

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018895
Article Type:	Research
Date Submitted by the Author:	01-Aug-2017
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
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Nutrition and metabolism, Paediatrics, Public health
Keywords:	EPIDEMIOLOGY, NUTRITION & DIETETICS, PREVENTIVE MEDICINE, PUBLIC HEALTH, SOCIAL MEDICINE

SCHOLARONE™  
Manuscripts

**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 <sup>a</sup>; Jérémie Botton, Associate Professor <sup>b,c</sup>; Anne-Lise Brantsæter, Senior researcher <sup>a</sup>; Margaretha Haugen, Senior researcher <sup>a</sup>; Jan Alexander, Senior researcher <sup>d</sup>; Helle Margrete Meltzer, Senior researcher <sup>d</sup>; Jonas Bacelis, PhD Candidate <sup>e</sup>; Anders Elfvin, Physician <sup>f</sup>; Bo Jacobsson, Professor/ Chief physician <sup>e,g</sup>; Verena Sengpiel, Associate Professor/Physician <sup>h</sup>

<sup>a</sup> 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

<sup>b</sup> 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

<sup>c</sup> Univ. Paris-Sud, Université Paris-Saclay, F-92296, Châtenay-Malabry, France

<sup>d</sup> Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

<sup>e</sup> Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

<sup>f</sup> Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

<sup>g</sup> Department of Genetics and Bioinformatics, Division of Health Data and Digitalization, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

<sup>h</sup> 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](mailto: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 ( $<50\text{mg/day}$ , 46%), women with average ( $50\text{-}199\text{mg/day}$ , 44%), high ( $\geq 200\text{-}299\text{mg/day}$ , 7%) and very high ( $\geq 300\text{mg/day}$ , 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  $>200\text{mg/day}$  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<sup>1</sup>. 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<sup>2</sup>. 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<sup>3</sup>. 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<sup>4</sup>. 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)<sup>5</sup>. 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)<sup>6</sup>.

Fetal growth and growth in infancy are important determinants for the development of obesity and for long-term cardiometabolic health<sup>7-9</sup>. Excess infant growth programs later obesity, fat mass, and risk of adult disease, independent of intrauterine growth<sup>10-15</sup>. 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<sup>16</sup>. This trend indicates that the probability of reaching the WHO global obesity target, of no rise in obesity by 2025, is close to zero<sup>16</sup>. 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<sup>17</sup>

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<sup>19 20</sup>. 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

1  
2  
3 Based on our previous findings on the association of prenatal caffeine exposure with fetal  
4 growth restriction<sup>5</sup> and the fetal programming hypothesis<sup>23</sup>, we hypothesized that prenatal  
5 caffeine exposure might affect postnatal growth. Thus, the objective of this study was to  
6 investigate the associations between maternal caffeine intake in pregnancy and child growth and  
7 risk of overweight up to age 8 years in a large prospective population-based cohort.  
8  
9

## 13 **Methods**

### 14 **Study population and ethical approval**

15 Our study was conducted within the Norwegian Mother and Child Cohort Study (MoBa), a  
16 prospective population-based pregnancy cohort study conducted by the Norwegian Institute of  
17 Public Health<sup>24</sup>. Pregnant women from all over Norway were recruited during 1999-2008 and  
18 40.6% of the invited women consented to participate. The cohort now includes 114,500 children,  
19 95,200 mothers and 75,200 fathers. Follow-up of the participants, after delivery, have been  
20 conducted at 6, 18, 36 months, 5, 7 and 8 years. Data used in this study are based on version 8 of  
21 the quality-assured data files, released for research in February 2014, with linkage to the Medical  
22 Birth Registry of Norway (MBRN). The data collection in MoBa was licensed by the Norwegian  
23 Data Inspectorate and approved by the Regional Committee for Medical Research Ethics. This  
24 study was approved by the Regional Committee for Medical Research Ethics in Southeastern  
25 Norway (2010/2683/REK Sør-øst A). All MoBA participants have provided a signed consent  
26 form.  
27  
28

29 After exclusion of multiple gestations, stillbirths, malformations and chromosomal  
30 abnormalities, 96,875 live-born singletons remained. Of these, 78,819 had answered the food  
31 frequency questionnaire developed and validated for MoBa and in use from 2002 and onwards.  
32 The eligible study population, with available information on maternal caffeine intake and all  
33 relevant covariates, constituted 62,034 mother-child pairs. Our final study population consisted of  
34 50,943 mother-child pairs with additional information on small for gestational age (SGA) and at  
35 least one postnatal measurement of weight or length/height. The cohort retention is presented in  
36 Supplementary Table 1. After 5 years, approximately 40% of the study population returned the  
37 questionnaire and had information on weight and height, while the distribution of mothers by  
38 caffeine intake level did not differ by follow-up age, meaning that loss to follow-up was not  
39 related to maternal caffeine intake in pregnancy.  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Maternal caffeine intake during pregnancy

Maternal caffeine intake estimation in MoBa has been described in detail previously by Sengpiel et al<sup>5</sup>. 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<sup>25</sup>. 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<sup>th</sup>-75<sup>th</sup> 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 ( $\geq$ 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<sup>26</sup>, 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<sup>27</sup>. 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.



1  
2  
3 We assessed excess infant weight gain by calculating the difference in gender-adjusted WHO  
4 weight-for-age z-scores between birth and age 1 year<sup>26</sup>. A z-score of >0.67 represents an upward  
5 crossing of the percentile<sup>28</sup>, referred to as excess growth<sup>29</sup>.  
6

7  
8 Individual growth trajectories for weight and length/height were obtained by modeling the  
9 overall growth from age 1 month to age 8 years, using the Jenss-Bayley growth curve model, a  
10 structural growth model based on a basic functional form of growth. This 4-parameter, non-linear  
11 model is suitable for describing growth of both weight and length/height during infancy and early  
12 childhood, up to age 8 years<sup>30</sup>, before growth starts to accelerate again at puberty. To assess  
13 individual growth trajectories, we applied a mixed-effect approach using the Stochastic  
14 Approximation of Expectation-Maximization (SAEM) algorithm<sup>31 32</sup>. We then calculated weight  
15 and length/height, body mass index (BMI) (weight (kg) divided by squared height (m)), as well  
16 as weight and height gain velocities at 14 age-points (1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4,  
17 5, 6, 7 and 8 years), using the growth model derivatives. As including birth weight in the model  
18 may influence the estimated trajectories, and in order to assess the effect of caffeine on early  
19 growth independently of its effect on birth size<sup>5</sup>, we did not include birth weight and length in the  
20 growth models. The correlation between measured and predicted anthropometrics ranged from  
21 0.85 to 0.99 for weight and from 0.95 to 0.98 for length/height (data not shown).  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31

32 We determined childhood overweight and/or obesity status, hereafter referred to as  
33 “overweight”, based on the model-predicted weight and height at two preschool-age (3 and 5  
34 years) and one school-age (8 years) time-point, using the International Obesity Task Force  
35 (IOTF) criteria<sup>33</sup>. Used BMI cut-offs and overweight prevalences are presented in Supplementary  
36 Table 3.  
37  
38  
39  
40  
41  
42

### 43 **Statistical analysis**

44 We used logistic regression models to examine associations between maternal caffeine intake  
45 and excess growth in infancy and childhood overweight. We used mixed-effect linear regression  
46 models with random intercept and slope for weight, height/length, BMI, weight and height gain  
47 velocities from ages 1 month to 8 years (14 age-points: 1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4,  
48 5, 6, 7 and 8 years). Low caffeine intake (0-49 mg/day) was the reference group. Covariates  
49 related to both maternal caffeine intake and excess growth in bivariate analysis were selected as  
50 confounders for adjustment: maternal age, maternal and paternal education, parity, pre-pregnancy  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 BMI, paternal BMI, maternal and paternal smoking during pregnancy, maternal energy intake  
4 and nausea/vomiting during pregnancy (Supplementary Table 4).

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

15  
16 Possible interaction effects were explored for child's gender, birth weight and SGA. SGA,  
17 defined as birth weight below the 10<sup>th</sup> percentile, according to population curves as described by  
18 Skjaerven et al<sup>35</sup>, was used. Birth weight was not considered in the excess growth analysis, as it is  
19 included in the excess growth calculation formula. In separate sensitivity analyses, i) we excluded  
20 SGA neonates, ii) excluded smokers during pregnancy, iii) excluded very high caffeine  
21 consumers, and iv) we assessed the association between maternal caffeine intake and childhood  
22 overweight, using the measured instead of predicted anthropometric data to define the outcome.

23  
24 The main analyses were performed with the Stata 14 statistical software (Stata Corporation,  
25 College Station, Texas) and R version 3.2.2<sup>36</sup> was used for the growth models.

## 26 27 28 **Patient involvement**

29  
30 No patients were involved in setting the research question or the outcome measures, nor were  
31 they involved in developing plans for design or implementation of the study. No patients were  
32 asked to advise on interpretation or writing up of results. There are no plans to disseminate the  
33 results of the research to study participants or the relevant patient community.

## 34 35 36 **Results**

### 37 38 39 ***Lifestyle and socio-demographic characteristics related to maternal caffeine intake during pregnancy***

40  
41 In our study population, 7.13% (n=3,633) and 3.21% (n=1,634) of women reported caffeine  
42 intake higher than 200mg/day and 300mg/day, respectively. The distribution of women not  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 included in the analysis, by caffeine intake level was similar to the included (low: 43%, average:  
4 46%, high: 8% and very high: 3%, Supplementary Table 1). The higher the caffeine intake, the  
5 higher the likelihood of a mother being older than 30 years, being multiparous, having gained  
6 more weight during pregnancy than recommended by the Institute of Medicine<sup>29</sup>, having a daily  
7 energy intake in the upper tertile, being a smoker and alcohol consumer during pregnancy and not  
8 suffering nausea and/or vomiting during pregnancy. Moreover, women with very high caffeine  
9 intake were more likely to have low education, have been obese before pregnancy and have  
10 partners who were obese and smokers, compared to those consuming less caffeine per day  
11 (Supplementary Table 4).  
12  
13  
14  
15  
16  
17

### 18 ***Prenatal caffeine exposure and excess growth in infancy***

19  
20 The prevalence of excess growth in infancy increased from 23% to 29% as prenatal caffeine  
21 intake increased from low to very high (Figure 1). After adjustment for confounders, children  
22 born to average, high and very high caffeine consumers had 1.15 (95%CI: 1.09, 1.22), 1.30  
23 (95%CI: 1.16,1.45) and 1.66 (95%CI: 1.42,1.93) higher odds of excess growth in infancy,  
24 compared with children born to low consumers (Table 1). Neither exclusion of mothers who  
25 smoked during pregnancy or SGA neonates modified the results. The positive association  
26 between caffeine intake as a continuous variable and the risk of excess growth in infancy was  
27 linear with no apparent threshold (Supplementary Figure 1).  
28  
29  
30  
31  
32  
33

### 34 ***Prenatal caffeine exposure and overweight in childhood***

35  
36 The prevalence of overweight increased by 5% at age 3 years, by 6% at age 5 years and by 3%  
37 at age 8 years with increasing prenatal caffeine exposure from low to very high (Figure 1).  
38 Children born to average, high and very high caffeine consumers had 1.05 (95%CI: 0.99,1.12),  
39 1.17 (95%CI: 1.05,1.30) and 1.44 (95%CI: 1.24,1.67) higher adjusted odds, respectively, for  
40 overweight at age 3 years, compared with children born to low caffeine consumers (Table 2).  
41 Similar odds ratios (OR) were found at age 5 years, but at age 8 years the respective risk was  
42 significant only for the highest caffeine consumption category (adjusted OR (aOR) 1.29; 95%CI  
43 1.04,1.61). Neither exclusion of mothers who smoked during pregnancy or SGA neonates  
44 modified the results. However, adjustment for birth weight slightly increased the odds  
45 (Supplementary Table 5). We found a linear association between maternal caffeine consumption  
46 as a continuous variable and the risk of overweight at ages 3 and 5 years with, again, higher OR  
47 at age 3 years than at age 5 years (Supplementary Figure 2). As there was a high degree of  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 concordance between overweight and/or obesity at ages 5 and 8 years, the plot at age 8 years  
4 overlapped with the one at age 5 years and was not included in Supplementary Figure 2.

### 6 ***Sensitivity analyses***

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

### 22 ***Prenatal caffeine exposure and growth up to 8 years***

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

### 46 **Discussion**

48 We found that any maternal caffeine intake during pregnancy was associated with a higher risk  
49 of excess growth in infancy and overweight in early childhood. In addition, caffeine intakes in  
50 pregnancy above the recommendation (200mg/day) were associated with modified growth  
51 trajectories from very early in life and maintained during childhood. More specifically, children  
52  
53  
54  
55  
56  
57  
58  
59

1  
2  
3 exposed prenatally to caffeine levels above 200mg/day had persistently higher weight-, BMI- and  
4 weight gain velocity up to 8 years of age.

### 6 ***Strengths and limitations of this study***

8 With the included 50,943 pregnancies, this is, so far, the largest study on the association of  
9 prenatal caffeine exposure and childhood growth parameters. It is the first to investigate effects  
10 on excess growth in infancy as well as growth velocities rather than just the size of the child, as  
11 well as critical age windows of diverging growth. Additional strengths include the prospective  
12 data collection, the comprehensive data on possible confounders and the assessment of caffeine  
13 intake from different sources. Nevertheless, our findings might be explained by residual  
14 confounding of non-accounted factors related to an overall unhealthy lifestyle and high caffeine  
15 consumption; though exclusion of smokers and very high caffeine consumers did not modify the  
16 results.  
17

18 In addition, the missing body size measurements were handled with the use of a growth model.  
19 The correlations between the measured and the predicted body size measurements were strong for  
20 at all ages. In sensitivity analyses restricted to the measured data, similar associations were found  
21 as with the predicted body size data (Supplementary Table 8). This provides some reassurance of  
22 the validity of the predicted anthropometrics. However, we still acknowledge the potential for  
23 outcome misclassification as only 23% of the cohort had anthropometric information at 8 years  
24 (Supplementary Table 3). At the time of release of the current data, 53% (27,142 children) of our  
25 study population had not reached the age of 8 years, and only 24% of missing anthropometric  
26 information at 8 years can be attributed to loss to follow-up. Furthermore, we found that maternal  
27 caffeine exposure was not related to loss to follow-up (Supplementary Table 3).  
28

29 The self-report of diet, which can induce misreporting, is a limitation. However, fair agreement  
30 between beverage intakes, particularly of coffee and tea, was found in a validation study based on  
31 food records and biomarkers<sup>25 37</sup>. Observational studies can never establish causality; however,  
32 our results fulfill some of the Hill's criteria for causation<sup>38</sup> with a strong association, consistent  
33 findings for major caffeine sources, a biological gradient with higher caffeine exposure being  
34 associated to abnormal growth, consistent findings in animal models and a plausible mechanism,  
35 i.e. fetal programming.  
36

37 Our study adds evidence to two previous epidemiological studies<sup>19 20</sup> that found an effect of  
38 prenatal caffeine exposure on child growth. In the study by Voerman et al., maternal caffeine  
39

1  
2  
3 intake above 360mg/day was associated with higher weight and BMI from birth to age 6 years,  
4 compared with intakes below 180mg/day<sup>19</sup>. In contrast to our findings, they found no association  
5 with overweight. Higher caffeine intake (360-540mg/day) during pregnancy was positively  
6 associated with body fat percentage and higher insulin levels in 6-year-olds. The exposure was  
7 assessed only by intakes of coffee and tea, which in our study also are the main but not the only  
8 caffeine contributors (78% of total caffeine intake). The median intake was double than in our  
9 study, resulting to a higher reference level (reference: <180mg/day, median: 117mg/day),  
10 providing less contrast between the compared exposure groups and less comparability to our  
11 study, as most of these women were not complying to the recommendation. Nevertheless, we  
12 found associations with adverse effects on child's growth even at low caffeine intakes, in the  
13 range of the recommendation, that are mostly due to consumption of foods and drinks other than  
14 coffee (chocolate, black tea, caffeinated sodas)<sup>5</sup>. Li et al. found likewise that any maternal  
15 caffeine intake was associated with an overall increased risk of obesity from ages 2 to 15 years,  
16 with an exposure range similar to the current study<sup>20</sup>. We have used similar approaches to study  
17 changes in individual growth trajectories, though with shorter follow-up. In addition, we  
18 provided age specific weight and BMI deviations, in order to find sensitive developmental  
19 windows when the association with the prenatal caffeine exposure exacerbated. There is no  
20 previous report of the association between caffeine intake in pregnancy and excess infant growth.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33

### 34 ***Potential mechanisms***

35  
36 Since excess growth in infancy, in itself, can be directly related to childhood obesity, adiposity<sup>39</sup>  
37 and an unfavorable adult cardio-metabolic profile<sup>40</sup>, the associations between prenatal caffeine  
38 exposure with overweight, body fat and insulin, found in this study and the previous reports,  
39 might be explained by excess infant growth. Putting together the previous findings in the MoBa  
40 study<sup>5</sup>, we have shown that children prenatally exposed to high caffeine levels are smaller at  
41 birth, grow faster in infancy and retain a higher weight throughout childhood without significant  
42 height differences, thus becoming overweight. These findings concur with the fetal programming  
43 of obesity hypothesis<sup>41</sup>. Nevertheless, the effect of prenatal caffeine exposure on postnatal growth  
44 and overweight was not dependent on birth weight. Hence, along with a healthy birth weight, it is  
45 important to identify the modifiable factors that can independently affect excess growth in  
46 infancy. A growing number of studies have shown that other prenatal factors, e.g. excess  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 gestational weight<sup>42</sup>, high (>3times/week) fish intake<sup>43</sup>, and postnatal factors, e.g. formula  
4 feeding and feeding schedule<sup>44</sup>, are associated with increased risk of excess growth in infancy.

5  
6 The biological plausibility supporting our findings is mainly provided by animal studies where,  
7 prenatal exposure to caffeine was shown to program the offspring towards excess growth and  
8 cardio-metabolic disorders through alterations i) in the hypothalamic-pituitary-adrenocortical axis  
9 that plays a key role in growth and metabolism<sup>45-47</sup>, ii) in regulation of adenosine and adenosine  
10 antagonists, which are important modulators of development<sup>48 492</sup> and iii) in the placental  
11 expression and transportation of leptin<sup>50</sup>, essential for appetite regulation.

12  
13 Although most pregnant women reduce their caffeine intake during pregnancy and few have  
14 caffeine intakes higher than 200 mg/day (10%), our results show associations between caffeine  
15 intakes below 200 mg/day and excess growth. The results add supporting evidence for the current  
16 advice to reduce caffeine intake during pregnancy and indicate that complete avoidance might  
17 actually be advisable. An absence of a “safe intake level” has been previously reported in the  
18 basis of associations between maternal caffeine intake and fetal growth restriction<sup>51</sup>.

19  
20 The association between prenatal caffeine exposure and overweight attenuated after 5 years,  
21 with only very high exposed children being at risk for overweight. Residual confounding due to  
22 postnatal factors related to overweight in late childhood might explain this attenuation.  
23 Nevertheless, adjustment for risk factors of being overweight at 8 years would introduce bias to  
24 the association under study. In addition, weight and height are screened from birth to 5 years in  
25 scheduled voluntarily appointments at the public health centers. Hence, a possible  
26 misclassification of outcome from anthropometrics after 5 years, might also explain the  
27 attenuation of the association.

28  
29 There are two studies showing effects of caffeine intake on body composition and  
30 cardiometabolic health<sup>19 52</sup>, with discrepant results. In the present study, we did not have any  
31 information on body composition. In addition, it is known that several genetic factors can  
32 contribute to variation in caffeine metabolism<sup>53</sup>, and studies in adults have shown that slower  
33 metabolism of caffeine is related to higher risk of cardiovascular disease<sup>54</sup>. On the other hand,  
34 during pregnancy, maternal caffeine clearance modified the association between maternal  
35 caffeine intake and fetal growth restriction, with faster clearance being more detrimental<sup>51</sup>. Thus,  
36 there is a need to investigate the programming effect of prenatal caffeine exposure on child and  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 adult body composition and cardiometabolic health, taking into account the genetic variation of  
4 maternal caffeine metabolism.  
5  
6  
7

## 8 **Conclusions**

9  
10 We found that the risk of excess infant growth and overweight in childhood-important risk  
11 factors for later cardio-metabolic disease- is increasing with maternal caffeine intake, with no  
12 apparent threshold. Maternal caffeine intake >200mg/day during pregnancy was associated with  
13 high weight gain velocity beginning from the first months of life and higher BMI throughout  
14 childhood. Our findings not only support the recommendation to limit caffeine intake during  
15 pregnancy (<200mg/day) but also indicate that complete avoidance might be advisable.  
16  
17  
18  
19  
20  
21

## 22 **Acknowledgements**

23 We are grateful to all the families in Norway who have participated in this ongoing cohort  
24 study.  
25  
26  
27  
28

## 29 **References**

- 30  
31 1. EFSA EFSA-PoDP, Nutrition and Allergies (NDA). Scientific Opinion on the safety of  
32 caffeine. *EFSA Journal* 2015;13(5)  
33  
34 2. Mort JR, Kruse HR. Timing of blood pressure measurement related to caffeine consumption.  
35 *Ann Pharmacother* 2008;42(1):105-10. doi: 10.1345/aph.1K337  
36  
37 3. Tomimatsu T, Lee SJ, Pena JP, et al. Maternal caffeine administration and cerebral  
38 oxygenation in near-term fetal sheep. *Reprod Sci* 2007;14(6):588-94. doi:  
39 10.1177/1933719107307717  
40  
41  
42 4. VKM. Risk assessment of "other substances"- Caffeine. Opinion of the Panel on Food  
43 Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics  
44 of the Norwegian Scientific Committee for Food Safety. Oslo, Norway, 2015.  
45  
46 5. Sengpiel V, Elind E, Bacelis J, et al. Maternal caffeine intake during pregnancy is associated  
47 with birth weight but not with gestational length: results from a large prospective  
48 observational cohort study. *BMC Med* 2013;11:42. doi: 10.1186/1741-7015-11-42  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 6. Rhee J, Kim R, Kim Y, et al. Maternal Caffeine Consumption during Pregnancy and Risk of  
4 Low Birth Weight: A Dose-Response Meta-Analysis of Observational Studies. *PloS one*  
5 2015;10(7):e0132334. doi: 10.1371/journal.pone.0132334  
6  
7
- 8 7. Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic  
9 review. *JAMA : the journal of the American Medical Association* 2008;300(24):2886-97.  
10 doi: 10.1001/jama.2008.886 [published Online First: 2008/12/26]  
11  
12
- 13 8. Lawlor DA, Ronalds G, Clark H, et al. Birth weight is inversely associated with incident  
14 coronary heart disease and stroke among individuals born in the 1950s: findings from the  
15 Aberdeen Children of the 1950s prospective cohort study. *Circulation*  
16 2005;112(10):1414-8. doi: 10.1161/CIRCULATIONAHA.104.528356  
17  
18  
19
- 20 9. Monasta L, Batty GD, Cattaneo A, et al. Early-life determinants of overweight and obesity: a  
21 review of systematic reviews. *Obesity reviews : an official journal of the International*  
22 *Association for the Study of Obesity* 2010;11(10):695-708. doi: 10.1111/j.1467-  
23 789X.2010.00735.x  
24  
25  
26
- 27 10. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and  
28 hopeful suggestions. *Acta paediatrica* 2006;95(8):904-8. doi:  
29 10.1080/08035250600719754  
30  
31
- 32 11. Baird J, Fisher D, Lucas P, et al. Being big or growing fast: systematic review of size and  
33 growth in infancy and later obesity. *BMJ* 2005;331(7522):929. doi:  
34 10.1136/bmj.38586.411273.E0  
35  
36  
37
- 38 12. Jones-Smith JC, Neufeld LM, Laraia B, et al. Early life growth trajectories and future risk for  
39 overweight. *Nutrition & diabetes* 2013;3:e60. doi: 10.1038/nutd.2012.32  
40  
41
- 42 13. Botton J, Heude B, Maccario J, et al. Postnatal weight and height growth velocities at  
43 different ages between birth and 5 y and body composition in adolescent boys and girls.  
44 *The American journal of clinical nutrition* 2008;87(6):1760-8.  
45  
46
- 47 14. Perng W, Hajj H, Belfort MB, et al. Birth Size, Early Life Weight Gain, and Midchildhood  
48 Cardiometabolic Health. *The Journal of pediatrics* 2016 doi: 10.1016/j.jpeds.2016.02.053  
49  
50
- 51 15. Ekelund U, Ong KK, Linne Y, et al. Association of weight gain in infancy and early  
52 childhood with metabolic risk in young adults. *The Journal of clinical endocrinology and*  
53 *metabolism* 2007;92(1):98-103. doi: 10.1210/jc.2006-1071  
54  
55  
56  
57  
58  
59

