HHS Public Access

Author manuscript

Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Paediatr Perinat Epidemiol. 2018 January ; 32(1): 55–67. doi:10.1111/ppe.12409.

Prevalence and contributors to low-grade inflammation in three U.S. populations of reproductive age women

Lindsey A. Sjaarda, PhD[1], **Rose G. Radin, PhD**[1], **Chandra Swanson, BS**[1], **Daniel L. Kuhr, BS**[1], **Sunni L. Mumford, PhD**[1], **Noya Galai, PhD**[2,3], **Robert M. Silver, MD**[4], **Jean Wactawski-Wende, PhD**[5], **Neil J. Perkins, PhD**[1], and **Enrique F. Schisterman, PhD**[1]

[1]Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

[2]Department of Statistics, University of Haifa, Haifa, Israel

[3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[4]Department of Obstetrics and Gynecology, University of Utah and Intermountain Healthcare, Salt Lake City, UT, United States

[5]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY

Abstract

Background—Inflammation, measured by high-sensitivity C-reactive protein (hsCRP), is linked to adverse reproductive outcomes. However, prevalence and predictors of low-grade inflammation are poorly understood among reproductive age women. Therefore, the current aim was to characterize: 1) the prevalence of elevated hsCRP and 2) whether the association of various demographic, anthropometric, lifestyle, and metabolic characteristics with higher hsCRP varies across populations of reproductive age women with varying risk profiles for adverse reproductive outcomes.

Methods—Bivariate analysis of characteristics among women ages 18–40 having hsCRP <2.0 vs. ≥2.0 mg/L in the BioCycle Study (N=259), the Effects of Aspirin in Gestation and Reproduction Trial (EAGeR) (N=1228), and the National Health and Nutrition Examination Survey (NHANES) (N=2173) were conducted. Multivariable regression analysis estimated the association of all characteristics to hsCRP within each cohort.

Results—Prevalence of hsCRP≥2 mg/L ranged from 20–40%. Age, BMI, waist circumference, blood pressure, lipids, glucose, and insulin were frequently higher in women with hsCRP≥2 mg/L. In multivariable models, however, only adiposity (BMI, waist circumference) was independently associated with hsCRP within all three cohorts. Some variables showed cohort-specific

Correspondence & requests for reprints to: Lindsey A. Sjaarda, PhD, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, 6710B Rockledge Drive, Bethesda, MD, 20817 USA. lindsey.sjaarda@nih.gov; Ph: 301-435-6897.

Conflicts of interest

The authors have no conflicts to disclose.

associations with higher hsCRP: white race (EAGeR), higher fasting glucose (BioCycle), and lesser education and employment (NHANES). The total characteristics explained 28–46% of the variation in hsCRP across the three cohorts.

Conclusions—Low-grade inflammation was common, including among predominantly non-obese women, affecting from 20–40% of reproductive age women. Given the potential to reduce inflammation through inexpensive, widely available therapies, examination of the impact of chronic inflammation on reproductive and pregnancy outcomes, as well as preventive interventions, are now needed.

Keywords

inflammation; premenopausal women; reproductive age; C-reactive protein; obesity; population health; fertility

Introduction

Inflammation is a risk factor for chronic diseases,[1–4] and is also associated with several adverse reproductive outcomes. Indeed, high-sensitivity C-reactive protein (hsCRP), a commonly used measure of inflammation,[5] is associated with an increased risk of recurrent pregnancy loss,[6] recurrent in-vitro fertilization failure,[7] preeclampsia,[8] gestational diabetes,[4] preterm birth,[9] and fetal growth restriction.[10] Better understanding the role of low-grade inflammation in reproduction may have significant value, given the potential for therapeutic use of widely available and effective anti-inflammatory treatments, for example, aspirin or statins, which are successfully used to prevent cardiovascular events in middle age adults with higher hsCRP.[3, 11] Moreover, preconception treatment with daily low-dose aspirin restored an observed decrement in pregnancy rates among women with low-grade inflammation, specifically resulting in a 31% increase in the clinical pregnancy rate in women with hsCRP ≥2 mg/L at study entry.[12]

However, the prevalence of low-grade inflammation among women of reproductive potential, as opposed to middle aged adults at risk for cardiovascular disease, and the factors which may contribute to moderately elevated hsCRP in this population are uncertain. Thus, in the current era of personalized medicine and available anti-inflammatory treatments, the goal of the present investigation was to identify presently undetected groups susceptible to low-grade inflammation, a potential treatment target to ultimately improve fertility and pregnancy health. Specifically, this study aimed to exploit data from three unique cohorts of reproductive age women with differing risk profiles for adverse reproductive and pregnancy outcomes: 1) healthy, reproductive age women not actively attempting pregnancy but who are at risk of becoming pregnant because of lack of oral contraception use and variable sexual activity, especially given that roughly half of pregnancies in the U.S. are not specifically planned;[13] 2) healthy, reproductive women actively attempting spontaneous pregnancy but with a history of pregnancy loss, a cohort particularly relevant to a large proportion of women trying to conceive since up to 20–30% of all conceptions end in loss; [14, 15] and 3) a population-representative sample of reproductive age women, including with morbidities and race-ethnic distributions underrepresented in the previous two selected populations. Therefore, within each cohort described above, the aim of the present

investigation was to: 1) characterize the prevalence of moderately elevated hsCRP and 2) evaluate whether the association of demographic, anthropometric, lifestyle, and metabolic characteristics with higher hsCRP varies across these cohorts of women.

Methods

Three distinct cohorts of reproductive age women were investigated: 1) 259 regularly menstruating, healthy women who were not using hormonal contraception and not attempting pregnancy (the BioCycle Study, 2005–2007);[16] 2) 1228 regularly menstruating, healthy women who were not using hormonal contraception and were actively attempting pregnancy with a history of 1–2 prior pregnancy losses as part of a clinical trial of low dose aspirin (the Effects of Aspirin in Gestation and Reproduction [EAGeR] trial, 2007–2012);[17] and 3) a U.S. nationally representative sample of reproductive-age women who were not pregnant, selected from the National Health And Nutrition Examination Survey (NHANES), 2005–2008.[18] For each cohort, the design, methods, and participant characteristics have been previously described. Study characteristics and methods that are relevant to the present analysis are summarized below. Supplemental Table 1 contains a detailed report of between-cohort differences in inclusion and exclusion criteria. Importantly, to assess the endogenous factors associated higher hsCRP among reproductive aged women, two of the three cohorts employed blood sampling during the menses phase of the menstrual cycle, as hsCRP has been shown to fall approximately 0.30 mg/L from menses to ovulation.[19] Another important source of higher hsCRP consistently noted in women that was excluded from this analysis, is the use of hormonal medication, where a difference of 1.25 mg/L has been noted between hormone replacement therapy users vs non-users.[20] hsCRP may also vary across season, with higher concentrations in winter to spring,[21, 22] but it is unclear whether this is attributable to seasonal variation in exposure to infection (e.g. cold and flu season), variation in vitamin D,[23] or something inherent to season such as photoperiod or temperature. Regardless, the present study was not able to account for season as a potential source of within-woman variation.

