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Monitoring caffeine intake in children with a questionnaire and urine collection: a cross-sectional study in a convenience sample in Switzerland

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Summary

Purpose: The objectives of this study were 1) to estimate caffeine intake and identify the main sources of intake using a dietary questionnaire, 2) to assess 24-hour urinary excretion of caffeine and its metabolites, and 3) to assess how self-reported intake estimates correlates with urinary excretion among children in Switzerland.

Methods: We conducted a cross-sectional study of children between 6 and 16 years of age in one region of Switzerland. The participants filled in a dietary questionnaire and collected a 24-hour urine sample. Caffeine intake was estimated with the questionnaire. Caffeine, paraxanthine, theophylline, and theobromine excretions were measured in the urine sample. Correlations between questionnaire-based intake and urinary excretion estimates were assessed using Pearson correlation coefficients.

Results: Ninety-one children were included in the analysis (mean age: 10.6 years; 43% female). The mean daily caffeine intake estimate derived from the diet questionnaire was 39 mg (range: 0-237), corresponding, when related to body weight, to 1.2 mg/kg (range: 0.0-6.3). Seven children (8%) had a caffeine intake above the upper recommended level of 3 mg/kg per day. The main sources of caffeine intake were cocoa milk (29%), chocolate (25%), soft drinks (11%), mocha yogurt (10%), tea (8%), and energy drinks (8%). The 24-hour urinary excretion of caffeine was 0.3 mg (range: 0.0-1.5), paraxanthine 1.4 mg (range: 0.0-7.1), theophylline 0.1 mg (range: 0.0-0.6), and theobromine 14.8 mg (range: 0.3-100.8). The correlations between estimates of caffeine intake and the 24-hour urinary excretion of caffeine was modest ($\rho = 0.21$, $p = 0.046$) and with the metabolites of caffeine were weak ($\rho = 0.09$-0.11, $p = 0.288$-0.423).

Conclusions: Caffeine intake in a sample of children in a region of Switzerland was relatively low. The major sources of intake were cocoa milk, chocolate and soft drinks. Self-reported

caffeine intake correlated weakly with urinary excretion of caffeine and some of its main metabolites.

Trial registration number: NCT02900261

Introduction

High caffeine intake can have several effects on the health of children and adolescents, such as headaches, stomach aches, appetite reduction, sleep disturbances, and dependence [1–6]. Caffeine is present in many plant-based beverages and foods, such as coffee, tea, and chocolate [7]. A growing source of caffeine in children are sugar-sweetened beverages, such as colas and energy drinks [3, 8–10]. As a result, intake has increased in children and adolescents in many countries over the last three decades [3, 11]. While caffeine intake has been assessed among children and adolescents in several studies in European countries [6, 12, 13] and in North America [9], there are no data for Switzerland.

How to monitor caffeine intake at a population level is a challenge. Nearly all studies assessing caffeine intake in children used dietary questionnaires. Although these questionnaires can be useful in epidemiological studies to describe the main sources of caffeine intake and to identify individuals with high intake, they rely on self-reported information and are subject to recall, misclassification, and measurement bias [14], especially when administered to children. Moreover, caffeine is present in many foods and drinks in quantities that can vary widely depending on the preparation [14] .

The measurement of the urinary excretion of caffeine and its metabolites has been proposed as an alternative to questionnaires [15, 16]. However, this method raises several challenges due to the complex metabolism of caffeine. Firstly, once absorbed, caffeine is metabolized in the liver, at different rates depending on the individuals [17], and into several metabolites before being excreted in urine. Of the total caffeine ingested, approximately 1-2% is excreted in the urine as caffeine, 4-7% as paraxanthine, 1% as theophylline, 2% as theobromine and the rest as further metabolites [18, 19]. Secondly, some of the metabolites of caffeine, such as theophylline and theobromine, do not exclusively originate from caffeine metabolism, but are

also present as such in other foods (e.g. in chocolate and tea [7]). Thirdly, caffeine metabolism varies greatly between individuals depending on genetic differences [20]. It is therefore important to evaluate to which extent urinary excretion of caffeine and its metabolites are correlated with caffeine dietary intake.

