HHS Public Access

Author manuscript

J Asthma. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:

J Asthma. 2022 November ; 59(11): 2127–2134. doi:10.1080/02770903.2021.1993250.

Urinary caffeine and caffeine metabolites, asthma, and lung function in a nationwide study of U.S. adults

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Abstract

Objective: Coffee intake has been inversely associated with asthma in adults. We examined the relation between urinary levels of caffeine or caffeine metabolites and asthma, lung function, and fractional exhaled nitric oxide (FeNO) in adults.

Methods: Cross-sectional study of 2,832 adults aged 18-79 years in the US National Health and Nutrition Examination Survey (NHANES). Multivariable logistic or linear regression was used for the analysis of urinary levels of caffeine or each of its three major metabolites (paraxanthine, theobromine, and theophylline) and current asthma, lung function, and FeNO.

Results: Subjects with urinary paraxanthine levels in the fourth quartile (Q4) had 53% lower odds of current asthma than those whose urinary paraxanthine levels were in the first quartile (Q1; 95% confidence = 0.22 to 1.00). Among never and former smokers, subjects with urinary theophylline levels above Q1 had 49% lower odds of current asthma than those whose urinary theophylline level was in Q1 (95% CI = 0.31 to 0.85). Among subjects without current asthma, each $\log_{10}$-unit increment in paraxanthine level was associated with a 0.83% increment in percent predicted (%pred) FEV_1 and a 1.27% increment in %pred FVC, while each $\log_{10}$-unit in theophylline was associated with a 1.24% increment in %pred FVC. Neither urinary caffeine nor any urinary caffeine metabolite was associated with bronchodilator response or FeNO.

Conclusions: Our findings suggest that two caffeine metabolites (theophylline and paraxanthine) may contribute to the previously reported inverse association between coffee intake and asthma in adults.

Keywords

Caffeine; caffeine metabolites; current asthma; lung function; FeNO; NHANES

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Declaration of interest

Dr. Celedón has received inhaled steroids from Merck in order to provide medications free of cost to participants in an NIH-funded study, unrelated to the current work. The other authors report no conflicts of interest.

Introduction

Caffeine is the most widely consumed psychoactive agent through dietary intake, largely through derivative beverages and foods such as coffee, tea, energy and soft drinks, and cocoa (1). In the United States (U.S.), 90% of adults consume coffee, which in turn contributes to ~64% of their average caffeine intake (2). Although caffeine intake impacts the cardiovascular and respiratory systems (3), moderate daily caffeine intake (up to 400 mg/day or about 4 cups of 8 oz. brewed coffee) has no proven adverse effects in healthy adults (4).

In three cross-sectional studies of adults, coffee consumption was associated with lower odds of asthma in Italy (5) and the U.S. (6) but not in France (7). Further, a single cross-sectional study of U.S. adults showed that coffee intake was positively associated with FEV_1 and FVC in never or former smokers but not in current smokers (8). However, none of those reports measured caffeine or caffeine metabolites in study participants.

Caffeine (1,3,7-trimethylxanthine) can be absorbed within 45 min after ingestion. Caffeine is primarily metabolized by CYP1A2 in the liver, where it undergoes successive demethylations and oxidations (9). The half-life of caffeine in adults is typically 2.5 to 5 h (9). The main products of the first steps in caffeine metabolism through demethylations are paraxanthine (1,7-dimethylxanthine), theobromine (3,7-dimethylxanthine), and theophylline (1,3-dimethylxanthine)(9). Caffeine and these primary metabolites are methylxanthines, a purine derived group of pharmacologic agents with bronchodilator properties (10). Caffeine has been used to treat apnea of prematurity (AOP) in infants (11) and shown to slightly improve lung function up to four hours post-ingestion in adults with mild to moderate asthma (12). While theophylline is a mild bronchodilator that has been used to treat asthma (13,14), there is limited and inconclusive evidence of any bronchodilator effects of theobromine (10). Although paraxanthine is the major caffeine metabolite, little is known about paraxanthine and asthma or lung function (9).

