Association of Prudent, Western, and Alternate Healthy Eating Index (AHEI-2010) dietary patterns with serum testosterone and sex hormone binding globulin levels in men

Lopez, David S ; Liu, Lydia ; Smith-Warner, Stephanie A ; Tsilidis, Konstantinos K ; Daniel, Carrie ; Baillargeon, Jacques ; Rohrmann, Sabine ; Platz, Elizabeth A ; Giovannucci, Edward

Abstract: PURPOSE The association of dietary patterns with testosterone (T) and sex hormone binding globulin (SHBG) levels remains unclear. We investigated the associations of dietary patterns with T and SHBG levels to determine whether these associations vary by obesity status. METHODS A cross-sectional analysis was conducted in 1376 middle-aged (≥ 40 years old) men of the Health Professionals Follow-up Study. Prudent (rich in whole grains and dietary fiber) and Western (rich in red meat and refined grains) diet scores were identified using principal component analysis. The Alternate Healthy Eating Index 2010 (AHEI-2010) score, a measure of overall diet quality, was defined based on foods and nutrients predictive of chronic disease risk. RESULTS We identified a weak inverse association between AHEI-2010 and T levels (P_{trend} = 0.07), but no associations with other dietary patterns. Null associations were observed between diet scores and SHBG. Obesity status appeared to modify the associations for the Prudent diet and AHEI-2010 with both T and SHBG ($P_{interaction} \leq 0.05$). T levels were lower (Q1 vs. Q4, 4.23 vs. 3.38) and SHBG higher (Q1 vs. Q4, 48.6 vs. 64.3) with adherence to a more prudent diet among obese men ($P_{trends} \leq 0.05$). CONCLUSION We observed a weak inverse association between AHEI-2010 and T levels. Null associations were identified for SHBG. Obesity status seemed to modulate associations of T and SHBG levels with diet scores, especially the AHEI-2010 and prudent diets. However, this research question warrants further investigation in prospective studies.

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Association of Prudent, Western, and Alternate Healthy Eating Index (AHEI-2010) dietary patterns with serum testosterone and sex hormone binding globulin levels in men

David S. Lopez[1,2], **Lydia Liu**[3], **Stephanie A. Smith-Warner**[3], **Konstantinos K. Tsilidis**[4,5], **Carrie Daniel**[6], **Jacques Baillargeon**[1], **Sabine Rohrmann**[7], **Elizabeth A. Platz**[8,9,10], **Edward Giovannucci**[3,11]

[1]Deparment of Preventive Medicine and Population Health, University of Texas Medical Branch, Galveston, TX, USA

[2]Department of Preventive Medicine and Population Health, UTMB Health School of Medicine, 301 University Blvd., Galveston, TX 77555-1153, USA

[3]Departments of Nutrition and Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[4]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

[5]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece

[6]Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[7]Department of Chronic Disease Epidemiology, Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich, Zurich, Switzerland

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

David S. Lopez, davlopez@utmb.edu.

Author contribution DSL and EG contributed to the study design, interpretation of the data, and writing and critical discussion of the manuscript draft. LL contributed to the statistical analysis of the study. All the other authors contributed to the interpretation, discussion, and editing of the manuscript draft.

Conflict of interest The authors declare no competing interests.

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Declarations

Ethics approval The protocols for the conduct of the Health Professionals Follow-Up Study (HPFS) were approved by the Institutional Review Board of the Harvard School of Public Health. Informed consent was obtained from all participants.

Informed consent We conducted a secondary data analysis using data from HPFS. HPFS obtained informed consents from participants that also included consent for publication.

[9]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

[10]Department of Urology and the James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[11]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital- Harvard Medical School, Boston, MA, USA

Abstract

Purpose—The association of dietary patterns with testosterone (T) and sex hormone binding globulin (SHBG) levels remains unclear. We investigated the associations of dietary patterns with T and SHBG levels to determine whether these associations vary by obesity status.

Methods—A cross-sectional analysis was conducted in 1376 middle-aged (≥40 years old) men of the Health Professionals Follow-up Study. Prudent (rich in whole grains and dietary fiber) and Western (rich in red meat and refined grains) diet scores were identified using principal component analysis. The Alternate Healthy Eating Index 2010 (AHEI-2010) score, a measure of overall diet quality, was defined based on foods and nutrients predictive of chronic disease risk.

Results—We identified a weak inverse association between AHEI-2010 and T levels (P_{trend} = 0.07), but no associations with other dietary patterns. Null associations were observed between diet scores and SHBG. Obesity status appeared to modify the associations for the Prudent diet and AHEI-2010 with both T and SHBG ($P_{interaction}$ ≤0.05). T levels were lower (Q1 vs. Q4, 4.23 vs. 3.38) and SHBG higher (Q1 vs. Q4, 48.6 vs. 64.3) with adherence to a more prudent diet among obese men (P_{trends} ≤0.05).

Conclusion—We observed a weak inverse association between AHEI-2010 and T levels. Null associations were identified for SHBG. Obesity status seemed to modulate associations of T and SHBG levels with diet scores, especially the AHEI-2010 and prudent diets. However, this research question warrants further investigation in prospective studies.

Keywords

Dietary pattern; Testosterone; SHBG; Men

Introduction

Testosterone (T) plays an important role in men's health, and its deficiency has been linked to poorer health and risk of a number of chronic diseases (e.g., cancer, diabetes, and cardiovascular diseases) [1, 2]. Studies over the last decade have demonstrated that one-third of men over 45 years of age experience low levels of T [3]. In the USA, there are approximately 2.4 million 40–69-year-old men with low T [4], and it is projected that by 2025, approximately 6.5 million American men aged 30 to 80 years will have low T, partly due to the increasing elderly population [3]. In parallel to the rising prevalence of low T, obesity (body mass index [BMI] ≥30 kg/m^2) prevalence has increased over time and now affects over 30% of American men [5]. In the last 10 years, several studies have investigated the associations between T and obesity; low levels of T and body fatness (as defined by BMI ≥30 kg/m^2, waist circumference ≥102 cm, or percent body fat ≥25%) are associated in

cross-sectional and prospective cohort studies [6, 7]. In addition, the relationship between T and obesity has been shown to be bidirectional: that is, low levels of T increase the risk of body fatness, and body fatness increases the risk of low levels of T [8].

