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Association Between Female Androgen Levels, Metabolic Syndrome, and Cardiovascular Disease: An NHANES Analysis (2013-2016)

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Background: The impact of androgens on metabolic diseases, cardiovascular diseases (CVD), and long-term mortality in the general female population remains poorly understood. This study, utilizing data from the National Health and Nutrition Examination Survey (NHANES) database managed by the Centers for Disease Control and Prevention, seeks to elucidate the relationship between androgen levels and metabolic syndrome (MS), CVD, and mortality in adult women.

Methods: After excluding ineligible individuals, descriptive analyses were conducted on demographic characteristics, metabolic-related indicators, and disease prevalence, based on the presence of high androgenemia and androgen quartile grouping. Logistic regression models were developed to assess the associations of androgen markers, including total testosterone (TT), Free Androgen Index (FAI), with MS, CVD, and cox regression models were used to explore the relationships with mortality.

Results: Our results show that, even without adjustment for age, age at menarche, marital status, and smoking status, both in patients with hyperandrogenemia and across the general population stratified by quartiles of FAI, higher androgen levels are associated with increased waist circumference, weight, Body Mass Index, fasting insulin, and the monocyte/high-density lipoprotein cholesterol ratio. In adjusted correlational analysis, MS remained positively correlated with FAI, even after controlling for age, tobacco use, and alcohol consumption. As FAI quartiles increased, the correlation strengthened, achieving an odds ratio (OR) of 1.45 (95% CI 1.04 to 2.02, P=0.03) in the highest quartile. This indicates that androgen levels are strongly associated with metabolic syndrome, with FAI proving more sensitive than TT.

Conclusion: The greater sensitivity of FAI may be attributed to its ability to reflect bioavailable testosterone more accurately than TT, underscoring its potential utility in clinical assessments of metabolic risk. This study found no significant correlation between androgen levels and CVD or mortality.

Keywords: androgen, free androgen index, metabolic syndrome, cardiovascular disease, NHANES

Introduction

Metabolic-related Diseases (MD) encompass a spectrum of disorders linked to abnormalities in glucose metabolism, insulin resistance, dyslipidemia, hypertension, and other metabolic disturbances.[1] These diseases originate from disruptions in metabolic pathways, including diabetes and impaired glucose tolerance due to carbohydrate metabolism issues, dyslipidemia from lipid metabolism disorders, and various diseases associated with protein and other metabolic pathways.[2] Metabolic Syndrome (MS) represents a collective manifestation of these disorders, with diagnostic criteria established by The National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III).[3] The core features of MS include insulin resistance, excessive accumulation of visceral fat, atherogenic dyslipidemia, and endothelial dysfunction. In the United States, the prevalence of MS is quite high, ranging from 24% to 34%; in China, in 2017, this figure was about 15.5%.[4] Cardiovascular Disease (CVD) has emerged as a leading systemic disease and significant cause of death both in the United States and globally,

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with deaths increasing by 12.5% over the past decade, now representing one-third of all global fatalities.[5] Over the past decade, the number of deaths from CVD worldwide has increased by 12.5%,[6] now accounting for one-third of all global deaths. Studies have shown that MS is an independent risk factor for CVD.[7] The proposal of MS aims to more effectively identify those high-risk populations that may develop type 2 diabetes and cardiovascular diseases.[8,9]

Despite female plasma containing only 5% to 10% of the androgen levels found in males,[10] these hormones play a crucial role in regulating metabolic functions. Disease affecting the gonads, adrenal glands, or hypothalamic-pituitary axis can disrupt androgen production and metabolism. Such disruptions may alter androgen concentrations in circulation, potentially leading to reproductive issues and metabolic complications, including cardiovascular diseases. These conditions are particularly relevant to MS, underscoring the systemic impact of androgen imbalances.[11] The impact of endogenous sex hormones on atherosclerosis, particularly regarding atherosclerotic cardiovascular disease (CVD), remains inconclusive. Evidence suggests that elevated serum testosterone may be linked to a decreased risk of CVD events in older men, while other studies indicate that lower levels of serum testosterone and estradiol are associated with increased mortality risk in this group. These findings collectively imply a potential association between androgen levels and CVD risk, though further investigation is needed to clarify this relationship.[12] High levels of androgen have profound effects on the metabolism of peripheral tissues such as fat, liver, pancreas, and muscle, as well as brain function.[13] Excessive androgen may enlarge adipocytes, making them prone to inflammation, macrophage infiltration, and apoptosis, thus impairing insulin sensitivity. Furthermore, high androgen levels disrupt lipid metabolism and inhibit fat breakdown, affecting pancreatic function potentially through systemic oxidative stress linked to enlarged fat cells, ultimately impairing β-cell function.[14,15] Androgens also modify metabolic regulation in the central nervous system through neuroendocrine pathways, such as altering hypothalamic signal transduction to decrease thermogenic activity in brown adipose tissue, exacerbating metabolic disorders,[16] and these enlarged fat cells are more susceptible to inflammation, macrophage infiltration, and apoptosis, thereby damaging insulin sensitivity. Moreover, excess androgen disrupts lipid metabolism and inhibits fat breakdown. It also directly affects pancreatic function, possibly related to systemic oxidative stress caused by the enlargement of fat cells, further damaging β-cell function.[17,18] Additionally, androgens can interfere with metabolic regulation in the central nervous system through neuroendocrine mechanisms,[19] for example, by altering signal transduction in the hypothalamus to reduce thermogenic activity in brown adipose tissue, thus exacerbating metabolic disorders.[20]

The utility of androgens as indicators for assessing metabolic status in the general female population remains uncertain. Recent meta-analyses reveal a gender-specific association between endogenous androgens and Metabolic Syndrome (MS), demonstrating that women diagnosed with MS exhibit elevated levels of total testosterone (TT) and free testosterone (FT) compared to their healthy counterparts. Despite these findings, comprehensive research is still required to elucidate the role and differential impact of androgen levels in normal and diseased states, including diabetes, hypertension, and metabolic syndrome. Such studies would help clarify whether adjustments in diagnostic and therapeutic approaches are warranted based on androgen levels.