Given a plausible role of caffeine or its metabolites on asthma but very limited evidence from large population-based studies, we examined the relation between urinary levels of caffeine and its primary metabolites (paraxanthine, theobromine, and theophylline) and asthma, lung function, and fractional exhaled nitric oxide (FeNO, a marker of eosinophilic airway inflammation) among adult participants in the U.S. National Health and Nutrition Examination Survey (NHANES).

Methods

Study design and study population

NHANES is a cross-sectional nationwide survey designed to assess the health and nutrition of the civilian non-institutionalized U.S. population, using a stratified multistage probability design to select a representative sample of such population. As part of the study design, ethnic minorities (non-Hispanic blacks, Hispanics, and Asians), low-income persons (at or below 130% of federal poverty level), and adults 80 years and older are oversampled to increase statistical power for data analysis in these groups. The NHANES protocol includes

health interviews, examination components, and laboratory tests administered by highly trained personnel. Urinary caffeine and caffeine metabolites were measured in a one-third subsample of adult participants. The flowchart for selection of participants from the 2009–2010 or 2011–2012 NHANES study cycles into the current analysis is shown in Figure E1 in the Online supplement. Of 11 603 participants aged 18 to 79 years, 2,832 had complete data on urinary caffeine and caffeine metabolites, current asthma, and relevant covariates, and were thus included in the current analysis. NHANES is approved by the Institutional Review Board of the National Center for Health Statistics of the Center for Disease Control and Prevention (CDC). Informed consent is obtained from all study participants. Further details of the methods, protocols, and definitions used in NHANES can be found at http://www.cdc.gov/nchs/nhanes.htm.

Urinary caffeine and caffeine metabolites

Urine samples were processed, stored, and shipped to the Centers for Disease Control (CDC) for analysis. Caffeine and its metabolites (paraxanthine, theobromine, and theophylline) were quantified in urine using of high-performance liquid chromatography-electrospray ionization-tandem quad-rupole mass spectrometry (HPLC-ESI-MS/MS) with stable isotope labeled internal standards. Levels below the lower limit of detection (LLOD) were divided by the square root of 2 (LLOD/sqrt[2]). Measures below the LLOD for caffeine, paraxanthine, theobromine, and theophylline were 142 (5.0%), 42 (1.5%), 14 (0.5%), and 80 (2.8%), respectively. All quality control (QC) procedures recommended by the manufacturers were followed. Because urinary caffeine and caffeine metabolites were measured by different instruments (same type of HPLC-ESI-MS/MS) for NHANES 2009–2010 and 2011–2012, regression equations recommended by NHANES to combine two study cycles of urine caffeine data were adopted. Urinary creatinine was measured by the Roche/Hitachi Modular P Chemistry Analyzer. Urinary caffeine and caffeine metabolites were divided by the urinary creatinine concentration to account for variation in dilution of spot urinary samples (i.e. caffeine to creatinine ratio in μmol/L). A detailed description of the approach used can be accessed at the NHANES Laboratory Method Files (15).

Outcomes

Current physician-diagnosed asthma (heretofore referred to as “current asthma”) was defined by a positive answer to both following questions: “Has a doctor or other health professional ever told you that you have asthma?” and “Do you still have asthma?”. Control subjects were participants without current asthma (i.e. those who reported never having had asthma diagnosed by a healthcare professional and those who reported having ever had asthma diagnosed by a healthcare professional but who denied still having asthma).

Eligible participants performed spirometry following American Thoracic Society and European Respiratory Society recommendations (16). The best forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were selected for analysis. Percent (%) predicted FEV_1, FVC and FEV_1/FVC were calculated using Global Lung Initiative 2012 equations that account for age, sex, race/ethnicity, and height (17). Participants were not eligible for spirometry if they had current chest pain or a physical problem with forceful expiration; were taking supplemental oxygen; had recent surgery of the eye, chest, or the abdomen;

had had a heart attack, stroke, or tuberculosis exposure; or had recently coughed up blood. Adults with a personal history of detached retina or a collapsed lung were also excluded. A total of 2,430 participants with (n = 189) and without (n = 2,241) current asthma were included in the analysis of lung function.

