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Clin Endocrinol (Oxf). Author manuscript; available in PMC 2011 April 1.

Published in final edited form as:
Clin Endocrinol (Oxf). 2010 April ; 72(4): 527–533. doi:10.1111/j.1365-2265.2009.03713.x.

Association of sex hormones and C-reactive protein levels in men

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Abstract

Objectives—The age-associated decline in sex hormone levels in men is paralleled by an increase in cardiovascular disease and associated risk factors including low grade chronic inflammation. The objective of this analysis was to investigate the association between sex hormone levels and C-reactive protein (CRP) in a population-based sample of men.

Design—Population-based, cross-sectional observational survey.

Participants—A multistage stratified design was used to recruit a random sample of 2,301 racially and ethnically diverse men age 30–79 years. Blood samples were obtained on 1,899 men. Analyses were conducted on 1,559 men with complete data on CRP and sex hormone levels.

Measurements—High sensitivity CRP levels. The association between CRP and sex hormone levels was assessed using multiple linear regression models.

Results—An inverse association was observed, in both bivariate and multivariate analyses, between CRP and total testosterone, free testosterone, and sex hormone-binding globulin (SHBG) levels. These associations remained statistically significant after adjusting for age, body mass index (BMI), comorbid conditions, and lifestyle factors. A positive trend between estradiol (total and free) and CRP levels was not statistically significant.

Conclusions—A robust, inverse dose-response correlation between testosterone and SHBG levels with CRP levels provides further evidence of a potential role of androgens in inflammatory processes.

Keywords

sex hormones; C-reactive protein; epidemiology

Introduction

The age-associated decline in sex hormone levels in men is paralleled by an increase in cardiovascular disease and associated risk factors.1 Low grade chronic inflammation has emerged as an independent predictor of cardiovascular events,2 and an increase in inflammatory status with age has been reported.3 Although a role of sex hormones in inflammatory processes has been hypothesized,4 few studies have investigated the

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association between sex hormone levels and inflammatory markers, and reported results have not been consistent. Cross-sectional data from the InCHIANTI study show an inverse association between total testosterone levels and soluble interleukin-6 receptor (sIL6r), but not with IL-6, TNF-α or IL-1β.5 In contrast, a recent cross-sectional analysis of 400 men age 40–80 years reports a positive association of C-reactive protein (CRP) levels with estradiol (E2) but not with total or bioavailable testosterone levels.6 Randomized trials of testosterone supplementation have shown a decrease in TNF-α and IL-1β levels,7 but no effect on CRP.8

Using data from the Boston Area Community Health (BACH) Survey, the objectives of this analysis were to investigate the association between CRP and sex hormone levels in a racially and ethnically diverse population-based sample of men.

Materials and Methods

Overall Design

The BACH survey is a population-based epidemiologic survey of a broad range of urologic symptoms and risk factors in a randomly selected sample. Detailed methods have been described elsewhere.9 In brief, BACH used a multi-stage stratified random sample to recruit approximately equal numbers of subjects according to age (30–39, 40–49, 50–59, 60–79 years), gender, and race/ethnic group (African American (Black), Hispanic, and Caucasian (White)). The BACH sample was recruited from April 2002 through June 2005. Interviews were completed with 63.3% of eligible subjects, resulting in a total sample of 5504 adults (2301 men, 3203 women, 1767 Black, 1877 Hispanic, 1859 White respondents). All protocols and informed consent procedures were approved by the New England Research Institutes' Institutional Review Board. All subjects provided written informed consent.

Data collection

Data were obtained during a 2-hour in-person interview, conducted by a trained (bilingual) phlebotomist/interviewer, generally in the subject's home. A venous blood sample (20 ml) was obtained and height, weight, and hip and waist circumference were measured along with self-reported information on medical and reproductive history, major comorbidities, lifestyle and psychosocial factors, and symptoms of urogynecological conditions. Two blood pressure measurements were obtained during the interview and were averaged. BACH participants were asked to gather all prescription, over-the-counter and alternative medications in the home used by them over the past 4 weeks for recording of the label information by the interviewer. Additionally, participants were asked separately if they were taking medications for specific indications, such as high cholesterol and high blood pressure.

