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Complete List of Authors:	Papadopoulou, Eleni; Norwegian Inst Publ Hlth, Department of Environmental Exposures and Epidemiology Botton, Jeremie; INSERM, Early Determinants of the Child's Health and Development Team (ORCHAD) Brantsaeter, Anne-Lise; Norwegian Institute of Public Health, Division of Environmental Medicine, Department of Exposure and Risk Assessment Haugen, Margaretha; Nasjonalt folkehelseinstitutt, Department of Environmental Exposures and Epidemiology Alexander, Jan; Norwegian Institute of Public Health, Office of the Director-General Meltzer, Helle Margrete; Nasjonalt folkehelseinstitutt Bacelis, Jonas ; Sahlgrenska universitetssjukhuset, Elfvin, Anders; Goteborgs universitet Sahlgrenska Akademin, Department of Pediatrics Jacobsson, Bo; Goteborgs universitet Sahlgrenska Akademin, Department of Obstetrics and Gynecology Sengpiel, Verena; Goteborgs universitet Sahlgrenska Akademin, Department of Obstetrics and Gynecology
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TITLE PAGE

Title: Maternal caffeine intake during pregnancy is associated with excess growth in infancy and overweight in childhood: results from a large prospective cohort study

Eleni Papadopoulou, Post-doctoral research fellow [a]; Jérémie Botton, Associate Professor [b,c]; Anne-Lise Brantsæter, Senior researcher [a] ; Margaretha Haugen, Senior researcher [a]; Jan Alexander, Senior researcher [d];Helle Margrete Meltzer, Senior researcher [d], Jonas Bacelis, PhD Candidate [e]; Anders Elfvin, Physician [f]; Bo Jacobsson, Professor/ Chief physician [e,g]; Verena Sengpiel, Associate Professor/Physician [h]

[a] Department of Environmental Exposure and Epidemiology, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[b] Early Determinants of the Child's Health and Development Team (ORCHAD), INSERM, UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Paris, F-75014 France

[c] Univ. Paris-Sud, Université Paris-Saclay, F-92296, Châtenay-Malabry, France

[d] Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[e] Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

[f] Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

[g] Department of Genetics and Bioinformatics, Division of Health Data and Digitalization, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[h] Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Östra, SE-416 85 Gothenburg, Sweden

Corresponding author:
Eleni Papadopoulou
Division of Infection Control and Environmental Health
Norwegian Institute of Public Health
P.O. Box 4404, Nydalen, NO-0403 Oslo, Norway
Phone number: +47 21076511
Fax number: +47 21076686
E-mail: eleni.papadopoulou@fhi.no

ABSTRACT

Objectives: To study the association between maternal caffeine intake during pregnancy and the child's weight gain and overweight risk up to 8 years.

Design: Prospective nationwide pregnancy cohort.

Setting: The Norwegian Mother and Child Cohort Study.

Participants: 50,943 mothers recruited from 2002 to 2009 and their children, after singleton pregnancies, with information about average caffeine intake assessed at mid-pregnancy.

Outcome measure: Child's body size information at 11 age-points from 6 weeks to 8 years. We defined excess growth in infancy as a WHO weight gain z-score of >0.67 from birth to age 1 year, and overweight according to the International Obesity Task Force. We used a growth model to assess individual growth trajectories.

Results: Compared to pregnant women with low caffeine intake (<50mg/day, 46%), women with average (50-199mg/day, 44%), high (≥200-299mg/day, 7%) and very high (≥300mg/day, 3%) caffeine intakes had an increased risk of their child experiencing excess growth in infancy, after adjustment for confounders (odds ratio (OR)=1.15, 95% Confidence Intervals (CI) 1.09-1.22), OR=1.30, 95%CI, 1.16-1.45, OR=1.66, 95%CI, 1.42-1.93, respectively). In-utero exposure to any caffeine was associated with higher risk of overweight at age 3 and 5 years, while, the association persisted at 8 years, only for very high exposures. Any caffeine intake was associated with increased body mass index from infancy to childhood. Children prenatally exposed to caffeine intake >200mg/day had consistently higher weight. Very high caffeine exposures were associated with higher weight gain velocity from infancy to age 8 years.

Conclusion: Any caffeine consumption during pregnancy is associated with excess infant growth and increased risk of overweight, mainly at pre-school ages. Maternal caffeine intake can modify overall weight growth trajectory from birth to 8 years. This study adds supporting evidence for the current advice to reduce caffeine intake during pregnancy and indicate that complete avoidance might be advisable.

Strengths and limitations of this study

- A strength of this study is the large sample size.
- Maternal caffeine intake was estimated from all possible food sources.
- This is the first study investigating the association between maternal caffeine intake and excess infant growth and growth velocity.
- Missing data from body size measurements were handled with a growth model.
- Limitations include self-reported dietary data and parental-reported measurements of height and weight after 2 years.

MANUSCRIPT

Introduction

Caffeine is the world's most widely consumed central nervous system stimulant. It occurs naturally or is added to foods and beverages, with coffee and tea as the most common and major sources[1]. After ingestion, caffeine is readily absorbed into the blood stream and distributed to the tissues. It is metabolized in the liver by the microsomal cytochrome P450[2]. During pregnancy, elimination of caffeine is prolonged and it rapidly passes all biological membranes, including the blood-brain and placenta barriers, resulting in exposure of the fetus[3]. A maximum intake level of caffeine for pregnant women has been stipulated by several authorities, most of which agree that it should not exceed 200 mg/day, based on the evidence of its adverse effects on miscarriage rates and fetal growth restriction[4]. The negative effects of caffeine consumption during pregnancy on fetal growth have been well documented in epidemiological studies, including a study within the Norwegian Mother and Child Cohort Study (MoBa)[5]. In a recent meta-analysis the highest, compared with the lowest, maternal caffeine intake level was associated with a 38% increased risk of low birth weight (< 2.5kg)[6].

Fetal growth and growth in infancy are important determinants for the development of obesity and for long-term cardiometabolic health [7-9]. Excess infant growth programs later obesity, fat mass, and risk of adult disease, independent of intrauterine growth [10-15]. The prevalence of metabolic disorders, including obesity, cardiovascular disease and type 2 diabetes is rapidly growing across the globe, with the number of obese people risen worldwide from 105 million in 1975 to 641 million in 2014[16]. This trend indicates that the probability of reaching the WHO global obesity target, of no rise in obesity by 2025, is close to zero[16]. There is compelling human and animal evidence supporting the "fetal programming" hypothesis, according to which in utero exposures permanently alter an organism's physiology and metabolism, leading to susceptibility to subsequent disease, including obesity and metabolic disorders, with transgenerational effects [17 18].

In-utero exposure to caffeine has been related to an increased risk of overweight and higher body fat in childhood, in two previous epidemiological studies [19 20]. However, the link between in-utero caffeine exposure and excess growth in infancy is yet to be studied, even though excess infant growth is an established risk factor in the etiology of obesity and cardio-metabolic disease [13 15 21 22].

Based on our previous findings on the association of prenatal caffeine exposure with fetal growth restriction[5] and the fetal programming hypothesis[23], we hypothesized that prenatal caffeine exposure might affect postnatal growth. Thus, the objective of this study was to investigate the associations between maternal caffeine intake in pregnancy and child growth and risk of overweight up to age 8 years in a large prospective population-based cohort.

Methods

Study population and ethical approval

Our study was conducted within the Norwegian Mother and Child Cohort Study (MoBa), a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health[24]. Pregnant women from all over Norway were recruited during 1999-2008 and 40.6% of the invited women consented to participate. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Follow-up of the participants, after delivery, have been conducted at 6, 18, 36 months, 5, 7 and 8 years. Data used in this study are based on version 8 of the quality-assured data files, released for research in February 2014, with linkage to the Medical Birth Registry of Norway (MBRN). The data collection in MoBa was licensed by the Norwegian Data Inspectorate and approved by the Regional Committee for Medical Research Ethics. This study was approved by the Regional Committee for Medical Research Ethics in Southeastern Norway (2010/2683/REK Sør-øst A). All MoBA participants have provided a signed consent form.

After exclusion of multiple gestations, stillbirths, malformations and chromosomal abnormalities, 96,875 live-born singletons remained. Of these, 78,819 had answered the food frequency questionnaire developed and validated for MoBa and in use from 2002 and onwards. The eligible study population, with available information on maternal caffeine intake and all relevant covariates, constituted 62,034 mother-child pairs. Our final study population consisted of 50,943 mother-child pairs with additional information on small for gestational age (SGA) and at least one postnatal measurement of weight or length/height. The cohort retention is presented in Supplementary Table 1. After 5 years, approximately 40% of the study population returned the questionnaire and had information on weight and height, while the distribution of mothers by caffeine intake level did not differ by follow-up age, meaning that loss to follow-up was not related to maternal caffeine intake in pregnancy.

Maternal caffeine intake during pregnancy

Maternal caffeine intake estimation in MoBa has been described in detail previously by Sengpiel et al[5]. In brief, self-reported intake of 255 dietary items was assessed at pregnancy week 22 with a food frequency questionnaire (FFQ) developed and validated for MoBa[25]. This is a semi-quantitative FFQ designed to record dietary habits during the first four to five months of gestation. Average, daily caffeine intake was calculated as the aggregated intake (in mg/day) from all available sources, including several types of coffee, black tea, caffeinated soft drinks, energy drinks, chocolate, chocolate milk, and sandwich spread, desserts, cakes and sweets containing cocoa. Supplementary Table 2 includes more details on the estimation of maternal caffeine intake. The median (25^{th} -75^{th} percentiles) caffeine intake was 57mg (23-120mg) for the included population and 64mg (25-129mg) for the non-included population with available caffeine information (n=11,091 mothers) ($p<0.001$ for Mann-Whitney test). We categorized caffeine intake, based on the calculated median as well as national and international recommendations for caffeine consumption during pregnancy, in four levels of caffeine intake: low (0-49mg/day), average (50-199mg/day), high (200-299mg/day) or very high (≥300mg/day).

Child postnatal growth and overweight

Mothers were asked to report weight and height/length, as documented in the child's health card, in six different questionnaires for eleven age-points: 6 weeks, 3, 6 and 8 months and 1, 1.5, 2, 3, 5, 7 and 8 years. From 6 weeks to 18 months, mothers were asked to refer to their child's health card, while for measurements from 2 to 8 years no specification was provided. Implausible anthropometrics were identified and excluded by separately implementing three different methods: i) by comparing with the WHO Growth Standards, as a weight-for-age or height-for-age z-score <6SD below or >6SD (5SD for weight) above the mean [26] , ii) by identifying measured values with a >|3SD| difference from the predicted value as derived from the Jenss-Bayley growth curve model model, and iii) by the conditional growth percentiles[27]. In total, 464,343 and 452,980 measurements of weight and height/length were reported for our study population. For weight, as for height/length, mothers reported seven repeated measurements per child, on average. More details on anthropometric measurements are presented in Supplementary Table 1.

We assessed excess infant weight gain by calculating the difference in gender-adjusted WHO weight-for-age z-scores between birth and age 1 year[26]. A z-score of >0.67 represents an upward crossing of the percentile[28], referred to as excess growth[29].

Individual growth trajectories for weight and length/height were obtained by modeling the overall growth from age 1 month to age 8 years, using the Jenss-Bayley growth curve model, a structural growth model based on a basic functional form of growth. This 4-parameter, non-linear model is suitable for describing growth of both weight and length/height during infancy and early childhood, up to age 8 years[30], before growth starts to accelerate again at puberty. To assess individual growth trajectories, we applied a mixed-effect approach using the Stochastic Approximation of Expectation-Maximization (SAEM) algorithm[31 32]. We then calculated weight and length/height, body mass index (BMI) (weight (kg) divided by squared height (m)), as well as weight and height gain velocities at 14 age-points (1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4, 5, 6, 7 and 8 years), using the growth model derivatives. As including birth weight in the model may influence the estimated trajectories, and in order to assess the effect of caffeine on early growth independently of its effect on birth size[5], we did not include birth weight and length in the growth models. The correlation between measured and predicted anthropometrics ranged from 0.85 to 0.99 for weight and from 0.95 to 0.98 for length/height (data not shown).

We determined childhood overweight and/or obesity status, hereafter referred to as "overweight", based on the model-predicted weight and height at two preschool-age (3 and 5 years) and one school-age (8 years) time-point, using the International Obesity Task Force (IOTF) criteria[33]. Used BMI cut-offs and overweight prevalences are presented in Supplementary Table 3.

Statistical analysis

We used logistic regression models to examine associations between maternal caffeine intake and excess growth in infancy and childhood overweight. We used mixed-effect linear regression models with random intercept and slope for weight, height/length, BMI, weight and height gain velocities from ages 1 month to 8 years (14 age-points: 1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4, 5, 6, 7 and 8 years). Low caffeine intake (0-49 mg/day) was the reference group. Covariates related to both maternal caffeine intake and excess growth in bivariate analysis were selected as confounders for adjustment: maternal age, maternal and paternal education, parity, pre-pregnancy

BMI, paternal BMI, maternal and paternal smoking during pregnancy, maternal energy intake and nausea/vomiting during pregnancy (Supplementary Table 4).

Furthermore, we studied caffeine intake with restricted cubic splines with four knots at percentiles 5, 35, 65 and 95, as recommended by Harrell[34], and corresponding to caffeine intakes of 6, 34, 91 and 253 mg/day, respectively. We used this variable to further study the non-linear association between the exposure and dichotomous outcomes in logistic regression models. The reference level of caffeine intake was set at 50mg/day, corresponding to the median intake in our study population. The associations were described graphically. Our main analysis consists of complete case analysis of 30,338 mother-child pairs for the risk of excess growth and of 50,943 mother-child pairs for all other growth outcomes. The cohort attrition due to loss to follow-up was addressed by the use of predicted anthropometric measurements.

Possible interaction effects were explored for child's gender, birth weight and SGA. SGA, defined as birth weight below the 10th percentile, according to population curves as described by Skjaerven et al[35], was used. Birth weight was not considered in the excess growth analysis, as it is included in the excess growth calculation formula. In separate sensitivity analyses, i) we excluded SGA neonates, ii) excluded smokers during pregnancy, iii) excluded very high caffeine consumers, and iv) we assessed the association between maternal caffeine intake and childhood overweight, using the measured instead of predicted anthropometric data to define the outcome.

The main analyses were performed with the Stata 14 statistical software (Stata Corporation, College Station, Texas) and R version 3.2.2 [36] was used for the growth models.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Lifestyle and socio-demographic characteristics related to maternal caffeine intake during pregnancy

In our study population, 7.13% (n=3,633) and 3.21% (n=1,634) of women reported caffeine intake higher than 200mg/day and 300mg/day, respectively. The distribution of women not

included in the analysis, by caffeine intake level was similar to the included (low: 43%, average: 46%, high: 8% and very high: 3%, Supplementary Table 1). The higher the caffeine intake, the higher the likelihood of a mother being older than 30 years, being multiparous, having gained more weight during pregnancy than recommended by the Institute of Medicine[29], having a daily energy intake in the upper tertile, being a smoker and alcohol consumer during pregnancy and not suffering nausea and/or vomiting during pregnancy. Moreover, women with very high caffeine intake were more likely to have low education, have been obese before pregnancy and have partners who were obese and smokers, compared to those consuming less caffeine per day (Supplementary Table 4).

Prenatal caffeine exposure and excess growth in infancy

The prevalence of excess growth in infancy increased from 23% to 29% as prenatal caffeine intake increased from low to very high (Figure 1). After adjustment for confounders, children born to average, high and very high caffeine consumers had 1.15 (95%CI: 1.09, 1.22), 1.30 (95%CI: 1.16,1.45) and 1.66 (95%CI: 1.42,1.93) higher odds of excess growth in infancy, compared with children born to low consumers (Table 1). Neither exclusion of mothers who smoked during pregnancy or SGA neonates modified the results. The positive association between caffeine intake as a continuous variable and the risk of excess growth in infancy was linear with no apparent threshold (Supplementary Figure 1).

Prenatal caffeine exposure and overweight in childhood

The prevalence of overweight increased by 5% at age 3 years, by 6% at age 5 years and by 3% at age 8 years with increasing prenatal caffeine exposure from low to very high (Figure 1). Children born to average, high and very high caffeine consumers had 1.05 (95%CI: 0.99,1.12), 1.17 (95%CI: 1.05,1.30) and 1.44 (95%CI: 1.24,1.67) higher adjusted odds, respectively, for overweight at age 3 years, compared with children born to low caffeine consumers (Table 2). Similar odds ratios (OR) were found at age 5 years, but at age 8 years the respective risk was significant only for the highest caffeine consumption category (adjusted OR (aOR) 1.29; 95%CI 1.04,1.61). Neither exclusion of mothers who smoked during pregnancy or SGA neonates modified the results. However, adjustment for birth weight slightly increased the odds (Supplementary Table 5). We found a linear association between maternal caffeine consumption as a continuous variable and the risk of overweight at ages 3 and 5 years with, again, higher OR at age 3 years than at age 5 years (Supplementary Figure 2). As there was a high degree of

concordance between overweight and/or obesity at ages 5 and 8 years, the plot at age 8 years overlapped with the one at age 5 years and was not included in Supplementary Figure 2.

Sensitivity analyses

In sensitivity analyses, we found similar results concerning the association of caffeine from different caffeine sources (black coffee, black tea, and soda drinks) with infant growth and overweight risk (Supplementary Table 6). When excluding very high caffeine consumers and using no coffee drinkers as the reference group, caffeine intake less than 300mg was still significantly associated with increased risk for excess infant growth and overweight (Supplementary Table 7). Finally, when growth data from actual measurements were used to assess the relationship between maternal caffeine intake and overweight at these age-points, similar trends and associations were observed (Supplementary Table 8).

Prenatal caffeine exposure and growth up to 8 years

In comparison with low exposure, both high and very high prenatal caffeine exposure were positively associated with a child's weight, weight gain velocity and BMI from the first month onwards (Figure 2). More specifically, children prenatally exposed to very high caffeine levels weighed 67-83g more in infancy (age 3 to 12 months), 110-136g more in toddlerhood (age 12 months to 3 years), 213-320g more at pre-school age (age 3 to 5 years) and 480g more at age 8 years, than children exposed to low caffeine levels (Table 3). Maternal caffeine intake during pregnancy, at any level above 50mg/day, was associated with higher BMI from ages 1 month to 8 years. Additional adjustment for birth weight provided better models (p-value<0.05 for likelihood ratio test between models with and without birth weight) and the estimates from these models are presented in Table 3. Whereas maternal caffeine intake during pregnancy was not associated with child height, it was related to higher height gain velocity up to age 3 months (Supplementary Table 9).

Discussion

We found that any maternal caffeine intake during pregnancy was associated with a higher risk of excess growth in infancy and overweight in early childhood. In addition, caffeine intakes in pregnancy above the recommendation (200mg/day) were associated with modified growth trajectories from very early in life and maintained during childhood. More specifically, children

exposed prenatally to caffeine levels above 200mg/day had persistently higher weight-, BMI- and weight gain velocity up to 8 years of age.

Strengths and limitations of this study

With the included 50,943 pregnancies, this is, so far, the largest study on the association of prenatal caffeine exposure and childhood growth parameters. It is the first to investigate effects on excess growth in infancy as well as growth velocities rather than just the size of the child, as well as critical age windows of diverging growth. Additional strengths include the prospective data collection, the comprehensive data on possible confounders and the assessment of caffeine intake from different sources. Nevertheless, our findings might be explained by residual confounding of non-accounted factors related to an overall unhealthy lifestyle and high caffeine consumption; though exclusion of smokers and very high caffeine consumers did not modify the results.

In addition, the missing body size measurements were handled with the use of a growth model. The correlations between the measured and the predicted body size measurements were strong for at all ages. In sensitivity analyses restricted to the measured data, similar associations were found as with the predicted body size data (Supplementary Table 8). This provides some reassurance of the validity of the predicted anthropometrics. However, we still acknowledge the potential for outcome misclassification as only 23% of the cohort had anthropometric information at 8 years (Supplementary Table 3). At the time of release of the current data, 53% (27,142 children) of our study population had not reached the age of 8 years, and only 24% of missing anthropometric information at 8 years can be attributed to loss to follow-up. Furthermore, we found that maternal caffeine exposure was not related to loss to follow-up (Supplementary Table 3).

The self-report of diet, which can induce misreporting, is a limitation. However, fair agreement between beverage intakes, particularly of coffee and tea, was found in a validation study based on food records and biomarkers[25 37]. Observational studies can never establish causality; however, our results fulfill some of the Hill's criteria for causation[38] with a strong association, consistent findings for major caffeine sources, a biological gradient with higher caffeine exposure being associated to abnormal growth, consistent findings in animal models and a plausible mechanism, i.e. fetal programing.

Our study adds evidence to two previous epidemiological studies[19 20] that found an effect of prenatal caffeine exposure on child growth. In the study by Voerman et al., maternal caffeine

intake above 360mg/day was associated with higher weight and BMI from birth to age 6 years, compared with intakes below 180mg/day[19]. In contrast to our findings, they found no association with overweight. Higher caffeine intake (360-540mg/day) during pregnancy was positively associated with body fat percentage and higher insulin levels in 6-year-olds. The exposure was assessed only by intakes of coffee and tea, which in our study also are the main but not the only caffeine contributors (78% of total caffeine intake). The median intake was double than in our study, resulting to a higher reference level (reference: <180mg/day, median: 117mg/day), providing less contrast between the compared exposure groups and less comparability to our study, as most of these women were not complying to the recommendation. Nevertheless, we found associations with adverse effects on child's growth even at low caffeine intakes, in the range of the recommendation, that are mostly due to consumption of foods and drinks other than coffee (chocolate, black tea, caffeinated sodas) [5]. Li et al. found likewise that any maternal caffeine intake was associated with an overall increased risk of obesity from ages 2 to 15 years, with an exposure range similar to the current study[20]. We have used similar approaches to study changes in individual growth trajectories, though with shorter follow-up. In addition, we provided age specific weight and BMI deviations, in order to find sensitive developmental windows when the association with the prenatal caffeine exposure exacerbated. There is no previous report of the association between caffeine intake in pregnancy and excess infant growth.

Potential mechanisms

Since excess growth in infancy, in itself, can be directly related to childhood obesity, adiposity[39] and an unfavorable adult cardio-metabolic profile[40], the associations between prenatal caffeine exposure with overweight, body fat and insulin, found in this study and the previous reports, might be explained by excess infant growth. Putting together the previous findings in the MoBa study[5], we have shown that children prenatally exposed to high caffeine levels are smaller at birth, grow faster in infancy and retain a higher weight throughout childhood without significant height differences, thus becoming overweight. These findings concur with the fetal programming of obesity hypothesis[41]. Nevertheless, the effect of prenatal caffeine exposure on postnatal growth and overweight was not dependent on birth weight. Hence, along with a healthy birth weight, it is important to identify the modifiable factors that can independently affect excess growth in infancy. A growing number of studies have shown that other prenatal factors, e.g. excess

gestational weight[42], high (>3times/week) fish intake [43],and postnatal factors, e.g. formula feeding and feeding schedule[44], are associated with increased risk of excess growth in infancy.

The biological plausibility supporting our findings is mainly provided by animal studies where, prenatal exposure to caffeine was shown to program the offspring towards excess growth and cardio-metabolic disorders through alterations i) in the hypothalamic-pituitary-adrenocortical axis that plays a key role in growth and metabolism[45-47], ii) in regulation of adenosine and adenosine antagonists, which are important modulators of development[48 492] and iii) in the placental expression and transportation of leptin[50], essential for appetite regulation.

Although most pregnant women reduce their caffeine intake during pregnancy and few have caffeine intakes higher than 200 mg/day (10%), our results show associations between caffeine intakes below 200 mg/day and excess growth. The results add supporting evidence for the current advice to reduce caffeine intake during pregnancy and indicate that complete avoidance might actually be advisable. An absence of a "safe intake level" has been previously reported in the basis of associations between maternal caffeine intake and fetal growth restriction[51].

The association between prenatal caffeine exposure and overweight attenuated after 5 years, with only very high exposed children being at risk for overweight. Residual confounding due to postnatal factors related to overweight in late childhood might explain this attenuation. Nevertheless, adjustment for risk factors of being overweight at 8 years would introduce bias to the association under study. In addition, weight and height are screened from birth to 5 years in scheduled voluntarily appointments at the public health centers. Hence, a possible misclassification of outcome from anthropometrics after 5 years, might also explain the attenuation of the association.

There are two studies showing effects of caffeine intake on body composition and cardiometabolic health [19 52], with discrepant results. In the present study, we did not have any information on body composition. In addition, it is known that several genetic factors can contribute to variation in caffeine metabolism[53], and studies in adults have shown that slower metabolism of caffeine is related to higher risk of cardiovascular disease[54]. On the other hand, during pregnancy, maternal caffeine clearance modified the association between maternal caffeine intake and fetal growth restriction, with faster clearance being more detrimental [51]. Thus, there is a need to investigate the programming effect of prenatal caffeine exposure on child and

adult body composition and cardiometabolic health, taking into account the genetic variation of maternal caffeine metabolism.

Conclusions

We found that the risk of excess infant growth and overweight in childhood-important risk factors for later cardio-metabolic disease- is increasing with maternal caffeine intake, with no apparent threshold. Maternal caffeine intake >200mg/day during pregnancy was associated with high weight gain velocity beginning from the first months of life and higher BMI throughout childhood. Our findings not only support the recommendation to limit caffeine intake during pregnancy (<200mg/day) but also indicate that complete avoidance might be advisable.

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BJ initiated this collaborative project, contributed to the study design and the interpretation of the results. VS defined the research question, contributed to the study design, database preparation and interpretation of the results. She is guarantor and had final responsibility for the decision to submit for publication. All authors read, revised and approved the final version of the paper.

Data sharing statement: No additional data are available. All data from the MoBa study are available to all qualified researchers/research groups in Norway and to international researchers who are collaborating with a Norwegian researcher.

