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Abstract

Objective To evaluate the association between lifestyle and dietary factors and serum concentrations of androgens in middle-aged healthy men.

Methods We conducted a cross-sectional analysis of the association of lifestyle factors with circulating concentrations of androstenedione (A-dione), 3-α-androstanediol glucuronide (A-diol-g), testosterone (T), SHBG (sex

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hormone-binding globulin), and free testosterone (FT) among 636 men in the European Prospective Investigation into Cancer and Nutrition.

Results Compared with the youngest age group (40–49 years), the oldest (70–79 years) had a higher mean concentration of SHBG (by 44%) and lower mean concentrations of A-diol-g (by 29%) FT (19%). Men in the highest BMI group (≥29.83 kg/m^2) had a higher mean A-diol-g concentration (by 38%) and lower mean concentration of T (by 20%) SHBG (29%) compared with the lowest (<24.16 kg/m^2). Current smokers had higher mean concentrations of T (by 13%), SHBG (14%), and A-dione (15%) compared with never smokers. Physical activity and dietary factors were not associated with androgen concentrations, although men in the highest fifth of alcohol intake had higher mean concentrations of A-dione (by 9%), FT (11%) compared with the lowest.

Conclusion Our results suggest that age, body weight, smoking, and alcohol intake are associated with circulating androgen concentrations in men.

Keywords Androstenedione · Androstanediol glucuronide · Testosterone · Sex hormone-binding globulin · Lifestyle factors · Diet

Abbreviations

A-dione	Androstenedione
A-diol-g	3-α-androstanediol glucuronide
BMI	Body mass index
CI	Confidence interval
DHT	Dihydrotestosterone
FT	Calculated free testosterone
LH	Luteinising hormone
SD	Standard deviation
T	Testosterone
SHBG	Sex hormone-binding globulin

Introduction

Androgens are steroid hormones that play an important role in men's health [1]. Low circulating androgen concentrations have been associated with an increased risk of heart disease [2], type II diabetes [3], osteoporosis [4], and hip fracture [5] by affecting the metabolism of blood lipids, glucose, and bone minerals. Androgens are also necessary for the development of male secondary sex characteristics and the normal growth of the prostate gland, and have been implicated in the development of prostate cancer [6], although the role of circulating levels in predicting risk is unclear [7]. The main circulating androgens are testosterone (T), androstenedione (A-dione), dihydrotestosterone (DHT, the most biologically active androgen) and its metabolite, androstanediol glucuronide (A-diol-g), which is often used as a surrogate marker for 5α-reductase activity and intra prostatic DHT activity [8].

Given the importance of androgens in the development of common diseases in adult men, identifying lifestyle factors that are associated with circulating androgen concentrations may help to understand the mechanism through which lifestyle factors influence disease risk. The aim of the current study is to examine the relationships between lifestyle and dietary factors and circulating androgen concentrations in a cross-sectional analysis of 636 middle-aged healthy men participating in the European Prospective Investigation into Cancer and Nutrition (EPIC).

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Materials and methods

Study subjects and data collection

Full details of EPIC recruitment procedures and the collection of baseline data, anthropometric measurements, and blood samples are provided elsewhere [9]. In brief, questionnaire data on dietary and non-dietary variables were collected between 1992 and 2000 from ~370,000 women and 150,000 men across 10 European countries, and a blood sample was collected from about 400,000 of these individuals.

All participants completed a questionnaire that included details of age, anthropometry (including height, body weight, waist and hip circumference), smoking, occupational and recreational physical activity, vigorous exercise, and other lifestyle factors. An index of total physical activity was calculated based on a cross-tabulation of recreational, household, and occupational physical activity and classified into four categories (i.e., inactive, moderately inactive, moderately active, and active) as described elsewhere [10]. In the present study, we combined the categories "moderately active" and "active" because of small numbers in the "active" category.

Height and weight were measured at recruitment, except for men in the Oxford "health-conscious" sub-cohort among whom height and weight were self-reported. Dietary intake during the year before enrolment was measured by validated country-specific dietary questionnaires designed to reflect local dietary habits. The questionnaires were self-administered in all centers except those in Greece, Spain, and Ragusa in Italy, where participants were interviewed using a computerised questionnaire. Questions were structured by meals on the questionnaires used in Italy and Spain, and by broad food groupings in the other centers. Participants were asked to report their average consumption of each food over the previous 12 months according to pre-coded categories that varied from never or less than once per month to six or more times per day.

