versus Puberty in Relation to Endogenous Sex Hormone Levels in Adult Women

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Abstract

Background—Socioeconomic adversity in early life is related to cardiovascular risk in adulthood; however, no studies have examined whether such adversity may be related to endogenous sex hormones—which are themselves associated with cardiovascular outcomes—or whether the timing of adversity exposures (childhood versus puberty) matters.

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The authors have no conflicts of interest to report.

Supplemental Digital Content 1. Table with complete results showing coefficients for all variables in the models. .doc

Objective—The goal of the current study was to separately examine neighborhood socioeconomic status (SES) during periods of childhood and puberty in relation to adulthood levels of endogenous sex hormones (estradiol [E_2], testosterone), sex hormone binding globulin (SHBG), and a derived index of bioavailable testosterone (free androgen index [FAI]).

Methods—In a sample of 143 premenopausal women (mean age 36.8 [*SD* = 5.5]; 51.7% White, 32.2% African American, 5.6% Latina, 7.0% Chinese, and 3.5% Filipina), retrospective reports of residential address information in designated periods of childhood and puberty was used to derive U.S. census-based neighborhood SES composite scores characterizing the socioeconomic environments of women during these periods.

Results—In covariate-adjusted analyses, higher neighborhood SES in puberty predicted higher levels of SHBG in adulthood, but neighborhood SES during childhood did not (standardized regression coefficient = .24, $p = .01$ vs. standardized regression coefficient = .04, $p = .75$, respectively). Neighborhood SES was not predictive of other hormones (E_2, testosterone, and FAI).

Discussion—The current findings suggest that puberty may be a time of particular vulnerability to the effects of neighborhood SES on SHBG levels, which have been previously linked to cardiovascular risk factor profiles and atherosclerotic disease progression.

Keywords

cardiovascular disease; early life adversity; life course; puberty; sex hormones; socioeconomic status

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Life course epidemiology as detailed in Lynch and Smith (2005) provides a valuable framework in considering how the timing of exposures over the life course—inclusive of a range of socio-environmental factors (Ben-Shlomo & Kuh, 2002)—relate to chronic disease outcomes in adulthood. Its consideration of exposures over the life course offers a bridge between work that has primarily focused on the prenatal environment (fetal origins hypothesis; Barker, 1992) and work emphasizing more proximal adulthood risk factors for disease. In this context, an abundant literature has shown that adverse exposures occurring in childhood predict cardiovascular disease outcomes, all-cause and disease-specific mortality, and intermediate health problems that lead to poorer long-term disease and mortality outcomes, including adulthood risk for obesity and central adiposity, conventional cardiovascular risk factors, and incident metabolic syndrome and type 2 diabetes (Alastalo et al., 2013; Danese et al., 2009; Galobardes, Lynch, & Smith, 2004, 2008; Galobardes, Smith, & Lynch, 2006; Janicki-Deverts, Cohen, Matthews, & Jacobs Jr., 2012; Lehman, Taylor, Kiefe, & Seeman, 2005, 2009; Midei & Matthews, 2011; Midei, Matthews, Chang, & Bromberger, 2013; Rich-Edwards et al., 2010; Riley, Wright, Jun, Hibert, & Rich-Edwards, 2010; Wegman & Stetler, 2009).

This body of work includes studies of longitudinal design examining changes in parameters of health and disease over time, studies that have employed “objective” measures of adversity (e.g., court records) and outcomes (e.g., death certificates). Studies have also attempted to isolate effects of adversity exposures in childhood from confounding factors by controlling for negative health practices and other related adulthood factors (e.g.,

socioeconomic status [SES])—raising the possibility that the influence of the early life environment on adulthood health may be etiological in nature. Models addressing the potential mechanisms that account for these links suggest there are adversity-related alterations in underlying biological systems known to be stress-responsive (Danese & McEwen, 2012; Miller, Chen, & Parker, 2011; Repetti, Taylor, & Seeman, 2002; Taylor, 2010; Taylor, Way, & Seeman, 2011). Such alterations—though adaptive in the short-term—are hypothesized to promote metabolic, hormonal, and immunological changes that can have profound long-term implications for compromised maintenance of health and increased risk for disease development.