The National Health and Nutrition Examination Survey (NHANES) is a nationwide cross-sectional survey executed by the Centers for Disease Control and Prevention to assess the health and nutritional status of the non-institutionalized civilian population in the United States. It utilizes a complex, stratified, multi-stage probability sampling design to ensure representative sampling of the entire US population. Participants undergo a detailed health interview, followed by a visit to a Mobile Examination Center (MEC), where they receive clinical tests, dietary interviews, and physical examinations. Data collected includes demographic information, physical examination results, and laboratory tests covering a wide array of health markers such as blood glucose and lipid levels. Participants also provide data through questionnaires on prescription drug use and overall health status. Ethical approval for NHANES is granted by the National Center for Health Statistics and Research Ethics Review Committee, adhering strictly to ethical guidelines. Informed consent is obtained from all participants prior to their inclusion in the survey.

Methods

Study Design and Population

This study included adult females from the NHANES database.

Inclusion and Exclusion Criteria

Inclusion Criteria: This study analyzes data from two NHANES cycles, 2013–2014 and 2015–2016, incorporating 11,763 participants lacking periodic hormonal data from other cycles.[21,22]

Exclusion Criteria: Excluded from the study were male participants; those aged 20 years or younger; individuals who had undergone bilateral oophorectomy; pregnant respondents at the time of the survey; participants missing key data such as sex hormone levels (Sex Hormone-Binding Globulin, TT), MS data, CVD data, mortality data; and those with abnormally high total testosterone levels. After applying these criteria, the final sample comprised 3520 participants. A detailed sample selection process is outlined in Figure 1 below.

Primary Study Indicators

Total Testosterone (TT), Free Androgen Index (FAI):The NHANES database utilizes isotope dilution liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS) to measure levels of serum total testosterone (TT) and estradiol (E^2), and employs chemiluminescence to measure concentrations of Sex Hormone Binding Globulin (SHBG). Based on previous studies, we indirectly assess circulating free testosterone (FT) levels by calculating the Free Androgen Index (FAI). The formula for calculating FAI is: Free Androgen Index (FAI) = [Total Testosterone (nmol/L) × 100 / SHBG (nmol/L)].[23] A FAI value above 6.1 is diagnosed as hyperandrogenemia.[24]

Key Related Indicators

1. Hypertension: Information on antihypertensive medication history from the questionnaire data and systolic/diastolic blood pressure from physical examination are collected. A systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg, or BPQ050A=1, indicates hypertension.[25]
2. Diabetes: Participants were classified based on their questionnaire responses to two items: "whether they had been informed by a physician of a diabetes diagnosis" and "whether they had been notified of borderline blood glucose levels." This classification resulted in three categories: no diabetes, prediabetes, and diabetes.
3. Hypercholesterolemia: Classification as having no hypercholesterolemia or undiagnosed hypercholesterolemia is based on whether a doctor has informed the participant of high cholesterol levels; being told to take prescription cholesterol medication; self-reporting current use of prescription cholesterol medication; LDL-C ≥ 160 mg/dL; Total Cholesterol (TC) ≥ 240 mg/dL.[26]

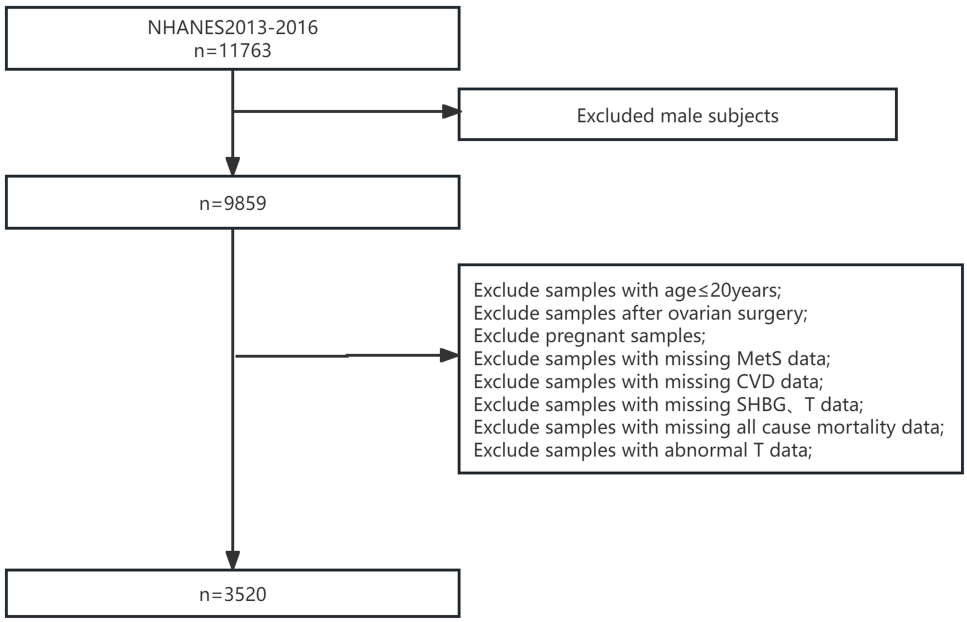

Figure 1 Sample selection flowchart.

4. Metabolic Syndrome: This study defines Metabolic Syndrome (MS) patients among the included population according to the diagnostic criteria set by the National Cholesterol Education Program (NCEP) as follows: 1) Hypertension (systolic blood pressure ≥130mmHg, diastolic blood pressure ≥85mmHg, or In response to the questionnaire item regarding "the presence of hypertension". the answer provided was"yes"); 2) High triglycerides (≥150mg/dL, or currently on lipid-lowering medication); 3) Low HDL cholesterol levels (women <50mg/dL, or currently on lipid-lowering medication); 4) Abdominal obesity (waist circumference women ≥88cm or men ≥102cm); or 5) High fasting blood glucose levels (≥100mg/dL or currently on medication for lowering blood sugar).[27]
5. Cardiovascular Related Diseases: Diagnosis of cardiovascular related diseases is derived from the NHANES database's MCQ and CDQ questionnaires, extracting history of coronary heart disease, congestive heart failure, heart attack, angina; meeting any of these criteria is diagnosed as CVD.[28,29]
6. Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR): This is the ratio of the count of monocytes in peripheral blood to HDL cholesterol (HDL-C), calculated based on laboratory measurements of peripheral blood monocyte counts and HDL-C levels.