For the BioCycle Study, 259 women from Western New York were recruited to participate for two menstrual cycles in a prospective study of cyclic changes in oxidative stress biomarkers, antioxidants, and endogenous reproductive hormones. Participants were regularly menstruating (cycles 21–35 days), age 18–44 years, with self-reported body mass index (BMI) 18–35 kg/m^2 at screening. BioCycle study exclusion criteria included use of oral contraceptives or short-acting hormonal treatments (e.g. patch, ring) during the preceding three months, use of longer-acting hormonal contraceptive medication (i.e., Depo-Provera, Norplant, intrauterine device) in the preceding 12 months, current use of vitamin and mineral supplements or prescription medications, pregnancy or breastfeeding in the preceding six months, currently attempting pregnancy, diagnosis of polycystic ovary syndrome (PCOS), infertility, or chronic medical conditions, and recent history of infections. The Health Sciences Institutional Review Board at the University at Buffalo approved the study; written informed consent was obtained from all participants.

The EAGeR trial enrolled 1,228 women at four U.S. medical centers in a randomized trial of preconception-initiated, daily low-dose aspirin and live birth. Participants were regularly

menstruating (cycles 21–42 days), age 18–40 years, and were actively attempting natural conception with a history of 1–2 documented pregnancy losses. Exclusion criteria included any indication or contra-indication for low-dose aspirin; diagnosis of PCOS, infertility, or chronic medical condition; and chronic use of NSAIDs. Institutional Review Board approval was obtained at each of the study sites, and all participants provided written informed consent. The trial was registered with ClinicalTrials.gov (NCT00467363).

The NHANES assesses the health and nutritional status of U.S. adults and children, obtaining a sample that is representative of the U.S. civilian, non-institutionalized population. To obtain data contemporaneous with the BioCycle and EAGeR studies, the present analysis used cross-sectional data from the 2005–2006 and 2007–2008 waves of NHANES. For the present analysis, the following exclusions were applied to the publicly available dataset (downloaded July 20, 2015): men, women ages <18 or >40 years, women who were pregnant as indicated either by self-report or positive result from a spot-urine pregnancy test, and women currently using hormonal contraception. These exclusions resulted in 1507 total women available for the present study. The present analysis accounted for the NHANES multi-stage sampling scheme and our additional inclusion criteria (women age 18–40 years who are not currently pregnant and not using hormonal contraception), producing results generalizable to U.S. women who meet these inclusion criteria. NHANES is conducted by the National Center for Health Statistics of the U.S. Centers for Disease Control and Prevention (CDC). The CDC Institutional Review Board approved the study and all participants provided informed consent.[18]

Data Collection

The BioCycle Study—The study baseline visit occurred on day 2 of the menstrual cycle (during menses). At this visit, demographic, reproductive history, and health behavior information was gathered through questionnaires, and fasting blood samples and anthropometric measures were collected by study staff.

The EAGeR trial—The study randomization visit (pre-aspirin treatment) occurred on day 2–4 of the menstrual cycle; questionnaires elicited data on participant demographics, reproductive history, and health behaviors. Anthropometric measures and untimed (i.e. random, majority non-fasting) blood samples were collected by study staff.

NHANES—At a study visit that was not timed to the menstrual cycle, trained interviewers collected data on participant demographics, medical and reproductive histories, current and past use of contraceptives, and health behaviors. Also, anthropometric measures and non-fasting blood samples were collected by study staff. Some participants (n=579) were selected to attend a morning medical examination visit where a fasting blood sample was collected.

Biospecimen analysis

The BioCycle Study—Serum hsCRP was measured using a chemiluminescent immunoassay (IMMULITE 2000 platform) sensitive to 0.3 mg per liter. Fasting serum total cholesterol, HDL cholesterol, and triglycerides were determined by an auto chemistry

analyzer. LDL cholesterol was determined using the Friedewald formula.[24] Fasting plasma glucose was assayed using a hexokinase-based methodology on a Beckman LX20 autoanalyzer. Fasting serum insulin was measured using a solid-phase competitive Chemiluminescent Enzymatic Immunoassay by Specialty Laboratories on the DPC Immulite 2000 analyzer.

The EAGeR Trial—Serum hsCRP was measured using an immunoturbidimetric assay using Roche COBAS 6000 autoanalyzer, with a limit of detection of 0.15 mg/L (Roche Diagnostics, Indianapolis, IN). Random total triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) concentrations were ascertained using Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Random plasma glucose was measured by a hexokinase based assay using a Roche COBAS 6000 chemistry analyzer. Random serum insulin was measured by sandwich immunoassay method using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN).

NHANES—Serum hsCRP was measured by latex-enhanced nephelometric assay on the Dade Behring Nephelometer II Analyzer System (Dade Behring Diagnostics, Inc., Somerville, New Jersey) with a limit of detection of 0.20 mg/L. Fasting total cholesterol and triglycerides were measured enzymatically in serum using either a Hitachi 717 or Hitachi 912 (Hitachi Global Storage Technologies, San Jose, CA) with a range of 3–800 mg/dL and 4–3000 mg/dL, respectively. HDL was measured directly using either a Hitachi 717 and 912 with a detection range of 3–120 mg/dL. LDL cholesterol was calculated using the Friedewald formula.[24] Fasting glucose was measured by hexokinase-mediated reaction with measurement of NADPH at 340 nm using a Roche/Hiatchi Analyzer (Roche Diagnostics, Indianapolis, IN). Insulin was measured with human insulin immunoassay using a SPECTRAmax™ 250 Microplate Spectrophotometer (Molecular Devices, Sunnyvale, CA) with a detection limit of <1 mU/L.