A study was conducted among children in Switzerland aiming to assess sodium intake and caffeine intake with dietary questionnaires and urine collections, and to compare these measurement methods. Results of the study on sodium intake have been previously published [21, 22]. For the present report, our specific objectives were: 1) to estimate caffeine intake and identify the main sources of intake using a dietary questionnaire, 2) to assess 24-hour urinary excretion of caffeine and its metabolites, and 3) to assess how self-reported intake estimates correlates with urinary excretion among children in Switzerland.

Materials and methods

Study design

This study was an observational cross-sectional study conducted in a convenience sample of children and aiming to assess sodium and caffeine intake. Detailed methods and results about sodium intake have been published previously [21, 22]. In short, any child between 6 and 16 years of age, without any disease or medication potentially altering the consumption and excretion of sodium or caffeine (e.g. diabetes, cardiovascular or gastro-intestinal problems, chronic kidney disease, renal insufficiency, taking diuretics, or under perfusion) and with sufficient knowledge of the local language to understand the content of the information forms, was eligible for inclusion. One hundred and one children were recruited between September 2016 and February 2018 at the Hospital of Valais in Sion and in several pediatric and primary care facilities in Valais, Switzerland.

Data collection

Upon enrolment, the children had their height and weight measured. The data collection was then conducted at home on the day chosen by the children and their parents. A semi-quantitative questionnaire focusing on the main dietary sources of caffeine eaten during one day was completed by the children, with the help of their parents if necessary. Potential sources of caffeine were caffeine containing sodas, iced tea, energy drinks, black or green tea, milk tea, coffee, expresso, decaffeinated coffee, milk coffee, cocoa milk, chocolate, coffee ice-cream, and mocha (coffee) yoghurt. Six different portion sizes were possible, with pictures to help the children identify the correct portion size. Moreover, the intake of medications and dietary supplements was recorded and their contents in caffeine checked. The questionnaire was adapted from existing dietary questionnaires [15, 23] and pre-tested for understanding and ease

of filling in with two children of 8 and 11 years of age (see questionnaires in **Appendix 1**). In parallel, one 24-hour urine sample was collected. The last urine void before going to bed on the day before the data collection was discarded and the time noted. From then onwards, all the urine during 24 hours was collected.

Laboratory analysis

Urine samples were stored between 4 and 8°C during urine collection and then between -20 and -80°C until analysis. Caffeine, paraxanthine, theobromine and theophylline were quantified by ultra-high performance liquid chromatography (Waters ACQUITY UPLC I-Class) coupled to electrospray ionization-tandem mass spectrometry (Waters Xevo TQ-S). The method was validated according to international guidelines using a stable isotope-labeled internal standard for each analyte (detailed method available upon request). Briefly, urine samples were diluted with deuterated internal standard (caffeine-D3, paraxanthine-D3 theophylline-D6, theobromine-D6) before injecting into a Acquity column (UPLC BEH Shield RP18 2.1 x 50 mm dp 1.7 µm Waters) using a gradient with two mobile phases (ammonium formate buffer 1mM pH4.0 and methanol). Nitrogen and Argon were used as desolvatation and collision gas, respectively. Parent and daughter ion (m/z) were 195 and 138.1; 181 and 124.1; 181 and 124.1; 181 and 67.1 for caffeine, paraxanthine, theophylline and theobromine, respectively; and 198.1 and 141.1; 184 and 124.1; 187 and 127.1; 187.1 and 70.1, respectively for their deuterated internal standards . Uncertainty of measurements varied between 7.6 and 8.2 % for all 4 compounds. The quantification limits were 10 ng/mL for caffeine, paraxanthine, and theophylline and 20 ng/mL for theobromine. The method was validated according to international guidelines using a stable isotope-labeled internal standard for each analyte.