The types of exposures in childhood that have been implicated are variable, but commonly include early life experiences reflecting greater socioeconomic disadvantage. Experiences such as lower parental education, poverty status, and substandard housing conditions have all been linked prospectively to adulthood cardiovascular health, including poorer cardiovascular risk factor profiles (Danese et al., 2009; Janicki-Deverts et al., 2012; Lehman et al., 2005, 2009) and increased incidence of cardiovascular disease (CVD) (Galobardes et al., 2006; Kittleson et al., 2006). For example, in the Coronary Artery Risk Development in Young Adults Study, women (but not men) who experienced greater socioeconomic disadvantage in early life exhibited greater increases in blood pressure over a 15-year period (Janicki-Deverts et al., 2012). Similarly, in a review of 40 studies examining CVD outcomes, results showed individuals who experienced greater socioeconomic disadvantage in early life were at increased adulthood risk for coronary heart disease (ischemic heart disease or myocardial infarction), stroke, angina, and atherosclerosis; although, associations with atherosclerosis were observed for women only (Galobardes et al., 2006).

To date, although study findings show strong associations between early life socioeconomic disadvantage and adulthood CVD risk, few studies have considered whether some of the long-term cardiovascular risk associated with early life socioeconomic adversity may be attributable to variations in endogenous sex hormones—which have themselves been linked prospectively to CVD risk (El Khoudary et al., 2012; Sutton-Tyrrell et al., 2005). For example, in the Study of Women's Health Across the Nation (SWAN), lower sex hormone-binding globulin (SHBG), lower estradiol (E_2) and higher free androgen index (FAI)—an estimate of unbound or biologically active testosterone—were related to CVD risk factors (e.g., greater inflammation, adverse lipid profiles) adjusted for body mass index (BMI) (Sutton-Tyrrell et al., 2005). Also in the SWAN, decreases in SHBG and E_2 levels over time were associated with increases in preclinical atherosclerotic disease marked by greater intima-medial thickness (IMT) and adventitial diameter (AD) progression, respectively, adjusted for CVD risk factors (El Khoudary et al., 2012). The direct and indirect mechanisms by which endogenous sex hormones influence CVD development remain focus of much interest. As described in Harman (2014), higher E_2 may afford cardio protection through its role in maintaining endothelial regulation via increases in nitric oxide (NO) synthesis and reductions in NO inhibitors (Li et al., 2004; Mendelsohn, 2002), as well as through the promotion of better lipid and adhesion molecule profiles (Hu et al., 2006; Störk, von Schacky, & Angerer, 2002; Tikkanen, 1996). Higher SHBG may afford cardio protection also through its role in lipid metabolism as well as its association with a reduction in risk for insulin resistance, metabolic syndrome, and type 2 diabetes (Haffner, Valdez,

Morales, Hazuda, & Stern, 1993; Mudali et al., 2005; Pugeat et al., 1995). Additionally, because SHBG binds androgens, SHGB levels may mark the availability of androgens with lower SHBG, indicating greater androgen availability; higher androgens are themselves related to an increase in risk for insulin resistance, metabolic syndrome, and type 2 diabetes (Oh, Barrett-Connor, Wedick, & Wingard, 2002; Torrens et al., 2009).

Study findings have also been limited by inconsistent definitions of "early life." In some studies, socioeconomic disadvantage in early life has been indexed broadly by reports of parental education/occupation in general, e.g., (Kittleson et al., 2006) or in "childhood" defined by the participant, e.g., (Janicki-Deverts et al., 2012); while in other studies, early life was limited to a specific, but arbitrary, age range (e.g., birth to 10 years) (Danese et al., 2009). To our knowledge, no studies have attempted to examine the period of puberty (versus childhood) distinctly, despite the potential importance of examining exposures during such a sensitive developmental period. Puberty reflects a discrete developmental period during which time a dynamic set of organizational events occur whereby sexual maturation and the potential for human reproduction is achieved. Specifically, decreases in inhibitory as well as increases in stimulatory inputs to the gonadotropin-releasing hormone (GnRH) pulse generator (Navarro, Castellano, García-Galiano, & Tena-Sempere, 2007; Ojeda et al., 2006)—the initiating event by which the hypothalamic-pituitary-gonadal (HPG) axis is activated—results in an increase in the pulsatile release of GnRH by neurons in the arcuate nucleus of the hypothalamus which, in turn, signals the gonadotrope cells of the anterior pituitary gland to synthesize and secrete gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Wildt, Marshall, & Knobil, 1980). Circulating LH and FSH then bind to receptors in the ovaries, promoting ovarian follicle maturation and the production of sex steroids to which the primary physical changes that occur in female puberty (i.e., acceleration in growth, development of secondary sexual characteristics, menarche, and ovulation) are attributable. It is plausible that adversity exposures during this period may have implications for reproductive functions relevant to hormone-related parameters of health and risk for disease longer term. Interestingly, findings in animal models are suggestive, showing that certain stressors—when experienced during puberty (but not before or after puberty)—cause alterations in hormone-dependent sexual behaviors that may be due to concomitant reductions in the expression of sex steroid receptors (Ismail, Garas, & Blaustein, 2011).