Statistical analysis

In each of the three studies, descriptive statistics of potentially relevant demographic, health, lifestyle, and reproductive history characteristics were calculated (including the total cohort for each: 259 for BioCycle, 1228 for EAGER, 1507 for NHANES). Then, bivariate analysis of each of these characteristics was conducted in women with lower versus higher hsCRP (<2 mg/L vs. 2–9.99 mg/L). Cut-points of hsCRP with demonstrated clinical utility for predicting cardiovascular disease risk in middle-aged adults define high risk as hsCRP ≥3 mg/L;[25] however, a lower cut-point of hsCRP ≥2 mg/L has been used to define ‘high’ hsCRP among adults considered to have low risk of cardiovascular disease (perhaps a more relevant population to presumably healthy premenopausal women).[26, 27] Furthermore, hsCRP 2–9.9 mg/L was the range that was associated with lower pregnancy rates in the EAGeR trial.[12] Women with hsCRP ≥10 mg/L were excluded from bivariate analyses, as well as regression model described below, as hsCRP ≥10 mg/L prompts retesting in clinical cardiovascular risk assessment and is consistent with acute phase inflammatory events (e.g. infection), as opposed to chronic low-grade inflammation.[28] Any hsCRP values identified as below the assay limit of detection were substituted with the assay limit of detection divided

by the square root of 2. Characteristics among women with lower (<2 mg/L) versus higher (2.0–9.99 mg/L) hsCRP (Table 2) were compared with Student's t-test for normally distributed continuous variables, Mann-Whitney U test for serum biomarkers which were not normally distributed, and Chi-square test for categorical variables.

In each cohort a generalized linear model of log-transformed hsCRP was fit as a function of all demographic, health, lifestyle, and reproductive history characteristics to examine the association of each characteristic to hsCRP across the three cohorts. The change in hsCRP per one unit change in a given variable (excluding log-transformed biomarkers) may be interpreted as a percent change in hsCRP (e.g. an increase of one BMI unit would result in a 9% increase in hsCRP in the BioCycle cohort). For independent variables which are log-transformed (i.e., lipid biomarkers, glucose, insulin), the percent change in hsCRP is expressed per one percent change in the independent variable (e.g. for each one percent increase in glucose, hsCRP increases by 1.93 percent in the BioCycle cohort). In each cohort, a multiple imputation procedure used a Markov chain Monte Carlo Method[29] to generate 20 complete datasets for all variables needed for the analysis (hsCRP and predictor variables, including demographics, health, lifestyle, and biomarkers). The multiple imputation model that was applied to the NHANES data also included variables denoting NHANES cluster and stratum. Among BioCycle participants, no variable was missing greater than 1%, except parity which was missing for 6 women (2.4%); missingness for any variable was less than 4% in the EAGeR cohort except education which was missing for 146 women (12.5%); and among NHANES participants, missingness for any variable was less than 10% except for income (10.2%), diastolic blood pressure (11.6%), systolic blood pressure (16.6%), smoking status (19.7%), and physical activity level (53.7%). Biomarkers included in the regression models also were log transformed for normality. Among the eligible NHANES participants, 579 women with fasting samples were included in the regression analysis. Analyses were conducted using SAS software (version 9.4; SAS Institute, Inc). For NHANES analyses, PROC SURVEYFREQ, PROC SURVEYMEANS, and PROC SURVEYREG were used, with appropriate sampling weights and variables to account for the additional exclusion criteria applied for the present analysis.[30] A *P*-value <0.05 was considered statistically significant in all tests, and a *P*-value <0.10 was considered marginally significant.

Results

Across the three cohorts, median (interquartile range) hsCRP ranged from 0.8 (0.4, 1.9) mg/L in the BioCycle Study to 1.4 (0.4, 3.9) mg/L in NHANES women. The prevalence of higher hsCRP (2.0–9.99 mg/L) was 20% in the BioCycle Study, 30% in the EAGeR trial cohort, and was 40% among women in NHANES (Table 1).

In bivariate analyses, certain factors were generally positively associated with higher hsCRP in all three cohorts (Table 2), including older age, higher BMI, larger waist circumference, higher blood pressure, higher lipids, and higher glucose and insulin concentrations. Reproductive history characteristics were inconsistently associated with higher hsCRP, where nearly twice higher parity was associated with having higher hsCRP in the BioCycle study, and earlier age at menarche was associated with higher hsCRP in the NHANES

cohort. Interestingly, smoking was only associated with higher hsCRP in NHANES; however, overall smoking prevalence was relatively low in the BioCycle and EAGeR cohorts compared to NHANES.

In multivariable models including all characteristics, adiposity measured by either BMI or waist circumference was independently associated with higher hsCRP within all three cohorts (Table 3). Specifically, each unit increase in BMI was associated with a 4–9% increase in hsCRP; this would translate to an increase in hsCRP of 0.3 to 0.7 ng/mL with an increase in five BMI units (a range separating BMI obesity categories), assuming a starting hsCRP concentration of 1.5 mg/mL. Also, some variables showed cohort-specific associations with higher hsCRP, such as white race in EAGeR women, though the estimate for white vs. non-white race was similar in the smaller BioCycle cohort. Also, higher fasting glucose was linked to higher hsCRP, but only in BioCycle. Women who were currently employed and who had completed at least a high school education had lower mean hsCRP in the NHANES cohort, but not in the other two cohorts. Of note, all BioCycle participants eligible for the linear regression analysis had at least a high school education. In contrast to the bivariate analyses, multivariable-adjusted models showed no independent association of hsCRP with age, nor with variables closely associated with age such as parity and marital status, nor was hsCRP associated with any lipid biomarker in any cohort.

The set of variables summarized in this report explained approximately 28% of the variation of hsCRP among EAGeR trial participants, 34% in the BioCycle participants, and 46% in NHANES participants (Table 3).

Comments

This study examined the prevalence and predictors of moderately elevated hsCRP (2–9.99 mg/L), as a marker of low-grade inflammation, across three distinct populations of reproductive-age women, and found that inflammation was common. Specifically, the prevalence ranged from 20–40%, with lower prevalence among cohorts selected to be healthy, including having lower adiposity, and higher prevalence in the general population. Adiposity as measured by BMI or waist circumference was independently associated with higher hsCRP in all three populations, even after considering multiple demographic, health, lifestyle, and reproductive history characteristics. Still, it is notable that low-grade inflammation was present in 1 in 5 women among the BioCycle cohort selected to be healthy and predominantly normal-weight. Furthermore, the total variance in hsCRP explained in reproductive age women ranged from 28–46%, indicating other unmeasured factors likely contribute to low-grade inflammation among this population.