Covariates

The covariates included in this study are: (1) Demographic basic information: age (years), race (White, Black, Mexican American, other races), education level (recoded as less than high school, high school or equivalent graduate, any college and college graduate or above), marital status (divorced, never married, married), poverty income ratio; (2) Physical examination: weight, height, BMI (Body Mass Index) (according to international standards, BMI < 18.5 kg/m² is underweight, 18.5 kg/m² ≤ BMI < 25 kg/m² is normal, 25 kg/m² ≤ BMI < 30 kg/m² is overweight, BMI ≥ 30 kg/m² is obese), waist circumference, blood pressure (average of systolic and diastolic pressure taken from three measurements); (3) Questionnaire data: smoking status (recoded based on SMQ040 questionnaire results as nonsmokers, ex-smokers, and current smokers), drinking history (recoded based on ALQ120U questionnaire results as regular drinkers, non-regular drinkers), age at menarche, menopausal status, years since menopause, number of pregnancies, number of births.[30]

Mortality Data

The National Death Index (NDI), maintained by the National Center for Health Statistics (NCHS), collects comprehensive death information including the cause of death, time of death, and copies of death certificates. It can be linked to the National Health and Nutrition Examination Survey (NHANES) database using unique identifiers of the study subjects to obtain detailed mortality data. This study has matched the NHANES III and NHANES 2013—2016 data with mortality data. Deaths were systematically classified using the International Statistical Classification of Diseases, 10th Revision (ICD-10). Specific outcomes analyzed in this study included all-cause mortality and deaths due to heart disease, categorized under ICD-10 codes I00-I09, I11, I13, and I20-I51.[31]

Statistical Analysis

Data cleaning and analysis in this study were performed using R Studio (version 4.2.3), a software environment for statistical computing and graphics. For covariates still missing after applying inclusion and exclusion criteria, multiple imputation was conducted using the mice package in R, followed by a sensitivity analysis to assess the impact of imputation on the dataset. The NHANES complex sampling design necessitated adjustments for stratification, clustering, and weighting in all statistical analyses. Given the complex sampling design of NHANES, all statistical analyses took into account sample stratification, clustering, and weights.

In descriptive analyses, continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range, while categorical variables were presented as frequencies and percentages. Comparisons between groups for normally distributed parameters were performed using ANOVA, while the Kruskal–Wallis test was used for non-parametric variables. A two-sided $p<0.05$ was considered statistically significant.

This study constructed three logistic models to assess the relationship between androgens and MS, CVD; Model 1 was unadjusted, Model 2 was adjusted for age, and Model 3 was adjusted for age, tobacco use, and alcohol use.

Three multivariable Cox proportional hazards regression models were constructed to evaluate the relationship between androgens and all-cause mortality as well as cardiovascular mortality; Model 1 was unadjusted, Model 2 was adjusted for age, and Model 3 was adjusted for age, tobacco use, and alcohol use.

Results

Characteristics of Study Participants

A total of 3520 participants were enrolled, with an average age of 48.6 ± 16.8 years, average TT concentration of 22.9 ± 13.7 ng/dL, and average FAI concentration of 1.5 ± 1.3. According to the diagnostic criteria for hyperandrogenemia based on FAI, 34 participants had high androgen levels. Among all participants, 1425 were diagnosed with MS, accounting for 40.5%; 334 had CVD, accounting for 9.5%. At the end of the follow-up period, 146 participants had died, accounting for 4.1%, of which 31 deaths were due to CVD, accounting for 21.2% of all causes of death. Detailed clinical characteristics of all participants are presented in Table 1.

Table 1 Baseline Characteristics of Participants with Hyperandrogenism

	Non-Hyperandrogenism N=3486	**Hyperandrogenism N=34**	***P*-value**
General data characteristics			
Age (years)	48.76 ± 16.76	31.29 ± 15.84	<0.001
Gravidity (times)	3.46 ± 2.07	3.24 ± 2.22	0.537
Parity (times)	2.31 ± 1.61	2.18 ± 1.83	0.627
Menarche (years)	12.72 ± 1.84	11.74 ± 1.14	0.002
Race			0.355
Mexican American	576 (16.52%)	6 (17.65%)	
Other Hispanic	446 (12.79%)	8 (23.53%)	
Non-Hispanic White	1250 (35.86%)	7 (20.59%)	
Non-Hispanic Black	714 (20.48%)	7 (20.59%)	
Non-Hispanic Asian	403 (11.56%)	5 (14.71%)	
Other Race	97 (2.78%)	1 (2.94%)	
PIR status			0.169
Low	882 (25.30%)	13 (38.24%)	
Medium	888 (25.47%)	9 (26.47%)	
High	1716 (49.23%)	12 (35.29%)	
Marital status			<0.001
Current	631 (18.11%)	18 (52.94%)	
Past	928 (26.64%)	5 (14.71%)	
Never	1925 (55.25%)	11 (32.35%)	
Education			0.450
<High school	768 (22.04%)	6 (17.65%)	
High school	731 (20.98%)	5 (14.71%)	
>High school	1986 (56.99%)	23 (67.65%)	
Drink			0.665
Rarely	1042 (29.89%)	9 (26.47%)	
Often	2444 (70.11%)	25 (73.53%)	
Smoke			0.028
Non-smoker	1843 (52.87%)	11 (32.35%)	
Former smoker	358 (10.27%)	3 (8.82%)	
Current smoker	1285 (36.86%)	20 (58.82%)	

(*Continued*)

Table 1 (Continued).

