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Levels of caffeine and its metabolites among U.S. smokers and nonsmokers

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ABSTRACT

Data from National Health and Nutrition Examination Survey for the years 2009–2010 were used to estimate the levels of caffeine and 14 of its metabolite among U.S. smokers and nonsmokers after adjustments were made for other factors that affect observed caffeine levels. In this study, when adjusted for daily caffeine intake, adjusted levels (AGM) of caffeine and its metabolites were not found to be statistically significantly different between smokers and nonsmokers. AGMs for caffeine and all of its metabolites were found to be statistically significantly higher ($p < 0.01$) among females aged ≥12 years than males. For caffeine, 1,3-dimethylxanthine, and 1,7-dimethylxanthine, those aged ≥20 years had statistically significantly higher ($p < 0.01$) AGM than those aged 12–19 years but the reverse was true for 7-methylxanthine and 3,7-dimethylxanthine ($p \leq 0.02$). The order of the AGMs by race/ethnicity was non-Hispanic whites > Hispanics > non-Hispanic blacks and most of the differences were statistically significant, at least between non-Hispanic whites and non-Hispanic blacks ($p < 0.01$). In general, there was a statistically significant positive association between the levels of caffeine and its metabolites and body mass index as well as daily caffeine intake. However, the levels of 7-methylxanthine were negatively associated with body mass index.

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1. Introduction

Intake of coffee and tea are the primary sources of caffeine (1,3,7-trimethylxanthine) though certain other beverages like cocoa, chocolate, cola products also contain caffeine. Caffeine has been shown to be associated with both beneficial and harmful health effects. Some of the reviews that have described these effects are by Higdon and Frei (2006), Bhatti et al. (2013) and Cano-Marquina et al. (2013).

Caffeine has been suggested to provide protection against development of type 2 diabetes among U.S. (Salazar-Martinez et al., 2004) as well as European cohorts (Rosengren et al., 2004; Tuomilehto et al., 2004; van Dam and Feskens, 2002). A recently published meta-analysis (Jiang et al., 2014) of several prospective studies reached the same conclusion. A recent review of controlled trials also reached the same conclusion (Whitehead and White, 2013). Other studies delineating the association between type 2 diabetes and caffeine intake/coffee consumption are by Bhupathiraju et al. (2013) and Natella and

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Scaccini (2012). A negative association between the risk of Parkinson disease and coffee consumption at certain doses has been suggested in quite a few studies (Ross et al., 2000; Ascherio et al., 2003, 2004). A negative dose response relationship between coffee consumption and risk of depression has also been observed (Lucas et al., 2011; Omagari et al., 2014; Ruusunen et al., 2010). Possible negative association between the risk of suicide and coffee consumption has also been investigated (Kawachi et al., 1996; Klatsky et al., 1993; Tanskanen et al., 2000; Silva et al., 2014). Other health benefits as listed by Higdon and Frei (2006) associated with coffee consumption/caffeine intake are decreased risk of colorectal cancer (Vitaglione et al., 2012; Michels et al., 2005), hepatic injury, cirrhosis (Gallus et al., 2002), and hepatocellular carcinoma (Johnson et al., 2011).

Contrary to what may be a widespread belief, there is no evidence that caffeine consumption is associated with an increased risk of arrhythmia (Caldeira et al., 2013; Klatsky et al., 2011). Caffeine is associated with increase in blood pressure among non-habitual coffee drinkers (Corti et al., 2002; Curatolo and Robertson, 1983; Freestone and Ramsay, 1982; Sharp and Benowitz, 1990), in particular among those who are hypertensive (Hartley et al., 2000) but not in habitual coffee drinkers (Corti et al., 2002; Sharp and Benowitz, 1990). Caffeine consumption is associated with arterial stiffness and the effect is synergistic with smoking (Vlachopoulos et al., 2004). While non-filtered coffee has been shown to have a hyperlipidemic effect (Jee et al., 2001), no such effect has been seen with the consumption of filtered coffee (Lopez-Garcia et al., 2006). A non-linear association between long-term coffee consumption and cardiovascular risk has been shown (Ding et al., 2014). Compared to no coffee consumption, moderate consumption of coffee has been shown to be associated with lower risk of stroke in prospective studies (Larson and Orsini, 2011).