A 30 ml blood sample was collected, according to a standardized protocol. Samples were kept at 5–10°C, protected from light, and transferred to a local laboratory for further processing and aliquoting, with the exception of subjects recruited through the Oxford centre, for which blood samples were collected throughout the UK and transported to the laboratory in Norfolk by mail at ambient temperature. Blood fractions (serum, plasma, red cells and buffy coat for DNA extraction) were aliquoted into 0.5 ml straws, which were heat-sealed at both ends and stored in liquid nitrogen tanks at −196°C, except in Denmark where samples were stored in 1 ml tubes in nitrogen vapor at −150°C.

The present cross-sectional study includes 636 men in seven European countries (Denmark, Germany, Greece, Italy, Netherlands, Spain, and the United Kingdom), almost all of whom were of Caucasian origin, and who were selected as control subjects in a nested case–control analysis of serum sex hormone concentrations and prostate cancer risk [11]. The case–control study used an incidence density sampling protocol for the selection of matched controls, such that men who became a case later could be included before disease onset as control subjects and each control could be sampled more than once. For the present analysis, we excluded two men who later became a case, in order to restrict the analysis to known cancer-free subjects and one observation for each of five duplicate controls, leaving data for 636 individuals. All participants gave written consent for future analyses of their blood samples and the study was approved by local ethics committees in the participating countries and the ethical review board of the International Agency for Research on Cancer (IARC).

Laboratory analyses

All hormone assays were performed at the laboratory of the Hormones and Cancer Team at IARC, Lyon, France. Androstenedione (A-dione) and androstanediol glucuronide (A-diol-g) were measured by a radio-immunoassay (RIA) with a double antibody system for the separation of free and bound antigen (Diagnostic Systems Laboratory Inc, Webster, TX). Serum testosterone (T) was measured by RIA (Immunotech, Marseilles, France). Sex hormone-binding globulin (SHBG) was measured by a solid phase "sandwich" immunoradiometric assay (Cis-Bio International, Gif-sur-Yvette, France). For quality control of serum samples, three additional sera were inserted into each batch. For some participants, particular hormone assay results were unavailable due to insufficient serum or due to assay failure. Mean intra- and inter-batch coefficients of variation (CV) were estimated to be 3.5% and 11.1% for A-dione, 4.1% and 9.9% for A-diol-g, 10.8% and 14.8% for T, and 7.7% and 12.2% for SHBG. An estimate of the concentration of free testosterone (FT) was derived from the measured concentrations of T and SHBG and assuming serum albumin concentration (43 g/l) to be constant between individuals, using the formula based on the law of mass action [12, 13]. We identified probable outliers by examining the distribution of each hormone. Three values for A-dione (two very low values and one very high value) and one value for each of T and FT were identified as obvious outliers and excluded from the analyses for the relevant hormones.

Statistical analyses

All hormone concentrations were natural-logarithmically transformed to approximate normal distributions. Partial correlation coefficients with adjustment for age at blood collection, laboratory batch, and center were used to

examine the correlations between hormone concentrations. Relationships between lifestyle and dietary variables and hormone concentrations were evaluated using analysis of variance (ANOVA) and multiple linear regression. Geometric mean hormone concentrations and their corresponding 95% confidence intervals (95% CI) are presented as back-transformed values. All analyses were adjusted for age at blood collection (continuous), BMI (continuous), smoking status (never, past, current, unknown), study recruitment center, and laboratory batch. Additional adjustments for other variables such as alcohol intake and total physical activity did not materially alter the observed results and were excluded from our final analysis. Food and nutrient intakes were divided into quintiles of intake. All energy-providing macronutrients were expressed as a percentage of energy intake using the nutrient density method [14], and all foods and nutrients, except for energy itself, were further adjusted for energy intake to produce an isoenergetic estimate of the effect of increasing intake on hormone concentrations. Analyses based on the energy decomposition (partition) model were also performed [15], but the results were similar to those of the nutrient density method and are not presented here. Tests of heterogeneity across categories were performed using the relevant *F*-test statistic from the ANOVA. To test for linear trend, the categorical variable was replaced by the corresponding continuous variable in the model. All tests were two-sided and, because of the large number of tests performed, a *p* value of less than 0.01 was considered statistically significant. All statistical analyses were performed using Stata version 9.0 (StataCorp LP, College Station, TX).

