Ambulatory blood pressure is associated with urinary caffeine and caffeine metabolites excretions

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A Swiss Kidney Project on Genes in Hypertension (SKIPOGH) study

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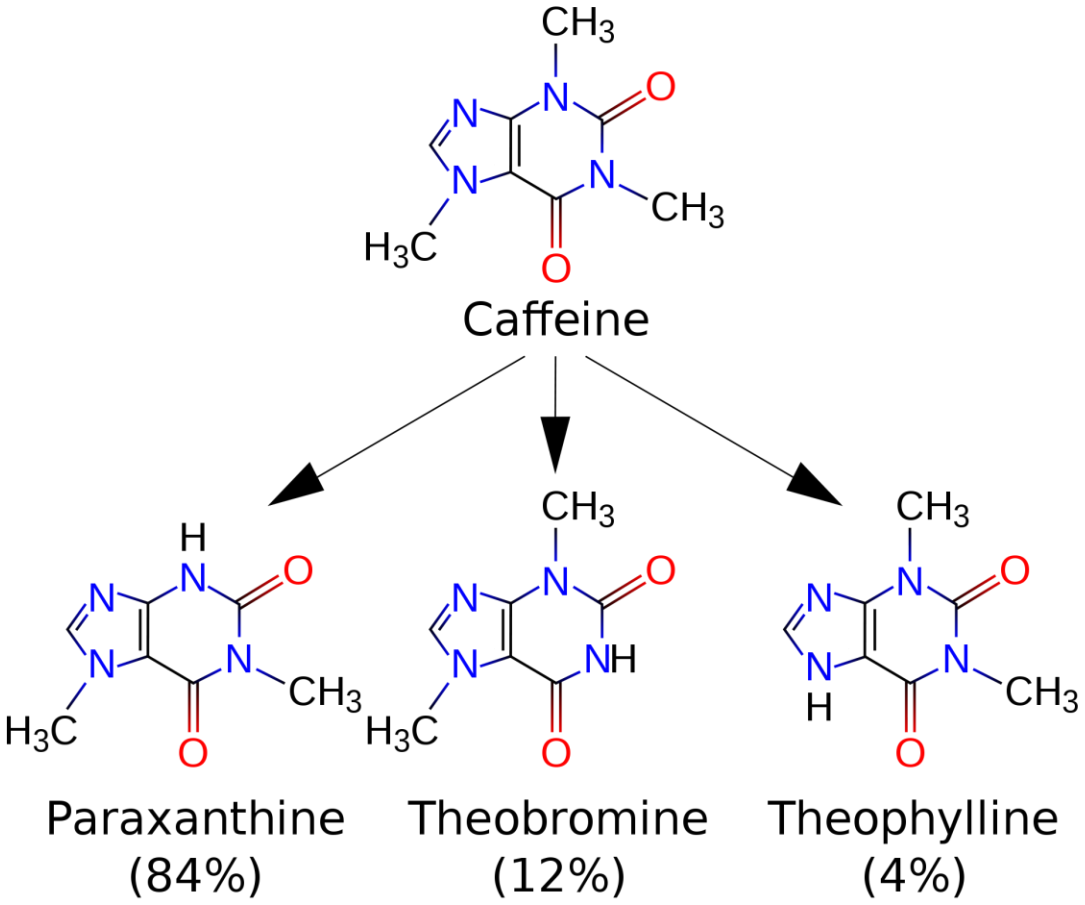
Background

- Caffeine is metabolized by the liver CYP1A2 enzyme into paraxanthine (about 80%), theobromine (about 12%), and theophylline (about 4%)

- Caffeine and caffeine metabolites are methylxanthines; a family of non-specific adenosine receptor antagonist with several properties including diuretic and natriuretic properties.

Wilcox CS et al. *JASN*. 1999

Caffeine
(1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione)



Background

- Studies on the effect of acute or chronic consumption of caffeine at dietary levels on blood pressure (BP) produced inconsistent results.

  Guessous I, Eap CB, & Bochud M. Curr Hypertens Rep. 2014

- High reported caffeine intake associated with a lower prevalence of hypertension only in non-smokers.

  Guessous et al. Hum Mol Genet. 2012

- Limitations so far:
  - use of reported caffeine intake instead of measured caffeine and caffeine metabolites.
  - use of office instead of ambulatory blood pressure measurement.

Objective and hypothesis

- Objective: to analyze the associations of ambulatory blood pressure with urinary caffeine and caffeine metabolites excretions in the general adult population.

- Hypothesis: caffeine and metabolites excretions are negatively associated with blood pressure via natriuretic and diuretic properties.