Declaration of transparency

EP as the lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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TABLES AND FIGURES

Figure 1. **Prevalence of excess growth in infancy and overweight/obesity at age 3, 5 and 8 years, in the whole population and by maternal caffeine intake during pregnancy**

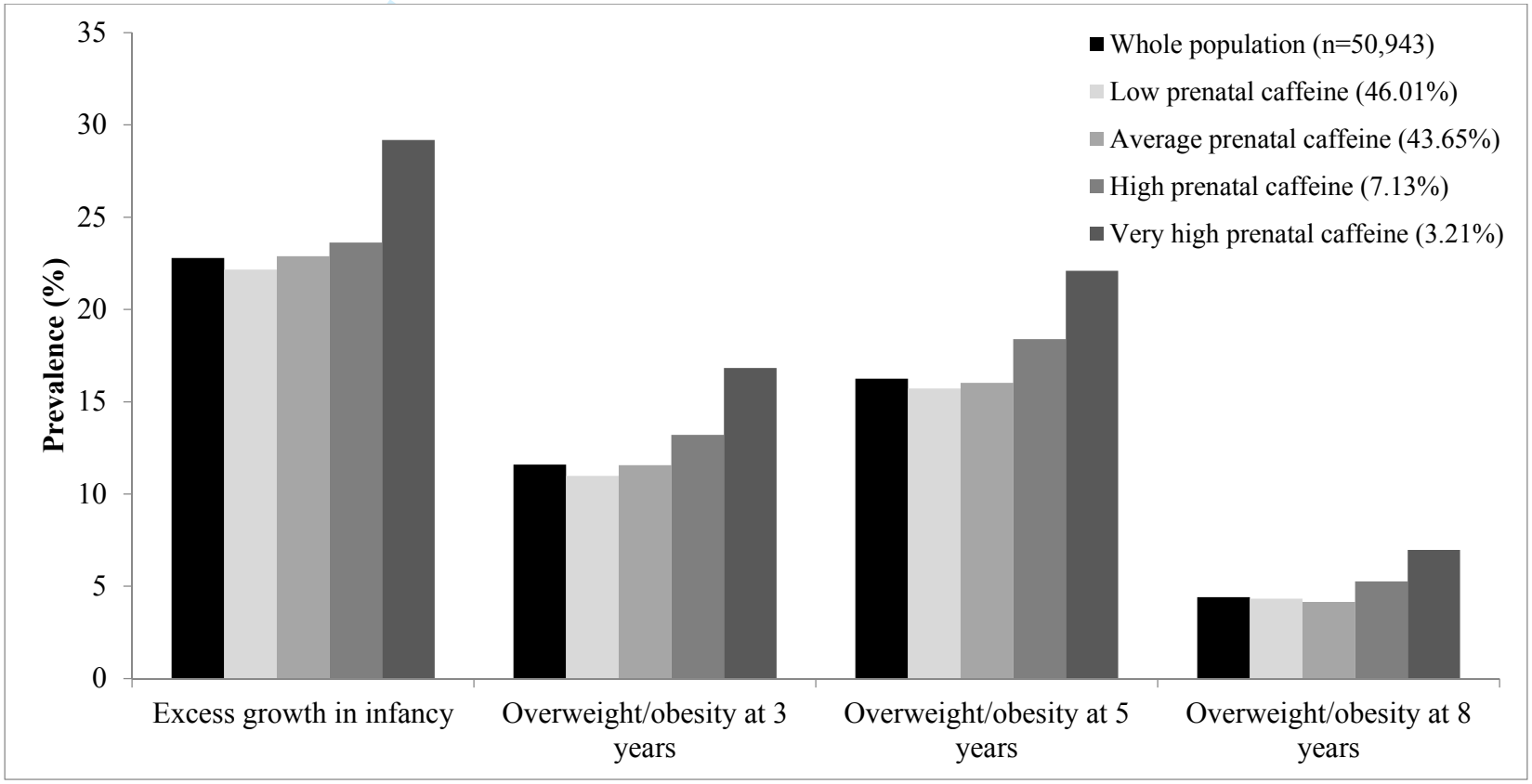


Table 1. **Maternal caffeine intake in pregnancy and risk of excess growth in infancy (from birth to age 12 months)**

	Risk of excess growth in infancy (from birth to age 12 months)[a]					
	All children (n=38,338)		After excluding smokers during pregnancy (n=35,672)		After excluding SGA neonates[b] (n=35,144)	
Maternal daily caffeine intake	OR	95% CI	OR	95% CI	OR	95% CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.15	1.09,1.22	1.15	1.08,1.22	1.14	1.07,1.22
High (200-299 mg)	1.30	1.16,1.45	1.32	1.17,1.49	1.25	1.11,1.41
Very high (≥300 mg)	1.66	1.42,1.93	1.58	1.30,1.91	1.67	1.41,1.97

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months.

[b] SGA according to Skjaerven et al.

Table 2. Maternal caffeine intake in pregnancy and risk of overweight/obesity at age 3, 5 and 8 years.

	Risk of overweight and/or obesity[a]					
	All children (n=50,943)					
	Age 3 years		Age 5 years		Age 8 years	
Maternal daily caffeine intake	OR	95% CI	OR	95% CI	OR	95% CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.05	0.99,1.12	1.00	0.95,1.06	0.95	0.86,1.04
High (200-299 mg)	1.17	1.05,1.30	1.12	1.02,1.23	1.11	0.94,1.31
Very high (≥300 mg)	1.44	1.24,1.67	1.29	1.13,1.47	1.29	1.04,1.61
After excluding smokers during pregnancy (n=47,036)						
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.05	0.99,1.12	1.00	0.95,1.06	0.92	0.84,1.02
High (200-299 mg)	1.17	1.04,1.32	1.10	1.00,1.23	1.08	0.89,1.29
Very high (≥300 mg)	1.50	1.25,1.79	1.31	1.12,1.54	1.30	1.00,1.70
After excluding SGA neonates (n=46,718) [b]						
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.06	0.99,1.12	1.01	0.95,1.06	0.96	0.87,1.05
High (200-299 mg)	1.18	1.05,1.32	1.14	1.03,1.25	1.11	0.94,1.32
Very high (≥300 mg)	1.48	1.28,1.72	1.32	1.15,1.51	1.36	1.09,1.69

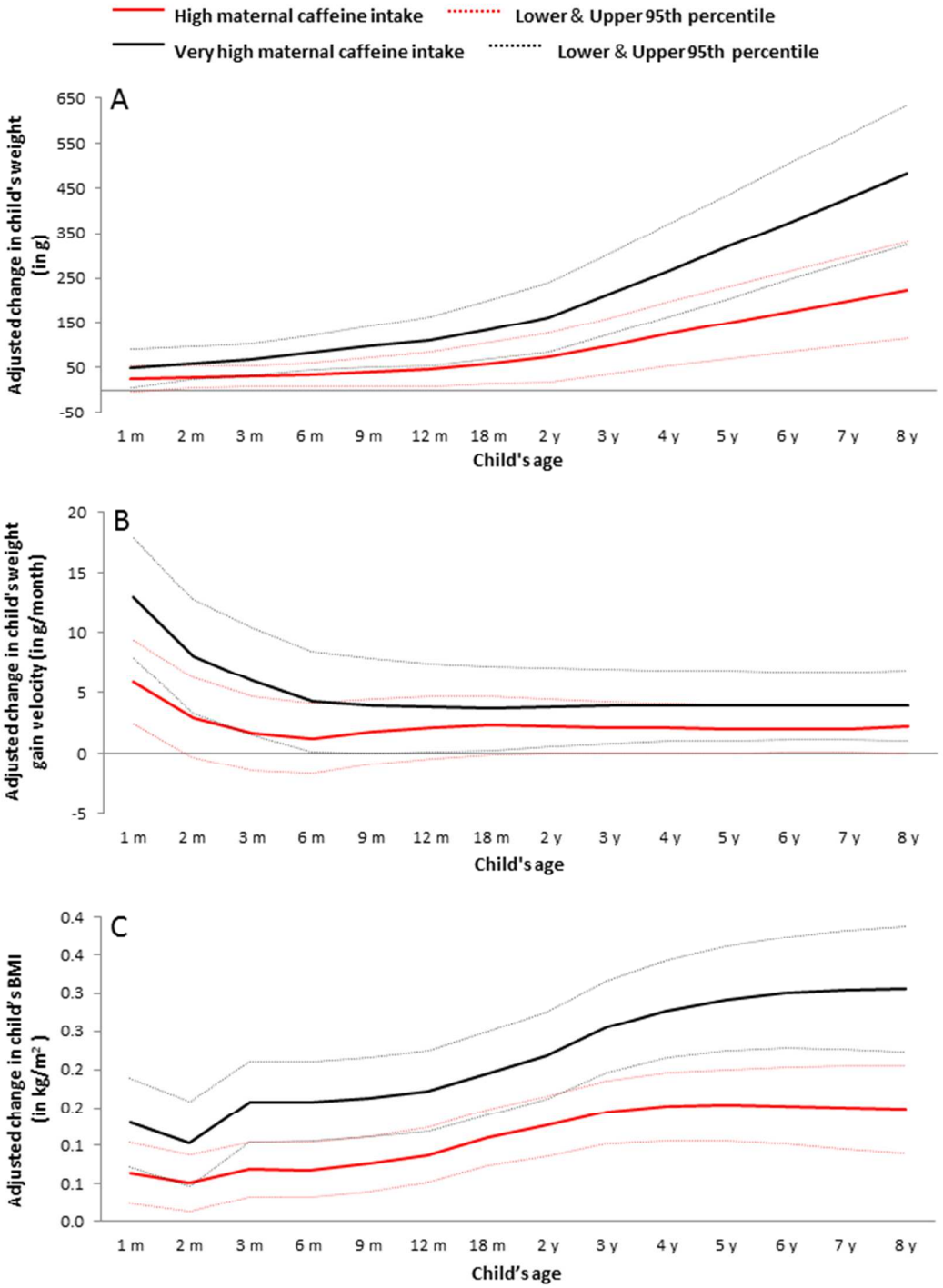
The same population was included at each age since the outcome was defined using model-derived anthropometrics.

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender

[a] Overweight and/or obesity in children, according to the International Obesity Task Force definition.

[b] SGA according to Skjaerven et al.

Figure 2. Maternal high (red) and very high (black) caffeine intake in pregnancy and adjusted change in children's a) weight (in g), b) weight gain velocity (in g/month) and c) body mass index (in kg/m^2), from age 1 month to 8 years (beta coefficients in solid lines and 95% confidence intervals in thin dashed lines). Low caffeine intake is the reference group.



Footnote: Models adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, nausea and/or vomiting during pregnancy, maternal smoking during pregnancy, gestational age, and birth weight

Table 3. Maternal caffeine intake in pregnancy and child's weight, weight gain velocity and body mass index (BMI) during childhood (n=50,943)

	Child's developmental period						
	Infancy		Toddlerhood		Pre-school age		School age
Maternal daily caffeine intake	3 m Beta (95%CI)	6 m Beta (95%CI)	12 m Beta (95%CI)	18 m Beta (95%CI)	3 y Beta (95%CI)	5 y Beta (95%CI)	8 y Beta (95%CI)
Weight (in g)							
Average (50-199 mg)	**14.1 (1.6,26.6)**	**15.1 (1.3,28.8)**	14.9 (-5.1,34.9)	14.8 (-9.3,38.9)	16.1 (-16.9,49.0)	18.2 (-24.0,60.5)	21.5 (-35.1,78.1)
High (200-299 mg)	**31.3 (7.5,55.1)**	**35.0 (8.8,61.1)**	**45.4 (7.3,83.5)**	**59.0 (13.1,104.8)**	**99.0 (36.3,161.7)**	**148.9 (68.4,229.4)**	**222.0 (114.1,329.8)**
Very high (≥300 mg)	**67.0 (32.5,101.6)**	**83.2 (45.3,121.1)**	**110.1 (55.2,165.0)**	**135.5 (69.5,201.5)**	**213.4 (123.3,303.6)**	**320.0 (204.4,435.6)**	**480.3 (325.5,635.1)**
Weight gain velocity (in g/month)							
Average (50-199 mg)	0.8(-0.8,2.4)	0.4(-1.2,1.9)	0.2(-1.2,1.5)	0.3(-1.0,1.5)	0.3(-0.7,1.4)	0.3(-0.7,1.4)	0.3(-0.7,1.4)
High (200-299 mg)	1. (-1.4,4.7)	1.2(-1.7,4.1)	2. (-0.4,4.7)	2.3(-0.1,4.7)	**2.1(0,4.3)**	**2.0(0.1,4.0)**	**2.2(0,4.0)**
Very high (≥300 mg)	**6.0(1.5,10.4)**	**4.3(0.2,8.5)**	**3.8(0.1,7.4)**	**3.7(0.3,7.1)**	**3.9(0.8,7.0)**	**3.9(1.1,6.8)**	**3.9(1.1,6.8)**
BMI (in kg/m^2)							
Average (50-199 mg)	**0.03 (0.01,0.05)**	**0.03 (0.01,0.05)**	**0.04 (0.02,0.06)**	**0.04 (0.02,0.06)**	**0.04 (0.02,0.06)**	**0.03 (0.01,0.06)**	0.02 (-0.01,0.05)
High (200-299 mg)	**0.07 (0.03,0.11)**	**0.07 (0.03,0.10)**	**0.09 (0.05,0.12)**	**0.11 (0.07,0.15)**	**0.14 (0.10,0.19)**	**0.15 (0.11,0.20)**	**0.15 (0.09,0.21)**
Very high (≥300 mg)	**0.16 (0.10,0.21)**	**0.16 (0.11,0.21)**	**0.17 (0.12,0.23)**	**0.20 (0.14,0.25)**	**0.26 (0.20,0.32)**	**0.29 (0.22,0.36)**	**0.31 (0.22,0.39)**

Abbreviations: Beta: beta coefficients, CI: confidence intervals

Infancy is defined as the period from birth to age 12 months, toddlerhood as the period from age 12 months to 3 years, pre-school age as the period from age 3 years to 5 years and school age as the period from age 5 years onwards.

Effect estimates derived from linear mixed effect models with input of all anthropometric information from age 1 month to 8 years and adjustment for: maternal age, parity, maternal education, pre-pregnancy BMI, nausea and/or vomiting during pregnancy, maternal smoking during pregnancy, paternal BMI, gestational age and birth weight

Supplementary Table 1. Estimation of caffeine intake during pregnancy in the Norwegian Mother and Child Cohort Study.

Food item containing caffeine	Reported frequency	Serving	Caffeine concentration (mg/100g of food)
Filtered coffee	Cups per day, week or months	1 cup (125ml)	57
Boiled/pressed coffee	Cups per day, week or months	1 cup (125ml)	57
Powdered instant coffee	Cups per day, week or months	1 cup (125ml)	40
Decaffeinated coffee	Cups per day, week or months	1 cup (125ml)	2
Caffe latte/cappuccino	Cups per day, week or months	1 cup (125ml)	21
Espresso	Cups per day, week or months	1 cup (125ml)	114
Black tea	Cups per day, week or months	1 cup (250ml)	16
Caffeinated soft drinks, sugar sweetened and artificially sweetened	Cups per day, week or months	1 glass (250 ml)	12
Energy drink	Cups per day, week or months	1 glass (250 ml)	15
Chocolate milk	Cups per day, week or months	1 glass (250 ml)	15
Chocolate, medium dark			38
Sandwich spreads with cocoa			13
Deserts with coca			3
Cakes with cocoa			4
Sweets with cocoa			9

Supplementary Table 2. Definitions of overweight and obesity

Reference	Description	Age (years)	Overweight and/or obesity (kg/m^2)		Prevalence (%)	
			Males	Females	Males	Females
International Obesity Task Force (IOTF) [1] (BMJ 2000 May 6; 320 (7244); 1240-Table 4)	Study-specific BMIs were calculated for age and sex	3	17.89	17.56	10.77	12.44
		5	17.42	17.15	14.30	18.28
		8	18.44	18.35	3.61	5.24

From Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ.* 2000;320(7244):1240-1243

Supplementary Table 3. Anthropometric measurements, maternal caffeine intake level and cohort attrition.

Measurement	Age (months)	Weight (kg)		Cohort retention	Height (cm)		Cohort retention	Maternal caffeine intake level			
								Low	Average	High	Very high
	Mean	N	Mean		N	Mean					
1	1.5	49672	5.0	98%	39175	57	77%	46%	44%	7%	3%
2	3.1	49912	6.4	98%	49122	62	96%	46%	44%	7%	3%
3	5.6	47047	7.9	92%	46640	68	92%	46%	44%	7%	3%
4	8.2	37612	8.8	74%	37493	71	74%	47%	43%	7%	3%
5	12.2	38660	9.9	76%	39046	76	77%	47%	43%	7%	3%
6	15.9	38757	10.9	76%	38842	81	76%	47%	43%	7%	3%
7	25.3	20485	13.0	40%	20855	89	41%	48%	42%	7%	3%
8	36.0	30588	15.1	60%	29747	97	58%	47%	43%	7%	3%
9	62.1	19340	20.0	38%	19768	113	39%	46%	44%	7%	3%
10	84.7	18699	25.1	37%	19550	126	38%	47%	43%	7%	3%
11	97.0	11685	28.7	23%	12312	132	24%	47%	42%	7%	4%

Supplementary Table 4. Parental and pregnancy-related characteristics by category of maternal caffeine intake during pregnancy (n=50,943)

	Maternal caffeine intake during pregnancy							
	Low caffeine intake (<50mg/day) N=23,437		Average caffeine intake (50-199mg/day) N=22,239		High caffeine intake (200-299mg/day) N=3,633		Very high caffeine intake (≥300mg/day) N=1,634	
	N	%	N	%	N	%	N	%
Maternal age (years)								
<20	247	1.1	94	0.4	20	0.6	6	0.4
20-29	12,426	53.0	8,643	38.9	1,185	32.6	474	29.0
≥30	10,764	45.9	13,502	60.7	2,428	66.8	1,154	70.6
Maternal education (years)								
<13	7,025	30.0	5,993	27.0	1,142	31.4	755	46.2
13-16	10,725	45.7	9,538	42.9	1,512	42.6	623	38.1
>16	5,687	24.3	6,708	30.1	979	27.0	256	15.7
Parity								
Primiparous	14,260	60.8	11,053	49.7	1,492	41.1	492	30.1
Multiparous	9,177	39.2	11,186	50.3	2,141	58.9	1,142	69.9
Pre-pregnancy BMI (kg/m^2)								
<18.5	690	2.9	644	2.9	89	2.5	44	2.7
18.5-24.9	15,466	66.0	14,893	67.0	2,416	66.5	999	61.1
25-29.9	5,071	21.6	4,838	21.7	785	21.6	406	24.9
≥30	2,210	9.4	1,864	8.4	343	9.4	185	11.3
Gestational weight gain according to IOM[1]								
Lower than recommended	4,663	19.9	4,165	18.7	587	16.1	273	16.7
Equal to recommended	7,125	30.4	6,737	30.3	1,016	28.0	433	26.5
Higher than recommended	11,649	49.7	11,337	51.0	2,030	55.9	928	56.8
Maternal daily energy intake (in tertiles, kcal)								
<2.000	9,211	39.3	6,791	30.5	802	22.1	347	21.2
2.000-2.500	7,803	33.3	7,619	34.3	1,137	31.3	458	28.1
>2.500	6,423	27.4	7,829	35.2	1,694	46.6	829	50.7
Maternal smoking during pregnancy								
Never	22,500	96.0	20,532	92.3	3,005	82.7	999	61.1
Ever	937	4.0	1,707	7.7	628	17.3	635	38.9
Maternal alcohol use during pregnancy								
Never	21,993	93.8	19,234	86.5	3,937	80.8	1,245	76.2
Ever	1,504	6.2	3,005	13.5	696	19.2	389	23.8
Nausea/vomiting in pregnancy								
Never	6,057	25.8	6,949	31.3	1,358	37.4	673	41.2

Ever	17,380	74.2	15,290	68.7	2,275	62.6	961	58.8
Paternal BMI (kg/m^2)								
<18.5	51	0.2	47	0.2	13	0.3	5	0.3
18.5-24.9	10,538	44.6	9,831	44.2	1,547	42.6	661	40.4
25-29.9	10,526	45.3	10,254	46.1	1,699	46.8	756	46.3
≥30	2,322	9.9	2,107	9.5	374	10.3	212	13.0
Paternal smoking during pregnancy								
Never	19,338	82.5	18,029	81.1	2,752	75.7	1,007	61.6
Ever	4,099	17.5	4,210	18.9	881	24.3	627	38.4

p-value<10^{-5} of chi square tests of all cross-tabulations presented in table

[1]IOM : Institute of Medicine

Supplementary Table 5. Maternal caffeine intake in pregnancy and risk of overweight/obesity at age 3, 5 and 8 years, after adjustment for birth weight.

	Risk of overweight and/or obesity [a], after additional adjustment for birth weight					
	Age 3 years		Age 5 years		Age 8 years	
Maternal daily caffeine intake	OR	95%CI	OR	95%CI	OR	95%CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	**1.08**	**1.02,1.15**	1.03	0.97,1.08	0.97	0.88,1.06
High (200-299 mg)	**1.21**	**1.09,1.36**	**1.16**	**1.05,1.28**	1.14	0.96,1.34
Very high (≥300 mg)	**1.53**	**1.32,1.78**	**1.36**	**1.19,1.55**	**1.35**	**1.09,1.68**

The same population was included at each age since the outcome was defined using model-derived anthropometrics.

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight

[a] Overweight and/or obesity in children, according to the International Obesity Task Force definition

Supplementary Table 6. Maternal caffeine intake during pregnancy from different sources and risk of excess growth in infancy (from birth to age 12 months) and overweight/obesity at age 3, 5 and 8 years

	Child's growth parameters											
	Excess growth[a]			Overweight/obesity at age 3 years[b]			Overweight/obesity at age 5 years[b]			Overweight/obesity at age 8 years[b]		
	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI
Caffeine from black coffee												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.18**	**1.11**	**1.26**	**1.18**	**1.11**	**1.26**	**1.12**	**1.05**	**1.18**	**1.11**	**1.00**	**1.23**
200-300	**1.31**	**1.06**	**1.62**	1.14	0.91	1.41	1.11	0.92	1.34	1.09	0.77	1.53
>300	**1.72**	**1.45**	**2.03**	**1.69**	**1.44**	**1.99**	**1.39**	**1.20**	**1.61**	**1.48**	**1.17**	**1.88**
Caffeine from black tea												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.11**	**1.01**	**1.21**	1.07	0.98	1.18	1.05	0.97	1.14	**1.20**	**1.04**	**1.38**
200-300	1.74	0.93	3.25	1.16	0.56	2.40	1.22	0.65	2.31	0.28	0.04	2.07
>300	1.67	0.50	5.54	0.86	0.20	3.75	0.86	0.25	2.97	NE		
Caffeine from soda drinks												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.20**	**1.08**	**1.33**	0.96	0.86	1.07	0.96	0.88	1.06	1.01	0.87	1.18
200-300	1.40	0.95	2.06	1.13	0.77	1.65	1.18	0.84	1.65	1.48	0.91	2.41
>300	1.21	0.22	6.58	0.48	0.06	3.79	0.73	0.16	3.34	NE		

NE: not estimated

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months. Model adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender, and mutually adjusted for maternal caffeine intake from black coffee, black tea and soda drinks.

[b] Overweight and/or obesity, according to International Obesity Task Force definition.

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight, and mutually adjusted for maternal caffeine intake from black coffee, black tea and soda drinks.

Supplementary Table 7. Sensitivity after excluding very high caffeine drinkers and using no black coffee drinkers (n=23,402) as the reference group.

	No coffee drinkers OR (95%CI)	Caffeine intake <199mg OR (95%CI)	Caffeine intake 200-299mg OR (95%CI)
Excess infant growth	1.00	1.07 (1.01,1.13)	1.25 (1.12,1.39)
Overweight			
3 years	1.00	1.12 (1.06,1.19)	1.21 (1.08,1.35)
5 years	1.00	1.08 (1.03,1.14)	1.17 (1.06,1.29)
8 years	1.00	1.02 (0.93,1.12)	1.15 (0.98,1.36)

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months.

[b] Overweight and/or obesity, according to International Obesity Task Force definition.

Models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender.

Supplementary Table 8. Maternal caffeine intake in early pregnancy and risk of overweight/obesity at pre-school (3-5 years) and school (6-8 years) age, using measured anthropometric values

	Risk of overweight and/or obesity at pre-school and school age[a]					
	Pre-school age (n=31,482)			School age (n=19,722)		
Maternal daily caffeine intake	N/% cases	OR	95% CI	N/% cases	OR	95% CI
Low (<50 mg)	14,723/13	1.00		9,204/12	1.00	
Average (50-199 mg)	13,706/14	1.06	0.99,1.14	8,471/12	1.03	0.93,1.13
High (200-299 mg)	2,135/16	**1.21**	**1.07,1.39**	1,386/14	1.13	0.95,1.35
Very high (≥300 mg)	918/20	**1.52**	**1.27,1.81**	664/18	**1.32**	**1.04,1.66**

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender

[a] Overweight and/or obesity, according to International Obesity Task Force definition.