Based on the NHANES protocol, participants whose baseline FEV_1/FVC was below the lower limit of normal (LLN)(18) and/or whose baseline FEV_1 was below 70% of the predicted value for their demographic characteristics underwent a repeat spirometry, 15 min after inhalation of albuterol. Participants were excluded from bronchodilator administration if they had recently used a short-acting inhaled β2-agonist or had a previous adverse reaction to albuterol; had a history of congenital heart disease, hypertension, major arrhythmias, or an implanted defibrillator; or were pregnant or breastfeeding. Bronchodilator response (BDR) was calculated as: ([post-bronchodilator FEV_1 - pre-bronchodilator FEV_1]/ pre-bronchodilator FEV_1) x 100. A total of 155 participants without current asthma and 23 participants with current asthma had BDR testing.

FeNO was measured using the Aerocrine NIOX MINO, a portable, hand-held NO analyzer (Aerocrine AB, Solna, Sweden). The NHANES protocol required two valid FeNO measurements that were reproducible in accordance with testing procedures recommended by the manufacturer and ATS (19). A total of 2,553 participants were included in the analysis of FeNO.

Statistical analysis

Primary sampling units and strata for the complex NHANES survey design were taken into account for data analysis. Sampling weights, stratification, and clusters provided in the NHANES dataset were incorporated into the analysis to obtain proper estimates and their standard errors. Two-sided Wald chi-square tests and t-tests were used for bivariate analyses. The Spearman's rank correlation coefficient (r) was used to examine the correlation between daily total caffeine intake and urinary caffeine and caffeine metabolites. Logistic regression was used for the multivariable analysis of urinary caffeine or each caffeine metabolite (as quartiles, due to skewness of the distribution) and current asthma, which was adjusted for known or potential confounders of the relation between caffeine or caffeine metabolites and current asthma or lung function. All models were adjusted for age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other Hispanic, or other), annual household income (< vs. ≥ $20 000 per year), body mass index (BMI, in kg/m^2), family history of asthma, serum cotinine, pack-years of smoking, and time of the day when the samples were collected (morning, afternoon, or evening). Daily total caffeine intake (mg) was obtained from the 24-h dietary recall interviews. Log10-transformed urinary levels of caffeine or caffeine metabolites were used for the analysis of lung function measures, BDR, and FeNO because of linear trends in bivariate analyses. Linear regression was used for the multivariable analysis of lung function, BDR, and FeNO, which was first conducted in all subjects and then separately in subjects with and without current asthma. Models for percent predicted lung function measures were adjusted for annual household income, BMI, serum cotinine, pack-years of cigarette smoking, use of oral or inhaled steroids in the past 2 days, time of the day when the samples were collected, and (in all subjects) an asthma diagnosis.

Models for BDR and FeNO were additionally adjusted for age, sex, and race and ethnicity (as no percent predicted values are available for these two outcomes).

Multicollinearity was assessed by examining the variance inflation factor and tolerance, which were <5 and >0.1, respectively, in all models. Model fitness was assessed using standard approaches. All statistical analyses were conducted using the SAS SURVEY procedure and SAS 9.4 software (SAS Institute Inc., Cary, NC).

Results

Table 1 shows a comparison of the main characteristics of study participants by current asthma. Compared to those without current asthma (n = 2,611), those with current asthma (n = 221) were more likely to be: female, non-Hispanic Black, and current smokers; to have an annual household income of less than $20 000 and to report a family history of asthma and hay fever episodes in the previous year; to have a higher BMI (or obese) and serum cotinine; to use oral or inhaled steroids in the previous 2 days; and to have lower %predicted lung function measures (FEV_1, FVC and FEV_1/FVC) but higher BDR. Among participants who had BDR testing, 22 (14%) without current asthma and 11 (57%) with current asthma had clinically significant BDR (an increment of ≥12% and ≥200 ml from baseline FEV1 after bronchodilator administration). Moreover, urinary paraxanthine was lower in subjects with current asthma than in those without. Among participants with current asthma, 46% had ≥1 asthma attack and 12% had ≥1 emergency room or urgent care visit for asthma in the previous year.