The current report describes an observational study of 143 premenopausal women (ages 25–45) in whom we employed a novel methodological approach to 1) isolate periods of assessment for childhood and puberty distinctly; and to 2) ascertain retrospective reports of residential address information to derive U.S. census-based variables characterizing the socioeconomic environments of women during these periods. The goal of the current study was to examine neighborhood socioeconomic status (SES) during periods of childhood and puberty in relation to adulthood levels of endogenous sex hormones (estradiol [E_2], testosterone), sex hormone-binding globulin (SHBG), and a derived index of bioavailable testosterone (free androgen index [FAI]) to determine whether socioeconomic adversity experienced during puberty may be uniquely related to CVD risk-associated hormone profiles.

Methods

Participants

The current sample included women who participated in a substudy of the Ovarian Aging (OVA) Study. The OVA Study was an investigation of genetic and environmental factors that influence the age-specific variability in reproductive aging among healthy, reproductive-age women (Bleil et al., 2014; Bleil, Gregorich, McConnell, Rosen, & Cedars, 2013; Rosen et al., 2013; Schuh-Huerta et al., 2012). Women were recruited from Kaiser Permanente of Northern California, a large, integrated health care delivery system that provides medical care to approximately one third the population of Northern California. Selection criteria for the OVA Study were ages 25–45, regular menses, having a uterus and both ovaries intact, and self-identification as White, African American, Latina, Chinese, or Filipina and speak/read English, Spanish, or Cantonese. Exclusions were major medical illnesses (i.e., cardiovascular diseases, chronic kidney or liver disease, diabetes, invasive cancer, chemotherapy or radiation therapy, epilepsy, systemic lupus erythematosus, or HIV-positive status), use of medications affecting the menstrual cycle within the three months prior to study participation, and current pregnancy/breastfeeding.

The OVA Study protocol included an in-person medical history interview, transvaginal ultrasound, anthropometric assessment, and blood draw. In addition, as a part of the substudy designed to retrospectively examine the neighborhood and family life environments of women in childhood, factors hypothesized to influence women's reproductive and general health, a subset of women comprising the first 270 of 1,019 total participants were administered a self-report questionnaire asking them to report the address of their residences in designated periods of childhood and puberty. A total of 143 participants with complete address information for periods of both childhood and puberty were retained for analysis in the current study. Excluded women (n = 127) were (a) 62 women who could not recall their addresses for both time periods; (b) 32 women who lived outside of the U.S. during the designated period(s); (c) 22 women who provided insufficient address information; and (d) 11 women who lived in rural areas that were not assigned U.S. census tract numbers. Institutional Review Board approval was obtained both from Kaiser Permanente and the University of California San Francisco, and all subjects provided informed, written consent.

Measures

Menarcheal age—In the context of an in-person medical history interview, women were asked to report the age of their first menstrual period. Retrospective reports of menarcheal age have been shown to be highly reliable (Bergsten-Brucefors, 1976; Koprowski, Coates, & Bernstein, 2001) with one study showing real-time adolescent reports correlated 0.79 with retrospective adulthood reports 33 years later (Must et al., 2002).