Moderately elevated hsCRP was prevalent and increased with decreasing exclusivity of the study populations examined. Specifically, in the NHANES cohort, designed to be nationally representative, the prevalence of moderately elevated hsCRP was 40%, whereas this rate was 20% among BioCycle participants. No generally accepted thresholds are established for defining elevated hsCRP in reproductive age women with relevance to optimal fertility and pregnancy health, and few studies have included reproductive age women when characterizing hsCRP. Therefore, it is challenging to compare the prevalence of hsCRP ≥ 2

mg/L characterized here to other studies. However, an earlier study of four large U.S. cohorts of apparently healthy adults reported a median hsCRP of 1.52 mg/L in women not using exogenous hormones. This is similar to the median hsCRP of 1.4 mg/L in the population-representative NHANES cohort reported here, though these prior studies represented predominantly Caucasian participants and included adults ages 40 to 84, as opposed to age 18–40 included in NHANES here.[5] Other cohorts of U.S. adults ages 30 to 65 exhibited median hsCRP of 3.2 mg/L in white women and 3.5 mg/L black women, well above our observations, though normal weight participants had median hsCRP of 1.7 mg/L in both racial groups.[31] Comparing our estimated median hsCRP levels with results from other countries, our estimated median values are consistent with a study of reproductive-age Australian women after accounting for exogenous estrogen use,[32] but values observed here are higher than reports from premenopausal women in Denmark[33] and Norway.[34] Besides differences in body composition, differences in diet and lifestyle could contribute to differences in hsCRP levels across nations. Lastly, the prevalence of hsCRP ≥ 10 mg/L observed in this study was similar to that observed in other studies, further supporting this range of hsCRP as being predominantly attributable to transient acute events (i.e. infection) and not chronic, systemic inflammation.[28, 32]

Our finding of a positive relationship between hsCRP and adiposity agrees with prior studies in other populations. Certainly the most consistently linked health factor to higher hsCRP is central body fat distribution,[35] and BMI,[32] as observed also in each of the three cohorts of women examined here, and independent of the multiple other factors examined. Though multiple metabolic markers, including lipids, glucose, and insulin, were also elevated in women with higher hsCRP, nearly all these associations disappeared when modeled simultaneously with adiposity and other factors. Of note, higher socioeconomic status, specifically employment and higher educational attainment, was associated with lower hsCRP in NHANES, consistent with prior studies.[36, 37] Observing this effect only among NHANES is likely attributable to the greater diversity in socioeconomic status among this nationally representative sample, evidenced by the greater variation in educational attainment than was seen in either the highly selected population in the EAGeR trial or BioCycle Study. Also, in the BioCycle population having the lowest BMI and waist circumference, only BMI was independently associated with hsCRP with somewhat larger estimates than in the other cohorts and with no association between hsCRP and waist circumference. In contrast, in the cohort of highest overall adiposity (NHANES), the beta coefficient for waist circumference was relatively larger and the estimate for BMI smaller than the other cohorts. Thus, perhaps in leaner women BMI is a more informative predictor of hsCRP whereas in women with greater adiposity, waist circumference is more informative to systemic inflammation. Similarly, fasting glucose was only independently related to hsCRP among the leaner, younger BioCycle participants, but was not informative in models of hsCRP in the other cohorts; though speculative, this finding may suggest that inflammation-associated dysmetabolism precedes development of excess adiposity with advancing age. Interestingly, white race (compared to non-white) was associated with increasing hsCRP among the EAGeR cohort, in contrast to prior reports indicating higher hsCRP in black women.[38, 39] Given the low proportion of non-white participants (approx. 5%) in the EAGeR cohort and lack of corroboration in the other, more racially diverse

cohorts included here, this is likely a chance finding. Collectively, these data indicate that overarching predictors of hsCRP appear similar among reproductive age women as in other populations, with the exception of age, which may be less relevant to chronic inflammation in younger women within a narrow age range as opposed to studies of all adult ages showing an positive relationship between age and hsCRP.[32]

Another implication of our study is that further research on a broader range of factors is still needed to identify other contributors to chronically elevated hsCRP in healthy, reproductive age women, as among the two populations of selected women with lower rates of obesity and no oral contraceptive use, the demographic, health, lifestyle, and reproductive characteristics explained less of the variation in hsCRP than they did in a nationally-representative sample of reproductive-age women. Potential candidates not assessed here may include nutrition,[40, 41] oral health or other chronic localized infection,[1] as well as potentially less explored factors such as psychological stress or pollution. Identifying the contribution of these alternative factors could aid in the development of preventive efforts. Given that moderately elevated hsCRP, which was significantly associated with diminished pregnancy rate,[12] was prevalent (20–40%) even among cohorts selected to be healthy, and moreover in the BioCycle cohort also to be of predominantly normal-weight, it remains important to interrogate other potential causes of chronic low-level inflammation in reproductive age women. Especially given that safe and effective anti-inflammatory treatments are available and have been applied in cardiovascular medicine, further investigation of the role of inflammation and anti-inflammatory treatments in the context of improving fertility and pregnancy health is warranted.

Limitations of this study include that the NHANES hsCRP measurements were not timed to the menses phase of the menstrual cycle, when hsCRP is reportedly highest, as was done in the other two cohorts. This difference potentially contributed to greater hsCRP variability, inter-cohort and within NHANES, and underestimation of higher hsCRP in the NHANES cohort.[19] Further, though hsCRP is a common clinical measure and all three studies utilized high-sensitivity hsCRP assays, differences in assay platforms may have impacted comparability across cohorts. Two of these three platforms were compared previously,[42] indicating that agreement between the IMMULITE platform (BioCycle) and the nephelometer (NHANES) was excellent at higher ranges of hsCRP (2–9.9 mg/L) but the IMMULITE platform used in BioCycle may produce somewhat higher values than in NHANES at the low range of hsCRP (<2 mg/L; e.g. 0.3 mg/L for nephlometer compared to 0.7 mg/L for IMMULITE, 0.9 mg/L for nephlometer vs. 1.3 mg/L for IMMULITE). Given that the lowest overall hsCRP concentrations were observed in BioCycle on the IMMULITE platform and such assay differences were only apparent below the cut-point of the low hsCRP category, it is unlikely that such assay variation was responsible for our findings in Tables 2 and 3. Because the hsCRP reported values tended to be lowest in BioCycle, and its method of measurement apparently produces slight over-estimates compared to what was used in NHANES, actual differences across cohorts in the rates of higher hsCRP may be larger than reported here. Given the consistent relationship observed here and elsewhere between hsCRP and body mass, more specific measures of adiposity (e.g. from dual energy x-ray absorptiometry, for example) would be useful to better examine these associations and should be considered in future studies. Also of note, this study assessed cross-sectional

correlations and does not intend to establish causality. All three cohorts had rigorous quality control of the hsCRP assay and other variables, a large sample size, and low frequency of missing data.

