

Study on Urinary Caffeine and Caffeine Metabolite Levels in American Adults with Coronary Heart Disease: A Cross-Sectional NHANES Study (2009-2014)

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Abstract

Background: In recent years, the impact of diet and lifestyle on coronary heart disease (CHD) has garnered significant attention. Caffeine, a common dietary component, and its metabolites may influence cardiovascular health.

Objective: This study aimed to investigate the association between urinary levels of caffeine and its metabolites and the incidence of CHD as well as to assess how these associations vary across different population groups.

Methods: Data from the NHANES database (2009-2014) were analyzed using multivariable logistic regression models and smooth curve fitting techniques. Participants were categorized into a control group (n = 5,005) and a CHD group (n = 222) based on CHD status. Urinary levels of caffeine and its metabolites were measured and recorded. Multivariable logistic regression was used to evaluate the association between urinary caffeine/metabolite levels and CHD incidence, while smooth curve fitting was employed to explore potential nonlinear relationships. A significance level of 5% was used to determine statistical significance.

Results: Higher urinary paraxanthine levels were associated with a lower risk of CHD. In contrast, elevated urinary caffeine levels were positively associated with CHD incidence among Mexican Americans, an association not observed in other racial/ethnic groups.

Conclusion: Lower urinary paraxanthine levels may reflect a reduced risk of CHD, while higher urinary caffeine levels could indicate an increased CHD risk in specific populations.

Keywords: Caffeine; Cardiovascular Disease; Coffee Metabolites; Race.

Introduction

In recent years, coronary heart disease (CHD) has become one of the leading causes of mortality, accounting for over 370,000 deaths annually.¹ In addition to traditional risk factors such as smoking, hyperlipidemia, hypertension, type 2 diabetes mellitus (T2DM), and obesity, emerging factors have also been identified, including systemic inflammation, gestational diabetes, preeclampsia, and early or surgical menopause.

Dietary modifications have been shown to reduce the incidence of CHD.² Natural pharmacological compounds — particularly caffeine — are often employed as complementary therapies for cardiovascular diseases.³ Coffee, the most

widely consumed beverage worldwide, contains caffeine (1,3,7-trimethylxanthine), which is primarily ingested through foods and beverages.^{4,5} Although caffeine may cause a transient increase in blood pressure among nonhabitual consumers, long-term coffee intake has been associated with a reduced risk of arrhythmias and heart failure, improved insulin sensitivity, and a lower risk of T2DM.

Several studies have reported an inverse relationship between coffee consumption and all-cause mortality. Habitual coffee drinking is associated with reduced risks of cardiovascular diseases and adverse cardiovascular outcomes, including CHD, congestive heart failure, and stroke. Long-term consumption has also been linked to lower risks of T2DM, depression, obesity, and certain cancers.^{6,7}

In particular, elevated urinary levels of caffeine and theophylline have been found to be negatively correlated with cardiovascular diseases,⁸ with the association being more pronounced in women.⁹ However, most current evidence is based on self-reported coffee consumption, which is subject to variation due to differences in brand, origin, and coffee type — all of which influence caffeine content. Few studies have examined the relationship between caffeine metabolites and cardiovascular disease, and many of those fail to account for

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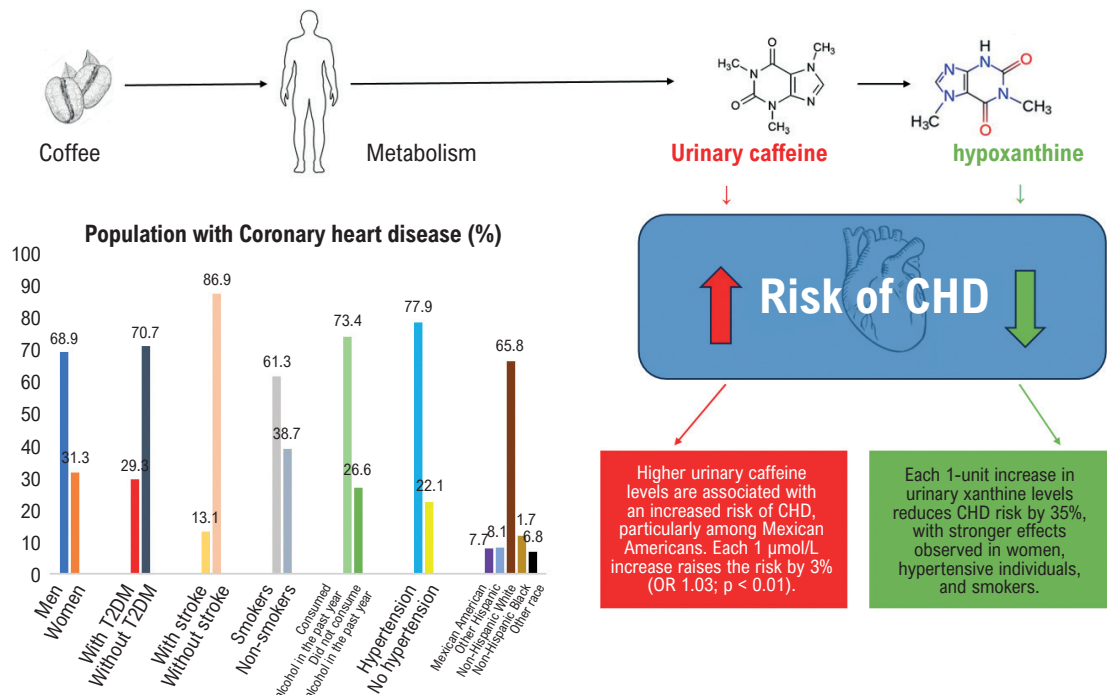
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Central Illustration: Study on Urinary Caffeine and Caffeine Metabolite Levels in American Adults with Coronary Heart Disease: A Cross-Sectional NHANES Study (2009-2014)



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CHD: coronary heart disease; T2DM: type 2 diabetes mellitus.

variability introduced by coffee type, origin, and production processes. Additionally, potential inaccuracies in self-reported data may affect the reliability of findings.

A reliable indicator of coffee intake is the concentration of caffeine and its metabolites excreted in urine. However, individual differences in caffeine metabolism can result in variability in circulating levels of caffeine and its metabolites. To better understand the association between urinary concentrations of caffeine and its metabolites and the presence of CHD, we conducted a cross-sectional analysis using data from the 2009-2014 National Health and Nutrition Examination Survey (NHANES). This study aimed to explore potential relationships between urinary biomarkers of caffeine exposure and CHD incidence.

Methods

Study population

NHANES is a cross-sectional nutritional survey conducted in the United States using a multistage, stratified probability sampling method. Approval for data collection and dissemination was granted by the National Center for Health

Statistics.¹⁰ We included data from adults aged 20 years and over who participated in NHANES between 2009 and 2014.¹¹ During and after data collection, we did not have access to any personally identifiable information.

A total of 30,468 participants were initially considered. After applying exclusion criteria, the final analysis included 5,227 participants. These criteria excluded individuals under the age of 20 ($n = 13,261$), individuals with incomplete data on CHD ($n = 67$) and individuals with missing data on caffeine and its metabolites ($n = 11,913$). After applying these exclusion criteria, 5,227 participants were included in the final analysis (Figure 1).