Sex hormone binding globulin (SHBG) is a glycoprotein synthesized in the liver that binds with high affinity to testosterone; therefore, SHBG plays a critical role in T physiology [9]. Low levels of SHBG have been independently associated with chronic disease risk, including metabolic syndrome, type 2 diabetes, and hormone-sensitive cancers such as those of the breast and prostate (null association) [10, 11]. Obesity is associated with lower levels of SHBG [6].

Beyond their role in obesity, dietary factors may also influence T and SHBG levels [12]. Previous studies have reported a number of significant associations between dietary patterns and hormone-related health outcomes (e.g., erectile dysfunction and semen quality) [13] and with risk for various chronic diseases [14, 15], suggesting that the aforementioned significant associations may be linked, in part, through the T pathway. Furthermore, the role of diet in circulating levels of T and SHBG among obese and non-obese men remains unclear, as previous studies have focused primarily on adjustment for BMI rather than examining the interaction of these three factors [12].

The research rationale to conduct this study was to better understand the potential role of diet in circulating levels of T and SHBG, and whether the presence of obesity, which has been linked to unhealthy diets and low levels of testosterone, can influence the role of diet as regards T and SHBG levels. To our knowledge, no previous study has simultaneously investigated the three dietary patterns, Prudent, AHEI-2010, and Western, in relation to serum T levels and examined whether these associations vary by obesity status. Therefore, in order to explore these issues, we conducted a cross-sectional analysis in the Health Professionals Follow-up Study (HPFS). Specifically, we examined two empirically derived dietary patterns, the Prudent diet (rich in whole grains and dietary fiber) and the Western diet (rich in red and processed meat and refined grains), and a modified dietary score based on national dietary recommendations, the Alternate Healthy Eating Index 2010 (AHEI-2010, a dietary score based on foods and nutrients predictive of chronic disease risk). We hypothesized that the Prudent and AHEI-2010 dietary patterns may potentially be associated with higher levels of T and SHBG, including those found in obese men, while the opposite would be observed with the Western diet.

Material and methods

Study population

The HPFS is an on-going prospective cohort study that started in 1986 with 51,529 middle-aged US male health professionals (dentists, pharmacists, optometrists, osteopath physicians, podiatrists, and veterinarians). Participants are followed up through mailed questionnaires every 2 years to obtain regular updates of their information on lifestyle and health outcomes, and every 4 years for assessment of their usual diet [16]. Follow-up rate for assessment of diseases is approximately 94%. During 1993 and 1995, 18,225 participants provided a blood sample, which was collected in blood tubes containing liquid EDTA

and shipped to the laboratory via overnight courier, chilled on ice. In the laboratory, the blood was centrifuged, divided into plasma, erythrocytes, and buffy coat, and stored in liquid nitrogen freezers. In the current study, we leveraged data from participants who were previously selected for a prior nested case–control study. Participants who were selected as cases and controls were matched by year of birth (± 1 year), timing of blood draw (midnight to before 9 am, 9 am to before noon, noon to before 4 pm, and 4 pm to before midnight), season (winter, spring, summer, and fall), and year (exact). The participants for this study were previously identified at different times of the on-going HPFS, and blood collection resulted in three assay batches, as follows: blood draw to 1996, 1996–1998, and 1998–2000. T levels have not consistently been associated with prostate cancer, except possibly at very low levels, while we previously conducted a similarly designed investigation of vitamin D and T [17, 18]. Due to the diurnal hormonal variation of serum T among men, we restricted the analysis to men whose blood samples were drawn in the morning (excluded $n = 236$). The institutional review board at Harvard T.H. Chan School of Public Health approved this study. All subjects signed a written informed consent form.

Assessment of testosterone, estradiol, and SHBG

Plasma concentrations of sex steroid hormones and sex hormone binding globulin (SHBG) were previously measured in Dr. Nader Rifai's laboratory at the Children's Hospital, Boston, MA, USA, in three assay batches. Total testosterone was measured using a competitive electrochemiluminescence immunoassay, estradiol was measured using a third-generation RIA, and SHBG was measured using a coated tube noncompetitive immunoradiometric assay. The mean intrapair correlation coefficients of variation were 4.9% for total testosterone, 5.2% for estradiol, and 10.7% for SHBG. Missing data occurred in only three samples due to low plasma volume. To assess the consistency of sex steroid hormone concentrations over time, total testosterone, estradiol, and SHBG were previously measured in 144 HPFS participants who were free of cancer diagnosis and who provided a blood sample in 1993/94 and again in 1997 (mean of 3.03 ± 0.46 years apart) [19]. Adjusting for age, race, and season of the year, the Spearman correlation coefficients were 0.68 for total testosterone, 0.55 for estradiol, and 0.74 for SHBG (all $P < 0.0001$) for the samples taken 3 years apart.

Dietary assessment

Information on dietary intake was obtained from study participants using a validated semi-quantitative food frequency questionnaire (FFQ) at baseline and every 4 years thereafter [20]. Participants reported how frequently they consumed a standard portion of a food item within the last year using nine response categories ranging from never or less than once per month to more than six times daily. The baseline FFQ was modified slightly over time to account for secular changes in food and cooking preferences. The FFQ at baseline contained 131 food items, while in 2010 it contained 148 items, with an average of 140 items across all FFQs. The correlation coefficients between the 1986 FFQ and two 7-day weighted dietary records in a sample of 323 men were 0.59 for red meat, 0.52 for processed meats, 0.67 for fruit, 0.26 for cruciferous vegetables, 0.28 for dark-yellow vegetables, 0.55 for green leafy vegetables, and 0.27 for whole grains.