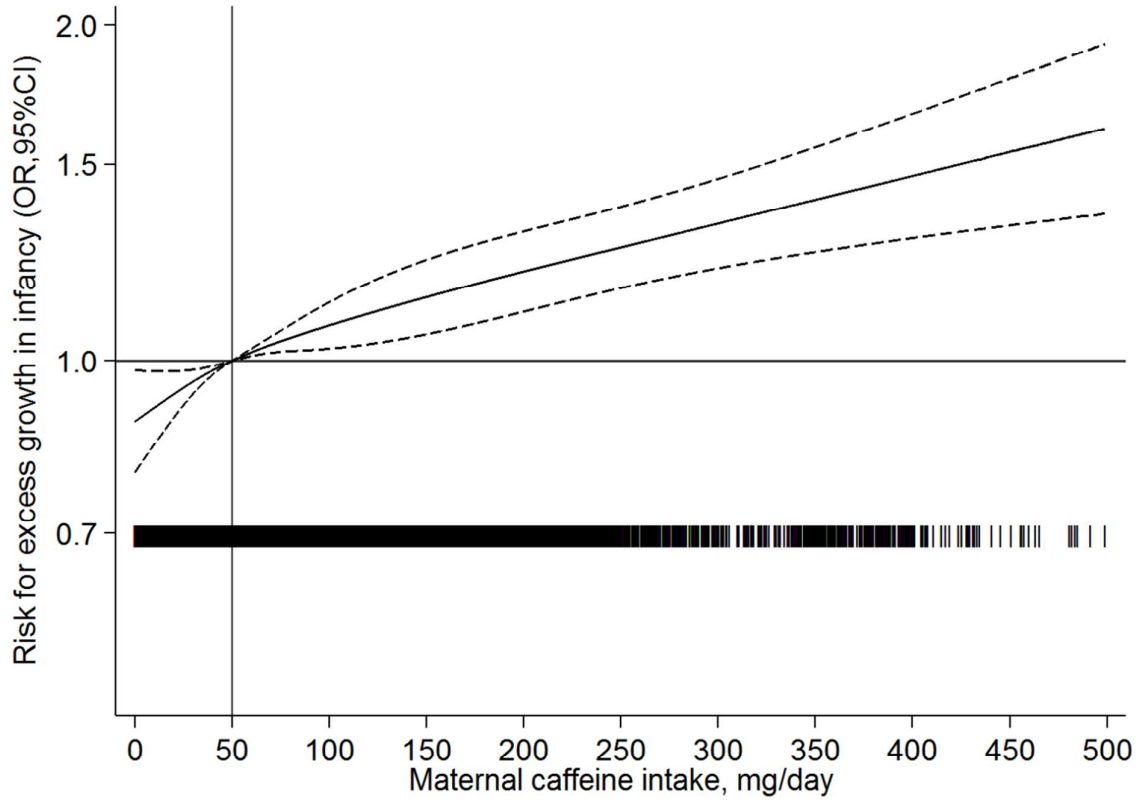
Supplementary Table 9. Maternal caffeine intake in early pregnancy and child's height and height gain velocity during childhood

Maternal daily caffeine intake	Child's developmental period: Infancy 3 m Beta (95%CI)	Infancy 6 m Beta (95%CI)	Toddlerhood 12 m Beta (95%CI)	Toddlerhood 18 m Beta (95%CI)	Pre-school age 3 y Beta (95%CI)	Pre-school age 5 y Beta (95%CI)	School age 8 y Beta (95%CI)
Height (in cm)							
Average (50-199 mg)	0.00 (-0.03,0.03)	0.00 (-0.04,0.03)	-0.03 (-0.07,0.02)	-0.04 (-0.09,0.00)	-0.05 (-0.10,0.01)	-0.02 (-0.09,0.05)	0.02 (-0.07,0.10)
High (200-299 mg)	-0.01 (-0.07,0.05)	-0.01 (-0.07,0.06)	-0.04 (-0.12,0.04)	-0.07 (-0.15,0.02)	-0.09 (-0.20,0.01)	-0.08 (-0.21,0.05)	-0.05 (-0.21,0.12)
Very high (≥300 mg)	-0.03 (-0.12,0.05)	-0.01 (-0.10,0.09)	0.00 (-0.12,0.11)	-0.02 (-0.15,0.10)	-0.09 (-0.24,0.07)	-0.13 (-0.31,0.06)	-0.17 (-0.41,0.07)
Height gain velocity (in mm/month)							
Average (50-199 mg)	**0.05 (0.02,0.09)**	-0.01 (-0.05,0.02)	-0.03 (-0.07,0.01)	-0.01 (-0.05,0.03)	0.02 (-0.02,0.06)	0.02 (-0.02,0.06)	0.02 (-0.02,0.07)
High (200-299 mg)	**0.08 (0.01,0.14)**	-0.01 (-0.08,0.05)	-0.05 (-0.12,0.02)	-0.04 (-0.11,0.04)	0.01 (-0.07,0.08)	0.02 (-0.06,0.09)	0.02 (-0.06,0.10)
Very high (≥300 mg)	**0.11 (0.01,0.21)**	0.04 (-0.06,0.14)	-0.04 (-0.14,0.06)	-0.06 (-0.16,0.05)	-0.04 (-0.15,0.07)	-0.03 (-0.14,0.08)	-0.03 (-0.15,0.09)

Abbreviations: Beta: beta coefficients, CI: confidence intervals

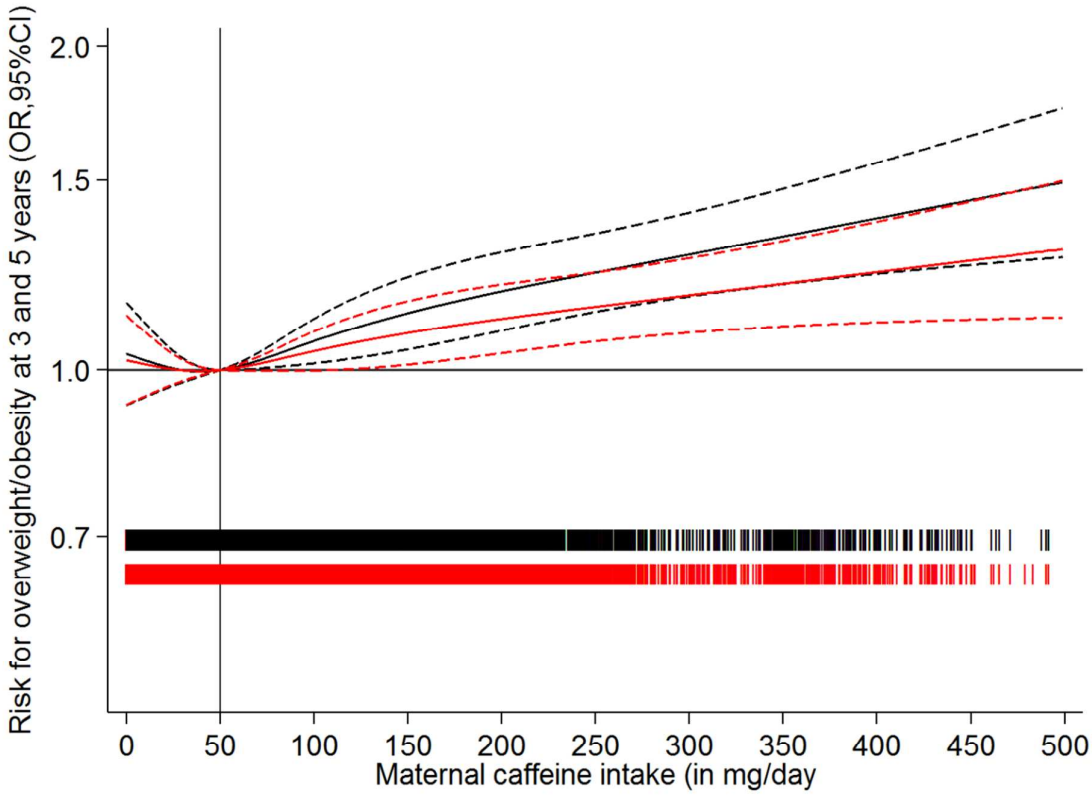
Effect estimates derive from linear mixed effect models with input of all anthropometric information from age 1month to 8 years and adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, nausea and/or vomiting during pregnancy, maternal smoking during pregnancy, gestational age, gender and birth weight

Supplementary Figure 1. Maternal caffeine intake on a continuous scale and risk of excess growth in infancy. Odds ratios (solid line) and 95% confidence intervals (dashed lines) derived from a logistic regression model using restricted cubic splines. The solid vertical line represents the reference value (50mg/day). The bar represents the children with excess growth.



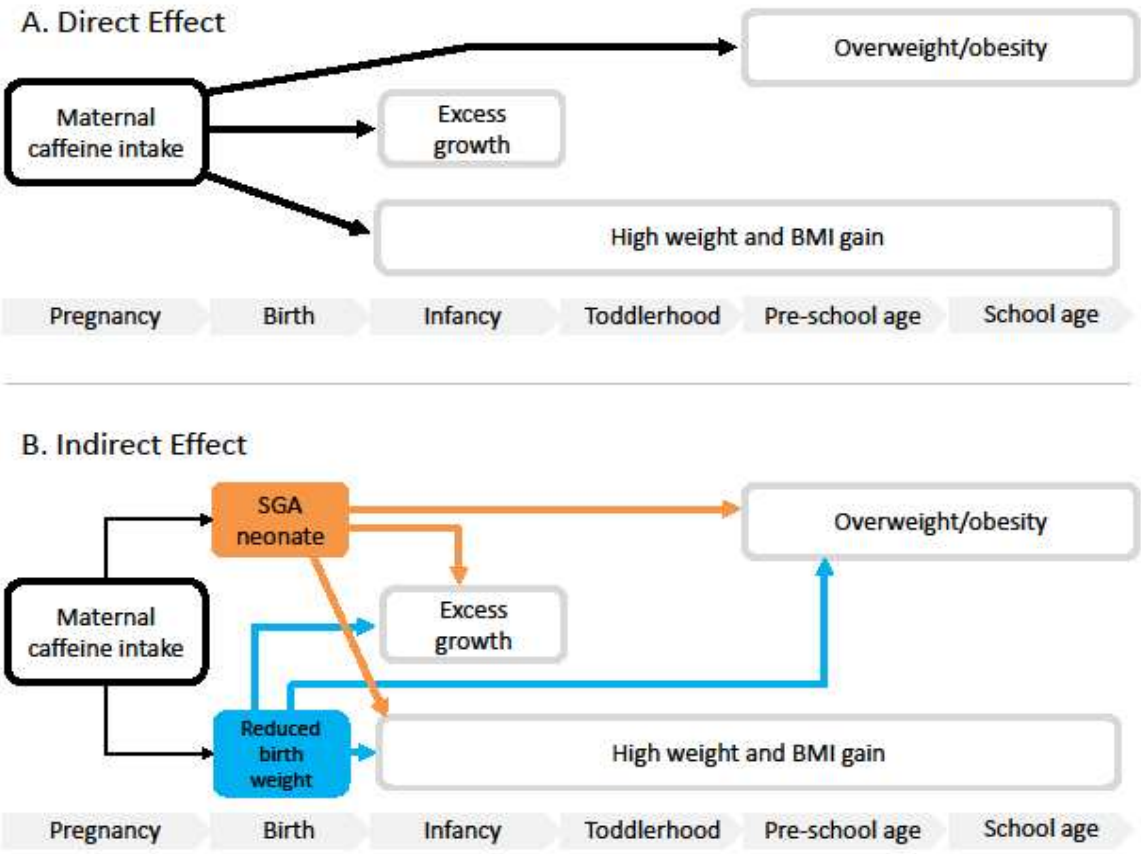
Footnote: all models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender and SGA according to Skjaerven et al.

Supplementary Figure 2. Maternal caffeine intake in continuous scale and risk for overweight/obesity at age 3 (black) and 5 years (red). Odds ratios (solid line) and the 95% confidence intervals (dashed lines) derived from a logistic regression model using restricted cubic splines. The solid vertical line represent the reference value (50mg/day). The bars represent the children with overweight/obesity.



Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight

Supplementary Figure 3. Simplified causal diagram for the direct and indirect associations between maternal caffeine intake during pregnancy and the studied outcomes, mediated by SGA and birth weight



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract This has been done in both subsections. The study is a prospective cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found This has been done. In the abstract, we have described our study design and setting, our study participants and in more detail, we have described the definition exposure and the main outcomes of interest. In a separate paragraph of the abstract, we have described the findings in details and have summarized the main finding in the conclusion section (page 2).
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported This has been done in the introduction. We have provided the rationale for our study as well as the literature to support it (page 3-4).
Objectives	3	State specific objectives, including any prespecified hypotheses This has been done in the last paragraph of the introduction (page 4, first paragraph).
Methods		
Study design	4	Present key elements of study design early in the paper Our study design was described in the first paragraph of the methods, subsection "Study population and ethical approval" (page 4).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection The setting, location, recruitment period and follow-up, as well as the database version used were described in the first paragraph of the methods section, along with the ethical approval of the study, subsection "Study population and ethical approval" (page 4).
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up The eligibility and inclusion criteria has been described the methods section subsection "Study population and ethical approval" (page 4).
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed This is not a matched study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. This has been done. The exposure has been described in details in the methods, subsection "Maternal caffeine intake during pregnancy" (page 5), as well as in Supplementary Table 2. The outcome has been described in details in the methods, subsection "Child postnatal growth and overweight" (pages 5-6) and in Supplementary Tables 1 and 3. Potential confounders and effect modifiers are described in the methods; in subsection "Statistical analysis" (pages 6-7).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group All these has been described in the methods section, in subsections "Maternal caffeine intake during pregnancy" and "Child postnatal growth and overweight" (pages 5-6). More information of data source for the exposure and outcome are presented in Supplemental Material.

Bias	9	Describe any efforts to address potential sources of bias Possible bias have been described in the "Child postnatal growth and overweight" subsection of methods (pages 5-6) and have been stressed in the study limitations and other parts of the discussion (pages 10-11).
Study size	10	Explain how the study size was arrived at The included study population is described in the "Study population and ethical approval" (page 4).
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Regarding the exposure, the choice of subgroups was explained at subsection "Maternal caffeine intake during pregnancy" (page 5) and how quantitative variable were handled was explained in the subsection "statistical analysis" (pages 6-7). Regarding the outcome, the choice of subgroups was explained at subsections "Child postnatal growth and overweight" (pages 5-6), as well in Supplemental material and how quantitative variable were handled was explained in the "Statistical analysis" (pages 6-7).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding This has been done in the "Statistical analysis" section (pages 6-7).
		(*b*) Describe any methods used to examine subgroups and interactions This has been done in the "Statistical analysis" section (pages 6-7).
		(*c*) Explain how missing data were addressed In the subsection "Statistical analysis" (page 6-7) we have described that we have conducted complete case analysis.
		(*d*) If applicable, explain how loss to follow-up was addressed This has been done in the "Statistical analysis" section (pages 6-7).
		(*e*) Describe any sensitivity analyses This has been done in the "Statistical analysis" section (pages 6-7).
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed This has been described in the "Study population and ethical approval" (page 4).
		(b) Give reasons for non-participation at each stage This has been described in the "Study population and ethical approval" (page 4).
		(c) Consider use of a flow diagram We have not provided a flow diagram.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders This was provided in the results, subsection "Lifestyle and socio-demographic characteristics related to maternal caffeine intake during pregnancy" (pages 7-8) and in Supplemental material (Table 4).
		(b) Indicate number of participants with missing data for each variable of interest This was provided in Supplemental material (Tables 1 and 4).
		(c) Summarise follow-up time (eg, average and total amount) This was provided in Supplemental material (Tables 1).
Outcome data	15*	Report numbers of outcome events or summary measures over time This was provided in Figure 1 and in Supplemental material (Table 1 and 3).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included This has been provided in the results section and in Tables 1, 2, 3).
		(*b*) Report category boundaries when continuous variables were categorized This has been done in the results section (pages 7-9) and in Figures and Tables.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses This was reported in the results section, subsection "sensitivity analyses" (page 9).
Discussion		
Key results	18	Summarise key results with reference to study objectives In the first paragraph of the discussion, we have summarized our key finding (pages 9-10).
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. In the discussion, subsection "Strengths and limitations of this study" as well as throughout the whole discussion section we have reported and discussed the limitations of our study (pages 9-12).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. In the conclusion section, we have summarized our results and provided an overall interpretation taking into account the strengths and the limitations of our study, as well as the biological plausibility (page 12). We have compared our findings with two previous studies investigating a similar hypothesis (pages 10-11) and we have discussed potential biological mechanisms (page 10).
Generalisability	21	Discuss the generalisability (external validity) of the study results Regarding the exposure, the major caffeine contributor is coffee and black tea and no large differences and/or similar variations by brand, are expected in different countries and populations of pregnant women. Regarding the outcome, we have used international cut-offs to define overweight and we have compared our growth data with the WHO growth Standards to define excess growth; hence, enhancing the external validity of our findings.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. Funding has been described in a specific point (page 14).

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Maternal caffeine intake during pregnancy is associated with excess growth in infancy and overweight in childhood: results from a large prospective cohort study

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Complete List of Authors:	Papadopoulou, Eleni; Norwegian Inst Publ Hlth, Department of Environmental Exposures and Epidemiology Botton, Jeremie; INSERM, Early Determinants of the Child's Health and Development Team (ORCHAD) Brantsaeter, Anne-Lise; Norwegian Institute of Public Health, Division of Environmental Medicine, Department of Exposure and Risk Assessment Haugen, Margaretha; Nasjonalt folkehelseinstitutt, Department of Environmental Exposures and Epidemiology Alexander, Jan; Norwegian Institute of Public Health, Office of the Director-General Meltzer, Helle Margrete; Nasjonalt folkehelseinstitutt Bacelis, Jonas ; Sahlgrenska universitetssjukhuset, Elfvin, Anders; Goteborgs universitet Sahlgrenska Akademin, Department of Pediatrics Jacobsson, Bo; Goteborgs universitet Sahlgrenska Akademin, Department of Obstetrics and Gynecology Sengpiel, Verena; Goteborgs universitet Sahlgrenska Akademin, Department of Obstetrics and Gynecology
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Keywords:	EPIDEMIOLOGY, NUTRITION & DIETETICS, PREVENTIVE MEDICINE, PUBLIC HEALTH, SOCIAL MEDICINE

TITLE PAGE

Title: Maternal caffeine intake during pregnancy is associated with excess growth in infancy and overweight in childhood: results from a large prospective cohort study

Eleni Papadopoulou, Post-doctoral research fellow [a]; Jérémie Botton, Associate Professor [b,c]; Anne-Lise Brantsæter, Senior researcher [a] ; Margaretha Haugen, Senior researcher [a]; Jan Alexander, Senior researcher [d];Helle Margrete Meltzer, Senior researcher [d], Jonas Bacelis, PhD Candidate [e]; Anders Elfvin, Physician [f]; Bo Jacobsson, Professor/ Chief physician [e,g]; Verena Sengpiel, Associate Professor/Physician [h]

[a] Department of Environmental Exposure and Epidemiology, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[b] Early Determinants of the Child's Health and Development Team (ORCHAD), INSERM, UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Paris, F-75014 France

[c] Univ. Paris-Sud, Université Paris-Saclay, F-92296, Châtenay-Malabry, France

[d] Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[e] Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

[f] Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

[g] Department of Genetics and Bioinformatics, Division of Health Data and Digitalization, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[h] Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Östra, SE-416 85 Gothenburg, Sweden

Corresponding author:
Eleni Papadopoulou
Division of Infection Control and Environmental Health
Norwegian Institute of Public Health
P.O. Box 4404, Nydalen, NO-0403 Oslo, Norway
Phone number: +47 21076511
Fax number: +47 21076686
E-mail: eleni.papadopoulou@fhi.no

ABSTRACT

Objectives: To study the association between maternal caffeine intake during pregnancy and the child's weight gain and overweight risk up to 8 years.

Design: Prospective nationwide pregnancy cohort.

Setting: The Norwegian Mother and Child Cohort Study.

Participants: 50,943 mothers recruited from 2002 to 2008 and their children, after singleton pregnancies, with information about average caffeine intake assessed at mid-pregnancy.

Outcome measure: Child's body size information at 11 age-points from 6 weeks to 8 years. We defined excess growth in infancy as a WHO weight gain z-score of >0.67 from birth to age 1 year, and overweight according to the International Obesity Task Force. We used a growth model to assess individual growth trajectories.

Results: Compared to pregnant women with low caffeine intake (<50mg/day, 46%), women with average (50-199mg/day, 44%), high (≥200-299mg/day, 7%) and very high (≥300mg/day, 3%) caffeine intakes had an increased risk of their child experiencing excess growth in infancy, after adjustment for confounders (odds ratio (OR)=1.15, 95% Confidence Intervals (CI) 1.09-1.22), OR=1.30, 95%CI, 1.16-1.45, OR=1.66, 95%CI, 1.42-1.93, respectively). In-utero exposure to any caffeine was associated with higher risk of overweight at age 3 and 5 years, while, the association persisted at 8 years, only for very high exposures. Any caffeine intake was associated with increased body mass index from infancy to childhood. Children prenatally exposed to caffeine intake >200mg/day had consistently higher weight. Very high caffeine exposures were associated with higher weight gain velocity from infancy to age 8 years.

Conclusion: Any caffeine consumption during pregnancy is associated with excess infant growth and increased risk of overweight, mainly at pre-school ages. Maternal caffeine intake may modify overall weight growth trajectory from birth to 8 years. This study adds supporting evidence for the current advice to reduce caffeine intake during pregnancy.

Strengths and limitations of this study

- A strength of this study is the large sample size.
- Maternal caffeine intake was estimated from all possible food sources.
- This is the first study investigating the association between maternal caffeine intake and excess infant growth and growth velocity.
- Missing data from body size measurements were handled with a growth model.
- Limitations include self-reported dietary data and parental-reported measurements of height and weight after 2 years.

MANUSCRIPT

Introduction

Caffeine is the world's most widely consumed central nervous system stimulant. It occurs naturally or is added to foods and beverages, with coffee and tea as the most common and major sources[1]. After ingestion, caffeine is readily absorbed into the blood stream and distributed to the tissues. It is metabolized in the liver by the microsomal cytochrome P450[2]. During pregnancy, elimination of caffeine is prolonged and it rapidly passes all biological membranes, including the blood-brain and placenta barriers, resulting in exposure of the fetus[3]. A maximum intake level of caffeine for pregnant women has been stipulated by several authorities, most of which agree that it should not exceed 200 mg/day, based on the evidence of its adverse effects on miscarriage rates and fetal growth restriction[1 4]. The negative effects of caffeine consumption during pregnancy on fetal growth have been well documented in epidemiological studies, including a study within the Norwegian Mother and Child Cohort Study (MoBa)[5]. In a recent meta-analysis the highest, compared with the lowest, maternal caffeine intake level was associated with a 38% increased risk of low birth weight (< 2.5kg)[6].

Fetal growth and growth in infancy are important determinants for the development of obesity and for long-term cardiometabolic health [7-9]. Excess infant growth programs later obesity, fat mass, and risk of adult disease, independent of intrauterine growth [10-15]. The prevalence of metabolic disorders, including obesity, cardiovascular disease and type 2 diabetes is rapidly growing across the globe, with the number of obese people risen worldwide from 105 million in 1975 to 641 million in 2014[16]. This trend indicates that the probability of reaching the WHO global obesity target, of no rise in obesity by 2025, is close to zero[16]. There is compelling human and animal evidence supporting the "fetal programming" hypothesis, according to which in utero exposures permanently alter an organism's physiology and metabolism, leading to susceptibility to subsequent disease, including obesity and metabolic disorders, with transgenerational effects [17 18].

In-utero exposure to caffeine has been related to an increased risk of overweight and higher body fat in childhood, in two previous epidemiological studies [19 20]. However, the link between in-utero caffeine exposure and excess growth in infancy is yet to be studied, even though excess infant growth is an established risk factor in the etiology of obesity and cardio-metabolic disease [13 15 21 22].

Based on our previous findings on the association of prenatal caffeine exposure with fetal growth restriction[5] and the fetal programming hypothesis[23], we hypothesized that prenatal caffeine exposure might affect postnatal growth. Thus, the objective of this study was to investigate the associations between maternal caffeine intake in pregnancy and child growth and risk of overweight up to age 8 years in a large prospective population-based cohort.

Methods

Study population and ethical approval

Our study was conducted within the Norwegian Mother and Child Cohort Study (MoBa), a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health[24]. Pregnant women from all over Norway were recruited during 1999-2008 and 40.6% of the invited women consented to participate. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Follow-up of the participants, after delivery, have been conducted at 6, 18, 36 months, 5, 7 and 8 years. Data used in this study are based on version 8 of the quality-assured data files, released for research in February 2014, with linkage to the Medical Birth Registry of Norway (MBRN). The data collection in MoBa was licensed by the Norwegian Data Inspectorate and approved by the Regional Committee for Medical Research Ethics. This study was approved by the Regional Committee for Medical Research Ethics in Southeastern Norway (2010/2683/REK Sør-øst A). All MoBA participants have provided a signed consent form.

After exclusion of multiple gestations, stillbirths, malformations and chromosomal abnormalities, 96,875 live-born singletons remained. Of these, 78,819 pregnant women had answered the food frequency questionnaire developed and validated for MoBa and in use from 2002 and onwards. The eligible study population, with available information on maternal caffeine intake and all relevant covariates, constituted 62,034 mother-child pairs. Our final study population consisted of 50,943 mother-child pairs with additional information on small for gestational age (SGA) and at least one postnatal measurement of weight or length/height. The cohort retention is presented in Supplementary Table 1. After 5 years, approximately 40% of the study population returned the questionnaire and had information on weight and height, while the distribution of mothers by caffeine intake level did not differ by follow-up age, meaning that loss to follow-up was not related to maternal caffeine intake in pregnancy.

Maternal caffeine intake during pregnancy

Maternal caffeine intake estimation in MoBa has been described in detail previously by Sengpiel et al[5]. In brief, self-reported intake of 255 dietary items was assessed at pregnancy week 22 with a food frequency questionnaire (FFQ) developed and validated for MoBa[25]. This is a semi-quantitative FFQ designed to record dietary habits during the first four to five months of gestation. Average, daily caffeine intake was calculated as the aggregated intake (in mg/day) from all available sources, including several types of coffee, black tea, caffeinated soft drinks, energy drinks, chocolate, chocolate milk, and sandwich spread, desserts, cakes and sweets containing cocoa. Supplementary Table 2 includes more details on the estimation of maternal caffeine intake. The median (25^{th} -75^{th} percentiles) caffeine intake was 57mg/day (23-120mg/day) for the included population and 64mg/day (25-129mg/day) for the non-included population with available caffeine information (n=11,091 mothers) ($p<0.001$ for Mann-Whitney test). We categorized caffeine intake, based on the calculated median as well as national and international recommendations for caffeine consumption during pregnancy, in four levels of caffeine intake: low (0-49mg/day), average (50-199mg/day), high (200-299mg/day) or very high (≥300mg/day).

Child postnatal growth and overweight

Anthropometric data

Weight and height/length measurements at eleven age-points (6 weeks, 3, 6 and 8 months and 1, 1.5, 2, 3, 5, 7 and 8 years) were reported. Up to 18 months the reported measurements were as documented in the child's health card, while for measurements from 2 to 8 years no specification was provided. Implausible anthropometrics were identified and excluded by separately implementing three different methods: i) by comparing with the WHO Growth Standards, as a weight-for-age or height-for-age z-score <6SD below or >6SD (5SD for weight) above the mean [26] , ii) by identifying measured values with a >|3SD| difference from the predicted value as derived from the Jenss-Bayley growth curve model model, and iii) by the conditional growth percentiles[27]. After exclusion of implausible values, 464,343 and 452,980 measurements of weight and height/length were reported for our study population. Seven repeated measurements per child were available on average, for both anthropometrics. More details on anthropometric measurements are presented in Supplementary Table 1.

Outcomes

First, we assessed excess infant weight gain by calculating the difference in gender-adjusted WHO weight-for-age z-scores between birth and age 1 year, using reported weights[26]. A z-score gain of >0.67 represents an upward crossing of the percentile line[28], referred to as excess growth[29].

Second, we determined childhood overweight, including obesity, at two preschool-age (3 and 5 years) and one school-age (8 years) time-point, using the International Obesity Task Force (IOTF) criteria[30]. Used BMI cut-offs and overweight prevalences are presented in Supplementary Table 3.

BMI was derived by growth models. Individual growth trajectories for weight and length/height were obtained by modeling the overall growth from age 1 month to age 8 years, using the Jenss-Bayley growth curve model, a structural growth model based on a basic functional form of growth. This 4-parameter, non-linear model is suitable for describing growth of both weight and length/height during infancy and early childhood, up to age 8 years[31], before growth starts to accelerate again at puberty. To assess individual growth trajectories, we applied a mixed-effect approach using the Stochastic Approximation of Expectation-Maximization (SAEM) algorithm[32] [33]. We then calculated weight and length/height, body mass index (BMI) (weight (kg) divided by squared height (m)), as well as weight and height gain velocities at 14 age-points (1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4, 5, 6, 7 and 8 years), using the growth model derivatives. These predicted anthropometrics were also assessed as outcomes.

As including birth weight in the model may influence the estimated trajectories, and in order to assess the effect of caffeine on early growth independently of its effect on birth size[5], we did not include birth weight and length in the growth models.

Statistical analysisWe used logistic regression models to examine associations between maternal caffeine intake in categories and excess growth in infancy and childhood overweight. Low caffeine intake (0-49 mg/day) was the reference group. Similar analysis was performed after modelling caffeine by restricted cubic splines with four knots at percentiles 5, 35, 65 and 95, as recommended by Harrell[34], and corresponding to caffeine intakes of 6, 34, 91 and 253 mg/day, respectively. The reference level of caffeine intake was set at 50mg/day, corresponding to the median intake in our study population. The associations were described graphically. Finally, we

used mixed-effect linear regression models with random intercept by child and a random slope for age to analyze associations between predicted weight, height/length, BMI, weight and height gain velocities from ages 1 month to 8 years (14 age-points: 1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4, 5, 6, 7 and 8 years). Covariates' effects have been models as fixed in the mixed-effect models. All regression models were adjusted for random effects of sibling clusters since some mothers participated with more than one pregnancy.

