Parental exposure to famine in early life and child overweight in offspring in Chinese populations

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Abstract

Background: Little is known about the transgenerational effect of nutrition deficiency in early life. This study aimed to evaluate the associations of fetal and childhood exposure to famine of parents with their offspring's risk of overweight during childhood.

Methods: This analysis included a total of 3734 participants of the China Health and Nutrition Survey aged 1-17 years whose fathers and/or mothers were born in 1955-1966. These children were classified into subgroups according to parental famine exposure status (unexposed and exposed) and timing (fetal-exposed and childhood-exposed). Random effects models were applied to evaluate the associations of parental famine exposure with body mass index (BMI) and overweight of offspring. Fractional polynomial functions were adopted to describe trajectories of BMI against age.

Results: Compared with children of unexposed parents, there was a lower risk of overweight among offspring of childhood-exposed fathers [OR(95%CI): 0.80 (0.61, 1.04)] or exposed parents [0.84 (0.68, 1.04)], particularly among male offspring, but not among those with exposed mothers only [0.98 (0.65, 1.47)]. For BMI, children with exposed mothers only had a slightly higher BMI [β(95%CI): 0.17 (-0.15, 0.49)], while those with exposed fathers only had no difference [-0.02 (-0.23, 0.19)] or exposed parents had a slightly lower BMI [-0.17 (-0.33, 0.00)] ($p< 0.05$ for interaction between maternal and paternal exposures). Stratified analysis showed little heterogeneity between male and female offspring, but the association between paternal childhood exposure to famine and lower overweight risk in offspring was more evident in high (vs low) paternal education group (p for interaction< 0.05).

Conclusions: The transgenerational associations of early-life exposure to famine with lower risks of child overweight may be via the paternal line and differ by the educational levels of parents. Further studies are warranted to confirm the results and reveal the biological mechanisms underlying.

Keywords: famine exposure; trans-generation; DOHaD; body mass index; childhood; overweight

Introduction

Child overweight, a high risk factor for metabolic and cardiovascular diseases in adulthood [1], is a major public health problem globally [2]. The epidemic of child overweight has been largely explained by a complex web of causation consisting of genetic susceptibility, intrauterine malnutrition, unbalanced energy intake and expenditure, and other factors [1]. In recent years, a growing number of studies demonstrated that the altered metabolisms in individuals exposed to malnutrition in early life not only influenced their subsequent risks of metabolic diseases [3], but also led to unhealthy phenotypes in their offspring through epigenetic inheritance approach [4].

The transgenerational effect of exposure to malnutrition in early life has been well-supported by animal experiments. One study has found that the male offspring (F2) of female rats (F1) whose mothers (F0) had restricted food during gestation inherited a phenotypic transgenerational tendency towards being overweight or obese in the juvenile period [5]. The adverse transgenerational effect on biometry and glucose metabolism of F1 and F2 progenies was also observed for female rats (F0) with low protein intake during gestation and/or lactation [6]. The metabolic dysregulation induced by malnourishment in F0 could be passed to two or more consecutive generations [7].

Evidence in humans is also accumulating. It has been suggested that maternal exposure to lead elicited an intergenerational effect on childhood overweight and obesity [8]. Maternal birthweight and body measurements during childhood were found to be associated with not only birthweight of their offspring [9, 10], but also birthweight of their grandchildren [11]. For paternal exposures, longer duration of pre-fatherhood betel chewing and smoking were independently associated with early occurrence of metabolic syndrome in offspring [12]; a negative association [13] and a positive (but non-significant) association [9] were found for paternal birthweight and growth with offspring's birthweight.

More evidence was derived from studies based on the Dutch [10, 14] and Chinese [15-17] famines, which provided unique opportunities of "natural experiments" to explore the intergenerational and transgenerational effects of malnutrition in early life. The 3-year Chinese Great famine occurred in 1959-61, based on which famine exposure status and timing in early life can be defined according to birth date. A recent study using the China Health and Nutrition Survey (CHNS) [16] found that parental exposure to famine (nutrition deficiency) in early-life was associated with increased body mass index (BMI) in adulthood among the male but not the female F2 generation. In our previous study also based on the CHNS data, we further observed higher risks of overweight and central obesity in adulthood among offspring of exposed mothers, but lower risks among offspring of childhood-exposed fathers, indicating heterogeneous effects of maternal and paternal exposures

[15].