Neighborhood SES—Childhood and puberty were defined with respect to each participant's age at menarche, reported retrospectively. Based on evidence suggesting that puberty begins two years prior to menarche on average and that sexual maturity (Tanner stage 5) is reached three years after menarche on average (Marshall & Tanner, 1969),

puberty was defined to be between two years prior and three years after menarche, and childhood was defined to be between birth and two years prior to menarche. For example, for a participant with a reported menarcheal age of 12, childhood was defined to be between 0–9 years of age and puberty was defined to be between 10–15 years of age. These age ranges were derived for each participant individually and presented in questionnaire format asking the participant to report her residential address(es) during each period. Women with multiple addresses within a given period were asked to identify the address at which she resided for the greatest number of years within the period. All women within complete or missing address information were contacted by phone to aid in the collection of this information. The midpoint of each age range was then associated with the most proximal decennial U.S. Census—the 1970, 1980, 1990, or 2000 U.S. Census as appropriate for the participant's age. The identified address for each period was entered into a web-based tool (Social Explorer, n.d.) to determine the corresponding census tract and then to use the tract to extract the specified SES variables. Only variables that were common to all four U.S. censuses were selected, including: (a) % of individuals with a high school diploma; (b) % of individuals >16 years of age in the work force who were unemployed; (c) median family income; (d) % of families below the poverty line; and (e) median value of owner-occupied housing units. For the Census variables pertaining to unemployment and poverty, distributions were multiplied by −1 to ensure higher scores reflected higher neighborhood socioeconomic status. (Note, however, the original distributions for these variables are reported in the descriptive analyses provided in Table 1.) Median family income and median value of owner-occupied housing units were adjusted for inflation to reflect 2010 dollars. Using the Consumer Price Index (CPI) provided by the U.S. Bureau of Labor Statistics, the adjustment (based on the percent change in price between indicated years) was computed by dividing the annual average CPI-U for 2010 by the annual average for the indicated earlier year. Factor analysis of the SES variables from nonredundant tracts was performed showing a single factor structure underlying—both for periods of childhood and puberty; variables accounted for 59.8% and 67.2% of the variance in the factors, respectively. On this basis, one neighborhood SES composite for each period was formed. The variables were first standardized and summed, then Blom transformed and restandardized to correct minor skew in the distributions.

Hormones—Between menstrual cycle days 2–4, blood was drawn for the analysis of E_2, testosterone, and SHBG. All were assayed with an automated chemiluminescent assay using the Bayer Diagnostics ACS: 180 (Bayer Diagnostics Corp., Tarrytown, NY). Coefficients of variation were as follows: E_2 ($CV_{intraassay}$: 6.5–6.9%, $CV_{interassay}$: 13.6–16.1%); testosterone ($CV_{intraassay}$: 2.9–4.0%, $CV_{interassay}$: 6.3–6.6%), and SHBG ($CV_{intraassay}$: 6.4–7.0%, $CV_{interassay}$: 6.9–8.9%). The FAI, an estimate of the quantity of unbound or biologically active testosterone, was calculated as testosterone/SHBG × 100.

Insulin resistance—Insulin resistance was indexed using the homeostasis model assessment of insulin resistance (HOMA-IR) calculated as insulin (uIU/mL) × glucose (mg/dL)/405 (Matthews et al., 1985). Assays for fasting glucose and insulin were performed by Quest Diagnostics (San Jose, CA). Fasting glucose was assayed by the glucose oxidase

method ($CV_{intraassay}$: 1.25–2.00%), and insulin was assayed using the Siemens Immulite (Tarrytown, NY) immunochemiluminometric assay ($CV_{intraassay}$: 3.64–6.64%).

Covariates—Covariates were age (in years);race/ethnicity (using White as the reference group), educational level (coded: 1 = less than high school (HS)/some HS; 2 = HS diploma/general educational development (GED) equivalent; 3 = s*ome college/associate's degree/vocational school*; 4 = *college graduate*; 5 = *graduate/professional degree (MS, PhD, MD, JD, DDS, MBA)*; household income (coded: 1 = *less than $5,000*; 2 = $5,000–$15,999; 3 = *$16,000–$24,999*; 4 = *$25,000–$34,999*; 5 = *$35,000–$49,999;* 6 = *$50,000–$74,999*; 7 = *$75,000–$99,999*; 8 = $*100,000–$149,999*; 9 = *$150,000–$199,999*; 10 = $*200,000 or more*); menarcheal age (in years), past use of a hormonal method of contraception (coded: 0 = *never used*; 1 = *positive history of use*); parity (0 = *no live births*; 1 = *one or more live births*), smoking (0 = *never smoked*; 1 = *current/past smoking*), body mass index (BMI) (kg/m^2) in adulthood, and retrospectively reported weight at age 18 (in lbs.).