Exposure factors

Theobromine (3,7-dimethylxanthine), theophylline (1,3-dimethylxanthine), and paraxanthine (1,7-dimethylxanthine) are the main human caffeine metabolites.¹² In this study, urinary concentrations of caffeine and its metabolites were used as exposure variables. Urine samples were collected between 10:00 a.m. and 12:00 p.m. after a 9-hour overnight fast. Samples were received, processed, and stored before being shipped to the Division of Laboratory Sciences at the National Center for Environmental

Health, Centers for Disease Control and Prevention, in Atlanta, Georgia, for analysis.

High-performance liquid chromatography-electrospray ionization-tandem quadrupole mass spectrometry was used in combination with stable isotope-labeled internal standards to quantify caffeine and its metabolites in urine.¹³ Data were then reviewed for quality; uncertain or incomplete values were returned to the laboratory for verification.

Outcome variable

The diagnosis of CAD was based on clinical records and imaging results, such as coronary angiography. Data were collected through computer-assisted personal interviews (CAPI) conducted by trained interviewers. The questionnaire and methodology are available on the NHANES website.

Covariates

The following covariates were included to adjust for potential confounders in the relationship between caffeine/metabolite levels and CHD: sex, age, race/ethnicity, history of hypertension, hypercholesterolemia, T2DM, stroke, and smoking (defined as having smoked at least 100 cigarettes in a lifetime). Additional variables included alcohol consumption (defined as at least 12 alcoholic drinks per year), physical activity (measured in metabolic equivalents of task [METs]), and body mass index (BMI, kg/m²).¹¹ BMI was calculated as weight (kg) divided by height squared (m²). Anthropometric measurements were obtained by trained health technicians at mobile examination centers, while other covariates were collected via the CAPI system.

Statistical analysis

Statistical analyses were performed using R software and EmpowerStats.¹⁴ A two-sided p-value < 0.05 was considered statistically significant. Continuous variables with missing data were excluded from the analysis, while missing categorical variables were treated as a separate category.

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test, supported by histogram visualization. If data followed a normal distribution, results were reported as mean ± SD, and independent-samples *t*-tests were used for group comparisons. For data not normally distributed, results were expressed as median and interquartile range (Q1-Q3), and group comparisons were performed using the Mann-Whitney *U* test. As detailed in Appendix 1, continuous variables in this study did not conform to a normal distribution.

Categorical variables were reported as absolute numbers (n) and percentages (%), and group differences were assessed using the chi-square test. When expected frequencies were <10, Fisher's exact test was applied.

Multivariable logistic regression analysis was used to examine the association between urinary levels of caffeine and its metabolites and the presence of CHD. For non-normally distributed continuous variables, data were divided into quartiles (Q1-Q4). Q1 represented the lowest 25% of values and was designated as the reference group. Q2, Q3, and Q4

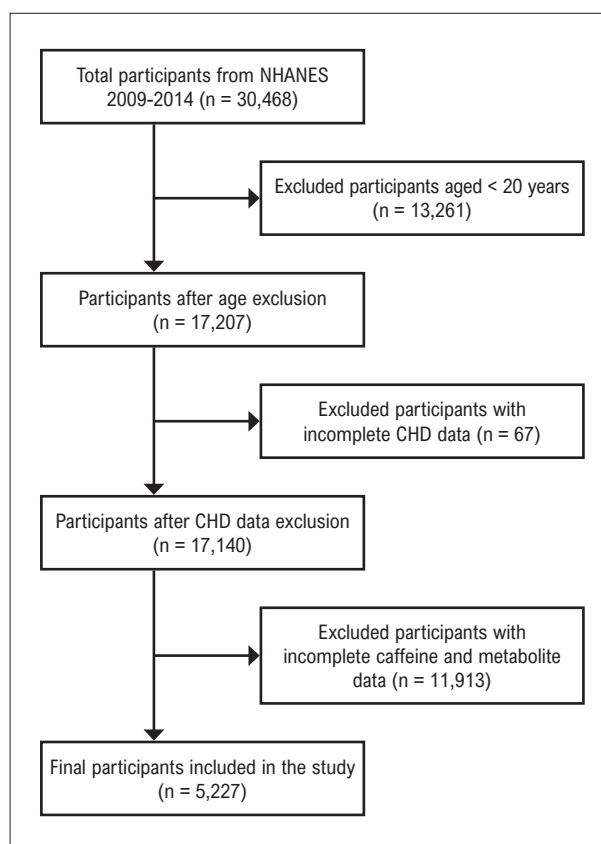


Figure 1 – Flowchart of participant selection process. CHD: coronary heart disease; NHANES: National Health and Nutrition Examination Survey.

represented progressively higher levels, enabling a clearer interpretation of trends across the distribution spectrum. Notably, Q4 referred to the highest 25% of data and was not part of a quintile division.

By grouping data into quartiles (Q1-Q4), we were able to clearly assess trends across the distribution of the variable of interest. Q1, representing the lowest 25% of values, served as the reference group and provided a baseline for comparison with the higher quartiles (Q2, Q3, and Q4). This approach allowed for a more detailed evaluation of how the variable behaves across progressively increasing levels. Q4, which represents the top 25% of data, highlighted the characteristics of the highest exposure group and its distinctions from the others. This method enhances the clarity of observed trends and patterns in the dataset.

We selected Q1 as the reference group because it represents the lowest exposure level, often associated with the lowest risk, making it suitable as a control group. The other quartiles (Q2-Q4) reflect increasing levels of exposure, which allows for a structured comparison across exposure gradients and improves the interpretability of differences between groups.

In this study, we constructed three models: model 1 was unadjusted; model 2 was adjusted for sex, age,

and race/ethnicity; model 3 was further adjusted for sex, age, race/ethnicity, height, history of hypertension, hypercholesterolemia, T2DM, and stroke, as well as smoking history (defined as smoking at least 100 cigarettes in a lifetime), alcohol consumption (≥ 12 alcoholic drinks/year), and BMI (kg/m^2).

These models were used to explore the association between urinary levels of caffeine and its metabolites and CHD while accounting for potential confounders. In addition, smooth curve fitting was applied to examine potential nonlinear relationships between caffeine/metabolite levels and CHD after adjustment. Subgroup analyses were also conducted to further explore these associations within specific population strata and to identify potential effect modifiers.

Ethical approval

This study was based on publicly available data from the NHANES, which is de-identified and accessible through the official NHANES website. Therefore, ethical approval was not required.

Results

Basic characteristics of the study population.

The normality test confirmed that the continuous variables did not follow a normal distribution (see Appendix 1). Therefore, non-normally distributed continuous variables are presented as medians and interquartile ranges (IQRs), and group comparisons were conducted using the Mann-Whitney U test. Categorical variables are expressed as frequencies and percentages (n, %) and were compared between groups using the chi-square test or Fisher's exact test when expected frequencies were < 10 . A p-value < 0.05 was considered statistically significant.