Results

Characteristics of the study subjects are shown in Table 1. The 636 men had a mean age of 61.4 years (range 43.6–77.0), a mean weight of 80.6 kg (range 46.8–136.4), and a

Table 1 Descriptive statistics of selected physiological, lifestyle and dietary factors and geometric means hormone concentrations among 636 men

Age and anthropometry	Mean (SD)
Age at blood collection (years)	61.4 (6.2)
Weight (kg)	80.6 (12.1)
Height (cm)	172.5 (7.0)
BMI (kg/m^2)	27.1 (3.6)
	Number (%)
Country	
Denmark	81 (12.7)
Germany	189 (29.7)
Greece	9 (1.4)
Italy	60 (9.4)
Netherlands	25 (3.9)
Spain	93 (14.6)
UK	179 (28.1)
Smoking status	
Never	169 (26.9)
Previous	284 (45.2)
Current	175 (27.9)
Total physical activity index	
Inactive	107 (17.1)
Moderately inactive	203 (32.5)
Active	315 (50.4)
Dietary factors	Mean (SD)
Total energy (MJ/day)	9.75 (2.82)
% energy from carbohydrate	40.9 (7.1)
% energy from starch	21.4 (6.1)
% energy from total sugars	18.1 (6.6)
% energy from protein	16.3 (2.9)
% energy from fat	33.8 (6.0)
% energy from saturated fat	12.6 (3.3)
% energy from monounsaturated fat	12.6 (3.3)
% energy from polyunsaturated fat	5.9 (2.0)
P:S ratio	0.50 (0.23)
Alcohol (g/day)	21.7 (26.2)
% energy from alcohol	6.4 (6.9)
Fiber (non-starch polysaccharides; g/day)	24.2 (8.4)
Calcium (mg/day)	961 (393)
Meat and meat products (g/day)	123.4 (66.8)
Red meat (g/day)	53.7 (40.6)
Fish and shellfish (g/day)	40.0 (37.5)
Milk (g/day)	206 (220)
Cheese (g/day)	33.0 (32.0)
Yoghurt (g/day)	41.3 (72.4)
Eggs (g/day)	19.9 (21.7)
Hormone	Geometric mean (95% CI)
Androstenedione (A-dione) (nmol/l)	4.67 (4.54-4.80)
Androstanediol-glucuronide (A-diol-g) (nmol/l)	12.9 (12.3-13.6)
Testosterone (T) (nmol/l)	15.8 (15.2-16.3)
Sex hormone-binding globulin (SHBG) (nmol/l)	42.7 (41.3-44.3)
Calculated free testosterone (FT) (pmol/l)	272 (263-281)

Number of missing values: A-dione (n = 4); A-diol-g (n = 2); T (n = 54); SHBG (n = 38); FT (n = 78); all dietary factors (n = 2, except starch, total sugars and calcium: n = 11); smoking status (n = 8); physical activity (n = 11)

mean BMI of 27.1 kg/m^2 (range 16.7–41.0). More than half of subjects come from Germany (29.7%) and the UK (28.1%). Twenty-seven percent of study subjects had never smoked, 45% were former smokers, and 28% were current smokers (who smoked a median of 15 cigarettes per day). About half of the men were physically active, one-third were moderately inactive and 17% were inactive. Dietary factors which mainly contributed to total energy intake were carbohydrate (40.9%) and fat (33.8%), followed by protein (16.3%) and alcohol (6.4%).

A wide variation in intake was observed for most foods and nutrients.

Pearson correlations between androgen concentrations, adjusted for age, batch and center, are shown in Table 2. Statistically significant positive associations ($p < 0.01$) were observed between all hormones, except between SHBG and each of A-dione, A-diol-g, and FT. The correlations remained essentially unchanged and statistically significant ($p < 0.01$) after further adjustment for BMI (results not shown).

The associations between lifestyle factors and serum androgen concentration are shown in Table 3.

Age

Age was negatively associated with FT and A-diol-g; compared with the youngest age group (40–49 years), men in the oldest age group (70–79 years) had a 19% lower mean concentration of FT and a 29% lower mean concentration of A-diol-g ($p_{trend} = 0.01$ for both hormones; Table 3). In contrast, the mean concentration of SHBG was 44% higher in the oldest age group compared with the youngest ($p_{trend} = 0.0001$). Concentrations of A-dione and of T were not significantly associated with age.