Analytical Plan

Primary analyses—In four separate linear regression equations, covariates were entered on Step 1 and the neighborhood SES composite was entered on Step 2 in predicting adulthood hormone outcomes (E_2, testosterone, SHBG, and FAI). Analyses were performed using the neighborhood SES composite in childhood and then repeated using the neighborhood SES composite in puberty.

Secondary analyses—In addition, secondary analyses were performed in which the same analyses described above were repeated but with HOMA-IR also included in the models. Inclusion of HOMA-IR enabled the examination of the neighborhood SES composites in relation to SHBG independently of insulin resistance to determine whether any effects of neighborhood SES on SHBG may be due to variations in insulin resistance—a possibility supported by study findings suggesting SHBG may index insulin resistance (Jayagopal et al., 2004; Loukovaara, Carson, & Adlercreutz, 1995).

Diagnostics—Assumptions of linear regression were evaluated using regression diagnostics incorporating both methods of visual inspection and quantitative guidelines (Institute for Digital Research and Education UCLA, n.d.). Linearity was assessed by inspection of partial regression plots of each predictor in relation to the dependent variable adjusted for the other predictors. Normality was assessed by inspection of histograms, Q-Q plots, and skewness/kurtosis values of residuals. Homoscedasticity was assessed by inspection of plots of residual versus predicted values. Multicollinearity was assessed by cutoffs for tolerance and variance inflation factor (VIF) values. Lastly, the potential influence of individual observations on the results was assessed by the Cook's *D* and DFBETA statistics. These efforts revealed minor violations in the normality of residuals (e.g., skewness/kurtosis values deviating from zero) due to slight positive skew in the distributions of the E_2 and FAI dependent variables. This was corrected by taking the natural log of the E_2 and FAI variables. In addition, a pattern was revealed in which an individual observation was noted to have considerable influence on the results. To illustrate, the DFBETA value showed that by including this observation (versus excluding it), the

coefficient for the neighborhood SES composite in puberty predicting SHBG decreased by −1.36 standard errors. Consistent with recommendations (Vittinghoff, Glidden, Shiboski, & McCulloch, 2012), sensitivity analyses are reported describing the results for all observations, as well as with this influential observation omitted.

Results

Sample Characteristics

As shown in Table 1, the sample was composed of 51.7% White, 32.2% African American, 5.6% Latina, 7.0% Chinese, and 3.5% Filipina women, and the mean age was 36.8 (*SD* = 5.5). When women with complete neighborhood SES data ($n = 143$) were compared to women with whom this information could not be derived ($n = 127$), no differences were observed for age, educational level, income level, menarcheal age, past use of a hormonal method of birth control, parity, smoking, BMI, weight at age 18, E_2, testosterone, SHBG, FAI, and HOMA-IR. However, African-American women were overrepresented ($\chi^2 = 5.4$, $p = .02$), and Latina and Chinese women were underrepresented ($\chi^2 = 7.5$, $p = .006$; $\chi^2 = 8.7$, $p = .003$, respectively) among the women with complete data due to a larger number of Latina and Chinese women living outside of the U.S. in periods of childhood/puberty.

Neighborhood descriptions are also summarized in Table 1. For assessments of neighborhood SES in childhood, 127 unique U.S. census tracts were represented in 54 counties. SES variables were drawn from the 1970, 1980, and 1990 U.S. Censuses for 45.5%, 48.3%, and 6.2% of the women, respectively. For assessments of neighborhood SES in puberty, 126 unique census tracts were represented in 52 counties. SES variables were drawn from the 1970, 1980, 1990, and 2000 US Censuses for 1.4%, 54.5%, 40.6%, and 3.5% of the women, respectively. Sixty-two (43.4%) women reported different addresses/tracts between periods of childhood and puberty. Bivariate correlations showed the neighborhood SES composites in periods of childhood and puberty were highly correlated ($r = .70$, $p < .001$).

Bivariate correlations among the dependent variables were as follows: E_2 was correlated with testosterone ($r = .08$, $p = .36$), SHBG ($r = .49$, $p < .0001$, and FAI ($r = -.38$, $p < .001$). Testosterone was correlated with SHBG ($r = .08$, $p = .33$) and FAI ($r = .49$, $p < .001$). SHBG was correlated with FAI ($r = -.79$, $p < .001$).

