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Maternal, but not paternal or grandparental, caffeine intake is associated with childhood obesity and adiposity: The Lifeways Cross-Generation Cohort Study

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ABSTRACT

Background: Maternal caffeine intake is associated with adverse birth outcomes, but its long-term influence on offspring adiposity outcomes is not well studied. Furthermore, few studies have investigated paternal and grandparental caffeine intake in relation to offspring outcomes.

Objective: To study the associations between maternal, paternal, and grandparental caffeine intake and offspring childhood adiposity.

Design: The core study sample consists of 558 mother-child pairs from the Lifeways Study. Caffeine intake was derived from relevant food items in a self-administered validated food frequency questionnaire in early pregnancy. Children's body mass index (BMI) and waist circumference (WC) were measured at 5- and 9-y follow-up. Childhood overall and central obesity were defined as age- and sex-specific BMI z-score > International Obesity Task Force cut-off and WC z-score > 90th percentile, respectively. Multiple linear and logistic regressions were used to assess associations.

Results: Study mothers had a mean age of 30.8 y and a mean prepregnancy BMI (kg/m²) of 23.7. In adjusted models, maternal caffeine intake was associated with a higher offspring BMI z-score [β (95% CI): 0.13 (0.06, 0.21) for year 5 and 0.17 (0.04, 0.29) for year 9; per 100 mg/d increment in maternal caffeine intake], WC z-score [β (95% CI): 0.09 (0.01, 0.17) for year 5 and 0.19 (0.05, 0.32) for year 9], and a higher risk of offspring overall obesity [OR (95% CI): 1.32 (1.11, 1.57) for year 5 and 1.44 (1.10, 1.88) for year 9] and central obesity [1.28 (1.02, 1.60) for year 5 and 1.62 (1.12, 2.34) for year 9]. The influence was stronger for coffee caffeine than tea caffeine. No consistent associations were observed for paternal and grandparental caffeine intake.

Conclusions: Maternal antenatal, but not paternal or grandparental, caffeine intake is associated with higher offspring adiposity and obesity risk at age 5 and 9 y, with stronger associations observed for coffee caffeine. This prospective observational study was registered

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Keywords: caffeine, coffee, tea, pregnancy, child, obesity, adiposity

Introduction

Childhood obesity has reached epidemic proportions worldwide (1). Being a complex problem, a multifaceted strategy should be adopted to lessen the burden associated with childhood obesity. The Developmental Origins of Health and Disease (DO-HaD) theory highlights the importance of optimizing maternal nutrition to positively influence offspring future health trajectory (2). The significance of prenatal care as a key strategy to prevent childhood obesity has also been highlighted in the recent

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Supplemental Figure 1 and Supplemental Tables 1–4 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

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Abbreviations used: FFQ, food frequency questionnaire; IOTF, International Obesity Task Force; WC, waist circumference; β , beta coefficient.

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Commission on Ending Childhood Obesity report commissioned by the WHO (3).

A well-balanced diet during pregnancy has been shown to be associated with better birth outcomes and reduced risk of excessive childhood adiposity for the offspring (4–7). However, whether caffeine-containing foods and beverages can be a component of a healthy diet during pregnancy is debatable. In general, neutral and inverse associations between caffeine intake and diseases have been reported in healthy populations (8, 9), whereas the reverse has been suggested for maternally consumed caffeine with regards to offspring outcomes (10, 11). Caffeine-containing foods and beverages are widely consumed even during pregnancy. Caffeine readily crosses the placental barrier and the main metabolizing enzyme (CYP 450) is absent in the placenta and fetus, raising concerns regarding caffeine accumulation and its potential harmful effects on fetal growth and development (12–14). As demonstrated in previous systematic and umbrella reviews (10, 11, 15–18), pregnancy is a vulnerable period during which the intake of caffeinated products should be limited.

Although many studies have established associations between maternal caffeine intake and adverse birth outcomes (13, 14), the potential long-term influence of perinatal caffeine consumption on offspring outcomes, such as childhood obesity, is less known. Furthermore, few studies have investigated the influence of paternal caffeine intake, and thus far no study has examined the cross-generational influence of grandparental caffeine intake. To this end, the Lifeways Cross-Generation Study, which collected dietary data for parents and grandparents, provides an unprecedented opportunity to examine these relations. Our objective in this study was 2-fold; first, to elucidate the influence of maternal caffeine intake on childhood adiposity and obesity. Second, to examine if any influence of maternally consumed caffeine is specific to in utero fetal exposure, we also investigated the relations between paternal and grandparental caffeine intake and offspring outcomes in a subsample.