Ethical considerations

Approval was obtained by the Ethics Committee of Canton de Vaud, Switzerland (CER-VD, identification number: 2015-01178). Written informed consent was obtained from the parent

(or legal guardian) of the child. Children below 14 years of age gave oral consent and children above 14 years of age gave written consent.

Statistical analysis

The caffeine content in each beverage and food group of the questionnaire was estimated using the mean caffeine contents of foods available in Swiss supermarkets, reported by the producers (see **Appendix 2**). The caffeine intake was calculated by adding the caffeine content of each beverage and food multiplied by its portion size. The caffeine intake per body weight was calculated. Caffeine intakes per body weight above 3 mg/kg/day, i.e., the maximum level recommended by the European Food Safety Authority (EFSA) (6), were considered high.

Urinary concentrations below the quantification limit were assumed to be 0 ng/mL. The total 24-hour urinary excretion of caffeine, paraxanthine, theobromine, theophylline, and creatinine were calculated by multiplying the concentration of caffeine in the 24-hour urine sample by the total volume of the sample and by adjusting for self-reported collection times to represent an exact 24-hour duration. A 24-hour creatinine excretion of less than 0.1 mmol per kilogram of body weight was considered an indication of incomplete 24-hour urine collection [24] and was corrected to equal to 0.1 mmol. The 24-hour excretion of caffeine and its metabolites were corrected using the same adjustment factor as for 24-hour creatinine excretion.

The Spearman correlation (ρ) between caffeine intake estimates from the questionnaires and the 24-hour urinary excretions of caffeine and its metabolites were calculated. Statistical analyses were conducted with R (version 3.5.2) and R Analytic Flow (version 3.0.4).

Results

The characteristics of the children recruited are shown in **Table 1**. Among the 101 children recruited, 94 collected the urine samples and 91 filled in the questionnaires. The analyses were conducted with the 91 children with complete data.

The statistics of caffeine intake and urine excretions of caffeine and its metabolites are shown in **Table 2**. The mean daily caffeine intake was 39 mg. The intake of caffeine per body weight was 1.2 mg/kg. Only 7 children (8%) had an average caffeine intakes above 3 mg/kg/day. There was no substantial correlation between total daily caffeine intake or caffeine intake per body weight and age ($\rho = 0.07$, $p = 0.513$, and $\rho = -0.18$, $p = 0.073$).

The contributions of each food and beverage containing caffeine to the total caffeine intake are shown in **Figure 1**. The main sources of caffeine intake were cocoa milk (29%), chocolate (25%), soft drinks (11%), mocha yogurt (10%), tea (8%), and energy drinks (8%).

The mean concentrations in the 24-hour urine samples were 0.3 mg/mL caffeine, 1.5 mg/mL paraxanthine, 0.1 mg/mL theophylline, and 14.8 mg/mL theobromine. Among all the 376 urine samples analyzed, caffeine and theophylline levels were below the quantification limit in 15 samples for caffeine and 7 for theophylline (none for paraxanthine nor for theobromine). The urinary concentration of caffeine in the 24-hour urine was highly correlated with the urinary concentrations of paraxanthine ($\rho = 0.82$, $p < 0.001$) and theophylline ($\rho = 0.83$, $p < 0.001$), but weakly correlated with the urinary concentration of theobromine ($\rho = 0.26$, $p = 0.014$).

The total 24-hour urinary excretion was 0.3 mg for caffeine, 1.4 mg for paraxanthine, 0.1 mg for theophylline, and 14.8 mg for theobromine. The total 24-hour urinary excretion of caffeine and its metabolites were weakly correlated with the caffeine intake estimates from the questionnaires (caffeine: $\rho = 0.21$, $p = 0.046$; paraxanthine: $\rho = 0.11$, $p = 0.294$; theophylline:

$\rho = 0.11$, $p = 0.288$; theobromine: $\rho = 0.09$, $p = 0.423$). Combining caffeine with paraxanthine, theophylline and/or theobromine did not provide higher correlations.