Participants in the CHD group were significantly older (median age: 72 [IQR: 63-80] years) than those in the control group (median age: 48 [IQR: 34-62] years; $p < 0.001$). The CHD group also had higher prevalences of hypertension, hypercholesterolemia, T2DM, and stroke as well as a greater history of smoking and alcohol consumption (all $p < 0.001$). Additionally, significant differences in ethnic distribution were observed between groups ($p = 0.001$).

Of the urinary metabolites analyzed, only paraxanthine levels differed significantly between groups ($p = 0.018$) (Table 1).

Association between urinary caffeine levels and CHD

The results of the association between urinary caffeine levels and CHD are presented in Table 2. In the unadjusted analysis, urinary caffeine levels as a continuous variable were not significantly associated with CHD (all $p > 0.05$). When caffeine levels were categorized into quartiles, individuals in the highest quartile (Q4) exhibited a statistically significant increase in CHD risk (OR 1.54; 95% CI 1.04-2.30; $p = 0.0318$) compared to those in the lowest quartile (Q1). This indicates that participants in Q4 had 54% higher odds of CHD than those in Q1.

Further analyses were stratified by sex and race/ethnicity. In the sex-stratified analysis, urinary caffeine levels were not significantly associated with CHD incidence in either men or women (OR 1.00; 95% CI 1.00-1.00; $p = 0.009$, which likely reflects model artifact or collinearity).

In the race-stratified analysis, a significant positive association was observed only among Mexican American participants, where each $1 \mu\text{mol}/\text{L}$ increase in urinary caffeine was associated with a 3% higher risk of CHD (OR 1.03; 95% CI 1.03-1.05; $p = 0.0081$). No statistically significant associations were found in other racial/ethnic groups (all $p > 0.05$).

These associations are visually represented in Figure 2A, which depicts a smoothed curve illustrating the relationship between urinary caffeine concentration and CHD incidence.

The associations between urinary caffeine metabolite levels and CHD are presented in Table 3.

The relationship between urinary caffeine metabolites and CHD is further explored using smooth curve fitting in Figure 2.

The results of the association between urinary caffeine metabolites and CHD are presented in Table 3. In Model 1, urinary levels of theophylline and theobromine showed no statistically significant association with CHD (all $p > 0.05$). When theophylline and theobromine levels were categorized into quartiles, no significant associations were observed across any model. After adjusting for potential confounders in Models 2 and 3, these findings remained nonsignificant. The smoothed curve fitting for theophylline and theobromine (Figures 2B and 2C, respectively) also demonstrated no clear association with CHD risk.

In contrast, urinary paraxanthine levels showed a significant inverse association with CHD in the unadjusted model (Model 1: OR 0.99; 95% CI 0.99-1.00; $p = 0.0177$). However, this association was no longer statistically significant after adjusting for covariates in Models 2 and 3.

To further assess the relationship, paraxanthine was also analyzed as a categorical variable divided into quartiles. In Model 1, individuals in the highest quartile of urinary paraxanthine (Q4) had a significantly lower risk of CHD compared to those in the lowest quartile (OR 0.65; 95% CI 0.43-0.97; $p = 0.036$). Nonetheless, this inverse association lost statistical significance after adjustment in Models 2 and 3 (all $p > 0.05$).

The urinary concentrations of theophylline, paraxanthine, theobromine, and caffeine were compared between the CHD group and the control group, as detailed in Table 4.

This analysis employed three models: an unadjusted model (Model 1), and two adjusted models — Model 2 (Adjust 1) and Model 3 (Adjust 2). Table 4 compares the urinary concentrations of four compounds (i.e., theophylline, paraxanthine, theobromine, and caffeine) between two groups: individuals without CHD (control group; $n = 5,005$) and those with CHD (CHD group; $n = 222$). For each compound, the difference in mean urinary concentration between the CHD group and the control group is presented, along with the corresponding 95% CI and p-value. The difference reflects the estimated average concentration difference between the two groups. The 95% CI provides

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Table 1 – Baseline characteristics and urinary levels of caffeine and its metabolites among study participants

Variable	CHD group (n = 222)	Control group (n = 5,005)	Standardized difference	p-value	Adjusted p-value (if applicable)*
Age (years)	72 (63 a 80)	48 (34 a 62)	1.5 (1.3 a 1.6)	<0.001	—
Sex			0.4 (0.3 a 0.6)	<0.001	—
Male	153 (68.9%)	2.390 (47.8%)			
Female	69 (31.1%)	2.615 (52.2%)			
Race/Ethnicity			0.5 (0.4 a 0.6)	<0.001	—
Mexican American	17 (7.7%)	700 (14.0%)			
Other Hispanic	18 (8.1%)	504 (10.1%)			
Non-Hispanic White	146 (65.8%)	2.111 (42.2%)			
Non-Hispanic Black	26 (11.7%)	1.074 (21.5%)			
Other/multi-racial	15 (6.8%)	616 (12.3%)			
Hypertension			1.0 (0.8 a 1.1)	<0.001	—
Yes	173 (77.9%)	1.735 (34.7%)			
No	48 (21.6%)	3.262 (65.2%)			
Do not know	1 (0.5%)	8 (0.2%)			
High cholesterol			1.0 (0.9 a 1.1)	<0.001	—
Yes	163 (73.4%)	1.552 (31.0%)			
No	56 (25.2%)	2.887 (57.7%)			
Do not know	3 (1.4%)	31 (0.6%)			
Missing	0 (0.0%)	535 (10.7%)			
T2DM			0.5 (0.4 a 0.6)	<0.001	—
Yes	65 (29.3%)	550 (11.0%)			
No	147 (66.2%)	4.333 (86.6%)			
Borderline	10 (4.5%)	117 (2.3%)			
Do not know	0 (0.0%)	5 (0.1%)			
Stroke			0.4 (0.3 a 0.5)	<0.001	—
Yes	29 (13.1%)	138 (2.8%)			
No	192 (86.5%)	4.864 (97.2%)			
Do not know	1 (0.5%)	3 (0.1%)			
Smoked ≥100 cigarettes (lifetime)			0.4 (0.2 a 0.5)	<0.001	—
Yes	136 (61.3%)	2.160 (43.2%)			
No	86 (38.7%)	2.844 (56.8%)			
Do not know	0 (0.0%)	1 (0.0%)			
≥12 alcoholic drinks/year			0.2 (0.0 a 0.3)	0.195	—
Yes	156 (70.3%)	3.278 (65.5%)			
No	54 (24.3%)	1.249 (25.0%)			
Do not know	0 (0.0%)	2 (0.0%)			
Missing	12 (5.4%)	476 (9.5%)			

Physical activity (MET)			0.4 (0.3 a 0.6)	<0.001	—
<4	91 (41.0%)	1.264 (25.3%)			
4-8	70 (31.5%)	1.392 (27.8%)			
≥8	61 (27.5%)	2.349 (46.9%)			
BMI (kg/m²)	28.86 (25.80 a 32.98)	28.00 (24.30 a 32.42)	0.2 (0.0 a 0.3)	0.023	0.007
Urinary theophylline (μmol/L)	1.645 (0.625 a 3.538)	1.88 (0.639 a 3.84)	0.1 (-0.1 a 0.2)	0.532	0.367
Urinary paraxanthine (μmol/L)	16.6 (4.738 a 29.325)	17.5 (5.72 a 37.4)	0.2 (0.0 a 0.3)	0.018	0.098
Urinary theobromine (μmol/L)	13.5 (6.285 a 29.8)	15.3 (6.36 a 34.0)	0.1 (-0.1 a 0.2)	0.367	0.289
Urinary caffeine (μmol/L)	5.465 (1.533 a 12.2)	4.23 (1.01 a 10.8)	0.1 (-0.0 a 0.2)	0.086	0.045

CHD: coronary heart disease; BMI: body mass index; MET: metabolic equivalent of task; T2DM: type 2 diabetes mellitus.