Our data provide the most comprehensive characterization of hsCRP in reproductive age women to date, including three separate populations which uniquely characterize women of reproductive potential in the U.S., and reveals consistent evidence for a relationship between adiposity and inflammation, independent of other demographic, metabolic, and health history variables. Of note, low-grade inflammation in this population was common, including among predominantly non-obese women, affecting from 20–40% of women of reproductive age. Given the great potential to reduce inflammation through inexpensive, widely available therapies, such as aspirin, statins, and non-steroidal anti-inflammatory drugs, expanded examination of the impact of chronic, low-grade inflammation prior to pregnancy on subsequent reproductive and pregnancy outcomes is needed. Establishing such relationships will ultimately aid in identifying appropriate preventive and treatment approaches to improve reproductive and pregnancy outcomes among reproductive age women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

The BioCycle Study was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health (contract # HHSN275200403394C).The EAGeR study was also supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (National Institutes of Health, Bethesda, MD, USA; contract numbers HHSN267200603423, HHSN267200603424, and HHSN267200603426). This work was also supported by the NIH Medical Research Scholars Program, a public-private partnership jointly supported by the NIH and generous contributions to the Foundation for the NIH by the Doris Duke Charitable Foundation (Grant #2014194), the American Association for Dental Research, the Colgate Palmolive Company, Genentech, and other private donors. For a complete list, visit the foundation website at http://www.fnih.org.

References

1. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nature Reviews Immunology. 2015; 15:30–44.
2. Libby P. Inflammation in atherosclerosis. Nature. 2002; 420:868–874. [PubMed: 12490960]
3. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. New England Journal of Medicine. 1997; 336:973–979. [PubMed: 9077376]
4. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. Journal of the American Medical Association. 2001; 286:327–334. [PubMed: 11466099]
5. Rifai N, Ridker PM. Population distributions of C-reactive protein in apparently healthy men and women in the United States: implication for clinical interpretation. Clinical Chemistry. 2003; 49:666–669. [PubMed: 12651826]

6. Boggess KA, Lieff S, Murtha AP, Moss K, Jared H, Beck J, et al. Maternal serum C-reactive protein concentration early in pregnancy and subsequent pregnancy loss. American Journal of Perinatolgoy. 2005; 22:299–304.
7. Levin I, Gamzu R, Mashiach R, Lessing JB, Amit A, Almog B. Higher C-reactive protein levels during IVF stimulation are associated with ART failure. Journal of Reproductive Immunology. 2007; 75:141–144. [PubMed: 17466381]
8. Mohaupt MG. C-reactive protein and its role in preeclampsia. Hypertension. 2015; 65:285–286. [PubMed: 25452476]
9. Pitiphat W, Gillman MW, Joshipura KJ, Williams PL, Douglass CW, Rich-Edwards JW. Plasma C-reactive protein in early pregnancy and preterm delivery. American Journal of Epidemiology. 2005; 162:1108–1113. [PubMed: 16236995]
10. Sorokin Y, Romero R, Mele L, Wapner RJ, Iams JD, Dudley DJ, et al. Maternal serum interleukin-6, C-reactive protein, and matrix metalloproteinase-9 concentrations as risk factors for preterm birth <32 weeks and adverse neonatal outcomes. American Journal of Perinatology. 2010; 27:631–640. [PubMed: 20195952]
11. Ridker PM. The JUPITER trial: results, controversies, and implications for prevention. Circulation Cardiovascular Quality and Outcomes. 2009; 2:279–285. [PubMed: 20031849]
12. Sjaarda LA, Radin RG, Silver RM, Mitchell EM, Mumford SL, Wilcox B, et al. Preconception low-dose aspirin restores diminished pregnancy and live birth rates in women with low grade inflammation: a secondary analysis of a randomized trial. Journal of Clinical Endocrinology and Metabolism. 2017; 102:1495–1504. [PubMed: 28323989]
13. Finer LB, Zolna MR. Unintended pregnancy in the United States: incidence and disparities, 2006. Contraception. 2011; 84:478–485. [PubMed: 22018121]
14. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. New England Journal of Medicine. 1988; 319:189–194. [PubMed: 3393170]
15. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertility & Sterility. 1996; 65:503–509. [PubMed: 8774277]
16. Wactawski-Wende J, Schisterman EF, Hovey KM, Howards PP, Browne RW, Hediger M, et al. BioCycle study: design of the longitudinal study of the oxidative stress and hormone variation during the menstrual cycle. Paediatric and Perinatal Epidemiology. 2009; 23:171–184. [PubMed: 19159403]
17. Schisterman EF, Silver RM, Perkins NJ, Mumford SL, Whitcomb BW, Stanford JB, et al. A randomised trial to evaluate the effects of low-dose aspirin in gestation and reproduction: design and baseline characteristics. Paediatric and Perinatal Epidemiology. 2013; 27:598–609. [PubMed: 24118062]
18. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National health and nutrition examination survey: plan and operations, 1999–2010. Vital Health Statistics Series 1, Programs and Collection Procedures. 2013:1–37.
19. Gaskins AJ, Wilchesky M, Mumford SL, Whitcomb BW, Browne RW, Wactawski-Wende J, et al. Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle Study. American Journal of Epidemiology. 2012; 175:423–431. [PubMed: 22306563]
20. Barinas-Mitchell E, Cushman M, Meilahn EN, Tracy RP, Kuller LH. Serum levels of C-reactive protein are associated with obesity, weight gain, and hormone replacement therapy in healthy postmenopausal women. American Journal of Epidemiology. 2001; 153:1094–1101. [PubMed: 11390329]
21. Liu B, Taioli E. Seasonal Variations of Complete Blood Count and Inflammatory Biomarkers in the US Population – Analysis of NHANES Data. PLoS One. 2015; 10:e0142382. [PubMed: 26544180]
22. Sung KC. Seasonal variation of C-reactive protein in apparently healthy Koreans. International Journal of Cardiology. 2006; 107:338–342. [PubMed: 16503255]
23. Calton EK, Keane KN, Raizel R, Rowlands J, Soares MJ, Newsholme P. Winter to summer change in vitamin D status reduces systemic inflammation and bioenergetic activity of human peripheral blood mononuclear cells. Redox Biology. 2017; 12:814–820. [PubMed: 28441630]