Hormones

Non-fasting blood samples were collected close to waking time (median time since awakening 3 h 38 min) to control for diurnal variation in hormone levels. Serum testosterone (T) and sex hormone-binding globulin (SHBG) levels were measured by competitive electrochemiluminescence immunoassays on the 2010 Elecsys system (Roche Diagnostics, Indianapolis, IN). All assays were previously approved by the Food and Drug Administration for clinical use. The lower limits of detection for T and SHBG were 0.07 nmol/L (2 ng/dL) and 3 nmol/L, respectively. Reference ranges are 9–27.8 nmol/L (260–801 ng/dL) for T and 14.5–48.4 nmol/L for SHBG. The inter-assay coefficients of variation (CV) for T at concentrations of 0.8, 9.5 and 24.3 nmol/L (24, 275, and 700 ng/dL) were 7.4, 2.2, and 1.7%, respectively. For SHBG at 16.5, 25, and 64 nmol/L, inter-assay CVs were 3.9, 2.4, and 2.2%, respectively. Estradiol (E2) was measured by the Mayo Clinic Core Laboratory (Rochester, MN) with liquid chromatography-tandem mass spectrometry. The lower limit of detection was 46 pmol/L (12.5 pg/mL). To reliably measure E2 levels in the

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low range, E2 values less than 46 pmol/L (12.5 pg/mL) were calculated by manual integration of chromatograms. The inter-assay CVs for E2 concentrations 4.6–220 pmol/L (1.25–60 pg/mL) ranged between 13.4–6.0%. Free testosterone (FT) and estradiol (FE2) concentrations were calculated from total T (TT) or E2 and SHBG concentrations using mass action equations assuming a fixed albumin concentration.10

High-sensitivity C-Reactive Protein (CRP) levels

The concentration of CRP was determined using an immunoturbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics - Indianapolis, IN), using reagents and calibrators from DiaSorin (Stillwater, MN). In this assay, an antigen-antibody reaction occurs between CRP in the sample and an anti-CRP antibody that has been sensitized to latex particles, and agglutination results. This antigen-antibody complex causes an increase in light scattering, which is detected spectrophotometrically, with the magnitude of the change being proportional to the concentration of CRP in the sample. Assays were performed at the Children's Hospital Medical Center Research Laboratories, Boston, MA, with a reported a sensitivity of 0.28 nmol/L (0.03 mg/L). The coefficients of variation at concentrations of 8.67, 29.24, and 127.43 nmol/L (0.91, 3.07, 13.38 mg/L) are 2.81, 1.61 and 1.1%, respectively.

Covariates

Potential confounders included in the analysis include sociodemographic, lifestyle factors, and comorbid conditions. Age was categorized by decades: 30–39, 40–49, 50–59, 60–69, and 70–79 years. Self reported race/ethnicity was defined as Black, Hispanic, or White. Body mass index (BMI) was categorized as <25.0, 25.0–29.9, and ≥30.0 kg/m^2. Physical activity was measured using the Physical Activity Scale for the Elderly (PASE) and was categorized as low (<100), medium (100–250), and high (>250). Alcohol consumption was defined as alcoholic drinks including beer, wine and hard liquor consumed per day: 0, <1, 1–2.9, ≥3 drinks per day. Smoking was defined as never smokers (smoked <100 cigarettes lifetime and not currently smoking), former smokers (smoked ≥100 cigarettes lifetime and currently non-smoker), and current smoker (smoked ≥100 cigarettes and currently a smoker). The socioeconomic status (SES) index was calculated using a combination of education and household income. SES was categorized as low (lower 25% of the distribution of the SES index), middle (middle 50% of the distribution), and high (upper 25% of the distribution). Comorbid conditions included in the analysis were heart disease, type 2 diabetes, hypertension, and depression. The presence of comorbidities was defined as a yes response to "Have you ever been told by a health care provider that you have or had…."? Heart disease was defined by self-report of myocardial infarction, angina, congestive heart failure, coronary artery bypass, or angioplasty stent. Participants reporting five or more depressive symptoms (out of 8) using the abbreviated Center for Epidemiological Studies – Depression (CES-D) scale were considered to have depressive symptoms. Medications included in the analysis were anti-inflammatory and other medications (both prescription and over the counter) that could affect CRP levels.11