Table 2 – Association between urinary caffeine levels (μmol/L) and CHD

Variable	Model 1, OR (95% CI), p-value	Model 2, OR (95% CI), p-value	Model 3, OR (95% CI), p-value
Caffeine (μmol/L)	1.01 (1.00-1.02). 0.0859	1.00 (0.99-1.01). 0.9476	0.99 (0.98-1.01). 0.3973
Caffeine quartiles			
Q1 (Reference)	—	—	—
Q2	1.37 (0.91-2.06). 0.1257	1.20 (0.78-1.85). 0.3998	1.13 (0.73-1.77). 0.5799
Q3	1.42 (0.95-2.13). 0.0874	1.18 (0.77-1.81). 0.4479	1.01 (0.65-1.59). 0.9487
Q4	1.54 (1.04-2.30). 0.0318	1.10 (0.72-1.68). 0.6571	0.94 (0.61-1.47). 0.8006
Sex			
Male	1.00 (1.00-1.00). 0.009	1.00 (1.00-1.00). 0.545	1.00 (1.00-1.00). 0.804
Female	1.00 (1.00-1.00). 0.721	1.00 (1.00-1.00). 0.282	1.00 (1.00-1.00). 0.155
Race/ethnicity			
Mexican American	1.03 (1.01-1.05). 0.0081	1.03 (1.00-1.05). 0.0700	1.02 (0.98-1.06). 0.2327
Other Hispanic	1.03 (0.99-1.07). 0.1409	1.02 (0.97-1.06). 0.4538	1.00 (0.95-1.05). 0.9737
Non-Hispanic White	0.99 (0.98-1.01). 0.3734	0.99 (0.97-1.01). 0.2670	0.98 (0.97-1.00). 0.0826
Non-Hispanic Black	1.00 (0.95-1.05). 0.9936	0.99 (0.94-1.04). 0.6900	0.99 (0.93-1.04). 0.6351

the range within which the true difference is likely to fall. A p-value < 0.05 indicates a statistically significant difference.

The results showed that theophylline in the non-adjusted model had a difference of -0.4 (-0.9 to 0.1; p = 0.0923), which did not reach statistical significance. In Adjust I, the difference was -0.8 (-1.5 to -0.1; p = 0.0196), which was significant. In Adjust II, the difference was -0.7 (-1.5 to -0.0; p = 0.0412), also significant. After adjustment, the concentration of theophylline in the CHD group was significantly lower than

in the control group. For paraxanthine, the non-adjusted model showed a difference of -4.8 (-8.0 to -1.7; p = 0.0028), which was significant. In Adjust I, the difference was -5.1 (-8.4 to -1.8; p = 0.0023), also significant. In Adjust II, the difference was -4.1 (-7.3 to -0.8; p = 0.0135), remaining significant. Paraxanthine levels were consistently lower in all models compared to the control group.

Theobromine in the non-adjusted model showed a difference of -2.5 (-8.2 to 3.2; p = 0.3925), which was not

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significant. In Adjust I, the difference was -0.1 (-5.9 to 5.7; $p = 0.9689$), not significant. In Adjust II, the difference remained -0.1 (-5.9 to 5.7; $p = 0.9770$), also not significant. There was no significant difference in the concentration of theobromine between the CHD group and the control group. Caffeine in the non-adjusted model showed a difference of 1.2 (-0.4 to 2.8; $p = 0.1327$), not significant. In Adjust I, the difference was -0.9 (-2.5 to 0.8; $p = 0.2966$), not significant. In Adjust II, the difference was -0.5 (-2.1 to 1.1; $p = 0.5534$), also not significant. After adjustment, there was no significant difference in caffeine concentration between the two groups.

Therefore, we can conclude that the concentrations of theophylline and paraxanthine in the CHD group were significantly lower than those in the control group, especially after adjustment, which still showed statistical significance. This suggests that these compounds may be associated with CHD. There was no significant difference in the concentrations of theobromine and caffeine between the two groups, indicating that these compounds may not be directly related to CHD.

The impact of the different adjustment models on the results was limited, but the adjusted results are more reliable.

Subgroup analysis

Table 5 presents the stratified analysis results of theophylline, paraxanthine, theobromine, and caffeine in different subgroups, including effect values, 95% CIs, and p -values. Through stratified analysis, differences in compound concentrations and their significance can be observed among different characteristic groups.

The subgroup variables analyzed included sex, age, race, presence of high blood pressure, high cholesterol levels, T2DM, BMI tertiles, history of stroke, smoking status, alcohol consumption in the past year, and MET score. The MET score was used to assess functional capacity: a score <4 reflects severe functional limitation and is strongly associated with increased cardiovascular risk; a score 4-6 indicates moderate limitation, often presenting as dyspnea or fatigue during moderate physical activity (e.g., walking short distances or