Methods

The design and recruitment process of Lifeways Cross-Generation Cohort Study has been described in detail elsewhere (19, 20). Briefly, Irish mothers were initially recruited by midwives during their first antenatal booking visits in two maternity hospitals in the Republic of Ireland between 2001 and 2003. A cohort of 1094 live births (of which 1070 are singletons) was born to the 1,082 recruited mothers. A total of 669 mothers consented to be followed-up at year 5, and maternal diets and offspring BMI information was available in 558 mother-child dyads, thus forming the core study sample for the current analysis. The participant flow chart is shown in **Supplemental Figure 1**. The Lifeways study has been granted ethical approval by ethical committees of the Coombe University Hospital, Dublin, University College Dublin, Irish College of General Practitioners and University College Hospital, Galway, Ireland; written informed consent was collected from all women upon recruitment.

Dietary assessment and derivation of caffeine intake

Assessment of habitual dietary intake of the Lifeways participants has been described in detail previously (21). Briefly,

the Lifeways mothers completed a self-administered semi-quantitative food frequency questionnaire (FFQ) (based on the European Prospective Investigation into Cancer and Nutrition instrument (22) which has been validated extensively in several populations (23)) during their first trimester of pregnancy. Adapted to reflect the Irish diet, the 149-item FFQ used in Lifeways was originally validated for use in the Irish population using food diaries and a protein biomarker in a volunteer sample (24) and incorporated into the Irish National Surveys of Lifestyle Attitudes and Nutrition 1998, 2002, 2007. For each food item, the participants indicated their average consumption frequency ranging from 'never or <1 per mo' to '6 + per d' during the first 12–16 weeks of pregnancy. These intake frequencies were converted into intake amounts (g/d) with standard portion sizes (25). Energy and nutrient intakes were calculated using an in-house software program (FFQ Software Ver 1.0; developed by the National Nutrition Surveillance Centre, School of Public Health, Physiotherapy and Sports Science, University College Dublin, Ireland), which linked frequency selections with the food equivalents in McCance and Widdowson Food Tables (25).

For caffeine intake estimation, relevant drink and food items were first identified from the FFQ (i.e., coffee, tea, soft drinks, and chocolate-containing foods and beverages). A caffeine intake variable was then derived by summing the caffeine content of these food groups based on previously published conversion values (14, 26–28) weighted by mothers' intakes (see **Supplemental Table 1** for conversion factors). The caffeine intake variable was also derived for a subset of study fathers and grandparents who completed the same FFQ.

Caffeine intake from all sources, coffee, and tea were also categorized to assess the potential differential influence of caffeine sources and dose on offspring weight status. The determination of category cut-offs (total caffeine: <50 mg/d, 50 to <100 mg/d, 100 to <200 mg/d, and ≥ 200 mg/d); coffee: nonconsumer, <200 mg/d, and ≥ 200 mg/d and tea: <50 mg/d, 50 to <100 mg/d, and ≥ 100 mg/d) were based on the distribution of intake (assessed by inspecting the histograms) in this population, as previously described (29), to ensure sufficient cases in each category for optimal statistical power especially for multiple logistic regressions. The current recommendation for caffeine intake during pregnancy in Ireland is <200 mg/d by the Food Safety Authority of Ireland (30).

Children's BMI and waist circumference determination

At age 5 and 9 y, the children's BMI and waist circumference (WC) measurements were collected by trained researchers using standardized tools and techniques. Weight, height, and WC were measured using a Tanita Digital Weighing Scale portable height measure, and a body tape with clear plastic slider, respectively. All tools were purchased from Chasmors Ltd. Detailed information on the anthropometric measurements of the study children has been previously described (31). Exact age of anthropometric measurement was also recorded during the visit. Childhood (general) overweight and obesity was defined according to the International Obesity Task Force (IOTF) (32) sex- and age-specific cut-offs to facilitate international

comparisons. Central obesity was defined as having age- and sex-standardized WC of over 90th percentile based on the 1990 British reference (33).