- 1  
2  
3 16. Collaboration NCDRF, Di Cesare M, Bentham J, et al. Trends in adult body-mass index in  
4 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based  
5 measurement studies with 19.2 million participants. *Lancet* 2016;387(10026):1377-96.  
6 doi: 10.1016/S0140-6736(16)30054-X  
7  
8
- 9  
10 17. Woo Baidal JA, Locks LM, Cheng ER, et al. Risk Factors for Childhood Obesity in the First  
11 1,000 Days: A Systematic Review. *Am J Prev Med* 2016;50(6):761-79. doi:  
12 10.1016/j.amepre.2015.11.012  
13  
14
- 15 18. Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and  
16 public health implications. *The American journal of clinical nutrition* 2011;94(6  
17 Suppl):1754S-58S. doi: 10.3945/ajcn.110.001206  
18  
19
- 20 19. Voerman E, Jaddoe VW, Gishti O, et al. Maternal caffeine intake during pregnancy, early  
21 growth, and body fat distribution at school age. *Obesity* 2016;24(5):1170-7. doi:  
22 10.1002/oby.21466  
23  
24
- 25 20. Li DK, Ferber JR, Odouli R. Maternal caffeine intake during pregnancy and risk of obesity in  
26 offspring: a prospective cohort study. *International journal of obesity* 2015;39(4):658-64.  
27 doi: 10.1038/ijo.2014.196  
28  
29
- 30 21. Barker DJ, Bagby SP. Developmental antecedents of cardiovascular disease: a historical  
31 perspective. *Journal of the American Society of Nephrology : JASN* 2005;16(9):2537-44.  
32 doi: 10.1681/ASN.2005020160  
33  
34
- 35 22. Gluckman PD, Cutfield W, Hofman P, et al. The fetal, neonatal, and infant environments-the  
36 long-term consequences for disease risk. *Early Hum Dev* 2005;81(1):51-9. doi:  
37 10.1016/j.earlhumdev.2004.10.003  
38  
39
- 40 23. Barker DJP. In utero programming of chronic disease. *Clinical Science* 1998;95:115-28.  
41  
42
- 43 24. Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child  
44 Cohort Study (MoBa). *International journal of epidemiology* 2016 [published Online  
45 First: April 10, 2016]  
46  
47
- 48 25. Brantsæter AL, Haugen M, Alexander J, et al. Validity of a new food frequency questionnaire  
49 for pregnant women in the Norwegian Mother and Child Cohort Study (MoBa).  
50 *MaternChild Nutr* 2008;4(1):28-43. doi: MCN103 [pii];10.1111/j.1740-  
51 8709.2007.00103.x [doi]  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1
- 2
- 3 26. WHO MGRSG. WHO Child Growth Standards: Length/height-for-age, weight-for-age,
- 4 weight-for-length, weight-for-height and body mass index-for-age: Methods and
- 5 development. Geneva: World Health Organization 2006.
- 6
- 7
- 8 27. Yang S, Hutcheon JA. Identifying outliers and implausible values in growth trajectory data.
- 9 *Annals of epidemiology* 2016;26(1):77-80 e1-2. doi: 10.1016/j.annepidem.2015.10.002
- 10
- 11 28. Ong KK, Ahmed ML, Emmett PM, et al. Association between postnatal catch-up growth and
- 12 obesity in childhood: prospective cohort study. *BMJ* 2000;320(7240):967-71. [published
- 13 Online First: 2001/02/07]
- 14
- 15 29. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a
- 16 systematic review. *Obesity reviews : an official journal of the International Association*
- 17 *for the Study of Obesity* 2005;6(2):143-54. doi: 10.1111/j.1467-789X.2005.00183.x
- 18
- 19 30. Jentsch RM, Bayley N. A mathematical method for studying the growth of a child. *Human*
- 20 *Biology* 1937;9:556-63.
- 21
- 22 31. Berkey CS. Comparison of two longitudinal growth models for preschool children.
- 23 *Biometrics* 1982;38(1):221-34.
- 24
- 25 32. Comets E, Lavenex A, Lavielle M. saemix: Stochastic Approximation Expectation
- 26 Maximization (SAEM) algorithm. 2014. [https://cran.r-](https://cran.r-project.org/web/packages/saemix/index.html)
- 27 [project.org/web/packages/saemix/index.html](https://cran.r-project.org/web/packages/saemix/index.html).
- 28
- 29 33. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness,
- 30 overweight and obesity. *Pediatric obesity* 2012;7(4):284-94. doi: 10.1111/j.2047-
- 31 6310.2012.00064.x
- 32
- 33 34. Harrell F. Regression Modeling Strategies: With Applications to Linear Models, Logistic
- 34 Regression, and Survival Analysis. 1 ed. New York: Springer-Verlag New York 2001.
- 35
- 36 35. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta*
- 37 *ObstetGynecolScand* 2000;79(6):440-49.
- 38
- 39 36. R: A language and environment for statistical computing [program]. Vienna, Austria: R
- 40 Foundation for Statistical Computing, 2016.
- 41
- 42 37. Brantsæter AL, Haugen M, Rasmussen SE, et al. Urine flavonoids and plasma carotenoids in
- 43 the validation of fruit, vegetable and tea intake during pregnancy in the Norwegian
- 44 Mother and Child Cohort Study (MoBa). *Public Health Nutr* 2007;10(8):838-47. doi:
- 45 S1368980007339037 [pii];10.1017/S1368980007339037 [doi]
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1  
2  
3 38. HILL AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION?  
4  
5 *ProcRSocMed* 1965;58:295-300.  
6  
7 39. Karaolis-Danckert N, Buyken AE, Bolzenius K, et al. Rapid growth among term children  
8 whose birth weight was appropriate for gestational age has a longer lasting effect on body  
9 fat percentage than on body mass index. *The American journal of clinical nutrition*  
10 2006;84(6):1449-55.  
11  
12 40. Leunissen RW, Kerkhof GF, Stijnen T, et al. Timing and tempo of first-year rapid growth in  
13 relation to cardiovascular and metabolic risk profile in early adulthood. *JAMA : the*  
14 *journal of the American Medical Association* 2009;301(21):2234-42. doi:  
15 10.1001/jama.2009.761  
16  
17 41. Barker DJ. Fetal origins of coronary heart disease. *BMJ* 1995;311(6998):171-74.  
18  
19 42. Subhan FB, Colman I, McCargar L, et al. Higher Pre-pregnancy BMI and Excessive  
20 Gestational Weight Gain are Risk Factors for Rapid Weight Gain in Infants. *Maternal and*  
21 *child health journal* 2017 doi: 10.1007/s10995-016-2246-z  
22  
23 43. Stratakis N, Roumeliotaki T, Oken E, et al. Fish Intake in Pregnancy and Child Growth: A  
24 Pooled Analysis of 15 European and US Birth Cohorts. *JAMA pediatrics*  
25 2016;170(4):381-90. doi: 10.1001/jamapediatrics.2015.4430  
26  
27 44. Mhrshahi S, Battistutta D, Magarey A, et al. Determinants of rapid weight gain during  
28 infancy: baseline results from the NOURISH randomised controlled trial. *BMC pediatrics*  
29 2011;11:99. doi: 10.1186/1471-2431-11-99 [published Online First: 2011/11/08]  
30  
31 45. Xu D, Zhang B, Liang G, et al. Caffeine-induced activated glucocorticoid metabolism in the  
32 hippocampus causes hypothalamic-pituitary-adrenal axis inhibition in fetal rats. *PloS one*  
33 2012;7(9):e44497. doi: 10.1371/journal.pone.0044497 [published Online First:  
34 2012/09/13]  
35  
36 46. Li J, Luo H, Wu Y, et al. Gender-specific increase in susceptibility to metabolic syndrome of  
37 offspring rats after prenatal caffeine exposure with post-weaning high-fat diet. *Toxicology*  
38 *and applied pharmacology* 2015;284(3):345-53. doi: 10.1016/j.taap.2015.03.002  
39  
40 47. Xu D, Wu Y, Liu F, et al. A hypothalamic-pituitary-adrenal axis-associated neuroendocrine  
41 metabolic programmed alteration in offspring rats of IUGR induced by prenatal caffeine  
42 ingestion. *Toxicology and applied pharmacology* 2012;264(3):395-403. doi:  
43 10.1016/j.taap.2012.08.016 [published Online First: 2012/09/11]  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 48. Buscariollo DL, Fang X, Greenwood V, et al. Embryonic caffeine exposure acts via A1  
4 adenosine receptors to alter adult cardiac function and DNA methylation in mice. *PloS*  
5 *one* 2014;9(1):e87547. doi: 10.1371/journal.pone.0087547  
6  
7  
8 49. Rivkees SA, Wendler CC. Adverse and protective influences of adenosine on the newborn  
9 and embryo: implications for preterm white matter injury and embryo protection.  
10 *Pediatric research* 2011;69(4):271-8. doi: 10.1203/PDR.0b013e31820efbcf [published  
11 Online First: 2011/01/14]  
12  
13  
14 50. Wu YM, Luo HW, Kou H, et al. Prenatal caffeine exposure induced a lower level of fetal  
15 blood leptin mainly via placental mechanism. *Toxicology and applied pharmacology*  
16 2015;289(1):109-16. doi: 10.1016/j.taap.2015.09.007  
17  
18  
19 51. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large  
20 prospective observational study. *BMJ* 2008;337:a2332. doi: 10.1136/bmj.a2332  
21 [published Online First: 2008/11/05]  
22  
23  
24 52. de Medeiros TS, Bernardi JR, de Brito ML, et al. Caffeine Intake During Pregnancy in  
25 Different Intrauterine Environments and its Association with Infant Anthropometric  
26 Measurements at 3 and 6 Months of Age. *Maternal and child health journal*  
27 2017;21(6):1297-307. doi: 10.1007/s10995-016-2230-7  
28  
29  
30 53. Cornelis MC, Kacprowski T, Menni C, et al. Genome-wide association study of caffeine  
31 metabolites provides new insights to caffeine metabolism and dietary caffeine-  
32 consumption behavior. *Hum Mol Genet* 2016;25(24):5472-82. doi: 10.1093/hmg/ddw334  
33  
34  
35 54. Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine.  
36 *Psychopharmacology* 2010;211(3):245-57. doi: 10.1007/s00213-010-1900-1  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **Funding statement:** The Norwegian Mother and Child Cohort Study is supported by the  
4 Norwegian Ministry of Health and Care Services and Ministry of Education and Research,  
5 NIH/NIEHS (contract no N01-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537- 01 and  
6 grant no.2 UO1 NS 047537-06A1). Verena Sengpiel has received grants from Stiftelsen Sigurd  
7 och Elsa Goljes Minnesfond (LA2013-0241 “Koffeinintag, födelsevikt och barnutfall”),  
8 Stiftelsen Fru Mary von Sydows, född Wijk, donationsfond (2014 “Koffeinintag, födelsevikt och  
9 barnutfall”) and Wilhelm och Martina Lundgrens Vetenskapsfond (1 vet1-119/2014:  
10 “Koffeinintag, födelsevikt och barnutfall”). The funding bodies were not involved in the design,  
11 implementation of the study or interpretation of the results.  
12  
13  
14  
15

16 **Competing interests statement:** *No competing interests.* All authors have completed the ICMJE  
17 uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any  
18 organisation for the submitted work; no financial relationships with any organisations that might  
19 have an interest in the submitted work in the previous three years; no other relationships or  
20 activities that could appear to have influenced the submitted work.  
21  
22  
23

24 **Contributorship statement:** EP contributed to study design, data analysis, and interpretation of  
25 the results and had the main responsibility of writing the paper. JBO contributed to the statistical  
26 analysis plan and database preparation and interpretation of the results. ALB contributed to study  
27 design, interpretation of the results and revising the paper. MH, JA, HMM contributed to the  
28 design of data collection tools, the study design and interpretation of the results. JBA contributed  
29 to the statistical analysis plan and database preparation. AE contributed to interpretation of the  
30 results.  
31

32  
33 BJ initiated this collaborative project, contributed to the study design and the interpretation of the  
34 results. VS defined the research question, contributed to the study design, database preparation  
35 and interpretation of the results. She is guarantor and had final responsibility for the decision to  
36 submit for publication. All authors read, revised and approved the final version of the paper.  
37  
38  
39

40 **Data sharing statement:** No additional data are available. All data from the MoBa study are  
41 available to all qualified researchers/research groups in Norway and to international researchers  
42 who are collaborating with a Norwegian researcher.  
43  
44

#### 45 **Declaration of transparency**

46  
47 EP as the lead author affirms that this manuscript is an honest, accurate, and transparent account  
48 of the study being reported; that no important aspects of the study have been omitted; and that  
49 any discrepancies from the study as planned (and, if relevant, registered) have been explained.  
50  
51  
52  
53

#### 54 **Licence to BMJ Publishing Group Limited (“BMJ Group”) for Publication**

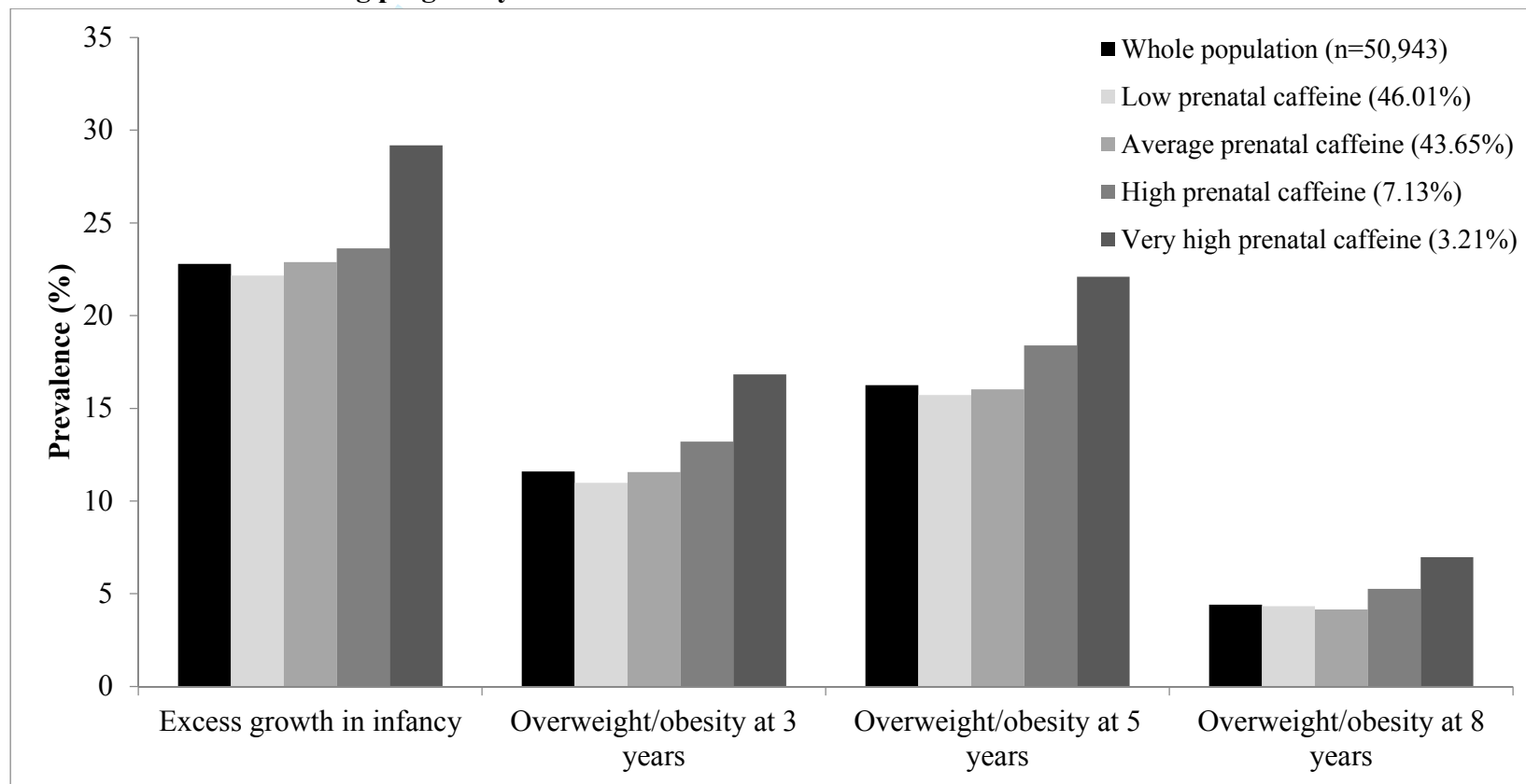
1  
2  
3 “I **Eleni Papadopoulou** The Corresponding Author of this article contained within the original  
4 manuscript which includes any diagrams & photographs within and any related or stand alone  
5 film submitted (the Contribution”) has the right to grant on behalf of all authors and does grant  
6 on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit  
7 this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products  
8 and to exploit all subsidiary rights, as set out in our licence set out at: [http://www.bmj.com/about-](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)  
9 [bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)  
10 [reuse.](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)”  
11

12 Please tick **one or more** boxes as appropriate:  
13

14 X I am one author signing on behalf of all co-owners of the Contribution.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**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**





1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

**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) <sup>a</sup>					
	All children (n=38,338)		After excluding smokers during pregnancy (n=35,672)		After excluding SGA neonates <sup>b</sup> (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

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

<sup>b</sup> 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 <sup>a</sup>					
	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) <sup>b</sup>					
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

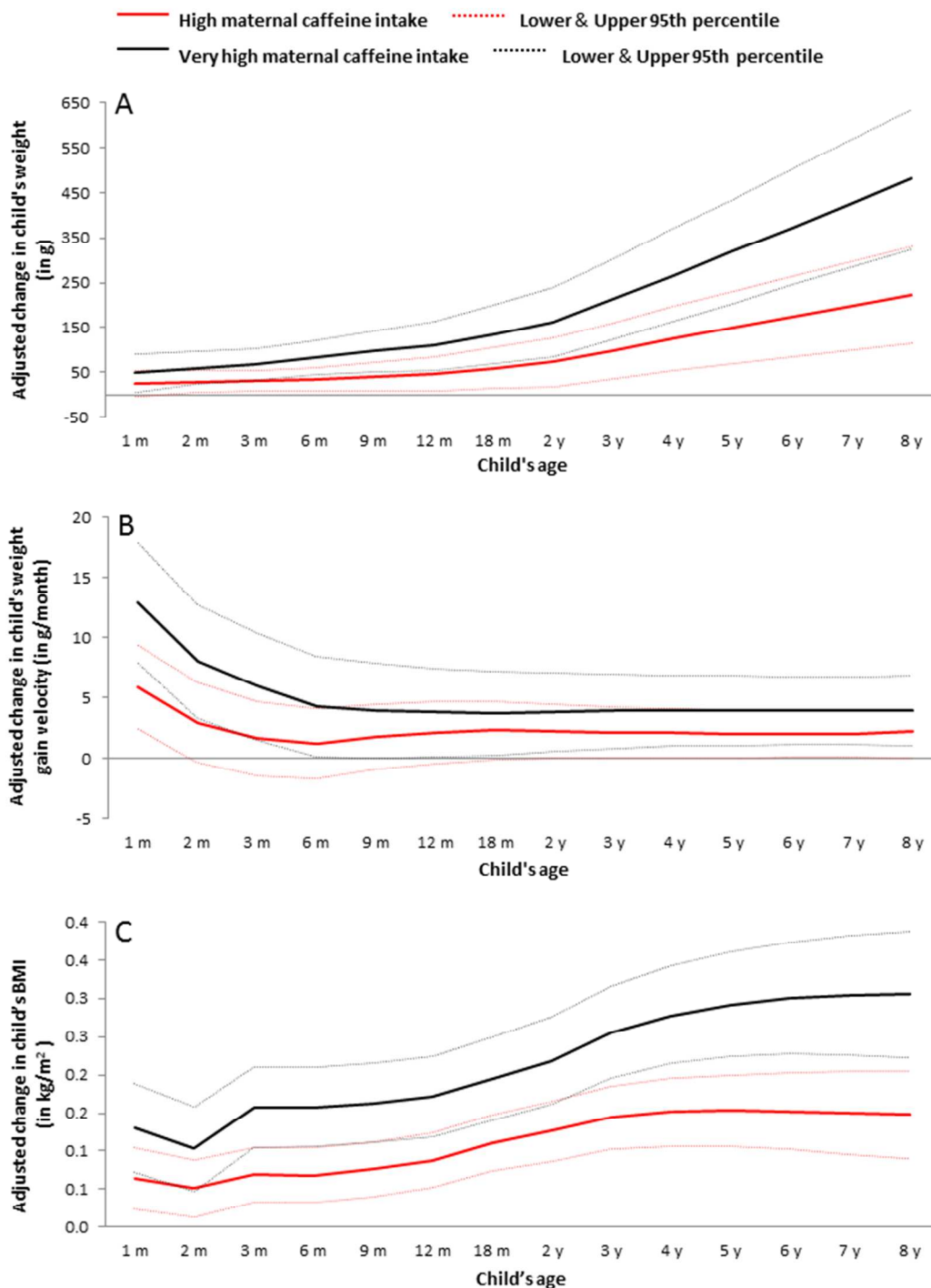
The same population was included at each age since the outcome was defined using model-derived anthropometrics.

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

<sup>a</sup> Overweight and/or obesity in children, according to the International Obesity Task Force definition.

<sup>b</sup> 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<sup>2</sup>), 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)**

Maternal daily caffeine intake	Child's developmental period						
	Infancy		Toddlerhood		Pre-school age		School age
	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)
<b><i>Weight (in g)</i></b>							
Average (50-199 mg)	<b>14.1</b> (1.6,26.6)	<b>15.1</b> (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)	<b>31.3</b> (7.5,55.1)	<b>35.0</b> (8.8,61.1)	<b>45.4</b> (7.3,83.5)	<b>59.0</b> (13.1,104.8)	<b>99.0</b> (36.3,161.7)	<b>148.9</b> (68.4,229.4)	<b>222.0</b> (114.1,329.8)
Very high (≥300 mg)	<b>67.0</b> (32.5,101.6)	<b>83.2</b> (45.3,121.1)	<b>110.1</b> (55.2,165.0)	<b>135.5</b> (69.5,201.5)	<b>213.4</b> (123.3,303.6)	<b>320.0</b> (204.4,435.6)	<b>480.3</b> (325.5,635.1)
<b><i>Weight gain velocity (in g/month)</i></b>							
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)	<b>2.1(0.4,3)</b>	<b>2.0(0.1,4.0)</b>	<b>2.2(0.4,4.0)</b>
Very high (≥300 mg)	<b>6.0(1.5,10.4)</b>	<b>4.3(0.2,8.5)</b>	<b>3.8(0.1,7.4)</b>	<b>3.7(0.3,7.1)</b>	<b>3.9(0.8,7.0)</b>	<b>3.9(1.1,6.8)</b>	<b>3.9(1.1,6.8)</b>
<b><i>BMI (in kg/m<sup>2</sup>)</i></b>							
Average (50-199 mg)	<b>0.03</b> (0.01,0.05)	<b>0.03</b> (0.01,0.05)	<b>0.04</b> (0.02,0.06)	<b>0.04</b> (0.02,0.06)	<b>0.04</b> (0.02,0.06)	<b>0.03</b> (0.01,0.06)	0.02 (-0.01,0.05)
High (200-299 mg)	<b>0.07</b> (0.03,0.11)	<b>0.07</b> (0.03,0.10)	<b>0.09</b> (0.05,0.12)	<b>0.11</b> (0.07,0.15)	<b>0.14</b> (0.10,0.19)	<b>0.15</b> (0.11,0.20)	<b>0.15</b> (0.09,0.21)
Very high (≥300 mg)	<b>0.16</b> (0.10,0.21)	<b>0.16</b> (0.11,0.21)	<b>0.17</b> (0.12,0.23)	<b>0.20</b> (0.14,0.25)	<b>0.26</b> (0.20,0.32)	<b>0.29</b> (0.22,0.36)	<b>0.31</b> (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 <sup>2</sup> )		Prevalence (%)	
			Males	Females	Males	Females
International Obesity Task Force (IOTF) <sup>1</sup> (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			
		Mean	N		Mean	N		Mean	Low	Average	High
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)		Average caffeine intake (50-199mg/day)		High caffeine intake (200-299mg/day)		Very high caffeine intake (≥300mg/day)	
	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 <sup>2</sup> )								
<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 <sup>1</sup>								
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 <sup>2</sup> )								
<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<sup>-5</sup> of chi square tests of all cross-tabulations presented in table

<sup>1</sup>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.

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

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

<sup>a</sup>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 <sup>a</sup>			Overweight/obesity at age 3 years <sup>b</sup>			Overweight/obesity at age 5 years <sup>b</sup>			Overweight/obesity at age 8 years <sup>b</sup>		
	OR	95% CI	CI	OR	95% CI	CI	OR	95% CI	CI	OR	95% CI	CI
Caffeine from black coffee												
0-50	1.00			1.00			1.00			1.00		
50-200	<b>1.18</b>	<b>1.11</b>	<b>1.26</b>	<b>1.18</b>	<b>1.11</b>	<b>1.26</b>	<b>1.12</b>	<b>1.05</b>	<b>1.18</b>	<b>1.11</b>	<b>1.00</b>	<b>1.23</b>
200-300	<b>1.31</b>	<b>1.06</b>	<b>1.62</b>	1.14	0.91	1.41	1.11	0.92	1.34	1.09	0.77	1.53
>300	<b>1.72</b>	<b>1.45</b>	<b>2.03</b>	<b>1.69</b>	<b>1.44</b>	<b>1.99</b>	<b>1.39</b>	<b>1.20</b>	<b>1.61</b>	<b>1.48</b>	<b>1.17</b>	<b>1.88</b>
Caffeine from black tea												
0-50	1.00			1.00			1.00			1.00		
50-200	<b>1.11</b>	<b>1.01</b>	<b>1.21</b>	1.07	0.98	1.18	1.05	0.97	1.14	<b>1.20</b>	<b>1.04</b>	<b>1.38</b>
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	<b>1.20</b>	<b>1.08</b>	<b>1.33</b>	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

<sup>a</sup> 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.

<sup>b</sup> 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	Caffeine intake <199mg	Caffeine intake 200-299mg
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Excess infant growth	1.00	1.07 (1.01,1.13)	1.25 (1.12,1.39)
<b>Overweight</b>			
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)

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

<sup>b</sup> 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 <sup>a</sup>					
	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	<b>1.21</b>	<b>1.07,1.39</b>	1,386/14	1.13	0.95,1.35
Very high (≥300 mg)	918/20	<b>1.52</b>	<b>1.27,1.81</b>	664/18	<b>1.32</b>	<b>1.04,1.66</b>

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

<sup>a</sup> Overweight and/or obesity, according to International Obesity Task Force definition.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

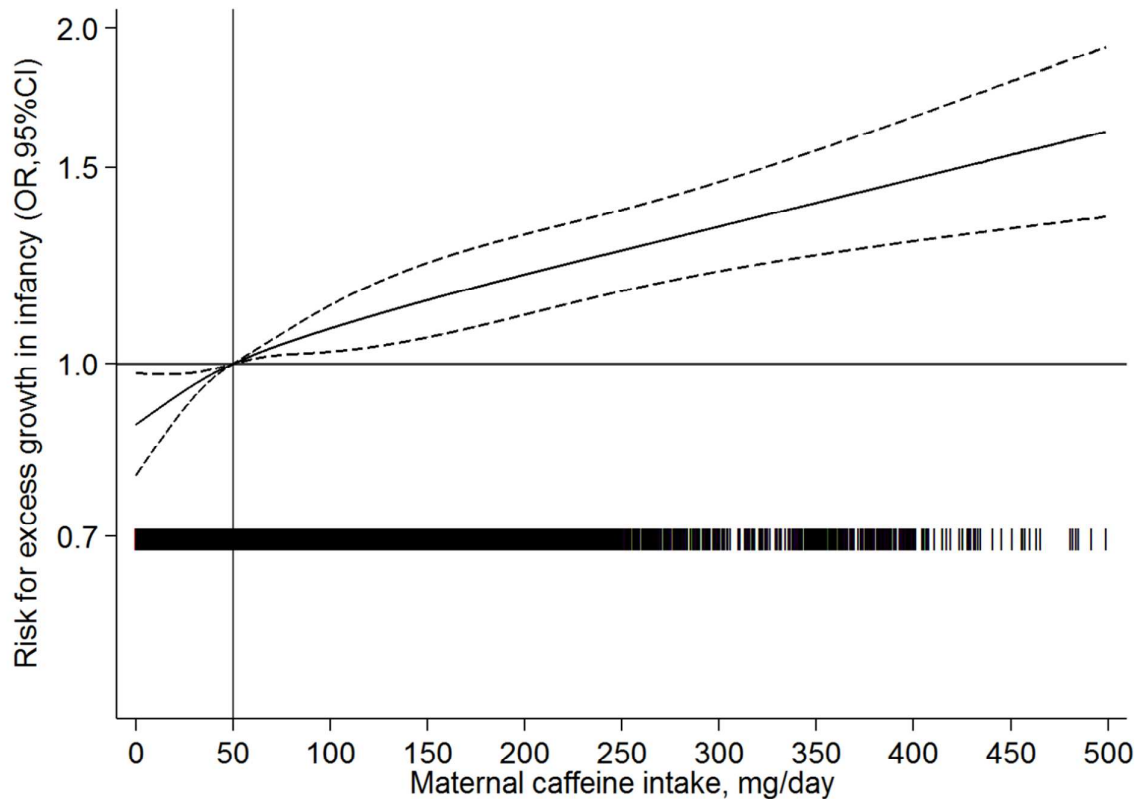
Supplementary Table 9. Maternal caffeine intake in early pregnancy and child’s height and height gain velocity during childhood

Maternal daily caffeine intake	Child’s developmental period							
	Infancy		Toddlerhood		Pre-school age		School age	
	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)	
<b>Height (in cm)</b>								
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)	
<b>Height gain velocity (in mm/month)</b>								
Average (50-199 mg)	<b>0.05</b> <b>(0.02,0.09)</b>	-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)	<b>0.08</b> <b>(0.01,0.14)</b>	-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)	<b>0.11</b> <b>(0.01,0.21)</b>	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

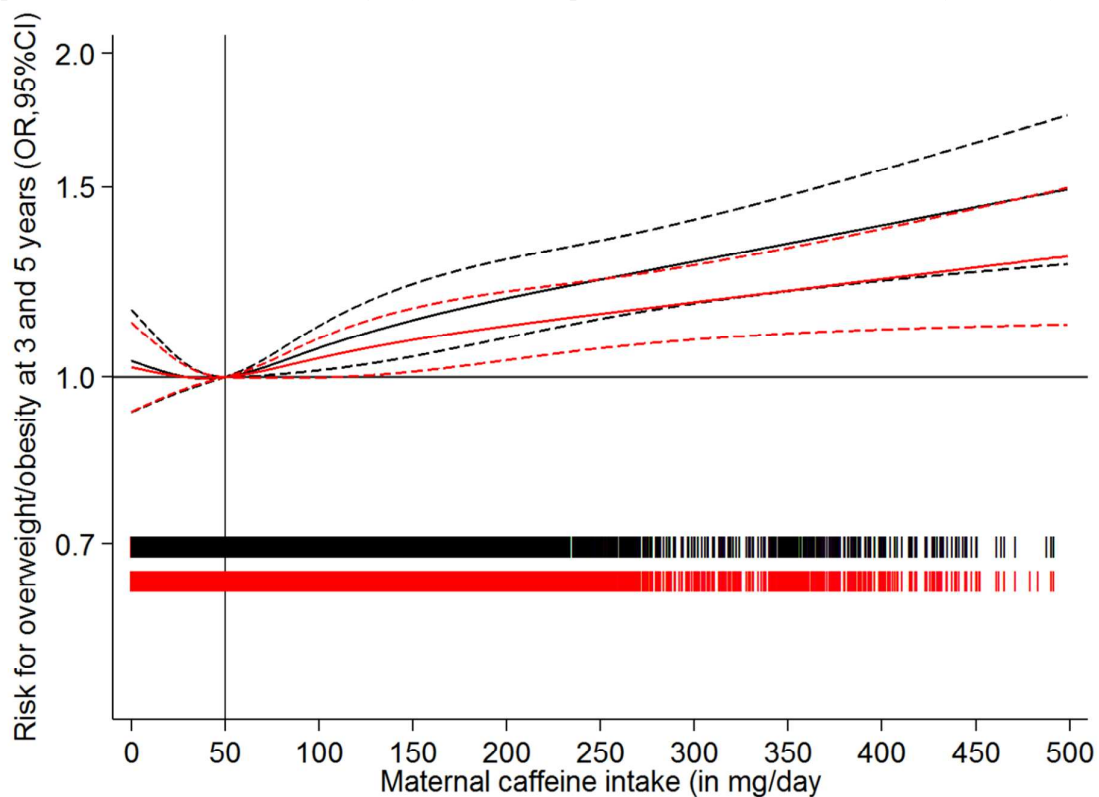
Effect estimates derive from linear mixed effect models with input of all anthropometric information from age 1 month to 8 years and adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, nausea and/or vomiting during pregnancy, maternal smoking during pregnancy, gestational age, gender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



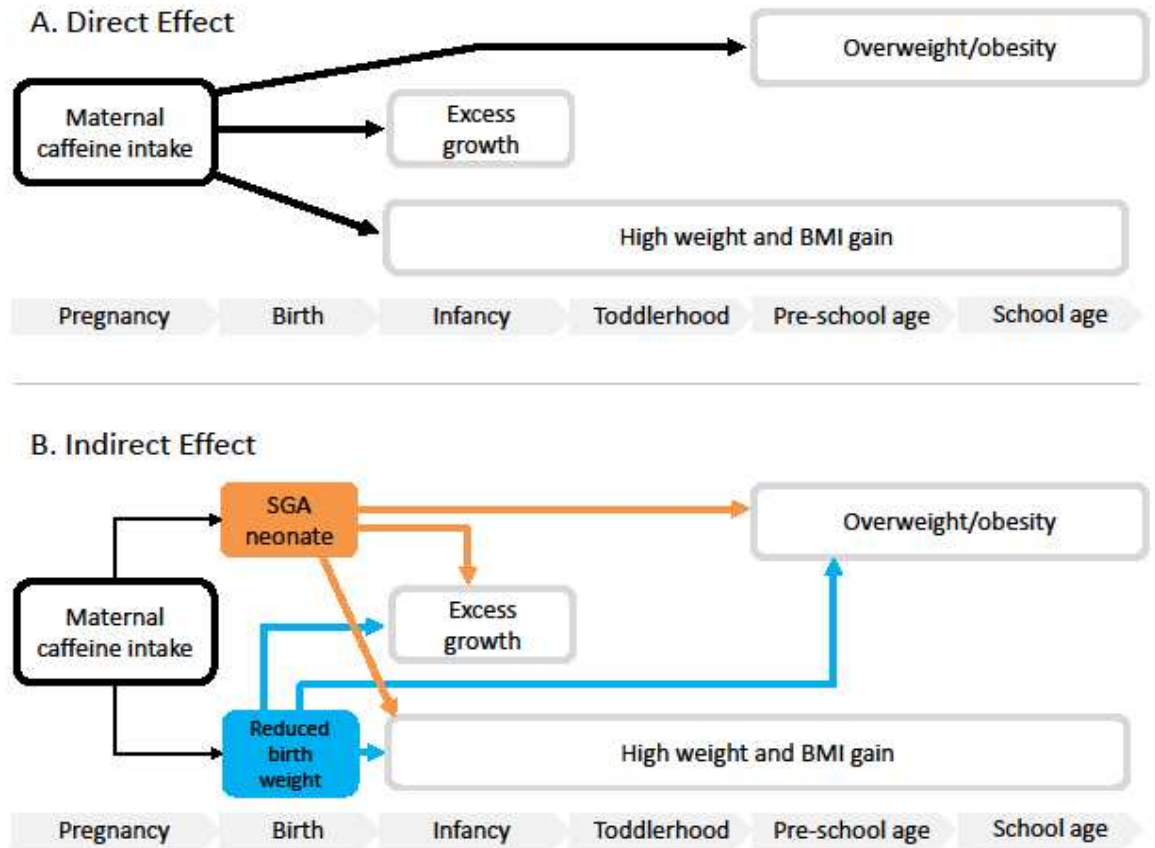
Footnote: all models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender and SGA according to Skjaerven et al.