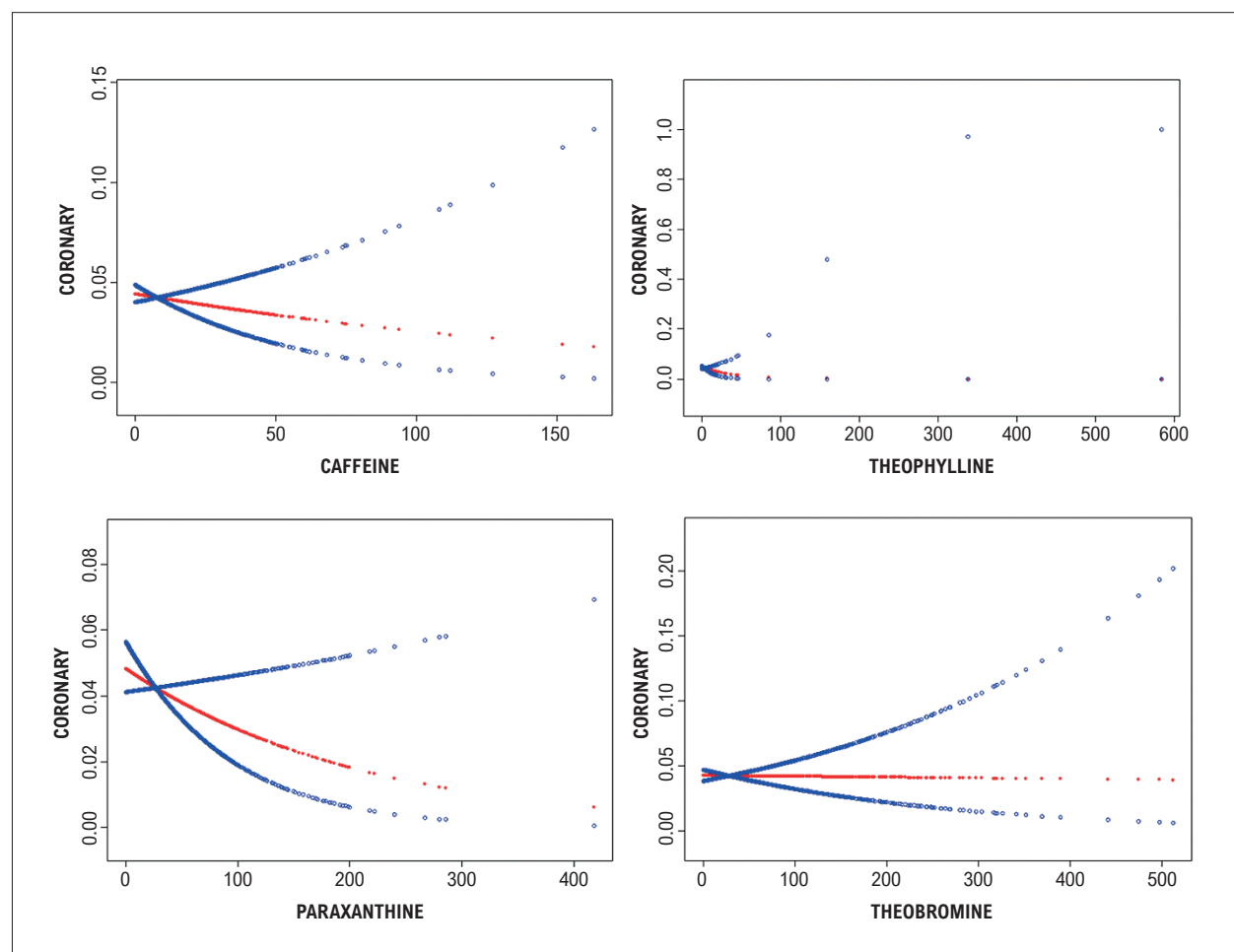


Figure 2 – Smoothed curve plots displaying the relationship between urinary levels of caffeine and its metabolites ($\mu\text{mol/L}$) and the incidence of CHD. The red line represents the fitted curve showing the estimated association, while the blue shaded area denotes the 95% CI. Models were adjusted for sex, age, race/ethnicity, hypertension, hypercholesterolemia, T2DM, stroke, smoking, alcohol consumption, and BMI. BMI: body mass index; CHD: coronary heart disease; T2DM: type 2 diabetes mellitus.

Table 3 – Association between urinary caffeine metabolite levels (μmol/L) and CHD

Variable	Model 1 OR (95% CI), p-value	Model 2 OR (95% CI), p-value	Model 3 OR (95% CI), p-value
Theophylline (μmol/L)	0.98 (0.93 to 1.02), 0.3320	0.98 (0.94 to 1.02), 0.3084	0.97 (0.93 to 1.02), 0.2592
Theophylline quartiles			
Q1 (Reference)	—	—	—
Q2	1.10 (0.76 to 1.59), 0.6243	1.00 (0.67 to 1.49), 0.9914	0.94 (0.62 to 1.42), 0.7712
Q3	0.94 (0.64 to 1.38), 0.7660	0.89 (0.59 to 1.34), 0.5788	0.83 (0.54 to 1.27), 0.3800
Q4	0.92 (0.63 to 1.36), 0.6883	0.90 (0.59 to 1.36), 0.6020	0.85 (0.55 to 1.31), 0.4527
Theobromine (μmol/L)	1.00 (0.99 to 1.00), 0.3674	1.00 (1.00 to 1.00), 0.6186	1.00 (1.00 to 1.00), 0.9285
Theobromine quartiles			
Q1 (Reference)	—	—	—
Q2	1.12 (0.77 to 1.62), 0.5605	1.19 (0.80 to 1.76), 0.3965	1.09 (0.73 to 1.64), 0.6724
Q3	1.09 (0.75 to 1.58), 0.6515	1.14 (0.76 to 1.70), 0.5217	1.10 (0.73 to 1.68), 0.6430
Q4	0.76 (0.51 to 1.14), 0.1816	0.84 (0.54 to 1.30), 0.4293	0.89 (0.57 to 1.40), 0.6291
Paraxanthine (μmol/L)	0.99 (0.99 to 1.00), 0.0177	1.00 (0.99 to 1.00), 0.1037	0.99 (0.99 to 1.00), 0.1154
Paraxanthine quartiles			
Q1 (Reference)	—	—	—
Q2	0.90 (0.62 to 1.31), 0.5866	0.76 (0.51 to 1.13), 0.1789	0.74 (0.49 to 1.11), 0.1461
Q3	1.01 (0.71 to 1.45), 0.9409	0.99 (0.67 to 1.45), 0.9396	0.97 (0.65 to 1.45), 0.8707
Q4	0.65 (0.43 to 0.97), 0.0360	0.68 (0.44 to 1.04), 0.0779	0.65 (0.42 to 1.03), 0.0655

CHD: coronary heart disease.

performing light work); a score >8 typically reflects low cardiovascular risk. Sample size (N) refers to the number of individuals in each subgroup. For each subgroup, the difference in concentration of four chemical compounds between individuals with CHD and the control group is shown, along with the 95% CI and the corresponding p-value to indicate statistical significance.

Stratified analysis revealed that in most subgroups the difference in theophylline concentration between individuals with CHD and controls was not statistically significant ($p > 0.05$). For instance, among individuals without hypertension, the observed difference was -1.3 (95% CI -4.8 to 2.2), with a p-value of 0.4758, indicating no significant association. Overall, theophylline levels did not differ meaningfully across subgroups. In contrast, paraxanthine showed a significant and relatively consistent difference across several subgroups. Among females, the difference was -7.4 ($p = 0.0379$), and among males, -4.8 ($p = 0.0538$). A pronounced difference was also observed in Non-Hispanic White individuals (-7.3, $p = 0.0034$), while no significant changes were detected in other racial groups. Among individuals with hypertension, the difference reached -9.7 ($p = 0.0299$), and in the high BMI group, it was -6.5 ($p = 0.0457$). Participants without a history of smoking showed a difference of -7.0 ($p = 0.0265$).

For participants with MET scores <4, the difference in paraxanthine concentration was -6.7 ($p = 0.0362$). This indicates that paraxanthine levels were significantly lower in most subgroups compared to the control group, with more notable differences observed among women, Non-Hispanic Whites, and individuals with specific health conditions such as hypertension, absence of smoking history, elevated BMI, and reduced functional capacity (low MET scores). In contrast, theobromine concentrations did not show statistically significant differences in any subgroup ($p > 0.05$), suggesting only a weak or inconsistent relationship with CHD. Caffeine, however, showed significant variation in a few subgroups: among males, the difference was 2.2 ($p = 0.0081$), while no significant difference was seen in females ($p = 0.7220$); among Mexican Americans, the difference reached 9.0 ($p = 0.0006$), with no significant findings in other racial categories. Additionally, individuals without T2DM showed a difference of 2.1 ($p = 0.0165$). These findings suggest that elevated caffeine concentrations may be more relevant in men, Mexican Americans, and those without T2DM, although this pattern was not consistent across all subgroups.