Covariates

Information on self-reported maternal height and prepregnancy weight, age at recruitment, cigarette smoking, and alcohol intake during the periconceptional period (including both reported current smokers/drinkers and women who have smoked/consumed alcohol within 3 mo of recruitment) were collected using a self-administered questionnaire at recruitment. Education status (tertiary or no tertiary education) and socio-economic status (proxied by eligibility to the General Medical Services Scheme, a robust indicator of social disadvantage in the Irish population (34) was collected using the same questionnaire. Prepregnancy BMI was derived using the formula weight/height². Information on birth weight, gestational age, and child gender was abstracted from hospital records.

Statistical analysis

Summary statistics were first generated for maternal and child characteristics. Differences in characteristics across maternal caffeine intake were assessed using one way-ANOVA for continuous variables and the chi-square test for categorical variables.

Associations between maternal intake of total caffeine (modeled continuously and in categories), caffeine from coffee and tea (categories), and offspring adiposity outcomes were investigated using multiple regression analyses (linear regressions for continuous outcomes and logistic regressions for binary outcomes). The following set of a priori selected confounders and covariates were adjusted: maternal socio-economic status and maternal cigarette smoking and alcohol intake during the periconceptional period, age at recruitment, education attainment, prepregnancy BMI, energy intake at the time of dietary assessment, and child gender. Missing covariates were multiply imputed using the chained equation (35), and regression coefficients from the 20 imputed datasets were subsequently pooled.

To investigate the specificity of in utero caffeine exposure, we used paternal caffeine intake as a negative control. To assess any intergenerational influence, grandparental caffeine intake and their associations with grandchildren's adiposity outcomes were studied. Furthermore, we investigated interactions between maternal caffeine intake with child gender and maternal BMI by including the corresponding multiplicative interaction terms in the model. We also investigated potential nonlinearity for the associations between maternal caffeine intake and offspring outcomes by including the quadratic terms of caffeine intake in the adjusted model. To examine if maternal caffeine intake-offspring adiposity associations were mediated by birth weight and gestational duration, we included these variables in the full model and assessed any attenuation of effect estimates. Further to the adjustment of energy intake, we also conducted sensitivity analysis adjusting for total maternal milk intake and sugar added to tea, coffee, and cereals. To ensure that our observed associations were not confounded by maternal dietary quality (measured by adherence to the Healthy Eating Index based on the FFQ data) and self-reported physical activity,

parental reports of childhood factors at the year 5 follow-up (time spent outdoors, time spent viewing television, and dietary quality), and any breastfeeding duration, we further adjusted for these variables in sensitivity analyses. In addition, we conducted analyses excluding mothers diagnosed with gestational diabetes (abstracted from obstetric record). Lastly, by using the leave-one-out modeling approach (36), we also explored the influence of per-serving-per-d substitution of maternal caffeinated beverages with alternative beverages in the FFQ (alcoholic beverages, sugar-sweetened beverages, and milk and malted milk drinks) on childhood adiposity outcomes.

Statistical analyses were conducted using the statistical software STATA version 13.1 (StataCorp). A two-sided *P* value of <0.05 was considered statistically significant.

Results

The characteristics of included participants according to increasing maternal intake of caffeine are presented in **Table 1**. Overall, the study mothers had a mean age of 30.8 y and a mean prepregnancy BMI of 23.7; most of them reported alcohol use during the periconceptional period (70%), compared with a lower proportion of cigarette smoking (26%). Mothers with a higher caffeine intake were older, more likely to consume alcohol, and to be nonprimiparous, compared with those with a lower caffeine intake (all *P* < 0.05).

As shown in **Table 2**, maternal caffeine intake was associated with higher sex- and age-specific BMI z-score [β (95% CI): 0.13 (0.06, 0.21) for year 5 and 0.17 (0.04, 0.29) for year 9; per 100 mg/d increment in maternal caffeine intake (~1 cup of coffee or 3 cups of tea)] and WC z-score [β (95% CI): 0.09 (0.01, 0.17) for year 5 and 0.19 (0.05, 0.32) for year 9]. When total caffeine intake was modeled in categories, similar trends were observed, and the associations were statistically significant for maternal caffeine intake of ≥ 200 mg/d [for BMI at year 5: 0.42 (0.13, 0.71) and year 9: 0.56 (0.09, 1.04); both *P*-trends <0.05] compared with <50 mg/d.