Statistical analysis

Descriptive statistics, proportions for categorical variables and mean and standard deviations (SD) for continuous variables, were used to describe the analysis sample. As the distribution of CRP levels was skewed, log (base 10) transformations of CRP levels were used. Log_{10}(CRP) levels were analyzed as a continuous variable. Additionally, CRP levels were categorized into three groups: <9.5 nmol/L (low cardiovascular risk), 9.5–28.5 nmol/L (moderate cardiovascular (CVD) risk), >28.5 nmol/L (high CVD risk).2 Similarly, sex hormone levels were log_{10} transformed. Serum hormone levels were analyzed as continuous variables. Scatter plots of CRP levels against sex hormone levels with locally weighted

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scatterplot smoothing (LOESS, smoothing parameter = 0.8) were used to assess graphically the linearity of the association. Multiple linear regression models were used to assess the association between sex hormones and CRP and to adjust for potential confounders.

Of the 2,301 men in BACH, blood samples were obtained for 1,899 (82.5%). A total of 12 men with missing or extreme values for T and SHBG were excluded from the analysis. Additionally, 281 men were missing E2. Of the remaining 1,607 men, 48 had at least one outlying hormone value with the largest groups outlying on FT (N=10) or SHBG (N=10). Analyses were conducted on a sample of 1,559 men with complete data on sex hormones and CRP. As results for T and SHBG were similar when conducted on the larger group of men with these measures available compared to the subgroup of men with complete data on all hormones and CRP, results are presented for the subgroup of 1,559 men. Of the 1,559 men included in the analysis, 87 (5.6%) had missing data on one or more covariates. Twenty-five multiple imputations were performed separately by race/ethnicity using all relevant variables to obtain plausible values for missing data on covariates included in the analysis. Observations were weighted as inversely proportional to their probability of selection. Weights were post-stratified to the Boston population according to the 2000 census. Analyses were conducted in version 9.1 of SAS (SAS Institute, Cary, NC, USA) and version 9.0.1 of SUDAAN (Research Triangle Institute, Research Triangle Park, NC, USA).

Results

Characteristics of the men included in the analysis are presented in Table 1 and descriptive statistics on sex hormones and CRP levels are included in Table 2. About 40% of men were overweight (BMI 25.0–29.9) and one-third were obese (BMI ≥30). About 30% of men were current smokers and 25% reported no alcohol consumption. Over half of the analysis sample reported use of anti-inflammatory or other medications that could affect CRP levels. Prevalence of heart disease and type 2 diabetes was similar at around 10%, while both depressive symptoms (14%) and hypertension (25%) were more common. One-third of men were at moderate cardiovascular risk (CRP levels 9.5–28.5 nmol/L) while almost 20% were at high risk (CRP >28.5 nmol/L).

Figure 1 presents scatterplots of CRP against sex hormone levels (TT, SHBG, and E2). These figures show an inverse association of CRP levels with both TT and SHBG. A similar association was observed with FT. In contrast, a slight trend in increased CRP was observed with increasing E2 and FE2 levels. Scatterplots presented in Figure 1 show fairly linear associations between CRP and sex hormone levels on the log scale. Table 3 presents crude and adjusted correlations between sex-hormones and CRP levels. Testosterone (both total and free) and SHBG levels were negatively associated with CRP levels (age- and BMI adjusted $r = -0.176$ for total T, $r = -.132$ for free T, and $r = -0.157$ for SHBG). E2 and free E2 were positively associated with CRP levels, but these associations were not statistically significant. These observed associations were robust and remained statistically significant in multivariate models. BMI had the largest impact on the association of CRP with T and SHBG level with changes of 35–40% in the regression coefficients after adding BMI to the model. Adjusting for waist circumference instead of BMI, similar results were observed. Additional covariates did not further attenuate the observed association. In contrast, no association was observed between E2 and CRP levels in either unadjusted or adjusted models. We also examined whether the ratio of TT to E2 was associated with CRP, the result was similar to the association between TT and CRP.