BMI, waist circumference, and waist:hip ratio

Men in the highest BMI quintile (≥29.83 kg/m^2) had lower mean concentrations of T (by 20%) and SHBG (by 28%) compared with men in the lowest quintile (BMI < 24.16 kg/m^2; $p_{trend} < 0.0001$ for both hormones). The concentration of FT did not vary monotonically across the categories of BMI, although there was a suggestion of an inverse association ($p_{trend} = 0.02$). A-dione concentration was not associated with BMI. In contrast, the mean concentration of A-diol-g was 38% higher in the highest BMI quintile compared with the lowest ($p_{trend} < 0.0001$; Table 3).

Waist circumference and waist:hip ratio were significantly positively associated with A-diol-g concentration and inversely associated with T and SHBG concentrations. However, after further adjusting for BMI, these associations were no longer statistically significant (data not shown).

Smoking status

Adjusting for BMI, compared with never smokers, current smokers had higher mean concentrations of A-dione (by 15%), T (by 13%), and SHBG (by 14%; $p_{heterogeneity} < 0.0001$, 0.02, and 0.008, respectively; Table 3). Smoking was not associated with concentrations of FT and A-diol-g.

Physical activity

Adjusting for BMI and smoking status, there was no association between physical activity and hormone concentrations, as measured by total physical activity (Table 3), or other indices such as leisure time activity, vigorous physical activity, and physical activity at work (data not shown).

Alcohol intake

Geometric mean-hormone concentrations by quintile of alcohol intake are shown in Table 3. Men in the highest quintile of alcohol intake (≥11% energy from alcohol) had higher mean concentrations of FT (by 11%) and A-dione (by 9%) compared with men with the lowest alcohol intake (<0.70% energy from alcohol), but there was no association for SHBG and T.

Partial correlation coefficients between log-transformed serum hormone concentrations and dietary factors are shown in Table 4. The only correlations that were statistically significant at the 1% level were those for FT ($r = 0.12$) and A-dione ($r = 0.11$) with alcohol consumption.

Other dietary intake

There was significant heterogeneity between mean A-dione concentrations by fifth of yoghurt intake (means from

Table 2 Partial correlations between log-transformed hormone concentrations, adjusted for age, batch, center, and BMI

	A-dione	A-diol-g	T	SHBG	FT
A-dione	1.00				
A-diol-g	0.28*	1.00			
T	0.35*	0.32*	1.00		
SHBG	0.10	0.11**	0.52*	1.00	
FT	0.37*	0.34*	0.80*	−0.08	1.00

A-dione androstenedione; *A-diol-g* androstanediol glucuronide; *T* testosterone; *SHBG* sex hormone-binding globulin; *FT* calculated free testosterone

* $p < 0.01$, ** $p = 0.01$

Table 3 Geometric mean hormone concentration (95% CI) by age, body mass index, smoking status, total physical activity index, and alcohol intake