Discussion

Summary of findings

Caffeine intake in a sample of children aged 6 to 16 years in a region of Switzerland was 39 mg per day, or 1.2 mg/kg body weight, which is relatively low. Only 8% of the children had a caffeine intake above the upper recommended level of 3 mg/kg per day. The principal sources of caffeine intake were cocoa milk, chocolate, and soft drinks. The caffeine intake estimated from a semi-quantitative questionnaire correlated weakly with 24-hour urinary excretion of caffeine and weakly correlated with 24-hour urinary excretion of paraxanthine, theophylline, and theobromine.

Comparison with other studies

In a review conducted by the EFSA, studies assessing caffeine intake among children and adolescents in European countries were identified [6]. The mean caffeine intakes in these studies were similar to our study, lying between 4 and 47 mg per day in children 3-9 years old and between 18 and 70 mg per day in children 10-18 years old [6]. The mean caffeine intakes per body weight ranged between 0.2 and 2.0 mg per day among children 3-9 years old and between 0.4 and 1.4 mg per day among children 10-18 years old [6]. And the proportion of children with intakes above recommended quantities ranged between 5% and 13% [6]. Similarly to our study, the first source of caffeine among children was chocolate, including cocoa drinks [6], as opposed to the United States, where sodas are the major sources of intake [25].

The few studies that have compared how caffeine intake correlates with urinary excretion of caffeine and its metabolites have also found modest correlations between reported intake and caffeine, paraxanthine, and theophylline urinary excretion and weak correlations with

theobromine urinary excretion [15, 16, 26] (which can be explained by the fact that theobromine is not solely a by-product of caffeine, but also present as such in foods such as chocolate [7]). A study among 598 adults in Switzerland found a correlation between a caffeine frequency questionnaire and 24-h hour excretion of caffeine ($\rho = 0.47$, $p < 0.001$), paraxanthine ($\rho = 0.53$, $p < 0.001$), and theophylline ($\rho = 0.52$, $p < 0.001$), but not of theobromine ($\rho = -0.02$, $p = 0.637$) [15]. A study among 2370 children and adults in the United States found a correlation between a 24-h recall and spot urine excretion of caffeine ($\rho = 0.59$, $p < 0.001$), paraxanthine ($\rho = 0.61$, $p < 0.001$), theophylline ($\rho = 0.63$, $p < 0.001$), and much weaker with theobromine ($\rho = 0.15$, $p < 0.001$)[16]. A study among 79 young Canadian adults found a correlation between a self-administered caffeine 24-h recall and 24-h hour excretion of caffeine biomarkers (r=0.28 to 0.52)[26].

Strengths and limitations

To our knowledge, this is the first study that assessed caffeine intake among children in Switzerland and compared it with simultaneous 24-hour urinary excretion of caffeine and its metabolites. We developed a specific questionnaire focusing on the main sources of caffeine for this population group and made it easy to complete and as accurate as possible.

However, there was a modest positive correlation between the self-reported caffeine intakes and the urinary excretion of caffeine and its metabolites, which could be explained by the limitations with both the questionnaire and the 24-hour urine collection. On one hand, the semi-quantitative questionnaire was dependent on the reporting and recall of the participant (which is especially challenging in children), and listed a definite amount of caffeine-containing drinks and foods, whose caffeine content of the foods were extrapolated from food composition tables. On the other hand, the 24-hour urine collection was performed only once per person, did not assess the inter-individual variations in the metabolization of caffeine [17], and in which only

the concentration caffeine and its three main metabolites were measured. In addition, we did not measure factors that could influence caffeine metabolism, such as liver function and genetic variations [20]. Moreover, for the 15 samples and 7 samples (out of 376 samples) who had caffeine and theophylline levels, respectively, below the quantification limit, a zero value was assigned. Although this concerns only a small proportion of patients, the correlation between urinary excretion of caffeine and theophylline and reported intake could be slightly higher than found in our study if a real value (i.e. lower than the limit of quantification but higher than zero) would have been assigned.