The methodology for defining a posteriori dietary patterns in the HPFS has been detailed previously [21]. In brief, food items were assigned to 40 pre-specified food groups based on nutrient profiles or cooking usage, as previously described. Next, we conducted principal component factor analysis [22] on the 40 food groups to identify dietary patterns. The obtained factors were rotated using orthogonal rotation to avoid dietary patterns being correlated with each other and to aid in interpretation. We used the eigenvalue (> 1), Scree test [23], and interpretability to determine the number of factors to retain. The first factor retained was positively associated with red meat, processed meat, refined grains, and high-fat dairy products and was labeled the "Western" dietary pattern; the second factor was associated with high intake of fruits, vegetables (leafy green, yellow, and cruciferous), tomatoes, garlic, legumes, poultry, fish, whole grains, other soups, salad dressing (oil/vinegar), water, and fruit juice and was labeled the "Prudent" dietary pattern. To calculate the factor score for each pattern for each participant, we summed the intake of the component food groups weighted by the factor loadings (the correlation coefficient between a food group and a particular dietary pattern).

The AHEI-2010, an a priori derived pattern based on existing evidence and dietary guidelines [14], was also calculated for each participant. The AHEI-2010 is a modified version of the HEI-2005, which incorporates current scientific evidence on dietary factors and risk of chronic diseases (e.g., type 2 diabetes, cardiovascular disease, and cancer). The score includes ten dietary components, classified as follows: six components for which high intake was considered desirable (vegetables, fruits, nuts and legumes, whole grains, long-chain omega-3 fatty acids, and polyunsaturated fat); one component for which moderate intake was considered to be desirable (alcohol); and three components for which avoidance or lowest intake was considered to be desirable (sugar sweetened beverages and fruit juice, red meat, and trans fat). Each component is scored from 0 to 10, with higher scores representing more optimal intake up to a maximum of 100 points.

Assessment of covariates

Age, weight, height, smoking status, total physical activity, and alcohol consumption were self-reported and obtained via mailed questionnaires. Energy intake was obtained via FFQs. Body mass index (BMI) was calculated based on weight and height (weight in kilograms divided by height in meters squared). Obesity was defined as BMI ≥30 kg/m^2. Participants were classified based on their smoking status as never, past, or current 1–14, 15–24, and ≥25 cigarettes per day. Total physical activity was derived from the metabolic equivalents per week. Alcohol consumption was categorized as grams per day, as follows: 0, 0.1–4.9, 5–14.9, 15–29.9, and ≥30.

Statistical analysis

A factor score for each dietary pattern was calculated for each participant. We categorized the continuous dietary pattern scores variable into quintiles. Geometric means and 95% confidence intervals (CIs) for total T concentrations were estimated by quintiles of the Prudent, Western, and AHEI dietary patterns using linear regression models. We used multivariable linear regression with robust variance (PROC MIXED with empirical statement) to investigate these associations. This method offers the flexibility to provide

a valid inference without assumption of a normal distribution for the dependent variables. Mean total T, estradiol, and SHBG concentrations were similar across batches. To test for linear trend, participants were assigned the median values of the specific dietary pattern quintiles, and the resulting variable was entered continuously to the model; the *P* value for linear trend was calculated using the Wald test. In the multivariable linear regression models, we adjusted for age, batch for potential residual confounding, BMI (kg/m^2, < 25; 25–29.9; 30 +), smoking habits (never, past, or current, 1–14, 15–24, and ≥25 cigarettes/d), total physical activity (metabolic equivalents/week, quintiles), alcohol consumption (g/d, 0; 0.1–4.9; 5–14.9; 15–29.9; and ≥30), and energy intake (kcal/d, quintiles) because these variables have been previously linked to T, estradiol, and SHBG levels, and dietary patterns. We further adjusted T results for estradiol levels because these hormones compete for binding with SHBG. Adjusted odds ratios (OR) and 95% CIs for low T (total testosterone ≤3.5 vs. > 3.5 ng/mL) were estimated in relation to quintiles of dietary patterns using logistic regression. As described above, all confounders, including estradiol and SHBG concentrations, were adjusted for in the logistic regression models to quantify the association between dietary patterns and low T.

Stratified analyses were conducted by obesity status (BMI < 30 vs. ≥30 kg/m^2) because BMI is known to influence T levels and the effects of diet may vary by BMI. Multiplicative interaction terms were incorporated in the models, and likelihood-ratio tests were used to test for interaction. All analyses were conducted with SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). All *P* values were 2-sided and $P < 0.05$ indicated statistical significance.

Results

Among the 1376 men in this analysis, those with the highest Prudent and AHEI-2010 dietary pattern scores were, on average, more likely to have lower BMI and SHBG levels, more likely to be physically active, and less likely to smoke and drink alcohol compared to men with the lowest Prudent and AHEI-2010 dietary pattern scores (Table 1). In contrast, men with the highest Western dietary pattern scores tended to have higher mean BMI and were more likely to smoke and drink alcohol than men with the lowest Western dietary pattern score and compared to men with high Prudent and AHEI-2010 dietary pattern scores (Supplemental Data, Fig. 1). Similarly, men with the highest Western dietary pattern score had higher mean estradiol levels when compared with men in the lowest Western dietary pattern score and when compared with men with the highest Prudent and AHEI-2010 dietary pattern scores.

Dietary pattern and T and SHBG levels

Prudent and Western dietary patterns' scores were not significantly associated with T levels after multivariable adjustment ($P_{trend} = 0.55$ and $P_{trend} = 0.69$, respectively). However, a marginally significant positive association was observed between the AHEI 2010 dietary pattern score and T levels ($P_{trend} = 0.07$). Men in the first two quintiles of AHEI-2010 (i.e., lower adherence to the dietary recommendations) had lower T levels compared to those in the three higher quintiles (Table 2 and Fig. 1). Non-significant associations were observed

between SHBG and the dietary scores (Table 2). These non-statistically significant results did not demonstrate a clear dose response or linear association between increasing quintiles of the dietary patterns and T levels. In the Prudent diet, T levels seem to be lower from the lowest to the highest quintile. However, in AHEI-2010, T levels were higher in quintile #3, but they were lower in the last two highest quintiles. Similarly, the Western diet showed a non-linear pattern with T levels.