The associations of maternal caffeine intake with the corresponding binary offspring outcomes are presented in **Table 3**. In keeping with our observations for continuous outcomes, a 100 mg/d increment in maternal caffeine intake was associated with higher risk of offspring overall overweight and obese status [OR (95% CI): 1.32 (1.11, 1.57) for year 5 and 1.44 (1.10, 1.88) for year 9] and central obesity [1.28 (1.02, 1.60) for year 5 and 1.62 (1.12, 2.34) for year 9]. Similarly, caffeine from coffee, but not tea, was associated with offspring overall overweight and obesity [year 9: 2.81 (1.14, 6.90); *P*-trend = 0.10; highest compared with lowest coffee caffeine intake] and central obesity [year 9: 4.57 (1.14, 18.24); *P*-trend = 0.046].

As seen in **Tables 4** and **5**, there was little suggestion of paternal caffeine intake influencing offspring adiposity outcomes, except for a trend towards association (*P* = 0.08) with offspring overweight and obese status at year 9. There was no evidence that grandparental caffeine intake had any impact on their grandchildren's adiposity outcomes.

Maternal BMI (all *P*-interaction ≥ 0.34) and child gender (all *P*-interaction ≥ 0.08) did not modify the relation between maternal caffeine intake and offspring adiposity outcomes. There was also little evidence of nonlinearity in our studied associations (all *P* ≥ 0.08). When birthweight or gestational age were included

TABLE 1 Characteristics of included Lifeways participants¹

	Total population (n = 558) ²	Caffeine intake categories				P value ³
		<50 mg/d (n = 108)	50 to <100 mg/d (n = 171)	100 to <200 mg/d (n = 192)	≥200 mg/d (n = 87)	
Maternal characteristics	—	—	—	—	—	
Maternal age at recruitment, y	30.8 ± 5.7	29.3 ± 6.2	30.6 ± 5.4	31.2 ± 5.5	32.3 ± 5.5	0.002
Maternal pre-pregnancy BMI, kg/m ²	23.7 ± 3.8	24.1 ± 4.5	24.0 ± 4.0	23.5 ± 3.4	23.4 ± 3.4	0.34
Eligibility to the General Medical Services Scheme	—	—	—	—	—	0.18
No	484 (88%)	86 (82%)	149 (89%)	169 (88%)	80 (92%)	
Yes	68 (12%)	19 (18%)	19 (11%)	23 (12%)	7 (8%)	
Education status	—	—	—	—	—	0.07
Below tertiary	263 (48%)	51 (48%)	84 (50%)	98 (52%)	30 (35%)	
Tertiary or above	288 (52%)	55 (52%)	85 (50%)	92 (48%)	56 (65%)	
Cigarette smoking during pregnancy	—	—	—	—	—	0.39
No	405 (74%)	82 (77%)	129 (77%)	134 (71%)	60 (70%)	
Yes	144 (26%)	24 (23%)	39 (23%)	55 (29%)	26 (30%)	
Alcohol use during pregnancy	—	—	—	—	—	0.017
No	164 (30%)	40 (38%)	54 (32%)	55 (29%)	15 (17%)	
Yes	391 (70%)	66 (62%)	116 (68%)	137 (71%)	72 (83%)	
Parity	—	—	—	—	—	0.020
Primiparous	234 (43%)	58 (56%)	70 (42%)	71 (37%)	35 (41%)	
Nonprimiparous	314 (57%)	46 (44%)	97 (58%)	120 (63%)	51 (59%)	
Child characteristics	—	—	—	—	—	
Child gender	—	—	—	—	—	0.79
Male	286 (51%)	52 (48%)	91 (53%)	96 (50%)	47 (54%)	
Female	272 (49%)	56 (52%)	80 (47%)	96 (50%)	40 (46%)	

¹ Values are mean ± SD for continuous variables or n (%) for categorical variables.

² Total number may not be 558 due to missing information: maternal age (n = 3); prepregnancy BMI (n = 80); eligibility to the General Medical Services Scheme (n = 6); maternal education status (n = 7); cigarettes smoking (n = 9); alcohol intake (n = 3); parity (n = 10).