These previous studies indicate the complexity of transgenerational effects of famine exposures in humans, particularly when phenotypes of offspring during adulthood were more likely affected by behavior and lifestyle factors in later life. Focusing on phenotypes of offspring during childhood may help better understand the transgenerational influence of famine exposure and related mechanisms. Therefore, we aimed to evaluate the associations of parental exposure to famine in early life (fetal and childhood) with BMI and risk of child overweight of their offspring using the CHNS data.

Methods

Study design and participants

The China Health and Nutrition Survey (CHNS) is an ongoing multipurpose longitudinal household survey initiated in 1989 with further nine waves. The details of the CHNS were described elsewhere [18]. Briefly, following a multistage random cluster sampling strategy, eligible subjects were enrolled from 12 provinces of China in 1989 to establish an open cohort, which was followed up in 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011, and 2015. The participants of each survey were required to provide information on demographic characteristics, socioeconomic status, general health status, lifestyle and other factors through a structured questionnaire, uptake physical examinations, and provide biological samples. All the data and samples were collected by trained health workers using standardized protocols.

The protocols adopted in each survey and the implementation process were approved by the Institutional Review Committees of the University of North Carolina at Chaple Hill, the National Institute of Nutrition and Health, and the Chinese Center for Disease Control and Prevention. Informed consent was obtained from each subject before the survey. The CHNS data can be accessed at the website of (https://www.cpc.unc.edu/projects/china).

Considering the household survey nature of the CHNS, we extracted 8972 fathers and 9791 mothers based on household ID and the relationship between family members first. Then we excluded all fathers and mothers whose spouses did not participate in any wave of the CHNS and those born before 1955 or after 1966. We further excluded those from Beijing, Chongqing, and Shanghai, the three autonomous cities not included in the sampling framework before 2009. We included children who were measured before age 18 years with eligible mothers or eligible fathers, respectively. And then we excluded non-biological offspring and those less than one year due to unavailable birth month. Considering the different protocols and stadiometers (or scales) for body measurements in the 1989 survey from those in subsequent surveys, we further excluded offspring

participating in the 1989 survey only. We also excluded offspring without body measurement data.

As shown in **Fig. S1**, three settings were included in this analysis: (1) 3121 offspring (1-17 years old) of 1956 fathers born in 1955-1966; (2) 3188 offspring of 1948 mothers born in 1955-1966; and (3) 2575 offspring of both parents (1589 fathers and 1588 mothers) born in 1955-1966. As a result, a total of 3734 offspring were included in this study, with an average of 2.67 repeated measurements. The offspring with two or more observations represented 80.0%, 79.8%, and 80.0% of all subjects in the three settings, while those having three or more observations accounted for 53.4%, 51.5%, and 53.7%, respectively.

Exposure to famine

Given that the Chinese Great Famine lasted for three years from 1959 to 1961, we defined the famine exposure status according to the birth year of parents (F1): unexposed (born in 1963-1966) and exposed (1958-1962), which included two exposure timing: fetal-exposed (1959-1962) and childhood-exposed (1955-1958), as described in previous studies [15, 17]. We further classified subjects (F2) into three groups according to famine exposure of their fathers or mothers: unexposed, fetal exposed, and childhood exposed (**Fig. S2**). For those whose both parents were born in 1955-1966, we classified them into four groups based on the exposure status of their parents: (1) neither parent exposed to famine (P0M0); (2) mother exposed only (P0M1); (3) father exposed only (P1M0); and (4) both parents exposed to famine (P1M1), and further into 8 groups according to the exposure timing of their parents. For example, the p1m2 group referred to the subjects with fetal-exposed fathers and childhood-exposed mothers. Due to no subject in the p0m2 group, the p0m1 group was factual the P0M1 group.