Figure E2 shows the correlation between daily total caffeine intake (mg) and caffeine and each of the three caffeine metabolites in urine samples from study participants. In this analysis, both paraxanthine and theophylline were moderately correlated with total dietary intake of caffeine (r > 0.50 and P < 0.01 in both instances), while there was a weak correlation between theobromine and caffeine (r = 0.27, P < 0.01).

The results of the multivariable analysis of urinary caffeine or caffeine metabolites and current asthma are shown in Table 2. Participants whose urinary paraxanthine level was in the fourth (highest) quartile had 53% lower odds of current asthma than those whose urinary paraxanthine level was in the first (lowest) quartile (95% confidence interval [CI] for the odds ratio [OR] = 0.22 to 1.00). Urinary levels of caffeine, theobromine, or theophylline were not associated with current asthma.

To reduce potential misclassification of chronic obstructive pulmonary disease (COPD) as asthma and to account for potential effects of smoking on theophylline metabolism (8,20), we repeated the analyses of current asthma after excluding current smokers and former smokers with ≥10 pack-years of smoking from the analysis. These analyses yielded similar results to those including all subjects, except for that of urinary theophylline, which suggested a potential threshold effect above the first quartile. Indeed, we found that never or former smokers whose urinary theophylline was above the first quartile had 49% lower odds of current asthma than those whose level was in the first quartile (95% CI for OR = 0.31 to 0.85). Because alcohol consumption can affect CYP1A2 activity (9), we also repeated the

multivariable analysis of current asthma in all subjects after additional adjustment for daily alcohol consumption (from a 24-h dietary recall), obtaining similar results (Table E1).

Table 3 shows the multivariable analysis of urinary levels of caffeine or its metabolites and lung function. In adults without current asthma, each log10-transformed unit increment in urinary paraxanthine was associated with a 00.83% increment in %predicted FEV_1 and a 1.27% increment in %predicted FVC. Similarly, each log10-transformed unit increment in urinary theophylline was associated with a 1.24% increment in %predicted FVC. In adults with current asthma, each log10-transformed unit increment in urinary theophylline was associated with a 2.40% decrement in %predicted FEV_1/FVC. We repeated this analysis using absolute values of lung function measures, obtaining similar results (Table E2).

Table 4 shows the results of the multivariable analysis of urinary caffeine or its metabolites and BDR. In this analysis, caffeine, paraxanthine, and theophylline were associated with increased BDR in adults with current asthma (**Model 1**). However, these associations became non-statistically significant ($P > 0.05$) after additional adjustment for baseline (pre-bronchodilator) FEV_1 (**Model 2**).

Next, we examined the relation between urinary caffeine or its metabolites and FeNO. In this analysis, neither urinary caffeine nor any caffeine metabolite was associated with FeNO, regardless of an asthma diagnosis (Table E3). Our results for lung function, BDR, and FeNO were essentially unchanged in analyses restricted to never or former smokers with <10 pack-years of cigarette smoking (data not shown).

We conducted a secondary analysis that matched 3 controls to each subject with clinically defined BDR ($n = 33$, including subjects with and without asthma, as shown in Table 1) by age, sex, race and ethnicity, BMI, and serum cotinine level. Although urinary levels of caffeine or caffeine metabolites were not significantly associated with asthma in this analysis, these results have to be cautiously interpreted due to very limited statistical power and potential misclassification of COPD as asthma (Table E4).

Discussion

To our knowledge, this is the first population-based study of urinary caffeine or its metabolites and current asthma, lung function, BDR, or FeNO. In a cohort of U.S. adults, we report that a urinary paraxanthine level in the highest quartile is associated with lower odds of current asthma and that a urinary theophylline level above the lowest quartile is associated with lower odds of current asthma in never or former smokers. Further, we show that urinary levels of both paraxanthine and theophylline are associated with small increments in FEV_1 and FVC in subjects without current asthma, and that urinary theophylline is associated with a small and reduction in FEV_1/FVC in subjects with current asthma. Neither urinary caffeine nor any urinary caffeine metabolite is associated with BDR or FeNO in this cohort.