Neighborhood SES and Adulthood Hormone Levels

Results of linear regression analyses (Table 2) showed that in covariate-adjusted models, neighborhood SES in childhood was unrelated to hormone levels in adulthood for E_2, testosterone, SHBG, and FAI. However, when analyses were repeated examining neighborhood SES in puberty, results showed that in covariate-adjusted models, higher neighborhood SES in puberty was related significantly to higher adulthood levels of SHBG (standardized regression coefficient $b^* = .24$, $p = .01$) but remained unrelated to adulthood levels of E_2, testosterone, and FAI. Examination of the model R^2 and R^2_{change} showed that neighborhood SES in puberty accounted for an additional 3.5% of the variance in adulthood SHBG levels beyond that explained by the covariates (28.3%). To account for having

conducted multiple statistical tests, the Holm-Bonferroni sequential correction test was performed. With this adjustment, the *p*-value remained significant ($p = .05$) for the reported association between neighborhood SES in puberty and adulthood SHBG levels.

Because diagnostic analyses (described in the Analytical Plan section above) revealed that an individual observation had considerable influence on the results, sensitivity analyses are also reported (Table 3) detailing how the results change with the omission of this observation. That is, with the omission of this observation, the association between neighborhood SES in puberty and adulthood levels of SHBG strengthened ($b^* = .36$, $p < .001$). In addition, a significant relationship emerged between higher neighborhood SES in puberty and lower adulthood levels of FAI ($b^* = -.22$, $p = .03$), and a nonsignificant trend emerged between higher neighborhood SES in puberty and higher adulthood levels of E_2 ($b^* = .20$, $p = .07$).

Based on evidence suggesting SHBG indexes insulin resistance (Jayagopal et al., 2004; Loukovaara et al., 1995), follow-up analyses were performed additionally, including HOMA-IR in the model. Results showed the relation between neighborhood SES in puberty and adulthood SHBG levels attenuated but remained statistically significant ($b^* = .22$, $p = .02$), indicating that the observed association is not entirely attributable to common variance with insulin resistance.

Complete results showing coefficients for all variables in the models are available (see Table, Supplemental Digital Content 1).

Discussion

Socioeconomic disadvantage in early life is a risk factor for CVD in adulthood (Danese et al., 2009; Galobardes et al., 2006; Janicki-Deverts et al., 2012; Kittleson et al., 2006; Lehman et al., 2005, 2009); however, no studies have examined whether such adversity may be related to endogenous sex hormones, which are themselves associated with cardiovascular outcomes (El Khoudary et al., 2012; Sutton-Tyrrell et al., 2005)—or whether the timing of adversity exposures matters. Results from the current study showed that higher neighborhood SES in puberty (but not childhood) was related to higher levels of SHBG in adulthood (adjusted for covariates: age, race/ethnicity, adulthood SES, menarcheal age, hormonal birth control use, parity, smoking, and adulthood and adolescent body composition), but was unrelated to E_2, testosterone, and FAI. Notably, lower SHBG levels have been related to poorer cardiovascular risk factor profiles, as well as the progression of preclinical atherosclerotic disease (El Khoudary et al., 2012; Sutton-Tyrrell et al., 2005).

Because linear regression diagnostics performed in the current study revealed the presence of an observation with considerable influence on the results, analyses were repeated with this observation omitted (see sensitivity analyses, Table 3). In these additional analyses, the results differed with an overall stronger pattern of association emerging in which neighborhood SES in puberty (but not childhood) was related to higher levels of SHBG in adulthood, *as well as* to lower adulthood levels of FAI and higher adulthood levels of E_2. Although these additional results must be interpreted with caution, there is an intriguing

overall pattern suggesting neighborhood SES adversity exposures, when experienced in puberty, uniquely may have a deleterious effect on adulthood hormone profiles relevant to cardiovascular risk. In other words, socioeconomic disadvantage appears to have a stronger impact on adulthood cardiovascular risk when experienced in puberty versus childhood. Although speculative, it is possible this may be due to the critical organizational processes that occur during puberty that, if disrupted, could impact the course of sexual maturation and associated hormonal and metabolic factors relevant to the development of adulthood cardio-metabolic diseases.