N3-demethylated paraxanthine (1,7-dimethylxanthine), N1-demethylated theobromine (3,7-dimethhylxanthine), and N7-demethylated theophylline (1,3-dimtheyl xanthine) are the three primary metabolites of caffeine (Miners and Birkett, 1996). CYP1A2 (Miners and Birkett, 1996) is the enzyme which is primarily responsible for metabolizing caffeine into paraxanthine, theobromine, and theophylline though eight other enzymes (Ou-Yang et al., 2000), namely, CYP1A1, CYP2A6, CYP2D6, CYP2E1, CYP3A4, CYP3A5, NAT2, and XO also contribute in metabolizing caffeine. Since, constituents in tobacco smoke induce CYP1A2 activity, smokers may be expected to eliminate caffeine faster than nonsmokers. However, Hukkanen et al. (2011) did not find nicotine exposure to affect elimination pharmacokinetics of paraxanthine, theobromine, and theophylline in a study of 12 healthy smokers exposed to 42 mg nicotine per day for 10 days via transdermal patches. However, it should be noted that these authors did not compare elimination kinetics of caffeine between smokers and nonsmokers. In another study, Joeres et al. (1988) found caffeine clearance among smokers to be 114 ± 40 mL/min and 64 ± 20 mL/min among nonsmokers.

Recently, for the first time, for the 2009–2010 cycle of National Health and Nutrition Examination Survey (NHANES, www.cdc.gov/nchs/nhanes.htm), data on the levels of caffeine and 14 of its metabolites in urine (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/CAFE_F.htm), as described in the next section, have been publically released. This study was undertaken to investigate how smoking affects the observed levels of caffeine and its metabolites in urine when adjustments are made for daily caffeine intake.

2. Materials and methods

Data were downloaded from demographic (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/DEMO_F.htm), caffeine data files (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/CAFE_F.htm), serum cotinine (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/COTNAL_F.htm), and body measures (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/BMX_F.htm) from NHANES for the survey years 2009–2010 and match merged. NHANES uses a complex, stratified, multistage, probability sampling designed as representative of the civilian, non-institutionalized U.S. population based on age, gender, and race/ethnicity (http://www.cdc.gov/nchs/nhanes.htm). Sampling weights are created in NHANES to account for the complex survey design, including oversampling, survey nonresponse, and post-stratification. Nonsmokers were defined as those who had serum cotinine concentrations below 10 ng/mL and smokers were defined as those who had serum cotinine concentrations $\geq$10 ng/mL. This classification has previously been used by Jain (2013). Laboratory methods to measure caffeine and its metabolites are provided elsewhere (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/CAFE_F.htm#Description_of_Laboratory_Methodology). Total dietary caffeine intake was used from the total dietary intake data files for the first day (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/DR1TOT_F.htm). Caffeine intake from the dietary supplements was used from total dietary supplement first day data files (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/DS1TOT_F.htm). For each participant, total caffeine intake was computed as the total intake from diet and dietary supplements. Data for the quantity of nicotine exposure, namely, number of days tobacco products were used during the last five days and number of cigarettes, cigars, and pipes smoked on the days they were smoked were also used (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/SMQRTU_F.htm).

In addition to caffeine, paraxanthine, theobromine, and theophylline, data were also available for 1-methylxanthine, 3-methylxanthie, 7-methylxanthine, 1,3,7-trimethyluric acid, 1,7-dimethyl uric acid, 3,7-dimethyl uric acid, 1-methyluric acid, 3-methylxanthie, 7-methyluric acid, and 5-acetylamino-6-amino-3-methyluracil (AAMU). Percent observations below the limit of detection (LOD) varied from a low of 80.2% for 3-methyluric acid to 100% for 1-methyuric acid. All observations below the limit of detection were imputed as LOD/Sqrt(2). There were a total of 2714 (133 males, 1381 females, 1186 non-Hispanic whites, 500 non-Hispanic blacks, 882 Hispanics, 146 other unclassified race/ethnicities, 1723 nonsmokers, and 473 smokers) participants for whom caffeine data were available. Smoking data was missing for 137 participants. The age distribution was: 318 6–11 years old, 397 12–19 years old, 1936 $\geq$20 years old. However, actual sample size used in regression models were smaller because of missing values for independent

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