Our study differs from prior reports in that we analyzed urinary levels of caffeine and caffeine metabolites. Our negative results do not support beneficial effects of caffeine *per se* on asthma or lung function in adults. An inverse association between self-reported estimated intake of coffee or caffeine has been found in some (5,6,21) but not all prior epidemiologic

studies (7), with some reporting a dose-response relationship. More recently, a population-based study of Korean adults with (n = 3,146) and without (n = 158 902) asthma showed that consuming coffee 1–2 times per day was associated with 13% decreased odds of asthma compared with no coffee consumption (21).

Consistent with potential beneficial effects of coffee on lung function, a prior study reported that consumption of at least 4 cups of coffee per day was associated with 2% to 3% increments in %predicted lung function measures (FEV_1 and FVC) in never and former smoking adults without known asthma, COPD, or emphysema (8). Moreover, a meta-analysis of six randomized controlled trials including a total of 55 subjects showed that caffeine led to a small increment in FEV_1 in adults with mild to moderate asthma up to two hours after consumption (but not afterwards) (7).

Caffeine is known to inhibit phosphodiesterase (PDE), modulate intracellular calcium levels, and act as an antagonist at adenosine receptors that can alter cyclic adenosine monophosphate (cAMP) regulation of nitric oxide (NO) synthase and NO production (22). Consistent with our results, two small, randomized crossover studies of nonsmoking adults with well-controlled asthma reported that caffeine intake (200 ml or 16 ounces of caffeinated coffee) was not associated with FeNO (23,24). On the other hand, two small interventional studies have yielded conflicting results for caffeine intake and FeNO, with one such study showing short-lived increased FeNO in 11 children with asthma (25) and another showing that caffeine was associated with reduced FeNO in 11 nonsmoking healthy adults (22).

Theophylline is a PDE inhibitor and mild bronchodilator that has been shown to have anti-inflammatory effects through upregulation of IL-10, inhibition of tumor necrosis factor-α (TNF-α), and reduced migration of eosinophils and $CD4^+$ lymphocytes into the airways (26). Further, cigarette smoking interacts with theophylline by increasing its clearance. Thus, our findings for current asthma in never or former smokers and FEV_1 or FVC in subjects without asthma are consistent with known interactions and effects of theophylline. The weak inverse association between urinary theophylline and FEV1/FVC in adults with asthma, is surprising and could be explained by reverse causation (i.e. if those who had worse asthma consumed more coffee). This association was also seen in participants who reported ≥1 emergency department visit for asthma in the previous year (data not shown), but these results must be cautiously interpreted due to small sample size.

Our findings for paraxanthine are novel and suggest that a high paraxanthine level is linked to lower odds of current or active asthma in adults. Although less studied than theophylline, paraxanthine has been shown to have immunoregulatory effects such as reduced production of interferon (IFN)-γ and IL-5 (27). Of the three major caffeine metabolites, paraxanthine has been shown to be the most potent inhibitor of transforming growth factor (TGF)-β related to fibrotic processes (28). Because TGF- β can mediate pro-inflammatory responses and fibrotic tissue remodeling in asthmatic airways (29), the mechanisms underlying potential effects of paraxanthines on asthma warrant further investigation.

We acknowledge several study limitations. First, we cannot examine temporal relationships in this cross-sectional analysis. Second, due to the relatively short half-lives of caffeine