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Discussion

Results from the BACH study demonstrate, in a community-based sample of men, an inverse association of CRP with total and free testosterone as well as SHBG. These associations remained statistically significant after adjusting for age, obesity, comorbid conditions, lifestyle factors, and prescription medications use. An association of E2 and CRP levels was not observed. These findings support the hypothesis that higher androgen levels may have an anti-inflammatory effect.

Results from previous observational studies of the association of sex hormone levels and inflammatory markers have not been consistent. Data from a study of 1,896 men with the metabolic syndrome but not type 2 diabetes conducted in Finland show an inverse association of T and SHBG with CRP levels after adjusting for age, BMI, comorbid conditions, and lifestyle factors.12 Similarly, a study of 70 men with type 2 diabetes reports an inverse association between bioavailable T and CRP levels.13 Data from the InCHIANTI study, a cross-sectional study of 497 men 65 yr and older, show an inverse association of between both total and bioavailable T and sIL6r but not with IL-6, TNF-α, IL-1β, or CRP levels.5 Data from the HAMLET (Hormonal changes in the Ageing MaLe: and Epidemiologic Taskforce) study on 400 men 40–80 years conducted in Germany reported a different pattern of association between sex hormones and CRP levels.6 The inverse association between T (total, free, or DHEAS) and CRP levels was not statistically significant while increased levels of both E2 and FE2 were associated with higher CRP levels. The estradiol and CRP association was attenuated but remained significant in multivariate models; however, this association was further attenuated and statistically non-significant after adjusting for intra-abdominal fat. A recent report from the InCHIANTI study shows a similar null result for the E2 and CRP association; however, a positive and statistically significant association was observed between estradiol and IL-6 levels.14 Finally, in an occupation-based sample of 715 middle-aged men (35–59 yrs), no association was observed between CRP and sex hormone levels, including TT, FT, SHBG, and E2.15

Data from studies of the effect of testosterone replacement therapy (TRT) on levels of inflammatory markers are not always consistent. A study of TRT among older men with androgen deficiency (TT <15 nmol/l) found a decrease in TNF-α and IL-1β levels after 1 month of treatment but no changes in CRP levels.7 A randomized trial among healthy older men (age>60 years) did not find a difference in inflammatory marker levels after 3 months of therapy.16 Similar results were reported by a randomized trial of TRT among hypogonadal men with type 2 diabetes after 3 months of treatment despite a baseline association of TT and FT with IL-6 and CRP levels.17 Finally a larger trial of men age 60–80 years with TT levels <13.7 nmol/l reported no change in CRP levels after testosterone supplementation for 26 weeks.8 While TRT seems to be associated with either a decrease or no change in levels of inflammatory markers, estrogen treatment in men with prostate cancer has been reported to increase CRP concentrations.18

The immunosuppressive effect of androgens is well established and the greater incidence of immune-mediated diseases in women and hypogonadal men is attributed to androgens down-regulating pro-inflammatory cytokines.4, 7 Although the association of sex hormone levels and cardiovascular events remains controversial,19 there is evidence from longitudinal studies showing low sex hormone levels as predictive of the development of the metabolic syndrome (a constellation of cardiovascular risk factors including dyslipidemia, hypertension, abdominal obesity, and insulin resistance) and type 2 diabetes.20, 21 Similar data on the association of E2 and cardiometabolic risk factors or outcomes is sparse. Elevated E2 levels have been associated with type 2 diabetes and increased insulin levels,22 however, the association with the metabolic syndrome has not been consistent.23, 24 While