Discussion

This 6-year, large-scale cross-sectional study provided insights summarized in Central Illustration, which highlights

Table 4 – Comparison of urinary caffeine and caffeine metabolite levels (μmol/L) between the CHD group and the control group

Metabolite	Group	Model 1, OR (95% CI), p-value	Model 2, OR (95% CI), p-value	Model 3, OR (95% CI), p-value
Theophylline	Control (n = 5,005)	Reference	Reference	Reference
	CHD (n = 222)	-0.4 (-0.9 to 0.1), 0.0923	-0.8 (-1.5 to -0.1), 0.0196	-0.7 (-1.5 to -0.0), 0.0412
Paraxanthine	Control (n = 5,005)	Reference	Reference	Reference
	CHD (n = 222)	-4.8 (-8.0 to -1.7), 0.0028	-5.1 (-8.4 to -1.8), 0.0023	-4.1 (-7.3 to -0.8), 0.0135
Theobromine	Control (n = 5,005)	Reference	Reference	Reference
	CHD (n = 222)	-2.5 (-8.2 to 3.2), 0.3925	-0.1 (-5.9 to 5.7), 0.9689	-0.1 (-5.9 to 5.7), 0.9770
Caffeine	Control (n = 5,005)	Reference	Reference	Reference
	CHD (n = 222)	1.2 (-0.4 to 2.8), 0.1327	-0.9 (-2.5 to 0.8), 0.2966	-0.5 (-2.1 to 1.1), 0.5534

CHD: coronary heart disease.

the key findings of the analysis. It illustrates significant baseline differences between individuals in the CHD group and those in the control group. Specifically, individuals with CHD were generally older and exhibited a higher prevalence of hypertension, hypercholesterolemia, T2DM, stroke, smoking, and alcohol consumption.

Analysis of urinary caffeine levels revealed a positive association with CHD incidence, particularly among the Mexican American population, where the association was more pronounced (OR 1.03; 95% CI 1.03-1.05; $p = 0.0081$). For each 1 μmol/L increase in urinary caffeine concentration, the risk of CHD increased by 3%, with statistical significance ($p < 0.01$). In contrast, no significant associations were identified between CHD and urinary levels of caffeine metabolites such as theobromine and theophylline. Both theophylline and hypoxanthine concentrations were significantly lower in the CHD group compared to controls.

Subgroup analyses revealed significant differences in hypoxanthine concentrations across various subgroups defined by sex, age, race, hypertension status, and smoking status — particularly among women, individuals with hypertension, and smokers. However, no significant subgroup differences were observed for theobromine or caffeine concentrations. These findings suggest that the relationship between urinary caffeine and CHD may be modulated by race and other physiological factors, and that hypoxanthine, a caffeine metabolite, may be linked to cardiovascular health. This study offers valuable insights for both clinical and basic research, supporting the identification and prevention of risk factors for CHD.

Previous studies have reported a positive association between coffee consumption and the risk of CHD (OR 1.35; 95% CI 1.05-1.73; $p = 0.017$) as well as an increased likelihood of developing hypertension.^{9,15} Moderate to excessive coffee intake has been linked to heightened inflammatory activity, which plays a key role in the pathogenesis of CHD.¹⁶ Excessive consumption of coffee, tea, and caffeine has also been associated with increased all-cause and cardiovascular mortality among individuals with existing cardiovascular conditions.¹⁷ Additionally, unfiltered coffee

may elevate serum triglyceride, cholesterol, and low-density lipoprotein (LDL) levels.^{18,19}

On the other hand, some studies suggest that coffee consumption is safe and does not increase mortality risk. The effects of various coffee preparation methods on cardiovascular outcomes and survival appear to differ. For example, decaffeinated coffee, ground coffee, and instant coffee have been associated with a significant reduction in cardiovascular disease incidence and mortality.²⁰ Ground and instant coffee without decaffeination have also been linked to a lower risk of cardiac arrhythmias. These findings suggest that the source and method of caffeine intake may influence research outcomes.²¹

In conclusion, our study used urinary levels of caffeine and its metabolites as objective indicators of actual coffee intake and found a positive association between urinary caffeine levels and the incidence of CHD (OR 1.54; 95% CI 1.04-2.3; $p = 0.0318$), supporting the validity of this approach. Moreover, we observed a negative association between urinary paraxanthine levels and CHD incidence. Individuals who consumed low (1-2 cups/day) or high (>2 cups/day) amounts of coffee had a reduced risk of death compared to non-coffee drinkers, with the greatest benefit observed among heavy coffee consumers.

Several mechanisms may help explain these findings. First, coffee is a complex beverage containing more than 100 bioactive compounds, with caffeine being the most prominent.^{22,23} Caffeine acutely stimulates the sympathetic nervous system by inhibiting phosphodiesterase, increasing intracellular calcium levels, and promoting the release of norepinephrine and adrenaline. These effects may enhance cardiovascular reserve and sustain coronary blood flow, potentially reducing the risk of CHD. Second, caffeine's antagonism of adenosine receptors may impair the expected increase in myocardial perfusion during physical activity.²⁴ Third, caffeine intake may help to regulate cardiovascular risk factors, particularly among non-smokers. Furthermore, coffee consumption has been linked to a potential protective effect against coronary artery calcification.²⁵ Fourth, the antioxidant properties of caffeine may