Methods

- **SKIPOGH-1** (Swiss Kidney Project on Genes in Hypertension) **study**:
  - multi-centric family and population-based study that examines the genetic determinants of BP in the adult Caucasian population randomly selected from the Cantons of Bern, Geneva, and the city of Lausanne, Switzerland

- Recruitment began in December 2009 and ended in April 2013.

- Data collected using:
  - 24-hour urine collection, with separate day and night collections.
  - standardized questionnaires and procedures

Methods: blood pressure measurement

- 24-hour blood pressure was measured using validated Diasys Integra devices (Novacor, Rueil-Malmaison, France).
- We used the awake and asleep periods as reported by participants to define day and night.
- Mean BP readings were then calculated using the valid 24-hour, daytime, and night-time measurements.

Methods: urinary caffeine and caffeine metabolites

- Quantification of caffeine and metabolites in urine samples was performed by ultra-high performance liquid chromatography (Waters ACQUITY UPLC I-Class) coupled to tandem mass spectrometry with electrospray ionization (Waters Xevo TQ-S).

- Caffeine urinary excretion is a validated measure of caffeine intake.

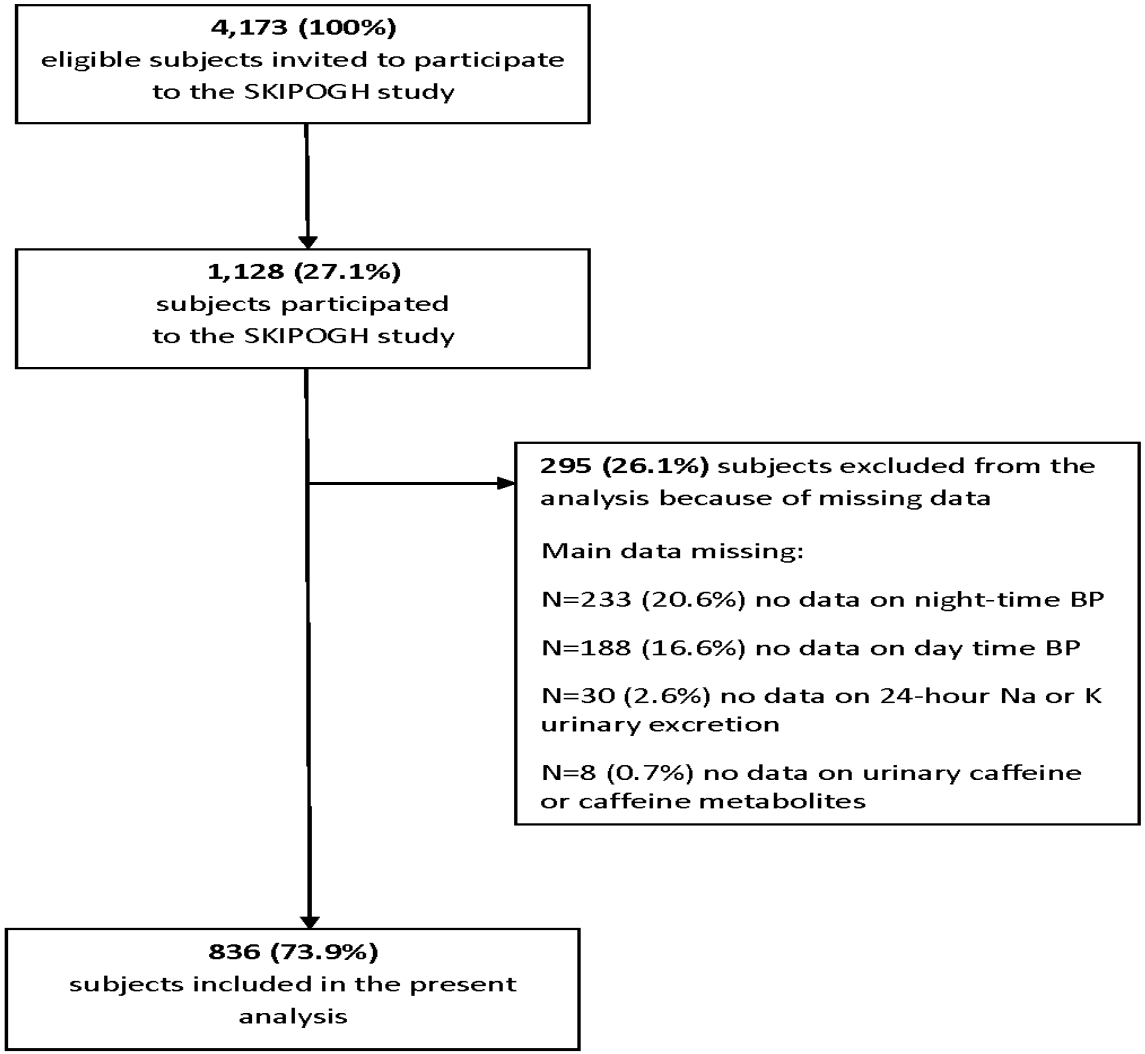
  Del Coso J et al. *Physiologie appliquee, nutrition et metabolisme*. 2011