³ P values were derived from one-way ANOVA for continuous variables and chi-square test for categorical variables.

in the models, effect estimates changed little (**Supplemental Table 2**), suggesting that mediation by the birth outcomes, if any, is minimal. The effect estimates between maternal caffeine intake and offspring adiposity outcomes remained practically unchanged with further adjustment for total maternal milk intake and sugar added to tea and coffee (**Supplemental Table 3**). Excluding mothers diagnosed with gestational diabetes did not change the results and conclusions (**Supplemental Table 3**). Similarly, results changed little with adjustment for maternal dietary quality and physical activity, or with further adjustment for childhood factors (**Supplemental Table 3**). In substitution analyses, the only significant association was between substitution of caffeinated beverages with milk and malted milk drinks and offspring WC z-score at year 9 ($\beta = -0.14$; 95% CI: $-0.26, -0.02$; per-serving-per-d substitution of caffeinated beverages with milk and malted milk drinks) (**Supplemental Table 4**). We did not ask about plain water intake, unfortunately, which could have been the optimal hydration source.

Discussion

This prospective study is one of the first to investigate the long-term influence of maternally and paternally consumed caffeine on offspring adiposity outcomes, and the first to examine the potential cross-generational influence of grandparental caffeine intake. Higher caffeine intake of mothers during pregnancy, but not that of fathers and grandparents, is associated with long-term

offspring adiposity (overall and central) outcomes at ages 5 and 9 y, suggesting the specificity of in utero influence of antenatal maternal caffeine intake.

There is a dearth of research investigating the long-term influence of maternally consumed caffeine on offspring growth, adiposity, and/or obesity outcomes. Out of 4 previous studies, 3 reported a direct association between maternal caffeine intake and offspring obesity and/or excessive childhood growth (37–39), whereas 1 did not find consistent associations (40). This could have been due to different assessment methods and year of study. The former 3 studies used questionnaires to ascertain caffeine intake, whereas the latter study used maternal serum concentration of paraxanthine, the primary metabolite of caffeine in humans. Although paraxanthine correlates well with very recent caffeine intake (40), it is less clear whether it can reflect longer-term habitual intake. Furthermore, that study was conducted in the 1960s, when the amount of caffeine intake and other lifestyle factors were potentially very different (40). For example, maternal pregnancy obesity was less common and maternal smoking, which affects caffeine metabolism, was much more common in the 1960s (40).

Studies reporting an association between maternal caffeine intake and childhood adiposity have been conducted in Norway, The Netherlands, and the USA (37–39), where coffee is the primary caffeine source (41). In contrast, tea is the main caffeine source in Ireland (41), thus providing an opportunity to study the potential differential influence of tea and coffee

TABLE 2 Associations of total maternal caffeine intakes with offspring weight status and waist circumference at 5 and 9 years¹

	BMI z-score		Waist circumference z-score	
	Year 5 (n = 558)	Year 9 (n = 283)	Year 5 (n = 557)	Year 9 (n = 269)
Total caffeine intake (per 100 mg/d increment)	0.13 (0.06, 0.21)***	0.17 (0.04, 0.29)*	0.09 (0.01, 0.17)*	0.19 (0.05, 0.32)**
<50 mg/d	Ref	Ref	Ref	Ref
50 to <100 mg/d	0.13 (-0.11, 0.37)	0.14 (-0.27, 0.55)	0.16 (-0.09, 0.41)	-0.06 (-0.46, 0.35)
100 to <200 mg/d	0.07 (-0.17, 0.31)	0.25 (-0.13, 0.64)	0.10 (-0.15, 0.34)	0.11 (-0.28, 0.49)
≥200 mg/d	0.42 (0.13, 0.71)**	0.56 (0.09, 1.04)*	0.28 (-0.02, 0.58)	0.36 (-0.12, 0.84)
P-trend	0.026	0.019	0.15	0.10
Caffeine from coffee	—	—	—	—
0 mg/d	Ref	Ref	Ref	Ref
<200 mg/d	-0.03 (-0.22, 0.15)	0.06 (-0.25, 0.36)	0.04 (-0.15, 0.23)	0.16 (-0.14, 0.46)
≥200 mg/d	0.32 (0.05, 0.59)	0.34 (-0.10, 0.79)	0.23 (-0.05, 0.51)	0.35 (-0.11, 0.81)
P-trend	0.11	0.16	0.14	0.13
Caffeine from tea	—	—	—	—
<50 mg/d	Ref	Ref	Ref	Ref
50 to <100 mg/d	0.05 (-0.15, 0.24)	0.06 (-0.27, 0.39)	0.06 (-0.14, 0.26)	-0.09 (-0.41, 0.24)
≥100 mg/d	0.12 (-0.11, 0.34)	0.07 (-0.30, 0.43)	0.03 (-0.20, 0.27)	0.23 (-0.13, 0.59)
P-trend	0.42	0.78	0.79	0.23