24. Tremblay AJ, Morrissette H, Gagne JM, Bergeron J, Gagne C, Couture P. Validation of the Friedewald formula for the determination of low-density lipoprotein cholesterol compared with beta-quantification in a large population. Clinical Biochemistry. 2004; 37:785–790. [PubMed: 15329317]
25. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107:499–511. [PubMed: 12551878]
26. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. Circulation. 2003; 108:2292–2297. [PubMed: 14609996]
27. Thompson AL, Koehler E, Herring AH, Paynter L, Du S, Zhang B, et al. Weight Gain Trajectories Associated With Elevated C-Reactive Protein Levels in Chinese Adults. Journal of the American Heart Association. 2016; 5:e003262. [PubMed: 27638785]
28. Smith SC Jr, Anderson JL, Cannon RO 3rd, Fadl YY, Koenig W, Libby P, et al. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: Report from the clinical practice discussion group. Circulation. 2004; 110:e550–553. [PubMed: 15611380]
29. Schafer, JL. Analysis of Incomplete Multivariate Data. New York: Chapman and Hall; 1997.
30. National Center for Health Statistics. NHANES Analyses Course. Hyattsville, MD: 2013. [cited 2017 February 22]; Available from: https://www.cdc.gov/nchs/tutorials/NHANES/NHANESAnalyses/NHANES_Analyses_intro.htm
31. Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, et al. Race and gender differences in C-reactive protein levels. Journal of the American College of Cardiology. 2005; 46:464–469. [PubMed: 16053959]
32. Hung J, Knuiman MW, Divitini ML, Davis T, Beilby JP. Prevalence and risk factor correlates of elevated C-reactive protein in an adult Australian population. American Journal of Cardiology. 2008; 101:193–198. [PubMed: 18178405]
33. Sorensen CJ, Pedersen OB, Petersen MS, Sorensen E, Kotze S, Thorner LW, et al. Combined oral contraception and obesity are strong predictors of low-grade inflammation in healthy individuals: results from the Danish Blood Donor Study (DBDS). PLoS One. 2014; 9:e88196. [PubMed: 24516611]
34. Laugsand LE, Asvold BO, Vatten LJ, Romundstad PR, Wiseth R, Hveem K, et al. Metabolic factors and high-sensitivity C-reactive protein: the HUNT study. European Journal of Preventive Cardiology. 2012; 19:1101–1110. [PubMed: 21775413]
35. Blum CA, Muller B, Huber P, Kraenzlin M, Schindler C, De Geyter C, et al. Low-grade inflammation and estimates of insulin resistance during the menstrual cycle in lean and overweight women. The Journal of Clinical Endocrinology and Metabolism. 2005; 90:3230–3235. [PubMed: 15797950]
36. Loucks EB, Sullivan LM, Hayes LJ, D'Agostino RB Sr, Larson MG, Vasan RS, et al. Association of educational level with inflammatory markers in the Framingham Offspring Study. American Journal of Epidemiology. 2006; 163:622–628. [PubMed: 16421236]
37. Panagiotakos DB, Pitsavos CE, Chrysohoou CA, Skoumas J, Toutouza M, Belegrinos D, et al. The association between educational status and risk factors related to cardiovascular disease in healthy individuals: The ATTICA study. Annals of Epidemiology. 2004; 14:188–194. [PubMed: 15036222]
38. Ferguson KK, McElrath TF, Chen YH, Mukherjee B, Meeker JD. Longitudinal profiling of inflammatory cytokines and C-reactive protein during uncomplicated and preterm pregnancy. American Journal of Reproductive Immunology. 2014; 72:326–336. [PubMed: 24807462]
39. Picklesimer AH, Jared HL, Moss K, Offenbacher S, Beck JD, Boggess KA. Racial differences in C-reactive protein levels during normal pregnancy. American Journal of Obstetrics and Gynecology. 2008; 199:523 e521–526. [PubMed: 18539258]

40. King DE, Mainous AG 3rd, Geesey ME, Woolson RF. Dietary magnesium and C-reactive protein levels. Journal of the American College of Nutrition. 2005; 24:166–171. [PubMed: 15930481]

41. Nanri A, Moore MA, Kono S. Impact of C-reactive protein on disease risk and its relation to dietary factors. Asian Pacific Journal of Cancer Prevention. 2007; 8:167–177. [PubMed: 17696726]

42. Roberts WL, Sedrick R, Moulton L, Spencer A, Rifai N. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Clinical Chem. 2000; 46:461–468. [PubMed: 10759469]

Table 1

Demographic, lifestyle and reproductive characteristics among three cohorts of reproductive age, U.S. women.[a]

Characteristics	BioCycle N=259	EAGeR N=1228	NHANES 2005–2008[b] N=1507
hsCRP, mg/L[c]	0.9 (0.8, 1)	1.3 (1.2, 1.4)	1.4 (1.2, 1.5)
hsCRP, mg/L[d]	0.8 (0.4, 1.9)	1.2 (0.6, 3.2)	1.4 (0.4, 3.9)
hsCRP < 2 mg/L	196 (75.7)	773 (63.0)	763 (50.6)
2 ≤ hsCRP < 10 mg/L	52 (20.1)	370 (30.1)	510 (40.4)
hsCRP ≥10 mg/L	9 (3.5)	63 (5.1)	136 (9.0)
hsCRP missing	2 (0.7)	22 (1.8)	98 (6.5)
Demographics			
Age, y	27.3 (26.3, 28.3)	28.7 (28.5, 29)	30.0 (29.5, 30.4)
Race: white (vs. non-white)	154 (59.5)	1162 (94.6)	886 (58.8)
Marital status: married or living with partner	66 (25.5)	1199 (97.6)	918 (60.9)
Education ≥ High School	258 (99.6)	1205 (98.1)	1221 (81.0)
Annual Household Income			
≥ $75,000	69 (26.8)	641 (52.2)	345 (22.9)
$20,000–$74,999	134 (51.8)	494 (40.2)	867 (57.5)
≤ $19,999	55 (21.4)	95 (7.7)	295 (19.6)
Currently employed	211 (81.6)	895 (72.9)	1028 (68.2)
Health & Lifestyle			
BMI, kg/m^2	24.1 (23.6, 24.5)	26.3 (26, 26.7)	28.1 (27.5, 28.8)
Waist circumference, cm	74.7 (73.7, 75.8)	86.8 (86, 87.7)	91.7 (90.2, 93.2)
Current smoker	10 (3.9)	151 (12.3)	399 (26.5)
Physical Activity, %			
Low (Walking)	25 (9.7)	322 (26.2)	574 (38.1)
Moderate (Moderate)	92 (35.5)	501 (40.8)	812 (53.9)
High (Vigorous)	142 (54.8)	405 (33.0)	121 (8.0)
Sleep duration <6 hours/night	15 (5.8)	33 (2.7)	217 (14.4)
Blood pressure, mmHg			
Systolic	99.2 (98.1, 100.3)	111.6 (110.9, 112.3)	110.1 (109.4, 110.9)
Diastolic	61.2 (60.2, 62.2)	72.6 (72, 73.2)	67.4 (66.6, 68.1)
Pulse, bpm	69.7 (68.7, 70.8)	73.0 (72.3, 73.6)	77 (76.3, 77.8)
Total cholesterol, mg/dL[d,e]	160 (146, 176)	163 (146, 184)	179 (159, 202)
HDL cholesterol, mg/dL[d,e]	49 (41, 58)	50 (43, 58)	55 (47, 65)
LDL cholesterol, mg/dL[d,e]	98 (87, 116)	99 (83, 118)	103 (83, 124)
Triglycerides, mg/dL[d,e]	53 (39, 72)	100 (73, 144)	87 (63, 126)
Glucose, mg/dL[d,e]	87 (83, 91)	81 (74, 88)	92 (87, 98)
Insulin, μU/mL[d,e]	6 (4, 8)	11 (6, 21)	8 (5, 13)