Logistic and linear mixed models were adjusted for variables related to both maternal caffeine intake and excess growth by bivariate analysis: maternal age, maternal education, parity, pre-pregnancy BMI, paternal BMI, maternal and paternal smoking during pregnancy, maternal energy intake and nausea/vomiting during pregnancy Gestational age and child's gender were also included in the models as a-priori covariates (Supplementary Table 4). Maternal height, paternal weight, paternal alcohol consumption and gestational diabetes (yes/no) were also considered but not included in the final models as they did not met the criteria. Our main analysis consists of complete case analysis of 38,338 mother-child pairs for the risk of excess growth and of 50,943 mother-child pairs for all other growth outcomes. The cohort attrition due to loss to follow-up was addressed by the use of predicted anthropometric measurements. The correlation between measured and predicted anthropometrics ranged from 0.85 to 0.99 for weight and from 0.95 to 0.98 for length/height (data not shown).. .

In separate sensitivity analyses, i) we excluded SGA neonates (SGA was defined as birth weight below the 10th percentile, according to population curves as described by Skjaerven et al[35]), ii) excluded smokers during pregnancy, iii) we adjusted for birth weight; only the overweight models and not the excess growth model, because birth weight is included in the excess growth calculation formula iv) explored caffeine intake by 3 main sources (i.e. from black coffee, black tea and soda drinks), v) excluded very high caffeine consumers, and vi) we assessed the association between maternal caffeine intake and childhood overweight, using the measured instead of predicted anthropometric data to define the outcome. Possible interactions with SGA and birth weight were tested with all studied outcomes. Since the associations between the outcomes and the interaction terms were not significant and the inclusion of the interaction term did not modified our results, we have not included these analyses in the manuscript.

Finally, we performed negative control analysis, using paternal caffeine intake as the negative control. Negative control analysis is a suggested method to test for the possibility of unmeasured

confounding. We have assumed that there is no direct association between the father's exposure during the pregnancy period and the child's outcome, and that the shared confounders are equally associated with the mother and the father's exposures [36 37]. We have calculated the caffeine intake of the father using the caffeine concentrations and serving sizes as used for the mother's calculations (Supplementary Table 1) for 5 food items: filtered coffee, boiled coffee, espresso coffee, caffeinated soft-drink with sugar or artificially sweetened. Only 16,455 (32%) fathers had available information.

The main analyses were performed with the Stata 14 statistical software (Stata Corporation, College Station, Texas) and R version 3.2.2 [38] was used for the growth models.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Lifestyle and socio-demographic characteristics related to maternal caffeine intake during pregnancy

In our study population, 7.13% (n=3,633) and 3.21% (n=1,634) of women reported caffeine intake higher than 200mg/day and 300mg/day, respectively. The distribution of women not included in the analysis, by caffeine intake level was similar to the included (low: 43%, average: 46%, high: 8% and very high: 3%). The higher the caffeine intake, the higher the likelihood of a mother being older than 30 years, being multiparous, having a daily energy intake in the upper tertile, being a smoker during pregnancy and not suffering nausea and/or vomiting during pregnancy. Moreover, women with very high caffeine intake were more likely to have low education, have been obese before pregnancy and have partners who were obese and smokers, compared to those consuming less caffeine per day (Supplementary Table 4).

Paternal median (5^{th} -95^{th} percentiles) intake was 193mg/day (0-493mg/day), with caffeine from coffee being the main contributor (median: 187 mg/day). Fathers were consuming statistical significantly more caffeine than their partners ($p<0.001$ for Wilcoxon matched-pairs signed-ranks test). The spearman correlation coefficient between maternal and paternal caffeine intakes was

0.15 (p-value<0.0001). However, paternal intake was increasing by increasing levels of maternal intake and 45% of mothers with very high intake were with partners in the highest quartile of caffeine intake (Supplementary Table 4).

Prenatal caffeine exposure and excess growth in infancy

The prevalence of excess growth in infancy increased from 23% to 29% as prenatal caffeine intake increased from low to very high (Figure 1). After adjustment for confounders, children born to average, high and very high caffeine consumers had 1.15 (95%CI: 1.09, 1.22), 1.30 (95%CI: 1.16,1.45) and 1.66 (95%CI: 1.42,1.93) higher odds of excess growth in infancy, compared with children born to low consumers (Table 1). Neither exclusion of mothers who smoked during pregnancy or SGA neonates modified the results. The positive association between caffeine intake as a continuous variable and the risk of excess growth in infancy was linear with no apparent threshold (Supplementary Figure 1).

Prenatal caffeine exposure and overweight in childhood

The prevalence of overweight increased by 5% at age 3 years, by 6% at age 5 years and by 3% at age 8 years with increasing prenatal caffeine exposure from low to very high (Figure 1). Children born to average, high and very high caffeine consumers had 1.05 (95%CI: 0.99,1.12), 1.17 (95%CI: 1.05,1.30) and 1.44 (95%CI: 1.24,1.67) higher adjusted odds, respectively, for overweight at age 3 years, compared with children born to low caffeine consumers (Table 2). Similar odds ratios (OR) were found at age 5 years, but at age 8 years the respective risk was significant only for the highest caffeine consumption category (adjusted OR (aOR) 1.29; 95%CI 1.04,1.61). Neither exclusion of mothers who smoked during pregnancy or SGA neonates modified the results. However, adjustment for birth weight slightly increased the odds (Supplementary Table 5). We found a linear association between maternal caffeine consumption as a continuous variable and the risk of overweight at ages 3 and 5 years with, again, higher OR at age 3 years than at age 5 years (Supplementary Figure 2). As there was a high degree of concordance between overweight and/or obesity at ages 5 and 8 years, the plot at age 8 years overlapped with the one at age 5 years and was not included in Supplementary Figure 2.

Sensitivity analyses

In sensitivity analyses, we found similar results concerning the association of caffeine from different caffeine sources (black coffee, black tea, and soda drinks) with infant growth and overweight risk (Supplementary Table 6). When excluding very high caffeine consumers and

using no coffee drinkers as the reference group, caffeine intake less than 300mg/day was still significantly associated with increased risk for excess infant growth and overweight (Supplementary Table 7). Finally, when growth data from actual measurements were used to assess the relationship between maternal caffeine intake and overweight at these age-points, similar trends and associations were observed (Supplementary Table 8).

Prenatal caffeine exposure and growth up to 8 years

In comparison with low exposure, both high and very high prenatal caffeine exposure were positively associated with a child's weight, weight gain velocity and BMI from the first month onwards (Figure 2). More specifically, children prenatally exposed to very high caffeine levels weighed 67-83g more in infancy (age 3 to 12 months), 110-136g more in toddlerhood (age 12 months to 3 years), 213-320g more at pre-school age (age 3 to 5 years) and 480g more at age 8 years, than children exposed to low caffeine levels (Table 3). Maternal caffeine intake during pregnancy, at any level above 50mg/day, was associated with higher BMI from ages 1 month to 8 years. Additional adjustment for birth weight provided better models (p-value<0.05 for likelihood ratio test between models with and without birth weight) and the estimates from these models are presented in Table 3. Whereas maternal caffeine intake during pregnancy was not associated with child height, it was related to higher height gain velocity up to age 3 months (Supplementary Table 9).

Negative control analysis: Paternal caffeine intake

We have explored the association between maternal and paternal caffeine intake without and with adjustment for paternal caffeine intake and the same for paternal intake. All models are adjusted for the same confounders as in the main analysis. We have explored the associations with excess infant growth (n=12,289) and overweight at 3 years (n=16,455) (Supplementary Figures 3 & 4). For both the risk of excess infant growth and overweight at 3 years, the association with maternal caffeine intake changed negligibly after adjusting for paternal intake. On the other hand, by using paternal caffeine intake as a negative control, the trend of the association with child's growth was similar to that of maternal caffeine intake, while the effect estimate was much lower.

Discussion

We found that any maternal caffeine intake during pregnancy was associated with a higher risk of excess growth in infancy and overweight in early childhood. In addition, caffeine intakes in

pregnancy above the recommendation (200mg/day) were associated with modified growth trajectories from very early in life and maintained during childhood. More specifically, children exposed prenatally to caffeine levels above 200mg/day had persistently higher weight-, BMI- and weight gain velocity up to 8 years of age.

Strengths and limitations of this study

With the included 50,943 pregnancies, this is, so far, the largest study on the association of prenatal caffeine exposure and childhood growth parameters. It is the first to investigate effects on excess growth in infancy as well as growth velocities rather than just the size of the child, as well as critical age windows of diverging growth. Additional strengths include the prospective data collection, the comprehensive data on possible confounders and the assessment of caffeine intake from different sources. Nevertheless, our findings might be explained by residual confounding of non-accounted factors related to an overall unhealthy lifestyle and high caffeine consumption; though exclusion of smokers and very high caffeine consumers did not modify the results. In an effort to control for the effect of unmeasured familial characteristics, we performed negative control analysis using the father's caffeine intake. The unchanged effect estimate of maternal caffeine intake after adjustment for paternal intake as well as the weak effect estimate of paternal caffeine intake, indicate minor bias by shared unmeasured confounders.

In addition, the missing body size measurements were handled with the use of a growth model. The correlations between the measured and the predicted body size measurements were strong for at all ages. In sensitivity analyses restricted to the measured data, similar associations were found as with the predicted body size data (Supplementary Table 8). This provides some reassurance of the validity of the predicted anthropometrics. However, we still acknowledge the potential for outcome misclassification as only 23% of the cohort had anthropometric information at 8 years (Supplementary Table 3). At the time of release of the current data, 53% (27,142 children) of our study population had not reached the age of 8 years, and only 24% of missing anthropometric information at 8 years can be attributed to loss to follow-up. Furthermore, we found that maternal caffeine exposure was not related to loss to follow-up (Supplementary Table 3).

The self-report of diet, which can induce misreporting, is a limitation. However, fair agreement between beverage intakes, particularly of coffee and tea, was found in a validation study based on food records and biomarkers[25 39]. Observational studies can never establish causality; however, our results fulfill some of the Bradford-Hill's criteria for causation[40] with a strong association,

consistent findings for major caffeine sources, a biological gradient with higher caffeine exposure being associated to abnormal growth, consistent findings in animal models and a plausible mechanism, i.e. fetal programing.

Our study adds evidence to two previous epidemiological studies[19 20] that found an effect of prenatal caffeine exposure on child growth. In the study by Voerman et al., maternal caffeine intake above 360mg/day was associated with higher weight and BMI from birth to age 6 years, compared with intakes below 180mg/day[19]. In contrast to our findings, they found no association with overweight. Higher caffeine intake (360-540mg/day) during pregnancy was positively associated with body fat percentage and higher insulin levels in 6-year-olds. The exposure was assessed only by intakes of coffee and tea, which in our study also are the main but not the only caffeine contributors (78% of total caffeine intake). The median intake was double than in our study, resulting to a higher reference level (reference: <180mg/day, median: 117mg/day), providing less contrast between the compared exposure groups and less comparability to our study, as most of these women were not complying to the recommendation. Nevertheless, we found associations with adverse effects on child's growth even at low caffeine intakes, in the range of the recommendation, that are mostly due to consumption of foods and drinks other than coffee (chocolate, black tea, caffeinated sodas) [5]. Li et al. found likewise that any maternal caffeine intake was associated with an overall increased risk of obesity from ages 2 to 15 years, with an exposure range similar to the current study[20]. We have used similar approaches to study changes in individual growth trajectories, though with shorter follow-up. In addition, we provided age specific weight and BMI deviations, in order to find sensitive developmental windows when the association with the prenatal caffeine exposure exacerbated. There is no previous report of the association between caffeine intake in pregnancy and excess infant growth.

Potential mechanisms

Since excess growth in infancy, in itself, can be directly related to childhood obesity, adiposity[41] and an unfavorable adult cardio-metabolic profile[42], the associations between prenatal caffeine exposure with overweight, body fat and insulin, found in this study and the previous reports, might be explained by excess infant growth. Putting together the previous findings in the MoBa study[5], we have shown that children prenatally exposed to high caffeine levels are smaller at birth, grow faster in infancy and retain a higher weight throughout childhood without significant height differences, thus becoming overweight (Supplementary Figure 5). These findings concur

with the fetal programming of obesity hypothesis[43]. Nevertheless, the effect of prenatal caffeine exposure on postnatal growth and overweight was not dependent on birth weight. Hence, along with a healthy birth weight, it is important to identify the modifiable factors that can independently affect excess growth in infancy, independent of fetal growth. A growing number of studies have shown that other prenatal factors, e.g. excess gestational weight[44], high (>3times/week) fish intake [45],and postnatal factors, e.g. formula feeding and feeding schedule[46], are associated with increased risk of excess growth in infancy. Recent research shows that some perinatal factors can also have a direct effect on postnatal growth, independent of effects on fetal growth, including parental body size, smoking during pregnancy and socioeconomic status [47-49].

The biological plausibility supporting our findings is mainly provided by animal studies where, prenatal exposure to caffeine was shown to program the offspring towards excess growth and cardio-metabolic disorders through alterations i) in the hypothalamic-pituitary-adrenocortical axis that plays a key role in growth and metabolism[50-52], ii) in regulation of adenosine and adenosine antagonists, which are important modulators of development[53 54] and iii) in the placental expression and transportation of leptin[55], essential for appetite regulation.

Although most pregnant women reduce their caffeine intake during pregnancy and few have caffeine intakes higher than 200 mg/day (10%), our results show associations between caffeine intakes below 200 mg/day and excess growth. The results add supporting evidence for the current advice to reduce caffeine intake during pregnancy and indicate that complete avoidance might actually be advisable. An absence of a "safe intake level" has been previously reported in the basis of associations between maternal caffeine intake and fetal growth restriction[56]. Nevertheless, the authors of a recent systematic review after critically assessing the evidence, concluded that a consumption of up to 300 mg caffeine/day in healthy pregnant women is generally not associated with adverse reproductive and developmental effects [57]. Postnatal growth and child's weight status were not included in this review. Our findings are in agreement with the previous studies assessing a similar hypothesis, with associations reported in caffeine intakes above, but even below, the comparator, indicating that an intake of 300mg/day might not be a safe level when growth is under study. Hence, more evidence is needed for the association between prenatal caffeine exposure and postnatal growth and an updated future critical assessment of such studies.

The association between prenatal caffeine exposure and overweight attenuated after 5 years, with only very high exposed children being at risk for overweight. Residual confounding due to postnatal factors related to overweight in late childhood might explain this attenuation. Nevertheless, adjustment for risk factors of being overweight at 8 years would introduce bias to the association under study. In addition, weight and height are screened from birth to 5 years in scheduled voluntarily appointments at the public health centers. Hence, a possible misclassification of outcome from anthropometrics after 5 years, might also explain the attenuation of the association.

There are two studies showing effects of caffeine intake on body composition and cardiometabolic health [19 58], with discrepant results. In the present study, we did not have any information on body composition. In addition, it is known that several genetic factors can contribute to variation in caffeine metabolism[59], and studies in adults have shown that slower metabolism of caffeine is related to higher risk of cardiovascular disease[60]. On the other hand, during pregnancy, maternal caffeine clearance modified the association between maternal caffeine intake and fetal growth restriction, with faster clearance being more detrimental [56]. More specifically, a genotype of rapid caffeine metabolism was associated with reduced birth weight while in women with a different polymorphism on the gene CYP1A2 C164A no effect was found [61]. Thus, there is a need to investigate the programming effect of prenatal caffeine exposure on child and adult body composition and cardiometabolic health, taking into account the genetic variation of maternal caffeine metabolism.

Conclusions

We found that the risk of excess infant growth and overweight in childhood-important risk factors for later cardio-metabolic disease- is increasing with maternal caffeine intake, with no apparent threshold. Maternal caffeine intake >200mg/day during pregnancy was associated with high weight gain velocity beginning from the first months of life and higher BMI throughout childhood. Our findings support the recommendation to limit caffeine intake during pregnancy (<200mg/day).

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BJ initiated this collaborative project, contributed to the study design and the interpretation of the results. VS defined the research question, contributed to the study design, database preparation and interpretation of the results. She is guarantor and had final responsibility for the decision to submit for publication. All authors read, revised and approved the final version of the paper.

Data sharing statement: No additional data are available. All data from the MoBa study are available to all qualified researchers/research groups in Norway and to international researchers who are collaborating with a Norwegian researcher.

Declaration of transparency

EP as the lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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TABLES

Table 1. **Maternal caffeine intake in pregnancy and risk of excess growth in infancy (from birth to age 12 months)**

	Risk of excess growth in infancy (from birth to age 12 months)[a]					
	All children (n=38,338)		After excluding smokers during pregnancy (n=35,672)		After excluding SGA neonates[b] (n=35,144)	
Maternal daily caffeine intake	OR	95% CI	OR	95% CI	OR	95% CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.15	1.09,1.22	1.15	1.08,1.22	1.14	1.07,1.22
High (200-299 mg)	1.30	1.16,1.45	1.32	1.17,1.49	1.25	1.11,1.41
Very high (≥300 mg)	1.66	1.42,1.93	1.58	1.30,1.91	1.67	1.41,1.97

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months.

[b] SGA according to Skjaerven et al.

Table 2. Maternal caffeine intake in pregnancy and risk of overweight/obesity at age 3, 5 and 8 years.

	Risk of overweight and/or obesity[a]					
	All children (n=50,943)					
	Age 3 years		Age 5 years		Age 8 years	
Maternal daily caffeine intake	OR	95% CI	OR	95% CI	OR	95% CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.05	0.99,1.12	1.00	0.95,1.06	0.95	0.86,1.04
High (200-299 mg)	1.17	1.05,1.30	1.12	1.02,1.23	1.11	0.94,1.31
Very high (≥300 mg)	1.44	1.24,1.67	1.29	1.13,1.47	1.29	1.04,1.61
After excluding smokers during pregnancy (n=47,036)						
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.05	0.99,1.12	1.00	0.95,1.06	0.92	0.84,1.02
High (200-299 mg)	1.17	1.04,1.32	1.10	1.00,1.23	1.08	0.89,1.29
Very high (≥300 mg)	1.50	1.25,1.79	1.31	1.12,1.54	1.30	1.00,1.70
After excluding SGA neonates (n=46,718) [b]						
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.06	0.99,1.12	1.01	0.95,1.06	0.96	0.87,1.05
High (200-299 mg)	1.18	1.05,1.32	1.14	1.03,1.25	1.11	0.94,1.32
Very high (≥300 mg)	1.48	1.28,1.72	1.32	1.15,1.51	1.36	1.09,1.69

The same population was included at each age since the outcome was defined using model-derived anthropometrics.
All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender
[a] Overweight and/or obesity in children, according to the International Obesity Task Force definition.
[b] SGA according to Skjaerven et al.

Table 3. Maternal caffeine intake in pregnancy and child's weight, weight gain velocity and body mass index (BMI) during childhood (n=50,943). Low caffeine intake is the reference group.

	Child's developmental period						
	Infancy		Toddlerhood		Pre-school age		School age
Maternal daily caffeine intake	3 m Beta (95%CI)	6 m Beta (95%CI)	12 m Beta (95%CI)	18 m Beta (95%CI)	3 y Beta (95%CI)	5 y Beta (95%CI)	8 y Beta (95%CI)
Weight (in g)							
Average (50-199 mg)	**14.1 (1.6,26.6)**	**15.1 (1.3,28.8)**	14.9 (-5.1,34.9)	14.8 (-9.3,38.9)	16.1 (-16.9,49.0)	18.2 (-24.0,60.5)	21.5 (-35.1,78.1)
High (200-299 mg)	**31.3 (7.5,55.1)**	**35.0 (8.8,61.1)**	**45.4 (7.3,83.5)**	**59.0 (13.1,104.8)**	**99.0 (36.3,161.7)**	**148.9 (68.4,229.4)**	**222.0 (114.1,329.8)**
Very high (≥300 mg)	**67.0 (32.5,101.6)**	**83.2 (45.3,121.1)**	**110.1 (55.2,165.0)**	**135.5 (69.5,201.5)**	**213.4 (123.3,303.6)**	**320.0 (204.4,435.6)**	**480.3 (325.5,635.1)**
Weight gain velocity (in g/month)							
Average (50-199 mg)	0.8(-0.8,2.4)	0.4(-1.2,1.9)	0.2(-1.2,1.5)	0.3(-1.0,1.5)	0.3(-0.7,1.4)	0.3(-0.7,1.4)	0.3(-0.7,1.4)
High (200-299 mg)	1. (-1.4,4.7)	1.2(-1.7,4.1)	2. (-0.4,4.7)	2.3(-0.1,4.7)	**2.1(0,4.3)**	**2.0(0.1,4.0)**	**2.2(0,4.0)**
Very high (≥300 mg)	**6.0(1.5,10.4)**	**4.3(0.2,8.5)**	**3.8(0.1,7.4)**	**3.7(0.3,7.1)**	**3.9(0.8,7.0)**	**3.9(1.1,6.8)**	**3.9(1.1,6.8)**
BMI (in kg/m^2)							
Average (50-199 mg)	**0.03 (0.01,0.05)**	**0.03 (0.01,0.05)**	**0.04 (0.02,0.06)**	**0.04 (0.02,0.06)**	**0.04 (0.02,0.06)**	**0.03 (0.01,0.06)**	0.02 (-0.01,0.05)
High (200-299 mg)	**0.07 (0.03,0.11)**	**0.07 (0.03,0.10)**	**0.09 (0.05,0.12)**	**0.11 (0.07,0.15)**	**0.14 (0.10,0.19)**	**0.15 (0.11,0.20)**	**0.15 (0.09,0.21)**
Very high (≥300 mg)	**0.16 (0.10,0.21)**	**0.16 (0.11,0.21)**	**0.17 (0.12,0.23)**	**0.20 (0.14,0.25)**	**0.26 (0.20,0.32)**	**0.29 (0.22,0.36)**	**0.31 (0.22,0.39)**

Abbreviations: Beta: beta coefficients, CI: confidence intervals

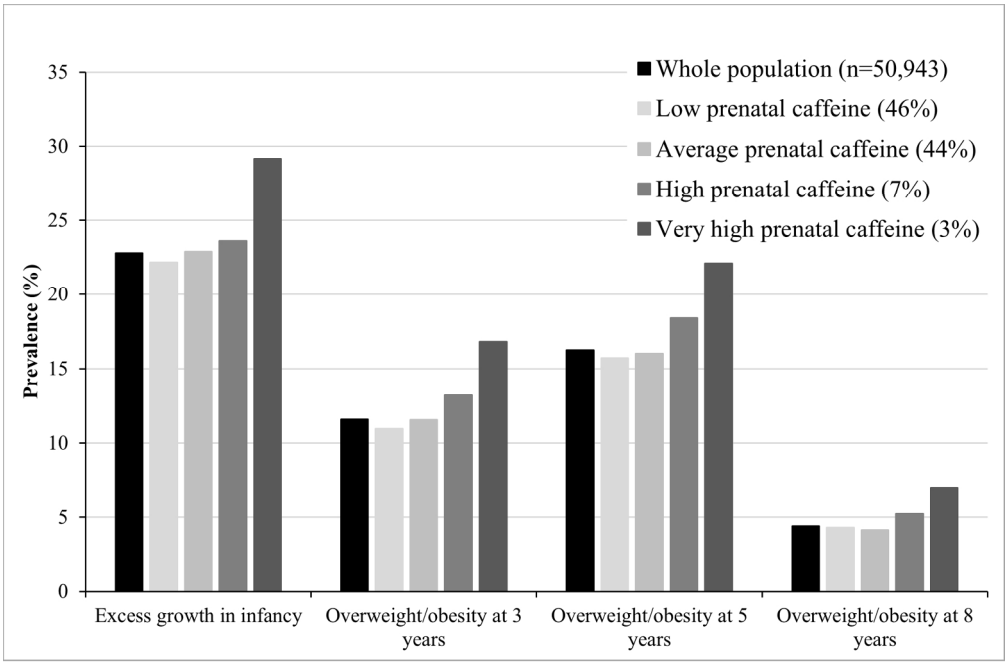
Infancy is defined as the period from birth to age 12 months, toddlerhood as the period from age 12 months to 3 years, pre-school age as the period from age 3 years to 5 years and school age as the period from age 5 years onwards.

Effect estimates derived from linear mixed effect models with input of all anthropometric information from age 1 month to 8 years and adjustment for: maternal age, parity, maternal education, pre-pregnancy BMI, nausea and/or vomiting during pregnancy, maternal smoking during pregnancy, paternal BMI, gestational age and birth weight. The effect estimates are adjusted mean changes of weight, weight gain velocity and BMI.

FIGURE LEGENDS

Figure 1. Prevalence of excess growth in infancy and overweight/obesity at age 3, 5 and 8 years, in the whole population and by maternal caffeine intake during pregnancy.

Figure 2. Maternal high (red) and very high (black) caffeine intake in pregnancy and adjusted change in children's a) weight (in g), b) weight gain velocity (in g/month) and c) body mass index (in kg/m^2), from age 1 month to 8 years (beta coefficients in solid lines and 95% confidence intervals in thin dashed lines). Low caffeine intake is the reference group.



Prevalence of excess growth in infancy and overweight/obesity at age 3, 5 and 8 years, in the whole population and by maternal caffeine intake during pregnancy.

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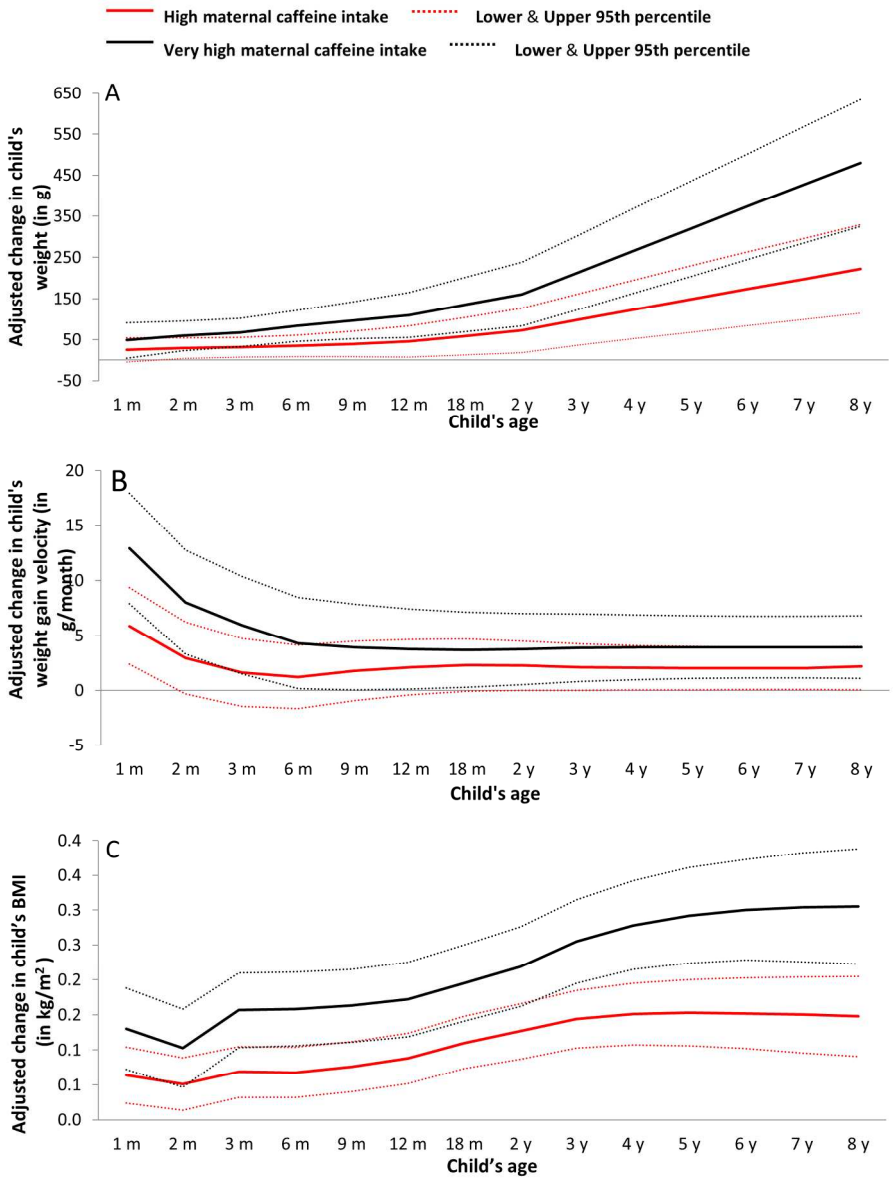

Maternal high (red) and very high (black) caffeine intake in pregnancy and adjusted change in children's a) weight (in g), b) weight gain velocity (in g/month) and c) body mass index (in kg/m2), from age 1 month to 8 years (beta coefficients in solid lines and 95% confidence intervals in thin dashed lines). Low caffeine intake is the reference group.