	Non-Hyperandrogenism N=3486	Hyperandrogenism N=34	*P*-value
Anthropometric measurement indicators			
Waist (cm)	98.71 ± 17.22	110.37 ± 16.39	<0.001
Weight (kg)	76.94 ± 21.42	97.36 ± 22.28	<0.001
Height (cm)	160.06 ± 7.18	163.12 ± 5.48	0.013
BMI (kg/m^2)	29.95 ± 7.73	36.56 ± 8.10	<0.001
BMI status			<0.001
Underweight	68 (1.95%)	1 (2.94%)	
Normal weight	968 (27.77%)	0 (0.00%)	
Overweight	930 (26.68%)	6 (17.65%)	
Obesity	1520 (43.60%)	27 (79.41%)	
Systolic blood pressure (mmHg)	123.45 ± 18.93	121.25 ± 13.24	0.500
Diastolic blood pressure (mmHg)	69.33 ± 12.14	69.31 ± 14.80	0.995
Laboratory indicators			
ApoB (g//L)	0.93 ± 0.29	0.85 ± 0.25	0.084
HDL-C (mg/dL)	57.93 ± 17.15	48.21 ± 18.64	0.001
LDL-C (mg/dL)	115.93 ± 45.28	98.03 ± 37.09	0.022
TG (mg/dL)	109.98 ± 100.25	132.85 ± 58.97	0.184
TC (mg/dL)	192.14 ± 41.43	184.12 ± 34.56	0.261
GLU (mg/dL)	106.93 ± 34.11	102.56 ± 25.36	0.456
INS (μU/mL)	13.79 ± 19.01	20.54 ± 14.13	0.039
Glycohemoglobin (%)	5.76 ± 1.12	5.68 ± 0.54	0.680
C-Reactive Protein (mg/L)	4.48 ± 6.48	4.78 ± 4.46	0.786
Monocyte number (1000 cells/uL)	0.55 ± 0.19	0.56 ± 0.13	0.807
TT (ng/dL)	22.62 ± 13.26	52.32 ± 21.48	<0.001
E^2 (pg/mL)	56.57 ± 86.94	66.88 ± 63.08	0.490
SHBG (nmol/L)	72.12 ± 46.96	23.30 ± 10.50	<0.001
FAI	1.41 ± 1.04	8.28 ± 2.79	<0.001
MHR	0.41 ± 0.20	0.49 ± 0.18	0.021
Classification of diseases			
Hypertension			0.725
No	1740 (49.91%)	18 (52.94%)	
Yes	1746 (50.09%)	16 (47.06%)	
Diabetes			0.249
No	2696 (77.34%)	26 (76.47%)	
Yes	426 (12.22%)	2 (5.88%)	
Borderline	364 (10.44%)	6 (17.65%)	
Hypercholesterolemia			0.119
No	2105 (60.38%)	25 (73.53%)	
Yes	1381 (39.62%)	9 (26.47%)	
MS Score			0.868
1	553 (15.86%)	4 (11.76%)	
2	1521 (43.63%)	17 (50.00%)	
3	995 (28.54%)	9 (26.47%)	
4	417 (11.96%)	4 (11.76%)	
MS			0.788
No	2074 (59.50%)	21 (61.76%)	
Yes	1412 (40.50%)	13 (38.24%)	

(*Continued*)

Table 1 (Continued).

	Non-Hyperandrogenism N=3486	Hyperandrogenism N=34	*P*-value
CVD			0.471
No	3154 (90.48%)	32 (94.12%)	
Yes	332 (9.52%)	2 (5.88%)	
Mortality endpoint analysis			
Death			0.223
No	3340 (95.81%)	34 (100.00%)	
Yes	146 (4.19%)	0 (0.00%)	
Cause of death			NA
Diseases of heart	31 (21.23%)	0 (%)	
Malignant neoplasms	29 (19.86%)	0 (%)	
Chronic lower respiratory diseases	10 (6.85%)	0 (%)	
Accidents	3 (2.05%)	0 (%)	
Cerebrovascular diseases	9 (6.16%)	0 (%)	
Alzheimer	5 (3.42%)	0 (%)	
Diabetes	8 (5.48%)	0 (%)	
Influenza and pneumonia	1 (0.68%)	0 (%)	
Kidney	4 (2.74%)	0 (%)	
Other	46 (31.51%)	0 (%)	

Abbreviations: PIR, poverty-to-income ratio; BMI, body mass index; ApoB, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; GLU, fasting blood glucose; INS, insulin; TT, total testosterone; E^2, estradiol; SHBG, sex hormone-binding globulin; FAI, free androgen index; MHR, monocyte to high-density lipoprotein cholesterol ratio; MS, metabolic syndrome; CVD, cardiovascular disease; NA, not available.

Compared to the normal androgen level group, patients with hyperandrogenemia were younger and had an earlier age at menarche. In anthropometric measures, women with hyperandrogenemia had significantly higher waist circumference, weight, and BMI than women without high androgen levels, with some differences being statistically significant ($p < 0.001$); in laboratory metabolic and hormone-related indicators, women with hyperandrogenemia had lower ApoB, HDL, LDL, and higher INS and MHR, all with statistical significance; in the incidence of related diseases, there were no significant statistical differences between the two groups in terms of diabetes, hypertension, hypercholesterolemia, CVD incidence, all-cause mortality, and cardiovascular mortality.

Clinical Characteristics After Stratification by FAI Quartiles

The clinical characteristics of subjects stratified by FAI quartiles are shown in Table 2. There are statistical differences in general data characteristics between different FAI quartiles, such as age, number of pregnancies and deliveries, age at menarche, race, economic status, education level, marital status, and smoking status. Without adjusting for these differences, in the anthropometric measurement indicators, BMI, waist circumference, and weight show an increasing trend with FAI quartiles; whereas in laboratory metabolic and hormone-related indicators, ApoB, HDL, and LDL show a decreasing trend with FAI values, and GLU, MHR, glycated hemoglobin, and CRP show an increasing trend, all with statistical significance; in the classification of diseases, diabetes shows an increasing trend, which is statistically significant; dyslipidemia, CVD, and all-cause mortality show a decreasing trend, which is also statistically significant.

Assessment of the Correlation Between TT and FAI with MS

Using complex weighted logistic regression, with the first quartile of FAI and TT as controls, the association between androgen levels and metabolic syndrome was explored. According to the models grouped by FAI quartiles, in model 2 adjusted for age, and in model 3 adjusted for age, tobacco use, and alcohol use, the prevalence of metabolic syndrome (MS) was positively correlated with FAI, and the correlation increased with FAI quartiles, all with statistical significance.