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



Only



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

	Item No	Recommendation
<b>Title and abstract</b>	1	<p>(a) Indicate the study's design with a commonly used term in the title or the abstract  <i>This has been done in both subsections. The study is a prospective cohort study.</i></p> <p>(b) Provide in the abstract an informative and balanced summary of what was done and what was found  <i>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).</i></p>
<b>Introduction</b>		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported  <i>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).</i></p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses  <i>This has been done in the last paragraph of the introduction (page 4, first paragraph).</i></p>
<b>Methods</b>		
Study design	4	<p>Present key elements of study design early in the paper  <i>Our study design was described in the first paragraph of the methods, subsection "Study population and ethical approval" (page 4).</i></p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  <i>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).</i></p>
Participants	6	<p>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  <i>The eligibility and inclusion criteria has been described the methods section subsection "Study population and ethical approval" (page 4).</i></p> <p>(b) For matched studies, give matching criteria and number of exposed and unexposed  <i>This is not a matched study.</i></p>
Variables	7	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.  <i>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).</i></p>
Data sources/ measurement	8*	<p>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  <i>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.</i></p>

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).
<b>Results</b>		
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 <a href="#">This has been provided in the results section and in Tables 1, 2, 3).</a>
		(b) Report category boundaries when continuous variables were categorized <a href="#">This has been done in the results section (pages 7-9) and in Figures and Tables.</a>
		(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 <a href="#">This was reported in the results section, subsection “sensitivity analyses” (page 9).</a>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives <a href="#">In the first paragraph of the discussion, we have summarized our key finding (pages 9-10).</a>
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. <a href="#">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).</a>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. <a href="#">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).</a>
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.
<b>Other information</b>		
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. <a href="#">Funding has been described in a specific point (page 14).</a>

\*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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018895.R1
Article Type:	Research
Date Submitted by the Author:	29-Nov-2017
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
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Nutrition and metabolism, Paediatrics, Public health
Keywords:	EPIDEMIOLOGY, NUTRITION & DIETETICS, PREVENTIVE MEDICINE, PUBLIC HEALTH, SOCIAL MEDICINE

SCHOLARONE™  
Manuscripts

1  
2  
3 1 **TITLE PAGE**

4 2 **Title: Maternal caffeine intake during pregnancy is associated with excess growth in**  
5 3 **infancy and overweight in childhood: results from a large prospective cohort study**

6 4 Eleni Papadopoulou, Post-doctoral research fellow <sup>a</sup>; Jérémie Botton, Associate Professor <sup>b,c</sup>;  
7 5 Anne-Lise Brantsæter, Senior researcher <sup>a</sup>; Margaretha Haugen, Senior researcher <sup>a</sup>; Jan  
8 6 Alexander, Senior researcher <sup>d</sup>; Helle Margrete Meltzer, Senior researcher <sup>d</sup>, Jonas Bacelis, PhD  
9 7 Candidate <sup>e</sup>; Anders Elfvin, Physician <sup>f</sup>; Bo Jacobsson, Professor/ Chief physician <sup>e,g</sup>; Verena  
10 8 Sengpiel, Associate Professor/Physician <sup>h</sup>

11 9  
12 10 <sup>a</sup> Department of Environmental Exposure and Epidemiology, Division of Infection Control and  
13 11 Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo,  
14 12 Norway

15 13 <sup>b</sup> Early Determinants of the Child's Health and Development Team (ORCHAD), INSERM,  
16 14 UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Paris, F-75014  
17 15 France

18 16 <sup>c</sup> Univ. Paris-Sud, Université Paris-Saclay, F-92296, Châtenay-Malabry, France

19 17 <sup>d</sup> Division of Infection Control and Environmental Health, Norwegian Institute of Public Health,  
20 18 PO Box 4404, N-0403, Oslo, Norway

21 19 <sup>e</sup> Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg,  
22 20 Östra, SE 416 85, Gothenburg, Sweden

23 21 <sup>f</sup> Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of  
24 22 Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

25 23 <sup>g</sup> Department of Genetics and Bioinformatics, Division of Health Data and Digitalization,  
26 24 Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

27 25 <sup>h</sup> Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Östra, SE-416 85  
28 26 Gothenburg, Sweden

29 27 **Corresponding author:**

30 28 Eleni Papadopoulou  
31 29 Division of Infection Control and Environmental Health  
32 30 Norwegian Institute of Public Health  
33 31 P.O. Box 4404, Nydalen, NO-0403 Oslo, Norway  
34 32 Phone number: +47 21076511  
35 33 Fax number: +47 21076686  
36 34 E-mail: [eleni.papadopoulou@fhi.no](mailto:eleni.papadopoulou@fhi.no)

1  
2  
3 35 **ABSTRACT**

4  
5 36 **Objectives:** To study the association between maternal caffeine intake during pregnancy and the  
6  
7 37 child's weight gain and overweight risk up to 8 years.

8  
9 38 **Design:** Prospective nationwide pregnancy cohort.

10  
11 39 **Setting:** The Norwegian Mother and Child Cohort Study.

12  
13 40 **Participants:** 50,943 mothers recruited from 2002 to 2008 and their children, after singleton  
14  
15 41 pregnancies, with information about average caffeine intake assessed at mid-pregnancy.

16  
17 42 **Outcome measure:** Child's body size information at 11 age-points from 6 weeks to 8 years. We  
18  
19 43 defined excess growth in infancy as a WHO weight gain z-score of  $>0.67$  from birth to age 1  
20  
21 44 year, and overweight according to the International Obesity Task Force. We used a growth model  
22  
23 45 to assess individual growth trajectories.

24  
25 46 **Results:** Compared to pregnant women with low caffeine intake ( $<50\text{mg/day}$ , 46%), women  
26  
27 47 with average ( $50\text{-}199\text{mg/day}$ , 44%), high ( $\geq 200\text{-}299\text{mg/day}$ , 7%) and very high ( $\geq 300\text{mg/day}$ ,  
28  
29 48 3%) caffeine intakes had an increased risk of their child experiencing excess growth in infancy,  
30  
31 49 after adjustment for confounders (odds ratio (OR)=1.15, 95% Confidence Intervals (CI) 1.09-  
32  
33 50 1.22), OR=1.30, 95%CI, 1.16-1.45, OR=1.66, 95%CI, 1.42-1.93, respectively). In-utero exposure  
34  
35 51 to any caffeine was associated with higher risk of overweight at age 3 and 5 years, while, the  
36  
37 52 association persisted at 8 years, only for very high exposures. Any caffeine intake was associated  
38  
39 53 with increased body mass index from infancy to childhood. Children prenatally exposed to  
40  
41 54 caffeine intake  $>200\text{mg/day}$  had consistently higher weight. Very high caffeine exposures were  
42  
43 55 associated with higher weight gain velocity from infancy to age 8 years.

44  
45 56 **Conclusion:** Any caffeine consumption during pregnancy is associated with excess infant growth  
46  
47 57 and increased risk of overweight, mainly at pre-school ages. Maternal caffeine intake may modify  
48  
49 58 overall weight growth trajectory from birth to 8 years. This study adds supporting evidence for  
50  
51 59 the current advice to reduce caffeine intake during pregnancy.

1  
2  
3 60 **Strengths and limitations of this study**  
4

- 5 61 • A strength of this study is the large sample size.  
6  
7 62 • Maternal caffeine intake was estimated from all possible food sources.  
8  
9 63 • This is the first study investigating the association between maternal caffeine intake and  
10 64 excess infant growth and growth velocity.  
11  
12 65 • Missing data from body size measurements were handled with a growth model.  
13  
14 66 • Limitations include self-reported dietary data and parental-reported measurements of  
15 67 height and weight after 2 years.  
16  
17 68

## 69 MANUSCRIPT

### 70 Introduction

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

84 Fetal growth and growth in infancy are important determinants for the development of obesity  
85 and for long-term cardiometabolic health<sup>7-9</sup>. Excess infant growth programs later obesity, fat  
86 mass, and risk of adult disease, independent of intrauterine growth<sup>10-15</sup>. The prevalence of  
87 metabolic disorders, including obesity, cardiovascular disease and type 2 diabetes is rapidly  
88 growing across the globe, with the number of obese people risen worldwide from 105 million in  
89 1975 to 641 million in 2014<sup>16</sup>. This trend indicates that the probability of reaching the WHO  
90 global obesity target, of no rise in obesity by 2025, is close to zero<sup>16</sup>. There is compelling human  
91 and animal evidence supporting the "fetal programming" hypothesis, according to which in utero  
92 exposures permanently alter an organism's physiology and metabolism, leading to susceptibility  
93 to subsequent disease, including obesity and metabolic disorders, with transgenerational effects<sup>17</sup>  
94<sup>18</sup>.

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



1  
2  
3 100 Based on our previous findings on the association of prenatal caffeine exposure with fetal  
4  
5 101 growth restriction<sup>5</sup> and the fetal programming hypothesis<sup>23</sup>, we hypothesized that prenatal  
6  
7 102 caffeine exposure might affect postnatal growth. Thus, the objective of this study was to  
8  
9 103 investigate the associations between maternal caffeine intake in pregnancy and child growth and  
10  
11 104 risk of overweight up to age 8 years in a large prospective population-based cohort.  
12

105

## 13 106 **Methods**

### 15 107 **Study population and ethical approval**

17 108 Our study was conducted within the Norwegian Mother and Child Cohort Study (MoBa), a  
18  
19 109 prospective population-based pregnancy cohort study conducted by the Norwegian Institute of  
20  
21 110 Public Health<sup>24</sup>. Pregnant women from all over Norway were recruited during 1999-2008 and  
22  
23 111 40.6% of the invited women consented to participate. The cohort now includes 114,500 children,  
24  
25 112 95,200 mothers and 75,200 fathers. Follow-up of the participants, after delivery, have been  
26  
27 113 conducted at 6, 18, 36 months, 5, 7 and 8 years. Data used in this study are based on version 8 of  
28  
29 114 the quality-assured data files, released for research in February 2014, with linkage to the Medical  
30  
31 115 Birth Registry of Norway (MBRN). The data collection in MoBa was licensed by the Norwegian  
32  
33 116 Data Inspectorate and approved by the Regional Committee for Medical Research Ethics. This  
34  
35 117 study was approved by the Regional Committee for Medical Research Ethics in Southeastern  
36  
37 118 Norway (2010/2683/REK Sør-øst A). All MoBA participants have provided a signed consent  
38  
39 119 form.

40  
41 120 After exclusion of multiple gestations, stillbirths, malformations and chromosomal  
42  
43 121 abnormalities, 96,875 live-born singletons remained. Of these, 78,819 pregnant women had  
44  
45 122 answered the food frequency questionnaire developed and validated for MoBa and in use from  
46  
47 123 2002 and onwards. The eligible study population, with available information on maternal caffeine  
48  
49 124 intake and all relevant covariates, constituted 62,034 mother-child pairs. Our final study  
50  
51 125 population consisted of 50,943 mother-child pairs with additional information on small for  
52  
53 126 gestational age (SGA) and at least one postnatal measurement of weight or length/height. The  
54  
55 127 cohort retention is presented in Supplementary Table 1. After 5 years, approximately 40% of the  
56  
57 128 study population returned the questionnaire and had information on weight and height, while the  
58  
59 129 distribution of mothers by caffeine intake level did not differ by follow-up age, meaning that loss  
60  
130 to follow-up was not related to maternal caffeine intake in pregnancy.

### 131 **Maternal caffeine intake during pregnancy**

132 Maternal caffeine intake estimation in MoBa has been described in detail previously by  
133 Sengpiel et al<sup>5</sup>. In brief, self-reported intake of 255 dietary items was assessed at pregnancy week  
134 22 with a food frequency questionnaire (FFQ) developed and validated for MoBa<sup>25</sup>. This is a  
135 semi-quantitative FFQ designed to record dietary habits during the first four to five months of  
136 gestation. Average, daily caffeine intake was calculated as the aggregated intake (in mg/day)  
137 from all available sources, including several types of coffee, black tea, caffeinated soft drinks,  
138 energy drinks, chocolate, chocolate milk, and sandwich spread, desserts, cakes and sweets  
139 containing cocoa. Supplementary Table 2 includes more details on the estimation of maternal  
140 caffeine intake. The median (25<sup>th</sup> -75<sup>th</sup> percentiles) caffeine intake was 57mg/day (23-  
141 120mg/day) for the included population and 64mg/day (25-129mg/day) for the non-included  
142 population with available caffeine information (n=11,091 mothers) (p<0.001 for Mann-Whitney  
143 test). We categorized caffeine intake, based on the calculated median as well as national and  
144 international recommendations for caffeine consumption during pregnancy, in four levels of  
145 caffeine intake: low (0-49mg/day), average (50-199mg/day), high (200-299mg/day) or very high  
146 ( $\geq 300$ mg/day).

### 148 **Child postnatal growth and overweight**

#### 149 *Anthropometric data*

150 Weight and height/length measurements at eleven age-points (6 weeks, 3, 6 and 8 months and 1,  
151 1.5, 2, 3, 5, 7 and 8 years) were reported. Up to 18 months the reported measurements were as  
152 documented in the child's health card, while for measurements from 2 to 8 years no specification  
153 was provided. Implausible anthropometrics were identified and excluded by separately  
154 implementing three different methods: i) by comparing with the WHO Growth Standards, as a  
155 weight-for-age or height-for-age z-score  $< 6SD$  below or  $> 6SD$  ( $5SD$  for weight) above the mean  
156 <sup>26</sup>, ii) by identifying measured values with a  $> |3SD|$  difference from the predicted value as  
157 derived from the Jemss-Bayley growth curve model model, and iii) by the conditional growth  
158 percentiles<sup>27</sup>. After exclusion of implausible values, 464,343 and 452,980 measurements of  
159 weight and height/length were reported for our study population. Seven repeated measurements  
160 per child were available on average, for both anthropometrics. More details on anthropometric  
161 measurements are presented in Supplementary Table 1.

## 162 **Outcomes**

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

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

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

182 As including birth weight in the model may influence the estimated trajectories, and in order to  
183 assess the effect of caffeine on early growth independently of its effect on birth size<sup>5</sup>, we did not  
184 include birth weight and length in the growth models.

185  
186 Statistical analysis We used logistic regression models to examine associations between  
187 maternal caffeine intake in categories and excess growth in infancy and childhood overweight.  
188 Low caffeine intake (0-49 mg/day) was the reference group. Similar analysis was performed after  
189 modelling caffeine by restricted cubic splines with four knots at percentiles 5, 35, 65 and 95, as  
190 recommended by Harrell<sup>34</sup>, and corresponding to caffeine intakes of 6, 34, 91 and 253 mg/day,  
191 respectively. The reference level of caffeine intake was set at 50mg/day, corresponding to the  
192 median intake in our study population. The associations were described graphically. Finally, we

1  
2  
3 193 used mixed-effect linear regression models with random intercept by child and a random slope  
4  
5 194 for age to analyze associations between predicted weight, height/length, BMI, weight and height  
6  
7 195 gain velocities from ages 1 month to 8 years (14 age-points: 1, 2, 3, 6, 9, 12 and 18 months and 2,  
8  
9 196 3, 4, 5, 6, 7 and 8 years). Covariates' effects have been models as fixed in the mixed-effect  
10  
11 197 models. All regression models were adjusted for random effects of sibling clusters since some  
12  
13 198 mothers participated with more than one pregnancy.

14 199 Logistic and linear mixed models were adjusted for variables related to both maternal caffeine  
15  
16 200 intake and excess growth by bivariate analysis: maternal age, maternal education, parity, pre-  
17  
18 201 pregnancy BMI, paternal BMI, maternal and paternal smoking during pregnancy, maternal  
19  
20 202 energy intake and nausea/vomiting during pregnancy Gestational age and child's gender were  
21  
22 203 also included in the models as a-priori covariates (Supplementary Table 4). Maternal height,  
23  
24 204 paternal weight, paternal alcohol consumption and gestational diabetes (yes/no) were also  
25  
26 205 considered but not included in the final models as they did not met the criteria. Our main analysis  
27  
28 206 consists of complete case analysis of 38,338 mother-child pairs for the risk of excess growth and  
29  
30 207 of 50,943 mother-child pairs for all other growth outcomes. The cohort attrition due to loss to  
31  
32 208 follow-up was addressed by the use of predicted anthropometric measurements. The correlation  
33  
34 209 between measured and predicted anthropometrics ranged from 0.85 to 0.99 for weight and from  
35  
36 210 0.95 to 0.98 for length/height (data not shown).. .

37 211 In separate sensitivity analyses, i) we excluded SGA neonates (SGA was defined as birth weight  
38  
39 212 below the 10<sup>th</sup> percentile, according to population curves as described by Skjaerven et al<sup>35</sup>), ii)  
40  
41 213 excluded smokers during pregnancy, iii) we adjusted for birth weight; only the overweight  
42  
43 214 models and not the excess growth model, because birth weight is included in the excess growth  
44  
45 215 calculation formula iv) explored caffeine intake by 3 main sources (i.e. from black coffee, black  
46  
47 216 tea and soda drinks), v) excluded very high caffeine consumers, and vi) we assessed the  
48  
49 217 association between maternal caffeine intake and childhood overweight, using the measured  
50  
51 218 instead of predicted anthropometric data to define the outcome. Possible interactions with SGA  
52  
53 219 and birth weight were tested with all studied outcomes. Since the associations between the  
54  
55 220 outcomes and the interaction terms were not significant and the inclusion of the interaction term  
56  
57 221 did not modified our results, we have not included these analyses in the manuscript.

58 222 Finally, we performed negative control analysis, using paternal caffeine intake as the negative  
59  
60 223 control. Negative control analysis is a suggested method to test for the possibility of unmeasured

1  
2  
3 224 confounding. We have assumed that there is no direct association between the father's exposure  
4  
5 225 during the pregnancy period and the child's outcome, and that the shared confounders are equally  
6  
7 226 associated with the mother and the father's exposures<sup>36 37</sup>. We have calculated the caffeine intake  
8  
9 227 of the father using the caffeine concentrations and serving sizes as used for the mother's  
10  
11 228 calculations (Supplementary Table 1) for 5 food items: filtered coffee, boiled coffee, espresso  
12  
13 229 coffee, caffeinated soft-drink with sugar or artificially sweetened. Only 16,455 (32%) fathers had  
14  
15 230 available information.

15 231 The main analyses were performed with the Stata 14 statistical software (Stata Corporation,  
16  
17 232 College Station, Texas) and R version 3.2.2<sup>38</sup> was used for the growth models.

### 19 233 **Patient involvement**

21 234 No patients were involved in setting the research question or the outcome measures, nor were  
22  
23 235 they involved in developing plans for design or implementation of the study. No patients were  
24  
25 236 asked to advise on interpretation or writing up of results. There are no plans to disseminate the  
26  
27 237 results of the research to study participants or the relevant patient community.

## 30 239 **Results**

### 31 240 *Lifestyle and socio-demographic characteristics related to maternal caffeine intake during* 32 33 241 *pregnancy*

35 242 In our study population, 7.13% (n=3,633) and 3.21% (n=1,634) of women reported caffeine  
36  
37 243 intake higher than 200mg/day and 300mg/day, respectively. The distribution of women not  
38  
39 244 included in the analysis, by caffeine intake level was similar to the included (low: 43%, average:  
40  
41 245 46%, high: 8% and very high: 3%). The higher the caffeine intake, the higher the likelihood of a  
42  
43 246 mother being older than 30 years, being multiparous, having a daily energy intake in the upper  
44  
45 247 tertile, being a smoker during pregnancy and not suffering nausea and/or vomiting during  
46  
47 248 pregnancy. Moreover, women with very high caffeine intake were more likely to have low  
48  
49 250 education, have been obese before pregnancy and have partners who were obese and smokers,  
50  
51 251 compared to those consuming less caffeine per day (Supplementary Table 4).

52 252 Paternal median (5<sup>th</sup> -95<sup>th</sup> percentiles) intake was 193mg/day (0-493mg/day), with caffeine from  
53  
54 253 coffee being the main contributor (median: 187 mg/day). Fathers were consuming statistical  
55  
56 254 significantly more caffeine than their partners (p<0.001 for Wilcoxon matched-pairs signed-ranks  
57  
58  
59  
60 test). The spearman correlation coefficient between maternal and paternal caffeine intakes was

1  
2  
3 255 0.15 ( $p$ -value<0.0001). However, paternal intake was increasing by increasing levels of maternal  
4 256 intake and 45% of mothers with very high intake were with partners in the highest quartile of  
5 257 caffeine intake (Supplementary Table 4).

### 8 258 ***Prenatal caffeine exposure and excess growth in infancy***

9  
10 259 The prevalence of excess growth in infancy increased from 23% to 29% as prenatal caffeine  
11 260 intake increased from low to very high (Figure 1). After adjustment for confounders, children  
12 261 born to average, high and very high caffeine consumers had 1.15 (95%CI: 1.09, 1.22), 1.30  
13 262 (95%CI: 1.16,1.45) and 1.66 (95%CI: 1.42,1.93) higher odds of excess growth in infancy,  
14 263 compared with children born to low consumers (Table 1). Neither exclusion of mothers who  
15 264 smoked during pregnancy or SGA neonates modified the results. The positive association  
16 265 between caffeine intake as a continuous variable and the risk of excess growth in infancy was  
17 266 linear with no apparent threshold (Supplementary Figure 1).

### 24 267 ***Prenatal caffeine exposure and overweight in childhood***

25 268 The prevalence of overweight increased by 5% at age 3 years, by 6% at age 5 years and by 3%  
26 269 at age 8 years with increasing prenatal caffeine exposure from low to very high (Figure 1).  
27 270 Children born to average, high and very high caffeine consumers had 1.05 (95%CI: 0.99,1.12),  
28 271 1.17 (95%CI: 1.05,1.30) and 1.44 (95%CI: 1.24,1.67) higher adjusted odds, respectively, for  
29 272 overweight at age 3 years, compared with children born to low caffeine consumers (Table 2).  
30 273 Similar odds ratios (OR) were found at age 5 years, but at age 8 years the respective risk was  
31 274 significant only for the highest caffeine consumption category (adjusted OR (aOR) 1.29; 95%CI  
32 275 1.04,1.61). Neither exclusion of mothers who smoked during pregnancy or SGA neonates  
33 276 modified the results. However, adjustment for birth weight slightly increased the odds  
34 277 (Supplementary Table 5). We found a linear association between maternal caffeine consumption  
35 278 as a continuous variable and the risk of overweight at ages 3 and 5 years with, again, higher OR  
36 279 at age 3 years than at age 5 years (Supplementary Figure 2). As there was a high degree of  
37 280 concordance between overweight and/or obesity at ages 5 and 8 years, the plot at age 8 years  
38 281 overlapped with the one at age 5 years and was not included in Supplementary Figure 2.

### 49 282 ***Sensitivity analyses***

50 283 In sensitivity analyses, we found similar results concerning the association of caffeine from  
51 284 different caffeine sources (black coffee, black tea, and soda drinks) with infant growth and  
52 285 overweight risk (Supplementary Table 6). When excluding very high caffeine consumers and  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 286 using no coffee drinkers as the reference group, caffeine intake less than 300mg/day was still  
4  
5 287 significantly associated with increased risk for excess infant growth and overweight  
6  
7 288 (Supplementary Table 7). Finally, when growth data from actual measurements were used to  
8  
9 289 assess the relationship between maternal caffeine intake and overweight at these age-points,  
10  
11 290 similar trends and associations were observed (Supplementary Table 8).

### 12 291 ***Prenatal caffeine exposure and growth up to 8 years***

13 292 In comparison with low exposure, both high and very high prenatal caffeine exposure were  
14  
15 293 positively associated with a child's weight, weight gain velocity and BMI from the first month  
16  
17 294 onwards (Figure 2). More specifically, children prenatally exposed to very high caffeine levels  
18  
19 295 weighed 67-83g more in infancy (age 3 to 12 months), 110-136g more in toddlerhood (age 12  
20  
21 296 months to 3 years), 213-320g more at pre-school age (age 3 to 5 years) and 480g more at age 8  
22  
23 297 years, than children exposed to low caffeine levels (Table 3). Maternal caffeine intake during  
24  
25 298 pregnancy, at any level above 50mg/day, was associated with higher BMI from ages 1 month to 8  
26  
27 299 years. Additional adjustment for birth weight provided better models (p-value<0.05 for likelihood  
28  
29 300 ratio test between models with and without birth weight) and the estimates from these models are  
30  
31 301 presented in Table 3. Whereas maternal caffeine intake during pregnancy was not associated with  
32  
33 302 child height, it was related to higher height gain velocity up to age 3 months (Supplementary  
34  
35 303 Table 9).