Another limitation is that the sample of this study was a convenience sample of children in one region of Switzerland, and was therefore not representative of the whole population of children in the country. One could assume that the caffeine intake and excretion in our sample could be lower than in the whole population of children in Switzerland due to sampling bias, participation bias, and the Hawthorne effect. The children and parents who accepted to participate in the study might have done so because they were more health conscious than the general population. Moreover, it is possible that since the participants knew that caffeine intake was measured, they could have limited their intake of caffeine containing foods during the data collection.

Implication and future research

The caffeine intake in our sample was similar to those previously reported in prior studies in children in Europe. However, in order to confirm the caffeine intake and the sources of caffeine among children in Switzerland, a larger study in different regions and including a wider age range of children would be useful.

Our results highlight the difficulty in identifying a reliable and convenient tool to monitor caffeine intake in children. In fact, it was not possible to assess the validity of the questionnaire or the urinary biomarkers [27, 28] to estimate caffeine intake, since there is currently no recognized gold standard to measure caffeine intake. Since a urinary biomarker could provide, at least in theory, less biased estimates of caffeine intake than a questionnaire [27, 28], it would be useful to validate a urinary biomarker for the monitoring of caffeine intake at a population level. To do so, a study in a controlled setting where participants ingest only foods and drinks with known amounts of caffeine and collect their urine over several days or even weeks, is needed, analogously to studies done to assess sodium intake and excretion in space flight simulations [29].

Conclusions

Caffeine intake in a sample of children between 6 and 16 years old in Switzerland was relatively low. The major sources of dietary intake were cocoa milk, chocolate and soft drinks. Urinary excretions of caffeine, theophylline, paraxanthine and theobromine were modestly correlated with self-reported caffeine intakes, highlighting the difficulty of identifying a reliable nutrition biomarker for caffeine intake. Further studies are needed to identify appropriate tools to assess caffeine intakes in children.

Supplementary files: Questionnaire and caffeine content of foods

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Conflicts of interest: The authors declare no conflicts of interest.

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Captions of tables and figures

Figure 1. Distribution of reported caffeine intakes (mg/kg/day) in children (n=91). Red line: Recommended maximum caffeine intake