Table 2 Baseline Characteristics of Participants with FAI Quartile

FAI Quartile	Q1 (0.031–0.714)	Q2 (0.714–1.144)	Q3 (1.144–1.841)	Q4 (1.841–17.948)	*P*-value
General data characteristics					
Age (years)	52.48 ± 17.27	50.90 ± 15.83	48.15 ± 16.06	42.85 ± 16.58	<0.001
Gravidity (times)	3.46 ± 2.14	3.66 ± 2.23	3.41 ± 1.98	3.29 ± 1.91	0.002
Parity (times)	2.28 ± 1.72	2.45 ± 1.63	2.31 ± 1.61	2.19 ± 1.48	0.008
Menarche (years)	12.91 ± 1.84	12.81 ± 1.89	12.60 ± 1.79	12.53 ± 1.81	<0.001
Race					0.001
Mexican American	124 (14.09%)	157 (17.84%)	155 (17.61%)	146 (16.59%)	
Other Hispanic	96 (10.91%)	113 (12.84%)	124 (14.09%)	121 (13.75%)	
Non-Hispanic White	360 (40.91%)	313 (35.57%)	284 (32.27%)	300 (34.09%)	
Non-Hispanic Black	165 (18.75%)	169 (19.20%)	203 (23.07%)	184 (20.91%)	
Non-Hispanic Asian	119 (13.52%)	102 (11.59%)	94 (10.68%)	93 (10.57%)	
Other Race	16 (1.82%)	26 (2.95%)	20 (2.27%)	36 (4.09%)	
PIR status					0.003
Low	195 (22.16%)	215 (24.43%)	230 (26.14%)	255 (28.98%)	
Medium	210 (23.86%)	223 (25.34%)	227 (25.80%)	237 (26.93%)	
High	475 (53.98%)	442 (50.23%)	423 (48.07%)	388 (44.09%)	
Marital status					<0.001
Current	129 (14.66%)	131 (14.92%)	166 (18.86%)	223 (25.34%)	
Past	268 (30.45%)	256 (29.16%)	236 (26.82%)	173 (19.66%)	
Never	483 (54.89%)	491 (55.92%)	478 (54.32%)	484 (55.00%)	
Education					0.397
<High school	201 (22.84%)	210 (23.86%)	186 (21.14%)	177 (20.14%)	
High school	170 (19.32%)	177 (20.11%)	193 (21.93%)	196 (22.30%)	
>High school	509 (57.84%)	493 (56.02%)	501 (56.93%)	506 (57.57%)	
Drink					<0.001
Rarely	276 (31.36%)	312 (35.45%)	244 (27.73%)	219 (24.89%)	
Often	604 (68.64%)	568 (64.55%)	636 (72.27%)	661 (75.11%)	
Smoke					<0.001
Non-smoker	493 (56.02%)	480 (54.55%)	475 (53.98%)	406 (46.14%)	
Former smoker	83 (9.43%)	98 (11.14%)	94 (10.68%)	86 (9.77%)	
Current smoker	304 (34.55%)	302 (34.32%)	311 (35.34%)	388 (44.09%)	
Anthropometric measurement indicators					
Waist (cm)	92.02 ± 15.24	96.82 ± 15.54	101.17 ± 17.39	105.27 ± 17.81	<0.001
Weight (kg)	68.42 ± 17.84	74.00 ± 18.48	79.90 ± 22.10	86.22 ± 22.99	<0.001
Height (cm)	159.71 ± 7.53	159.66 ± 7.34	160.16 ± 6.81	160.83 ± 6.91	0.002
BMI (kg/m^2)	26.76 ± 6.48	29.00 ± 6.83	31.06 ± 7.88	33.24 ± 8.19	<0.001
BMI status					<0.001
Underweight	33 (3.75%)	15 (1.70%)	12 (1.36%)	9 (1.02%)	
Normal weight	394 (44.77%)	267 (30.34%)	194 (22.05%)	113 (12.84%)	
Overweight	233 (26.48%)	265 (30.11%)	226 (25.68%)	212 (24.09%)	
Obesity	220 (25.00%)	333 (37.84%)	448 (50.91%)	546 (62.05%)	
Systolic blood pressure (mmHg)	124.59 ± 20.65	124.00 ± 18.91	123.62 ± 19.28	121.50 ± 16.33	0.004
Diastolic blood pressure (mmHg)	68.56 ± 12.45	68.98 ± 12.54	70.12 ± 12.32	69.64 ± 11.28	0.036
Laboratory indicators					
ApoB (g/L)	0.95 ± 0.31	0.94 ± 0.28	0.93 ± 0.31	0.91 ± 0.27	0.042
HDL –C (mg/dL)	63.71 ± 18.16	59.88 ± 17.84	55.84 ± 16.07	51.92 ± 14.09	<0.001
LDL-C (mg/dL)	119.56 ± 49.12	117.40 ± 42.52	115.49 ± 46.85	110.60 ± 41.62	<0.001
TG (mg/dL)	105.51 ± 152.75	107.66 ± 73.35	111.21 ± 73.51	116.44 ± 76.26	0.110

(*Continued*)

Table 2 (Continued).