¹Values are β (95% CI) from linear regressions. Regressions were adjusted for maternal socio-economic status, education attainment, cigarette smoking and alcohol consumption during periconceptional period, age at recruitment, parity, prepregnancy BMI; regressions for different caffeine sources were additionally mutually adjusted for each other; the outcomes were intrinsically adjusted for child gender and age at measurement.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

caffeine in a high tea consumption setting. Our results indicate stronger associations between higher intakes of coffee caffeine with higher adiposity and obesity risk in offspring than tea caffeine, suggestive perhaps that components other than caffeine in coffee, a beverage with an array of active components (42), might have more important influences on offspring postnatal adiposity. However, as with other studies, we have previously shown that tea caffeine is associated with lower birth sizes and

adverse birth outcomes (29). Thus, it may be that caffeine has a more immediate influence on birth outcomes whereas other components in coffee may influence postnatal offspring adiposity through other independent pathways. This notion is supported by a lack of mediation effect by birth weight and gestational age on the maternal caffeine-offspring postnatal adiposity associations. The lack of or lesser influence of tea caffeine on longer-term offspring outcomes should be replicated in other studies with a

TABLE 3 Associations of tea and coffee caffeine with offspring overweight status and central obesity at 5 and 9 y¹

	Overweight/obesity (IOTF)		Central obesity (WC >90 th percentile)	
	Year 5 (n = 558)	Year 9 (n = 283)	Year 5 (n = 557)	Year 9 (n = 269)
Total caffeine intake (per 100 mg/d increment)	1.32 (1.11, 1.57)**	1.44 (1.10, 1.88)**	1.28 (1.02, 1.60)*	1.62 (1.12, 2.34)*
<50 mg/d	Ref	Ref	Ref	Ref
50 to <100 mg/d	0.87 (0.49, 1.54)	1.01 (0.39, 2.66)	1.14 (0.49, 2.62)	0.76 (0.15, 3.84)
100 to <200 mg/d	1.13 (0.64, 1.97)	1.29 (0.53, 3.15)	0.91 (0.38, 2.16)	1.24 (0.31, 5.05)
≥200 mg/d	1.83 (0.95, 3.52) ^{T1}	2.76 (0.99, 7.66) ^{T2}	1.86 (0.74, 4.70)	3.22 (0.68, 15.25)
P-trend	0.05	0.042	0.35	0.08
Caffeine from coffee	—	—	—	—
0 mg/d	Ref	Ref	Ref	Ref
<200 mg/d	0.86 (0.56, 1.34)	1.05 (0.53, 2.07)	0.95 (0.49, 1.82)	1.98 (0.68, 5.70)
≥200 mg/d	1.93 (1.06, 3.52)	2.81 (1.14, 6.90)*	1.93 (0.84, 4.44)	4.57 (1.14, 18.24)*
P-trend	0.17	0.10	0.26	0.046
Caffeine from tea	—	—	—	—
<50 mg/d	Ref	Ref	Ref	Ref
50 to <100 mg/d	0.97 (0.61, 1.52)	0.76 (0.36, 1.60)	1.27 (0.64, 2.50)	0.55 (0.16, 1.90)
≥100 mg/d	1.31 (0.78, 2.21)	1.61 (0.74, 3.50)	1.47 (0.67, 3.21)	1.84 (0.58, 5.83)
P-trend	0.46	0.27	0.41	0.21

IOTF, International Obesity Task Force; WC, waist circumference.