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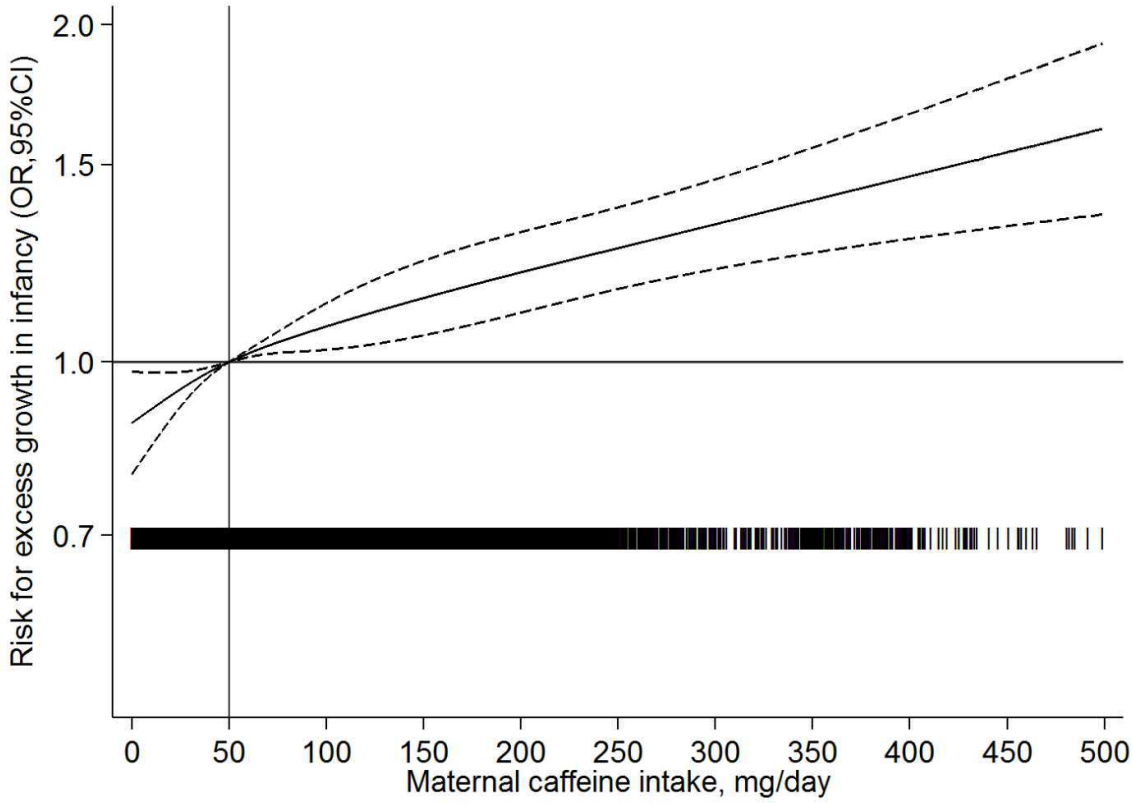
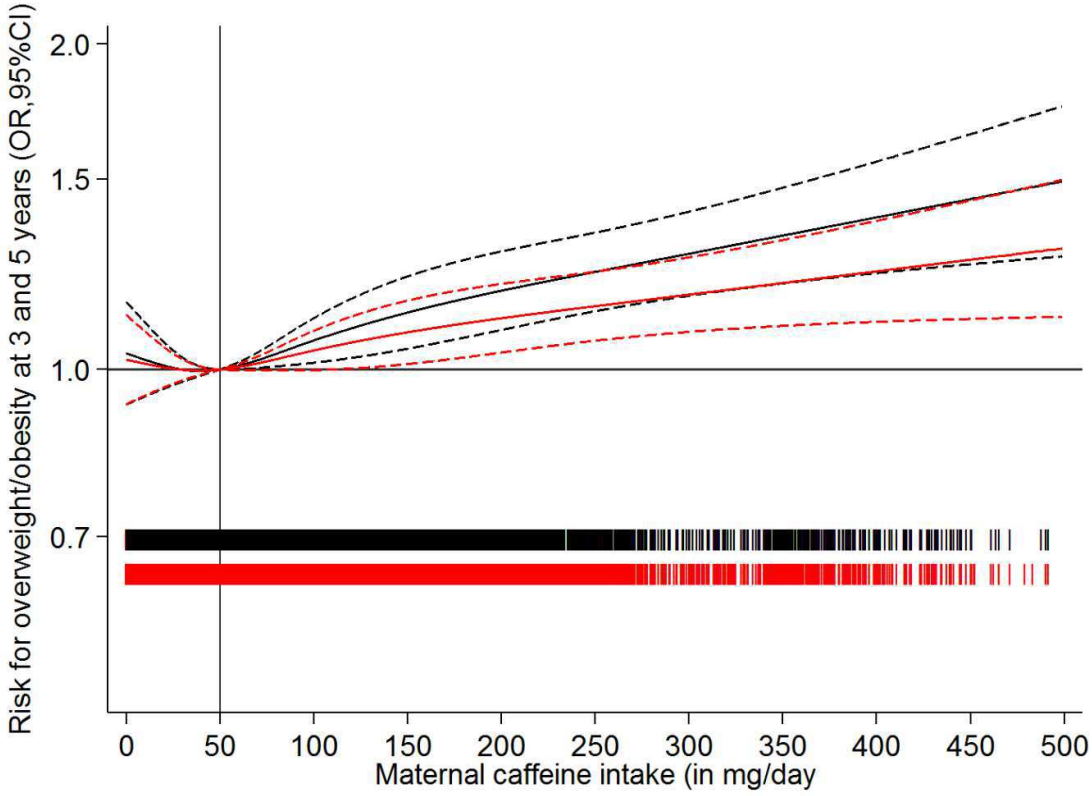
Supplementary Figure 1. Maternal caffeine intake on a continuous scale and risk of excess growth in infancy. Odds ratios (solid line) and 95% confidence intervals (dashed lines) derived from a logistic regression model using restricted cubic splines. The solid vertical line represents the reference value (50mg/day). The bar represents the children with excess growth.



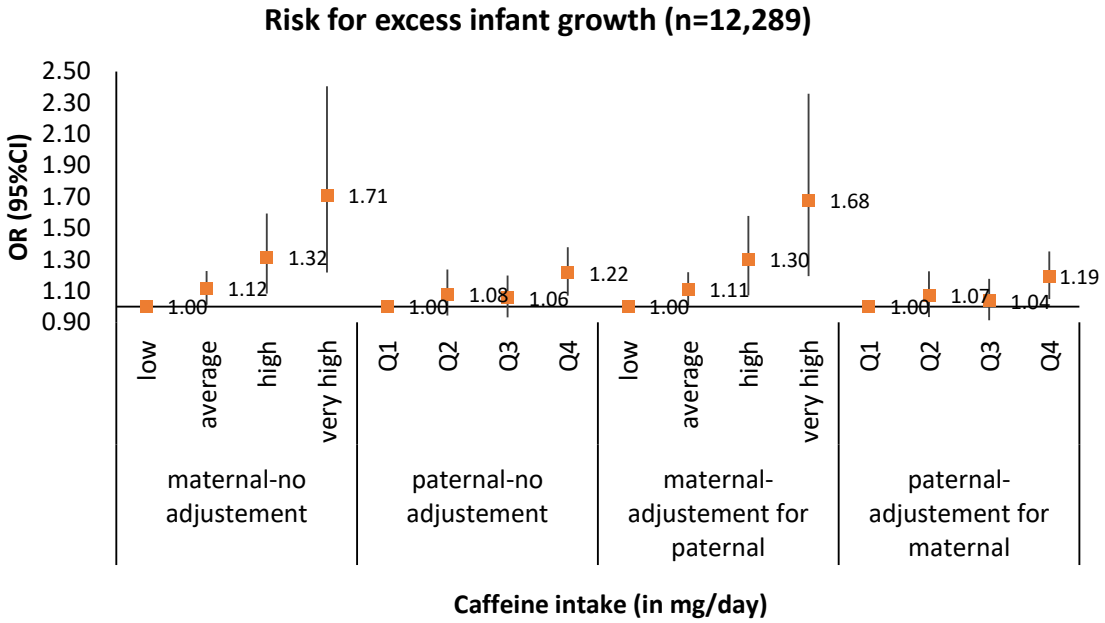
Footnote: all models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender and SGA according to Skjaerven et al.

Supplementary Figure 2. Maternal caffeine intake in continuous scale and risk for overweight/obesity at age 3 (black) and 5 years (red). Odds ratios (solid line) and the 95% confidence intervals (dashed lines) derived from a logistic regression model using restricted cubic splines. The solid vertical line represent the reference value (50mg/day). The bars represent the children with overweight/obesity.



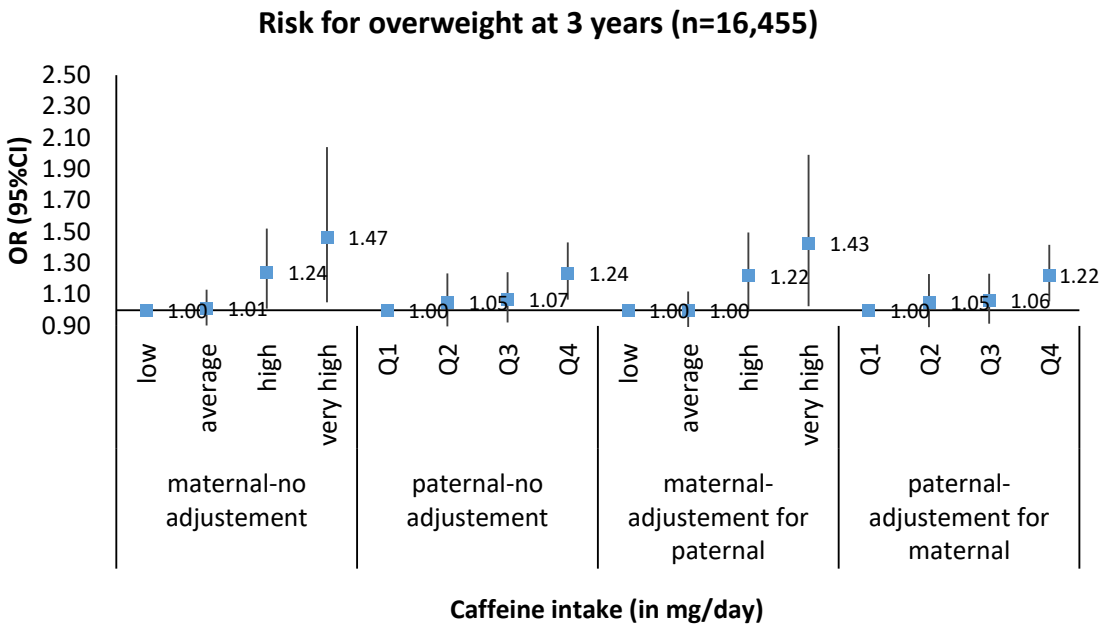
Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight

Supplementary Figure 3. Association between maternal and paternal caffeine intake during pregnancy and excess infant growth.



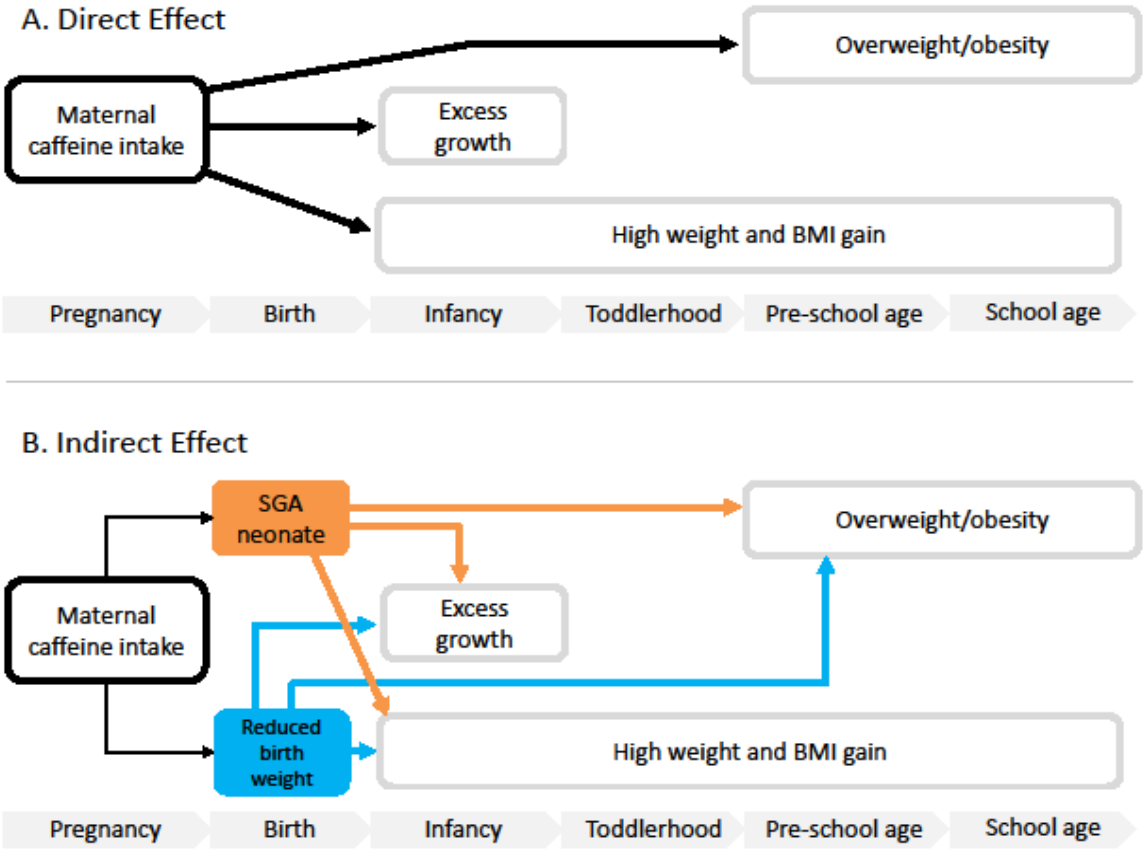
Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender.

Supplementary Figure 4. Association between maternal and paternal caffeine intake during pregnancy and overweight at 3 years.



Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender.

Supplementary Figure 5. Simplified causal diagram for the direct and indirect associations between maternal caffeine intake during pregnancy and the studied outcomes, mediated by SGA and birth weight



Supplementary Table 1. Anthropometric measurements, maternal caffeine intake level and cohort retention.

Measurement	Age (months)	Weight (kg)		Cohort retention	Height (cm)		Cohort retention	Maternal caffeine intake level			
								Low	Average	High	Very high
	Mean	N	Mean		N	Mean					
1	1.5	49672	5.0	98%	39175	57	77%	46%	44%	7%	3%
2	3.1	49912	6.4	98%	49122	62	96%	46%	44%	7%	3%
3	5.6	47047	7.9	92%	46640	68	92%	46%	44%	7%	3%
4	8.2	37612	8.8	74%	37493	71	74%	47%	43%	7%	3%
5	12.2	38660	9.9	76%	39046	76	77%	47%	43%	7%	3%
6	15.9	38757	10.9	76%	38842	81	76%	47%	43%	7%	3%
7	25.3	20485	13.0	40%	20855	89	41%	48%	42%	7%	3%
8	36.0	30588	15.1	60%	29747	97	58%	47%	43%	7%	3%
9	62.1	19340	20.0	38%	19768	113	39%	46%	44%	7%	3%
10	84.7	18699	25.1	37%	19550	126	38%	47%	43%	7%	3%
11	97.0	11685	28.7	23%	12312	132	24%	47%	42%	7%	4%

Supplementary Table 2. Estimation of caffeine intake during pregnancy in the Norwegian Mother and Child Cohort Study.

Food item containing caffeine	Reported frequency	Serving	Caffeine concentration (mg/100g of food)
Filtered coffee	Cups per day, week or months	1 cup (125ml)	57
Boiled/pressed coffee	Cups per day, week or months	1 cup (125ml)	57
Powdered instant coffee	Cups per day, week or months	1 cup (125ml)	40
Decaffeinated coffee	Cups per day, week or months	1 cup (125ml)	2
Caffe latte/cappuccino	Cups per day, week or months	1 cup (125ml)	21
Espresso	Cups per day, week or months	1 cup (125ml)	114
Black tea	Cups per day, week or months	1 cup (250ml)	16
Caffeinated soft drinks, sugar sweetened and artificially sweetened	Cups per day, week or months	1 glass (250 ml)	12
Energy drink	Cups per day, week or months	1 glass (250 ml)	15
Chocolate milk	Cups per day, week or months	1 glass (250 ml)	15
Chocolate, medium dark			38
Sandwich spreads with cocoa			13
Deserts with coca			3
Cakes with cocoa			4
Sweets with cocoa			9

Supplementary Table 3. Definitions of overweight and obesity

Reference	Description	Age (years)	Overweight and/or obesity (kg/m^2)		Prevalence (%) [a]	
			Males	Females	Males	Females
International Obesity Task Force (IOTF) [1] (BMJ 2000 May 6; 320 (7244); 1240-Table 4)	Study-specific BMIs were calculated for age and sex	3	17.89	17.56	10.77	12.44
		5	17.42	17.15	14.30	18.28
		8	18.44	18.35	3.61	5.24

[a] Based on BMI calculated from the predicted anthropometric data.

From Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240-1243

Supplementary Table 4. Parental and pregnancy-related characteristics by category of maternal caffeine intake during pregnancy (n=50,943)

	Maternal caffeine intake during pregnancy							
	Low caffeine intake (<50mg/day) N=23,437		Average caffeine intake (50-199mg/day) N=22,239		High caffeine intake (200-299mg/day) N=3,633		Very high caffeine intake (≥300mg/day) N=1,634	
	N	%	N	%	N	%	N	%
Maternal age (years)								
<20	247	1.1	94	0.4	20	0.6	6	0.4
20-29	12,426	53.0	8,643	38.9	1,185	32.6	474	29.0
≥30	10,764	45.9	13,502	60.7	2,428	66.8	1,154	70.6
Maternal education (years)								
<13	7,025	30.0	5,993	27.0	1,142	31.4	755	46.2
13-16	10,725	45.7	9,538	42.9	1,512	42.6	623	38.1
>16	5,687	24.3	6,708	30.1	979	27.0	256	15.7
Parity								
Primiparous	14,260	60.8	11,053	49.7	1,492	41.1	492	30.1
Multiparous	9,177	39.2	11,186	50.3	2,141	58.9	1,142	69.9
Pre-pregnancy BMI (kg/m^2)								
<18.5	690	2.9	644	2.9	89	2.5	44	2.7
18.5-24.9	15,466	66.0	14,893	67.0	2,416	66.5	999	61.1
25-29.9	5,071	21.6	4,838	21.7	785	21.6	406	24.9
≥30	2,210	9.4	1,864	8.4	343	9.4	185	11.3
Maternal daily energy intake (in tertiles, kcal)								
<2.000	9,211	39.3	6,791	30.5	802	22.1	347	21.2
2.000-2.500	7,803	33.3	7,619	34.3	1,137	31.3	458	28.1
>2.500	6,423	27.4	7,829	35.2	1,694	46.6	829	50.7
Maternal smoking during pregnancy								
Never	22,500	96.0	20,532	92.3	3,005	82.7	999	61.1
Ever	937	4.0	1,707	7.7	628	17.3	635	38.9
Nausea/vomiting in pregnancy								
Never	6,057	25.8	6,949	31.3	1,358	37.4	673	41.2
Ever	17,380	74.2	15,290	68.7	2,275	62.6	961	58.8
Paternal BMI (kg/m^2)								
<18.5	51	0.2	47	0.2	13	0.3	5	0.3
18.5-24.9	10,538	44.6	9,831	44.2	1,547	42.6	661	40.4
25-29.9	10,526	45.3	10,254	46.1	1,699	46.8	756	46.3
≥30	2,322	9.9	2,107	9.5	374	10.3	212	13.0
Paternal smoking during pregnancy								
Never	19,338	82.5	18,029	81.1	2,752	75.7	1,007	61.6
Ever	4,099	17.5	4,210	18.9	881	24.3	627	38.4

Paternal caffeine intake								
1st quartile	2,253	(29%)	1,504	(20%)	168	(15%)	44	(14%)
2nd quartile	1,605	(21%)	1,495	(20%)	202	(18%)	51	(16%)
3rd quartile	1,950	(26%)	2,186	(30%)	356	(33%)	82	(25%)
4th quartile	1,832	(24%)	2,211	(30%)	371	(34%)	145	(45%)
Child's gender								
Boys	11,821	50.4	11,430	51.4	1.871	51.5	820	50.2
Girls	11,616	49.6	10,809	48.6	1.762	48.5	814	49.8
Gestational age (in weeks, median, IQR)	40.1	1.9	40.3	1.9	40.3	1.9	40.3	1.7

p-value<10^{-5} of chi square tests of all cross-tabulations presented in table

[1]IOM : Institute of Medicine

Supplementary Table 5. Maternal caffeine intake in pregnancy and risk of overweight/obesity at age 3, 5 and 8 years, after adjustment for birth weight.

	Risk of overweight and/or obesity [a], after additional adjustment for birth weight					
	Age 3 years		Age 5 years		Age 8 years	
Maternal daily caffeine intake	OR	95%CI	OR	95%CI	OR	95%CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	**1.08**	**1.02,1.15**	1.03	0.97,1.08	0.97	0.88,1.06
High (200-299 mg)	**1.21**	**1.09,1.36**	**1.16**	**1.05,1.28**	1.14	0.96,1.34
Very high (≥300 mg)	**1.53**	**1.32,1.78**	**1.36**	**1.19,1.55**	**1.35**	**1.09,1.68**

The same population was included at each age since the outcome was defined using model-derived anthropometrics.

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight

[a] Overweight and/or obesity in children, according to the International Obesity Task Force definition

Supplementary Table 6. Maternal caffeine intake during pregnancy from different sources and risk of excess growth in infancy (from birth to age 12 months) and overweight/obesity at age 3, 5 and 8 years

	Child's growth parameters											
	Excess growth[a]			Overweight/obesity at age 3 years[b]			Overweight/obesity at age 5 years[b]			Overweight/obesity at age 8 years[b]		
	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI
Caffeine from black coffee												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.18**	**1.11**	**1.26**	**1.18**	**1.11**	**1.26**	**1.12**	**1.05**	**1.18**	**1.11**	**1.00**	**1.23**
200-300	**1.31**	**1.06**	**1.62**	1.14	0.91	1.41	1.11	0.92	1.34	1.09	0.77	1.53
>300	**1.72**	**1.45**	**2.03**	**1.69**	**1.44**	**1.99**	**1.39**	**1.20**	**1.61**	**1.48**	**1.17**	**1.88**
Caffeine from black tea												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.11**	**1.01**	**1.21**	1.07	0.98	1.18	1.05	0.97	1.14	**1.20**	**1.04**	**1.38**
200-300	1.74	0.93	3.25	1.16	0.56	2.40	1.22	0.65	2.31	0.28	0.04	2.07
>300	1.67	0.50	5.54	0.86	0.20	3.75	0.86	0.25	2.97	NE		
Caffeine from soda drinks												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.20**	**1.08**	**1.33**	0.96	0.86	1.07	0.96	0.88	1.06	1.01	0.87	1.18
200-300	1.40	0.95	2.06	1.13	0.77	1.65	1.18	0.84	1.65	1.48	0.91	2.41
>300	1.21	0.22	6.58	0.48	0.06	3.79	0.73	0.16	3.34	NE		

NE: not estimated

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months. Model adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender, and mutually adjusted for maternal caffeine intake from black coffee, black tea and soda drinks.

[b] Overweight and/or obesity, according to International Obesity Task Force definition.

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight, and mutually adjusted for maternal caffeine intake from black coffee, black tea and soda drinks.

Supplementary Table 7. Sensitivity after excluding very high caffeine drinkers and using no black coffee drinkers (n=23,402) as the reference group.

	No coffee drinkers OR (95%CI)	Caffeine intake <199mg OR (95%CI)	Caffeine intake 200-299mg OR (95%CI)
Excess infant growth	1.00	1.07 (1.01,1.13)	1.25 (1.12,1.39)
Overweight			
3 years	1.00	1.12 (1.06,1.19)	1.21 (1.08,1.35)
5 years	1.00	1.08 (1.03,1.14)	1.17 (1.06,1.29)
8 years	1.00	1.02 (0.93,1.12)	1.15 (0.98,1.36)

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months.

[b] Overweight and/or obesity, according to International Obesity Task Force definition.

Models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender.

Supplementary Table 8. Maternal caffeine intake in early pregnancy and risk of overweight/obesity at pre-school (3-5 years) and school (6-8 years) age, using measured anthropometric values

	Risk of overweight and/or obesity at pre-school and school age[a]					
	Pre-school age (n=31,482)			School age (n=19,722)		
Maternal daily caffeine intake	N/% cases	OR	95% CI	N/% cases	OR	95% CI
Low (<50 mg)	14,723/13	1.00		9,204/12	1.00	
Average (50-199 mg)	13,706/14	1.06	0.99,1.14	8,471/12	1.03	0.93,1.13
High (200-299 mg)	2,135/16	**1.21**	**1.07,1.39**	1,386/14	1.13	0.95,1.35
Very high (≥300 mg)	918/20	**1.52**	**1.27,1.81**	664/18	**1.32**	**1.04,1.66**

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender

[a] Overweight and/or obesity, according to International Obesity Task Force definition.