metabolites (< 8 h) (30), spot urinary samples do not account for daily and seasonal variability or long-term intake of caffeine. Thus, we cannot examine long-term effects of caffeine or its metabolites. Repeated measures of caffeine consumption and urinary caffeine and its metabolites would be helpful to understand caffeine metabolism and its health or functional consequences. Third, we had limited statistical power in analysis restricted to subjects with asthma, particularly for BDR (n = 23). Fourth, we could not account for factors affecting caffeine pharmacokinetics such as liver function, use of medications, and genetic variants. It has been suggested that caffeine intake, metabolism, and functional effects can be influenced by a large variety of exogenous and endogenous factors (9). For example, polymorphisms in the CYP1A2 gene have been shown to downregulate theophylline metabolism in patients with asthma (31). Fifth, misclassification of asthma is possible (32). However, self-reported current asthma has been previously validated and is extensively used in epidemiologic studies. Moreover, we obtained similar results in a sensitivity analysis excluding current smokers and former smokers with ≥10 pack-years of smoking. Lastly, we cannot exclude residual confounding by unmeasured risk factors or behaviors. Although we adjusted the analysis for only one indicator of socioeconomic status (annual household income) because of collinearity with other indicators, we obtained similar results in multivariable models adjusting for health insurance coverage instead of annual income (Data not shown).

Pending confirmation in longitudinal studies, our overall results in a cohort of U.S. adults suggest that prior reports of an inverse association between coffee intake and asthma may be explained by two caffeine metabolites (theophylline and paraxanthine). Moreover, our results suggest weak and non-clinically significant effects of caffeine or any caffeine metabolite on lung function in this cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Dr. Celedón's contribution was supported by grants HL117191, HL152475, and MD011764 from the U.S. National Institutes of Health. Dr. Han's contribution was supported by grant MD011764. Dr. Forno's contribution was supported by HL 149693.

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Table 1.

Characteristics of 2,832 adult participants in NHANES (2009–2012).

Characteristics	Without current asthma (*n* = 2,611)	With current asthma (*n* = 221)	*P*-value
Age (years)	46.0 ± 0.6	43.2 ± 1.7	0.13
Female sex	1331 (50.2)	146 (66.1)	<0.01
Race and ethnicity			<0.01
Non-Hispanic White	1104 (67.8)	106 (70.8)	
Non-Hispanic Black	554 (10.7)	67 (16.4)	
Mexican American/Other Hispanic	674 (13.9)	32 (8.5)	
Other	279 (7.6)	16 (4.3)	
Private health insurance coverage	1372 (63.6)	98 (58.2)	0.12
Annual household income < $20,000	542 (13.8)	71 (25.7)	<0.01
Family history of asthma	463 (17.5)	108 (44.0)	<0.01
Body mass index, kg/m^2	28.8 ± 0.2	30.9 ± 0.6	<0.01
Obesity	993 (36.1)	117 (43.3)	0.05
Hay fever in the previous year	370 (16.8)	63 (29.9)	<0.01
Serum cotinine level, ng/ml *	0.25 ± 0.03	0.59 ± 0.20	0.02
Smoking status			0.01
Never	1516 (54.5)	103 (48.5)	
Former	548 (19.7)	44 (20.6)	
Current	547 (17.9)	74 (30.8)	
Pack-years of cigarette smoking	6.8 ± 0.5	8.4 ± 1.4	0.26
Use of oral or inhaled steroids, past 2 days	41 (1.9)	62 (35.6)	<0.01
% predicted prebronchodilator FEV_1	97.9 ± 0.5	89.5 ± 2.6	<0.01
% predicted prebronchodilator FVC	101.5 ± 0.4	97.6 ± 1.6	0.02
% predicted prebronchodilator FEV_1/FVC	96.2 ± 0.2	90.9 ± 1.8	<0.01
prebronchodilator FEV_1/FVC (%)	78.1 ± 0.2	74.8 ± 1.6	0.03
Fractional exhaled nitric oxide, ppb	16.1 ± 0.5	17.9 ± 1.4	0.13
Bronchodilator response (BDR), % †	6.16 ± 0.69	13.4 ± 2.37	<0.01
BD*R* ≥ 12% and 200 ml	22 (14.4)	11 (56.5)	0.02