Methods: statistical analyses

- Mixed linear models were used to explore the associations of
  - Quartiles of urinary caffeine/metabolites excretions
  - log-transformed caffeine /metabolites excretions

  with ambulatory systolic and diastolic blood pressure, while adjusting for major confounders and exploring effect modification.

Results

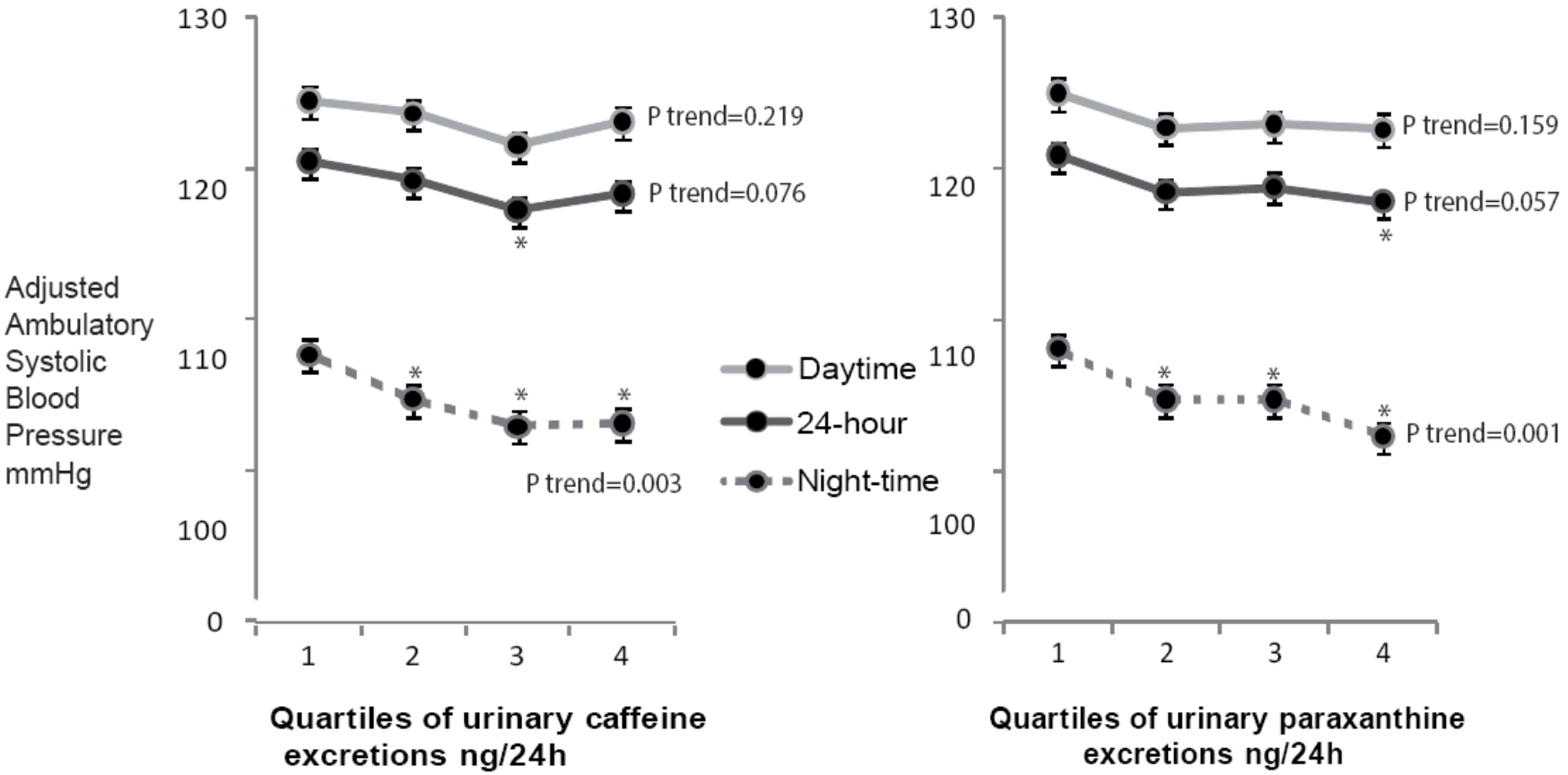

4,173 (100%)
eligible subjects invited to participate to the SKIPOGH study
1,128 (27.1%)
subjects participated to the SKIPOGH study
295 (26.1%) subjects excluded from the analysis because of missing data
Main data missing:
N=233 (20.6%) no data on night-time BP
N=188 (16.6%) no data on day time BP
N=30 (2.6%) no data on 24-hour Na or K urinary excretion
N=8 (0.7%) no data on urinary caffeine or caffeine metabolites
836 (73.9%)
subjects included in the present analysis