Supplementary Table 9. Maternal caffeine intake in early pregnancy and child's height and height gain velocity during childhood

	Child's developmental period						
	Infancy		Toddlerhood		Pre-school age		School age
	3 m	6 m	12 m	18 m	3 y	5 y	8 y
Maternal daily caffeine intake	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)
Height (in cm)							
Average (50-199 mg)	0.00 (-0.03,0.03)	0.00 (-0.04,0.03)	-0.03 (-0.07,0.02)	-0.04 (-0.09,0.00)	-0.05 (-0.10,0.01)	-0.02 (-0.09,0.05)	0.02 (-0.07,0.10)
High (200-299 mg)	-0.01 (-0.07,0.05)	-0.01 (-0.07,0.06)	-0.04 (-0.12,0.04)	-0.07 (-0.15,0.02)	-0.09 (-0.20,0.01)	-0.08 (-0.21,0.05)	-0.05 (-0.21,0.12)
Very high (≥300 mg)	-0.03 (-0.12,0.05)	-0.01 (-0.10,0.09)	0.00 (-0.12,0.11)	-0.02 (-0.15,0.10)	-0.09 (-0.24,0.07)	-0.13 (-0.31,0.06)	-0.17 (-0.41,0.07)
Height gain velocity (in mm/month)							
Average (50-199 mg)	**0.05 (0.02,0.09)**	-0.01 (-0.05,0.02)	-0.03 (-0.07,0.01)	-0.01 (-0.05,0.03)	0.02 (-0.02,0.06)	0.02 (-0.02,0.06)	0.02 (-0.02,0.07)
High (200-299 mg)	**0.08 (0.01,0.14)**	-0.01 (-0.08,0.05)	-0.05 (-0.12,0.02)	-0.04 (-0.11,0.04)	0.01 (-0.07,0.08)	0.02 (-0.06,0.09)	0.02 (-0.06,0.10)
Very high (≥300 mg)	**0.11 (0.01,0.21)**	0.04 (-0.06,0.14)	-0.04 (-0.14,0.06)	-0.06 (-0.16,0.05)	-0.04 (-0.15,0.07)	-0.03 (-0.14,0.08)	-0.03 (-0.15,0.09)

Abbreviations: Beta: beta coefficients, CI: confidence intervals

Effect estimates derive from linear mixed effect models with input of all anthropometric information from age 1month to 8 years and adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, nausea and/or vomiting during pregnancy, maternal smoking during pregnancy, gestational age, gender and birth weight

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract This has been done in both subsections. The study is a prospective cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found This has been done. In the abstract, we have described our study design and setting, our study participants and in more detail, we have described the definition exposure and the main outcomes of interest. In a separate paragraph of the abstract, we have described the findings in details and have summarized the main finding in the conclusion section (page 2).
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported This has been done in the introduction. We have provided the rationale for our study as well as the literature to support it (page 3-4).
Objectives	3	State specific objectives, including any prespecified hypotheses This has been done in the last paragraph of the introduction (page 4, first paragraph).
Methods		
Study design	4	Present key elements of study design early in the paper Our study design was described in the first paragraph of the methods, subsection "Study population and ethical approval" (page 4).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection The setting, location, recruitment period and follow-up, as well as the database version used were described in the first paragraph of the methods section, along with the ethical approval of the study, subsection "Study population and ethical approval" (page 4).
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up The eligibility and inclusion criteria has been described the methods section subsection "Study population and ethical approval" (page 4).
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed This is not a matched study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. This has been done. The exposure has been described in details in the methods, subsection "Maternal caffeine intake during pregnancy" (page 5), as well as in Supplementary Table 2. The outcome has been described in details in the methods, subsection "Child postnatal growth and overweight" (pages 5-6) and in Supplementary Tables 1 and 3. Potential confounders and effect modifiers are described in the methods; in subsection "Statistical analysis" (pages 6-7).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group All these has been described in the methods section, in subsections "Maternal caffeine intake during pregnancy" and "Child postnatal growth and overweight" (pages 5-6). More information of data source for the exposure and outcome are presented in Supplemental Material.

Bias	9	Describe any efforts to address potential sources of bias Possible bias have been described in the "Child postnatal growth and overweight" subsection of methods (pages 5-6) and have been stressed in the study limitations and other parts of the discussion (pages 10-11).
Study size	10	Explain how the study size was arrived at The included study population is described in the "Study population and ethical approval" (page 4).
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Regarding the exposure, the choice of subgroups was explained at subsection "Maternal caffeine intake during pregnancy" (page 5) and how quantitative variable were handled was explained in the subsection "statistical analysis" (pages 6-7). Regarding the outcome, the choice of subgroups was explained at subsections "Child postnatal growth and overweight" (pages 5-6), as well in Supplemental material and how quantitative variable were handled was explained in the "Statistical analysis" (pages 6-7).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding This has been done in the "Statistical analysis" section (pages 6-7).
		(*b*) Describe any methods used to examine subgroups and interactions This has been done in the "Statistical analysis" section (pages 6-7).
		(*c*) Explain how missing data were addressed In the subsection "Statistical analysis" (page 6-7) we have described that we have conducted complete case analysis.
		(*d*) If applicable, explain how loss to follow-up was addressed This has been done in the "Statistical analysis" section (pages 6-7).
		(*e*) Describe any sensitivity analyses This has been done in the "Statistical analysis" section (pages 6-7).
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed This has been described in the "Study population and ethical approval" (page 4).
		(b) Give reasons for non-participation at each stage This has been described in the "Study population and ethical approval" (page 4).
		(c) Consider use of a flow diagram We have not provided a flow diagram.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders This was provided in the results, subsection "Lifestyle and socio-demographic characteristics related to maternal caffeine intake during pregnancy" (pages 7-8) and in Supplemental material (Table 4).
		(b) Indicate number of participants with missing data for each variable of interest This was provided in Supplemental material (Tables 1 and 4).
		(c) Summarise follow-up time (eg, average and total amount) This was provided in Supplemental material (Tables 1).
Outcome data	15*	Report numbers of outcome events or summary measures over time This was provided in Figure 1 and in Supplemental material (Table 1 and 3).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included This has been provided in the results section and in Tables 1, 2, 3).
		(*b*) Report category boundaries when continuous variables were categorized This has been done in the results section (pages 7-9) and in Figures and Tables.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses This was reported in the results section, subsection "sensitivity analyses" (page 9).
Discussion		
Key results	18	Summarise key results with reference to study objectives In the first paragraph of the discussion, we have summarized our key finding (pages 9-10).
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. In the discussion, subsection "Strengths and limitations of this study" as well as throughout the whole discussion section we have reported and discussed the limitations of our study (pages 9-12).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. In the conclusion section, we have summarized our results and provided an overall interpretation taking into account the strengths and the limitations of our study, as well as the biological plausibility (page 12). We have compared our findings with two previous studies investigating a similar hypothesis (pages 10-11) and we have discussed potential biological mechanisms (page 10).
Generalisability	21	Discuss the generalisability (external validity) of the study results Regarding the exposure, the major caffeine contributor is coffee and black tea and no large differences and/or similar variations by brand, are expected in different countries and populations of pregnant women. Regarding the outcome, we have used international cut-offs to define overweight and we have compared our growth data with the WHO growth Standards to define excess growth; hence, enhancing the external validity of our findings.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. Funding has been described in a specific point (page 14).

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Maternal caffeine intake during pregnancy is associated with excess growth in infancy and overweight in childhood: results from a large prospective cohort study

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TITLE PAGE

Title: Maternal caffeine intake during pregnancy is associated with excess growth in infancy and overweight in childhood: results from a large prospective cohort study

Eleni Papadopoulou, Post-doctoral research fellow [a]; Jérémie Botton, Associate Professor [b,c]; Anne-Lise Brantsæter, Senior researcher [a] ; Margaretha Haugen, Senior researcher [a]; Jan Alexander, Senior researcher [d];Helle Margrete Meltzer, Senior researcher [d], Jonas Bacelis, PhD Candidate [e]; Anders Elfvin, Physician [f]; Bo Jacobsson, Professor/ Chief physician [e,g]; Verena Sengpiel, Associate Professor/Physician [h]

[a] Department of Environmental Exposure and Epidemiology, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[b] Early Determinants of the Child's Health and Development Team (ORCHAD), INSERM, UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Paris, F-75014 France

[c] Univ. Paris-Sud, Université Paris-Saclay, F-92296, Châtenay-Malabry, France

[d] Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[e] Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

[f] Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

[g] Department of Genetics and Bioinformatics, Division of Health Data and Digitalization, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

[h] Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Östra, SE-416 85 Gothenburg, Sweden

Corresponding author:
Eleni Papadopoulou
Division of Infection Control and Environmental Health
Norwegian Institute of Public Health
P.O. Box 4404, Nydalen, NO-0403 Oslo, Norway
Phone number: +47 21076511
Fax number: +47 21076686
E-mail: eleni.papadopoulou@fhi.no

ABSTRACT

Objectives: To study the association between maternal caffeine intake during pregnancy and the child's weight gain and overweight risk up to 8 years.

Design: Prospective nationwide pregnancy cohort.

Setting: The Norwegian Mother and Child Cohort Study.

Participants: 50,943 mothers recruited from 2002 to 2008 and their children, after singleton pregnancies, with information about average caffeine intake assessed at mid-pregnancy.

Outcome measure: Child's body size information at 11 age-points from 6 weeks to 8 years. We defined excess growth in infancy as a WHO weight gain z-score of >0.67 from birth to age 1 year, and overweight according to the International Obesity Task Force. We used a growth model to assess individual growth trajectories.

Results: Compared to pregnant women with low caffeine intake (<50mg/day, 46%), women with average (50-199mg/day, 44%), high (≥200-299mg/day, 7%) and very high (≥300mg/day, 3%) caffeine intakes had an increased risk of their child experiencing excess growth in infancy, after adjustment for confounders (odds ratio (OR)=1.15, 95% Confidence Intervals (CI) 1.09-1.22), OR=1.30, 95%CI, 1.16-1.45, OR=1.66, 95%CI, 1.42-1.93, respectively). In-utero exposure to any caffeine was associated with higher risk of overweight at age 3 and 5 years, while, the association persisted at 8 years, only for very high exposures. Any caffeine intake was associated with increased body mass index from infancy to childhood. Children prenatally exposed to caffeine intake >200mg/day had consistently higher weight. Very high caffeine exposures were associated with higher weight gain velocity from infancy to age 8 years.

Conclusion: Any caffeine consumption during pregnancy is associated with excess infant growth and increased risk of overweight, mainly at pre-school ages. Maternal caffeine intake may modify overall weight growth trajectory from birth to 8 years. This study adds supporting evidence for the current advice to reduce caffeine intake during pregnancy.

Strengths and limitations of this study

- A strength of this study is the large sample size.
- Maternal caffeine intake was estimated from all possible food sources.
- This is the first study investigating the association between maternal caffeine intake and excess infant growth and growth velocity.
- Missing data from body size measurements were handled with a growth model.
- Limitations include self-reported dietary data and parental-reported measurements of height and weight after 2 years.

MANUSCRIPT

Introduction

Caffeine is the world's most widely consumed central nervous system stimulant. It occurs naturally or is added to foods and beverages, with coffee and tea as the most common and major sources[1]. After ingestion, caffeine is readily absorbed into the blood stream and distributed to the tissues. It is metabolized in the liver by the microsomal cytochrome P450[2]. During pregnancy, elimination of caffeine is prolonged and it rapidly passes all biological membranes, including the blood-brain and placenta barriers, resulting in exposure of the fetus[3]. A maximum intake level of caffeine for pregnant women has been stipulated by several authorities, most of which agree that it should not exceed 200 mg/day, based on the evidence of its adverse effects on miscarriage rates and fetal growth restriction[1 4]. The negative effects of caffeine consumption during pregnancy on fetal growth have been well documented in epidemiological studies, including a study within the Norwegian Mother and Child Cohort Study (MoBa)[5]. In a recent meta-analysis the highest, compared with the lowest, maternal caffeine intake level was associated with a 38% increased risk of low birth weight (< 2.5kg)[6].

Fetal growth and growth in infancy are important determinants for the development of obesity and for long-term cardiometabolic health [7-9]. Excess infant growth programs later obesity, fat mass, and risk of adult disease, independent of intrauterine growth [10-15]. The prevalence of metabolic disorders, including obesity, cardiovascular disease and type 2 diabetes is rapidly growing across the globe, with the number of obese people risen worldwide from 105 million in 1975 to 641 million in 2014[16]. This trend indicates that the probability of reaching the WHO global obesity target, of no rise in obesity by 2025, is close to zero[16]. There is compelling human and animal evidence supporting the "fetal programming" hypothesis, according to which in utero exposures permanently alter an organism's physiology and metabolism, leading to susceptibility to subsequent disease, including obesity and metabolic disorders, with transgenerational effects [17 18].

In-utero exposure to caffeine has been related to an increased risk of overweight and higher body fat in childhood, in two previous epidemiological studies [19 20]. However, the link between in-utero caffeine exposure and excess growth in infancy is yet to be studied, even though excess infant growth is an established risk factor in the etiology of obesity and cardio-metabolic disease [13 15 21 22].

Based on our previous findings on the association of prenatal caffeine exposure with fetal growth restriction[5] and the fetal programming hypothesis[23], we hypothesized that prenatal caffeine exposure might affect postnatal growth. Thus, the objective of this study was to investigate the associations between maternal caffeine intake in pregnancy and child growth and risk of overweight up to age 8 years in a large prospective population-based cohort.

Methods

Study population and ethical approval

Our study was conducted within the Norwegian Mother and Child Cohort Study (MoBa), a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health[24]. Pregnant women from all over Norway were recruited during 1999-2008 and 40.6% of the invited women consented to participate. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Follow-up of the participants, after delivery, have been conducted at 6, 18, 36 months, 5, 7 and 8 years. Data used in this study are based on version 8 of the quality-assured data files, released for research in February 2014, with linkage to the Medical Birth Registry of Norway (MBRN). The data collection in MoBa was licensed by the Norwegian Data Inspectorate and approved by the Regional Committee for Medical Research Ethics. This study was approved by the Regional Committee for Medical Research Ethics in Southeastern Norway (2010/2683/REK Sør-øst A). All MoBA participants have provided a signed consent form.

After exclusion of multiple gestations, stillbirths, malformations and chromosomal abnormalities, 96,875 live-born singletons remained. Of these, 78,819 pregnant women had answered the food frequency questionnaire developed and validated for MoBa and in use from 2002 and onwards. The eligible study population, with available information on maternal caffeine intake and all relevant covariates, constituted 62,034 mother-child pairs. Our final study population consisted of 50,943 mother-child pairs with additional information on small for gestational age (SGA) and at least one postnatal measurement of weight or length/height. The cohort retention is presented in Supplementary Table 1. After 5 years, approximately 40% of the study population returned the questionnaire and had information on weight and height, while the distribution of mothers by caffeine intake level did not differ by follow-up age, meaning that loss to follow-up was not related to maternal caffeine intake in pregnancy.

Maternal caffeine intake during pregnancy

Maternal caffeine intake estimation in MoBa has been described in detail previously by Sengpiel et al[5]. In brief, self-reported intake of 255 dietary items was assessed at pregnancy week 22 with a food frequency questionnaire (FFQ) developed and validated for MoBa[25]. This is a semi-quantitative FFQ designed to record dietary habits during the first four to five months of gestation. Average, daily caffeine intake was calculated as the aggregated intake (in mg/day) from all available sources, including several types of coffee, black tea, caffeinated soft drinks, energy drinks, chocolate, chocolate milk, and sandwich spread, desserts, cakes and sweets containing cocoa. Supplementary Table 2 includes more details on the estimation of maternal caffeine intake. The median (25^{th} -75^{th} percentiles) caffeine intake was 57mg/day (23-120mg/day) for the included population and 64mg/day (25-129mg/day) for the non-included population with available caffeine information (n=11,091 mothers) ($p<0.001$ for Mann-Whitney test). We categorized caffeine intake, based on the calculated median as well as national and international recommendations for caffeine consumption during pregnancy, in four levels of caffeine intake: low (0-49mg/day), average (50-199mg/day), high (200-299mg/day) or very high (≥300mg/day).

Child postnatal growth and overweight

Anthropometric data

Weight and height/length measurements at eleven age-points (6 weeks, 3, 6 and 8 months and 1, 1.5, 2, 3, 5, 7 and 8 years) were reported. Up to 18 months the reported measurements were as documented in the child's health card, while for measurements from 2 to 8 years no specification was provided. Implausible anthropometrics were identified and excluded by separately implementing three different methods: i) by comparing with the WHO Growth Standards, as a weight-for-age or height-for-age z-score <6SD below or >6SD (5SD for weight) above the mean [26] , ii) by identifying measured values with a >|5SD| difference from the predicted value as derived from the Jenss-Bayley growth curve model, and iii) by the conditional growth percentiles[27]. After exclusion of implausible values, 464,343 and 452,980 measurements of weight and height/length were reported for our study population. Seven repeated measurements per child were available on average, for both anthropometrics. More details on anthropometric measurements are presented in Supplementary Table 1.

Outcomes

First, we assessed excess infant weight gain by calculating the difference in gender-adjusted WHO weight-for-age z-scores between birth and age 1 year, using reported weights[26]. A z-score gain of >0.67 represents an upward crossing of the percentile line[28], referred to as excess growth[29].

Second, we determined childhood overweight, including obesity, at two preschool-age (3 and 5 years) and one school-age (8 years) time-point, using the International Obesity Task Force (IOTF) criteria[30]. Used BMI cut-offs and overweight prevalences are presented in Supplementary Table 3.

BMI was derived by growth models. Individual growth trajectories for weight and length/height were obtained by modeling the overall growth from age 1 month to age 8 years, using the Jenss-Bayley growth curve model, a structural growth model based on a basic functional form of growth. This 4-parameter, non-linear model is suitable for describing growth of both weight and length/height during infancy and early childhood, up to age 8 years[31], before growth starts to accelerate again at puberty. To assess individual growth trajectories, we applied a mixed-effect approach using the Stochastic Approximation of Expectation-Maximization (SAEM) algorithm[32] [33]. We then calculated weight and length/height, body mass index (BMI) (weight (kg) divided by squared height (m)), as well as weight and height gain velocities at 14 age-points (1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4, 5, 6, 7 and 8 years), using the growth model derivatives. These predicted anthropometrics were also assessed as outcomes.

As including birth weight in the model may influence the estimated trajectories, and in order to assess the effect of caffeine on early growth independently of its effect on birth size[5], we did not include birth weight and length in the growth models.

Statistical analysis

We used logistic regression models to examine associations between maternal caffeine intake in categories and excess growth in infancy and childhood overweight. Low caffeine intake (0-49 mg/day) was the reference group. Similar analysis was performed after modelling caffeine by restricted cubic splines with four knots at percentiles 5, 35, 65 and 95, as recommended by Harrell[34], and corresponding to caffeine intakes of 6, 34, 91 and 253 mg/day, respectively. The reference level of caffeine intake was set at 50mg/day, corresponding to the median intake in our

study population. The associations were described graphically. Finally, we used mixed-effect linear regression models with random intercept by child and a random slope for age to analyze associations between predicted weight, height/length, BMI, weight and height gain velocities from ages 1 month to 8 years (14 age-points: 1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4, 5, 6, 7 and 8 years). Covariates' effects have been models as fixed in the mixed-effect models. All regression models were adjusted for random effects of sibling clusters since some mothers participated with more than one pregnancy.

Logistic and linear mixed models were adjusted for variables related to both maternal caffeine intake and excess growth by bivariate analysis: maternal age, maternal education, parity, pre-pregnancy BMI, paternal BMI, maternal and paternal smoking during pregnancy, maternal energy intake and nausea/vomiting during pregnancy. Gestational age and child's gender were also included in the models as a-priori covariates (Supplementary Table 4). Maternal height, paternal weight, paternal alcohol consumption and gestational diabetes (yes/no) were also considered but not included in the final models as they did not met the criteria. Our main analysis consists of complete case analysis of 38,338 mother-child pairs for the risk of excess growth and of 50,943 mother-child pairs for all other growth outcomes. The cohort attrition due to loss to follow-up was addressed by the use of predicted anthropometric measurements. The correlation between measured and predicted anthropometrics ranged from 0.85 to 0.99 for weight and from 0.95 to 0.98 for length/height (data not shown).

In separate sensitivity analyses, i) we excluded SGA neonates (SGA was defined as birth weight below the 10th percentile, according to population curves as described by Skjaerven et al[35]), ii) excluded smokers during pregnancy, iii) we adjusted for birth weight; only the overweight models and not the excess growth model, because birth weight is included in the excess growth calculation formula iv) explored caffeine intake by 3 main sources (i.e. from black coffee, black tea and soda drinks), v) excluded very high caffeine consumers, and vi) we assessed the association between maternal caffeine intake and childhood overweight, using the measured instead of predicted anthropometric data to define the outcome. Possible interactions with SGA and birth weight were tested with all studied outcomes. Since the associations between the outcomes and the interaction terms were not significant and the inclusion of the interaction term did not modified our results, we have not included these analyses in the manuscript.

Finally, we performed negative control analysis, using paternal caffeine intake as the negative control. Negative control analysis is a suggested method to test for the possibility of unmeasured confounding. We have assumed that there is no direct association between the father's exposure during the pregnancy period and the child's outcome, and that the shared confounders are equally associated with the mother and the father's exposures [36 37]. We have calculated the caffeine intake of the father using the caffeine concentrations and serving sizes as used for the mother's calculations (Supplementary Table 2) for 5 food items: filtered coffee, boiled coffee, espresso coffee, caffeinated soft-drink with sugar or artificially sweetened. Only 16,455 (32%) fathers had available information.

The main analyses were performed with the Stata 14 statistical software (Stata Corporation, College Station, Texas) and R version 3.2.2 [38] was used for the growth models.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Lifestyle and socio-demographic characteristics related to maternal caffeine intake during pregnancy

In our study population, 7.13% (n=3,633) and 3.21% (n=1,634) of women reported caffeine intake higher than 200mg/day and 300mg/day, respectively. The distribution of women not included in the analysis, by caffeine intake level was similar to the included (low: 43%, average: 46%, high: 8% and very high: 3%). The higher the caffeine intake, the higher the likelihood of a mother being older than 30 years, being multiparous, having a daily energy intake in the upper tertile, being a smoker during pregnancy and not suffering nausea and/or vomiting during pregnancy. Moreover, women with very high caffeine intake were more likely to have low education, have been obese before pregnancy and have partners who were obese and smokers, compared to those consuming less caffeine per day (Supplementary Table 4).

Paternal median (5^{th} -95^{th} percentiles) intake was 193mg/day (0-493mg/day), with caffeine from coffee being the main contributor (median: 187 mg/day). Fathers were consuming statistical

significantly more caffeine than their partners ($p<0.001$ for Wilcoxon matched-pairs signed-ranks test). The spearman correlation coefficient between maternal and paternal caffeine intakes was 0.15 (p-value<0.0001). However, paternal intake was increasing by increasing levels of maternal intake and 45% of mothers with very high intake were with partners in the highest quartile of caffeine intake (Supplementary Table 4).

Prenatal caffeine exposure and excess growth in infancy

The prevalence of excess growth in infancy increased from 23% to 29% as prenatal caffeine intake increased from low to very high (Figure 1). After adjustment for confounders, children born to average, high and very high caffeine consumers had 1.15 (95%CI: 1.09, 1.22), 1.30 (95%CI: 1.16, 1.45) and 1.66 (95%CI: 1.42,1.93) higher odds of excess growth in infancy, compared with children born to low consumers (Table 1). Neither exclusion of mothers who smoked during pregnancy or SGA neonates modified the results. The positive association between caffeine intake as a continuous variable and the risk of excess growth in infancy was linear with no apparent threshold (Supplementary Figure 1).

Prenatal caffeine exposure and overweight in childhood

The prevalence of overweight increased by 5% at age 3 years, by 6% at age 5 years and by 3% at age 8 years with increasing prenatal caffeine exposure from low to very high (Figure 1). Children born to average, high and very high caffeine consumers had 1.05 (95%CI: 0.99,1.12), 1.17 (95%CI: 1.05,1.30) and 1.44 (95%CI: 1.24,1.67) higher adjusted odds, respectively, for overweight at age 3 years, compared with children born to low caffeine consumers (Table 2). Similar odds ratios (OR) were found at age 5 years, but at age 8 years the respective risk was significant only for the highest caffeine consumption category (adjusted OR (aOR) 1.29; 95%CI 1.04,1.61). Neither exclusion of mothers who smoked during pregnancy or SGA neonates modified the results. However, adjustment for birth weight slightly increased the odds (Supplementary Table 5). We found a linear association between maternal caffeine consumption as a continuous variable and the risk of overweight at ages 3 and 5 years with, again, higher OR at age 3 years than at age 5 years (Supplementary Figure 2). As there was a high degree of concordance between overweight and/or obesity at ages 5 and 8 years, the plot at age 8 years overlapped with the one at age 5 years and was not included in Supplementary Figure 2.

Sensitivity analyses

In sensitivity analyses, we found similar results concerning the association of caffeine from different caffeine sources (black coffee, black tea, and soda drinks) with infant growth and overweight risk (Supplementary Table 6). When excluding very high caffeine consumers and using no coffee drinkers as the reference group, caffeine intake less than 300mg/day was still significantly associated with increased risk for excess infant growth and overweight (Supplementary Table 7). Finally, when growth data from actual measurements were used to assess the relationship between maternal caffeine intake and overweight at these age-points, similar trends and associations were observed (Supplementary Table 8).

Prenatal caffeine exposure and growth up to 8 years

In comparison with low exposure, both high and very high prenatal caffeine exposure were positively associated with a child's weight, weight gain velocity and BMI from the first month onwards (Figure 2). More specifically, children prenatally exposed to very high caffeine levels weighed 67-83g more in infancy (age 3 to 12 months), 110-136g more in toddlerhood (age 12 months to 3 years), 213-320g more at pre-school age (age 3 to 5 years) and 480g more at age 8 years, than children exposed to low caffeine levels (Table 3). Maternal caffeine intake during pregnancy, at any level above 50mg/day, was associated with higher BMI from ages 1 month to 8 years. Additional adjustment for birth weight provided better models (p-value<0.05 for likelihood ratio test between models with and without birth weight) and the estimates from these models are presented in Table 3. Whereas maternal caffeine intake during pregnancy was not associated with child height, it was related to higher height gain velocity up to age 3 months (Supplementary Table 9).

Negative control analysis: Paternal caffeine intake

We have explored the association between maternal and paternal caffeine intake without and with adjustment for paternal caffeine intake and the same for paternal intake. All models are adjusted for the same confounders as in the main analysis. We have explored the associations with excess infant growth (n=12,289) and overweight at 3 years (n=16,455) (Supplementary Figures 3 & 4). For both the risk of excess infant growth and overweight at 3 years, the association with maternal caffeine intake changed negligibly after adjusting for paternal intake. On the other hand, by using paternal caffeine intake as a negative control, the trend of the association with child's growth was similar to that of maternal caffeine intake, while the effect estimate was much lower.