Table 5 – Subgroup analysis

Subgroup	N	Theophylline	Paraxanthine	Theobromine	Caffeine
Sex					
Male	2,543	-0.4 (-2.7 to 1.8) 0.7161	-4.8 (-9.8 to 0.1) 0.0538	0.4 (-6.0 to 6.8) 0.9105	2.2 (0.6 to 3.8) 0.0081
Female	2,684	-0.7 (-1.7 to 0.4) 0.2290	-7.4 (-14.5 to -0.4) 0.0379	-6.7 (-16.5 to 3.1) 0.1791	-0.5 (-3.1 to 2.1) 0.7220
Age group (years)					
18-39	1,685	-0.9 (-3.6 to 1.9) 0.5380	-11.0 (-37.5 to 15.4) 0.4137	-17.7 (-53.9 to 18.5) 0.3381	-3.9 (-11.3 to 3.6) 0.3106
40-57	1,740	-0.6 (-1.7 to 0.5) 0.2582	-2.0 (-13.3 to 9.3) 0.7259	-8.8 (-23.3 to 5.8) 0.2373	0.9 (-2.6 to 4.4) 0.6177
58-80	1,802	-0.8 (-3.3 to 1.7) 0.5434	-3.6 (-7.7 to 0.5) 0.0882	2.0 (-3.8 to 7.8) 0.5072	0.3 (-1.5 to 2.1) 0.7589
Race					
Mexican American	717	1.7 (-0.0 to 3.4) 0.0531	3.1 (-12.4 to 18.5) 0.6971	3.7 (-12.0 to 19.4) 0.6447	9.0 (3.9 to 14.1) 0.0006
Other Hispanic	522	0.0 (-1.4 to 1.5) 0.9699	1.2 (-12.3 to 14.8) 0.8565	-5.4 (-22.1 to 11.3) 0.5295	3.3 (-1.0 to 7.6) 0.1348
Non-Hispanic White	2,257	-1.1 (-3.6 to 1.4) 0.3858	-7.3 (-12.2 to -2.4) 0.0034	-4.9 (-12.3 to 2.5) 0.1936	-0.9 (-2.8 to 1.1) 0.3745
Non-Hispanic Black	1,100	-0.7 (-1.6 to 0.2) 0.1460	-7.7 (-18.3 to 2.9) 0.1538	-7.7 (-22.1 to 6.7) 0.2933	-0.0 (-3.1 to 3.0) 0.9936
Other / Multiracial	631	-0.3 (-1.9 to 1.2) 0.6714	-2.6 (-19.8 to 14.6) 0.7695	-7.0 (-27.6 to 13.6) 0.5071	1.7 (-2.8 to 6.1) 0.4658
Hypertension					
Yes	1,908	0.1 (-0.5 to 0.7) 0.8032	-1.4 (-5.6 to 2.9) 0.5379	1.5 (-4.2 to 7.2) 0.6026	1.5 (-0.2 to 3.3) 0.0869
No	3,310	-1.3 (-4.8 to 2.2) 0.4758	-9.7 (-18.5 to -1.0) 0.0299	-7.2 (-19.2 to 4.7) 0.2365	-1.5 (-4.3 to 1.3) 0.2977
Do not know	9	—	—	—	—
High Cholesterol Level					
Yes	1,715	-0.2 (-0.7 to 0.3) 0.4859	-3.7 (-8.3 to 1.0) 0.1196	-1.6 (-8.3 to 5.0) 0.6333	1.0 (-0.8 to 2.8) 0.2794
No	2,943	-0.7 (-3.8 to 2.4) 0.6428	-7.0 (-15.1 to 1.1) 0.0924	-3.6 (-14.0 to 6.7) 0.4927	-0.4 (-3.1 to 2.4) 0.7814
Do not know	34	-0.5 (-4.8 to 3.9) 0.8378	-13.2 (-57.1 to 30.7) 0.5605	-14.6 (-68.1 to 38.9) 0.5969	0.0 (-12.4 to 12.4) 0.9987
Missing	535	—	—	—	—
T2DM					
Yes	615	-0.4 (-1.2 to 0.4) 0.3501	-6.8 (-13.6 to 0.0) 0.0513	0.1 (-8.5 to 8.7) 0.9758	-1.0 (-3.6 to 1.7) 0.4773
No	4,480	-0.2 (-1.8 to 1.4) 0.7934	-2.6 (-7.6 to 2.3) 0.2998	-0.9 (-7.5 to 5.7) 0.7801	2.1 (0.4 to 3.8) 0.0165
Borderline	127	-3.2 (-22.6 to 16.3) 0.7500	-8.0 (-28.2 to 12.3) 0.4417	-11.2 (-50.9 to 28.6) 0.5830	-0.6 (-9.3 to 8.0) 0.8841
Do not know	5	—	—	—	—

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BMI

Low (13.4 ≤ BMI ≤ 25.69)	1,724	-1.0 (-5.1 to 3.0) 0.6270	-5.9 (-14.0 to 2.2) 0.1543	-2.6 (-13.4 to 8.2) 0.6394	-0.6 (-3.2 to 2.1) 0.6778
Middle (25.7 ≤ BMI ≤ 30.59)	1,750	-0.2 (-2.1 to 1.7) 0.8438	-2.9 (-9.6 to 3.8) 0.3952	-0.5 (-9.6 to 8.5) 0.9080	1.9 (-0.6 to 4.3) 0.1384
High (30.7 ≤ BMI ≤ 82.1)	1,753	-0.3 (-1.0 to 0.4) 0.4031	-6.5 (-12.8 to -0.1) 0.0457	-4.9 (-13.6 to 3.7) 0.2616	1.5 (-0.7 to 3.7) 0.1743

Stroke

Yes	167	-1.0 (-3.8 to 1.7) 0.4676	-4.6 (-13.8 to 4.6) 0.3249	-6.3 (-17.6 to 5.0) 0.2746	-1.1 (-5.5 to 3.3) 0.6228
No	5,056	-0.3 (-1.8 to 1.1) 0.6445	-4.1 (-8.4 to 0.3) 0.0663	-1.2 (-7.0 to 4.6) 0.6889	1.3 (-0.2 to 2.8) 0.0862
Do not know	4	—	—	—	—

Smoked at least 100 cigarettes in life

Yes	2,296	-0.1 (-1.6 to 1.4) 0.8906	-4.8 (-10.1 to 0.6) 0.0805	1.0 (-5.4 to 7.5) 0.7546	1.8 (-0.1 to 3.7) 0.0675
No	2,930	-1.1 (-3.5 to 1.3) 0.3891	-7.0 (-13.1 to -0.8) 0.0265	-6.0 (-15.1 to 3.1) 0.1957	-0.3 (-2.4 to 1.8) 0.7948
Do not know	1	—	—	—	—

At least 12 alcoholic drinks in the past year

Yes	3,434	-0.4 (-2.2 to 1.3) 0.6268	-4.7 (-9.7 to 0.3) 0.0677	-1.4 (-7.9 to 5.0) 0.6600	0.9 (-0.9 to 2.7) 0.3292
No	1,303	-0.5 (-3.2 to 2.1) 0.6935	-5.5 (-12.8 to 1.8) 0.1398	-4.9 (-15.9 to 6.1) 0.3797	1.8 (-0.4 to 4.0) 0.1138
Do not know	2	—	—	—	—
Missing	488	-0.5 (-2.0 to 1.0) 0.5035	-7.1 (-22.3 to 8.1) 0.3581	-5.8 (-29.3 to 17.7) 0.6281	1.7 (-3.3 to 6.6) 0.5120

MET

<4	1,355	-0.6 (-2.8 to 1.7) 0.6099	-6.7 (-12.9 to -0.4) 0.0362	-4.8 (-12.8 to 3.2) 0.2381	1.6 (-0.8 to 4.0) 0.1847
4-8	1,462	-0.5 (-1.5 to 0.4) 0.2511	-3.6 (-10.3 to 3.0) 0.2818	2.0 (-6.4 to 10.5) 0.6361	-0.1 (-2.4 to 2.2) 0.9365
≥8	2,410	-0.0 (-3.1 to 3.1) 0.9958	-1.3 (-9.3 to 6.6) 0.7388	-0.7 (-11.9 to 10.5) 0.8991	1.8 (-0.8 to 4.4) 0.1730

BMI: body mass index; MET: metabolic equivalent of task.

protect endothelial cells from damage, thereby reducing the risk of CHD. Finally, phenolic compounds in coffee — especially hydroxycinnamic acids — may exert cardiovascular benefits through anti-inflammatory and antioxidant effects. In contrast, short-term consumption of unfiltered coffee may raise serum levels of triglycerides, cholesterol, and LDL.¹⁸

In this large-scale cross-sectional study, we identified a negative association between urinary caffeine levels and the incidence of CHD among Mexican Americans, a pattern not observed in other ethnic groups. This disparity may reflect differences in CHD prevalence across racial groups.²⁶ Additionally, genetic variability may influence individual

responses to caffeine. For instance, a study by Happonen et al.²⁷ suggested that specific genetic polymorphisms — such as variants in the *COMT* gene — may modulate caffeine's effects on cardiovascular outcomes. Prior research²⁸ also indicates that elevated plasma caffeine levels in men are linked to reduced stress-induced myocardial blood flow and flow reserve, whereas similar hemodynamic changes were not observed in women. However, our findings did not reveal any sex-related differences. These observations highlight the need for further high-quality, large-scale randomized controlled trials that incorporate genetic data to better understand how gene polymorphisms may influence the relationship between caffeine and cardiovascular health.