Participants characteristics

	ALL (N=836, 100%)
Male gender, %	409 (48.9)
Smokers, %	188 (22.5)
Anti-hypertensive treatment, %	132 (15.8)
Age, mean (SD)	47.8 (17.5)
Urinary methylxanthine excretions (24h)	
Caffeine median (IQR) , microgram/24h	3140.3 (3967.8)
Paraxanthine median (IQR), microgram/24h	10177.5 (10966.8)
Theophylline median (IQR), microgram/24h	935.0 (999.2)
Theobromine median (IQR), microgram/24h	11134.6 (12498.3)
Ambulatory blood pressure (mm Hg)	
Day SBP (SD)	124.0 (14.7)
Night SBP (SD)	107.5 (14.4)
Day DBP (SD)	81.1 (9.6)
Night DBP (SD)	68.1 (8.3)

DBP: diastolic blood pressure; IQR: interquartile range; SBP: systolic blood pressure; SD: standard deviation.

Associations of 24h, day, night SBP with urinary caffeine/paraxanthine excretions quartiles



*P value <0.05 compared to (lowest) quartile 1 (reference)

Adjusted for age, sex, BMI, study center, contraceptive use, diabetes, current alcohol use, smoking, GFR (CKD-EPI), blood Na^+ and K^+, and Na^+ and K^+ excretion.

IUMSP

Institut universitaire de médecine sociale et préventive, Lausanne

Associations of systolic BP with 24h urinary methylanthines excretions

		Beta, SE	P value
Caffeine*	SBP 24h	-0.642, 0.296	0.030
	SBP day	-0.505, 0.313	0.107
	SBP night	-1.107, 0.315	<0.001
Paraxanthine*	SBP 24h	-0.718, 0.343	0.036
	SBP day	-0.545, 0.362	0.132
	SBP night	-1.376, 0.364	<0.001
Theophylline*	SBP 24h	-0.633, 0.341	0.064
	SBP day	-0.458, 0.360	0.204
	SBP night	-1.183, 0.363	0.001
Theobromine*	SBP 24h	0.302, 0.338	0.372
	SBP day	0.325, 0.357	0.363
	SBP night	0.003, 0.361	0.993

Models are adjusted for age, sex, BMI, study center, contraceptive use, diabetes, current alcohol use and smoking, GFR (CKD-EPI), anti-hypertensive treatment, blood Na^+ and K^+, and Na+ and K^+ excretion. *log-transformed

No clear associations of diastolic BP with 24-hour urinary methylanthines excretions

		Beta, SE	P value
Caffeine*	DBP 24h	0.252, 0.182	0.166
	DBP day	0.342, 0.202	0.091
	DBP night	-0.074, 0.183	0.686
Paraxanthine*	DBP 24h	0.353, 0.211	0.094
	DBP day	0.442, 0.234	0.059
	DBP night	-0.039, 0.212	0.851
Theophylline*	DBP 24h	0.391, 0.209	0.062
	DBP day	0.530, 0.232	0.022
	DBP night	-0.032, 0.211	0.881
Theobromine*	DBP 24h	0.237, 0.208	0.254
	DBP day	0.263, 0.230	0.254
	DBP night	-0.015, 0.209	0.942

Models are adjusted for age, sex, BMI, study center, contraceptive use, diabetes, current alcohol use and smoking, GFR (CKD-EPI), anti-hypertensive treatment, blood Na^+ and K^+, and Na+ and K^+ excretion. *log-transformed

Limitations

- Cross-sectional design.
- *CYP1A2* genetic information was not available in the present analysis.
- Reverse causality (e.g., participants with high BP may be advised to intake less caffeine) cannot be excluded.

Conclusions

- Ambulatory systolic blood pressure was negatively associated with urinary caffeine and caffeine metabolites, paraxanthine and theophylline, in adults from the general population.

- Given the ubiquitous nature of caffeinated beverages and foods in the population, our results may have important public health implications.