We also evaluated the associations of Prudent, Western, and AHEI-2010 dietary patterns with low T (defined as total testosterone ≤3.5 ng/mL). There were no statistically significant associations with low T for any of the dietary patterns (P_{trend} ≥0.49 for the 3 diets, Supplemental Data, Fig. 2–4).

Dietary pattern and T and SHBG levels by obesity status

Figures 2a, b, and c show associations of Prudent, AHEI-2010, and Western dietary patterns with T levels stratified by obesity status (BMI ≥30 kg/m^2). As expected, obese men had substantially lower T levels compared to overweight and normal weight men (Fig. 2a, b, c and Online Supplemental Table 1). Suggestive interactions between obesity and Prudent ($P_{interaction}$ = 0.05, Fig. 2a) and AHEI-2010 ($P_{interaction}$ = 0.05, Fig. 2b) dietary patterns were observed to be in association with T levels. Among non-obese men, neither dietary pattern was associated with T levels. However, among obese men, the Prudent dietary pattern (P_{trend} = 0.05, Fig. 2a) and AHEI-2010 (P_{trend} = 0.09, Fig. 2b) were similarly inversely associated with T levels, albeit these associations were not statistically significant. The Western dietary pattern was not significantly associated with T levels by obesity status (Fig. 2c). In general, in both Prudent and AHEI-2010 dietary patterns among obese men, T levels appeared to be lower from lowest to highest quintile. However, the opposite was observed with the Western diet.

The association between SHBG concentrations and dietary patterns also varied by obesity status, with normal weight/overweight men having higher SHBG concentrations compared to obese men (Fig. 3a, b, c). We found significant interactions between obesity and the Prudent ($P_{interaction}$ = 0.01, Fig. 3a) and AHEI-2010 ($P_{interaction}$ = 0.04, Fig. 3b) dietary patterns in association with SHBG level. We saw a positive association between the Prudent diet and SHBG level among obese men (P_{trend} = 0.03, Fig. 3a), but not among non-obese men. We also observed a suggestive positive trend in the association between AHEI-2010 and SHBG level among obese men, although this trend was not statistically significant (P_{trend} = 0.17, Fig. 3b). The association between the Western dietary pattern and SHBG levels appeared to be modified by obesity status, but it did not reach statistical significance ($P_{interaction}$ = 0.07, Fig. 3c). In general, in both Prudent and AHEI-2010 dietary patterns among obese men, SHBG levels were shown to be higher from lowest to highest quintile. However, no clear pattern was observed with the Western diet.

We conducted further analysis of the association of T/SHBG ratio levels with the dietary patterns, including stratification by obesity status (Supplemental Tables 2 and 3). We did not find a clear pattern in these associations, and the *P* value for interactions did not reach statistical significance.

Discussion

In this cross-sectional analysis of 1376 middle-aged male health professionals, we did not detect any statistically significant associations between three dietary patterns (namely, Prudent, Western, and AHEI-2010) and T and SHBG levels overall, although a weak association was observed between AHEI-2010 and T levels. However, the associations of Prudent and AHEI-2010 dietary patterns with T (marginally) and SHBG levels were modified by BMI. Obese men had lower levels of T and SHBG compared to men who were not obese, irrespective of dietary pattern. Among obese men, higher scores on the Prudent and possibly AHEI-2010 dietary patterns were associated with lower T levels, whereas SHBG levels were higher with higher scores in the Prudent dietary pattern.

Dietary patterns have received increasing attention in the field of disease prevention because they account for the complexity of nutrient and food interactions within diets that may contribute to alterations in metabolism [24]. Overall, the associations between healthy diets and T and SHBG levels have been inconsistent [25] and only a few studies have evaluated associations with the dietary patterns we examined [13, 26–28]. Among these studies, two recent cross-sectional studies from NHANES found conflicting results, one reporting [26] that men adhering to a low-fat diet or a Mediterranean diet (n = 1221) had lower serum testosterone levels, while the second [27] did not find a significant association between HEI and testosterone and SHBG levels. Another study of 336 men [13] reported that increased adherence to the Prudent diet pattern was associated with higher levels of T after adjusting for sexual abstinence, age, smoking, past diseases, and alcohol consumption. A smaller cross-sectional study of 215 healthy (non-obese) men found no association between the Western dietary pattern and T levels [28], as we observed both overall and among non-obese men. Furthermore, studies that evaluated other healthy diets (e.g., vegetarian and vegan diets) have reported inconsistent findings for T and SHBG [25, 29].

Our stratified analysis by obesity status showed that T levels were lower among obese men than among non-obese men, as seen in previous studies [6, 30], irrespective of the diet. However, among obese men, we observed an inverse association between the Prudent dietary pattern and T levels. Notably, our results may reflect the potential influence of diet in men already in the obese state. In contrast, the Prudent diet over many years or decades may reduce rates of obesity, and obesity has been linked to reduced T levels [31]. Therefore, long-term adherence to the Prudent diet can potentially lead to higher T levels by lowering BMI. The mechanisms (e.g., causal, reverse causality, and residual confounding) via which the Prudent diet, or other healthy diets, is associated with lower T levels remain not well understood and have not been confirmed or replicated in larger studies [32, 33].