Characteristics	BioCycle N=259	EAGeR N=1228	NHANES 2005–2008[b] N=1507
Reproductive Health History			
Age at menarche, y	12.5 (12.3, 12.6)	12.8 (12.6, 12.9)	12.6 (12.5, 12.7)
Parous	68 (26.1)	657 (53.5)	1025 (68)
Number of live births			
0	191 (73.9)	571 (46.5)	482 (32.0)
1	14 (5.5)	443 (36.1)	285 (18.9)
2	28 (10.7)	214 (17.4)	404 (26.8)
≥3	26 (9.9)	0 (0.0)	336 (22.3)
Number of pregnancies not ending in live birth			
0	243 (93.7)	0 (0.0)	1034 (68.6)
1	16 (6.3)	825 (67.2)	271 (18.0)
2	0.0	403 (32.8)	118 (7.8)
≥3	0.0	0 (0.0)	84 (5.6)

[a] Data are n (%) or mean (95% confidence interval [CI]), unless otherwise noted.

[b] NHANES cohort excluding women using hormonal contraception; use of hormonal contraceptives was an exclusion criteria for BioCycle and EAGeR.

[c] Statistics are presented as geometric mean (95% CI).

[d] Statistics are presented as median (IQR).

[e] BioCycle and NHANES 2005–2008 biomarker measure is a fasting value; EAGeR is not a fasting value.

Table 2

Demographic, lifestyle, and reproductive history by hsCRP level in three cohorts of reproductive age, U.S. women.[a]

	BioCycle		EAGeR		NHANES[b]	
	Low, hsCRP <2	**High, hsCRP 2–9.9**	**Low CRP hsCRP <2**	**High, hsCRP 2–9.9**	**Low CRP hsCRP <2**	**High, hsCRP 2–9.9**
	N=196	**N=52**	**N=773**	**N=370**	**N=763**	**N=510**
hsCRP, mg/L[c]	**0.5 (0.4)**	**3.6 (1.4)**	**0.6 (0.5)**	**3.9 (1.6)**	0.5 (0.02)	3.9 (0.1)
Demographics						
Age, y	**26.3 (7.9)**	**30.4 (8.5)**	**28.5 (4.7)**	**29.2 (5.0)**	29.8 (0.3)	30.6 (0.3)
Race: white (vs. non-white)	56.6	71.2 *	94.0	96.2	61.9	56.4
Marital status: married or living with partner	**21.4**	**38.5**	98.3	95.9	62.2	64.8
Education ≥ High School	100	100	98.8	97.5	**84.2**	**76.7**
Annual Household Income						
≥ $75,000	25.8	26.9	55.4	47.3	26.7	21.4
$20,000–$74,999	49.5	61.5	37.2	44.3	57.1	57.3
≤ $19,999	24.7	11.5	7.4	8.4	16.2	21.3
Currently employed	81.7	81.3	75.1	76.9	71.1	66.4 *
Health & Lifestyle						
BMI, kg/m^2	**23.1 (3.3)**	**26.9 (4.1)**	**23.9 (4.5)**	**30.2 (6.4)**	**24.2 (0.2)**	**31.4 (0.4)**
Waist circumference, cm	**72.5 (7.3)**	**81.0 (9.1)**	**81.4 (11.3)**	**96.0 (15.8)**	**83.4 (0.5)**	**99.6 (1.0)**
Current smoker	4.1	3.8	11.2	13.9	**22.4**	**31.0**
Physical Activity						
Low	9.7	9.6	24.1	28.6	42.2	33.9
Moderate	38.3	28.8	41.8	39.5	48.2	58.8
High	52.0	61.5	34.2	31.9	9.6	7.4
Sleep duration <6 hours	6.2	5.9	2.0	4.1	**10.2**	**19.5**
Blood pressure, mmHg						
Systolic	98.5 (8.6)	101.1 (8.1) *	**109.4 (11.0)**	**115.2 (12.8)**	**108.0 (0.5)**	**112.2 (0.7)**
Diastolic	60.8 (8.1)	61.8 (8.4)	**71.2 (11.9)**	**75.2 (9.6)**	66.5 (0.4)	67.8 (0.7) *
Pulse, bpm	69.7 (8.2)	68.6 (7.3)	**71.6 (10.6)**	**75.4 (13.1)**	75.6 (0.6)	77.8 (0.6)
Total cholesterol, mg/dL[d,e]	**159 (143, 175)**	**168 (152, 187)**	**161 (145, 180)**	**167 (150, 191)**	**174 (154, 195)**	**183 (164, 211)**

	BioCycle		EAGeR		NHANES[b]	
	Low, hsCRP <2	**High, hsCRP 2–9.9**	**Low CRP hsCRP <2**	**High, hsCRP 2–9.9**	**Low CRP hsCRP <2**	**High, hsCRP 2–9.9**
	N=196	**N=52**	**N=773**	**N=370**	**N=763**	**N=510**
HDL, mg/dL[d,e]	49 (41, 58)	47 (42, 57)	**52 (45, 60)**	**45 (39, 53)**	**60 (50, 69)**	**50 (44, 58)**
LDL, mg/dL[d,e]	98 (84, 112)	107 (92, 124)*	**97 (81, 113)**	**106 (88, 123)**	**95 (80, 114)**	**110 (91, 134)**
Triglycerides, mg/dL[d,e]	**50 (38, 69)**	**60 (46, 84)**	**92 (68, 125)**	**124 (86, 185)**	**72 (54, 100)**	**106 (73, 144)**
Glucose, mg/dL[d,e]	**84 (81, 89)**	**87 (82, 91)**	**80 (72, 86)**	**83 (76, 91)**	**90 (86, 96)**	**94 (89, 100)**
Insulin, μU/mL[d,e]	6 (4, 8)	6 (5, 10)	**10 (6, 18)**	**15 (8, 29)**	**6 (4, 9)**	**10 (8, 17)**
Reproductive Health History						
Age at menarche, y	12.4 (1.2)	12.5 (1.5)	12.8 (1.5)	12.8 (4.8)	**12.7 (0.1)**	**12.4 (0.1)**
Parous	**21.1**	**40.4**	51.5	57.0	66.1	72.3
Number of live births						
0	**78.9**	**59.6**	48.5	43.0	33.9	27.7
1	**4.2**	**9.6**	35.7	37.0	18.6	18.5
2	**10.5**	**9.6**	15.8	20.0	27.7	25.2
≥ 3	**6.3**	**21.2**	0.0	0.0	19.8	28.6
Number of pregnancies not ending in live birth						
0	94.0	93.3	0.0	0.0*	67.5	69.3
1	6.0	6.7	69.2	64.1*	19.3	16.2
2	0.0	0.0	30.8	35.9*	8.6	7.4
≥ 3	0.0	0.0	0.0	0.0*	4.5	7.1