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data from the Framingham Heart Study have suggested that men with higher E2 are at lower risk of cardiovascular events,25 other longitudinal studies have found either no association between E2 and CVD (Rancho-Bernardo and Caerphilly studies)26, 27 or reported an increase in the risk of stroke (Honolulu-Asia Aging Study)28 or progression of atherosclerosis (Atherosclerosis and Insulin Resistance study).29 The robust inverse association between testosterone and CRP levels observed in the present study provides further evidence supporting the hypothesis that modulation of inflammatory processes may be one of the pathways by which androgens affect cardiometabolic risk. As BACH is presently a cross-sectional study, the temporal sequence of causality or specific mechanisms of action cannot be assessed by means of cross-sectional data alone. Thus, we cannot exclude the alternative hypothesis that low androgen levels may be a consequence of inflammation. Longitudinal studies as well as investigation of the association of sex hormones and additional inflammatory markers are warranted to confirm the role of androgens in inflammatory processes.

Strengths of the BACH study include a community-based random sample across a wide age range (30–79 years), inclusion of large numbers of minority participants representative of Black and Hispanic populations, and a wide range of covariates including sociodemographic, lifestyle, and health variables, which can be adjusted for in the analysis. Although the effect of anti-inflammatory medications are controlled for in the present analysis, the effect of the treatment of comorbid conditions, which could have further attenuated CRP levels, are not accounted for in this analysis. Additionally, information on recent hospitalization was not collected. However, a full analysis of the potential influence of medication use in general on CRP levels is beyond the scope of this paper. The potential confounding effect of insulin, a negative modulator of SHBG, on the androgens and CRP association could not be assessed as insulin levels were not measured in the present study. History of comorbid conditions was assessed by self-report with the potential for reporting and/or recall bias; however, previous research has demonstrated the reliability and validity of self-report for heart disease, diabetes, and hypertension.30 The BACH study was limited geographically to the Boston area. However, comparison of sociodemographic and health-related variables from BACH with other large regional (Boston Behavioral Risk Factor Surveillance System) and national (National Health Interview Survey) surveys have shown that the BACH estimates are comparable to national trends on key health related variables. Although BACH measured demographics, medications and comorbidities in detail, residual confounding in this observational study cannot be excluded as the explanation for these associations.

In summary, results from the present study demonstrate a robust inverse correlation of T (both total and free) and SHBG with CRP levels. Although cross-sectional, these findings provide further evidence supporting the hypothesis that modulation of inflammatory processes is a potential pathway by which androgens could affect cardiometabolic risk and associated conditions such as the metabolic syndrome, diabetes, and cardiovascular disease.

Acknowledgments

Funding: This work was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) DK 56842. Analyses for the current manuscript were supported through an unrestricted educational grant to New England Research Institutes, Inc. from GlaxoSmithKline. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health. The Corresponding Author retains the right to provide a copy of the final manuscript to the NIH upon acceptance for publication, for public archiving in PubMed Central as soon as possible but no later than 12 months after publication.

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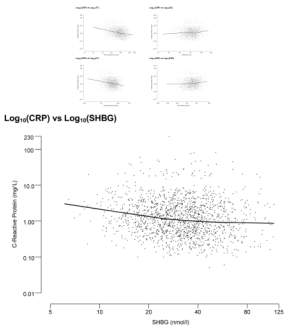

Figure 1.
Scatter plots of Log_{10} transformed C-reactive protein levels by Log_{10} transformed sex hormone levels with LOESS curve

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Table 1

Characteristics of the analysis sample (N=1,559).

	N (weighted %)
Age (years)	
30–39	418 (37.1%)
40–49	454 (25.5%)
50–59	353 (17.9%)
60–69	220 (12.4%)
70–79	114 (7.0%)
Race/Ethnicity*	
Black	429 (27.5%)
Hispanic	515 (33.0%)
White	615 (39.5%)
Socioeconomic Status	
Low	632 (22.8%)
Middle	641 (48.3%)
High	286 (28.9%)
Body Mass Index (kg/m2)	
<25.0	407 (26.8%)
25.0–29.9	612 (39.5%)
30.0+	541 (33.7%)
Physical Activity (PASE)	
Low (<100)	434 (25.4%)
Middle (100–250)	731 (47.2%)
High (250+)	394 (27.5%)
Smoking	
Never	600 (39.4%)
Former	455 (29.4%)
Current	503 (31.2%)
Alcohol Consumption (drinks/day)	
None	499 (24.8%)
<1	575 (41.1%)
1–2.9	311 (25.2%)
3+	174 (8.9%)
Heart disease (% Yes)	152 (9.4%)
Diabetes (% Yes)	190 (9.7%)
High blood pressure (% Yes)	481 (25.8%)
Depression (% Yes)	259 (14.1%)
Anti-inflammatory medication** (% Yes)	732 (53.5%)
Current cancer treatment (% Yes)	16 (1.4%)
Taking hormone medication (% Yes)	25 (1.4%)