Characteristics	Without current asthma (*n* = 2,611)	With current asthma (*n* = 221)	*P*-value
≥1 asthma attack in the previous year	-	113 (46.3)	-
≥1 emergency department visit for asthma in theprevious year	-	37 (12.2)	-
Taken prescribed asthma medications, past 3 months	-	140 (65.0)	-
Urinary creatinine, mg/dL *	95.2 ± 2.9	101.9 ± 5.4	0.60
Daily total caffeine consumption (mg)	184.0 ± 8.7	188.5 ± 20.8	0.82
Urinary caffeine and caffeine metabolites μmol/L) *			
Caffeine (1,3,7-trimethylxanthine)	3.6 ± 0.2	2.7 ± 0.5	0.52
Paraxanthine (1,7-dimethylxanthine)	14.7 ± 0.6	11.1 ± 1.7	0.02
Theobromine (3,7-dimethylxanthine)	16.2 ± 0.6	15.2 ± 1.9	0.86
Theophylline (1,3-dimethylxanthine)	1.7 ± 0.1	1.5 ± 0.2	0.25

Results are shown as mean ± standard error (SE) for continuous variables, and as N (%) for binary variables. P values for comparison between subjects with and without current asthma.

* Results are shown as geometric mean (GM) ± SE for GM.

† 178 participants had BDR measures (*n* = 155 for no asthma and *n* = 23 for current asthma).

Table 2.

Multivariable analysis of urinary caffeine and urinary caffeine metabolites and current asthma.

	All participants (*n* = 2,832)	Never smokers or former smokers with *h*< 10 pack-years of cigarette smoking (*n* = 2,033)
Urinary caffeine and caffeine metabolites	**Odds ratio (95% confidence interval), P-value**	
Caffeine		
Quartile 1	1.0 (Ref)	1.0 (Ref)
Quartile 2	1.11 (0.71 to 1.75), 0.63	0.92 (0.52 to 1.63), 0.77
Quartile 3	0.79 (0.45 to1.37), 0.39	0.67 (0.36 to 1.26), 0.21
Quartile 4	0.76 (0.36 to 1.62), 0.47	0.63 (0.26 to 1.51), 0.29
Paraxanthine		
Quartile 1	1.0 (Ref)	1.0 (Ref)
Quartile 2	0.84 (0.52 to 1.35), 0.45	0.62 (0.32, 1.20), 0.16
Quartile 3	1.02 (0.55 to 1.88), 0.94	0.82 (0.43 to 1.57), 0.54
Quartile 4	**0.47 (0.22 to 1.00), 0.05**	**0.38 (0.18 to 0.83), 0.02**
Theobromine		
Quartile 1	1.0 (Ref)	1.0 (Ref)
Quartile 2	1.16 (0.75 to 1.81), 0.50	1.52 (0.85 to 2.72), 0.15
Quartile 3	0.85 (0.53 to 1.38), 0.50	1.13 (0.60 to 2.12), 0.71
Quartile 4	0.84 (0.41 to 1.71), 0.61	0.71 (0.33 to 1.52), 0.36
Theophylline		
Quartile 1	1.0 (Ref)	1.0 (Ref)
Quartile 2	0.70 (0.46 to 1.07), 0.10	**0.51 (0.31 to 0.85), 0.01**
Quartile 3	0.82 (0.47 to 1.46), 0.49	0.69 (0.39 to 1.22), 0.19
Quartile 4	0.62 (0.34 to 1.11), 0.11	0.55 (0.29 to 1.06), 0.07

The urinary level of caffeine or each of its metabolites was divided by urinary creatinine level. All models adjusted for age, sex, race and ethnicity, annual household income, body mass index, family history of asthma, serum cotinine, pack-years of cigarette smoking (in all participants), and time of the day when the samples were collected.

Table 3.

Multivariable analysis of urinary caffeine or caffeine metabolites and lung function measures by asthma diagnosis.