¹Values are OR (95% CI) from logistic regressions. Regressions were adjusted for maternal socio-economic status, education attainment, cigarette smoking and alcohol consumption during periconceptional period, age at recruitment, parity, prepregnancy BMI; regressions for different caffeine sources were additionally mutually adjusted for each other; the outcomes were intrinsically adjusted for child gender and age at measurement.

^{T1} $P = 0.07$, ^{T2} $P = 0.05$, * $P < 0.05$, ** $P < 0.01$.

TABLE 4 Associations of parental and grandparental total caffeine intake with BMI and waist circumference (WC) at 5 and 9 y¹

	BMI z-score		WC z-score	
	Year 5	Year 9	Year 5	Year 9
MGM	0.06 (−0.06, 0.18)	−0.004 (−0.19, 0.18)	−0.01 (−0.01, 0.11)	0.05 (−0.15, 0.25)
MGF	−0.01 (−0.18, 0.16)	−0.23 (−0.54, 0.09)	0.03 (−0.14, 0.20)	−0.15 (−0.52, 0.22)
PGM	−0.1 (−0.24, 0.04)	−0.15 (−0.32, 0.02)	−0.07 (−0.20, 0.06)	−0.08 (−0.25, 0.09)
PGF	0.19 (−0.05, 0.44)	0.03 (−0.32, 0.38)	0.01 (−0.26, 0.28)	−0.3 (−0.64, 0.05)
P	−0.01 (−0.1, 0.09)	−0.02 (−0.13, 0.09)	−0.06 (−0.15, 0.04)	−0.004 (−0.12, 0.11)
M	0.13 (0.06, 0.21)***	0.17 (0.04, 0.29)*	0.09 (0.01, 0.17)*	0.19 (0.05, 0.32)**

¹Regressions were adjusted for maternal socio-economic status, education attainment, cigarette smoking and alcohol consumption during periconceptional period, age at recruitment, parity, prepregnancy BMI; regressions for different caffeine sources were additionally mutually adjusted for each other; the outcomes were intrinsically adjusted for child gender and age at measurement. Values are β (95% CI) from linear regressions. Year 5 (BMI: MGM = 173; MGF = 99; PGM = 96; PGF = 57; P = 214; M = 558) (WC: MGM = 172; MGF = 88; PGM = 97; PGF = 58; P = 212; M = 557). Year 9 (BMI: MGM = 102; MGF = 63; PGM = 68; PGF = 40; P = 145; M = 283) (WC: MGM = 99; MGF = 58; PGM = 63; PGF = 37; P = 137; M = 269). MGM, maternal grandmother; MGF, maternal grandfather; PGM, paternal grandmother; PGF, paternal grandfather; P, paternal; M, maternal.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

similar caffeine consumption pattern (e.g., the UK), since both tea and coffee caffeine were reported to affect postnatal growth in the recent Norwegian study (39). Furthermore, although not statistically significant, the directions of associations between maternal tea caffeine intake and offspring adiposity are in general similar to those of coffee caffeine in our study, as mirrored in the US study comparing binary tea intake (tea consumer compared with nonconsumer) (37).

As described earlier, the observed influence of caffeine or other coffee components on offspring postnatal adiposity was not mediated by birth weight. Cross-generational epigenetic influence through grandparental caffeine consumption is unlikely, although the sample size of grandparents in our study is not large and should be confirmed in other studies. Our results suggest that the influence of parental caffeine intake on long-term offspring adiposity outcomes is likely specific to in utero exposure as paternal and grandparental caffeine intake were not significantly associated with the studied outcomes. That maternally consumed caffeine can affect long-term offspring adiposity and growth appears biologically plausible through metabolic programming via alteration of offspring brain functions and appetite regulation, with most evidence arising from animal studies. For instance, in utero exposure to maternally consumed caffeine has been shown to alter lipid and glucose metabolism and functions of the hypothalamic-pituitary-adrenal (HPA) axis in offspring rats

(43, 44). Furthermore, a reduced fetal blood leptin concentration, important in appetite regulation, was observed for pregnant rats administered caffeine, mainly through reduction in placental leptin expression and transportation (45). Other components in coffee may also influence appetite. For instance, decaffeinated coffee has been shown to acutely decrease hunger by increasing the satiety hormone peptide YY in healthy male volunteers (46). Nonetheless, the potential transgenerational effects of these components were less studied compared with caffeine.