*unweighted

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** Anti-inflammatory and other medications that may could affect CRP levels: Blood form & coagulant/anti-platelet agent (clopidogrel, ticlopidine); Cardiovascular/antilipemics/hmg-coa reductase inhibitors (statins); Non-statin anti-cholesterol drugs; Beta-blockers; Calcium channel blockers; Select ACE inhibitors (captopril, ramipril, fosinopril); Rosiglitazone, pioglitazone; Angiotensin II receptor agonists (Losartan, Valsartan, Irbesartan, Olmesartan, Candesartan, Telmisartan); Aspirin; Naproxen; Ibuprofen

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Table 2

Descriptive statistics for sex hormones and C-reactive protein (CRP) levels.

		Geometric Mean ± SD or Median (Interquartile range) or N (%)
Total T (nmol/L)	Geometric Mean ± SD	13.75 ± 1.55
	Median (Interquartile range)	14.47 (10.44, 18.98)
Free T (nmol/L)	Geometric Mean ± SD	0.29 ± 1.52
	Median (Interquartile range)	0.29 (0.23, 0.38)
SHBG (nmol/L)	Geometric Mean ± SD	0.29 ± 1.52
	Median (Interquartile range)	30.47 (22.16, 41.53)
Estradiol (pmol/L)	Geometric Mean ± SD	79.62 ± 1.52
	Median (Interquartile range)	82.23 (61.31, 108.29)
Free estradiol (pmol/L)	Geometric Mean ± SD	2.26 ± 1.53
	Median (Interquartile range)	2.34 (1.75, 3.09)
CRP (nmol/L)	Geometric Mean ± SD	10.69 ± 3.22
	Median (Interquartile range)	10.29 (4.67, 22.95)
	<9.5 nmol/L	688 (47.2%)
	9.5–28.5 nmol/L	533 (33.1%)
	>28.5 nmol/L	338 (19.7%)

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Table 3

Association of $\log_{10}$ transformed sex-hormones and $\log_{10}$ transformed CRP levels. Pearson correlations and 95% confidence intervals. (N=1,559)

	Crude	p-value	Age-adjusted	p-value	Age and BMI-adjusted	p-value	Multivariate-adjusted*	p-value
Total T	−0.282 (−0.368, −0.196)	<0.001	−0.277 (−0.366, −0.187)	<0.001	−0.176 (−0.266, −0.087)	<0.001	−0.184 (−0.259, −0.110)	<0.001
Free T	−0.234 (−0.315, −0.154)	<0.001	−0.221 (−0.318, −0.124)	<0.001	−0.132 (−0.223, −0.040)	0.005	−0.129 (−0.207, −0.051)	0.001
SHBG	−0.164 (−0.241, −0.088)	<0.001	−0.263 (−0.347, −0.180)	<0.001	−0.157 (−0.235, −0.078)	<0.001	−0.176 (−0.245, −0.107)	<0.001
E2	0.065 (−0.042, 0.173)	0.24	0.061 (−0.047, 0.168)	0.27	0.040 (−0.060, 0.139)	0.44	0.027 (−0.066, 0.120)	0.57
Free E2	0.092 (−0.017, 0.201)	0.099	0.103 (−0.007, 0.213)	0.07	0.063 (−0.038, 0.164)	0.22	0.054 (−0.038, 0.147)	0.25

*adjusted for age, BMI, SES, smoking status, alcohol intake, heart disease, high blood pressure, depression, diabetes, current cancer treatment, anti-inflammatory medication