	All participants (*n* = 2,430)	Without current asthma (*n* = 2,241)	With current asthma (*n* = 189)
Lung function measures		**β (95% confidence interval), P-value**	
Caffeine			
% predicted FEV_1	0.06 (−0.83, 0.96), 0.89	0.22 (−0.58, 1.02), 0.58	−0.55 (−4.19, 3.09), 0.76
% predicted FVC	0.59 (−0.24, 1.41), 0.16	0.61 (−0.23, 1.45), 0.15	0.84 (−2.08, 3.75), 0.56
% predicted FEV_1/FVC	−0.54 (−1.29, 0.21), 0.15	−0.39 (−1.08, 0.31), 0.26	−1.52 (−3.38, 0.34), 0.11
Paraxanthine			
% predicted FEV_1	0.52 (−0.20, 1.43), 0.13	**0.83 (0.02, 1.65), 0.04**	−1.08 (−5.56, 3.40), 0.63
% predicted FVC	**1.21 (0.41, 2.02), <0.01**	**1.27 (0.40, 2.13), <0.01**	0.81 (−2.75, 4.38), 0.65
% predicted FEV_1/FVC	−0.58 (−1.32, 0.16), 0.12	−0.41 (−1.10, 0.28), 0.24	−1.98 (−4.37, 0.42), 0.10
Theobromine			
% predicted FEV_1	0.04 (−1.09, 1.17), 0.94	0.11 (−1.16, 1.38), 0.86	−1.33 (−7.16, 4.50), 0.65
% predicted FVC	0.35 (−0.62 , 1.32), 0.47	0.26 (−0.90, 1.42), 0.65	1.04 (−3.06, 5.14), 0.61
% predicted FEV_1/FVC	−0.32 (−1.01, 0.37), 0.35	−0.16 (−0.75, 0.43), 0.58	−2.50 (−5.78, 0.78), 0.13
Theophylline			
% predicted FEV_1	0.46 (−0.50, 1.43), 0.34	0.70 (−0.20, 1.61), 0.12	−0.30 (−4.06, 3.46), 0.87
% predicted FVC	**1.24 (0.31, 2.18), 0.01**	**1.24 (0.27, 2.21), 0.01**	2.20 (−0.68, 5.10), 0.13
% predicted FEV_1/FVC	−0.77 (−1.64, 0.10), 0.08	−0.53 (−1.37, 0.31), 0.21	**−2.40 (−4.48, −0.33), 0.02**

Urinary levels of caffeine or its metabolites were first divided by the urinary creatinine level and then log10-transformed.

All models adjusted for annual household income, body mass index, serum cotinine, pack-years of cigarette smoking, use of oral or inhaled steroids in the past 2 days, time of the day when the samples were collected, and (in all participants) asthma diagnosis.

Table 4.

Multivariable analysis of urinary caffeine and caffeine metabolites and bronchodilator response.

	Model 1	Model 2
Bronchodilator response (%)	**β, (95% confidence interval), P-value**	
Participants without current asthma (*n* = 155)		
Caffeine	−0.49 (−2.76 to 1.78), 0.66	−1.16 (−3.09, 0.77), 0.23
Paraxanthine	−0.43 (−3.23, 2.37), 0.76	−1.08 (−2.53, 1.38), 0.38
Theobromine	0.12 (−1.82, 2.05), 0.90	−0.60 (−2.66, 1.46), 0.56
Theophylline	−0.78 (−3.63, 2.07), 0.58	−1.70 (−4.11, 0.72), 0.16
Participants with current asthma (*n* = 23)		
Caffeine	**5.16 (1.36, 8.95), <0.01**	2.32 (−0.48, 5.12), 0.10
Paraxanthine	**5.38 (1.28, 9.48), 0.01**	2.71 (−0.08, 5.49), 0.06
Theobromine	3.41 (−0.71, 7.54), 0.10	2.45 (−0.73, 5.64), 0.13
Theophylline	**6.98 (2.28, 11.69), <0.01**	3.32 (−0.18, 6.82), 0.06

Urinary levels of caffeine or its metabolites were first divided by the urinary creatinine level and then log10-transformed.

All models adjusted for age, sex, race and ethnicity, annual household income, body mass index, serum cotinine, pack-years of cigarette smoking, use of oral or inhaled steroids in the past 2 days, and time of the day when the samples were collected. Model 2 was additionally adjusted for pre-bronchodilator FEV_1.