Discussion

We found that any maternal caffeine intake during pregnancy was associated with a higher risk of excess growth in infancy and overweight in early childhood. In addition, caffeine intakes in pregnancy above the recommendation (200mg/day) were associated with modified growth trajectories from very early in life and maintained during childhood. More specifically, children exposed prenatally to caffeine levels above 200mg/day had persistently higher weight-, BMI- and weight gain velocity up to 8 years of age.

Strengths and limitations of this study

With the included 50,943 pregnancies, this is, so far, the largest study on the association of prenatal caffeine exposure and childhood growth parameters. It is the first to investigate effects on excess growth in infancy as well as growth velocities rather than just the size of the child, as well as critical age windows of diverging growth. Additional strengths include the prospective data collection, the comprehensive data on possible confounders and the assessment of caffeine intake from different sources. Nevertheless, our findings might be explained by residual confounding of non-accounted factors related to an overall unhealthy lifestyle and high caffeine consumption; though exclusion of smokers and very high caffeine consumers did not modify the results. In an effort to control for the effect of unmeasured familial characteristics, we performed negative control analysis using the father's caffeine intake. The unchanged effect estimate of maternal caffeine intake after adjustment for paternal intake as well as the weak effect estimate of paternal caffeine intake, indicate minor bias by shared unmeasured confounders.

In addition, the missing body size measurements were handled with the use of a growth model. In sensitivity analyses restricted to the measured data, similar associations were found as with the predicted body size data (Supplementary Table 8). This provides some reassurance of the validity of the predicted anthropometrics. However, we still acknowledge the potential for outcome misclassification as only 23% of the cohort had anthropometric information at 8 years (Supplementary Table 1). At the time of release of the current data, 53% (27,142 children) of our study population had not reached the age of 8 years, and only 24% of missing anthropometric information at 8 years can be attributed to loss to follow-up. Furthermore, we found that maternal caffeine exposure was not related to loss to follow-up (Supplementary Table 1).

The self-report of diet, which can induce misreporting, is a limitation. However, fair agreement between beverage intakes, particularly of coffee and tea, was found in a validation study based on food records and biomarkers[25 39]. Observational studies can never establish causality; however, our results fulfill some of the Bradford-Hill's criteria for causation[40] with a strong association, consistent findings for major caffeine sources, a biological gradient with higher caffeine exposure being associated to abnormal growth, consistent findings in animal models and a plausible mechanism, i.e. fetal programing.

Our study adds evidence to two previous epidemiological studies[19 20] that found an effect of prenatal caffeine exposure on child growth. In the study by Voerman et al., maternal caffeine intake above 360mg/day was associated with higher weight and BMI from birth to age 6 years, compared with intakes below 180mg/day[19]. In contrast to our findings, they found no association with overweight. Higher caffeine intake (360-540mg/day) during pregnancy was positively associated with body fat percentage and higher insulin levels in 6-year-olds. The exposure was assessed only by intakes of coffee and tea, which in our study also are the main but not the only caffeine contributors (78% of total caffeine intake). The median intake was double than in our study, resulting to a higher reference level (reference: <180mg/day, median: 117mg/day), providing less contrast between the compared exposure groups and less comparability to our study, as most of these women were not complying to the recommendation. Nevertheless, we found associations with adverse effects on child's growth even at low caffeine intakes, in the range of the recommendation, that are mostly due to consumption of foods and drinks other than coffee (chocolate, black tea, caffeinated sodas) [5]. Li et al. found likewise that any maternal caffeine intake was associated with an overall increased risk of obesity from ages 2 to 15 years, with an exposure range similar to the current study[20]. We have used similar approaches to study changes in individual growth trajectories, though with shorter follow-up. In addition, we provided age specific weight and BMI deviations, in order to find sensitive developmental windows when the association with the prenatal caffeine exposure exacerbated. There is no previous report of the association between caffeine intake in pregnancy and excess infant growth.

Potential mechanisms

Since excess growth in infancy, in itself, can be directly related to childhood obesity, adiposity[41] and an unfavorable adult cardio-metabolic profile[42], the associations between prenatal caffeine exposure with overweight, body fat and insulin, found in this study and the previous reports,

might be explained by excess infant growth. Putting together the previous findings in the MoBa study[5], we have shown that children prenatally exposed to high caffeine levels are smaller at birth, grow faster in infancy and retain a higher weight throughout childhood without significant height differences, thus becoming overweight (Supplementary Figure 5). These findings concur with the fetal programming of obesity hypothesis[43]. Nevertheless, the effect of prenatal caffeine exposure on postnatal growth and overweight was not dependent on birth weight. Hence, along with a healthy birth weight, it is important to identify the modifiable factors that can independently affect excess growth in infancy, independent of fetal growth. A growing number of studies have shown that other prenatal factors, e.g. excess gestational weight[44], high (>3times/week) fish intake [45],and postnatal factors, e.g. formula feeding and feeding schedule[46], are associated with increased risk of excess growth in infancy. Recent research shows that some perinatal factors can also have a direct effect on postnatal growth, independent of effects on fetal growth, including parental body size, smoking during pregnancy and socioeconomic status [47-49].

The biological plausibility supporting our findings is mainly provided by animal studies where, prenatal exposure to caffeine was shown to program the offspring towards excess growth and cardio-metabolic disorders through alterations i) in the hypothalamic-pituitary-adrenocortical axis that plays a key role in growth and metabolism[50-52], ii) in regulation of adenosine and adenosine antagonists, which are important modulators of development[53 54] and iii) in the placental expression and transportation of leptin[55], essential for appetite regulation.

Although most pregnant women reduce their caffeine intake during pregnancy and few have caffeine intakes higher than 200 mg/day (10%), our results show associations between caffeine intakes below 200 mg/day and excess growth. The results add supporting evidence for the current advice to reduce caffeine intake during pregnancy and indicate that complete avoidance might actually be advisable. An absence of a "safe intake level" has been previously reported in the basis of associations between maternal caffeine intake and fetal growth restriction[56]. Nevertheless, the authors of a recent systematic review after critically assessing the evidence, concluded that a consumption of up to 300 mg caffeine/day in healthy pregnant women is generally not associated with adverse reproductive and developmental effects [57]. Postnatal growth and child's weight status were not included in this review. Our findings are in agreement with the previous studies assessing a similar hypothesis, with associations reported in caffeine intakes above, but even below, the comparator, indicating that an intake of 300mg/day might not be a

safe level when growth is under study. Given that overweight in childhood is not a rare condition and the number of children highly exposed to caffeine during pregnancy is large, even a small increase in the risk of overweight due to caffeine can result into a large proportion of children becoming overweight, assuming that the effect was causal. Hence, more evidence is needed for the association between prenatal caffeine exposure and postnatal growth and an updated future critical assessment of such studies.

The association between prenatal caffeine exposure and overweight attenuated after 5 years, with only very high exposed children being at risk for overweight. Residual confounding due to postnatal factors related to overweight in late childhood might explain this attenuation. Nevertheless, adjustment for risk factors of being overweight at 8 years would introduce bias to the association under study. In addition, weight and height are screened from birth to 5 years in scheduled voluntarily appointments at the public health centers. Hence, a possible misclassification of outcome from anthropometrics after 5 years, might also explain the attenuation of the association.

There are two studies showing effects of caffeine intake on body composition and cardiometabolic health [19 58], with discrepant results. In the present study, we did not have any information on body composition. In addition, it is known that several genetic factors can contribute to variation in caffeine metabolism[59], and studies in adults have shown that slower metabolism of caffeine is related to higher risk of cardiovascular disease[60]. On the other hand, during pregnancy, maternal caffeine clearance modified the association between maternal caffeine intake and fetal growth restriction, with faster clearance being more detrimental [56]. More specifically, a genotype of rapid caffeine metabolism was associated with reduced birth weight while in women with a different polymorphism on the gene CYP1A2 C164A no effect was found [61]. Thus, there is a need to investigate the programming effect of prenatal caffeine exposure on child and adult body composition and cardiometabolic health, taking into account the genetic variation of maternal caffeine metabolism.

Conclusions

We found that the risk of excess infant growth and overweight in childhood-important risk factors for later cardio-metabolic disease- is increasing with maternal caffeine intake, with no apparent threshold. Maternal caffeine intake >200mg/day during pregnancy was associated with

high weight gain velocity beginning from the first months of life and higher BMI throughout childhood. Our findings support the recommendation to limit caffeine intake during pregnancy (<200mg/day).

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BJ initiated this collaborative project, contributed to the study design and the interpretation of the results. VS defined the research question, contributed to the study design, database preparation and interpretation of the results. She is guarantor and had final responsibility for the decision to submit for publication. All authors read, revised and approved the final version of the paper.

Data sharing statement: No additional data are available. All data from the MoBa study are available to all qualified researchers/research groups in Norway and to international researchers who are collaborating with a Norwegian researcher.

Declaration of transparency

EP as the lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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TABLES

Table 1. **Maternal caffeine intake in pregnancy and risk of excess growth in infancy (from birth to age 12 months)**

	Risk of excess growth in infancy (from birth to age 12 months)[a]					
	All children (n=38,338)		After excluding smokers during pregnancy (n=35,672)		After excluding SGA neonates[b] (n=35,144)	
Maternal daily caffeine intake	OR	95% CI	OR	95% CI	OR	95% CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.15	1.09,1.22	1.15	1.08,1.22	1.14	1.07,1.22
High (200-299 mg)	1.30	1.16,1.45	1.32	1.17,1.49	1.25	1.11,1.41
Very high (≥300 mg)	1.66	1.42,1.93	1.58	1.30,1.91	1.67	1.41,1.97

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months.

[b] SGA according to Skjaerven et al.

Table 2. Maternal caffeine intake in pregnancy and risk of overweight/obesity at age 3, 5 and 8 years.

	Risk of overweight and/or obesity[a]					
	All children (n=50,943)					
	Age 3 years		Age 5 years		Age 8 years	
Maternal daily caffeine intake	OR	95% CI	OR	95% CI	OR	95% CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.05	0.99,1.12	1.00	0.95,1.06	0.95	0.86,1.04
High (200-299 mg)	1.17	1.05,1.30	1.12	1.02,1.23	1.11	0.94,1.31
Very high (≥300 mg)	1.44	1.24,1.67	1.29	1.13,1.47	1.29	1.04,1.61
After excluding smokers during pregnancy (n=47,036)						
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.05	0.99,1.12	1.00	0.95,1.06	0.92	0.84,1.02
High (200-299 mg)	1.17	1.04,1.32	1.10	1.00,1.23	1.08	0.89,1.29
Very high (≥300 mg)	1.50	1.25,1.79	1.31	1.12,1.54	1.30	1.00,1.70
After excluding SGA neonates (n=46,718) [b]						
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	1.06	0.99,1.12	1.01	0.95,1.06	0.96	0.87,1.05
High (200-299 mg)	1.18	1.05,1.32	1.14	1.03,1.25	1.11	0.94,1.32
Very high (≥300 mg)	1.48	1.28,1.72	1.32	1.15,1.51	1.36	1.09,1.69

The same population was included at each age since the outcome was defined using model-derived anthropometrics.
All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender
[a] Overweight and/or obesity in children, according to the International Obesity Task Force definition.
[b] SGA according to Skjaerven et al.

Table 3. Maternal caffeine intake in pregnancy and child's weight, weight gain velocity and body mass index (BMI) during childhood (n=50,943). Low caffeine intake is the reference group.

	Child's developmental period						
	Infancy		Toddlerhood		Pre-school age		School age
Maternal daily caffeine intake	3 m Beta (95%CI)	6 m Beta (95%CI)	12 m Beta (95%CI)	18 m Beta (95%CI)	3 y Beta (95%CI)	5 y Beta (95%CI)	8 y Beta (95%CI)
Weight (in g)							
Average (50-199 mg)	**14.1 (1.6,26.6)**	**15.1 (1.3,28.8)**	14.9 (-5.1,34.9)	14.8 (-9.3,38.9)	16.1 (-16.9,49.0)	18.2 (-24.0,60.5)	21.5 (-35.1,78.1)
High (200-299 mg)	**31.3 (7.5,55.1)**	**35.0 (8.8,61.1)**	**45.4 (7.3,83.5)**	**59.0 (13.1,104.8)**	**99.0 (36.3,161.7)**	**148.9 (68.4,229.4)**	**222.0 (114.1,329.8)**
Very high (≥300 mg)	**67.0 (32.5,101.6)**	**83.2 (45.3,121.1)**	**110.1 (55.2,165.0)**	**135.5 (69.5,201.5)**	**213.4 (123.3,303.6)**	**320.0 (204.4,435.6)**	**480.3 (325.5,635.1)**
Weight gain velocity (in g/month)							
Average (50-199 mg)	0.8(-0.8,2.4)	0.4(-1.2,1.9)	0.2(-1.2,1.5)	0.3(-1.0,1.5)	0.3(-0.7,1.4)	0.3(-0.7,1.4)	0.3(-0.7,1.4)
High (200-299 mg)	1. (-1.4,4.7)	1.2(-1.7,4.1)	2. (-0.4,4.7)	2.3(-0.1,4.7)	**2.1(0,4.3)**	**2.0(0.1,4.0)**	**2.2(0,4.0)**
Very high (≥300 mg)	**6.0(1.5,10.4)**	**4.3(0.2,8.5)**	**3.8(0.1,7.4)**	**3.7(0.3,7.1)**	**3.9(0.8,7.0)**	**3.9(1.1,6.8)**	**3.9(1.1,6.8)**
BMI (in kg/m^2)							
Average (50-199 mg)	**0.03 (0.01,0.05)**	**0.03 (0.01,0.05)**	**0.04 (0.02,0.06)**	**0.04 (0.02,0.06)**	**0.04 (0.02,0.06)**	**0.03 (0.01,0.06)**	0.02 (-0.01,0.05)
High (200-299 mg)	**0.07 (0.03,0.11)**	**0.07 (0.03,0.10)**	**0.09 (0.05,0.12)**	**0.11 (0.07,0.15)**	**0.14 (0.10,0.19)**	**0.15 (0.11,0.20)**	**0.15 (0.09,0.21)**
Very high (≥300 mg)	**0.16 (0.10,0.21)**	**0.16 (0.11,0.21)**	**0.17 (0.12,0.23)**	**0.20 (0.14,0.25)**	**0.26 (0.20,0.32)**	**0.29 (0.22,0.36)**	**0.31 (0.22,0.39)**

Abbreviations: Beta: beta coefficients, CI: confidence intervals

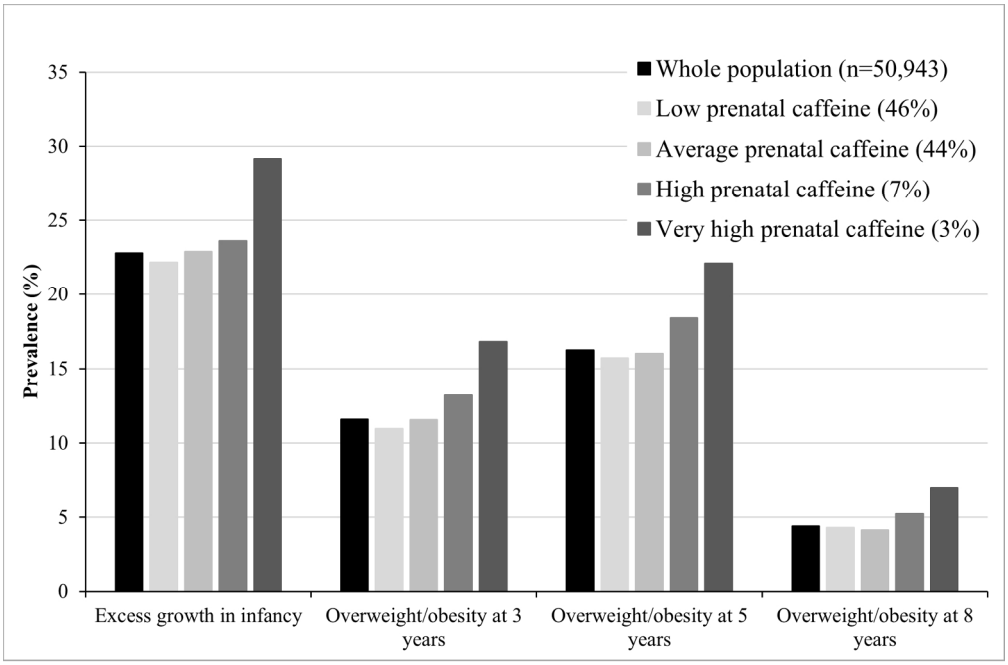
Infancy is defined as the period from birth to age 12 months, toddlerhood as the period from age 12 months to 3 years, pre-school age as the period from age 3 years to 5 years and school age as the period from age 5 years onwards.

Effect estimates derived from linear mixed effect models with input of all anthropometric information from age 1 month to 8 years and adjustment for: maternal age, parity, maternal education, pre-pregnancy BMI, nausea and/or vomiting during pregnancy, maternal smoking during pregnancy, paternal BMI, gestational age and birth weight. The effect estimates are adjusted mean changes of weight, weight gain velocity and BMI.

FIGURE LEGENDS

Figure 1. Prevalence of excess growth in infancy and overweight/obesity at age 3, 5 and 8 years, in the whole population and by maternal caffeine intake during pregnancy.

Figure 2. Maternal high (red) and very high (black) caffeine intake in pregnancy and adjusted change in children's a) weight (in g), b) weight gain velocity (in g/month) and c) body mass index (in kg/m^2), from age 1 month to 8 years (beta coefficients in solid lines and 95% confidence intervals in thin dashed lines). Low caffeine intake is the reference group.



Prevalence of excess growth in infancy and overweight/obesity at age 3, 5 and 8 years, in the whole population and by maternal caffeine intake during pregnancy.

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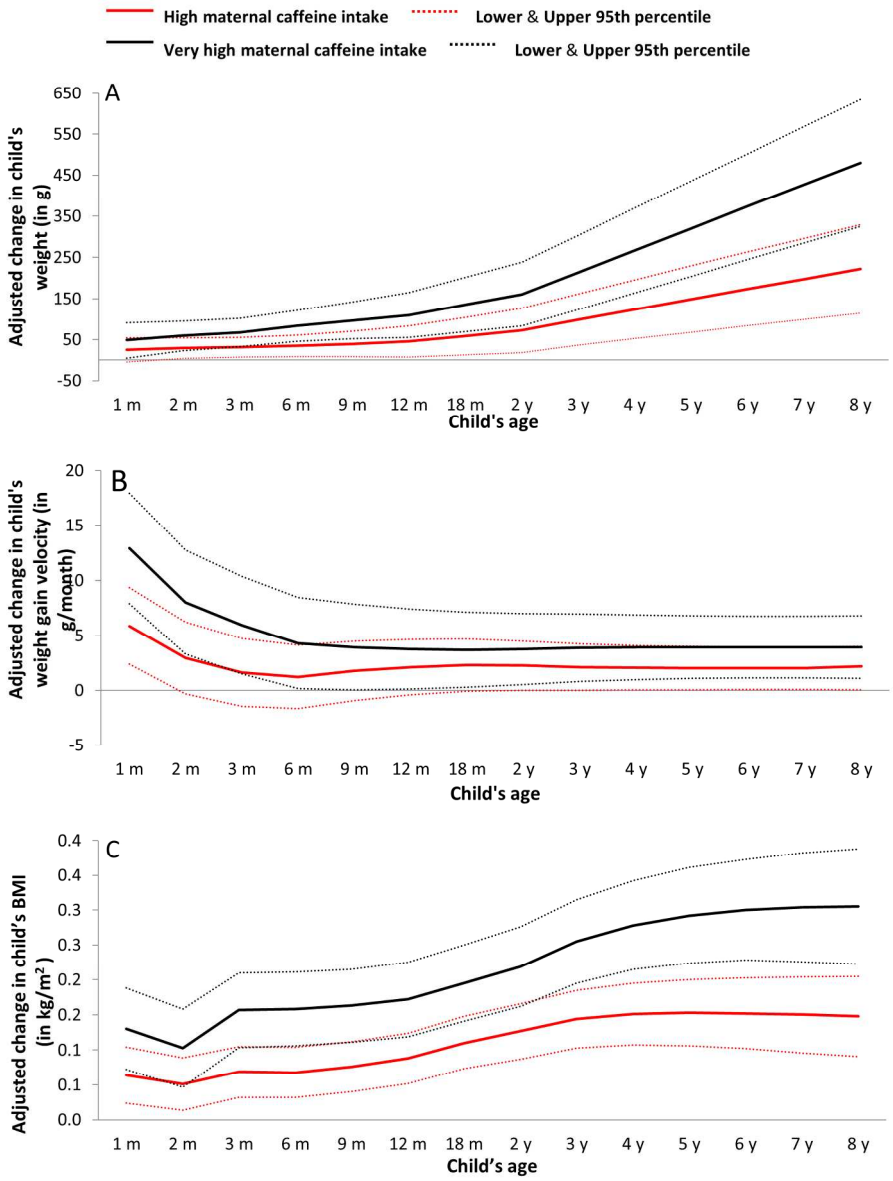

Maternal high (red) and very high (black) caffeine intake in pregnancy and adjusted change in children's a) weight (in g), b) weight gain velocity (in g/month) and c) body mass index (in kg/m2), from age 1 month to 8 years (beta coefficients in solid lines and 95% confidence intervals in thin dashed lines). Low caffeine intake is the reference group.

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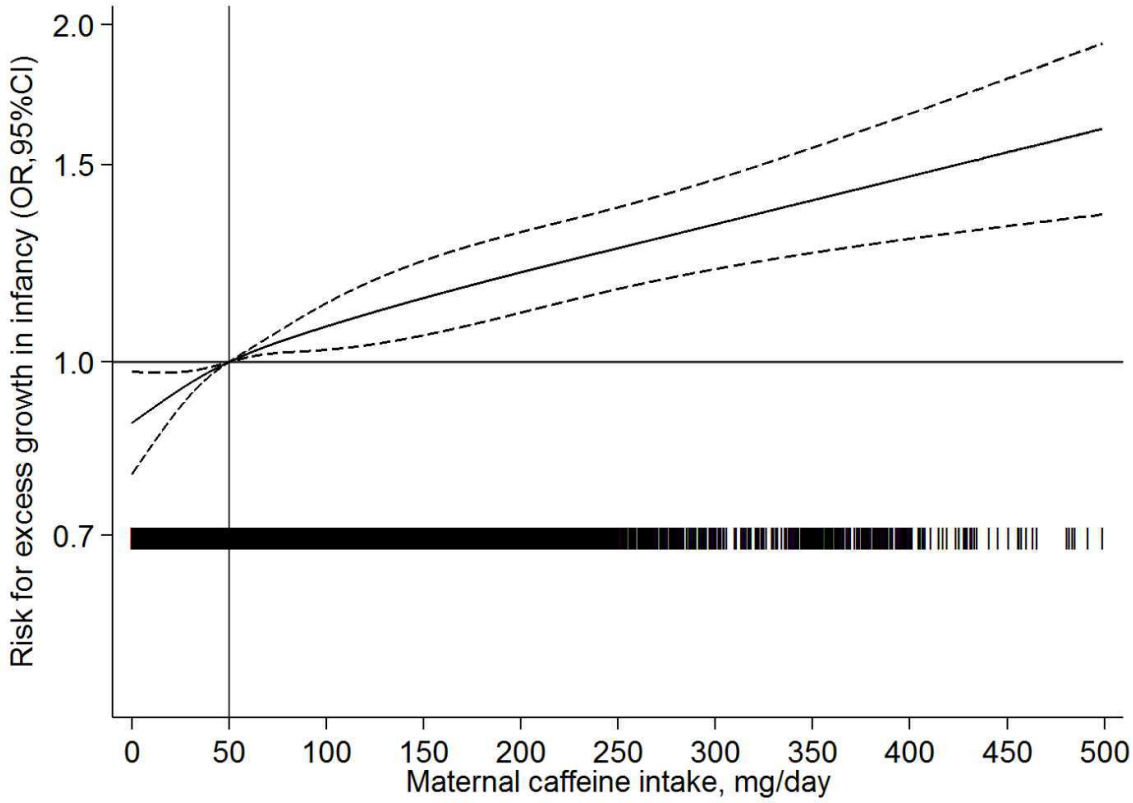
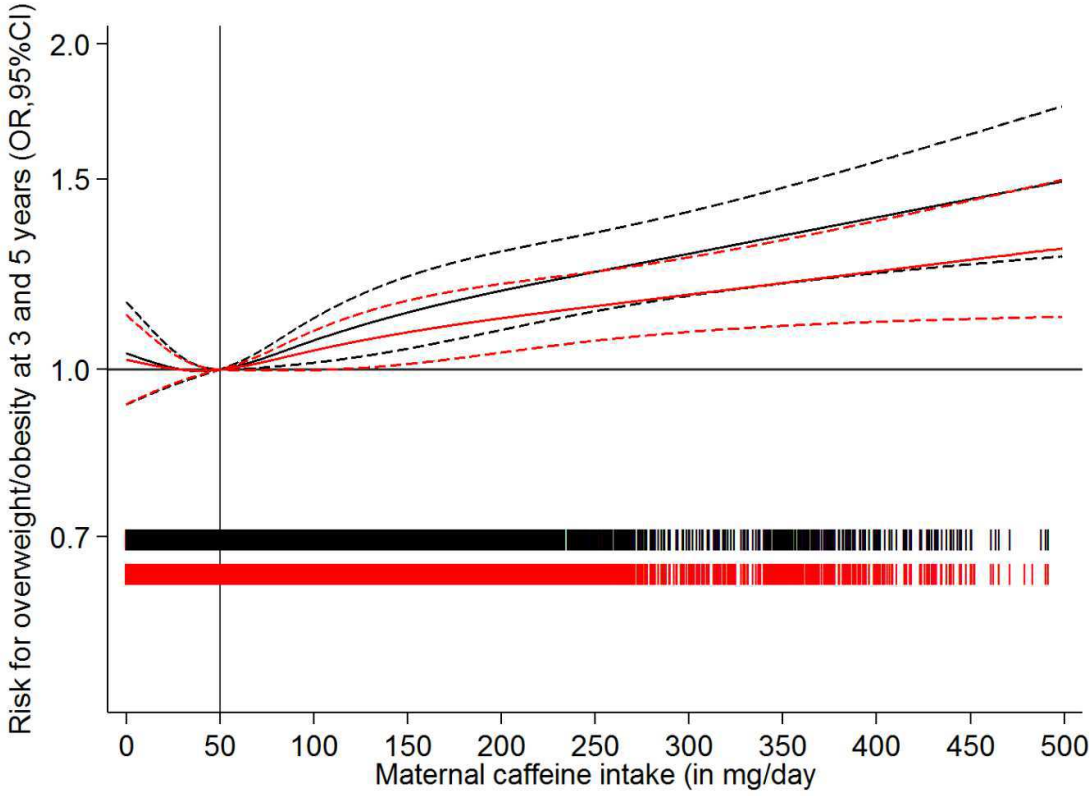
Supplementary Figure 1. Maternal caffeine intake on a continuous scale and risk of excess growth in infancy. Odds ratios (solid line) and 95% confidence intervals (dashed lines) derived from a logistic regression model using restricted cubic splines. The solid vertical line represents the reference value (50mg/day). The bar represents the children with excess growth.