### 36 304 ***Negative control analysis: Paternal caffeine intake***

37 305 We have explored the association between maternal and paternal caffeine intake without and with  
38  
39 306 adjustment for paternal caffeine intake and the same for paternal intake. All models are adjusted  
40  
41 307 for the same confounders as in the main analysis. We have explored the associations with excess  
42  
43 308 infant growth (n=12,289) and overweight at 3 years (n=16,455) (Supplementary Figures 3 & 4).  
44  
45 309 For both the risk of excess infant growth and overweight at 3 years, the association with maternal  
46  
47 310 caffeine intake changed negligibly after adjusting for paternal intake. On the other hand, by using  
48  
49 311 paternal caffeine intake as a negative control, the trend of the association with child's growth was  
50  
51 312 similar to that of maternal caffeine intake, while the effect estimate was much lower.

## 52 313 **Discussion**

53 314 We found that any maternal caffeine intake during pregnancy was associated with a higher risk  
54  
55 315 of excess growth in infancy and overweight in early childhood. In addition, caffeine intakes in  
56  
57  
58  
59  
60

1  
2  
3 317 pregnancy above the recommendation (200mg/day) were associated with modified growth  
4 318 trajectories from very early in life and maintained during childhood. More specifically, children  
5 319 exposed prenatally to caffeine levels above 200mg/day had persistently higher weight-, BMI- and  
6 320 weight gain velocity up to 8 years of age.  
7  
8  
9

### 10 321 ***Strengths and limitations of this study***

11 322 With the included 50,943 pregnancies, this is, so far, the largest study on the association of  
12 323 prenatal caffeine exposure and childhood growth parameters. It is the first to investigate effects  
13 324 on excess growth in infancy as well as growth velocities rather than just the size of the child, as  
14 325 well as critical age windows of diverging growth. Additional strengths include the prospective  
15 326 data collection, the comprehensive data on possible confounders and the assessment of caffeine  
16 327 intake from different sources. Nevertheless, our findings might be explained by residual  
17 328 confounding of non-accounted factors related to an overall unhealthy lifestyle and high caffeine  
18 329 consumption; though exclusion of smokers and very high caffeine consumers did not modify the  
19 330 results. In an effort to control for the effect of unmeasured familial characteristics, we performed  
20 331 negative control analysis using the father's caffeine intake. The unchanged effect estimate of  
21 332 maternal caffeine intake after adjustment for paternal intake as well as the weak effect estimate of  
22 333 paternal caffeine intake, indicate minor bias by shared unmeasured confounders.  
23  
24  
25  
26  
27  
28  
29  
30  
31

32 334 In addition, the missing body size measurements were handled with the use of a growth model.  
33 335 The correlations between the measured and the predicted body size measurements were strong for  
34 336 at all ages. In sensitivity analyses restricted to the measured data, similar associations were found  
35 337 as with the predicted body size data (Supplementary Table 8). This provides some reassurance of  
36 338 the validity of the predicted anthropometrics. However, we still acknowledge the potential for  
37 339 outcome misclassification as only 23% of the cohort had anthropometric information at 8 years  
38 340 (Supplementary Table 3). At the time of release of the current data, 53% (27,142 children) of our  
39 341 study population had not reached the age of 8 years, and only 24% of missing anthropometric  
40 342 information at 8 years can be attributed to loss to follow-up. Furthermore, we found that maternal  
41 343 caffeine exposure was not related to loss to follow-up (Supplementary Table 3).  
42  
43  
44  
45  
46  
47  
48  
49

50 344 The self-report of diet, which can induce misreporting, is a limitation. However, fair agreement  
51 345 between beverage intakes, particularly of coffee and tea, was found in a validation study based on  
52 346 food records and biomarkers<sup>25 39</sup>. Observational studies can never establish causality; however,  
53 347 our results fulfill some of the Bradford-Hill's criteria for causation<sup>40</sup> with a strong association,  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 348 consistent findings for major caffeine sources, a biological gradient with higher caffeine exposure  
4  
5 349 being associated to abnormal growth, consistent findings in animal models and a plausible  
6  
7 350 mechanism, i.e. fetal programming.

8 351 Our study adds evidence to two previous epidemiological studies<sup>19 20</sup> that found an effect of  
9  
10 352 prenatal caffeine exposure on child growth. In the study by Voerman et al., maternal caffeine  
11  
12 353 intake above 360mg/day was associated with higher weight and BMI from birth to age 6 years,  
13  
14 354 compared with intakes below 180mg/day<sup>19</sup>. In contrast to our findings, they found no association  
15  
16 355 with overweight. Higher caffeine intake (360-540mg/day) during pregnancy was positively  
17  
18 356 associated with body fat percentage and higher insulin levels in 6-year-olds. The exposure was  
19  
20 357 assessed only by intakes of coffee and tea, which in our study also are the main but not the only  
21  
22 358 caffeine contributors (78% of total caffeine intake). The median intake was double than in our  
23  
24 359 study, resulting to a higher reference level (reference: <180mg/day, median: 117mg/day),  
25  
26 360 providing less contrast between the compared exposure groups and less comparability to our  
27  
28 361 study, as most of these women were not complying to the recommendation. Nevertheless, we  
29  
30 362 found associations with adverse effects on child's growth even at low caffeine intakes, in the  
31  
32 363 range of the recommendation, that are mostly due to consumption of foods and drinks other than  
33  
34 364 coffee (chocolate, black tea, caffeinated sodas)<sup>5</sup>. Li et al. found likewise that any maternal  
35  
36 365 caffeine intake was associated with an overall increased risk of obesity from ages 2 to 15 years,  
37  
38 366 with an exposure range similar to the current study<sup>20</sup>. We have used similar approaches to study  
39  
40 367 changes in individual growth trajectories, though with shorter follow-up. In addition, we  
41  
42 368 provided age specific weight and BMI deviations, in order to find sensitive developmental  
43  
44 369 windows when the association with the prenatal caffeine exposure exacerbated. There is no  
45  
46 370 previous report of the association between caffeine intake in pregnancy and excess infant growth.

### 43 371 ***Potential mechanisms***

44 372 Since excess growth in infancy, in itself, can be directly related to childhood obesity, adiposity<sup>41</sup>  
45  
46 373 and an unfavorable adult cardio-metabolic profile<sup>42</sup>, the associations between prenatal caffeine  
47  
48 374 exposure with overweight, body fat and insulin, found in this study and the previous reports,  
49  
50 375 might be explained by excess infant growth. Putting together the previous findings in the MoBa  
51  
52 376 study<sup>5</sup>, we have shown that children prenatally exposed to high caffeine levels are smaller at  
53  
54 377 birth, grow faster in infancy and retain a higher weight throughout childhood without significant  
55  
56 378 height differences, thus becoming overweight (Supplementary Figure 5). These findings concur

1  
2  
3 379 with the fetal programming of obesity hypothesis<sup>43</sup>. Nevertheless, the effect of prenatal caffeine  
4  
5 380 exposure on postnatal growth and overweight was not dependent on birth weight. Hence, along  
6  
7 381 with a healthy birth weight, it is important to identify the modifiable factors that can  
8  
9 382 independently affect excess growth in infancy, independent of fetal growth. A growing number of  
10  
11 383 studies have shown that other prenatal factors, e.g. excess gestational weight<sup>44</sup>, high  
12  
13 384 (>3times/week) fish intake<sup>45</sup>, and postnatal factors, e.g. formula feeding and feeding schedule<sup>46</sup>,  
14  
15 385 are associated with increased risk of excess growth in infancy. Recent research shows that some  
16  
17 386 perinatal factors can also have a direct effect on postnatal growth, independent of effects on fetal  
18  
19 387 growth, including parental body size, smoking during pregnancy and socioeconomic status<sup>47-49</sup>.

20  
21 388 The biological plausibility supporting our findings is mainly provided by animal studies where,  
22  
23 389 prenatal exposure to caffeine was shown to program the offspring towards excess growth and  
24  
25 390 cardio-metabolic disorders through alterations i) in the hypothalamic-pituitary-adrenocortical axis  
26  
27 391 that plays a key role in growth and metabolism<sup>50-52</sup>, ii) in regulation of adenosine and adenosine  
28  
29 392 antagonists, which are important modulators of development<sup>53 54</sup> and iii) in the placental  
30  
31 393 expression and transportation of leptin<sup>55</sup>, essential for appetite regulation.

32  
33 394 Although most pregnant women reduce their caffeine intake during pregnancy and few have  
34  
35 395 caffeine intakes higher than 200 mg/day (10%), our results show associations between caffeine  
36  
37 396 intakes below 200 mg/day and excess growth. The results add supporting evidence for the current  
38  
39 397 advice to reduce caffeine intake during pregnancy and indicate that complete avoidance might  
40  
41 398 actually be advisable. An absence of a “safe intake level” has been previously reported in the  
42  
43 399 basis of associations between maternal caffeine intake and fetal growth restriction<sup>56</sup>.  
44  
45 400 Nevertheless, the authors of a recent systematic review after critically assessing the evidence,  
46  
47 401 concluded that a consumption of up to 300 mg caffeine/day in healthy pregnant women is  
48  
49 402 generally not associated with adverse reproductive and developmental effects<sup>57</sup>. Postnatal growth  
50  
51 403 and child’s weight status were not included in this review. Our findings are in agreement with the  
52  
53 404 previous studies assessing a similar hypothesis, with associations reported in caffeine intakes  
54  
55 405 above, but even below, the comparator, indicating that an intake of 300mg/day might not be a  
56  
57 406 safe level when growth is under study. Hence, more evidence is needed for the association  
58  
59 407 between prenatal caffeine exposure and postnatal growth and an updated future critical  
60  
61 408 assessment of such studies.

1  
2  
3 409 The association between prenatal caffeine exposure and overweight attenuated after 5 years,  
4  
5 410 with only very high exposed children being at risk for overweight. Residual confounding due to  
6  
7 411 postnatal factors related to overweight in late childhood might explain this attenuation.  
8  
9 412 Nevertheless, adjustment for risk factors of being overweight at 8 years would introduce bias to  
10  
11 413 the association under study. In addition, weight and height are screened from birth to 5 years in  
12  
13 414 scheduled voluntarily appointments at the public health centers. Hence, a possible  
14  
15 415 misclassification of outcome from anthropometrics after 5 years, might also explain the  
16  
17 416 attenuation of the association.

17 417 There are two studies showing effects of caffeine intake on body composition and  
18  
19 418 cardiometabolic health<sup>19 58</sup>, with discrepant results. In the present study, we did not have any  
20  
21 419 information on body composition. In addition, it is known that several genetic factors can  
22  
23 420 contribute to variation in caffeine metabolism<sup>59</sup>, and studies in adults have shown that slower  
24  
25 421 metabolism of caffeine is related to higher risk of cardiovascular disease<sup>60</sup>. On the other hand,  
26  
27 422 during pregnancy, maternal caffeine clearance modified the association between maternal  
28  
29 423 caffeine intake and fetal growth restriction, with faster clearance being more detrimental<sup>56</sup>. More  
30  
31 424 specifically, a genotype of rapid caffeine metabolism was associated with reduced birth weight  
32  
33 425 while in women with a different polymorphism on the gene CYP1A2 C164A no effect was found  
34  
35 426<sup>61</sup>. Thus, there is a need to investigate the programming effect of prenatal caffeine exposure on  
36  
37 427 child and adult body composition and cardiometabolic health, taking into account the genetic  
38  
39 428 variation of maternal caffeine metabolism.  
40

## 409 430 **Conclusions**

41 431 We found that the risk of excess infant growth and overweight in childhood-important risk  
42  
43 432 factors for later cardio-metabolic disease- is increasing with maternal caffeine intake, with no  
44  
45 433 apparent threshold. Maternal caffeine intake >200mg/day during pregnancy was associated with  
46  
47 434 high weight gain velocity beginning from the first months of life and higher BMI throughout  
48  
49 435 childhood. Our findings support the recommendation to limit caffeine intake during pregnancy  
50  
51 436 (<200mg/day).

## 53 438 **Acknowledgements**

439 We are grateful to all the families in Norway who have participated in this ongoing cohort  
440 study.

441

## 442 References

- 443 1. EFSA EFSA-PoDP, Nutrition and Allergies (NDA). Scientific Opinion on the safety of caffeine. *EFSA*  
444 *Journal* 2015;13(5)
- 445 2. Mort JR, Kruse HR. Timing of blood pressure measurement related to caffeine consumption. *Ann*  
446 *Pharmacother* 2008;42(1):105-10. doi: 10.1345/aph.1K337
- 447 3. Tomimatsu T, Lee SJ, Pena JP, et al. Maternal caffeine administration and cerebral oxygenation in  
448 near-term fetal sheep. *Reprod Sci* 2007;14(6):588-94. doi: 10.1177/1933719107307717
- 449 4. VKM. Risk assessment of "other substances"– Caffeine. Opinion of the Panel on Food Additives,  
450 Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian  
451 Scientific Committee for Food Safety. Oslo, Norway, 2015.
- 452 5. Sengpiel V, Elind E, Bacelis J, et al. Maternal caffeine intake during pregnancy is associated with birth  
453 weight but not with gestational length: results from a large prospective observational cohort  
454 study. *BMC Med* 2013;11:42. doi: 10.1186/1741-7015-11-42
- 455 6. Rhee J, Kim R, Kim Y, et al. Maternal Caffeine Consumption during Pregnancy and Risk of Low Birth  
456 Weight: A Dose-Response Meta-Analysis of Observational Studies. *PloS one*  
457 2015;10(7):e0132334. doi: 10.1371/journal.pone.0132334
- 458 7. Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic review.  
459 *JAMA : the journal of the American Medical Association* 2008;300(24):2886-97. doi:  
460 10.1001/jama.2008.886 [published Online First: 2008/12/26]
- 461 8. Lawlor DA, Ronalds G, Clark H, et al. Birth weight is inversely associated with incident coronary heart  
462 disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of  
463 the 1950s prospective cohort study. *Circulation* 2005;112(10):1414-8. doi:  
464 10.1161/CIRCULATIONAHA.104.528356
- 465 9. Monasta L, Batty GD, Cattaneo A, et al. Early-life determinants of overweight and obesity: a review of  
466 systematic reviews. *Obesity reviews : an official journal of the International Association for the*  
467 *Study of Obesity* 2010;11(10):695-708. doi: 10.1111/j.1467-789X.2010.00735.x
- 468 10. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful  
469 suggestions. *Acta paediatrica* 2006;95(8):904-8. doi: 10.1080/08035250600719754
- 470 11. Baird J, Fisher D, Lucas P, et al. Being big or growing fast: systematic review of size and growth in  
471 infancy and later obesity. *BMJ* 2005;331(7522):929. doi: 10.1136/bmj.38586.411273.E0
- 472 12. Jones-Smith JC, Neufeld LM, Laraia B, et al. Early life growth trajectories and future risk for  
473 overweight. *Nutrition & diabetes* 2013;3:e60. doi: 10.1038/nutd.2012.32
- 474 13. Botton J, Heude B, Maccario J, et al. Postnatal weight and height growth velocities at different ages  
475 between birth and 5 y and body composition in adolescent boys and girls. *The American journal*  
476 *of clinical nutrition* 2008;87(6):1760-8.
- 477 14. Perng W, Hajj H, Belfort MB, et al. Birth Size, Early Life Weight Gain, and Midchildhood  
478 Cardiometabolic Health. *The Journal of pediatrics* 2016 doi: 10.1016/j.jpeds.2016.02.053
- 479 15. Ekelund U, Ong KK, Linne Y, et al. Association of weight gain in infancy and early childhood with  
480 metabolic risk in young adults. *The Journal of clinical endocrinology and metabolism*  
481 2007;92(1):98-103. doi: 10.1210/jc.2006-1071
- 482 16. Collaboration NCDRF, Di Cesare M, Bentham J, et al. Trends in adult body-mass index in 200 countries  
483 from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2  
484 million participants. *Lancet* 2016;387(10026):1377-96. doi: 10.1016/S0140-6736(16)30054-X

- 1  
2  
3 485 17. Woo Baidal JA, Locks LM, Cheng ER, et al. Risk Factors for Childhood Obesity in the First 1,000 Days: A  
4 486 Systematic Review. *Am J Prev Med* 2016;50(6):761-79. doi: 10.1016/j.amepre.2015.11.012  
5 487 18. Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public  
6 488 health implications. *The American journal of clinical nutrition* 2011;94(6 Suppl):1754S-58S. doi:  
7 489 10.3945/ajcn.110.001206  
8 490 19. Voerman E, Jaddoe VW, Gishti O, et al. Maternal caffeine intake during pregnancy, early growth, and  
9 491 body fat distribution at school age. *Obesity* 2016;24(5):1170-7. doi: 10.1002/oby.21466  
10 492 20. Li DK, Ferber JR, Odouli R. Maternal caffeine intake during pregnancy and risk of obesity in offspring:  
11 493 a prospective cohort study. *International journal of obesity* 2015;39(4):658-64. doi:  
12 494 10.1038/ijo.2014.196  
13 495 21. Barker DJ, Bagby SP. Developmental antecedents of cardiovascular disease: a historical perspective.  
14 496 *Journal of the American Society of Nephrology : JASN* 2005;16(9):2537-44. doi:  
15 497 10.1681/ASN.2005020160  
16 498 22. Gluckman PD, Cutfield W, Hofman P, et al. The fetal, neonatal, and infant environments-the long-  
17 499 term consequences for disease risk. *Early Hum Dev* 2005;81(1):51-9. doi:  
20 500 10.1016/j.earlhumdev.2004.10.003  
21 501 23. Barker DJP. In utero programming of chronic disease. *Clinical Science* 1998;95:115-28.  
22 502 24. Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort  
23 503 Study (MoBa). *International journal of epidemiology* 2016 [published Online First: April 10, 2016]  
24 504 25. Brantsæter AL, Haugen M, Alexander J, et al. Validity of a new food frequency questionnaire for  
25 505 pregnant women in the Norwegian Mother and Child Cohort Study (MoBa). *Matern Child Nutr*  
26 506 2008;4(1):28-43. doi: MCN103 [pii];10.1111/j.1740-8709.2007.00103.x [doi]  
27 507 26. WHO MGRSG. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-  
28 508 length, weight-for-height and body mass index-for-age: Methods and development. Geneva:  
29 509 World Health Organization 2006.  
30 510 27. Yang S, Hutcheon JA. Identifying outliers and implausible values in growth trajectory data. *Annals of*  
31 511 *epidemiology* 2016;26(1):77-80 e1-2. doi: 10.1016/j.annepidem.2015.10.002  
32 512 28. Ong KK, Ahmed ML, Emmett PM, et al. Association between postnatal catch-up growth and obesity in  
33 513 childhood: prospective cohort study. *BMJ* 2000;320(7240):967-71. [published Online First:  
34 514 2001/02/07]  
35 515 29. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a  
36 516 systematic review. *Obesity reviews : an official journal of the International Association for the*  
37 517 *Study of Obesity* 2005;6(2):143-54. doi: 10.1111/j.1467-789X.2005.00183.x  
38 518 30. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight  
39 519 and obesity. *Pediatric obesity* 2012;7(4):284-94. doi: 10.1111/j.2047-6310.2012.00064.x  
40 520 31. Jenss RM, Bayley N. A mathematical method for studying the growth of a child. *Human Biology*  
41 521 1937;9:556-63.  
42 522 32. Berkey CS. Comparison of two longitudinal growth models for preschool children. *Biometrics*  
43 523 1982;38(1):221-34.  
44 524 33. Comets E, Lavenue A, Lavielle M. saemix: Stochastic Approximation Expectation Maximization (SAEM)  
45 525 algorithm. 2014. <https://cran.r-project.org/web/packages/saemix/index.html>.  
46 526 34. Harrell F. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression,  
47 527 and Survival Analysis. 1 ed. New York: Springer-Verlag New York 2001.  
48 528 35. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta*  
49 529 *ObstetGynecolScand* 2000;79(6):440-49.  
50 530 36. Richmond RC, Al-Amin A, Smith GD, et al. Approaches for drawing causal inferences from  
51 531 epidemiological birth cohorts: a review. *Early Hum Dev* 2014;90(11):769-80. doi:  
52 532 10.1016/j.earlhumdev.2014.08.023  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 533 37. Brew BK, Gong T, Williams DM, et al. Using fathers as a negative control exposure to test the  
4 534 Developmental Origins of Health and Disease Hypothesis: A case study on maternal distress and  
5 535 offspring asthma using Swedish register data. *Scandinavian journal of public health*  
6 536 2017;45(17\_suppl):36-40. doi: 10.1177/1403494817702324  
7  
8 537 38. R: A language and environment for statistical computing [program]. Vienna, Austria: R Foundation for  
9 538 Statistical Computing, 2016.  
10 539 39. Brantsæter AL, Haugen M, Rasmussen SE, et al. Urine flavonoids and plasma carotenoids in the  
11 540 validation of fruit, vegetable and tea intake during pregnancy in the Norwegian Mother and Child  
12 541 Cohort Study (MoBa). *Public Health Nutr* 2007;10(8):838-47. doi: S1368980007339037  
13 542 [pii];10.1017/S1368980007339037 [doi]  
14 543 40. HILL AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *ProcRSocMed*  
15 544 1965;58:295-300.  
16 545 41. Karaolis-Danckert N, Buyken AE, Bolzenius K, et al. Rapid growth among term children whose birth  
17 546 weight was appropriate for gestational age has a longer lasting effect on body fat percentage  
18 547 than on body mass index. *The American journal of clinical nutrition* 2006;84(6):1449-55.  
19 548 42. Leunissen RW, Kerkhof GF, Stijnen T, et al. Timing and tempo of first-year rapid growth in relation to  
20 549 cardiovascular and metabolic risk profile in early adulthood. *JAMA : the journal of the American*  
21 550 *Medical Association* 2009;301(21):2234-42. doi: 10.1001/jama.2009.761  
22 551 43. Barker DJ. Fetal origins of coronary heart disease. *BMJ* 1995;311(6998):171-74.  
23 552 44. Subhan FB, Colman I, McCargar L, et al. Higher Pre-pregnancy BMI and Excessive Gestational Weight  
24 553 Gain are Risk Factors for Rapid Weight Gain in Infants. *Maternal and child health journal* 2017  
25 554 doi: 10.1007/s10995-016-2246-z  
26 555 45. Stratakis N, Roumeliotaki T, Oken E, et al. Fish Intake in Pregnancy and Child Growth: A Pooled  
27 556 Analysis of 15 European and US Birth Cohorts. *JAMA pediatrics* 2016;170(4):381-90. doi:  
28 557 10.1001/jamapediatrics.2015.4430  
29 558 46. Mahrshahi S, Battistutta D, Magarey A, et al. Determinants of rapid weight gain during infancy:  
30 559 baseline results from the Nourish randomised controlled trial. *BMC pediatrics* 2011;11:99. doi:  
31 560 10.1186/1471-2431-11-99 [published Online First: 2011/11/08]  
32 561 47. Liu JX, Xu X, Liu JH, et al. Association of maternal gestational weight gain with their offspring's  
33 562 anthropometric outcomes at late infancy and 6 years old: mediating roles of birth weight and  
34 563 breastfeeding duration. *International journal of obesity* 2017 doi: 10.1038/ijo.2017.183  
35 564 48. Hindmarsh PC, Geary MP, Rodeck CH, et al. Factors predicting ante- and postnatal growth. *Pediatric*  
36 565 *research* 2008;63(1):99-102. doi: 10.1203/PDR.0b013e31815b8e8f  
37 566 49. Morgen CS, Angquist L, Baker JL, et al. Prenatal risk factors influencing childhood BMI and overweight  
38 567 independent of birth weight and infancy BMI: a path analysis within the Danish National Birth  
39 568 Cohort. *International journal of obesity* 2017 doi: 10.1038/ijo.2017.217  
40 569 50. Xu D, Zhang B, Liang G, et al. Caffeine-induced activated glucocorticoid metabolism in the  
41 570 hippocampus causes hypothalamic-pituitary-adrenal axis inhibition in fetal rats. *PloS one*  
42 571 2012;7(9):e44497. doi: 10.1371/journal.pone.0044497 [published Online First: 2012/09/13]  
43 572 51. Li J, Luo H, Wu Y, et al. Gender-specific increase in susceptibility to metabolic syndrome of offspring  
44 573 rats after prenatal caffeine exposure with post-weaning high-fat diet. *Toxicology and applied*  
45 574 *pharmacology* 2015;284(3):345-53. doi: 10.1016/j.taap.2015.03.002  
46 575 52. Xu D, Wu Y, Liu F, et al. A hypothalamic-pituitary-adrenal axis-associated neuroendocrine metabolic  
47 576 programmed alteration in offspring rats of IUGR induced by prenatal caffeine ingestion.  
48 577 *Toxicology and applied pharmacology* 2012;264(3):395-403. doi: 10.1016/j.taap.2012.08.016  
49 578 [published Online First: 2012/09/11]  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 579 53. Buscariollo DL, Fang X, Greenwood V, et al. Embryonic caffeine exposure acts via A1 adenosine  
4 580 receptors to alter adult cardiac function and DNA methylation in mice. *PLoS one*  
5 581 2014;9(1):e87547. doi: 10.1371/journal.pone.0087547  
6 582  
7 583 54. Rivkees SA, Wendler CC. Adverse and protective influences of adenosine on the newborn and  
8 584 embryo: implications for preterm white matter injury and embryo protection. *Pediatric research*  
9 585 2011;69(4):271-8. doi: 10.1203/PDR.0b013e31820efbcf [published Online First: 2011/01/14]  
10 586  
11 587 55. Wu YM, Luo HW, Kou H, et al. Prenatal caffeine exposure induced a lower level of fetal blood leptin  
12 588 mainly via placental mechanism. *Toxicology and applied pharmacology* 2015;289(1):109-16. doi:  
13 589 10.1016/j.taap.2015.09.007  
14 590  
15 591 56. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective  
16 592 observational study. *BMJ* 2008;337:a2332. doi: 10.1136/bmj.a2332 [published Online First:  
17 593 2008/11/05]  
18 594  
19 595 57. Wikoff D, Welsh BT, Henderson R, et al. Systematic review of the potential adverse effects of caffeine  
20 596 consumption in healthy adults, pregnant women, adolescents, and children. *Food and chemical*  
21 597 *toxicology : an international journal published for the British Industrial Biological Research*  
22 598 *Association* 2017;109(Pt 1):585-648. doi: 10.1016/j.fct.2017.04.002  
23 599  
24 600 58. de Medeiros TS, Bernardi JR, de Brito ML, et al. Caffeine Intake During Pregnancy in Different  
25 601 Intrauterine Environments and its Association with Infant Anthropometric Measurements at 3  
26 602 and 6 Months of Age. *Maternal and child health journal* 2017;21(6):1297-307. doi:  
27 603 10.1007/s10995-016-2230-7  
28 604  
29 605 59. Cornelis MC, Kacprowski T, Menni C, et al. Genome-wide association study of caffeine metabolites  
30 606 provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. *Hum*  
31 607 *Mol Genet* 2016;25(24):5472-82. doi: 10.1093/hmg/ddw334  
32 608  
33 609 60. Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine.  
34 610 *Psychopharmacology* 2010;211(3):245-57. doi: 10.1007/s00213-010-1900-1  
35 611  
36 612 61. Norwegian Mother and Child Study: Norwegian Institute of Public Health; [Available from:  
37 613 [http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea\\_5811&MainArea\\_5811=5895:0:15,3046:1:0:0:::0:02010](http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5895:0:15,3046:1:0:0:::0:02010).  
38 614  
39 615  
40 616  
41 617  
42 618  
43 619  
44 620  
45 621  
46 622  
47 623  
48 624  
49 625  
50 626  
51 627  
52 628  
53 629  
54 630  
55 631  
56 632  
57 633  
58 634  
59 635  
60 636

1  
2  
3 609 **Funding statement:** The Norwegian Mother and Child Cohort Study is supported by the  
4 610 Norwegian Ministry of Health and Care Services and Ministry of Education and Research,  
5 611 NIH/NIEHS (contract no N01-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537- 01 and  
6 612 grant no.2 UO1 NS 047537-06A1). Verena Sengpiel has received grants from Stiftelsen Sigurd  
7 613 och Elsa Goljes Minnesfond (LA2013-0241 “Koffeinintag, födelsevikt och barnutfall”),  
8 614 Stiftelsen Fru Mary von Sydows, född Wijk, donationsfond (2014 “Koffeinintag, födelsevikt och  
9 615 barnutfall”) and Wilhelm och Martina Lundgrens Vetenskapsfond (1 vet1-119/2014:  
10 616 “Koffeinintag, födelsevikt och barnutfall”). The funding bodies were not involved in the design,  
11 617 implementation of the study or interpretation of the results.  
12 618

13 619 **Competing interests statement:** *No competing interests.* All authors have completed the ICMJE  
14 620 uniform disclosure form at [www.icmje.org/doi\\_disclosure.pdf](http://www.icmje.org/doi_disclosure.pdf) and declare: no support from any  
15 621 organisation for the submitted work; no financial relationships with any organisations that might  
16 622 have an interest in the submitted work in the previous three years; no other relationships or  
17 623 activities that could appear to have influenced the submitted work.  
18 624

19 625 **Contributorship statement:** EP contributed to study design, data analysis, and interpretation of  
20 626 the results and had the main responsibility of writing the paper. JBO contributed to the statistical  
21 627 analysis plan and database preparation and interpretation of the results. ALB contributed to study  
22 628 design, interpretation of the results and revising the paper. MH, JA, HMM contributed to the  
23 629 design of data collection tools, the study design and interpretation of the results. JBA contributed  
24 630 to the statistical analysis plan and database preparation. AE contributed to interpretation of the  
25 631 results.  
26 632 BJ initiated this collaborative project, contributed to the study design and the interpretation of the  
27 633 results. VS defined the research question, contributed to the study design, database preparation  
28 634 and interpretation of the results. She is guarantor and had final responsibility for the decision to  
29 635 submit for publication. All authors read, revised and approved the final version of the paper.  
30 636

31 637 **Data sharing statement:** No additional data are available. All data from the MoBa study are  
32 638 available to all qualified researchers/research groups in Norway and to international researchers  
33 639 who are collaborating with a Norwegian researcher.