Anthropometric measurements

During each survey, height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) was measured for all participants with lightweight clothing and without shoes. BMI was calculated as measured weight in kilograms divided by measured height in meters squared (kg/m^2).

The parents (F1) with BMI≥ 25 kg/m^2 were identified as overweight according to the World Health Organization (WHO) criteria [19]. The offspring (F2) were considered being overweight if their BMI were at or above the 85^{th} percentile of BMI of children (aged 1-17 years) at the same age by sex according to the results of the National Survey of Child Growth and Development in China [20].

Covariates

The severity of famine exposure was defined according to the total fertility loss in each province from 1958 to 1965 [21]. Six provinces were identified as having suffered more severe famine: *Liaoning*, *Shandong*, *Jiangsu*, *Hunan*, *Henan,* and *Guizhou*, as published previously [17].

Physical activity (PA) level was evaluated using a structured questionnaire [18] and classified into *no working ability (age<7 years), very light, light, moderate, heavy,* and *very heavy* based on the metabolic equivalent of task hours [22], and then combined as three groups for data analysis: light (no working ability, very light, and light), moderate (moderate), and heavy (heavy and very heavy).

Energy intake was calculated according to the Chinese Food Composition Table (version 2002 and 2004 for the corresponding survey) based on three consecutive 24-h diet recall and weighted household food inventory and wastage collected in the CHNS [23].

Maternal and paternal educational levels were classified into the low (*junior high school or below*) or high (*senior high school or above*) groups, based on which parental educational attainment was defined as low (*neither parent obtained senior high school education or above*) or high levels (*at least one parent had senior high school education or above*).

Statistical analysis

Data were presented as mean ± standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables. Analysis of Variance (ANOVA) and Chi-square tests were used to compare the characteristics of parents or offspring by famine exposure status of parents. Of these variables, missing values for energy intake were observed among 558 of 9959 offspring (5.6%), and were imputed using age- and sex-specific average levels of energy intake. No missing value was found for other variables.

First, mean and 95% confidence interval (95%CI) of BMI of offspring (F2) by sex and famine exposure status of their parents (F1) using Linear regression models adjusting for age. Second, we applied linear mixed effect models to BMI and generalized linear mixed effect models (GLMM) to overweight, with a random intercept taking into account of the repeated measurements. These models allow for subjects measured with different frequencies or timing. Beta coefficients (95%Cis) were estimated to compare the differences in BMI between the famine-exposed and unexposed groups, while odds ratios (OR) and 95%CIs were computed to evaluate the associations of parental exposure to famine with the risk of overweight in offspring. Fractional polynomial functions were adopted to describe trajectories of BMI against age. Based on the Akaike's information criterion and

the Bayesian Information Criterion statistics, the best-fitting fractional polynomials include age^2 and age^3.

Sex, age at survey, and residence (rural/urban) of offspring were adjusted in all models. Parental BMI at the interview closest to the birth of their surveyed offspring, parental educational level, as well as birth year of mothers (in analysis for paternal exposure only) or birth year of fathers (in analysis for maternal exposure only) were also treated as potential confounders in respective models. We further adjusted for years of education, energy intake, and PA level of offspring, but did not find any substantial changes in the results. Thus, we mainly presented the results of the models without these covariates. The potential modifying effects of educational levels of parents in the associations were evaluated in stratified analyses by maternal, paternal, and parental educational levels.

Sensitivity analyses were performed by: (1) focusing on offspring with both parents born in 1955-1966; (2) including offspring from rural areas only; (3) including offspring from areas suffering from more severe famine only; (4) including offspring with two or more observations; and (5) excluding offspring of parents born in 1958 or 1963.

All analyses were performed using SAS version 9.4 and R version 4.2.

Results

Demographics of F1 parents and F2 offspring observations by parental famine exposure status

Table S1 summarizes the main characteristics of F1 parents. In both fathers and mothers, the unexposed group was younger than the fetal-exposed and the childhood-exposed groups and had a lower educational level. The fetal-exposed group was found with a slightly higher BMI and prevalence of overweight in both mothers and fathers (p> 0.05). A similar pattern in characteristics was observed among fathers and mothers who were both born in 1955-1966.