FAI Quartile	Q1 (0.031–0.714)	Q2 (0.714–1.144)	Q3 (1.144–1.841)	Q4 (1.841–17.948)	*P*-value
TC (mg/dL)	191.04 ± 41.13	195.74 ± 38.04	193.58 ± 46.07	187.87 ± 39.44	<0.001
GLU (mg/dL)	102.73 ± 27.86	107.09 ± 34.00	108.85 ± 37.76	108.88 ± 35.44	<0.001
INS (μU/mL)	11.47 ± 14.57	13.80 ± 20.52	13.54 ± 14.90	16.62 ± 23.95	<0.001
Glycohemoglobin (%)	5.61 ± 0.88	5.76 ± 1.17	5.83 ± 1.23	5.83 ± 1.14	<0.001
C-Reactive Protein (mg/L)	3.63 ± 5.53	4.06 ± 5.96	4.86 ± 6.11	5.38 ± 7.88	<0.001
Monocyte number (1000 cells/uL)	0.53 ± 0.18	0.55 ± 0.20	0.55 ± 0.18	0.58 ± 0.18	<0.001
E^2 (pg/mL)	43.03 ± 101.16	53.98 ± 79.45	58.43 ± 83.53	71.23 ± 78.68	<0.001
SHBG (nmol/L)	113.99 ± 59.93	75.35 ± 35.08	55.74 ± 25.51	41.52 ± 19.92	<0.001
MHR	0.35 ± 0.17	0.39 ± 0.22	0.42 ± 0.19	0.47 ± 0.21	<0.001
Classification of diseases					
Hypertension					0.056
No	431 (48.98%)	415 (47.16%)	441 (50.11%)	471 (53.52%)	
Yes	449 (51.02%)	465 (52.84%)	439 (49.89%)	409 (46.48%)	
Diabetes					<0.001
No	720 (81.82%)	691 (78.52%)	664 (75.45%)	647 (73.52%)	
Yes	91 (10.34%)	107 (12.16%)	114 (12.95%)	116 (13.18%)	
Borderline	69 (7.84%)	82 (9.32%)	102 (11.59%)	117 (13.30%)	
Hypercholesterolemia					0.007
No	508 (57.73%)	519 (58.98%)	529 (60.11%)	574 (65.23%)	
Yes	372 (42.27%)	361 (41.02%)	351 (39.89%)	306 (34.77%)	
MS Score					0.235
1	137 (15.57%)	134 (15.23%)	137 (15.57%)	149 (16.93%)	
2	396 (45.00%)	371 (42.16%)	382 (43.41%)	389 (44.20%)	
3	253 (28.75%)	278 (31.59%)	237 (26.93%)	236 (26.82%)	
4	94 (10.68%)	97 (11.02%)	124 (14.09%)	106 (12.05%)	
MS					0.373
No	533 (60.57%)	505 (57.39%)	519 (58.98%)	538 (61.14%)	
Yes	347 (39.43%)	375 (42.61%)	361 (41.02%)	342 (38.86%)	
CVD					<0.001
No	767 (87.16%)	798 (90.68%)	807 (91.70%)	814 (92.50%)	
Yes	113 (12.84%)	82 (9.32%)	73 (8.30%)	66 (7.50%)	
Mortality endpoint analysis					
Death					0.029
No	833 (94.66%)	837 (95.11%)	849 (96.48%)	855 (97.16%)	
Yes	47 (5.34%)	43 (4.89%)	31 (3.52%)	25 (2.84%)	
Cause of death					0.398
Diseases of heart	12 (25.53%)	6 (13.95%)	8 (25.81%)	5 (20.00%)	
Malignant neoplasms	8 (17.02%)	9 (20.93%)	6 (19.35%)	6 (24.00%)	
Chronic lower respiratory diseases	6 (12.77%)	3 (6.98%)	1 (3.23%)	0 (0.00%)	
Accidents	0 (0.00%)	3 (6.98%)	0 (0.00%)	0 (0.00%)	
Cerebrovascular diseases	3 (6.38%)	2 (4.65%)	2 (6.45%)	2 (8.00%)	
Alzheimer	3 (6.38%)	0 (0.00%)	2 (6.45%)	0 (0.00%)	
Diabetes	2 (4.26%)	1 (2.33%)	2 (6.45%)	3 (12.00%)	
Influenza and pneumonia	1 (2.13%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Kidney	2 (4.26%)	1 (2.33%)	0 (0.00%)	1 (4.00%)	
Other	10 (21.28%)	18 (41.86%)	10 (32.26%)	8 (32.00%)	

Abbreviations: PIR, poverty-to-income ratio; BMI, body mass index; ApoB, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; GLU, fasting blood glucose; INS, insulin; TT, total testosterone; E^2, estradiol; SHBG, sex hormone-binding globulin; FAI, free androgen index; MHR, monocyte to high-density lipoprotein cholesterol ratio; MS, metabolic syndrome; CVD, cardiovascular disease; NA, not available.

In the models grouped by TT quartiles, in model 1, the prevalence of MS was negatively correlated with TT, with statistical significance, but in models 2 and 3, there was no significant statistical correlation. Detailed results of the correlations are presented in Table 3.

Assessment of the Correlation Between TT and FAI with CVD

Using complex weighted logistic regression, with the first quartile of FAI and TT as controls, the association between androgen levels and CVD was explored. In the models grouped by FAI quartiles, in the unadjusted Model 1, the second and third quartiles of FAI showed a negative correlation with CVD, with statistical significance, while in Models 2 and 3, the correlation did not show significant statistical meaning. In the models grouped by TT quartiles, in Model 1, the prevalence of CVD was negatively correlated with TT, with statistical significance, but in Models 2 and 3, there was no significant statistical correlation. Detailed results of the correlations are presented in Table 4.

Table 3 Correlation Between FAI and TT with Metabolic Syndrome

	Q1	Q2	Q3	Q4
FAI Quartiles				
Model 1	1	1.15 (0.95,1.40)0.15	1.09 (0.89,1.35)0.40	1.04 (0.77,1.40)0.80
OR (95% CI) *P*-value				
Model 2	1	1.28 (1.03,1.59)0.02	1.34 (1.06,1.69)0.01	1.45 (1.04,2.02)0.03
OR (95% CI) *P*-value				
Model 3	1	1.29 (1.04,1.61)0.02	1.33 (1.05,1.68)0.02	1.45 (1.04,2.02)0.03
OR (95% CI) *P*-value				
TT Quartiles				
Model 1	1	0.75 (0.62,0.92)0.00	0.52 (0.41,0.65)0.00	0.52 (0.36,0.73)0.00
OR (95% CI) *P*-value				
Model 2	1	1.01 (0.81,1.26)0.91	0.82 (0.63,1.06)0.12	0.93 (0.63,1.37)0.71
OR (95% CI) *P*-value				
Model 3	1	1.02 (0.82,1.27)0.85	0.83 (0.64,1.07)0.15	0.94 (0.64,1.39)0.76
OR (95% CI) *P*-value				

Notes: Model 1 unadjusted, Model 2 adjusted for age, and Model 3 adjusted for age, tobacco use, and alcohol use.
Abbreviations: TT, total testosterone; FAI, free androgen index; CI, confidence intervals; OR, odds radio.