[a] Data are % and mean (standard deviation), unless otherwise noted. Significant differences (P<0.05) noted in bold font; and

* indicates marginal difference (P<0.10) between low and high hsCRP for a given characteristic within an individual study population. Significant testing was conducted using Fisher exact test for categorical variables; t-test for parametric continuous variables (e.g. age); Wilcoxon-Mann-Whitney U test for biomarkers in Biocycle and EAGeR studies, and F-test for natural-log-transformed biomarkers in NHANES study.

[b] NHANES cohort excluding women using hormonal contraception; use of hormonal contraceptives was an exclusion criteria for BioCycle and EAGeR.

[c] Statistics are presented as geometric mean (SD).

[d] Statistics are presented as median (IQR).

[e] BioCycle and NHANES 2005–2008 biomarker measure is a fasting value; EAGeR is not a fasting value.

Table 3

Regression coefficients (95% confidence intervals) describing predictors of log(hsCRP) within each cohort of reproductive age, U.S. women with hsCRP < 10 mg/L).[a]

Characteristics	BioCycle N=250	EAGeR N=1165	NHANES[b] 2005–2008 N=579
Demographics			
Age, y	0.00 (−0.02, 0.03)	0.01 (0.00, 0.02)	0.01 (−0.01, 0.04)
Race, white (vs. non-white)	0.25 (−0.04, 0.54)	**0.28 (0.03, 0.54)**	−0.09 (−0.30, 0.12)
Marital status, married or living with partner	−0.11 (−0.51, 0.28)	−0.13 (−0.52, 0.26)	0.01 (−0.19, 0.22)
Education ≥ High School	_[c]	0.21 (−0.24, 0.66)	**−0.26 (−0.46, −0.06)**
Annual Household Income			
≥ $75,000	−0.09 (−0.38, 0.21)	−0.06 (−0.17, 0.06)	−0.04 (−0.31, 0.23)
$20,000–$74,999	0.00 (ref)	0.00 (ref)	0.00 (ref)
≤ $19,999	−0.02 (−0.34, 0.31)	−0.19 (−0.42, 0.04)	−0.01 (−0.25, 0.24)
Currently employed (vs. not employed)	0.15 (−0.17, 0.47)	0.01 (−0.13, 0.15)	**−0.20 (−0.39, −0.01)**
Health & Lifestyle			
BMI, kg/m^2	**0.09 (0.03, 0.15)**	**0.05 (0.03, 0.07)**	**0.04 (0.01, 0.07)**
Waist circumference, cm	0.03 (−0.01, 0.06)	**0.01 (0.00, 0.02)**	**0.03 (0.01, 0.04)**
Current smoker	−0.02 (−0.64, 0.61)	−0.01 (−0.19, 0.18)	0.16 (−0.01, 0.42)
Physical Activity			
Low (Walking)	0.15 (−0.28, 0.57)	0.03 (−0.11, 0.17)	−0.06 (−0.32, 0.19)
Moderate (Moderate)	0.00 (ref)	0.00 (ref)	0.00 (ref)
High (Vigorous)	0.16 (−0.10, 0.43)	−0.03 (−0.16, 0.10)	−0.14 (−0.48, 0.20)
Sleep duration <6 hours/night (vs. ≥6)	−0.31 (−0.83, 0.22)	0.32 (−0.03, 0.67)	−0.03 (−0.30, 0.24)
Blood pressure, mmHg			
Systolic	0.01 (−0.02, 0.02)	0.00 (0.00, 0.01)	0.00 (−0.01, 0.01)
Diastolic	−0.02 (−0.04, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
Pulse, bpm	0.00 (−0.02, 0.02)	0.00 (0.00, 0.01)	0.00 (−0.01, 0.01)
Total cholesterol, mg/dL[d]	5.70 (−0.93, 12.30)	−0.57 (−1.61, 0.46)	0.96 (−1.89, 3.80)
HDL cholesterol, mg/dL[d]	−1.56 (−3.77, 0.66)	−0.11 (−0.55, 0.32)	−0.74 (−1.63, 0.15)
LDL cholesterol, mg/dL [d]	−3.40 (−7.40, 0.61)	0.39 (−0.17, 0.96)	−0.22 (−1.85, 1.41)
Triglycerides, mg/dL[d]	−0.41 (−1.01, 0.20)	0.19 (−0.04, 0.41)	−0.14 (−0.49, 0.22)
Glucose, mg/dL[d]	**1.93 (0.12, 3.74)**	0.26 (−0.13, 0.64)	0.20 (−0.47, 0.86)
Insulin, μU/mL[d]	−0.06 (−0.33, 0.21)	0.02 (−0.06, 0.11)	0.01 (−0.17, 0.19)
Reproductive Health History			
Parous	0.29 (−0.16, 0.73)	0.02 (−0.10, 0.14)	0.12 (−0.20, 0.43)
R^2	0.34	0.28	0.46

[a]Statistics are β estimates (95% CI) from a linear model with natural log(hsCRP) as the dependent variable and all variables listed in the first column entered as independent variables. All biomarkers were log-transformed for analysis. Missing data were imputed via a multiple imputation procedure that produced 20 replicates, and the results from each cohort were summarized over these replicates. Significant associations are bolded.

[b] NHANES cohort excluding women using hormonal contraception; use of hormonal contraceptives was an exclusion criteria for BioCycle and EAGeR. The present analysis accounted for the NHANES multi-stage sampling scheme and our additional exclusion criteria with appropriate samplings weights and variables, producing results generalizable to U.S. women who meet these inclusion criteria.

[c] All BioCycle participants eligible for the multivariable linear model had completed at least a high school education.

[d] BioCycle and NHANES 2005–2008 biomarker measures are fasting (i.e., only women among the NHANES fasting subsample were included in this analysis); EAGeR biomarkers are not fasting.