In particular, evidence suggests that SHBG may index insulin resistance (Jayagopal et al., 2004; Loukovaara et al., 1995) which, interestingly, is increased as a normal part of puberty (Ball et al., 2006). Greater insulin resistance may persist among girls who experience more SES-related adversity in puberty—putting them at risk for subsequent weight gain and other downstream deleterious effects associated with insulin resistance (Lustig, 2006). In the current study, effects of neighborhood SES in puberty on SHBG levels in adulthood attenuated but remained statistically significant when HOMA-IR was covaried, providing partial support for a potential mechanistic role of insulin resistance. Additionally, the potential role of SHBG levels in linking SES-related adversity exposures in puberty to adulthood cardiovascular risk may result from its role in marking the availability of androgens. In the current study, higher neighborhood SES in puberty was also related to lower adulthood levels of FAI (albeit in the follow-up analyses only), and FAI is an established risk factor for cardiovascular risk. Although, to our knowledge, no studies having examined early life adversity exposures in relation to androgens directly, correlates of early life adversity (i.e., depressive symptomatology) have been associated with androgen excess (Sher et al., 2014; Vogel, Klaiber, & Broverman, 1978).

Future longitudinal studies using larger samples are necessary to further assess the feasibility and validity/reliability of using this methodological approach, as well as to replicate the current findings. Future studies are also necessary to begin to understand the biological mechanisms by which it may be possible for adversity-related exposures to disrupt optimal pubertal maturation. It is not clear why adversity related exposures might promote a hormonal profile in adulthood that is associated with an increase in cardiovascular risk. Although the current study adjusted for numerous potentially confounding variables (age, race/ethnicity, adulthood SES, menarcheal age, hormonal birth control use, parity, smoking, and adulthood and adolescent body composition), it remains possible that third variables unmeasured in the current study might account for the observed associations between neighborhood SES in puberty and adulthood hormone levels. Finally, future studies should include better characterization of the prenatal environment and attempt to achieve greater precision in defining the period of puberty, as well as linking it in time with relevant adversity exposures.

Limitations

The study was observational and the sample size was small. However, the current study reflected a preliminary effort to implement a novel methodological strategy to isolate assessment periods of childhood and puberty distinctly, and to use retrospectively reported

information about residential addresses to ascertain objective information about the socioeconomic environments of women during these important developmental periods. Notably, 81% of women were able to recall their address information and neighborhood SES variables were able to be derived for the majority (66%) of these women. Moreover, women with complete neighborhood SES information did not differ from women with missing data except on race/ethnicity (because the Latina and Chinese women were more likely to live outside the U.S. during childhood/puberty), suggesting the sample was not significantly biased in its representation of the full cohort.

Prenatal exposures that have been shown to have important effects on adulthood health, including a range of intrauterine factors and birth weight (Barker, 1992), were not available for analysis in the current study. Additionally, the methodology for the specification of periods of childhood and puberty was customized around each participant's menarcheal age but was based on the *average* length of pubertal development. Although the rate of pubertal maturation is obviously variable, the current study did not have the data necessary to account for individual differences in pubertal tempo. The methodology was also limited because the midpoints of the childhood and puberty time intervals were taken and then linked with data from decennial censuses. Therefore, there could be a mismatch of several years between the year that was identified as the midpoint of a participant's age in childhood or puberty (e.g., 1982) and the closest decennial year (e.g., 1980).

Conclusions

Socioeconomic disadvantage in early life is a risk factor for CVD in adulthood, yet no studies have examined potential effects of early life SES on endogenous sex hormones (commonly linked to CVD outcomes) or attempted to isolate "early life" exposures more precisely. Therefore, the goal of the current study was to implement a novel methodological strategy to isolate periods of assessment for childhood and puberty distinctly so as to ascertain objective information about the socioeconomic environments of women during these important developmental periods in relation to adulthood levels of endogenous sex hormones. Results of the current study showed higher neighborhood SES in puberty (but not childhood) were related to higher SHBG levels in adulthood—independently of adjustment for relevant covariates. Implications are that puberty may be a time of particular vulnerability to the effects of neighborhood SES on SHBG levels which, when lower, have previously been linked to poorer cardiovascular risk factor profiles and atherosclerotic disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge preparation of this manuscript and the research described here were supported by NIH/NICHD and NIH/NIA (R01 HD044876); NIH/NIA (K08 AG03575); NIH/UCSF-CTSI (UL1 RR024131); and the Robert Wood Johnson Foundation (045820). The funders had no involvement in the execution of the study, data analyses, or manuscript preparation.