#### 640 **Declaration of transparency**

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

644  
645 **Licence to BMJ Publishing Group Limited (“BMJ Group”) for Publication**



1  
2  
3 646 “I **Eleni Papadopoulou** The Corresponding Author of this article contained within the original  
4 647 manuscript which includes any diagrams & photographs within and any related or stand alone  
5 648 film submitted (the Contribution”) has the right to grant on behalf of all authors and does grant  
6 649 on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit  
7 650 this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products  
8 651 and to exploit all subsidiary rights, as set out in our licence set out at: [http://www.bmj.com/about-](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)  
9 652 [bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)  
10 653 [reuse.](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)”  
11 654

12 Please tick **one or more** boxes as appropriate:  
13

14 655 X I am one author signing on behalf of all co-owners of the Contribution.  
15  
16  
17 656  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 **TABLES**  
6  
7

8 **Table 1. Maternal caffeine intake in pregnancy and risk of excess growth in infancy (from birth to age 12 months)**  
9

	Risk of excess growth in infancy (from birth to age 12 months) <sup>a</sup>					
	All children (n=38,338)		After excluding smokers during pregnancy (n=35,672)		After excluding SGA neonates <sup>b</sup> (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

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

25 <sup>a</sup> Excess growth is defined as a WHO weight-for-age z-score difference >0.67 between birth and age 12 months.

26 <sup>b</sup> SGA according to Skjaerven et al.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

**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 <sup>a</sup>					
	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) <sup>b</sup>					
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

<sup>a</sup> Overweight and/or obesity in children, according to the International Obesity Task Force definition.

<sup>b</sup> 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.**

Maternal daily caffeine intake	Child's developmental period						
	Infancy		Toddlerhood		Pre-school age		School age
	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)
<b><i>Weight (in g)</i></b>							
Average (50-199 mg)	<b>14.1</b> <b>(1.6,26.6)</b>	<b>15.1</b> <b>(1.3,28.8)</b>	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)	<b>31.3</b> <b>(7.5,55.1)</b>	<b>35.0</b> <b>(8.8,61.1)</b>	<b>45.4</b> <b>(7.3,83.5)</b>	<b>59.0</b> <b>(13.1,104.8)</b>	<b>99.0</b> <b>(36.3,161.7)</b>	<b>148.9</b> <b>(68.4,229.4)</b>	<b>222.0</b> <b>(114.1,329.8)</b>
Very high ( $\geq 300$ mg)	<b>67.0</b> <b>(32.5,101.6)</b>	<b>83.2</b> <b>(45.3,121.1)</b>	<b>110.1</b> <b>(55.2,165.0)</b>	<b>135.5</b> <b>(69.5,201.5)</b>	<b>213.4</b> <b>(123.3,303.6)</b>	<b>320.0</b> <b>(204.4,435.6)</b>	<b>480.3</b> <b>(325.5,635.1)</b>
<b><i>Weight gain velocity (in g/month)</i></b>							
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)	<b>2.1(0.4,3)</b>	<b>2.0(0.1,4.0)</b>	<b>2.2(0.4,0)</b>
Very high ( $\geq 300$ mg)	<b>6.0(1.5,10.4)</b>	<b>4.3(0.2,8.5)</b>	<b>3.8(0.1,7.4)</b>	<b>3.7(0.3,7.1)</b>	<b>3.9(0.8,7.0)</b>	<b>3.9(1.1,6.8)</b>	<b>3.9(1.1,6.8)</b>
<b><i>BMI (in kg/m<sup>2</sup>)</i></b>							
Average (50-199 mg)	<b>0.03</b> <b>(0.01,0.05)</b>	<b>0.03</b> <b>(0.01,0.05)</b>	<b>0.04</b> <b>(0.02,0.06)</b>	<b>0.04</b> <b>(0.02,0.06)</b>	<b>0.04</b> <b>(0.02,0.06)</b>	<b>0.03</b> <b>(0.01,0.06)</b>	0.02 (-0.01,0.05)
High (200-299 mg)	<b>0.07</b> <b>(0.03,0.11)</b>	<b>0.07</b> <b>(0.03,0.10)</b>	<b>0.09</b> <b>(0.05,0.12)</b>	<b>0.11</b> <b>(0.07,0.15)</b>	<b>0.14</b> <b>(0.10,0.19)</b>	<b>0.15</b> <b>(0.11,0.20)</b>	<b>0.15</b> <b>(0.09,0.21)</b>
Very high ( $\geq 300$ mg)	<b>0.16</b> <b>(0.10,0.21)</b>	<b>0.16</b> <b>(0.11,0.21)</b>	<b>0.17</b> <b>(0.12,0.23)</b>	<b>0.20</b> <b>(0.14,0.25)</b>	<b>0.26</b> <b>(0.20,0.32)</b>	<b>0.29</b> <b>(0.22,0.36)</b>	<b>0.31</b> <b>(0.22,0.39)</b>

Abbreviations: Beta: beta coefficients, CI: confidence intervals

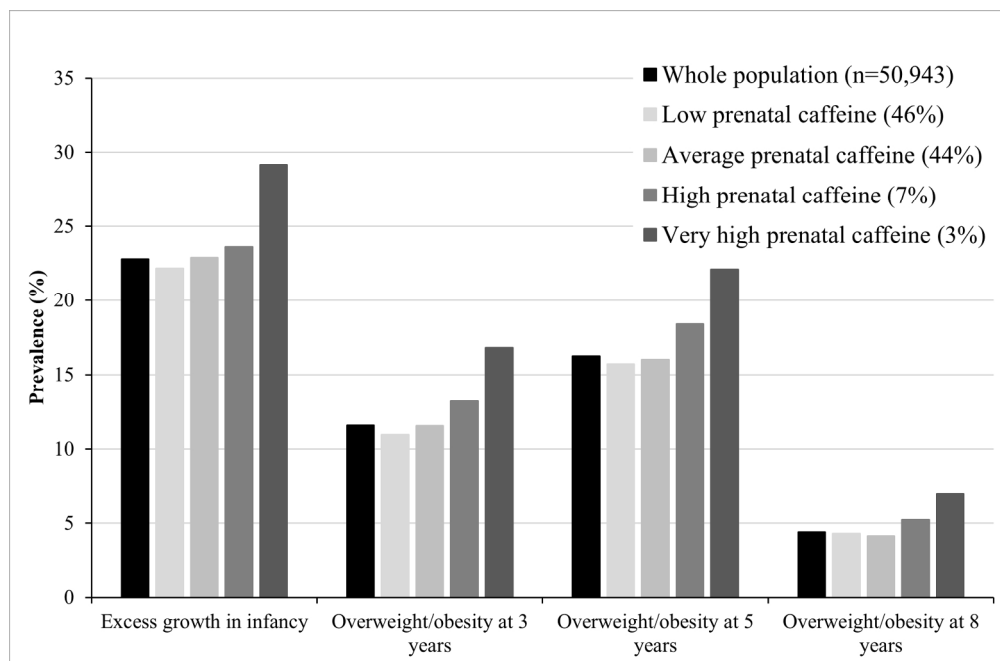
Infancy is defined as the period from birth to age 12 months, toddlerhood as the period from age 12 months to 3 years, pre-school age as the period from age 3 years to 5 years and school age as the period from age 5 years onwards.

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.

1  
2  
3 **FIGURE LEGENDS**  
4  
5  
6

7 **Figure 1.** Prevalence of excess growth in infancy and overweight/obesity at age 3, 5 and 8 years, in the whole population and by  
8 maternal caffeine intake during pregnancy.  
9

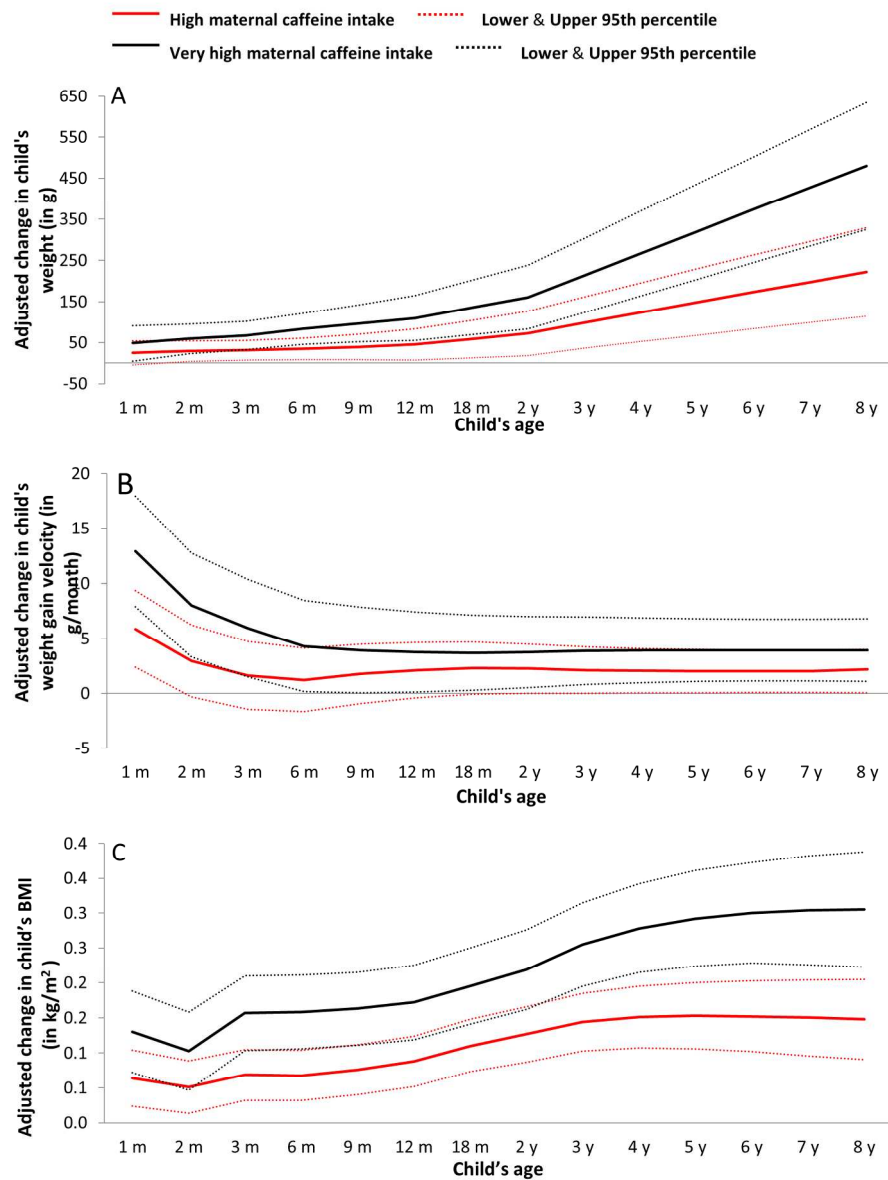
10  
11 **Figure 2.** Maternal high (red) and very high (black) caffeine intake in pregnancy and adjusted change in children's a) weight (in g), b)  
12 weight gain velocity (in g/month) and c) body mass index (in kg/m<sup>2</sup>), from age 1 month to 8 years (beta coefficients in solid lines and  
13 95% confidence intervals in thin dashed lines). Low caffeine intake is the reference group.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47



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.

172x114mm (300 x 300 DPI)

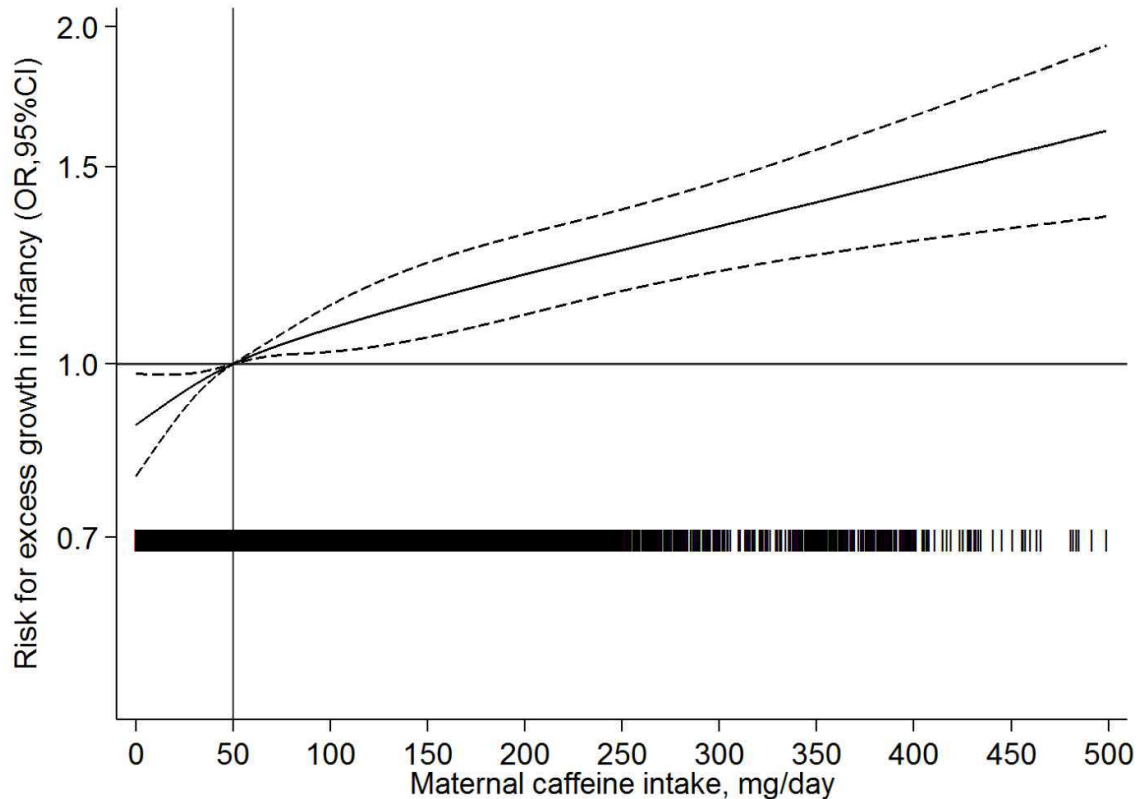
View only



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<sup>2</sup>), 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.

172x228mm (300 x 300 DPI)

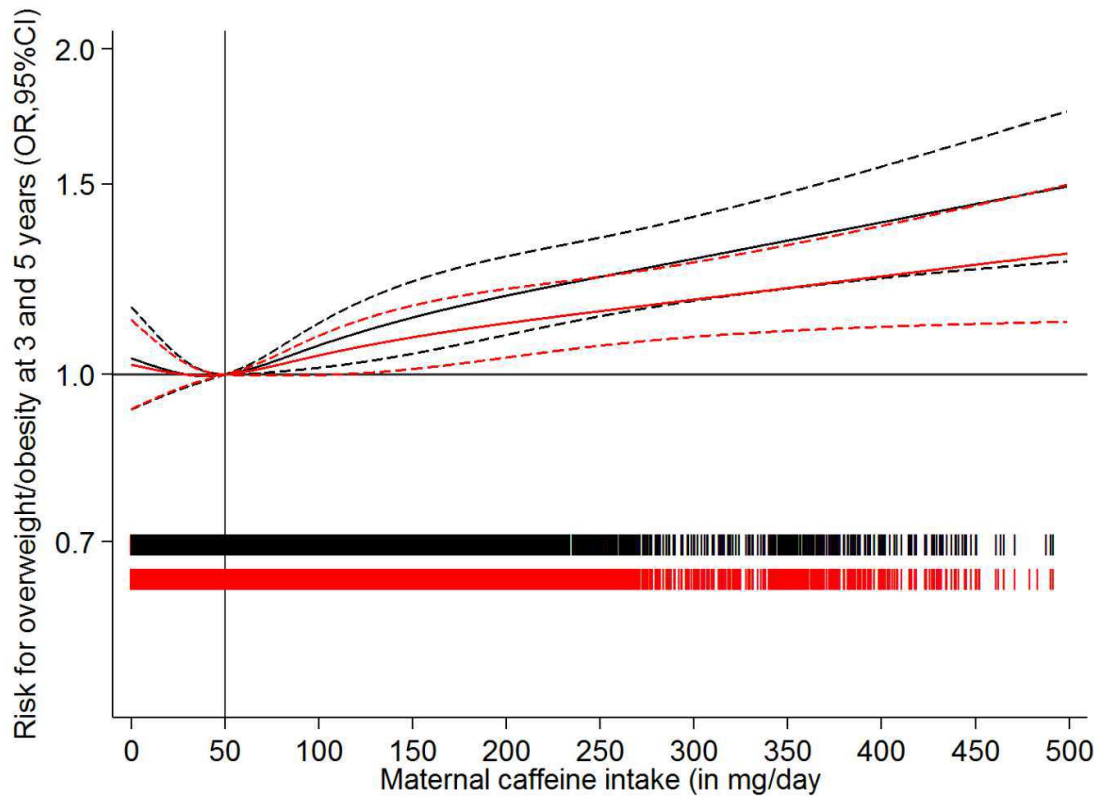
Supplementary Figure 1. Maternal caffeine intake on a continuous scale and risk of excess growth in infancy. Odds ratios (solid line) and 95% confidence intervals (dashed lines) derived from a logistic regression model using restricted cubic splines. The solid vertical line represents the reference value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

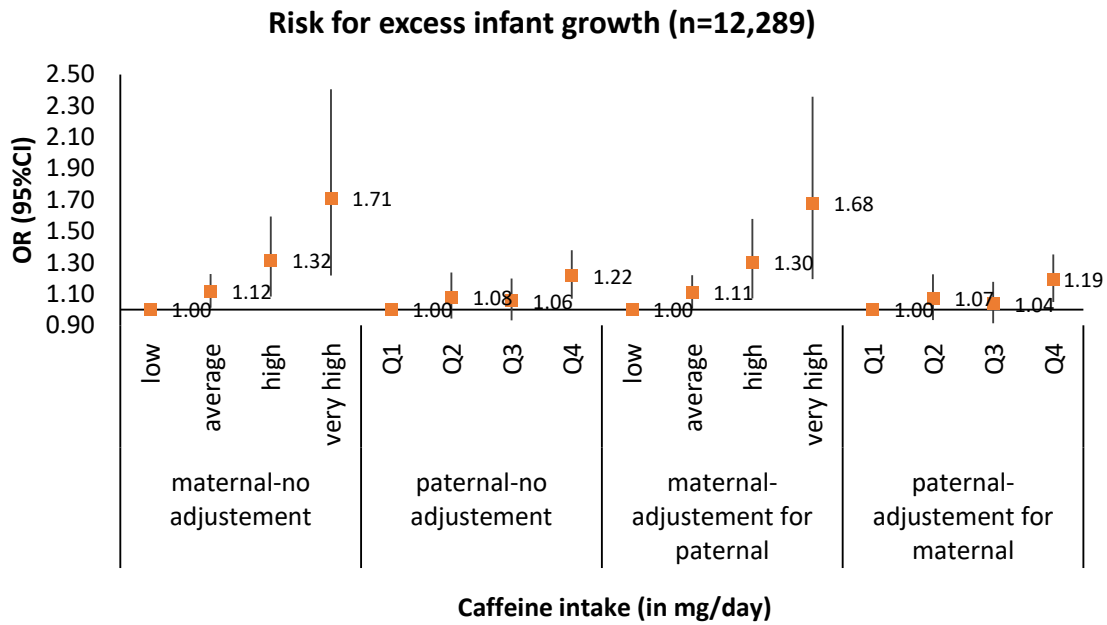


Supplementary Figure 2. Maternal caffeine intake in continuous scale and risk for overweight/obesity at age 3 (black) and 5 years (red). Odds ratios (solid line) and the 95% confidence intervals (dashed lines) derived from a logistic regression model using restricted cubic splines. The solid vertical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



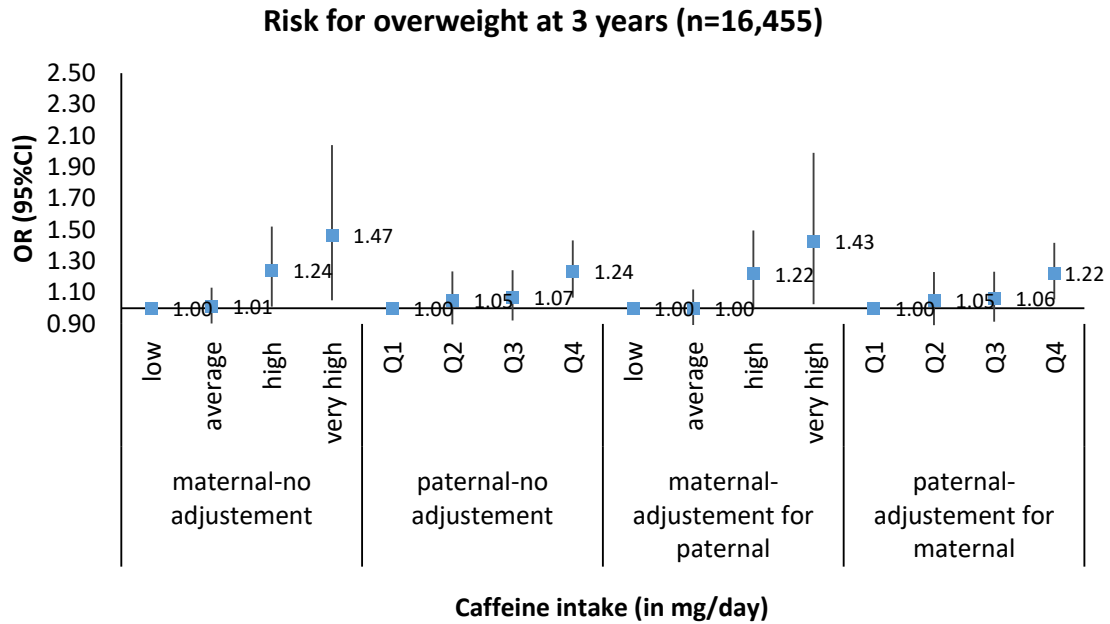
Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age, gender and birth weight

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



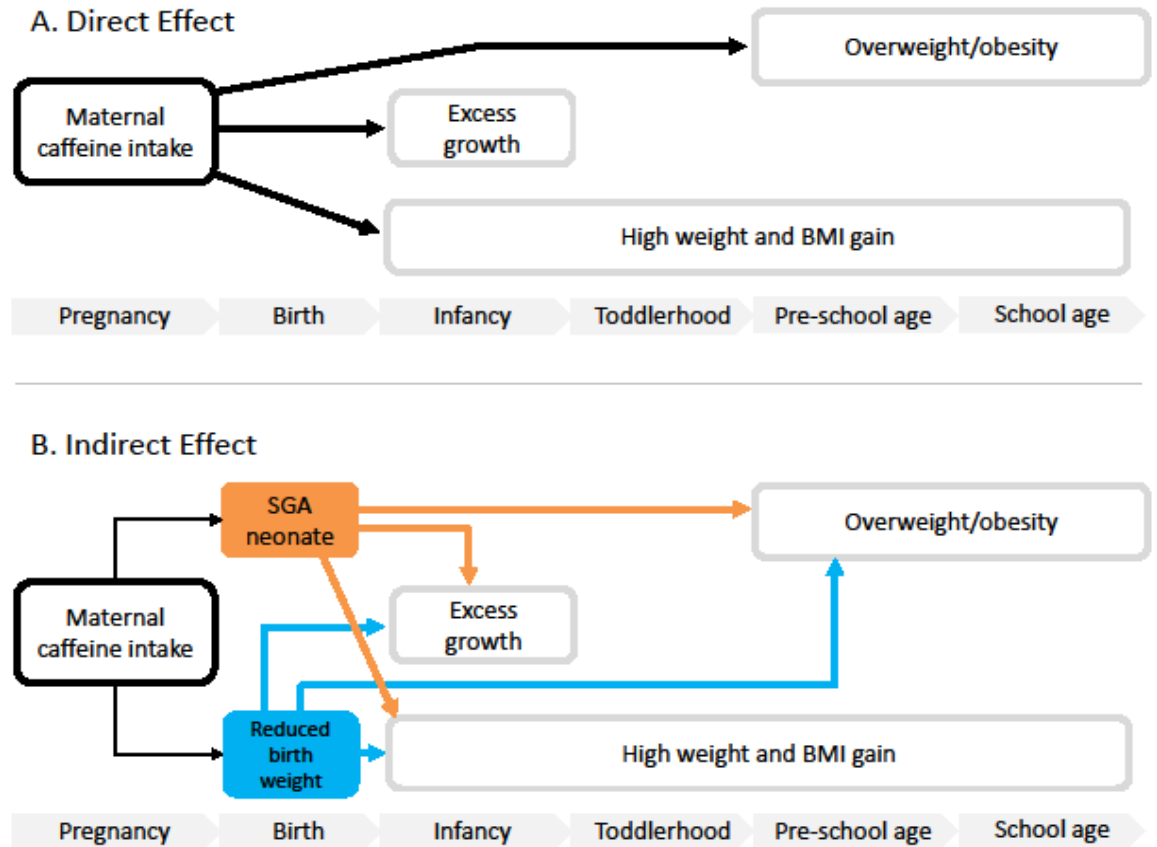
Footnote: All models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender.

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



only

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			
	Mean	N	Mean	N		Mean	N		Low	Average	High	Very high
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 <sup>2</sup> )		Prevalence (%) <sup>a</sup>	
			Males	Females	Males	Females
International Obesity Task Force (IOTF) <sup>1</sup>	Study-specific BMIs were calculated for age and sex	3	17.89	17.56	10.77	12.44
(BMJ 2000 May 6; 320 (7244); 1240-1243)		5	17.42	17.15	14.30	18.28
Table 4)		8	18.44	18.35	3.61	5.24

<sup>a</sup>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)		Average caffeine intake (50-199mg/day)		High caffeine intake (200-299mg/day)		Very high caffeine intake (≥300mg/day)	
	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 <sup>2</sup> )								
<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 <sup>2</sup> )								
<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

1 <sup>st</sup> quartile	2,253	(29%)	1,504	(20%)	168	(15%)	44	(14%)
2 <sup>nd</sup> quartile	1,605	(21%)	1,495	(20%)	202	(18%)	51	(16%)
3 <sup>rd</sup> quartile	1,950	(26%)	2,186	(30%)	356	(33%)	82	(25%)
4 <sup>th</sup> 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<sup>-5</sup> of chi square tests of all cross-tabulations presented in table

<sup>1</sup>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.

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

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

<sup>a</sup> 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 <sup>a</sup>			Overweight/obesity at age 3 years <sup>b</sup>			Overweight/obesity at age 5 years <sup>b</sup>			Overweight/obesity at age 8 years <sup>b</sup>		
	OR	95% CI	CI	OR	95% CI	CI	OR	95% CI	CI	OR	95% CI	CI
Caffeine from black coffee												
0-50	1.00			1.00			1.00			1.00		
50-200	<b>1.18</b>	<b>1.11</b>	<b>1.26</b>	<b>1.18</b>	<b>1.11</b>	<b>1.26</b>	<b>1.12</b>	<b>1.05</b>	<b>1.18</b>	<b>1.11</b>	<b>1.00</b>	<b>1.23</b>
200-300	<b>1.31</b>	<b>1.06</b>	<b>1.62</b>	1.14	0.91	1.41	1.11	0.92	1.34	1.09	0.77	1.53
>300	<b>1.72</b>	<b>1.45</b>	<b>2.03</b>	<b>1.69</b>	<b>1.44</b>	<b>1.99</b>	<b>1.39</b>	<b>1.20</b>	<b>1.61</b>	<b>1.48</b>	<b>1.17</b>	<b>1.88</b>
Caffeine from black tea												
0-50	1.00			1.00			1.00			1.00		
50-200	<b>1.11</b>	<b>1.01</b>	<b>1.21</b>	1.07	0.98	1.18	1.05	0.97	1.14	<b>1.20</b>	<b>1.04</b>	<b>1.38</b>
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	<b>1.20</b>	<b>1.08</b>	<b>1.33</b>	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

<sup>a</sup> 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.