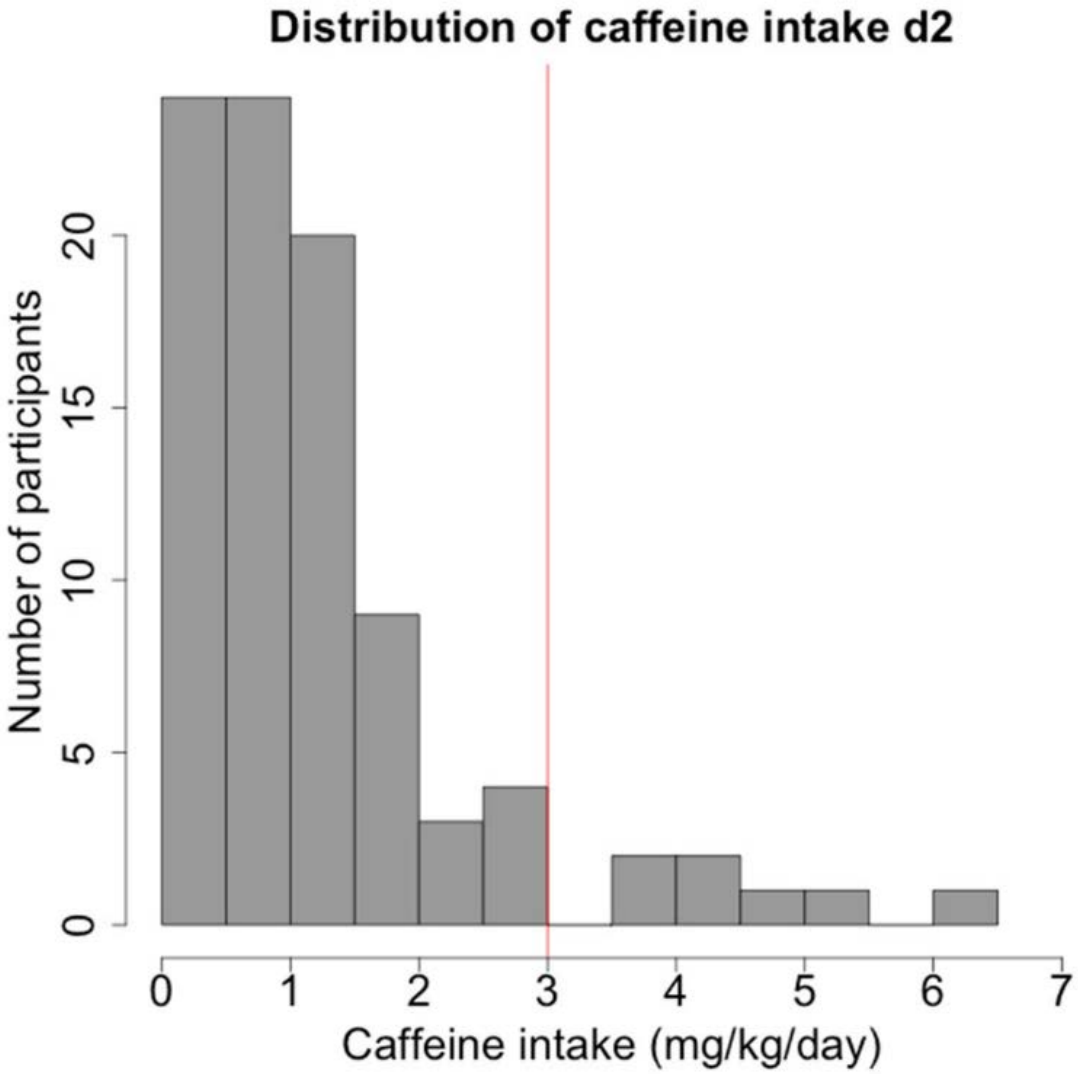
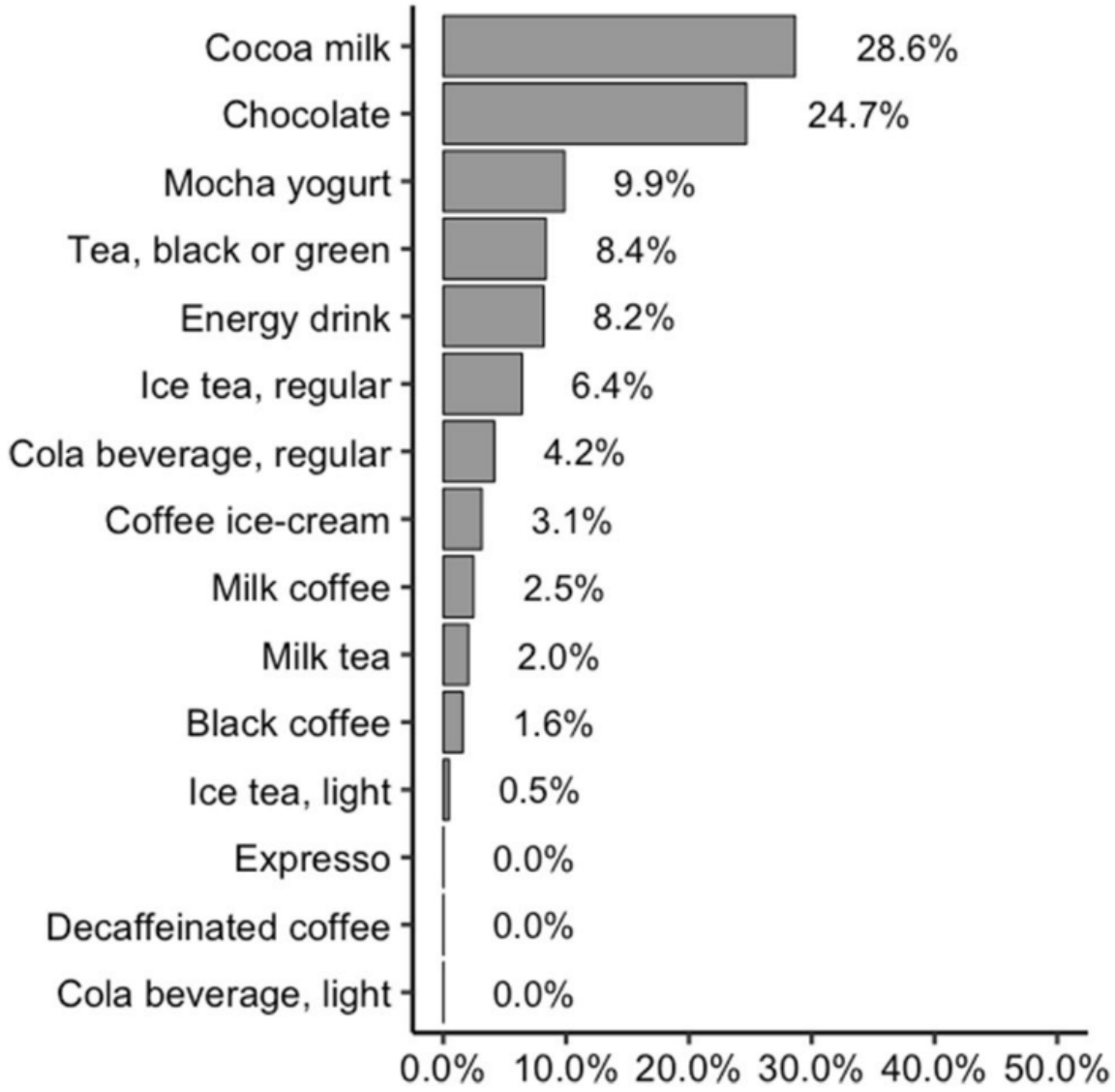