Age group (years)	A-dione (nmol/l)		A-diol-g (nmol/l)		T (nmol/l)		SHBG (nmol/l)		FT (pmol/l)	
	n	Mean[a]	*n*	Mean[a]	*n*	Mean[a]	*n*	Mean[a]	*n*	Mean[a]
40–49	17	4.90 (4.17–5.76)	17	14.3 (10.7–19.1)	15	16.0 (12.9–19.7)	16	34.8 (28.1–43.2)	15	313 (254–385)
50–59	250	4.71 (4.51–4.92)	251	13.6 (12.6–14.7)	235	15.2 (14.3–16.1)	238	39.7 (37.2–42.3)	224	279 (262–297)
60–69	295	4.70 (4.52–4.89)	296	13.1 (12.2–14.0)	268	16.1 (15.2–17.0)	274	44.4 (41.9–46.9)	255	267 (253–282)
70—79	70	4.32 (3.83–4.86)	70	10.1 (8.2–12.6)	64	16.5 (13.6–20.0)	70	50.0 (41.4–60.3)	64	255 (212–308)
$p_{\text{heterogeneity}}$		0.59		0.13		0.57		0.02		0.44
$p_{\text{linear trend}}$		0.25		0.01		0.65		0.0001		0.01
% change per one year increase	−0.34 (−0.92 to 0.24)		−1.37 (−2.40 to −0.32)		0.19 (−0.63 to 1.02)		1.73 (0.86 to 2.60)		−1.07 (−1.89 to −0.25)	
Body mass index (kg/m^2)	*n*	Mean[b]	*n*	Mean[b]	*n*	Mean[b]	*n*	Mean[b]	*n*	Mean[b]
Q1: <24.16	128	4.65 (4.40−4.92)	128	10.8 (9.8−12.0)	114	16.9 (15.7−18.2)	119	49.4 (46.0−53.2)	109	269 (250−289)
Q2: ≥24.16–<25.76	127	4.70 (4.44−4.97)	125	12.3 (11.1−13.7)	119	17.8 (16.6−19.1)	123	47.7 (44.3−51.4)	116	291 (271−312)
Q3: ≥25.76–<27.62	126	4.57 (4.32−4.83)	127	12.7 (11.5−14.0)	116	15.6 (14.5−16.7)	120	42.7 (39.7−46.0)	112	272 (253−292)
Q4: ≥27.62–<29.83	126	4.67 (4.42−4.95)	127	14.3 (12.9−15.9)	115	15.3 (14.2−16.4)	118	39.6 (36.7−42.7)	109	271 (251−291)
Q5: ≥29.83	125	4.75 (4.48−5.03)	127	14.9 (13.4−16.5)	118	13.5 (12.6−14.6)	118	35.5 (32.9−38.3)	112	256 (238−275)
$p_{\text{heterogeneity}}$		0.92		0.0001		<0.0001		<0.0001		0.22
$p_{\text{linear trend}}$		0.55		<0.0001		<0.0001		<0.0001		0.02
% change per 1 kg/m^2 increase	0.22 (−0.49 to 0.94)		2.75 (1.44 to 4.08)		−2.85 (−3.71 to −1.98)		−3.53 (−4.43 to −2.62)		−1.08 (−1.97 to −0.19)	
Smoking status	*n*	Mean[c]	*n*	Mean[c]	*n*	Mean[c]	*n*	Mean[c]	*n*	Mean[c]
Never	169	4.48 (4.26–4.70)	169	12.4 (11.4–13.6)	154	15.1 (14.2–16.0)	162	41.0 (38.5–43.6)	150	268 (252–285)
Previous	280	4.51 (4.34–4.69)	283	13.2 (12.3–14.1)	259	15.4 (14.7–16.2)	264	41.5 (39.5–43.6)	246	272 (259–285)
Current	175	5.16 (4.91–5.41)	174	13.1 (12.0–14.3)	161	17.0 (15.9–18.0)	164	46.6 (43.7–49.7)	154	274 (258–292)
$p_{\text{heterogeneity}}$		<0.0001		0.57		0.02		0.008		0.89
% difference[d]		15.2		5.6		12.5		13.8		2.2
Total physical activity index	*n*	Mean[e]	*n*	Mean[e]	*n*	Mean[e]	*n*	Mean[e]	*n*	Mean[e]
Inactive	107	4.61 (4.33–4.91)	107	12.8 (11.4–14.3)	99	15.7 (14.5–17.0)	102	42.7 (39.3–46.4)	95	273 (252–296)
Moderately inactive	201	4.63 (4.43–4.84)	202	12.8 (11.8–13.8)	180	15.4 (14.5–16.3)	185	41.7 (39.2–44.2)	172	266 (251–282)
Active	313	4.70 (4.54–4.87)	314	13.1 (12.3–13.9)	292	15.9 (15.2–16.6)	301	43.2 (41.3–45.3)	281	273 (261–286)
$p_{\text{heterogeneity}}$		0.82		0.89		0.67		0.63		0.76