Table 1 shows the characteristics of F2 offspring at surveys. Age at survey, birth year, years of education, energy intake, and PA level in F2 offspring differed by famine exposure status of parents.

Trajectories of BMI along age in offspring by parental famine exposure status

Fig. 1 illustrates the age trajectories of BMI by parental famine exposure status in boys and girls. A “J-shape” trajectories was observed in all subgroups, with a monotonically decreasing trend before 5-6 years and an increasing trend thereafter (p< 0.05 for interaction with age).

Associations between parental famine exposure and offspring’s BMI

As shown in **Table 2**, mean BMI of offspring differed by paternal exposure status and timing (all *p values*<0.05). Offspring with fetal or childhood-exposed fathers had a lower BMI than those with unexposed fathers. After adjusting for potential confounders, a lower mean BMI was observed only in male offspring [β (95%CI): -0.43 (-0.72, -0.14)]. No significant difference in BMI was observed in offspring by exposure status of their mothers.

Further analysis demonstrated a lower BMI in offspring with exposed parents (P1M1) [-0.17 (-0.33, -0.00)] and a slightly higher BMI among those with exposed mothers only (P0M1) [0.17 (-0.15, 0.49)] than those with unexposed parents (P0M0). Regarding the exposure timing, compared with the P0M0 group, the offspring of fetal-exposed parents (p1m1) [-0.23 (-0.45, -0.02)] and male offspring of childhood-exposed parents (p2m2] [-0.33 (-0.61, -0.06)] had a lower BMI, while male offspring of fetal-exposed fathers and childhood-exposed mothers (p1m2) had a higher BMI [0.68 (0.06, 1.30)]. However, there was no heterogeneity in the relationships between boys and girls (p> 0.05 for interaction).

Associations between parental famine exposure and offspring's risk of overweight

Fig. 2 shows that the prevalence of overweight was lower in offspring of childhood-exposed fathers (9.5%) or mothers (8.8%) than those of unexposed fathers (14.7%) or mothers (13.8%) (p < 0.05). The prevalence was also lower in offspring with exposed parents (P1M1) (10.7%) than those with unexposed parents (P0M0) (13.6%). After adjusting for potential confounders, a lower risk of overweight was found for the p2m2 group compared with the P0M0 group, but not for any other exposed subgroups relative to respective unexposed groups. Stratified analyses by sex showed lower odds of overweight in boys of childhood-exposed fathers [OR (95%CI): 0.59 (0.40, 0.87)], in the male P1M1 group [0.71 (0.53, 0.95)] and the male p2m2 group [0.52 (0.34, 0.79)]. No association was found among female offspring, although no sex-heterogeneity was observed in the population. Additionally adjustment for years of education, energy intake and physical activity of offspring did not change the results substantially (**Table S2**).

A similar association pattern was observed among offspring with both parents born in 1955-1966, and a significant interaction was observed between paternal and maternal exposure to famine on BMI in male offspring (p< 0.05) (**Table 3**).

Modifying effect of parental educational level

As shown in **Table S3**, no modifying effect was observed for maternal or paternal educational

levels alone. However, parental educational level was found to modify the transgenerational associations of maternal, paternal and parental exposures. As presented in **Table 4**, the associations of famine exposures with offspring's BMI were significant only among those with highly educated parents ($p< 0.05$ for all interactions). A more pronounced association of maternal famine exposure with overweight was also observed among offspring with highly educated parents, with p for interaction with maternal famine exposure less than 0.05 (**Fig. 3**).

Sensitivity analyses

Including participants from rural areas or areas suffering severe famine, or those with two or more observations, or excluding those whose mothers or fathers were born in 1958 or 1963 did not change the transgenerational association pattern substantially, but obtained attenuated associations probably due to smaller sample size, as presented in **Table S4** to **S6**.

Discussion

In this longitudinal study focusing on the potential influence of parental exposure to the Chinese Great Famine in early-life on BMI and child overweight of their offspring, we found: 1) an inverse association of paternal childhood-exposure to famine with male offspring's BMI and overweight; and 2) a modifying effect of parental educational level in the transgenerational associations, with a stronger association among those with highly educated parents for maternal, paternal or parental exposure with offspring's BMI, and for maternal famine exposure with offspring's overweight.