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TABLE 1

Sample Description

Characteristic	*M*	(*SD*)	Range
Age (yrs)	36.8	(5.5)	25.1 – 45.1
BMI (kg/m^2)	26.7	(7.4)	17.2 – 54.9
Menarcheal age (yrs)	12.5	(1.5)	9 – 17
Weight at age 18 (lbs)	130.8	(27.9)	92 – 253
Neighborhood: Childhood[a]			
Median family income[b]	62,924	(27,439)	13,797 – 250,257
Median housing unit value[b]	196,183	(113,312)	17,984 –721,570
% Individuals with HS diploma	68.5	(17.9)	22.0 – 97.8
% Individuals unemployed	6.3	(4.1)	1.4 – 23.8
% Families below poverty line	10.3	(12.4)	0.0 – 75.0
Neighborhood: Puberty[a]			
Median family income[b]	69,230	(30,391)	13,782–172,897
Median housing unit value[b]	296,944	(164,305)	72,774–834,187
% Individuals with HS diploma	77.1	(15.5)	30.0–98.2
% Individuals unemployed	6.5	(4.4)	0.0–22.6
% Families below poverty line	9.7	(11.3)	0.0–47.7
HOMA-IR	1.4	(1.4)	0.18 – 6.76
Hormones			
E_2	45.1	(27.1)	7.4 – 153.0
Testosterone	49.3	(14.5)	20.1 – 90.5
SHBG	48.4	(21.7)	9.2 – 115.9
FAI	1.2	(0.7)	0.3 – 3.7
	n	**(%)**	
College-educated (yes)	99	(69.2)	
Household income (≥ $50,000)	84	(58.7)	
Past hormonal contraceptive use (yes)	113	(79.0)	
Live births (≥ 1)	41	(28.7)	
Current/past smoking (yes)	38	(26.6)	
Race/ethnicity			
White	74	(51.7)	
African American	46	(32.2)	
Latina	8	(5.6)	
Chinese	10	(7.0)	
Filipina	5	(3.5)	

Note. *N* = 143. ; BMI = body mass index. E_2= estradiol; FAI = free androgen index; HOMA-IR = homeostasis model assessment of insulin resistance; HS = high school; SHBG = sex hormone binding globulin. USD = U. S. dollars.

[a]Values are census tract characteristics.

[b] Values adjusted for inflation to reflect 2010 USDs.

TABLE 2

Regression Models for E_2, Testosterone, SHBG, and FAI: Coefficients for Socioeconomic Status during Childhood and Puberty

Period	DV	*b**	*b*	95% CI[a]	*p*
Childhood	E_2	.13	.07	[−0.05, 0.19]	.22
	Testosterone	.01	.10	[−2.96, 3.17]	.95
	SHBG	.04	.75	[−3.42, 4.92]	.72
	FAI	−.001	.000	[−0.10, 0.10]	.99
Puberty	E_2	.18	.10	[−0.02, 0.21]	.09
	Testosterone	.04	.58	− [2.42, 3.58]	.70
	SHBG	.24	5.14	[1.16, 9.12]	.01
	FAI	−.16	−.08	[−0.18, 0.02]	.10

Note. N = 143. ***b**** = standardized regression coefficient; CI = confidence interval; DV = dependent variable; E_2 = estradiol; FAI = free androgen index; SHBG = sex hormone binding globulin. Covariates included age, race/ethnicity, educational level, household income, menarcheal age, past use of a hormonal method of contraception, parity, smoking, BMI in adulthood, retrospectively reported weight at age 18.

[a]Confidence interval for the unstandardized coefficient.

TABLE 3

Sensitivity of Regression Models During Puberty: One Influential Observation Omitted

DV	*b**	*b*	95% CI[a]	*p*
E_2	.20	0.11	[−0.01, 0.23]	.07
Testosterone	.06	0.84	[−2.35, 4.03]	.60
SHBG	.36	7.74	[3.72, 11.75]	< .001
FAI	−.22	−0.12	[−0.22, −0.01]	.03

Note. n = 142. ***b**** = standardized regression coefficient; CI = confidence interval; DV = dependent variable; E_2= estradiol; FAI = free androgen index; SHBG = sex hormone binding globulin. Covariates included age, race/ethnicity, educational level, household income, menarcheal age, past use of a hormonal method of contraception, parity, smoking, BMI in adulthood, retrospectively reported weight at age 18. Models including the observation flagged as influential are shown in Table 2 for the puberty period.

[a]Confidence interval for the unstandardized coefficient.