Table 3 continued

% energy from alcohol	*n*	Mean[f]	*n*	Mean[f]	*n*	Mean[f]	*n*	Mean[f]	*n*	Mean[f]
Q1: <0.70	126	4.57 (4.31–4.84)	127	12.4 (11.1–13.8)	116	16.1 (15.0–17.4)	120	46.3 (42.9–50.0)	112	263 (244–283)
Q2: ≥0.70–<2.96	126	4.53 (4.27–4.79)	127	12.9 (11.6–14.3)	116	14.9 (13.8–16.0)	119	42.6 (39.5–45.9)	113	254 (237–273)
Q3: ≥2.96–<5.78	126	4.57 (4.32–4.83)	126	12.5 (11.3–13.8)	116	15.7 (14.6–16.8)	121	42.8 (39.8–46.0)	112	266 (248–286)
Q4 : ≥5.78–<11.34	127	4.77 (4.51–5.04)	127	13.0 (11.8–14.4)	117	16.1 (15.0–17.3)	118	41.4 (38.5–44.6)	111	287 (267–308)
Q5: ≥11.34	125	4.96 (4.68–5.26)	125	14.0 (12.6–15.5)	115	16.1 (14.9–17.3)	118	40.7 (37.6–43.9)	108	291 (270–314)
$p_{heterogeneity}$		0.19		0.56		0.48		0.21		0.08
p_{trend}		0.0074		0.15		0.33		0.15		0.0097
% change per 1 SD increase	3.80 (1.01 to 6.66)		3.71 (−1.29 to 8.95)		1.77 (−1.75 to 5.42)		−2.62 (−6.06 to 0.95)		4.78 (1.15 to 8.53)	

[a] Adjusted for center, batch, BMI, and smoking status

[b] Adjusted for center, batch, age, and smoking status

[c] Adjusted for center, batch, age, and BMI

[d] Percentage difference in mean hormone concentrations for current smokers compared with never smokers

[e] Adjusted for center, batch, age, BMI, and smoking status

[f] Adjusted for center, batch, age, BMI, smoking status, and energy intake

lowest to highest fifth 5.17, 4.56, 4.44, 4.55, and 4.38 nmol/l; $p_{heterogeneity} = 0.0004$). However, the corresponding trend test was not statistically significant at the 1% level.

Discussion

We examined the relationships between lifestyle, dietary factors, and serum androgen concentrations among 636 healthy middle-aged men living in Europe using a cross-sectional study design.

Age

Our finding of a substantial age-related increase in SHBG is well-documented [16, 17] and corresponds well with the decline in FT, which has been reported in both cross-sectional [1, 18, 19] and longitudinal studies [16, 17, 20]. In agreement with our results, a decrease in A-diol-g with increasing age has also been reported [1, 21, 22].

Our results, as well as some previous studies [1, 18, 23], show no strong age-dependent decline in T in men aged 40 or older. Therefore, the reduction in circulating FT with increasing age might largely reflect the age-related increase in SHBG concentration, although hypogonadism-related mechanisms for an age-dependent decline in circulating T have been proposed [24–26]. The mechanisms through which SHBG increases with age remains to be clarified but may relate to the age-related reduction in circulating IGF-I concentrations [27–29].

BMI

Overweight/obesity was significantly associated with the circulating concentrations of several androgens. In agreement with previous studies, we found increasing BMI to be associated with a reduction in T [17, 19, 30–35] and SHBG [17, 19, 21, 32–37] and an increase in A-diol-g concentrations [1, 22, 34, 36]. The inverse association of BMI with SHBG may be partly explained by the inhibition of hepatic SHBG synthesis and release by raised insulin levels [28]. It is thought that a reduction in SHBG with weight gain leads to a down-regulation of T production via negative feedback, so as to maintain a relatively constant FT concentration [1, 19, 25, 30]. In addition to the effect of SHBG on T, it has also been suggested that T production may be reduced due to a reduction in LH pulse amplitude [38], and an increased conversion rate of T to estradiol in adipose tissue [30]. The observed increase in A-diol-g in overweight men is in accordance with some previous studies [1, 22, 36], but not all [21]. It has been proposed that circulating A-diol-g concentration may indirectly

Table 4 Correlations between log-transformed serum hormone concentrations and dietary factors

Nutrient/food	A-dione	A-diol-g	T	SHBG	FT
Total energy	−0.06	0.03	−0.02	0.03	−0.02
% energy from carbohydrate	0.00	0.01	0.00	0.07	−0.05
% energy from starch	−0.04	−0.01	−0.05	−0.01	−0.06
% energy from total sugars	0.03	0.02	0.05	0.11	−0.03
% energy from protein	−0.10	−0.03	−0.09	−0.07	−0.05
% energy from fat	−0.08	−0.05	0.00	0.01	−0.03
% energy from saturated fat	−0.07	−0.03	−0.03	0.03	−0.06
% energy from monounsaturated fat	−0.01	−0.04	0.04	0.01	0.04
% energy from polyunsaturated fat	−0.10	−0.05	−0.03	−0.03	−0.03
P:S ratio	−0.04	−0.02	0.00	−0.01	−0.01
% energy from alcohol	0.11*	0.06	0.04	−0.06	0.12*
Fiber (non-starch polysaccharides)	−0.03	−0.05	0.01	0.04	−0.01
Calcium	−0.07	−0.04	−0.08	−0.01	−0.09
Meat and meat products	−0.04	0.06	0.02	−0.02	0.03
Red meat	−0.01	0.03	0.01	0.05	−0.03
Fish and shellfish	0.05	−0.03	0.03	−0.04	0.08
Milk	−0.01	−0.06	−0.06	0.04	−0.10
Cheese	−0.03	−0.03	−0.07	−0.08	−0.04
Yoghurt	−0.06	0.04	0.00	0.00	0.00
Eggs	−0.04	0.00	−0.05	0.02	−0.06