In our previous study using the CHNS data, we found a higher risk of overweight among adult offspring of exposed mothers, but a lower risk in adult offspring of childhood-exposed fathers [15]. In this study, we observed a similar negative association of paternal exposure with child overweight of offspring, but a null association for maternal exposure. The significant interaction between paternal and maternal exposures was also observed in an observational study, in which offspring of fathers prenatally exposed to Dutch Famine, but not those of the exposed mothers, had higher body weight and risk of obesity than offspring of unexposed parents [14]. Our results support the hypothesis of Paternal Origins of Health and Disease (*POHaD*) [24].

Regarding the maternal exposure, however, we did not find a similar positive association in the offspring, but a lower BMI and a lower risk of overweight among children of parents with higher educational level. The results were consistent with a previous study, in which the high educational level of parents was associated with a lower BMI of their children [25]. Compared with children of

less-educated parents, those having better-educated parents are more likely to have healthy lifestyles, such as healthy food habits [26], and more time to play sports [27], which may counteract the adverse transgenerational effects of famine exposure. Our results highlighted the importance of parenting style and indicate the potential to break the transgenerational vicious circles by developing interventions on the modifiable factors.

However, parental educational level did not modify the negative associations of paternal exposure with offspring's risk of overweight. Its modifying effects on BMI appeared less evident for childhood exposure. The son preference in Chinese culture which allowed the boys to receive more care and nutrition [28] may partly account for the difference.

The transgenerational effect of famine exposure in early life has been found to be fulfilled through an epigenetic approach in animal experiments. It was reported that *in utero* nutritional scarcity of F1 embryos led to epigenetic changes in a subset of imprinted genes [29] and altered locus-specific germline DNA methylome [30] in F1 adult males. The effects of the alternations may persist for decades and can be transmitted cross generations, which is called "metabolic memory", leading to vicious circles of metabolic disorders [31]. In a recent animal experiment, offspring of trained male mice were observed to have a similar DNA methylation profile at the *PI3Kca*, *IGF2,* and *H19* loci present in the progenitor sperm, indicating that exercise-induced epigenetic changes in the paternal germline may contribute to the transgenerational transmission [32]. So far, however, no evidence was derived from humans. The associations of paternal exposure with male offspring's BMI and overweight found in this study indicate the inheritance of paternal line exposure and the involvement of germline epigenetic changes. Further studies in humans are warranted to better understand the biological mechanisms underlying our results.

To the best of our knowledge, this is the first study to systematically evaluate the transgenerational effects of famine exposure on child overweight of offspring, and for the first time find the modifying effect of parental educational level. Our results benefit from several strengths of the study. First, the study was based on the CHNS, a large-scale longitudinal survey covering most regions of China, which makes our subjects a representative sample of the Chinese populations. Second, the big sample size allowed us to evaluate the joint and independent influence of maternal and paternal exposures in two stages of early-life (fetal and childhood) and to explore potential effect modifiers. Finally, the application of the fractional polynomial functions in trajectories of BMI and the GLMM with fractional polynomials to deal with repeated binary outcomes (overweight) in this study facilitate the control of potential confounders and guarantee the accuracy of the association evaluations based on the complicated database of the CHNS.

There are several limitations. First, we used the birth year of parents to define the famine exposure status and timing in early life, which may lead to non-differential misclassification bias. However, the unchanged results in sensitivity analyses excluding parents born in 1958 or 1963 have minimized our concerns about the bias. Second, despite the large sample size of the study, the small number of subjects and observations in the subgroups classified by exposure timing and other covariates has limited the statistical power to evaluate the associations in specific subpopulations. Moreover, as the weight of sampling of the CHNS was not considered in this study, selection bias could not be excluded. These potential biases, however, may just influence the external validity of our results, but not the internal validity. Finally, to reduce the potential bias derived from the heterogeneous age distribution across subgroups, we adjusted for age at survey of offspring in all analyses. However, the residual confounding effects of age and other unrecognized confounders may still exist.