Our study adds to the limited literature; in contrast to most previous reports our population has a different caffeine consumption pattern and thus potentially different confounding structure. The prospective nature of our investigation establishes the temporal sequence between exposure and outcomes. We also used a multiple imputation method to handle missing covariate information and utilized paternal caffeine intake as a negative control. To the best of our knowledge, this is the first investigation of associations between grandparental caffeine intake and offspring outcomes. Nevertheless, our results should be interpreted in view of some limitations. As with any observational study our results could have been affected by residual confounding, particularly due to uncollected variables on shared familial environment between mothers and children. However, the lack of association for paternal caffeine intake as a negative control provides some evidence against this explanation.

TABLE 5 Associations of parental caffeine intake with obesity and central obesity at 5 and 9 y¹

	Overweight/obese (IOTF)		Central obesity (WC > 90 th percentile)	
	Year 5	Year 9	Year 5	Year 9
P	0.85 (0.65, 1.11)	1.33 (0.97, 1.82) ^T	1.20 (0.87, 1.66)	1.001 (0.52, 1.92)
M	1.32 (1.11, 1.57)**	1.44 (1.10, 1.88)**	1.28 (1.02, 1.60)*	1.62 (1.12, 2.34)*

¹Regressions were adjusted for maternal socio-economic status, education attainment, cigarette smoking and alcohol consumption during periconceptional period, age at recruitment, parity, prepregnancy BMI; regressions for different caffeine sources were additionally mutually adjusted for each other; the outcomes were intrinsically adjusted for child gender and age at measurement. Values are OR (95% CI) from logistic regressions; only performed for maternal and paternal exposure due to insufficient cases for grandparental exposure. Sample size: Year 5 (BMI: P = 214; M = 558) (WC: P = 212; M = 557). Year 9 (BMI: P = 145; M = 283) (WC: P = 137; M = 269). P, paternal; M, maternal.

^TP = 0.08, * $P < 0.05$, ** $P < 0.01$.

Randomized controlled trials are needed to confirm causation, although subjecting pregnant women to potentially harmful substances could be unethical and thus to date, no clinical trial has assessed the long-term influence of maternally consumed caffeine on offspring outcomes. Compared with mothers with a live birth excluded from the current analysis due to missing child BMI data, included mothers had a higher mean caffeine intake, were older, more likely to have attained tertiary education, have higher socio-economic status, and less likely to smoke (**Supplemental Table 5**), suggesting that the included mothers were generally healthier. No differences in parity, alcohol use, prepregnancy BMI and child gender, birthweight, and gestational age at birth were evident. Furthermore, the internal validity of the observed caffeine-adiposity relations should not have been affected.

Measurement errors due to recall limitation could have compromised the accuracy of caffeine intake estimation assessed using self-reported dietary intakes. However, self-report of major caffeine sources such as coffee and tea is in general reported to be reasonably reliable and accurate (47, 48). Moreover, it is likely that any measurement error is nondifferential (thus biasing results towards null) in nature given the prospective design of our analyses. We did not consider energy drinks in deriving total caffeine intake, but only <3% of adults reported consuming energy drinks in the 2000s according to a national Irish dietary survey (49). Due to the window of recruitment (12–16 weeks of gestation) some study mothers have reported first trimester caffeine intake exclusively, whereas others have reported their intakes up until very early second trimester, potentially resulting in greater measurement errors. Furthermore, since only early pregnancy caffeine intake data were available in our study, there is potential concern on their representativeness of the whole pregnancy exposure. Based on previous studies which collected information across trimesters, we would expect our caffeine exposure range to be lower than that during late pregnancy, but the difference in intake is likely modest (13, 14). Nonetheless, information on caffeine intake in all 3 trimesters of pregnancy should be collected in future studies to identify potential critical periods of the influence of maternal caffeine intake on offspring development.

In conclusion, our study makes a significant and novel contribution to the scarce literature and demonstrates that maternal, but not paternal and grandparental, caffeine intake is associated with higher offspring adiposity and obesity risk at ages 5 and 9 y, with stronger associations observed for caffeine from coffee. In view of consistent results from other observational studies and pending confirmation from randomized controlled trials, it is prudent to limit antenatal intake of caffeinated products, especially coffee, for optimal offspring adiposity.

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