In this study, obese men overall had low levels of SHBG, this being consistent with previous studies [34, 35]. Furthermore, among obese men, SHBG levels were higher with scores for the Prudent (statistically significant) and AHEI-2010 (statistically non-significant) diets. The Prudent diet has been reported to have a direct effect on liver function by reducing fatty liver, lowering insulin levels, and preventing the development of insulin resistance and diabetes [36–38], and this could potentially lead to higher production of SHBG levels by the liver. In support of this hypothesis, a previous study in the HPFS demonstrated that the

consumption of the Prudent dietary pattern was associated with risk factor reduction for type 2 diabetes [39].

When studying T levels, it is important to consider that SHBG binds circulating sex steroids with high affinity, and approximately 60% of circulating T is tightly bound to SHBG [40]. The production and regulation of SHBG by the liver vary by age as well as by hormonal, metabolic, and nutritional factors [9, 41]. Therefore, the relationship between T and SHBG is of considerable importance, as any variation in SHBG concentrations will influence circulating levels of T and, subsequently, the diagnosis of T deficiency (or low levels of T). Low SHBG levels are strongly associated with the metabolic syndrome, type 2 diabetes, and obesity [42–44]. Furthermore, emerging evidence suggests that SHBG may exert independent effects on chronic diseases, including diabetes, through its own receptor [40]. On the basis of our study, we suggest that the differential association of the Prudent dietary pattern with T (negative) and SHBG (positive) levels may have independent offsetting beneficial health effects, such as potentially reducing the likelihood of metabolic syndrome, diabetes, and other chronic diseases. However, this hypothesis cannot be substantiated through our cross-sectional analysis. A previous study in the HPFS showed that among obese men, adherence to the Prudent diet was associated with a reduced risk of coronary heart disease [45]. This finding may suggest that although a more prudent diet is associated with lower T levels in obese men, the overall benefits of a prudent diet on health outcomes are positive. This suggestion was also recently presented in another cross-sectional study in NHANES [26] which found that men adhering to a low-fat diet had lower serum T levels.

Several factors derived from previous investigations merit further discussion in the present study [46, 47]. The concomitant relationship between declining T and increasing SHBG levels has previously been identified in longitudinal population-based studies of aging [46–48]. In addition to obesity, it is proposed that aging may influence the relationship between T and SHBG. In the European Male Aging Study, a mean increase in SHBG of approximately 50% was observed between the ages of 40 and 75 years [49]. Therefore, we suggest that aging could have played a role in the findings of our current study, as the mean age of the male population was > 60 years old and the mean level of SHBG was > 70 nmol/L (normal range of SHBG is 20–60 nmol/L) [9]. It is still unclear why SHBG increases with age, but previous studies have proposed that it may relate to the age-associated decline in levels of growth hormone and/or insulin-like growth factor-I levels (IGF-1) [8, 29]. Due to the cross-sectional nature of our statistical analyses, the interplay between T, SHBG, age, and dietary patterns is likely to be teased out in future longitudinal studies.

Our study has several limitations. First, we relied on a single measurement of total T, which was measured by immunoassay: this method is thought to have lower accuracy and sensitivity than HPLC tandem mass spectrometry, considered the gold standard. Second, although we adjusted for several potential confounders, there is still the possibility of confounding from information that was not collected in this study (e.g., prevalence of hypogonadism, use of T therapy, and androgen deprivation therapy). However, such confounders are relatively rare, and it is unlikely that they would fully account for the observed findings regarding the relationship between diet and T. Third, the FFQ is based on self-reported dietary intake, which is liable to measurement error. Nonetheless, FFQs

are generally considered to be adequate to assess broad dietary patterns. Fourth, due to limited information, we could not assess the effect of other major organs on circulating testosterone levels, such as liver and kidney function [36, 37]. Fifth, the HPFS includes a large number of non-Hispanic White men with professional degrees; therefore, the findings from this study cannot be generalized to understudy populations, such as non-Hispanic Black and Hispanic men. Sixth, although we observed marginal associations, these may be due to chance or residual confounding, which are inherent in the cross-sectional design. Seven, previous studies have reported that diet and sex steroid hormones display great variability throughout the lifespan of men; however, this study was not able to capture the latter variability, nor previous exposures before adoption of a healthy diet. Finally, due to the cross-sectional design of our study, we could not confirm causality or directionality of the relationships between T, SHBG, dietary pattern, obesity, or lipid profiles. We leveraged data from participants who were previously selected for a nested case–control study on prostate cancer; however, the collection of the blood samples of this study to derive the sex steroid hormone information was obtained before the disease developed. This has the potential to move the associations toward null. Furthermore, previous studies that have capitalized on pool analysis of prospective cohort studies have found that testosterone levels are not consistently associated with prostate cancer, except possibly at very low levels. The above observations necessitate further investigation in longitudinal and interventional studies.

Despite the above-mentioned limitations, the current study has several strengths given that the HPFS follows a rigorous protocol with extensive quality control procedures for the collection of the exposures (i.e., validated FFQ to derive dietary patterns [20, 24, 50]), outcome of interest, and the potential-confounding factors considered in this study.