<sup>b</sup> 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	Caffeine intake <199mg	Caffeine intake 200-299mg
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Excess infant growth	1.00	1.07 (1.01,1.13)	1.25 (1.12,1.39)
<b>Overweight</b>			
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)

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

<sup>b</sup> 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

Maternal daily caffeine intake	Risk of overweight and/or obesity at pre-school and school age <sup>a</sup>					
	Pre-school age (n=31,482)			School age (n=19,722)		
	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	<b>1.21</b>	<b>1.07,1.39</b>	1,386/14	1.13	0.95,1.35
Very high (≥300 mg)	918/20	<b>1.52</b>	<b>1.27,1.81</b>	664/18	<b>1.32</b>	<b>1.04,1.66</b>

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

<sup>a</sup> 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)
<b>Height (in cm)</b>							
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 ( $\geq 300$ 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)
<b>Height gain velocity (in mm/month)</b>							
Average (50-199 mg)	<b>0.05</b> <b>(0.02,0.09)</b>	-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)	<b>0.08</b> <b>(0.01,0.14)</b>	-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 ( $\geq 300$ mg)	<b>0.11</b> <b>(0.01,0.21)</b>	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 1 month 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
<b>Title and abstract</b>	1	<p>(a) Indicate the study's design with a commonly used term in the title or the abstract  <i>This has been done in both subsections. The study is a prospective cohort study.</i></p> <p>(b) Provide in the abstract an informative and balanced summary of what was done and what was found  <i>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).</i></p>
<b>Introduction</b>		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported  <i>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).</i></p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses  <i>This has been done in the last paragraph of the introduction (page 4, first paragraph).</i></p>
<b>Methods</b>		
Study design	4	<p>Present key elements of study design early in the paper  <i>Our study design was described in the first paragraph of the methods, subsection "Study population and ethical approval" (page 4).</i></p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  <i>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).</i></p>
Participants	6	<p>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  <i>The eligibility and inclusion criteria has been described the methods section subsection "Study population and ethical approval" (page 4).</i></p> <p>(b) For matched studies, give matching criteria and number of exposed and unexposed  <i>This is not a matched study.</i></p>
Variables	7	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.  <i>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).</i></p>
Data sources/ measurement	8*	<p>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  <i>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.</i></p>

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).
<b>Results</b>		
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 <a href="#">This has been provided in the results section and in Tables 1, 2, 3).</a>
		(b) Report category boundaries when continuous variables were categorized <a href="#">This has been done in the results section (pages 7-9) and in Figures and Tables.</a>
		(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 <a href="#">This was reported in the results section, subsection “sensitivity analyses” (page 9).</a>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives <a href="#">In the first paragraph of the discussion, we have summarized our key finding (pages 9-10).</a>
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. <a href="#">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).</a>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. <a href="#">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).</a>
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.
<b>Other information</b>		
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. <a href="#">Funding has been described in a specific point (page 14).</a>

\*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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018895.R2
Article Type:	Research
Date Submitted by the Author:	09-Jan-2018
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
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Nutrition and metabolism, Paediatrics, Public health
Keywords:	EPIDEMIOLOGY, NUTRITION & DIETETICS, PREVENTIVE MEDICINE, PUBLIC HEALTH, SOCIAL MEDICINE

SCHOLARONE™  
Manuscripts

1  
2  
3 1 **TITLE PAGE**

4 2 **Title: Maternal caffeine intake during pregnancy is associated with excess growth in**  
5 3 **infancy and overweight in childhood: results from a large prospective cohort study**

6 4 Eleni Papadopoulou, Post-doctoral research fellow <sup>a</sup>; Jérémie Botton, Associate Professor <sup>b,c</sup>;  
7 5 Anne-Lise Brantsæter, Senior researcher <sup>a</sup> ; Margaretha Haugen, Senior researcher <sup>a</sup>; Jan  
8 6 Alexander, Senior researcher <sup>d</sup>; Helle Margrete Meltzer, Senior researcher <sup>d</sup>, Jonas Bacelis, PhD  
9 7 Candidate <sup>e</sup>; Anders Elfvin, Physician <sup>f</sup>; Bo Jacobsson, Professor/ Chief physician <sup>e,g</sup>; Verena  
10 8 Sengpiel, Associate Professor/Physician <sup>h</sup>

11 9  
12 10 <sup>a</sup> Department of Environmental Exposure and Epidemiology, Division of Infection Control and  
13 11 Environmental Health, Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo,  
14 12 Norway

15 13 <sup>b</sup> Early Determinants of the Child's Health and Development Team (ORCHAD), INSERM,  
16 14 UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Paris, F-75014  
17 15 France

18 16 <sup>c</sup> Univ. Paris-Sud, Université Paris-Saclay, F-92296, Châtenay-Malabry, France

19 17 <sup>d</sup> Division of Infection Control and Environmental Health, Norwegian Institute of Public Health,  
20 18 PO Box 4404, N-0403, Oslo, Norway

21 19 <sup>e</sup> Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg,  
22 20 Östra, SE 416 85, Gothenburg, Sweden

23 21 <sup>f</sup> Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of  
24 22 Gothenburg, Östra, SE 416 85, Gothenburg, Sweden

25 23 <sup>g</sup> Department of Genetics and Bioinformatics, Division of Health Data and Digitalization,  
26 24 Norwegian Institute of Public Health, PO Box 4404, N-0403, Oslo, Norway

27 25 <sup>h</sup> Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Östra, SE-416 85  
28 26 Gothenburg, Sweden

29 27 **Corresponding author:**

30 28 Eleni Papadopoulou  
31 29 Division of Infection Control and Environmental Health  
32 30 Norwegian Institute of Public Health  
33 31 P.O. Box 4404, Nydalen, NO-0403 Oslo, Norway  
34 32 Phone number: +47 21076511  
35 33 Fax number: +47 21076686  
36 34 E-mail: [eleni.papadopoulou@fhi.no](mailto:eleni.papadopoulou@fhi.no)

1  
2  
3 35 **ABSTRACT**

4  
5 36 **Objectives:** To study the association between maternal caffeine intake during pregnancy and the  
6  
7 37 child's weight gain and overweight risk up to 8 years.

8  
9 38 **Design:** Prospective nationwide pregnancy cohort.

10  
11 39 **Setting:** The Norwegian Mother and Child Cohort Study.

12  
13 40 **Participants:** 50,943 mothers recruited from 2002 to 2008 and their children, after singleton  
14  
15 41 pregnancies, with information about average caffeine intake assessed at mid-pregnancy.

16  
17 42 **Outcome measure:** Child's body size information at 11 age-points from 6 weeks to 8 years. We  
18  
19 43 defined excess growth in infancy as a WHO weight gain z-score of  $>0.67$  from birth to age 1  
20  
21 44 year, and overweight according to the International Obesity Task Force. We used a growth model  
22  
23 45 to assess individual growth trajectories.

24  
25 46 **Results:** Compared to pregnant women with low caffeine intake ( $<50\text{mg/day}$ , 46%), women  
26  
27 47 with average ( $50\text{-}199\text{mg/day}$ , 44%), high ( $\geq 200\text{-}299\text{mg/day}$ , 7%) and very high ( $\geq 300\text{mg/day}$ ,  
28  
29 48 3%) caffeine intakes had an increased risk of their child experiencing excess growth in infancy,  
30  
31 49 after adjustment for confounders (odds ratio (OR)=1.15, 95% Confidence Intervals (CI) 1.09-  
32  
33 50 1.22), OR=1.30, 95%CI, 1.16-1.45, OR=1.66, 95%CI, 1.42-1.93, respectively). In-utero exposure  
34  
35 51 to any caffeine was associated with higher risk of overweight at age 3 and 5 years, while, the  
36  
37 52 association persisted at 8 years, only for very high exposures. Any caffeine intake was associated  
38  
39 53 with increased body mass index from infancy to childhood. Children prenatally exposed to  
40  
41 54 caffeine intake  $>200\text{mg/day}$  had consistently higher weight. Very high caffeine exposures were  
42  
43 55 associated with higher weight gain velocity from infancy to age 8 years.

44  
45 56 **Conclusion:** Any caffeine consumption during pregnancy is associated with excess infant growth  
46  
47 57 and increased risk of overweight, mainly at pre-school ages. Maternal caffeine intake may modify  
48  
49 58 overall weight growth trajectory from birth to 8 years. This study adds supporting evidence for  
50  
51 59 the current advice to reduce caffeine intake during pregnancy.

1  
2  
3 60 **Strengths and limitations of this study**  
4

- 5 61 • A strength of this study is the large sample size.  
6  
7 62 • Maternal caffeine intake was estimated from all possible food sources.  
8  
9 63 • This is the first study investigating the association between maternal caffeine intake and  
10 64 excess infant growth and growth velocity.  
11  
12 65 • Missing data from body size measurements were handled with a growth model.  
13  
14 66 • Limitations include self-reported dietary data and parental-reported measurements of  
15 67 height and weight after 2 years.  
16  
17 68

## 69 MANUSCRIPT

### 70 Introduction

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

84 Fetal growth and growth in infancy are important determinants for the development of obesity  
85 and for long-term cardiometabolic health<sup>7-9</sup>. Excess infant growth programs later obesity, fat  
86 mass, and risk of adult disease, independent of intrauterine growth<sup>10-15</sup>. The prevalence of  
87 metabolic disorders, including obesity, cardiovascular disease and type 2 diabetes is rapidly  
88 growing across the globe, with the number of obese people risen worldwide from 105 million in  
89 1975 to 641 million in 2014<sup>16</sup>. This trend indicates that the probability of reaching the WHO  
90 global obesity target, of no rise in obesity by 2025, is close to zero<sup>16</sup>. There is compelling human  
91 and animal evidence supporting the "fetal programming" hypothesis, according to which in utero  
92 exposures permanently alter an organism's physiology and metabolism, leading to susceptibility  
93 to subsequent disease, including obesity and metabolic disorders, with transgenerational effects<sup>17</sup>  
94<sup>18</sup>.

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

1  
2  
3 100 Based on our previous findings on the association of prenatal caffeine exposure with fetal  
4 101 growth restriction<sup>5</sup> and the fetal programming hypothesis<sup>23</sup>, we hypothesized that prenatal  
5 102 caffeine exposure might affect postnatal growth. Thus, the objective of this study was to  
6 103 investigate the associations between maternal caffeine intake in pregnancy and child growth and  
7 104 risk of overweight up to age 8 years in a large prospective population-based cohort.  
8  
9  
10  
11  
12

105

## 106 **Methods**

### 107 **Study population and ethical approval**

108 Our study was conducted within the Norwegian Mother and Child Cohort Study (MoBa), a  
109 prospective population-based pregnancy cohort study conducted by the Norwegian Institute of  
110 Public Health<sup>24</sup>. Pregnant women from all over Norway were recruited during 1999-2008 and  
111 40.6% of the invited women consented to participate. The cohort now includes 114,500 children,  
112 95,200 mothers and 75,200 fathers. Follow-up of the participants, after delivery, have been  
113 conducted at 6, 18, 36 months, 5, 7 and 8 years. Data used in this study are based on version 8 of  
114 the quality-assured data files, released for research in February 2014, with linkage to the Medical  
115 Birth Registry of Norway (MBRN). The data collection in MoBa was licensed by the Norwegian  
116 Data Inspectorate and approved by the Regional Committee for Medical Research Ethics. This  
117 study was approved by the Regional Committee for Medical Research Ethics in Southeastern  
118 Norway (2010/2683/REK Sør-øst A). All MoBA participants have provided a signed consent  
119 form.

120 After exclusion of multiple gestations, stillbirths, malformations and chromosomal  
121 abnormalities, 96,875 live-born singletons remained. Of these, 78,819 pregnant women had  
122 answered the food frequency questionnaire developed and validated for MoBa and in use from  
123 2002 and onwards. The eligible study population, with available information on maternal caffeine  
124 intake and all relevant covariates, constituted 62,034 mother-child pairs. Our final study  
125 population consisted of 50,943 mother-child pairs with additional information on small for  
126 gestational age (SGA) and at least one postnatal measurement of weight or length/height. The  
127 cohort retention is presented in Supplementary Table 1. After 5 years, approximately 40% of the  
128 study population returned the questionnaire and had information on weight and height, while the  
129 distribution of mothers by caffeine intake level did not differ by follow-up age, meaning that loss  
130 to follow-up was not related to maternal caffeine intake in pregnancy.

### 131 **Maternal caffeine intake during pregnancy**

132 Maternal caffeine intake estimation in MoBa has been described in detail previously by  
133 Sengpiel et al<sup>5</sup>. In brief, self-reported intake of 255 dietary items was assessed at pregnancy week  
134 22 with a food frequency questionnaire (FFQ) developed and validated for MoBa<sup>25</sup>. This is a  
135 semi-quantitative FFQ designed to record dietary habits during the first four to five months of  
136 gestation. Average, daily caffeine intake was calculated as the aggregated intake (in mg/day)  
137 from all available sources, including several types of coffee, black tea, caffeinated soft drinks,  
138 energy drinks, chocolate, chocolate milk, and sandwich spread, desserts, cakes and sweets  
139 containing cocoa. Supplementary Table 2 includes more details on the estimation of maternal  
140 caffeine intake. The median (25<sup>th</sup> -75<sup>th</sup> percentiles) caffeine intake was 57mg/day (23-  
141 120mg/day) for the included population and 64mg/day (25-129mg/day) for the non-included  
142 population with available caffeine information (n=11,091 mothers) (p<0.001 for Mann-Whitney  
143 test). We categorized caffeine intake, based on the calculated median as well as national and  
144 international recommendations for caffeine consumption during pregnancy, in four levels of  
145 caffeine intake: low (0-49mg/day), average (50-199mg/day), high (200-299mg/day) or very high  
146 ( $\geq 300$ mg/day).

### 148 **Child postnatal growth and overweight**

#### 149 *Anthropometric data*

150 Weight and height/length measurements at eleven age-points (6 weeks, 3, 6 and 8 months and 1,  
151 1.5, 2, 3, 5, 7 and 8 years) were reported. Up to 18 months the reported measurements were as  
152 documented in the child's health card, while for measurements from 2 to 8 years no specification  
153 was provided. Implausible anthropometrics were identified and excluded by separately  
154 implementing three different methods: i) by comparing with the WHO Growth Standards, as a  
155 weight-for-age or height-for-age z-score <6SD below or >6SD (5SD for weight) above the mean  
156 <sup>26</sup>, ii) by identifying measured values with a >|5SD| difference from the predicted value as  
157 derived from the Jemss-Bayley growth curve model, and iii) by the conditional growth  
158 percentiles<sup>27</sup>. After exclusion of implausible values, 464,343 and 452,980 measurements of  
159 weight and height/length were reported for our study population. Seven repeated measurements  
160 per child were available on average, for both anthropometrics. More details on anthropometric  
161 measurements are presented in Supplementary Table 1.



## 162 **Outcomes**

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

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

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

182 As including birth weight in the model may influence the estimated trajectories, and in order to  
183 assess the effect of caffeine on early growth independently of its effect on birth size<sup>5</sup>, we did not  
184 include birth weight and length in the growth models.

185

## 186 **Statistical analysis**

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

1  
2  
3 193 study population. The associations were described graphically. Finally, we used mixed-effect  
4  
5 194 linear regression models with random intercept by child and a random slope for age to analyze  
6  
7 195 associations between predicted weight, height/length, BMI, weight and height gain velocities  
8  
9 196 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  
10  
11 197 and 8 years). Covariates' effects have been models as fixed in the mixed-effect models. All  
12  
13 198 regression models were adjusted for random effects of sibling clusters since some mothers  
14  
15 199 participated with more than one pregnancy.

16 200 Logistic and linear mixed models were adjusted for variables related to both maternal caffeine  
17  
18 201 intake and excess growth by bivariate analysis: maternal age, maternal education, parity, pre-  
19  
20 202 pregnancy BMI, paternal BMI, maternal and paternal smoking during pregnancy, maternal  
21  
22 203 energy intake and nausea/vomiting during pregnancy. Gestational age and child's gender were  
23  
24 204 also included in the models as a-priori covariates (Supplementary Table 4). Maternal height,  
25  
26 205 paternal weight, paternal alcohol consumption and gestational diabetes (yes/no) were also  
27  
28 206 considered but not included in the final models as they did not met the criteria. Our main analysis  
29  
30 207 consists of complete case analysis of 38,338 mother-child pairs for the risk of excess growth and  
31  
32 208 of 50,943 mother-child pairs for all other growth outcomes. The cohort attrition due to loss to  
33  
34 209 follow-up was addressed by the use of predicted anthropometric measurements. The correlation  
35  
36 210 between measured and predicted anthropometrics ranged from 0.85 to 0.99 for weight and from  
37  
38 211 0.95 to 0.98 for length/height (data not shown).

39 212 In separate sensitivity analyses, i) we excluded SGA neonates (SGA was defined as birth weight  
40  
41 213 below the 10<sup>th</sup> percentile, according to population curves as described by Skjaerven et al<sup>35</sup>), ii)  
42  
43 214 excluded smokers during pregnancy, iii) we adjusted for birth weight; only the overweight  
44  
45 215 models and not the excess growth model, because birth weight is included in the excess growth  
46  
47 216 calculation formula iv) explored caffeine intake by 3 main sources (i.e. from black coffee, black  
48  
49 217 tea and soda drinks), v) excluded very high caffeine consumers, and vi) we assessed the  
50  
51 218 association between maternal caffeine intake and childhood overweight, using the measured  
52  
53 219 instead of predicted anthropometric data to define the outcome. Possible interactions with SGA  
54  
55 220 and birth weight were tested with all studied outcomes. Since the associations between the  
56  
57 221 outcomes and the interaction terms were not significant and the inclusion of the interaction term  
58  
59 222 did not modified our results, we have not included these analyses in the manuscript.

1  
2  
3 223 Finally, we performed negative control analysis, using paternal caffeine intake as the negative  
4  
5 224 control. Negative control analysis is a suggested method to test for the possibility of unmeasured  
6  
7 225 confounding. We have assumed that there is no direct association between the father's exposure  
8  
9 226 during the pregnancy period and the child's outcome, and that the shared confounders are equally  
10  
11 227 associated with the mother and the father's exposures<sup>36 37</sup>. We have calculated the caffeine intake  
12  
13 228 of the father using the caffeine concentrations and serving sizes as used for the mother's  
14  
15 229 calculations (Supplementary Table 2) for 5 food items: filtered coffee, boiled coffee, espresso  
16  
17 230 coffee, caffeinated soft-drink with sugar or artificially sweetened. Only 16,455 (32%) fathers had  
18  
19 231 available information.

20  
21 232 The main analyses were performed with the Stata 14 statistical software (Stata Corporation,  
22  
23 233 College Station, Texas) and R version 3.2.2<sup>38</sup> was used for the growth models.

### 23 234 **Patient involvement**

24  
25 235 No patients were involved in setting the research question or the outcome measures, nor were  
26  
27 236 they involved in developing plans for design or implementation of the study. No patients were  
28  
29 237 asked to advise on interpretation or writing up of results. There are no plans to disseminate the  
30  
31 238 results of the research to study participants or the relevant patient community.

## 31 239 32 33 240 **Results**

### 34 35 241 *Lifestyle and socio-demographic characteristics related to maternal caffeine intake during* 36 37 242 *pregnancy*

38  
39 243 In our study population, 7.13% (n=3,633) and 3.21% (n=1,634) of women reported caffeine  
40  
41 244 intake higher than 200mg/day and 300mg/day, respectively. The distribution of women not  
42  
43 245 included in the analysis, by caffeine intake level was similar to the included (low: 43%, average:  
44  
45 246 46%, high: 8% and very high: 3%). The higher the caffeine intake, the higher the likelihood of a  
46  
47 247 mother being older than 30 years, being multiparous, having a daily energy intake in the upper  
48  
49 248 tertile, being a smoker during pregnancy and not suffering nausea and/or vomiting during  
50  
51 249 pregnancy. Moreover, women with very high caffeine intake were more likely to have low  
52  
53 250 education, have been obese before pregnancy and have partners who were obese and smokers,  
54  
55 251 compared to those consuming less caffeine per day (Supplementary Table 4).

56  
57 252 Paternal median (5<sup>th</sup> -95<sup>th</sup> percentiles) intake was 193mg/day (0-493mg/day), with caffeine from  
58  
59 253 coffee being the main contributor (median: 187 mg/day). Fathers were consuming statistical

1  
2  
3 254 significantly more caffeine than their partners ( $p < 0.001$  for Wilcoxon matched-pairs signed-ranks  
4 test). The spearman correlation coefficient between maternal and paternal caffeine intakes was  
5 255 0.15 ( $p$ -value  $< 0.0001$ ). However, paternal intake was increasing by increasing levels of maternal  
6 256 intake and 45% of mothers with very high intake were with partners in the highest quartile of  
7 257 caffeine intake (Supplementary Table 4).  
8  
9 258

### 11 259 ***Prenatal caffeine exposure and excess growth in infancy***

12 260 The prevalence of excess growth in infancy increased from 23% to 29% as prenatal caffeine  
13 261 intake increased from low to very high (Figure 1). After adjustment for confounders, children  
14 262 born to average, high and very high caffeine consumers had 1.15 (95%CI: 1.09, 1.22), 1.30  
15 263 (95%CI: 1.16, 1.45) and 1.66 (95%CI: 1.42, 1.93) higher odds of excess growth in infancy,  
16 264 compared with children born to low consumers (Table 1). Neither exclusion of mothers who  
17 265 smoked during pregnancy or SGA neonates modified the results. The positive association  
18 266 between caffeine intake as a continuous variable and the risk of excess growth in infancy was  
19 267 linear with no apparent threshold (Supplementary Figure 1).  
20  
21 268

### 22 269 ***Prenatal caffeine exposure and overweight in childhood***

23 270 The prevalence of overweight increased by 5% at age 3 years, by 6% at age 5 years and by 3%  
24 271 at age 8 years with increasing prenatal caffeine exposure from low to very high (Figure 1).  
25 272 Children born to average, high and very high caffeine consumers had 1.05 (95%CI: 0.99, 1.12),  
26 273 1.17 (95%CI: 1.05, 1.30) and 1.44 (95%CI: 1.24, 1.67) higher adjusted odds, respectively, for  
27 274 overweight at age 3 years, compared with children born to low caffeine consumers (Table 2).  
28 275 Similar odds ratios (OR) were found at age 5 years, but at age 8 years the respective risk was  
29 276 significant only for the highest caffeine consumption category (adjusted OR (aOR) 1.29; 95%CI  
30 277 1.04, 1.61). Neither exclusion of mothers who smoked during pregnancy or SGA neonates  
31 278 modified the results. However, adjustment for birth weight slightly increased the odds  
32 279 (Supplementary Table 5). We found a linear association between maternal caffeine consumption  
33 280 as a continuous variable and the risk of overweight at ages 3 and 5 years with, again, higher OR  
34 281 at age 3 years than at age 5 years (Supplementary Figure 2). As there was a high degree of  
35 282 concordance between overweight and/or obesity at ages 5 and 8 years, the plot at age 8 years  
36 283 overlapped with the one at age 5 years and was not included in Supplementary Figure 2.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52

### 53 284 ***Sensitivity analyses***

1  
2  
3 284 In sensitivity analyses, we found similar results concerning the association of caffeine from  
4 285 different caffeine sources (black coffee, black tea, and soda drinks) with infant growth and  
5 286 overweight risk (Supplementary Table 6). When excluding very high caffeine consumers and  
6 287 using no coffee drinkers as the reference group, caffeine intake less than 300mg/day was still  
7 288 significantly associated with increased risk for excess infant growth and overweight  
8 289 (Supplementary Table 7). Finally, when growth data from actual measurements were used to  
9 290 assess the relationship between maternal caffeine intake and overweight at these age-points,  
10 291 similar trends and associations were observed (Supplementary Table 8).

### 17 292 ***Prenatal caffeine exposure and growth up to 8 years***

18 293 In comparison with low exposure, both high and very high prenatal caffeine exposure were  
19 294 positively associated with a child's weight, weight gain velocity and BMI from the first month  
20 295 onwards (Figure 2). More specifically, children prenatally exposed to very high caffeine levels  
21 296 weighed 67-83g more in infancy (age 3 to 12 months), 110-136g more in toddlerhood (age 12  
22 297 months to 3 years), 213-320g more at pre-school age (age 3 to 5 years) and 480g more at age 8  
23 298 years, than children exposed to low caffeine levels (Table 3). Maternal caffeine intake during  
24 299 pregnancy, at any level above 50mg/day, was associated with higher BMI from ages 1 month to 8  
25 300 years. Additional adjustment for birth weight provided better models (p-value<0.05 for likelihood  
26 301 ratio test between models with and without birth weight) and the estimates from these models are  
27 302 presented in Table 3. Whereas maternal caffeine intake during pregnancy was not associated with  
28 303 child height, it was related to higher height gain velocity up to age 3 months (Supplementary  
29 304 Table 9).

### 39 305 ***Negative control analysis: Paternal caffeine intake***

40 306 We have explored the association between maternal and paternal caffeine intake without and with  
41 307 adjustment for paternal caffeine intake and the same for paternal intake. All models are adjusted  
42 308 for the same confounders as in the main analysis. We have explored the associations with excess  
43 309 infant growth (n=12,289) and overweight at 3 years (n=16,455) (Supplementary Figures 3 & 4).  
44 310 For both the risk of excess infant growth and overweight at 3 years, the association with maternal  
45 311 caffeine intake changed negligibly after adjusting for paternal intake. On the other hand, by using  
46 312 paternal caffeine intake as a negative control, the trend of the association with child's growth was  
47 313 similar to that of maternal caffeine intake, while the effect estimate was much lower.

1  
2  
3 3144  
5 315 **Discussion**

6 316 We found that any maternal caffeine intake during pregnancy was associated with a higher risk  
7 317 of excess growth in infancy and overweight in early childhood. In addition, caffeine intakes in  
8 318 pregnancy above the recommendation (200mg/day) were associated with modified growth  
9 319 trajectories from very early in life and maintained during childhood. More specifically, children  
10 320 exposed prenatally to caffeine levels above 200mg/day had persistently higher weight-, BMI- and  
11 321 weight gain velocity up to 8 years of age.

12 322 ***Strengths and limitations of this study***

13 323 With the included 50,943 pregnancies, this is, so far, the largest study on the association of  
14 324 prenatal caffeine exposure and childhood growth parameters. It is the first to investigate effects  
15 325 on excess growth in infancy as well as growth velocities rather than just the size of the child, as  
16 326 well as critical age windows of diverging growth. Additional strengths include the prospective  
17 327 data collection, the comprehensive data on possible confounders and the assessment of caffeine  
18 328 intake from different sources. Nevertheless, our findings might be explained by residual  
19 329 confounding of non-accounted factors related to an overall unhealthy lifestyle and high caffeine  
20 330 consumption; though exclusion of smokers and very high caffeine consumers did not modify the  
21 331 results. In an effort to control for the effect of unmeasured familial characteristics, we performed  
22 332 negative control analysis using the father's caffeine intake. The unchanged effect estimate of  
23 333 maternal caffeine intake after adjustment for paternal intake as well as the weak effect estimate of  
24 334 paternal caffeine intake, indicate minor bias by shared unmeasured confounders.

25 335 In addition, the missing body size measurements were handled with the use of a growth model.  
26 336 In sensitivity analyses restricted to the measured data, similar associations were found as with the  
27 337 predicted body size data (Supplementary Table 8). This provides some reassurance of the validity  
28 338 of the predicted anthropometrics. However, we still acknowledge the potential for outcome  
29 339 misclassification as only 23% of the cohort had anthropometric information at 8 years  
30 340 (Supplementary Table 1). At the time of release of the current data, 53% (27,142 children) of our  
31 341 study population had not reached the age of 8 years, and only 24% of missing anthropometric  
32 342 information at 8 years can be attributed to loss to follow-up. Furthermore, we found that maternal  
33 343 caffeine exposure was not related to loss to follow-up (Supplementary Table 1).