Table 4 Correlation Between FAI and TT with CVD

	Q1	Q2	Q3	Q4
FAI Quartiles				
Model 1	1	0.73 (0.54,1.01)0.05	0.69 (0.48,0.99)0.04	0.73 (0.41,1.31)0.30
OR (95% CI) *P*-value				
Model 2	1	0.78 (0.56,1.08)0.13	0.79 (0.54,1.15)0.22	0.91 (0.49,1.69)0.77
OR (95% CI) *P*-value				
Model 3	1	0.80 (0.58,1.11)0.19	0.78 (0.53,1.14)0.20	0.89 (0.48,1.65)0.72
OR (95% CI) *P*-value				
TT Quartiles				
Model 1	1	0.71 (0.52,0.97)0.03	0.43 (0.29,0.64)0.00	0.52 (0.29,0.93)0.03
OR (95% CI) *P*-value				
Model 2	1	0.93 (0.67,1.28)0.64	0.64 (0.43,0.97)0.03	0.84 (0.46,1.52)0.56
OR (95% CI) *P*-value				
Model 3	1	0.93 (0.67,1.28)0.64	0.66 (0.44,1.00)0.05	0.86 (0.47,1.58)0.64
OR (95% CI) *P*-value				

Notes: Model 1 unadjusted, Model 2 adjusted for age, and Model 3 adjusted for age, tobacco use, and alcohol use.
Abbreviations: TT, total testosterone; FAI, free androgen index; CI, confidence intervals; OR, odds radio.

Assessment of the Correlation Between TT and FAI with All-Cause Mortality and Cardiac Mortality

Using complex weighted COX regression models, with the first quartile of FAI and TT as controls, the association between androgen levels and all-cause mortality and cardiac mortality was explored. In the three models grouped by quartiles of FAI and TT, there was no significant statistical correlation between both and all-cause mortality and CVD mortality. The results of the correlations are detailed in Tables 5 and 6.

Table 5 Correlation Between FAI and All-Cause Mortality, Cardiac Mortality

	Quartiles of FAI			
	Q1	Q2	Q3	Q4
All-cause mortality				
Model 1	1	1.09(0.69,1.74)0.70	0.96(0.51,1.80)0.91	1.42(0.48,4.20)0.52
HR (95% CI) *P*-value				
Model 2	1	1.22(0.77,1.93)0.40	1.18(0.63,2.19)0.61	1.83(0.62,5.40)0.28
HR (95% CI) *P*-value				
Model 3	1	1.23(0.78,1.95)0.38	1.18(0.63,2.21)0.60	1.82(0.62,5.39)0.28
HR (95% CI) *P*-value				
CVD mortality				
Model 1	1	0.44(0.14,1.36)0.15	0.55(0.11,2.74)0.46	0.13(0.00,4.02)0.25
HR (95% CI) *P*-value				
Model 2	1	0.45(0.15,1.40)0.17	0.42(0.09,2.09)0.29	0.08(0.00,2.27)0.14
HR (95% CI) *P*-value				
Model 3	1	0.48(0.15,1.46)0.20	0.43(0.08,2.22)0.32	0.05(0.00,1.50)0.08
HR (95% CI) *P*-value				

Notes: Model 1 unadjusted, Model 2 adjusted for age, and Model 3 adjusted for age, tobacco use, and alcohol use.
Abbreviations: FAI, free androgen index; CI, confidence intervals; HR, hazard ratio.

Table 6 Correlation Between TT and All-Cause Mortality, Cardiac Mortality

	Quartiles of TT			
	Q1	Q2	Q3	Q4
All-cause mortality				
Model 1	1	0.64(0.41,1.02)0.06	0.58(0.34,0.99)0.04	0.55(0.24,1.26)0.16
HR (95% CI) *P*-value				
Model 2	1	0.94(0.59,1.50)0.80	0.96(0.56,1.63)0.87	0.94(0.41,2.21)0.88
HR (95% CI) *P*-value				
Model 3	1	0.92(0.58,1.47)0.73	0.95(0.56,1.63)0.86	0.92(0.41,2.08)0.84
HR (95% CI) *P*-value				
CVD mortality				
Model 1	1	1.50(0.48,4.64)0.48	2.34(0.57,9.60)0.24	5.88(0.65,53.11)0.11
HR (95% CI) *P*-value				
Model 2	1	1.86(0.58,5.90)0.29	3.20(0.75,13.62)0.11	6.89(0.73,65.08)0.09
HR (95% CI) *P*-value				
Model 3	1	1.63(0.50,5.31)0.42	2.83(0.67,12.01)0.16	3.05(0.30,31.02)0.35
HR (95% CI) *P*-value				

Notes: Model 1 unadjusted, Model 2 adjusted for age, and Model 3 adjusted for age, tobacco use, and alcohol use.
Abbreviations: TT, total testosterone; CI, confidence intervals; HR, hazard ratio.

Discussion

In this cross-sectional study based on 2013–2016 NHANES data, we explored the association between female androgen indicators (TT, FAI) and metabolic status, cardiovascular risks, and long-term mortality. Our initial findings indicate that higher androgen levels correlate with increased waist circumference, weight, Body Mass Index (BMI), insulin levels (INS), and Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR) across all population quartiles and in women with high androgenemia, even prior to adjusting for age, menarche, marital status, and smoking habits. MHR is a well-established marker of inflammation and oxidative stress, linked to the prognosis of various conditions, including PCOS, corneal diseases, chronic obstructive pulmonary disease, diabetes, and CVD.[32] Our previous studies have clarified the relevance of MHR to the occurrence of MS, pre-obesity, and prediabetes in peri-menopausal and postmenopausal women, indicating its predictive value for these metabolic diseases. These results suggest that androgens significantly influence obesity, insulin regulation, and inflammatory responses in the body.[33] Further stratification by FAI quartiles revealed that higher androgen levels also correlate with elevated blood glucose, glycated hemoglobin, and C-reactive protein (CRP) levels, indicating a strong association with glucose metabolism and inflammatory states, consistent with prior research.[34]