Conclusions

In summary, we found no statistically significant associations between three dietary patterns (Prudent, Western, and AHEI-2010) and T and SHBG levels overall, although a weak association was observed between AHEI-2010 and T levels. While obesity was associated with lower T and SHBG levels, irrespective of the dietary pattern, among obese men, the Prudent diet was shown to contribute to lower T levels and higher SHBG levels. The possible health effects of these associations require further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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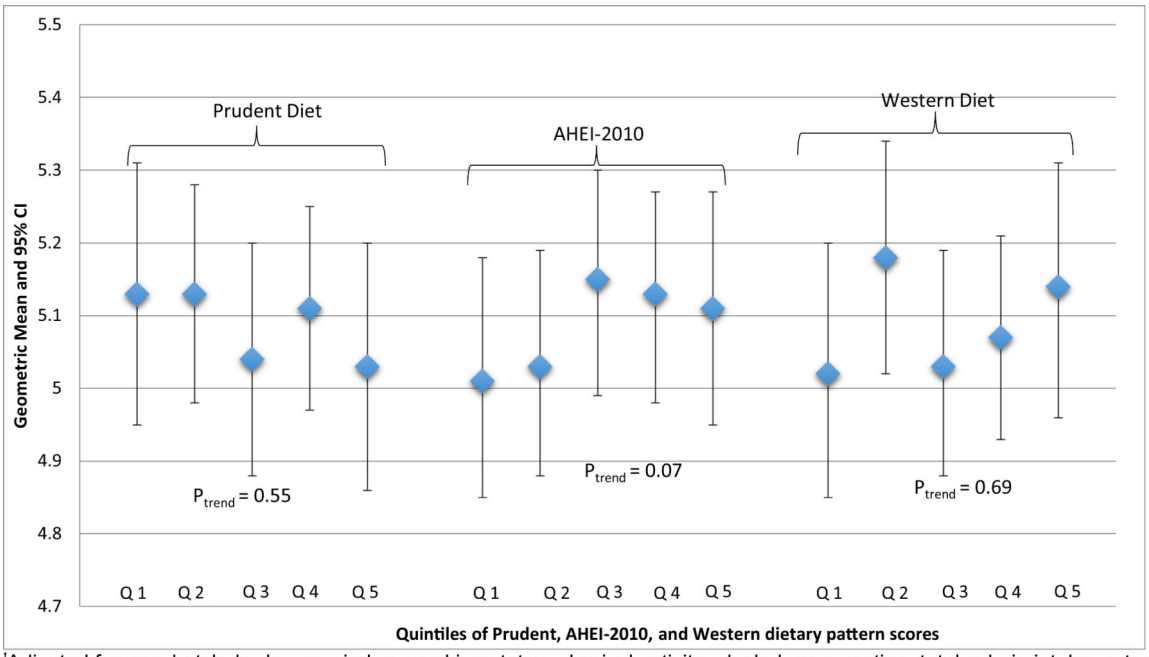
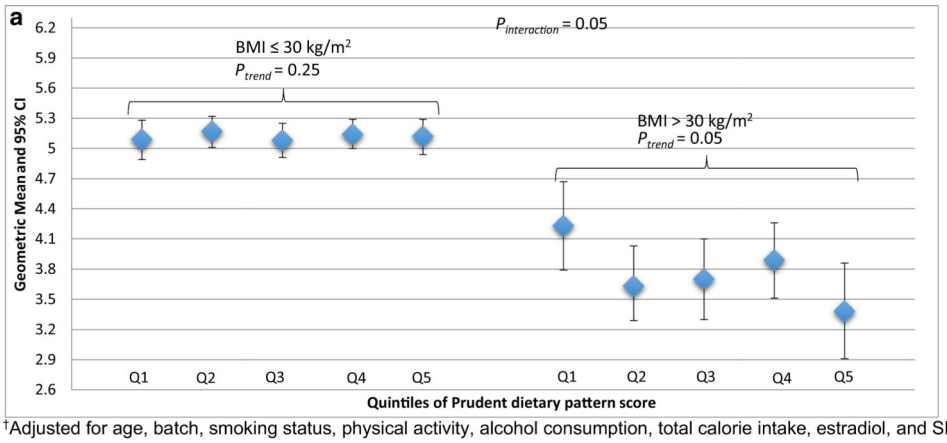


[†]Adjusted for age, batch, body mass index, smoking status, physical activity, alcohol consumption, total calorie intake, estradiol, and SHBG

Fig. 1.

Association[□] of quintiles of Prudent, AHEI-2010, and Western dietary patterns with total testosterone concentration (ng/mL) in 1376 men ≥40 years old in the Health Professionals Follow-up Study. [□]Adjusted for age, batch, body mass index, smoking status, physical activity, alcohol consumption, total calorie intake, estradiol, and SHBG



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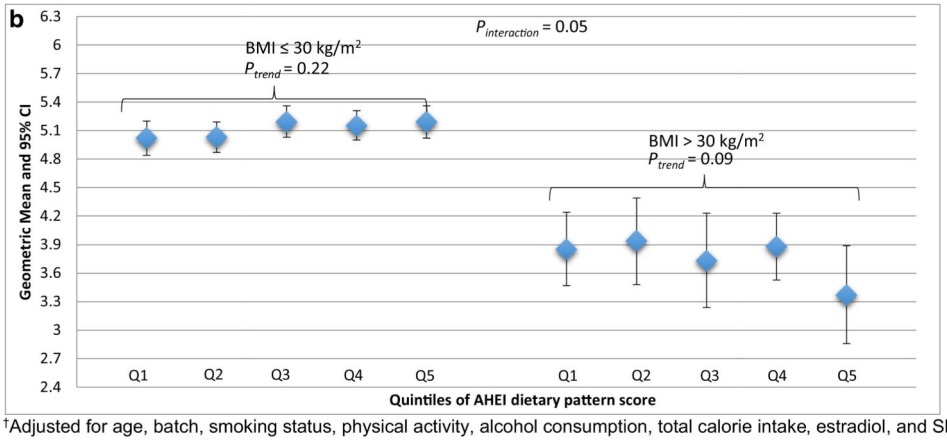