Regression analysis showed that the concentrations of theophylline and hypoxanthine were significantly lower in the CHD group compared to the control group. This difference remained statistically significant after adjustment, suggesting a potential association between these compounds and CHD. No significant differences were observed in the concentrations of theobromine and caffeine between groups, indicating that these compounds may not be directly related to CHD.

Theophylline is a secondary metabolite of caffeine, and its reduced levels may reflect impaired metabolic function. For example, individuals with CHD may experience decreased liver function or overall metabolic capacity, resulting in lower theophylline production. Additionally, systemic inflammation or oxidative stress — common in cardiovascular conditions — may disrupt the metabolic pathways of theophylline. The increase in theophylline levels after adjustment suggests that confounders such as age, sex, and BMI may have masked a true association in unadjusted models. The marked reduction in theophylline concentration highlights its potential diagnostic value. Future studies could incorporate genomic data, such as *CYP1A2* gene variants, to assess whether changes in theophylline levels can predict CHD risk or serve as markers for therapeutic monitoring.

Across all models, xanthine levels were consistently and significantly lower in the CHD group (difference range: -4.1 to -5.1, $p < 0.05$), both before and after adjustment, indicating a strong and potentially independent link to CHD with limited influence from confounders. This finding supports its potential use as a standalone metabolic marker for CHD. Theobromine and caffeine concentrations did not differ significantly between groups, suggesting they may not be directly involved in cardiovascular metabolic processes or that their effects may be obscured by diet and lifestyle factors.

In future research, paraxanthine could be included in early screening biomarker panels for CHD. Personalized diagnostic approaches may be developed by integrating genomic data and creating targeted prevention and management strategies that account for sex, race, and metabolic profiles, based on the regulatory roles of theophylline and hypoxanthine.

Subgroup analysis revealed that paraxanthine was the only compound significantly reduced across most groups, particularly among women, individuals with hypertension, those with high BMI, and those with low MET scores. These findings suggest that paraxanthine may serve as a key potential biomarker for CHD. As the primary metabolite of caffeine, paraxanthine is known to exert anti-inflammatory effects and regulate lipid metabolism. Its marked decrease in individuals with CHD may reflect elevated inflammatory markers or impaired metabolic pathways commonly associated with cardiovascular conditions.

In hypertensive individuals and those with elevated BMI, higher levels of metabolic stress may contribute to reduced paraxanthine levels, likely linked to lipid metabolism disturbances, impaired liver function, and systemic inflammation. The significant reduction of paraxanthine in women, hypertensive patients, and those with severe functional limitations may indicate gender-specific metabolic responses and the compounding effect of hypertension on

the metabolic profile of CHD. The statistical significance observed among Non-Hispanic Whites may reflect interethnic differences in metabolic enzyme activity, lifestyle patterns, and disease susceptibility.

Future research will focus on large-scale cohort studies to further validate xanthine as a reliable biomarker for CHD. No statistically significant differences were observed in the concentrations of theophylline and theobromine, indicating a weaker association with CHD. Theophylline, an intermediate metabolite of caffeine, is heavily influenced by genetic and hepatic enzyme activity (notably polymorphisms in the *CYP1A2* gene). Since these metabolic pathways are not directly involved in cardiovascular pathophysiology, changes in their concentrations may not be sensitive indicators of CHD. Additionally, theophylline's longer half-life may dampen the effects of transient metabolic fluctuations.

Theobromine, a cocoa-derived alkaloid and secondary caffeine metabolite, has low metabolic efficiency and relatively stable levels in the body, making it less likely to reflect cardiovascular metabolic shifts. Caffeine concentration differences were only significant in select subgroups, with no consistent trend overall, suggesting a weak or indirect association with CHD or confounding from external factors. The elevated caffeine levels in males may be explained by higher intake (e.g., greater coffee consumption) and faster metabolic rates, while in females, estrogen may modulate caffeine metabolism, reducing observed differences.

The significantly higher levels in Mexican Americans may be attributed to population-specific polymorphisms in caffeine-metabolizing genes, as well as cultural and dietary habits. Additionally, elevated caffeine levels in non-diabetic individuals suggest that T2DM may impair caffeine clearance through disrupted metabolism. Taken together, the observed reduction in xanthine levels may represent a valuable metabolic marker for CHD, supporting its use in early screening and clinical intervention. Identifying subgroup-specific patterns may also facilitate the development of personalized strategies for prevention and disease management.

Our study offers several strengths. First, it utilizes data from NHANES to perform a large-sample analysis, effectively minimizing bias associated with small sample sizes. Second, data were stratified by sex, age, and race, and multivariable confounders such as hypertension and BMI were considered in the regression analysis. This approach enabled a more precise investigation into the relationship between urinary caffeine and its metabolites and the incidence of CHD. Third, rather than relying on self-reported caffeine intake through questionnaires, we used urinary concentrations of caffeine and its metabolites as exposure variables, thereby avoiding recall bias, misclassification, and variability in food sources. Fourth, by constructing multiple models and incorporating a range of covariates, we were able to generate more robust and reliable findings regarding the association between caffeine, its metabolites, and CHD.

Nonetheless, this study has certain limitations. First, being a cross-sectional study, it cannot establish a causal relationship between caffeine metabolites and CHD. Second, the participants were primarily from the United States, which may

limit the generalizability of the findings to other populations. Third, due to the NHANES stratification strategy and the relatively low prevalence of CHD, the number of cases in the CHD group was limited, potentially introducing bias into the results. Therefore, future longitudinal studies and multi-regional, multi-center investigations are needed to confirm these findings and further elucidate the relationship between caffeine, its metabolites, and CHD.

Conclusion

This study found an inverse association between urinary paraxanthine levels and the risk of CHD. In contrast, urinary caffeine levels were positively associated with CHD among Mexican Americans, while no significant association was observed in other ethnic groups. Overall, higher urinary caffeine concentrations were associated with increased CHD incidence, although this trend was not evident in sex-stratified analyses. These findings may contribute to clinical prediction and diagnosis; however, further large-scale prospective studies are needed to confirm these results.

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Author Contributions

Conception and design of the research: Li Q, Ke G, Liu M; Acquisition of data: Li Q, Ke G; Analysis and interpretation

of the data and Statistical analysis: Li Q; Obtaining financing and Critical revision of the manuscript for content: Chen Y; Writing of the manuscript: Li Q, Liu M.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Data Availability

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

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