Partial correlation coefficients are adjusted for age at blood collection, center, batch, BMI, smoking status and total energy intake, and are based on 630 (A-dione), 632 (A-diol-g), 580 (T), 596 (SHBG) and 556 (FT) observations for all nutrients and foods except for starch, total sugars and calcium, for which data was unavailable for Greece ($n = 9$)

* $p < 0.01$

reflect peripheral androgen action [39] and 5α-reductase enzyme activities I and II, which are generally correlated with a production of DHT in the skin and in the prostate gland [8, 40]. Therefore, excess body weight might stimulate peripheral androgen metabolism, while lowering overall T concentrations [41, 42].

Smoking

Current smokers had higher concentrations of A-dione, T, and SHBG than non-smokers, while the levels of A-diol-g and FT were unrelated to smoking. Our results are consistent with some previous studies, showing a high level of A-dione [36, 43, 44], T [1, 17, 19, 36, 43, 45], and SHBG [1, 17, 19, 36] in current smokers compared with never smokers. No substantial alteration in levels of A-diol-g [1, 22, 36] and FT [1, 17, 46] due to smoking has also been reported in previous studies. Little is known about the mechanisms through which smoking may alter circulating androgen concentrations, but it has been suggested that oxidative stress [47] and/or a suppression of 21- and/or 11β-hydroxylase activity [44] may be involved.

Physical activity

We observed no association between physical activity and hormone concentrations, which is consistent with some [19, 22, 48] but not all cross-sectional studies [1, 17, 45, 49]. In addition, evidence from intervention studies that physical activity influences circulating androgen levels is highly inconsistent and may relate to differences in the type and duration of the intervention [50–52].

Alcohol

Alcohol consumption was not associated with serum T concentration, which is consistent with a previous study [53], although others have reported an inverse association [54, 55]. The positive association of alcohol intake with FT appeared to be most likely a result of the small decrease in SHBG, which again is consistent with some [17, 36, 56] but not all studies [19]. Our finding of a positive association of alcohol intake with A-dione may be due to chance because of the number of statistical tests performed, but warrants further study.

Other dietary factors

Although several previous studies have suggested relationships between dietary factors and serum androgens, such as an increase in SHBG with increasing dietary fiber [36, 37] and dietary fat [56], an increase in T with increasing polyunsaturated fatty acid intake [56], and a decrease in T with a low fat-high fiber diet [57], we found no clear associations in the current study, in line with our previous report [1].

Limitations and strengths of this study

Due to the cross-sectional nature of the study design, the results were based on information assessed at one point in time and any within-person variation may lead to attenuation of the associations. Our study contained a relatively large number of healthy participants recruited from seven countries in the EPIC study. Our results for aging and BMI are in agreement with the majority of previous studies, and this suggests high reliability of measurements of serum androgens in the current study. Physical activity and dietary factors (except alcohol consumption) were not significantly associated with hormone concentrations; this may be, because there is little or no effect of physical activity and diet, although it is possible that weak associations have been missed due to measurement error in these variables.

Conclusion

In summary, we found a considerable reduction in circulating FT with increasing age, reflecting elevated SHBG concentration at older ages. Overweight/obesity was associated with a higher concentration of A-diol-g and a substantial reduction in SHBG, leading to a down-regulation of the secretion of T through negative feedback to maintain a constant FT concentration. Smoking was associated with higher concentrations of A-dione, T, and SHBG, and there were weak-positive associations between A-dione and FT and alcohol consumption. However, there was no evidence of an association between other dietary factors or physical activity and serum androgen concentrations.

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