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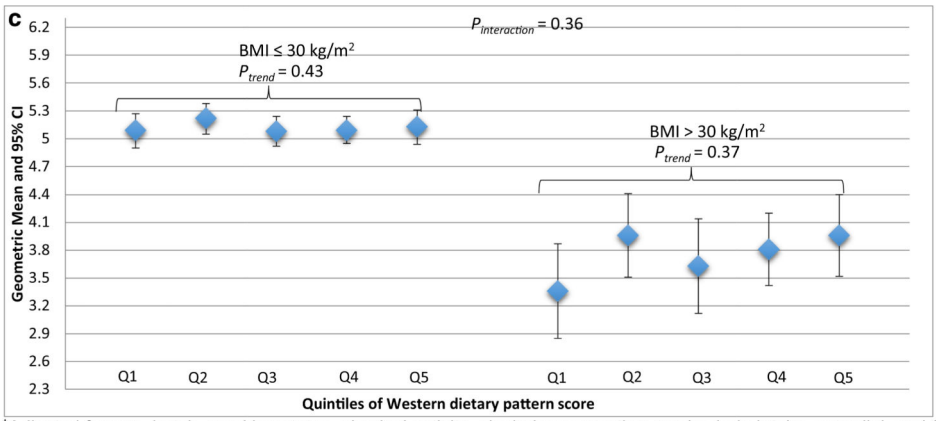
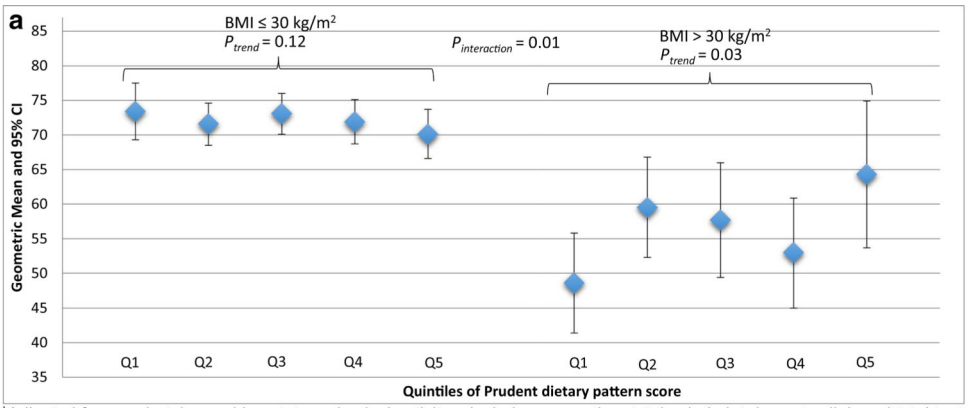


‡Adjusted for age, batch, smoking status, physical activity, alcohol consumption, total calorie intake, estradiol, and SHBG

Fig. 2.

a Association† of quintiles of prudent dietary patterns with total testosterone concentration (ng/mL) stratified by obesity status (BMI > 30 kg/m^2) in 1376 men ≥40 years old in the Health Professionals Follow-up Study. †Adjusted for age, batch, smoking status, physical activity, alcohol consumption, total calorie intake, estradiol, and SHBG. **b** Association† of quintiles of AHEI-2010 dietary score with total testosterone concentration (ng/mL) stratified by obesity status (BMI > 30 kg/m^2) in 1376 men ≥40 years old in the Health Professionals Follow-up Study. †Adjusted for age, batch, smoking status, physical activity,

alcohol consumption, total calorie intake, estradiol, and SHBG. **c** Association[†] of quintiles of Western dietary pattern with total testosterone concentration (ng/mL) stratified by obesity status (BMI > 30 kg/m^2) in 1376 men ≥40 years old in the Health Professionals Follow-up Study. [†]Adjusted for age, batch, smoking status, physical activity, alcohol consumption, total calorie intake, estradiol, and SHBG



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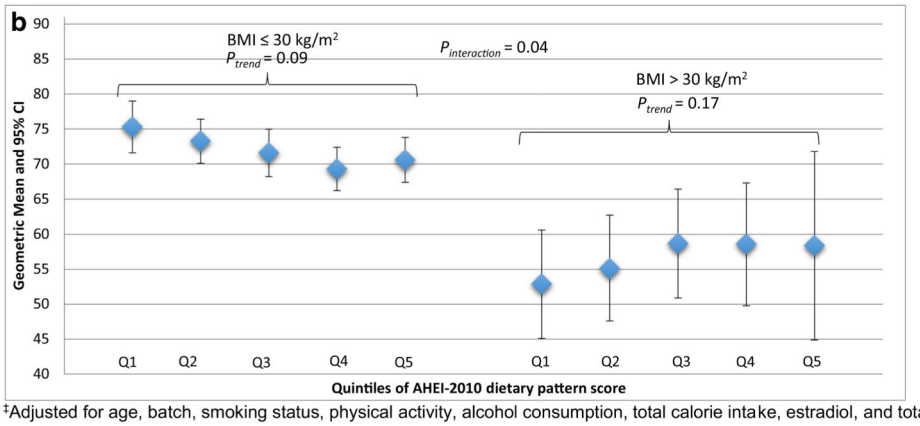

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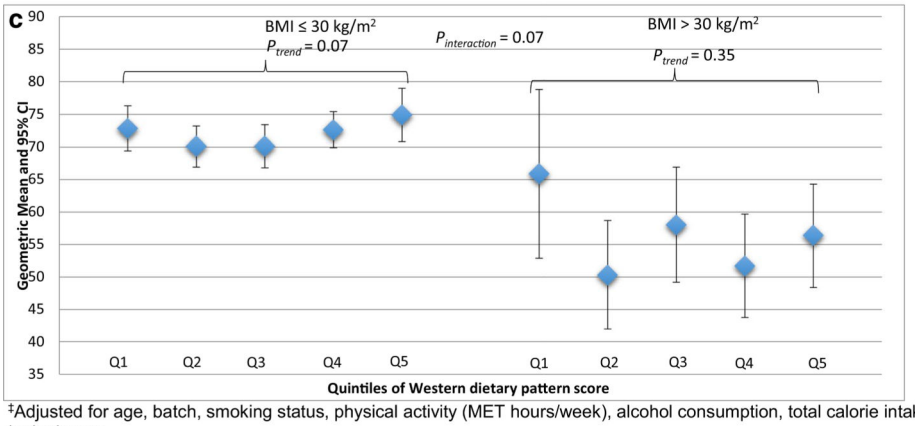

‡Adjusted for age, batch, smoking status, physical activity (MET hours/week), alcohol consumption, total calorie intake, estradiol, and total testosterone

Fig. 3.