1  
2  
3 344 The self-report of diet, which can induce misreporting, is a limitation. However, fair agreement  
4  
5 345 between beverage intakes, particularly of coffee and tea, was found in a validation study based on  
6  
7 346 food records and biomarkers<sup>25 39</sup>. Observational studies can never establish causality; however,  
8  
9 347 our results fulfill some of the Bradford-Hill's criteria for causation<sup>40</sup> with a strong association,  
10  
11 348 consistent findings for major caffeine sources, a biological gradient with higher caffeine exposure  
12  
13 349 being associated to abnormal growth, consistent findings in animal models and a plausible  
14  
15 350 mechanism, i.e. fetal programming.

15 351 Our study adds evidence to two previous epidemiological studies<sup>19 20</sup> that found an effect of  
16  
17 352 prenatal caffeine exposure on child growth. In the study by Voerman et al., maternal caffeine  
18  
19 353 intake above 360mg/day was associated with higher weight and BMI from birth to age 6 years,  
20  
21 354 compared with intakes below 180mg/day<sup>19</sup>. In contrast to our findings, they found no association  
22  
23 355 with overweight. Higher caffeine intake (360-540mg/day) during pregnancy was positively  
24  
25 356 associated with body fat percentage and higher insulin levels in 6-year-olds. The exposure was  
26  
27 357 assessed only by intakes of coffee and tea, which in our study also are the main but not the only  
28  
29 358 caffeine contributors (78% of total caffeine intake). The median intake was double than in our  
30  
31 359 study, resulting to a higher reference level (reference: <180mg/day, median: 117mg/day),  
32  
33 360 providing less contrast between the compared exposure groups and less comparability to our  
34  
35 361 study, as most of these women were not complying to the recommendation. Nevertheless, we  
36  
37 362 found associations with adverse effects on child's growth even at low caffeine intakes, in the  
38  
39 363 range of the recommendation, that are mostly due to consumption of foods and drinks other than  
40  
41 364 coffee (chocolate, black tea, caffeinated sodas)<sup>5</sup>. Li et al. found likewise that any maternal  
42  
43 365 caffeine intake was associated with an overall increased risk of obesity from ages 2 to 15 years,  
44  
45 366 with an exposure range similar to the current study<sup>20</sup>. We have used similar approaches to study  
46  
47 367 changes in individual growth trajectories, though with shorter follow-up. In addition, we  
48  
49 368 provided age specific weight and BMI deviations, in order to find sensitive developmental  
50  
51 369 windows when the association with the prenatal caffeine exposure exacerbated. There is no  
52  
53 370 previous report of the association between caffeine intake in pregnancy and excess infant growth.

### 50 371 ***Potential mechanisms***

51 372 Since excess growth in infancy, in itself, can be directly related to childhood obesity, adiposity<sup>41</sup>  
52  
53 373 and an unfavorable adult cardio-metabolic profile<sup>42</sup>, the associations between prenatal caffeine  
54  
55 374 exposure with overweight, body fat and insulin, found in this study and the previous reports,

1  
2  
3 375 might be explained by excess infant growth. Putting together the previous findings in the MoBa  
4 study<sup>5</sup>, we have shown that children prenatally exposed to high caffeine levels are smaller at  
5 376 birth, grow faster in infancy and retain a higher weight throughout childhood without significant  
6 377 height differences, thus becoming overweight (Supplementary Figure 5). These findings concur  
7 378 with the fetal programming of obesity hypothesis<sup>43</sup>. Nevertheless, the effect of prenatal caffeine  
8 379 exposure on postnatal growth and overweight was not dependent on birth weight. Hence, along  
9 380 with a healthy birth weight, it is important to identify the modifiable factors that can  
10 381 independently affect excess growth in infancy, independent of fetal growth. A growing number of  
11 382 studies have shown that other prenatal factors, e.g. excess gestational weight<sup>44</sup>, high  
12 383 (>3times/week) fish intake<sup>45</sup>, and postnatal factors, e.g. formula feeding and feeding schedule<sup>46</sup>,  
13 384 are associated with increased risk of excess growth in infancy. Recent research shows that some  
14 385 perinatal factors can also have a direct effect on postnatal growth, independent of effects on fetal  
15 386 growth, including parental body size, smoking during pregnancy and socioeconomic status<sup>47-49</sup>.

16 387  
17 388 The biological plausibility supporting our findings is mainly provided by animal studies where,  
18 389 prenatal exposure to caffeine was shown to program the offspring towards excess growth and  
19 390 cardio-metabolic disorders through alterations i) in the hypothalamic-pituitary-adrenocortical axis  
20 391 that plays a key role in growth and metabolism<sup>50-52</sup>, ii) in regulation of adenosine and adenosine  
21 392 antagonists, which are important modulators of development<sup>53 54</sup> and iii) in the placental  
22 393 expression and transportation of leptin<sup>55</sup>, essential for appetite regulation.

23 394 Although most pregnant women reduce their caffeine intake during pregnancy and few have  
24 395 caffeine intakes higher than 200 mg/day (10%), our results show associations between caffeine  
25 396 intakes below 200 mg/day and excess growth. The results add supporting evidence for the current  
26 397 advice to reduce caffeine intake during pregnancy and indicate that complete avoidance might  
27 398 actually be advisable. An absence of a “safe intake level” has been previously reported in the  
28 399 basis of associations between maternal caffeine intake and fetal growth restriction<sup>56</sup>.  
29 400 Nevertheless, the authors of a recent systematic review after critically assessing the evidence,  
30 401 concluded that a consumption of up to 300 mg caffeine/day in healthy pregnant women is  
31 402 generally not associated with adverse reproductive and developmental effects<sup>57</sup>. Postnatal growth  
32 403 and child’s weight status were not included in this review. Our findings are in agreement with the  
33 404 previous studies assessing a similar hypothesis, with associations reported in caffeine intakes  
34 405 above, but even below, the comparator, indicating that an intake of 300mg/day might not be a



1  
2  
3 406 safe level when growth is under study. Given that overweight in childhood is not a rare condition  
4  
5 407 and the number of children highly exposed to caffeine during pregnancy is large, even a small  
6  
7 408 increase in the risk of overweight due to caffeine can result into a large proportion of children  
8  
9 409 becoming overweight, assuming that the effect was causal. Hence, more evidence is needed for  
10  
11 410 the association between prenatal caffeine exposure and postnatal growth and an updated future  
12  
13 411 critical assessment of such studies.

14 412 The association between prenatal caffeine exposure and overweight attenuated after 5 years,  
15  
16 413 with only very high exposed children being at risk for overweight. Residual confounding due to  
17  
18 414 postnatal factors related to overweight in late childhood might explain this attenuation.  
19  
20 415 Nevertheless, adjustment for risk factors of being overweight at 8 years would introduce bias to  
21  
22 416 the association under study. In addition, weight and height are screened from birth to 5 years in  
23  
24 417 scheduled voluntarily appointments at the public health centers. Hence, a possible  
25  
26 418 misclassification of outcome from anthropometrics after 5 years, might also explain the  
27  
28 419 attenuation of the association.

29 420 There are two studies showing effects of caffeine intake on body composition and  
30  
31 421 cardiometabolic health<sup>19 58</sup>, with discrepant results. In the present study, we did not have any  
32  
33 422 information on body composition. In addition, it is known that several genetic factors can  
34  
35 423 contribute to variation in caffeine metabolism<sup>59</sup>, and studies in adults have shown that slower  
36  
37 424 metabolism of caffeine is related to higher risk of cardiovascular disease<sup>60</sup>. On the other hand,  
38  
39 425 during pregnancy, maternal caffeine clearance modified the association between maternal  
40  
41 426 caffeine intake and fetal growth restriction, with faster clearance being more detrimental<sup>56</sup>. More  
42  
43 427 specifically, a genotype of rapid caffeine metabolism was associated with reduced birth weight  
44  
45 428 while in women with a different polymorphism on the gene CYP1A2 C164A no effect was found  
46  
47 429<sup>61</sup>. Thus, there is a need to investigate the programming effect of prenatal caffeine exposure on  
48  
49 430 child and adult body composition and cardiometabolic health, taking into account the genetic  
50  
51 431 variation of maternal caffeine metabolism.

52  
53  
54  
55 432  
56  
57  
58  
59  
60  
433 **Conclusions**  
434 We found that the risk of excess infant growth and overweight in childhood-important risk  
435 factors for later cardio-metabolic disease- is increasing with maternal caffeine intake, with no  
436 apparent threshold. Maternal caffeine intake >200mg/day during pregnancy was associated with

1  
2  
3 437 high weight gain velocity beginning from the first months of life and higher BMI throughout  
4 438 childhood. Our findings support the recommendation to limit caffeine intake during pregnancy  
5 439 (<200mg/day).  
6  
7  
8  
9

440

## 441 **Acknowledgements**

11 442 We are grateful to all the families in Norway who have participated in this ongoing cohort  
12 443 study.  
13  
14

444

## 445 **References**

- 18 446 1. EFSA EFSA-PoDP, Nutrition and Allergies (NDA). Scientific Opinion on the safety of caffeine. *EFSA*  
19 447 *Journal* 2015;13(5)
- 21 448 2. Mort JR, Kruse HR. Timing of blood pressure measurement related to caffeine consumption. *Ann*  
22 449 *Pharmacother* 2008;42(1):105-10. doi: 10.1345/aph.1K337
- 23 450 3. Tomimatsu T, Lee SJ, Pena JP, et al. Maternal caffeine administration and cerebral oxygenation in  
24 451 near-term fetal sheep. *Reprod Sci* 2007;14(6):588-94. doi: 10.1177/1933719107307717
- 25 452 4. VKM. Risk assessment of "other substances"— Caffeine. Opinion of the Panel on Food Additives,  
26 453 Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian  
27 454 Scientific Committee for Food Safety. Oslo, Norway, 2015.
- 29 455 5. Sengpiel V, Elind E, Bacelis J, et al. Maternal caffeine intake during pregnancy is associated with birth  
30 456 weight but not with gestational length: results from a large prospective observational cohort  
31 457 study. *BMC Med* 2013;11:42. doi: 10.1186/1741-7015-11-42
- 32 458 6. Rhee J, Kim R, Kim Y, et al. Maternal Caffeine Consumption during Pregnancy and Risk of Low Birth  
33 459 Weight: A Dose-Response Meta-Analysis of Observational Studies. *PloS one*  
34 460 2015;10(7):e0132334. doi: 10.1371/journal.pone.0132334
- 35 461 7. Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic review.  
36 462 *JAMA : the journal of the American Medical Association* 2008;300(24):2886-97. doi:  
37 463 10.1001/jama.2008.886 [published Online First: 2008/12/26]
- 39 464 8. Lawlor DA, Ronalds G, Clark H, et al. Birth weight is inversely associated with incident coronary heart  
40 465 disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of  
41 466 the 1950s prospective cohort study. *Circulation* 2005;112(10):1414-8. doi:  
42 467 10.1161/CIRCULATIONAHA.104.528356
- 43 468 9. Monasta L, Batty GD, Cattaneo A, et al. Early-life determinants of overweight and obesity: a review of  
44 469 systematic reviews. *Obesity reviews : an official journal of the International Association for the*  
45 470 *Study of Obesity* 2010;11(10):695-708. doi: 10.1111/j.1467-789X.2010.00735.x
- 46 471 10. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful  
47 472 suggestions. *Acta paediatrica* 2006;95(8):904-8. doi: 10.1080/08035250600719754
- 49 473 11. Baird J, Fisher D, Lucas P, et al. Being big or growing fast: systematic review of size and growth in  
50 474 infancy and later obesity. *BMJ* 2005;331(7522):929. doi: 10.1136/bmj.38586.411273.E0
- 51 475 12. Jones-Smith JC, Neufeld LM, Laraia B, et al. Early life growth trajectories and future risk for  
52 476 overweight. *Nutrition & diabetes* 2013;3:e60. doi: 10.1038/nutd.2012.32
- 53 477 13. Botton J, Heude B, Maccario J, et al. Postnatal weight and height growth velocities at different ages  
54 478 between birth and 5 y and body composition in adolescent boys and girls. *The American journal*  
55 479 *of clinical nutrition* 2008;87(6):1760-8.

- 1  
2  
3 480 14. Perng W, Hajj H, Belfort MB, et al. Birth Size, Early Life Weight Gain, and Midchildhood  
4 481 Cardiometabolic Health. *The Journal of pediatrics* 2016 doi: 10.1016/j.jpeds.2016.02.053  
5 482 15. Ekelund U, Ong KK, Linne Y, et al. Association of weight gain in infancy and early childhood with  
6 483 metabolic risk in young adults. *The Journal of clinical endocrinology and metabolism*  
7 484 2007;92(1):98-103. doi: 10.1210/jc.2006-1071  
8 485 16. Collaboration NCDRF, Di Cesare M, Bentham J, et al. Trends in adult body-mass index in 200 countries  
9 486 from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2  
10 487 million participants. *Lancet* 2016;387(10026):1377-96. doi: 10.1016/S0140-6736(16)30054-X  
11 488 17. Woo Baidal JA, Locks LM, Cheng ER, et al. Risk Factors for Childhood Obesity in the First 1,000 Days: A  
12 489 Systematic Review. *Am J Prev Med* 2016;50(6):761-79. doi: 10.1016/j.amepre.2015.11.012  
13 490 18. Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public  
14 491 health implications. *The American journal of clinical nutrition* 2011;94(6 Suppl):1754S-58S. doi:  
15 492 10.3945/ajcn.110.001206  
16 493 19. Voerman E, Jaddoe VW, Gishti O, et al. Maternal caffeine intake during pregnancy, early growth, and  
17 494 body fat distribution at school age. *Obesity* 2016;24(5):1170-7. doi: 10.1002/oby.21466  
18 495 20. Li DK, Ferber JR, Odouli R. Maternal caffeine intake during pregnancy and risk of obesity in offspring:  
19 496 a prospective cohort study. *International journal of obesity* 2015;39(4):658-64. doi:  
20 497 10.1038/ijo.2014.196  
21 498 21. Barker DJ, Bagby SP. Developmental antecedents of cardiovascular disease: a historical perspective.  
22 499 *Journal of the American Society of Nephrology : JASN* 2005;16(9):2537-44. doi:  
23 500 10.1681/ASN.2005020160  
24 501 22. Gluckman PD, Cutfield W, Hofman P, et al. The fetal, neonatal, and infant environments-the long-  
25 502 term consequences for disease risk. *Early Hum Dev* 2005;81(1):51-9. doi:  
26 503 10.1016/j.earlhumdev.2004.10.003  
27 504 23. Barker DJP. In utero programming of chronic disease. *Clinical Science* 1998;95:115-28.  
28 505 24. Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort  
29 506 Study (MoBa). *International journal of epidemiology* 2016 [published Online First: April 10, 2016]  
30 507 25. Brantsæter AL, Haugen M, Alexander J, et al. Validity of a new food frequency questionnaire for  
31 508 pregnant women in the Norwegian Mother and Child Cohort Study (MoBa). *Matern Child Nutr*  
32 509 2008;4(1):28-43. doi: MCN103 [pii];10.1111/j.1740-8709.2007.00103.x [doi]  
33 510 26. WHO MGRSG. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-  
34 511 length, weight-for-height and body mass index-for-age: Methods and development. Geneva:  
35 512 World Health Organization 2006.  
36 513 27. Yang S, Hutcheon JA. Identifying outliers and implausible values in growth trajectory data. *Annals of*  
37 514 *epidemiology* 2016;26(1):77-80 e1-2. doi: 10.1016/j.annepidem.2015.10.002  
38 515 28. Ong KK, Ahmed ML, Emmett PM, et al. Association between postnatal catch-up growth and obesity in  
39 516 childhood: prospective cohort study. *BMJ* 2000;320(7240):967-71. [published Online First:  
40 517 2001/02/07]  
41 518 29. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a  
42 519 systematic review. *Obesity reviews : an official journal of the International Association for the*  
43 520 *Study of Obesity* 2005;6(2):143-54. doi: 10.1111/j.1467-789X.2005.00183.x  
44 521 30. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight  
45 522 and obesity. *Pediatric obesity* 2012;7(4):284-94. doi: 10.1111/j.2047-6310.2012.00064.x  
46 523 31. Jenss RM, Bayley N. A mathematical method for studying the growth of a child. *Human Biology*  
47 524 1937;9:556-63.  
48 525 32. Berkey CS. Comparison of two longitudinal growth models for preschool children. *Biometrics*  
49 526 1982;38(1):221-34.

- 1  
2  
3 527 33. Comets E, Lavenu A, Lavielle M. saemix: Stochastic Approximation Expectation Maximization (SAEM)  
4 528 algorithm. 2014. <https://cran.r-project.org/web/packages/saemix/index.html>.
- 5 529 34. Harrell F. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression,  
6 530 and Survival Analysis. 1 ed. New York: Springer-Verlag New York 2001.
- 7 531 35. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta*  
8 532 *ObstetGynecolScand* 2000;79(6):440-49.
- 9 533 36. Richmond RC, Al-Amin A, Smith GD, et al. Approaches for drawing causal inferences from  
10 534 epidemiological birth cohorts: a review. *Early Hum Dev* 2014;90(11):769-80. doi:  
11 535 10.1016/j.earlhumdev.2014.08.023
- 12 536 37. Brew BK, Gong T, Williams DM, et al. Using fathers as a negative control exposure to test the  
13 537 Developmental Origins of Health and Disease Hypothesis: A case study on maternal distress and  
14 538 offspring asthma using Swedish register data. *Scandinavian journal of public health*  
15 539 2017;45(17\_suppl):36-40. doi: 10.1177/1403494817702324
- 16 540 38. R: A language and environment for statistical computing [program]. Vienna, Austria: R Foundation for  
17 541 Statistical Computing, 2016.
- 18 542 39. Brantsæter AL, Haugen M, Rasmussen SE, et al. Urine flavonoids and plasma carotenoids in the  
19 543 validation of fruit, vegetable and tea intake during pregnancy in the Norwegian Mother and Child  
20 544 Cohort Study (MoBa). *Public Health Nutr* 2007;10(8):838-47. doi: S1368980007339037  
21 545 [pii];10.1017/S1368980007339037 [doi]
- 22 546 40. HILL AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *ProcRSocMed*  
23 547 1965;58:295-300.
- 24 548 41. Karaolis-Danckert N, Buyken AE, Bolzenius K, et al. Rapid growth among term children whose birth  
25 549 weight was appropriate for gestational age has a longer lasting effect on body fat percentage  
26 550 than on body mass index. *The American journal of clinical nutrition* 2006;84(6):1449-55.
- 27 551 42. Leunissen RW, Kerkhof GF, Stijnen T, et al. Timing and tempo of first-year rapid growth in relation to  
28 552 cardiovascular and metabolic risk profile in early adulthood. *JAMA : the journal of the American*  
29 553 *Medical Association* 2009;301(21):2234-42. doi: 10.1001/jama.2009.761
- 30 554 43. Barker DJ. Fetal origins of coronary heart disease. *BMJ* 1995;311(6998):171-74.
- 31 555 44. Subhan FB, Colman I, McCargar L, et al. Higher Pre-pregnancy BMI and Excessive Gestational Weight  
32 556 Gain are Risk Factors for Rapid Weight Gain in Infants. *Maternal and child health journal* 2017  
33 557 doi: 10.1007/s10995-016-2246-z
- 34 558 45. Stratakis N, Roumeliotaki T, Oken E, et al. Fish Intake in Pregnancy and Child Growth: A Pooled  
35 559 Analysis of 15 European and US Birth Cohorts. *JAMA pediatrics* 2016;170(4):381-90. doi:  
36 560 10.1001/jamapediatrics.2015.4430
- 37 561 46. Mahrshahi S, Battistutta D, Magarey A, et al. Determinants of rapid weight gain during infancy:  
38 562 baseline results from the NOURISH randomised controlled trial. *BMC pediatrics* 2011;11:99. doi:  
39 563 10.1186/1471-2431-11-99 [published Online First: 2011/11/08]
- 40 564 47. Liu JX, Xu X, Liu JH, et al. Association of maternal gestational weight gain with their offspring's  
41 565 anthropometric outcomes at late infancy and 6 years old: mediating roles of birth weight and  
42 566 breastfeeding duration. *International journal of obesity* 2017 doi: 10.1038/ijo.2017.183
- 43 567 48. Hindmarsh PC, Geary MP, Rodeck CH, et al. Factors predicting ante- and postnatal growth. *Pediatric*  
44 568 *research* 2008;63(1):99-102. doi: 10.1203/PDR.0b013e31815b8e8f
- 45 569 49. Morgen CS, Angquist L, Baker JL, et al. Prenatal risk factors influencing childhood BMI and overweight  
46 570 independent of birth weight and infancy BMI: a path analysis within the Danish National Birth  
47 571 Cohort. *International journal of obesity* 2017 doi: 10.1038/ijo.2017.217
- 48 572 50. Xu D, Zhang B, Liang G, et al. Caffeine-induced activated glucocorticoid metabolism in the  
49 573 hippocampus causes hypothalamic-pituitary-adrenal axis inhibition in fetal rats. *PloS one*  
50 574 2012;7(9):e44497. doi: 10.1371/journal.pone.0044497 [published Online First: 2012/09/13]

- 1  
2  
3 575 51. Li J, Luo H, Wu Y, et al. Gender-specific increase in susceptibility to metabolic syndrome of offspring  
4 576 rats after prenatal caffeine exposure with post-weaning high-fat diet. *Toxicology and applied*  
5 577 *pharmacology* 2015;284(3):345-53. doi: 10.1016/j.taap.2015.03.002  
6 578  
7 579 52. Xu D, Wu Y, Liu F, et al. A hypothalamic-pituitary-adrenal axis-associated neuroendocrine metabolic  
8 580 programmed alteration in offspring rats of IUGR induced by prenatal caffeine ingestion.  
9 581 *Toxicology and applied pharmacology* 2012;264(3):395-403. doi: 10.1016/j.taap.2012.08.016  
10 582 [published Online First: 2012/09/11]  
11 583 53. Buscariollo DL, Fang X, Greenwood V, et al. Embryonic caffeine exposure acts via A1 adenosine  
12 584 receptors to alter adult cardiac function and DNA methylation in mice. *PLoS one*  
13 585 2014;9(1):e87547. doi: 10.1371/journal.pone.0087547  
14 586 54. Rivkees SA, Wendler CC. Adverse and protective influences of adenosine on the newborn and  
15 587 embryo: implications for preterm white matter injury and embryo protection. *Pediatric research*  
16 588 2011;69(4):271-8. doi: 10.1203/PDR.0b013e31820efbcf [published Online First: 2011/01/14]  
17 589 55. Wu YM, Luo HW, Kou H, et al. Prenatal caffeine exposure induced a lower level of fetal blood leptin  
18 590 mainly via placental mechanism. *Toxicology and applied pharmacology* 2015;289(1):109-16. doi:  
19 591 10.1016/j.taap.2015.09.007  
20 592 56. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective  
21 593 observational study. *BMJ* 2008;337:a2332. doi: 10.1136/bmj.a2332 [published Online First:  
22 594 2008/11/05]  
23 595 57. Wikoff D, Welsh BT, Henderson R, et al. Systematic review of the potential adverse effects of caffeine  
24 596 consumption in healthy adults, pregnant women, adolescents, and children. *Food and chemical*  
25 597 *toxicology : an international journal published for the British Industrial Biological Research*  
26 598 *Association* 2017;109(Pt 1):585-648. doi: 10.1016/j.fct.2017.04.002  
27 599 58. de Medeiros TS, Bernardi JR, de Brito ML, et al. Caffeine Intake During Pregnancy in Different  
30 600 Intrauterine Environments and its Association with Infant Anthropometric Measurements at 3  
31 601 and 6 Months of Age. *Maternal and child health journal* 2017;21(6):1297-307. doi:  
32 602 10.1007/s10995-016-2230-7  
33 603 59. Cornelis MC, Kacprowski T, Menni C, et al. Genome-wide association study of caffeine metabolites  
34 604 provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. *Hum*  
35 605 *Mol Genet* 2016;25(24):5472-82. doi: 10.1093/hmg/ddw334  
36 606 60. Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine.  
37 607 *Psychopharmacology* 2010;211(3):245-57. doi: 10.1007/s00213-010-1900-1  
38 608 61. Norwegian Mother and Child Study: Norwegian Institute of Public Health; [Available from:  
39 609 [http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea\\_5811&MainArea\\_5811=5895:0:15,3046:1:0:0:::0:02010](http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5895:0:15,3046:1:0:0:::0:02010).  
40  
41  
42

610

611

1  
2  
3 612 **Funding statement:** The Norwegian Mother and Child Cohort Study is supported by the  
4 613 Norwegian Ministry of Health and Care Services and Ministry of Education and Research,  
5 614 NIH/NIEHS (contract no N01-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537- 01 and  
6 615 grant no.2 UO1 NS 047537-06A1). Verena Sengpiel has received grants from Stiftelsen Sigurd  
7 616 och Elsa Goljes Minnesfond (LA2013-0241 “Koffeinintag, födelsevikt och barnutfall”),  
8 617 Stiftelsen Fru Mary von Sydows, född Wijk, donationsfond (2014 “Koffeinintag, födelsevikt och  
9 618 barnutfall”) and Wilhelm och Martina Lundgrens Vetenskapsfond (1 vet1-119/2014:  
10 619 “Koffeinintag, födelsevikt och barnutfall”). The funding bodies were not involved in the design,  
11 620 implementation of the study or interpretation of the results.  
12  
13  
14 621

15 622 **Competing interests statement:** *No competing interests.* All authors have completed the ICMJE  
16 623 uniform disclosure form at [www.icmje.org/doi\\_disclosure.pdf](http://www.icmje.org/doi_disclosure.pdf) and declare: no support from any  
17 624 organisation for the submitted work; no financial relationships with any organisations that might  
18 625 have an interest in the submitted work in the previous three years; no other relationships or  
19 626 activities that could appear to have influenced the submitted work.  
20  
21  
22 627

23 628 **Contributorship statement:** EP contributed to study design, data analysis, and interpretation of  
24 629 the results and had the main responsibility of writing the paper. JBO contributed to the statistical  
25 630 analysis plan and database preparation and interpretation of the results. ALB contributed to study  
26 631 design, interpretation of the results and revising the paper. MH, JA, HMM contributed to the  
27 632 design of data collection tools, the study design and interpretation of the results. JBA contributed  
28 633 to the statistical analysis plan and database preparation. AE contributed to interpretation of the  
29 634 results.

30 635 BJ initiated this collaborative project, contributed to the study design and the interpretation of the  
31 636 results. VS defined the research question, contributed to the study design, database preparation  
32 637 and interpretation of the results. She is guarantor and had final responsibility for the decision to  
33 638 submit for publication. All authors read, revised and approved the final version of the paper.  
34 639

35 640 **Data sharing statement:** No additional data are available. All data from the MoBa study are  
36 641 available to all qualified researchers/research groups in Norway and to international researchers  
37 642 who are collaborating with a Norwegian researcher.  
38  
39

#### 40 643 **Declaration of transparency**

41 644 EP as the lead author affirms that this manuscript is an honest, accurate, and transparent account  
42 645 of the study being reported; that no important aspects of the study have been omitted; and that  
43 646 any discrepancies from the study as planned (and, if relevant, registered) have been explained.  
44  
45  
46

#### 47 647 **Licence to BMJ Publishing Group Limited (“BMJ Group”) for Publication**

1  
2  
3 649 “I **Eleni Papadopoulou** The Corresponding Author of this article contained within the original  
4 650 manuscript which includes any diagrams & photographs within and any related or stand alone  
5 651 film submitted (the Contribution”) has the right to grant on behalf of all authors and does grant  
6 652 on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit  
7 653 this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products  
8 654 and to exploit all subsidiary rights, as set out in our licence set out at: [http://www.bmj.com/about-](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)  
9 655 [bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)  
10 656 [reuse.](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)”  
11 657

12 Please tick **one or more** boxes as appropriate:  
13

14 658 X I am one author signing on behalf of all co-owners of the Contribution.  
15  
16  
17 659

## 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) <sup>a</sup>					
	All children (n=38,338)		After excluding smokers during pregnancy (n=35,672)		After excluding SGA neonates <sup>b</sup> (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

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

<sup>b</sup> 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 <sup>a</sup>					
	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) <sup>b</sup>					
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

<sup>a</sup> Overweight and/or obesity in children, according to the International Obesity Task Force definition.