Conclusion

This exploratory analysis demonstrated transgenerational associations of famine exposure in early-life with child overweight through paternal line in Chinese populations. The results contributed to our understanding of the adverse influence of malnutrition in early life and the complexity of its potential mechanisms. Our study also highlights the importance of parenting style and improving nutrition in pregnant women and children. Further studies are warranted to confirm our findings, ideally from different populations.

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Author contributions: WHX, LL and YFY designed the study and critically revised the manuscript; WYY analyzed data and wrote the original paper; WYY and LL contributed to data analysis; All authors contributed to the final manuscript; All authors had full access to all of the data in the study; WHX and LL had primary responsibility for final content.

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Figure legends

Fig. 1 Fitted trajectories of body mass index (BMI) of offspring along age by parental exposure to famine in early life. (A) Male offspring of fathers born in 1955-1966; (B) Female offspring of fathers born in 1955-1966; (C) Male offspring of mothers born in 1955-1966; (D) Female offspring of mothers born in 1955-1966; (E) Male offspring with both parents born in 1955-1966; (F) Female offspring with both parents born in 1955-1966.

The BMI (kg/m2) trajectories fitted by linear mixed effect models with fractional polynomials for age (years) with a random intercept taking into account of the repeated measurements. All p values for interaction with age < 0.05.

P0: unexposed fathers; P1: fetal-exposed fathers; P2: childhood-exposed fathers; M0: unexposed mothers; M1: fetal-exposed mothers; M2: childhood-exposed mothers; P0M0: neither parent exposed to famine; P0M1: maternal exposed only; P1M0: paternal exposed only; P1M1: both parents exposed to famine.

Fig. 2 Associations of famine exposure of F1 parents with the risk of childhood overweight in F2 offspring

[a] P0M0: neither parents exposed to famine; P0M1: maternal exposed only; P1M0: paternal exposed only; P1M1: both parents exposed to famine. [b] p0m1: unexposed father and fetal-exposed mother; p1m0: fetal-exposed father and unexposed mother; p1m1: both parents fetal-exposed to famine; p1m2: fetal-exposed father and childhood-exposed mother; p2m0: childhood-exposed father and unexposed mother; p2m1: childhood-exposed father and fetal-exposed mother; p2m2: both parents childhood-exposed to famine.

All OR (95%CI) derived from generalized linear mixed effect models with fractional polynomials for age adjusting for sex and residence area (urban/rural) of offspring, parental educational level, BMI of both parents at the interview closest to the birth of F2 offspring, and for birth year of mothers (in the analysis for paternal exposure) or birth year of fathers (in the analysis for maternal exposure).

Fig. 3 Associations of famine exposure of F1 parents with the risk of childhood overweight in F2 offspring by parental educational level

Low education: both parents completed junior high school or lower; High education: at least one parent completed senior high school or above.

[a] P0M0: neither parents exposed to famine; P0M1: maternal exposed only; P1M0: paternal exposed only; P1M1: both parents exposed to famine. [b] p0m1: unexposed father and fetal-exposed mother; p1m0: fetal-exposed father and unexposed mother; p1m1: both parents fetal-exposed to famine; p1m2: fetal-exposed father and childhood-exposed mother; p2m0: childhood-exposed father and unexposed mother; p2m1: childhood-exposed father and fetal-exposed mother; p2m2: both parents childhood-exposed to famine.

All OR (95%CI) derived from generalized linear mixed effect models with fractional polynomials for age adjusting for sex and residence area (urban/rural) of offspring, BMI of both parents at the interview closest to the birth of F2 offspring, and for birth year of mothers (in the analysis for paternal exposure) or birth year of fathers (in the analysis for maternal exposure).