a Association† of quintiles of prudent dietary patterns with SHBG concentration (ng/mL) stratified by obesity status (BMI > 30 kg/m^2) in 1376 men ≥40 years old in the Health Professionals Follow-up Study. †Adjusted for age, batch, smoking status, physical activity, alcohol consumption, total calorie intake, estradiol, and total testosterone. **b** Association† of quintiles of AHEI-2010 dietary score with SHBG concentration (ng/mL) stratified by obesity status (BMI > 30 kg/m^2) in 1376 men ≥40 years old in the Health Professionals Follow-up Study. †Adjusted for age, batch, smoking status, physical activity, alcohol

consumption, total calorie intake, estradiol, and total testosterone. **c** Association[†] of quintiles of Western dietary pattern with SHBG concentration (ng/mL) stratified by obesity status (BMI > 30 kg/m^2) in 1376 men ≥40 years old in the Health Professionals Follow-up Study. [†]Adjusted for age, batch, smoking status, physical activity (MET hours/week), alcohol consumption, total calorie intake, estradiol, and total testosterone

Table 1

Distribution of participants' characteristics by quintiles of Prudent, Western, and AHEI-2010* dietary patterns in 1376 men ≥40 years old in the Health Professionals Follow-up Study

	Prudent (*n* = 1,376)			Western (*n* = 1,376)			AHEI-2010 (*n* = 1,376)		
	Q1 (*n* = 213)	Q3 (*n* = 280)	Q5 (*n* = 313)	Q1 (*n* = 270)	Q3 (*n* = 269)	Q5 (*n* = 271)	Q1 (*n* = 239)	Q3 (*n* = 277)	Q5 (*n* = 293)
Age (y), mean (SD)	63.8 (8.0)	65.8 (7.4)	67.0 (7.1)	66.0 (8.0)	65.1 (7.8)	66.0 (7.0)	64.4 (8.0)	65.4 (7.7)	66.3 (7.1)
BMI[a] (kg/m^2), mean (SD)	26.3 (3.3)	26.0 (4.0)	25.5[c] (3.7)	25.3 (3.3)	25.9 (3.6)	26.8[c] (4.0)	26.5 (4.1)	26.2 (3.3)	25.1[c] (3.2)
Physical activity (MET/wk), mean (SD)	29.70 (30.5)	34.22 (33.4)	51.71[c] (47.6)	42.0 (49.1)	38.80 (42.5)	40.30 (37.6)	31.90 (36.7)	37.80 (37.6)	50.00[c] (53.6)
Smoking status, %									
Never	37	45	46	47	45	41[b]	44	40	46
Past	54	47	46	49	47	52	45	53	48
Current	7	4	4[b]	0.0	6	6[c]	8	3	3[c]
Alcohol intake (g/day), mean (SD)	17.5 (17.6)	9.9 (13.0)	9.3[c] (13.7)	10.2 (13.3)	10.9 (12.4)	14.3[c] (19.3)	14.3 (19.5)	12.3 (14.8)	10.7[b] (11.1)
Estradiol (pmol/L), mean (SD)	30.6 (9.9)	32.6 (10.2)	32.1 (9.0)	31.3 (10.5)	31.9 (9.2)	33.1[b] (10.0)	31.7 (10.1)	32.7 (10.4)	31.9 (10.0)
Sex hormone binding globulin concentration (SHBG, nmol/L), mean (SD)	81.0 (55.8)	75.6 (50.4)	68.8[b] (49.7)	75.8 (54.3)	71.7 (45.6)	77.3 (54.5)	80.7 (55.4)	71.6 (51.6)	71.9[b] (50.4)
Total testosterone concentration (ng/mL)	4.80 (1.8)	4.80 (1.8)	4.80 (1.8)	4.90 (1.8)	4.70 (1.7)	4.90 (1.8)	4.80 (1.8)	4.80 (1.8)	4.90 (1.8)

AHEI, Alternate Healthy Eating Index 2010

[a] BMI, weight (kg)/height (m)^2

[b] $P_{\text{linear trend}} < 0.05$

[c] $P_{\text{linear trend}} < 0.01$

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Table 2

Association of Prudent, AHEI-2010, and Western dietary patterns with total testosterone levels and sex hormone binding globulin levels in 1376 men ≥40 years old in the Health Professionals Follow-up Study

Dietary patterns	Q1		Q2		Q3		Q4		Q5		P_{trend}
	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI	
Total testosterone (ng/mL)											
Prudent diet											
Model[a]	5.13	4.95, 5.31	5.13	4.98, 5.28	5.04	4.88, 5.20	5.11	4.97, 5.25	5.03	4.86, 5.2	0.55
AHEI-2010 diet											
Model[a]	5.01	4.85, 5.18	5.03	4.88, 5.19	5.15	4.99, 5.30	5.13	4.98, 5.27	5.11	4.95, 5.27	0.07
Western diet											
Model[a]	5.02	4.85, 5.2	5.18	5.02, 5.34	5.03	4.88, 5.19	5.07	4.93, 5.21	5.14	4.96, 5.31	0.69
Sex hormone binding globulin (nmol/L)											
Prudent diet											
Model[b]	70.22	66.5, 74	69.90	67.0, 72.9	71.90	69.0, 74.8	70.21	67.2, 73.3	69.90	66.4, 73.4	0.59
AHEI-2010 diet											
Model[b]	73.30	69.8, 76.7	71.20	68.2, 74.1	70.11	66.9, 73.3	68.12	65.2,71.1	69.50	66.3, 72.6	0.26
Western diet											
Model[b]	72.00	68.5, 75.4	68.30	65.4,71.3	69.10	66.0, 72.2	70.30	67.7, 72.9	72.90	69.1,76.7	0.19

[a]Multivariable analyses adjusted for age, batch, body mass index, smoking status, physical activity, alcohol consumption, total calorie intake, estradiol, and SHBG

[b]Multivariable analyses adjusted for age, batch, body mass index, smoking status, physical activity, alcohol consumption, total calorie intake, estradiol, and total testosterone