<sup>b</sup> 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.**

Maternal daily caffeine intake	Child's developmental period						
	Infancy		Toddlerhood		Pre-school age		School age
	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)
<b><i>Weight (in g)</i></b>							
Average (50-199 mg)	<b>14.1</b> <b>(1.6,26.6)</b>	<b>15.1</b> <b>(1.3,28.8)</b>	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)	<b>31.3</b> <b>(7.5,55.1)</b>	<b>35.0</b> <b>(8.8,61.1)</b>	<b>45.4</b> <b>(7.3,83.5)</b>	<b>59.0</b> <b>(13.1,104.8)</b>	<b>99.0</b> <b>(36.3,161.7)</b>	<b>148.9</b> <b>(68.4,229.4)</b>	<b>222.0</b> <b>(114.1,329.8)</b>
Very high (≥300 mg)	<b>67.0</b> <b>(32.5,101.6)</b>	<b>83.2</b> <b>(45.3,121.1)</b>	<b>110.1</b> <b>(55.2,165.0)</b>	<b>135.5</b> <b>(69.5,201.5)</b>	<b>213.4</b> <b>(123.3,303.6)</b>	<b>320.0</b> <b>(204.4,435.6)</b>	<b>480.3</b> <b>(325.5,635.1)</b>
<b><i>Weight gain velocity (in g/month)</i></b>							
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)	<b>2.1(0.4,3)</b>	<b>2.0(0.1,4.0)</b>	<b>2.2(0.4,0)</b>
Very high (≥300 mg)	<b>6.0(1.5,10.4)</b>	<b>4.3(0.2,8.5)</b>	<b>3.8(0.1,7.4)</b>	<b>3.7(0.3,7.1)</b>	<b>3.9(0.8,7.0)</b>	<b>3.9(1.1,6.8)</b>	<b>3.9(1.1,6.8)</b>
<b><i>BMI (in kg/m<sup>2</sup>)</i></b>							
Average (50-199 mg)	<b>0.03</b> <b>(0.01,0.05)</b>	<b>0.03</b> <b>(0.01,0.05)</b>	<b>0.04</b> <b>(0.02,0.06)</b>	<b>0.04</b> <b>(0.02,0.06)</b>	<b>0.04</b> <b>(0.02,0.06)</b>	<b>0.03</b> <b>(0.01,0.06)</b>	0.02 (-0.01,0.05)
High (200-299 mg)	<b>0.07</b> <b>(0.03,0.11)</b>	<b>0.07</b> <b>(0.03,0.10)</b>	<b>0.09</b> <b>(0.05,0.12)</b>	<b>0.11</b> <b>(0.07,0.15)</b>	<b>0.14</b> <b>(0.10,0.19)</b>	<b>0.15</b> <b>(0.11,0.20)</b>	<b>0.15</b> <b>(0.09,0.21)</b>
Very high (≥300 mg)	<b>0.16</b> <b>(0.10,0.21)</b>	<b>0.16</b> <b>(0.11,0.21)</b>	<b>0.17</b> <b>(0.12,0.23)</b>	<b>0.20</b> <b>(0.14,0.25)</b>	<b>0.26</b> <b>(0.20,0.32)</b>	<b>0.29</b> <b>(0.22,0.36)</b>	<b>0.31</b> <b>(0.22,0.39)</b>

Abbreviations: Beta: beta coefficients, CI: confidence intervals

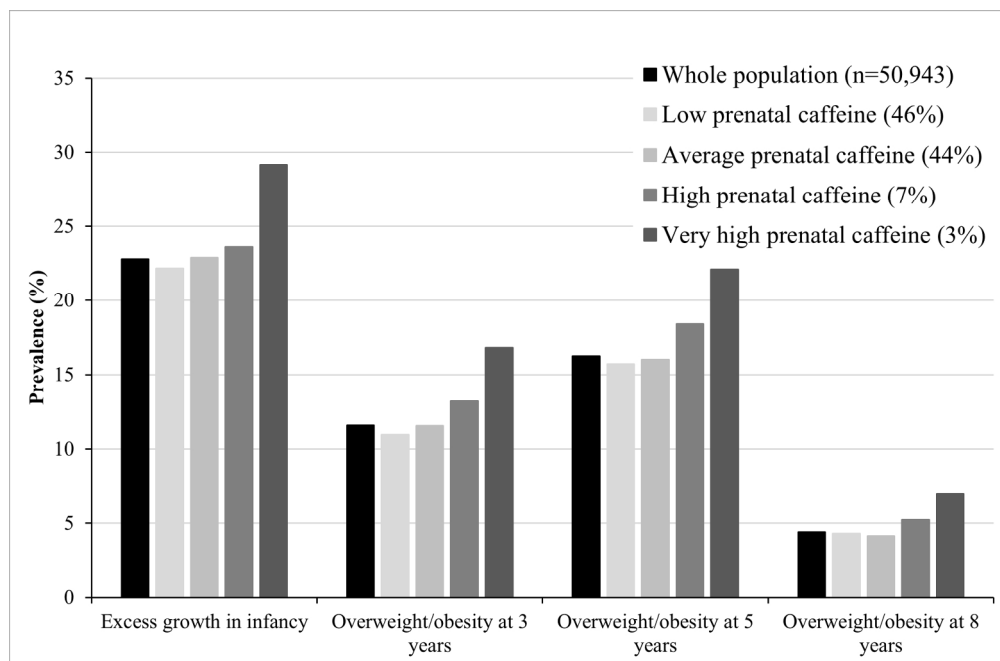
Infancy is defined as the period from birth to age 12 months, toddlerhood as the period from age 12 months to 3 years, pre-school age as the period from age 3 years to 5 years and school age as the period from age 5 years onwards.

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.

1  
2  
3 **FIGURE LEGENDS**  
4  
5  
6

7 **Figure 1.** Prevalence of excess growth in infancy and overweight/obesity at age 3, 5 and 8 years, in the whole population and by  
8 maternal caffeine intake during pregnancy.  
9

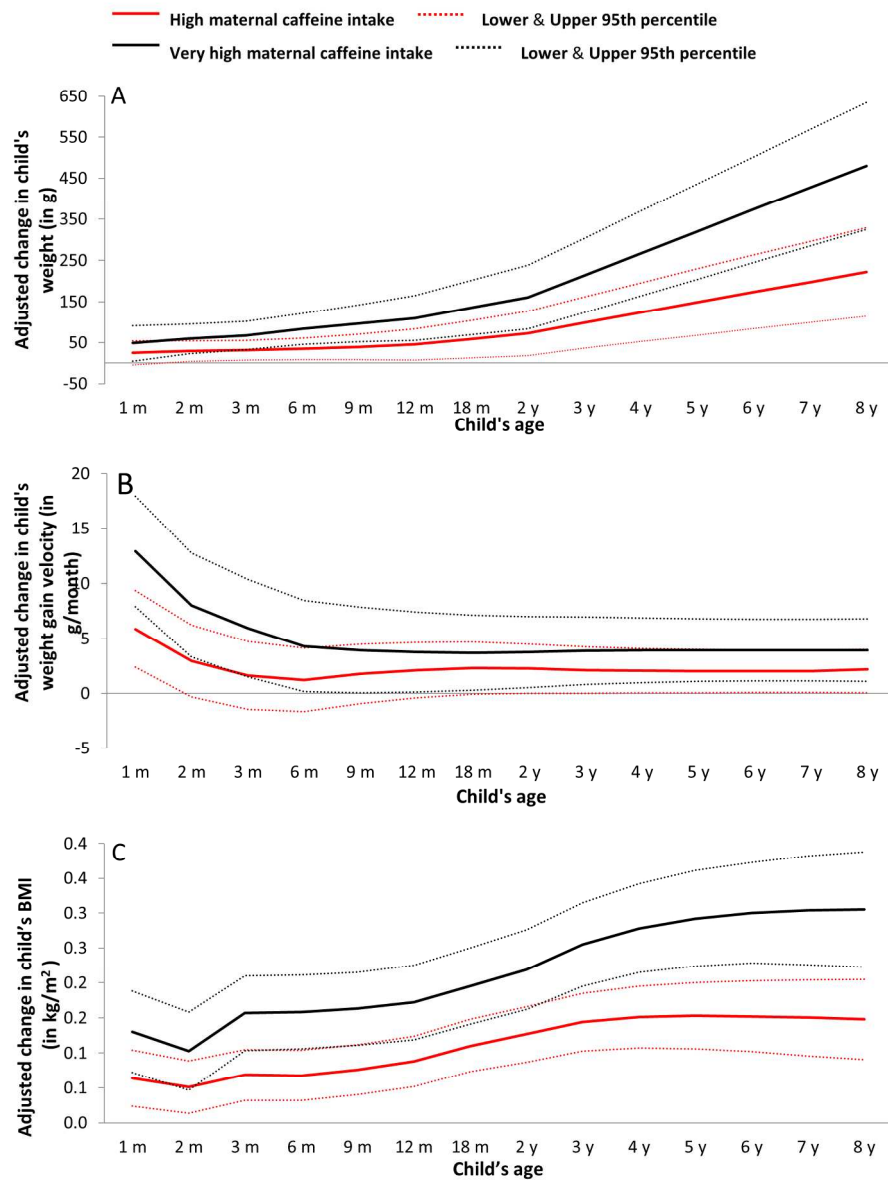
10  
11 **Figure 2.** Maternal high (red) and very high (black) caffeine intake in pregnancy and adjusted change in children's a) weight (in g), b)  
12 weight gain velocity (in g/month) and c) body mass index (in kg/m<sup>2</sup>), from age 1 month to 8 years (beta coefficients in solid lines and  
13 95% confidence intervals in thin dashed lines). Low caffeine intake is the reference group.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47



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.

172x114mm (300 x 300 DPI)

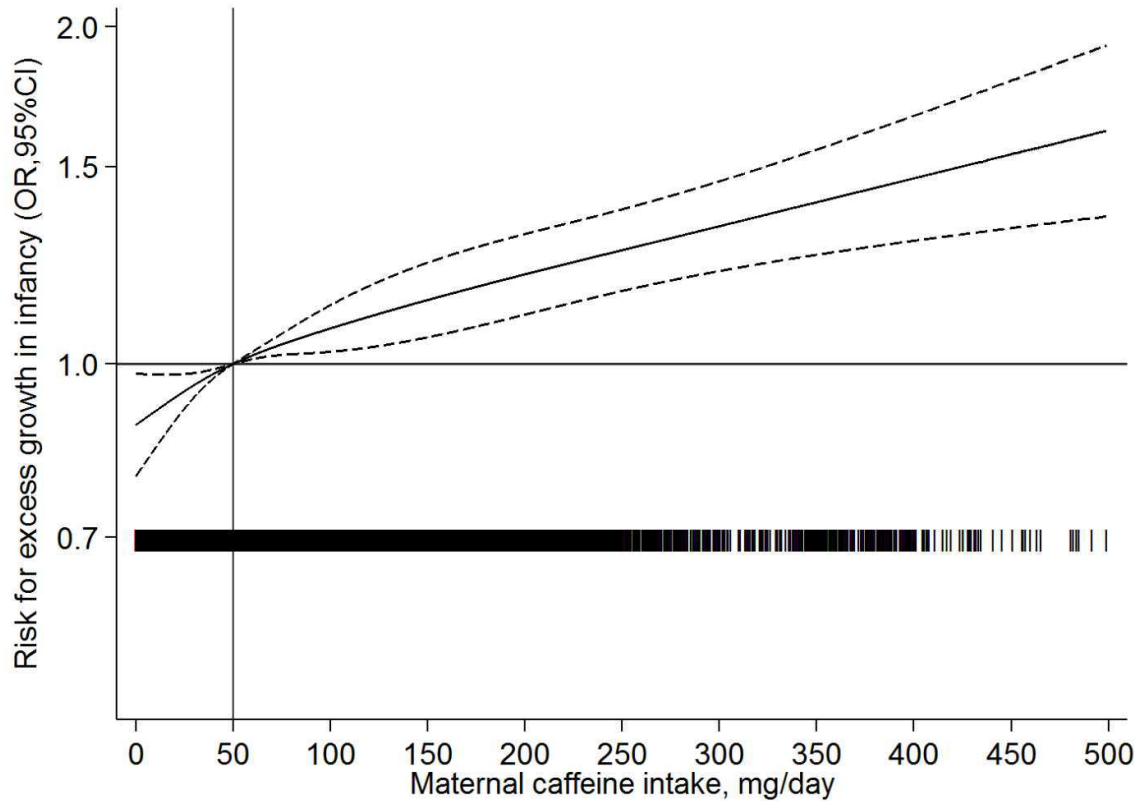
View only



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<sup>2</sup>), 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.

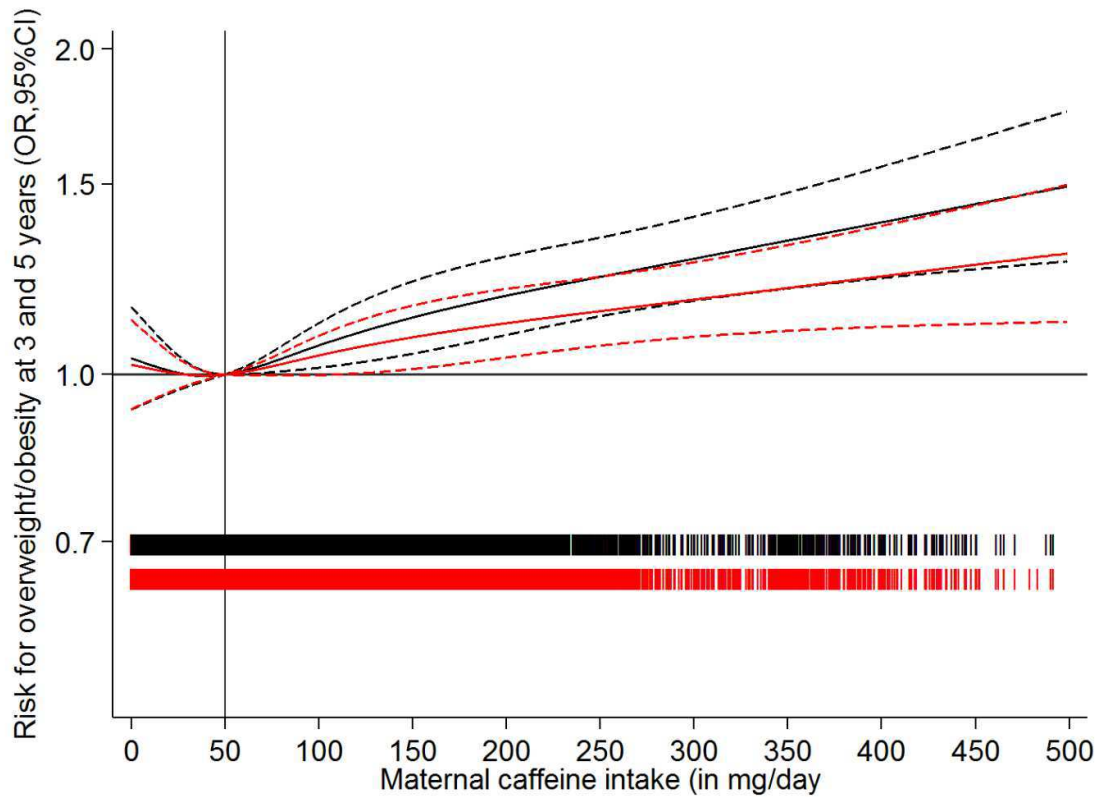
172x228mm (300 x 300 DPI)

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.



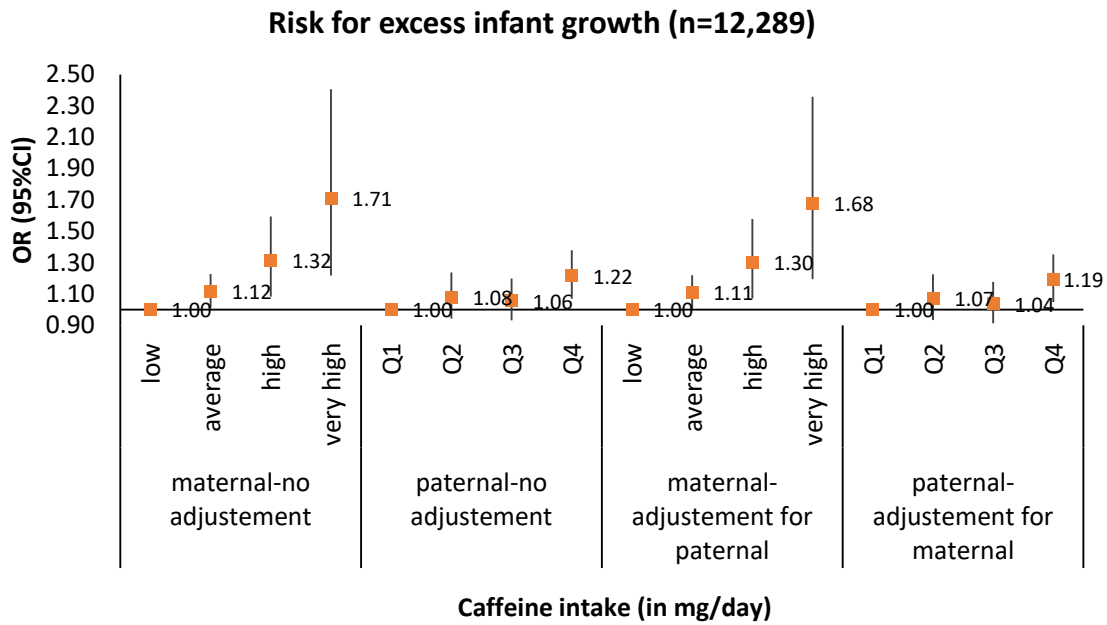
Footnote: all models adjusted for maternal age, parity, parental education, pre-pregnancy BMI, total energy intake, nausea and/or vomiting during pregnancy, paternal BMI, parental smoking during pregnancy, gestational age and gender and SGA according to Skjaerven et al.

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

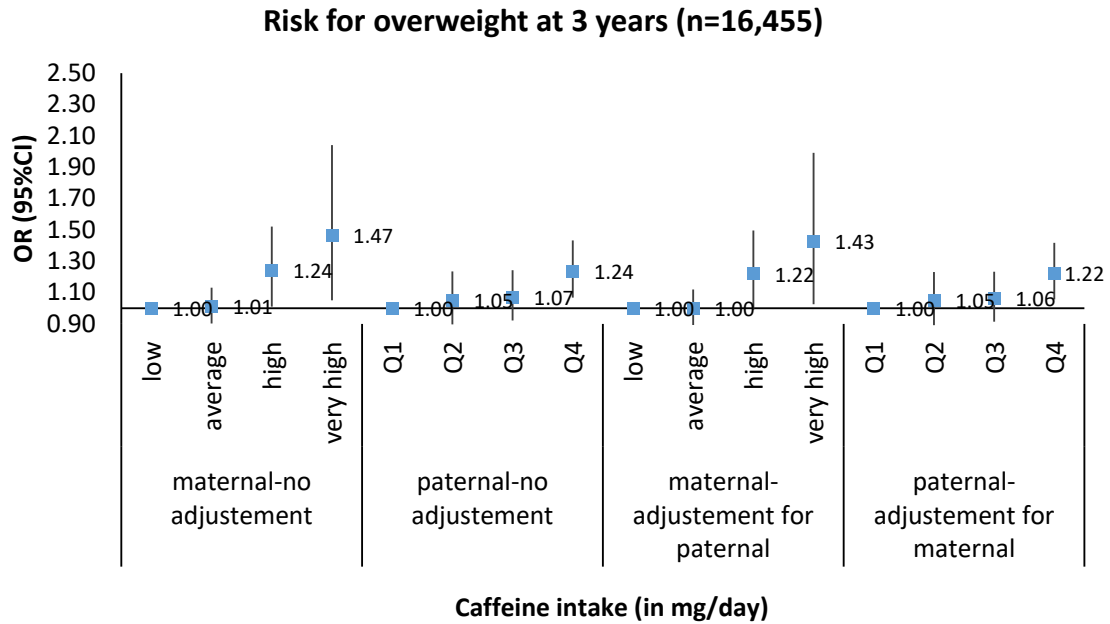
Supplementary Figure 3. Association between maternal and paternal caffeine intake during pregnancy and excess infant growth.



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.

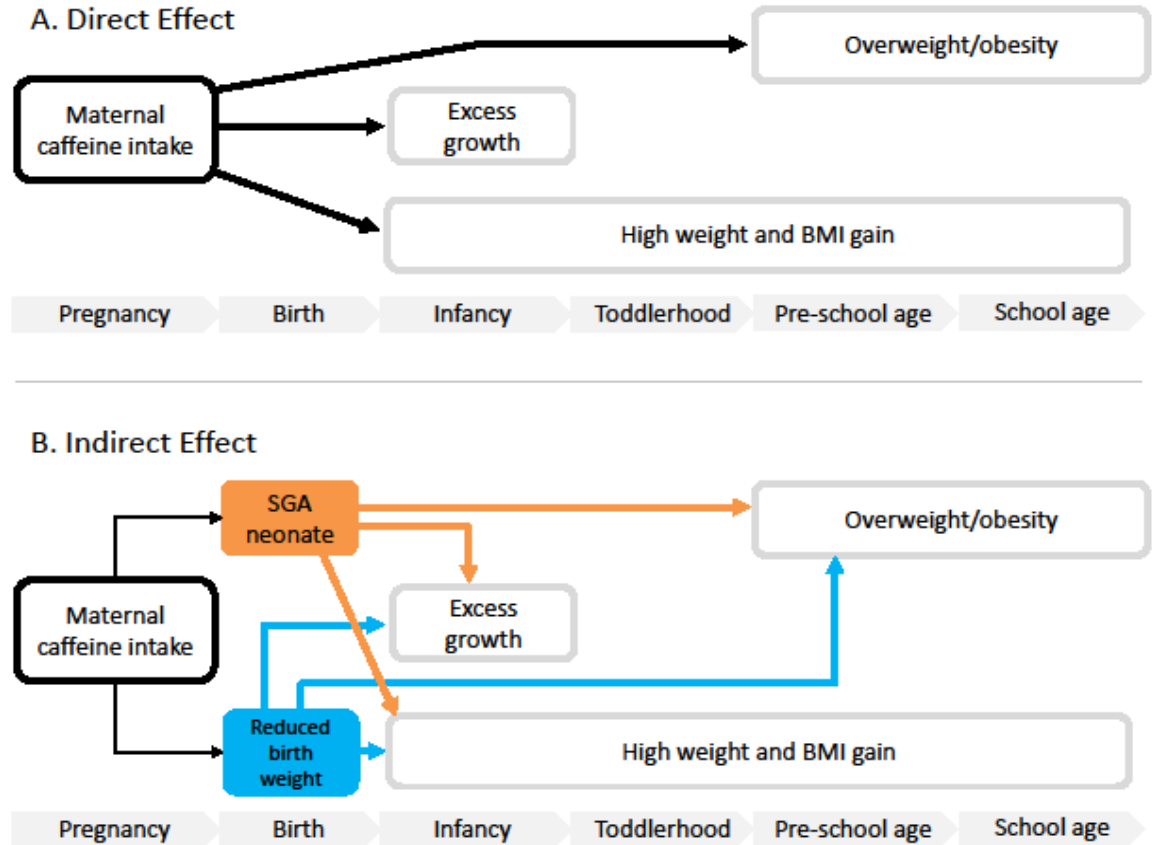


Supplementary Figure 4. Association between maternal and paternal caffeine intake during pregnancy and overweight at 3 years.



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



only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

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%

For peer review only

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 <sup>2</sup> )		Prevalence (%) <sup>a</sup>	
			Males	Females	Males	Females
International Obesity Task Force (IOTF) <sup>1</sup>	Study-specific BMIs were calculated for age and sex	3	17.89	17.56	10.77	12.44
(BMJ 2000 May 6; 320 (7244); 1240-1243)		5	17.42	17.15	14.30	18.28
Table 4)		8	18.44	18.35	3.61	5.24

<sup>a</sup>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)		Average caffeine intake (50-199mg/day)		High caffeine intake (200-299mg/day)		Very high caffeine intake (≥300mg/day)	
	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 <sup>2</sup> )								
<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 <sup>2</sup> )								
<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

1 <sup>st</sup> quartile	2,253	(29%)	1,504	(20%)	168	(15%)	44	(14%)
2 <sup>nd</sup> quartile	1,605	(21%)	1,495	(20%)	202	(18%)	51	(16%)
3 <sup>rd</sup> quartile	1,950	(26%)	2,186	(30%)	356	(33%)	82	(25%)
4 <sup>th</sup> 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<sup>-5</sup> of chi square tests of all cross-tabulations presented in table

<sup>1</sup>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.

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

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

<sup>a</sup> 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 <sup>a</sup>			Overweight/obesity at age 3 years <sup>b</sup>			Overweight/obesity at age 5 years <sup>b</sup>			Overweight/obesity at age 8 years <sup>b</sup>		
	OR	95% CI	CI	OR	95% CI	CI	OR	95% CI	CI	OR	95% CI	CI
Caffeine from black coffee												
0-50	1.00			1.00			1.00			1.00		
50-200	<b>1.18</b>	<b>1.11</b>	<b>1.26</b>	<b>1.18</b>	<b>1.11</b>	<b>1.26</b>	<b>1.12</b>	<b>1.05</b>	<b>1.18</b>	<b>1.11</b>	<b>1.00</b>	<b>1.23</b>
200-300	<b>1.31</b>	<b>1.06</b>	<b>1.62</b>	1.14	0.91	1.41	1.11	0.92	1.34	1.09	0.77	1.53
>300	<b>1.72</b>	<b>1.45</b>	<b>2.03</b>	<b>1.69</b>	<b>1.44</b>	<b>1.99</b>	<b>1.39</b>	<b>1.20</b>	<b>1.61</b>	<b>1.48</b>	<b>1.17</b>	<b>1.88</b>
Caffeine from black tea												
0-50	1.00			1.00			1.00			1.00		
50-200	<b>1.11</b>	<b>1.01</b>	<b>1.21</b>	1.07	0.98	1.18	1.05	0.97	1.14	<b>1.20</b>	<b>1.04</b>	<b>1.38</b>
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	<b>1.20</b>	<b>1.08</b>	<b>1.33</b>	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

<sup>a</sup> 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.

<sup>b</sup> 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	Caffeine intake <199mg	Caffeine intake 200-299mg
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Excess infant growth	1.00	1.07 (1.01,1.13)	1.25 (1.12,1.39)
<b>Overweight</b>			
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)

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

<sup>b</sup> 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

Maternal daily caffeine intake	Risk of overweight and/or obesity at pre-school and school age <sup>a</sup>					
	Pre-school age (n=31,482)			School age (n=19,722)		
	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	<b>1.21</b>	<b>1.07,1.39</b>	1,386/14	1.13	0.95,1.35
Very high (≥300 mg)	918/20	<b>1.52</b>	<b>1.27,1.81</b>	664/18	<b>1.32</b>	<b>1.04,1.66</b>

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

<sup>a</sup> 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		Toddlerhood		Pre-school age		School age
	3 m	6 m	12 m	18 m	3 y	5 y	8 y
	Beta	Beta	Beta	Beta	Beta	Beta	Beta
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
<b>Height (in cm)</b>							
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 ( $\geq 300$ 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)
<b>Height gain velocity (in mm/month)</b>							
Average (50-199 mg)	<b>0.05</b> ( <b>0.02,0.09</b> )	-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)	<b>0.08</b> ( <b>0.01,0.14</b> )	-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 ( $\geq 300$ mg)	<b>0.11</b> ( <b>0.01,0.21</b> )	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 1 month 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
<b>Title and abstract</b>	1	<p>(a) Indicate the study's design with a commonly used term in the title or the abstract  <i>This has been done in both subsections. The study is a prospective cohort study.</i></p> <p>(b) Provide in the abstract an informative and balanced summary of what was done and what was found  <i>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).</i></p>
<b>Introduction</b>		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported  <i>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).</i></p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses  <i>This has been done in the last paragraph of the introduction (page 4, first paragraph).</i></p>
<b>Methods</b>		
Study design	4	<p>Present key elements of study design early in the paper  <i>Our study design was described in the first paragraph of the methods, subsection "Study population and ethical approval" (page 4).</i></p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  <i>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).</i></p>
Participants	6	<p>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  <i>The eligibility and inclusion criteria has been described the methods section subsection "Study population and ethical approval" (page 4).</i></p> <p>(b) For matched studies, give matching criteria and number of exposed and unexposed  <i>This is not a matched study.</i></p>
Variables	7	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.  <i>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).</i></p>
Data sources/ measurement	8*	<p>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  <i>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.</i></p>

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).
<b>Results</b>		
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 <a href="#">This has been provided in the results section and in Tables 1, 2, 3).</a>
		(b) Report category boundaries when continuous variables were categorized <a href="#">This has been done in the results section (pages 7-9) and in Figures and Tables.</a>
		(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 <a href="#">This was reported in the results section, subsection “sensitivity analyses” (page 9).</a>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives <a href="#">In the first paragraph of the discussion, we have summarized our key finding (pages 9-10).</a>
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. <a href="#">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).</a>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. <a href="#">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).</a>
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.
<b>Other information</b>		
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. <a href="#">Funding has been described in a specific point (page 14).</a>

\*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>.