Figure 2. Contribution (%) of individual foods and beverages to total reported caffeine intake in children (n=91).



381 **Table 1. Characteristics of the participants (n=91)**

Table 1 Characteristics of the participants ($n = 91$)

	Means (SD) or percentages	Range
Age (years)	10.6 (2.9)	6–16
Female (%)	42.9%	
Height (cm)	142 (17)	113–186
Weight (kg)	36.1 (14.1)	17.4–88.0
Body mass index (kg/m^2)	17.3 (3.9)	12.5–37.2
Overweight (%)	15.4%	

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384 **Table 2. Intake and urine excretion statistics (n=91)**

Table 2 Intake and urine excretion statistics ($n = 91$)

	Mean	SD	Min	25th quantile	Median	75th quantile	Max
Questionnaire							
Caffeine intake (mg/day)	39	38	0	15	31	47	237
Caffeine intake per bodyweight (mg/kg/day)	1.2	1.2	0.0	0.3	0.9	1.3	6.3
Urine							
Caffeine concentration (mg/mL)	0.3	0.3	0.0	0.1	0.2	0.3	1.6
Paraxanthine concentration (mg/mL)	1.5	1.6	0.0	0.6	1.1	2.0	11.8
Theophylline concentration (mg/mL)	0.1	0.1	0.0	0.0	0.1	0.1	0.6
Theobromine concentration (mg/mL)	14.8	13.5	0.3	7.3	12.0	19.8	100.8
24-h caffeine excretion (mg/24 h)	0.3	0.3	0.0	0.1	0.2	0.4	1.5
24-h paraxanthine excretion (mg/24 h)	1.4	1.4	0.0	0.4	1.0	1.9	7.1
24-h theophylline excretion (mg/24 h)	0.1	0.1	0.0	0.0	0.1	0.1	0.6
24-h theobromine excretion (mg/24 h)	14.8	13.5	0.3	5.2	12.0	17.2	59.9

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