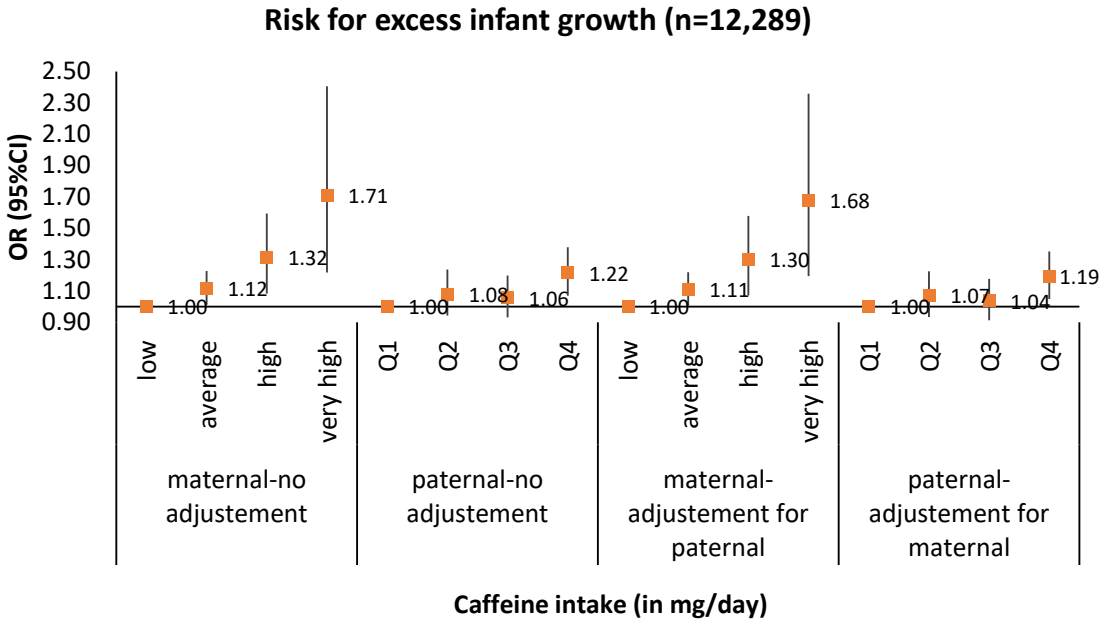
Footnote: all models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender and SGA according to Skjaerven et al.

Supplementary Figure 2. Maternal caffeine intake in continuous scale and risk for overweight/obesity at age 3 (black) and 5 years (red). Odds ratios (solid line) and the 95% confidence intervals (dashed lines) derived from a logistic regression model using restricted cubic splines. The solid vertical line represent the reference value (50mg/day). The bars represent the children with overweight/obesity.



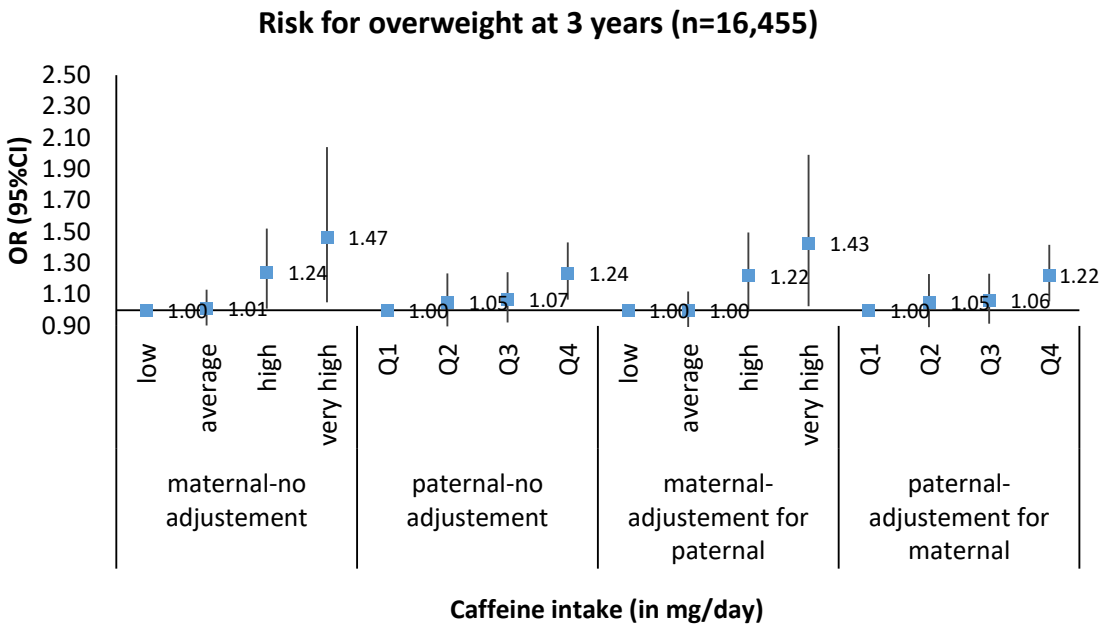
Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight

Supplementary Figure 3. Association between maternal and paternal caffeine intake during pregnancy and excess infant growth.



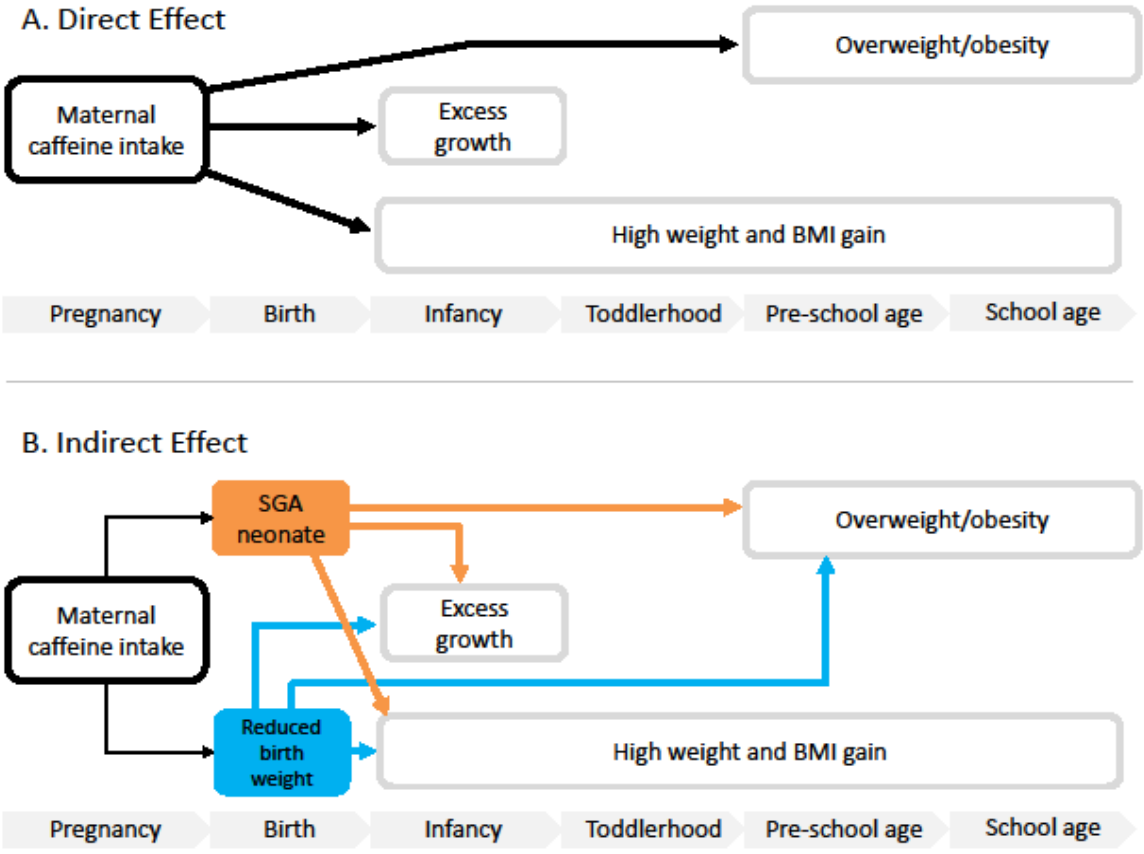
Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender.

Supplementary Figure 4. Association between maternal and paternal caffeine intake during pregnancy and overweight at 3 years.



Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender.

Supplementary Figure 5. Simplified causal diagram for the direct and indirect associations between maternal caffeine intake during pregnancy and the studied outcomes, mediated by SGA and birth weight



Supplementary Table 1. Anthropometric measurements, maternal caffeine intake level and cohort retention.

Measurement	Target age	Age (months)	Weight (kg)		Cohort retention	Height (cm)		Cohort retention	Maternal caffeine intake level				
		Mean	N	Mean		N	Mean		N	Low	Average	High	Very high
1	6 months	1.5	49672	5.0	98%	39175	57	77%	49672	46%	44%	7%	3%
2	3 months	3.1	49912	6.4	98%	49122	62	96%	49912	46%	44%	7%	3%
3	5-6 months	5.6	47047	7.9	92%	46640	68	92%	47047	46%	44%	7%	3%
4	8 months	8.2	37612	8.8	74%	37493	71	74%	37612	47%	43%	7%	3%
5	1 year	12.2	38660	9.9	76%	39046	76	77%	38660	47%	43%	7%	3%
6	15-18 months	15.9	38757	10.9	76%	38842	81	76%	38757	47%	43%	7%	3%
7	2 years	25.3	20485	13.0	40%	20855	89	41%	20485	48%	42%	7%	3%
8	3 years	36.0	30588	15.1	60%	29747	97	58%	30588	47%	43%	7%	3%
9	5 years	62.1	19340	20.0	38%	19768	113	39%	19340	46%	44%	7%	3%
10	7 years	84.7	18699	25.1	37%	19550	126	38%	18699	47%	43%	7%	3%
11	8 years	97.0	11685	28.7	23%	12312	132	24%	11685	47%	42%	7%	4%

Supplementary Table 2. Estimation of caffeine intake during pregnancy in the Norwegian Mother and Child Cohort Study.

Food item containing caffeine	Reported frequency	Serving	Caffeine concentration (mg/100g of food)
Filtered coffee	Cups per day, week or months	1 cup (125ml)	57
Boiled/pressed coffee	Cups per day, week or months	1 cup (125ml)	57
Powdered instant coffee	Cups per day, week or months	1 cup (125ml)	40
Decaffeinated coffee	Cups per day, week or months	1 cup (125ml)	2
Caffe latte/cappuccino	Cups per day, week or months	1 cup (125ml)	21
Espresso	Cups per day, week or months	1 cup (125ml)	114
Black tea	Cups per day, week or months	1 cup (250ml)	16
Caffeinated soft drinks, sugar sweetened and artificially sweetened	Cups per day, week or months	1 glass (250 ml)	12
Energy drink	Cups per day, week or months	1 glass (250 ml)	15
Chocolate milk	Cups per day, week or months	1 glass (250 ml)	15
Chocolate, medium dark			38
Sandwich spreads with cocoa			13
Deserts with coca			3
Cakes with cocoa			4
Sweets with cocoa			9

Supplementary Table 3. Definitions of overweight and obesity

Reference	Description	Age (years)	Overweight and/or obesity (kg/m^2)		Prevalence (%) [a]	
			Males	Females	Males	Females
International Obesity Task Force (IOTF) [1] (BMJ 2000 May 6; 320 (7244); 1240-Table 4)	Study-specific BMIs were calculated for age and sex	3	17.89	17.56	10.77	12.44
		5	17.42	17.15	14.30	18.28
		8	18.44	18.35	3.61	5.24

[a] Based on BMI calculated from the predicted anthropometric data.

From Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240-1243

Supplementary Table 4. Parental and pregnancy-related characteristics by category of maternal caffeine intake during pregnancy (n=50,943)

	Maternal caffeine intake during pregnancy							
	Low caffeine intake (<50mg/day) N=23,437		Average caffeine intake (50-199mg/day) N=22,239		High caffeine intake (200-299mg/day) N=3,633		Very high caffeine intake (≥300mg/day) N=1,634	
	N	%	N	%	N	%	N	%
Maternal age (years)								
<20	247	1.1	94	0.4	20	0.6	6	0.4
20-29	12,426	53.0	8,643	38.9	1,185	32.6	474	29.0
≥30	10,764	45.9	13,502	60.7	2,428	66.8	1,154	70.6
Maternal education (years)								
<13	7,025	30.0	5,993	27.0	1,142	31.4	755	46.2
13-16	10,725	45.7	9,538	42.9	1,512	42.6	623	38.1
>16	5,687	24.3	6,708	30.1	979	27.0	256	15.7
Parity								
Primiparous	14,260	60.8	11,053	49.7	1,492	41.1	492	30.1
Multiparous	9,177	39.2	11,186	50.3	2,141	58.9	1,142	69.9
Pre-pregnancy BMI (kg/m^2)								
<18.5	690	2.9	644	2.9	89	2.5	44	2.7
18.5-24.9	15,466	66.0	14,893	67.0	2,416	66.5	999	61.1
25-29.9	5,071	21.6	4,838	21.7	785	21.6	406	24.9
≥30	2,210	9.4	1,864	8.4	343	9.4	185	11.3
Maternal daily energy intake (in tertiles, kcal)								
<2.000	9,211	39.3	6,791	30.5	802	22.1	347	21.2
2.000-2.500	7,803	33.3	7,619	34.3	1,137	31.3	458	28.1
>2.500	6,423	27.4	7,829	35.2	1,694	46.6	829	50.7
Maternal smoking during pregnancy								
Never	22,500	96.0	20,532	92.3	3,005	82.7	999	61.1
Ever	937	4.0	1,707	7.7	628	17.3	635	38.9
Nausea/vomiting in pregnancy								
Never	6,057	25.8	6,949	31.3	1,358	37.4	673	41.2
Ever	17,380	74.2	15,290	68.7	2,275	62.6	961	58.8
Paternal BMI (kg/m^2)								
<18.5	51	0.2	47	0.2	13	0.3	5	0.3
18.5-24.9	10,538	44.6	9,831	44.2	1,547	42.6	661	40.4
25-29.9	10,526	45.3	10,254	46.1	1,699	46.8	756	46.3
≥30	2,322	9.9	2,107	9.5	374	10.3	212	13.0
Paternal smoking during pregnancy								
Never	19,338	82.5	18,029	81.1	2,752	75.7	1,007	61.6
Ever	4,099	17.5	4,210	18.9	881	24.3	627	38.4

Paternal caffeine intake								
1st quartile	2,253	(29%)	1,504	(20%)	168	(15%)	44	(14%)
2nd quartile	1,605	(21%)	1,495	(20%)	202	(18%)	51	(16%)
3rd quartile	1,950	(26%)	2,186	(30%)	356	(33%)	82	(25%)
4th quartile	1,832	(24%)	2,211	(30%)	371	(34%)	145	(45%)
Child's gender								
Boys	11,821	50.4	11,430	51.4	1.871	51.5	820	50.2
Girls	11,616	49.6	10,809	48.6	1.762	48.5	814	49.8
Gestational age (in weeks, median, IQR)	40.1	1.9	40.3	1.9	40.3	1.9	40.3	1.7

p-value<10^{-5} of chi square tests of all cross-tabulations presented in table

[1]IOM : Institute of Medicine

Supplementary Table 5. Maternal caffeine intake in pregnancy and risk of overweight/obesity at age 3, 5 and 8 years, after adjustment for birth weight.

	Risk of overweight and/or obesity [a], after additional adjustment for birth weight					
	Age 3 years		Age 5 years		Age 8 years	
Maternal daily caffeine intake	OR	95%CI	OR	95%CI	OR	95%CI
Low (<50 mg)	1.00		1.00		1.00	
Average (50-199 mg)	**1.08**	**1.02,1.15**	1.03	0.97,1.08	0.97	0.88,1.06
High (200-299 mg)	**1.21**	**1.09,1.36**	**1.16**	**1.05,1.28**	1.14	0.96,1.34
Very high (≥300 mg)	**1.53**	**1.32,1.78**	**1.36**	**1.19,1.55**	**1.35**	**1.09,1.68**

The same population was included at each age since the outcome was defined using model-derived anthropometrics.

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight

[a] Overweight and/or obesity in children, according to the International Obesity Task Force definition

Supplementary Table 6. Maternal caffeine intake during pregnancy from different sources and risk of excess growth in infancy (from birth to age 12 months) and overweight/obesity at age 3, 5 and 8 years

	Child's growth parameters											
	Excess growth[a]			Overweight/obesity at age 3 years[b]			Overweight/obesity at age 5 years[b]			Overweight/obesity at age 8 years[b]		
	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI
Caffeine from black coffee												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.18**	**1.11**	**1.26**	**1.18**	**1.11**	**1.26**	**1.12**	**1.05**	**1.18**	**1.11**	**1.00**	**1.23**
200-300	**1.31**	**1.06**	**1.62**	1.14	0.91	1.41	1.11	0.92	1.34	1.09	0.77	1.53
>300	**1.72**	**1.45**	**2.03**	**1.69**	**1.44**	**1.99**	**1.39**	**1.20**	**1.61**	**1.48**	**1.17**	**1.88**
Caffeine from black tea												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.11**	**1.01**	**1.21**	1.07	0.98	1.18	1.05	0.97	1.14	**1.20**	**1.04**	**1.38**
200-300	1.74	0.93	3.25	1.16	0.56	2.40	1.22	0.65	2.31	0.28	0.04	2.07
>300	1.67	0.50	5.54	0.86	0.20	3.75	0.86	0.25	2.97	NE		
Caffeine from soda drinks												
0-50	1.00			1.00			1.00			1.00		
50-200	**1.20**	**1.08**	**1.33**	0.96	0.86	1.07	0.96	0.88	1.06	1.01	0.87	1.18
200-300	1.40	0.95	2.06	1.13	0.77	1.65	1.18	0.84	1.65	1.48	0.91	2.41
>300	1.21	0.22	6.58	0.48	0.06	3.79	0.73	0.16	3.34	NE		

NE: not estimated

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months. Model adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender, and mutually adjusted for maternal caffeine intake from black coffee, black tea and soda drinks.

[b] Overweight and/or obesity, according to International Obesity Task Force definition.

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight, and mutually adjusted for maternal caffeine intake from black coffee, black tea and soda drinks.

Supplementary Table 7. Sensitivity after excluding very high caffeine drinkers and using no black coffee drinkers (n=23,402) as the reference group.

	No coffee drinkers OR (95%CI)	Caffeine intake <199mg OR (95%CI)	Caffeine intake 200-299mg OR (95%CI)
Excess infant growth	1.00	1.07 (1.01,1.13)	1.25 (1.12,1.39)
Overweight			
3 years	1.00	1.12 (1.06,1.19)	1.21 (1.08,1.35)
5 years	1.00	1.08 (1.03,1.14)	1.17 (1.06,1.29)
8 years	1.00	1.02 (0.93,1.12)	1.15 (0.98,1.36)

[a] Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months.

[b] Overweight and/or obesity, according to International Obesity Task Force definition.

Models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender.

Supplementary Table 8. Maternal caffeine intake in early pregnancy and risk of overweight/obesity at pre-school (3-5 years) and school (6-8 years) age, using measured anthropometric values

	Risk of overweight and/or obesity at pre-school and school age[a]					
	Pre-school age (n=31,482)			School age (n=19,722)		
Maternal daily caffeine intake	N/% cases	OR	95% CI	N/% cases	OR	95% CI
Low (<50 mg)	14,723/13	1.00		9,204/12	1.00	
Average (50-199 mg)	13,706/14	1.06	0.99,1.14	8,471/12	1.03	0.93,1.13
High (200-299 mg)	2,135/16	**1.21**	**1.07,1.39**	1,386/14	1.13	0.95,1.35
Very high (≥300 mg)	918/20	**1.52**	**1.27,1.81**	664/18	**1.32**	**1.04,1.66**

All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender

[a] Overweight and/or obesity, according to International Obesity Task Force definition.

Supplementary Table 9. Maternal caffeine intake in early pregnancy and child's height and height gain velocity during childhood

	Child's developmental period						
	Infancy		Toddlerhood		Pre-school age		School age
Maternal daily caffeine intake	3 m Beta (95%CI)	6 m Beta (95%CI)	12 m Beta (95%CI)	18 m Beta (95%CI)	3 y Beta (95%CI)	5 y Beta (95%CI)	8 y Beta (95%CI)
Height (in cm)							
Average (50-199 mg)	0.00 (-0.03,0.03)	0.00 (-0.04,0.03)	-0.03 (-0.07,0.02)	-0.04 (-0.09,0.00)	-0.05 (-0.10,0.01)	-0.02 (-0.09,0.05)	0.02 (-0.07,0.10)
High (200-299 mg)	-0.01 (-0.07,0.05)	-0.01 (-0.07,0.06)	-0.04 (-0.12,0.04)	-0.07 (-0.15,0.02)	-0.09 (-0.20,0.01)	-0.08 (-0.21,0.05)	-0.05 (-0.21,0.12)
Very high (≥300 mg)	-0.03 (-0.12,0.05)	-0.01 (-0.10,0.09)	0.00 (-0.12,0.11)	-0.02 (-0.15,0.10)	-0.09 (-0.24,0.07)	-0.13 (-0.31,0.06)	-0.17 (-0.41,0.07)
Height gain velocity (in mm/month)							
Average (50-199 mg)	**0.05 (0.02,0.09)**	-0.01 (-0.05,0.02)	-0.03 (-0.07,0.01)	-0.01 (-0.05,0.03)	0.02 (-0.02,0.06)	0.02 (-0.02,0.06)	0.02 (-0.02,0.07)
High (200-299 mg)	**0.08 (0.01,0.14)**	-0.01 (-0.08,0.05)	-0.05 (-0.12,0.02)	-0.04 (-0.11,0.04)	0.01 (-0.07,0.08)	0.02 (-0.06,0.09)	0.02 (-0.06,0.10)
Very high (≥300 mg)	**0.11 (0.01,0.21)**	0.04 (-0.06,0.14)	-0.04 (-0.14,0.06)	-0.06 (-0.16,0.05)	-0.04 (-0.15,0.07)	-0.03 (-0.14,0.08)	-0.03 (-0.15,0.09)

Abbreviations: Beta: beta coefficients, CI: confidence intervals

Effect estimates derive from linear mixed effect models with input of all anthropometric information from age 1month to 8 years and adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, nausea and/or vomiting during pregnancy, maternal smoking during pregnancy, gestational age, gender and birth weight

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract This has been done in both subsections. The study is a prospective cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found This has been done. In the abstract, we have described our study design and setting, our study participants and in more detail, we have described the definition exposure and the main outcomes of interest. In a separate paragraph of the abstract, we have described the findings in details and have summarized the main finding in the conclusion section (page 2).
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported This has been done in the introduction. We have provided the rationale for our study as well as the literature to support it (page 3-4).
Objectives	3	State specific objectives, including any prespecified hypotheses This has been done in the last paragraph of the introduction (page 4, first paragraph).
Methods		
Study design	4	Present key elements of study design early in the paper Our study design was described in the first paragraph of the methods, subsection "Study population and ethical approval" (page 4).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection The setting, location, recruitment period and follow-up, as well as the database version used were described in the first paragraph of the methods section, along with the ethical approval of the study, subsection "Study population and ethical approval" (page 4).
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up The eligibility and inclusion criteria has been described the methods section subsection "Study population and ethical approval" (page 4).
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed This is not a matched study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. This has been done. The exposure has been described in details in the methods, subsection "Maternal caffeine intake during pregnancy" (page 5), as well as in Supplementary Table 2. The outcome has been described in details in the methods, subsection "Child postnatal growth and overweight" (pages 5-6) and in Supplementary Tables 1 and 3. Potential confounders and effect modifiers are described in the methods; in subsection "Statistical analysis" (pages 6-7).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group All these has been described in the methods section, in subsections "Maternal caffeine intake during pregnancy" and "Child postnatal growth and overweight" (pages 5-6). More information of data source for the exposure and outcome are presented in Supplemental Material.

Bias	9	Describe any efforts to address potential sources of bias Possible bias have been described in the "Child postnatal growth and overweight" subsection of methods (pages 5-6) and have been stressed in the study limitations and other parts of the discussion (pages 10-11).
Study size	10	Explain how the study size was arrived at The included study population is described in the "Study population and ethical approval" (page 4).
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Regarding the exposure, the choice of subgroups was explained at subsection "Maternal caffeine intake during pregnancy" (page 5) and how quantitative variable were handled was explained in the subsection "statistical analysis" (pages 6-7). Regarding the outcome, the choice of subgroups was explained at subsections "Child postnatal growth and overweight" (pages 5-6), as well in Supplemental material and how quantitative variable were handled was explained in the "Statistical analysis" (pages 6-7).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding This has been done in the "Statistical analysis" section (pages 6-7).
		(*b*) Describe any methods used to examine subgroups and interactions This has been done in the "Statistical analysis" section (pages 6-7).
		(*c*) Explain how missing data were addressed In the subsection "Statistical analysis" (page 6-7) we have described that we have conducted complete case analysis.
		(*d*) If applicable, explain how loss to follow-up was addressed This has been done in the "Statistical analysis" section (pages 6-7).
		(*e*) Describe any sensitivity analyses This has been done in the "Statistical analysis" section (pages 6-7).
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed This has been described in the "Study population and ethical approval" (page 4).
		(b) Give reasons for non-participation at each stage This has been described in the "Study population and ethical approval" (page 4).
		(c) Consider use of a flow diagram We have not provided a flow diagram.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders This was provided in the results, subsection "Lifestyle and socio-demographic characteristics related to maternal caffeine intake during pregnancy" (pages 7-8) and in Supplemental material (Table 4).
		(b) Indicate number of participants with missing data for each variable of interest This was provided in Supplemental material (Tables 1 and 4).
		(c) Summarise follow-up time (eg, average and total amount) This was provided in Supplemental material (Tables 1).
Outcome data	15*	Report numbers of outcome events or summary measures over time This was provided in Figure 1 and in Supplemental material (Table 1 and 3).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included This has been provided in the results section and in Tables 1, 2, 3).
		(*b*) Report category boundaries when continuous variables were categorized This has been done in the results section (pages 7-9) and in Figures and Tables.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses This was reported in the results section, subsection "sensitivity analyses" (page 9).
Discussion		
Key results	18	Summarise key results with reference to study objectives In the first paragraph of the discussion, we have summarized our key finding (pages 9-10).
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. In the discussion, subsection "Strengths and limitations of this study" as well as throughout the whole discussion section we have reported and discussed the limitations of our study (pages 9-12).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. In the conclusion section, we have summarized our results and provided an overall interpretation taking into account the strengths and the limitations of our study, as well as the biological plausibility (page 12). We have compared our findings with two previous studies investigating a similar hypothesis (pages 10-11) and we have discussed potential biological mechanisms (page 10).
Generalisability	21	Discuss the generalisability (external validity) of the study results Regarding the exposure, the major caffeine contributor is coffee and black tea and no large differences and/or similar variations by brand, are expected in different countries and populations of pregnant women. Regarding the outcome, we have used international cut-offs to define overweight and we have compared our growth data with the WHO growth Standards to define excess growth; hence, enhancing the external validity of our findings.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. Funding has been described in a specific point (page 14).

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.