Androgens significantly influence adipose tissue distribution, demonstrating notable sexual dimorphism. This effect is mediated by the hormonal balance between androgens and estrogens, which bind to specific receptors and modulate both the distribution and function of adipose tissue. Adipose tissue plays a core role in the pathophysiology of obesity-dependent type 2 diabetes and metabolic syndrome.[35] Recent genomic and proteomic studies reveal that steroids alter not just the distribution but also the functional characteristics of adipose tissue. Specifically, analyses of visceral omental fat from severely obese women with androgen excess have demonstrated significant alterations in gene expression and protein profiles compared to those in non-obese women.[36] These differences involve multiple biological pathways such as insulin, oxidative stress, inflammation, immune function, and adipocyte differentiation.[37] A 12-year prospective study in Sweden identified higher levels of free testosterone as an independent risk factor for the development and progression of type 2 diabetes in postmenopausal women, correlating elevated testosterone levels with impaired glucose tolerance. A meta-analysis suggested that free testosterone levels are associated with the risk of type 2 diabetes in women, possibly because testosterone levels reduce healthy women's overall glucose uptake in response to insulin stimulation, leading to insulin resistance.[38] Previous studies have demonstrated that statin therapy positively impacts serum lipid profiles and reduces levels of testosterone, DHEA, DHEA-S, and androstenedione. These changes are linked to improvements in hyperandrogenism and an increase in the FSH/LH ratio, which are accompanied by reductions in menstrual irregularities and infertility commonly observed in patients with PCOS.[39]

In the correlation analysis adjusted for age, tobacco use, and alcohol consumption, a positive relationship remained between Metabolic Syndrome (MS) and the Free Androgen Index (FAI), with the correlation coefficient increasing across FAI quartiles and reaching a peak of 1.45 (95% CI 1.04–2.02, P=0.03) in the highest quartile. In typical conditions, testosterone (T) circulates in three forms: Approximately 85% is tightly bound to sex hormone-binding globulin (SHBG), 10–15% is loosely bound to albumin, and about 1% exists as free testosterone (FT), which is biologically active. The Free Androgen Index (FAI) estimates the level of FT, thereby serving as a reliable marker for biologically active androgens and aiding in the prediction of MS risk.[40] Androgen synthesis and metabolism in females primarily occur in the ovaries, with significant contributions from the adrenal glands. Tumors of the adrenal glands and ovaries that secrete androgens can lead to abnormally high levels of androgens in the blood, which is different from the high androgenemia caused by functional diseases we usually see and its impact on the body. Therefore, we excluded study subjects with abnormally high testosterone levels. Previous studies have shown that excessive body fat is a decisive factor in the occurrence and development of MS,[13] and testosterone levels play an important role in its regulation, as described above, female androgens are closely related to fat distribution, impaired glucose tolerance, pancreatic dysfunction, etc, also indicating that female androgens, especially FAI, are closely related to MS.[41]

In our study, after adjusting for age, tobacco use, and alcohol use, no statistically significant correlation was found between androgens and CVD, all-cause mortality, and cardiac-specific mortality. The impact of androgens on the development of cardiovascular diseases remains a subject of ongoing debate in the scientific community. While some research indicates that high androgen levels do not increase the risk of major vascular diseases, abdominal aortic plaques,

myocardial infarction, or stroke,[42] other studies suggest a higher prevalence of hypertension, cerebrovascular diseases, and an increased risk of coronary heart disease and stroke among women with elevated androgen levels.[42] The relationship between endogenous androgen levels and the risk of coronary heart disease in women is still inconclusive.[43] Recent studies on postmenopausal women in the general population have found that high concentrations of testosterone are related to risk factors for cardiovascular diseases, such as dyslipidemia, obesity, and elevated plasma glucose levels, which may lead to vascular arteriosclerosis.[44] Conversely, some cohort studies have found that higher endogenous testosterone levels are linked to decreased carotid atherosclerosis and lower rates of all-cause mortality and cardiovascular events in both premenopausal and postmenopausal women.[45] Proteomic studies have shown that patients with polycystic ovary syndrome (PCOS) have elevated levels of ApoE, complement C3, and heparin cofactor II (HCFII), along with reduced ApoM levels. This protein dysregulation may impair the protective effects of HDL-C, potentially contributing to increased atherosclerosis and heightened cardiovascular risk.[46] Analyses of related randomized controlled trials have not shown an increased CVD risk in women receiving testosterone treatment.[47] Our study included a small number of CVD patients and deaths, and further large-scale cohort studies are needed.

The strength of our study lies in utilizing a large cross-sectional database from the United States, which, with its relatively large sample size and long-term follow-up of cardiovascular events and deaths, provided robust data for our analysis. Additionally, by adjusting for potential confounding factors such as socioeconomic status, diet, lifestyle factors, and history of tobacco and alcohol use, we were able to enhance the validity of our conclusions.

Our study has some limitations. As it is based on a large cross-sectional national database in the United States, it cannot entirely eliminate the potential for residual confounding factors. Additionally, the questionnaire results from the database provide limited information on conditions like polycystic ovary syndrome. We also cannot exclude measurement errors and residual or unknown confounding or spurious effects caused by unmeasured variables.

In summary, our study, utilizing NHANES data from 2013 to 2016, demonstrates a significant association between female androgens, metabolic indicators, and cardiovascular diseases. Our findings suggest that androgen levels significantly influence glucose metabolism and inflammatory states, with FAI emerging as a more sensitive marker for metabolic syndrome than TT. However, the small sample size for CVD limited our ability to establish a correlation between androgen levels and CVD, pointing to the need for further large-scale cohort studies.

Conclusion

Androgen levels are closely associated with glucose metabolism and inflammatory status. Notably, the Free Androgen Index (FAI) proves to be a more sensitive indicator for metabolic syndrome than Total Testosterone (TT). However, this study found no significant correlation between androgen levels and either cardiovascular disease (CVD) or all-cause mortality.

Data Sharing Statement

The following information was supplied regarding data availability: Data is available at the NHANES database (https://www.cdc.gov/nchs/nhanes/).

Ethics Approval and Consent to Participate

The studies involving humans were approved by the National Center for Health Statistics Ethics Review Board. The studies were conducted according to local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. The Ethics Committee of Zhongda Hospital Southeast University waived the necessity of ethical approval for this study, as the NHANES is a publicly accessible database.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author reports no conflicts of interest in this work.

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