Table 1 Characteristics of offspring by maternal, paternal and parental exposure to famine in early life

	Paternal exposure (n=3121)			$p^{\dagger}$	Maternal exposure (n=3188)			$p^{\dagger}$	Parental exposure (n=2575)[a]				$p^{\dagger}$
	Unexposed	Fetal-exposed	Childhood-exposed		Unexposed	Fetal-exposed	Childhood-exposed		P0M0	P0M1	P1M0	P1M1	
N (subjects)	1191	826	1104		1230	901	1057		695	126	427	1327	
Women (n, %)	546 (45.8)	377 (45.6)	558 (50.5)	*<0.01*	553 (45.0)	419 (46.5)	522 (49.4)	*<0.01*	308 (44.3)	55 (43.7)	196 (45.9)	652 (49.1)	*<0.01*
N (observations)	3356	2264	2843		3438	2460	2541		1930	373	1211	3429	
Age at survey	9.0 ± 4.4	9.4 ± 4.3	10.3 ± 4.0	*<0.01*	9.0 ± 4.4	9.6 ± 4.1	10.9 ± 3.8	*<0.01*	9.0 ± 4.4	9.2 ± 4.2	9.1 ± 4.3	10.1 ± 4.0	*<0.01*
Birth year(range)	1982-2010	1978-2011	1974-2007	*<0.01*	1981-2010	1977-2005	1974-2004	*<0.01*	1982-2010	1983-2004	1981-2004	1975-2005	*<0.01*
Years of education	3.8 ± 3.4	4.0 ± 3.4	4.4 ± 3.3	*<0.01*	3.8 ± 3.4	4.1 ± 3.4	4.8 ± 3.1	*<0.01*	3.8 ± 3.4	4.0 ± 3.4	3.8 ± 3.4	4.4 ± 3.3	*<0.01*
Physical activity (n, %)				*<0.01*				*<0.01*					*<0.01*
Light	1249 (37.2)	757 (33.5)	668 (23.5)		1290 (37.5)	754 (30.7)	478 (18.8)		734 (38.0)	136 (36.5)	444 (36.7)	862 (25.2)	
Medium	2065 (61.5)	1472 (65.0)	2097 (73.8)		2106 (61.3)	1666 (67.7)	1956 (77.0)		1167 (60.5)	233 (62.4)	758 (62.6)	2483 (72.4)	
Heavy	45 (1.3)	35 (1.5)	78 (2.7)		42 (1.2)	40 (1.6)	107 (4.2)		29 (1.5)	4 (1.1)	9 (0.7)	84 (2.4)	
Energy intake (kcal/d)													
Boys	1748 ± 640	1847 ± 653	1945 ± 637	*<0.01*	1755 ± 637	1873 ± 637	2049 ± 639	*<0.01*	1736 ± 627	1952 ± 619	1828 ± 651	1917 ± 637	*<0.01*
Girls	1587 ± 550	1669 ± 554	1838 ± 575	*<0.01*	1606 ± 545	1730 ± 550	1914 ± 607	*<0.01*	1586 ± 547	1745 ± 541	1639 ± 548	1808 ± 572	*<0.01*

Data presented as mean±SD for continuous variables or N (%) for categorical variables.

[†] *p* value for ANOVA (continuous variables) or Chi-squared tests (categorical variables).

[a]P0M0: neither parent exposed to famine; P0M1: maternal exposed only; P1M0: paternal exposed only; P1M1: both parents exposed to famine.

Table 2 Mean BMI in offspring by parental exposure to famine

	No. of observations	BMI (kg/m^2, mean with 95%CI)[†]			Difference in BMI (kg/m^2, β with 95%CI)[‡]			*p* for interaction with sex
		All offspring	Boys	Girls	All offspring	Boys	Girls	
Paternal exposure								*0.081*
Unexposed	3356	17.1 (17.0, 17.2)	17.2 (17.1, 17.3)	16.9 (16.8, 17.0)	Ref	Ref	Ref	
Fetal exposed	2264	16.9 (16.8, 17.0)*	17.0 (16.9, 17.1)*	16.8 (16.6, 16.9)	-0.09 (-0.26, 0.08)	-0.19 (-0.42, 0.04)	0.01 (-0.24, 0.26)	
Childhood exposed	2843	16.7 (16.6, 16.8)*	16.6 (16.5, 16.8)*	16.7 (16.5, 16.8)*	-0.20 (-0.41, 0.01)	-0.43 (-0.72, -0.14)	0.05 (-0.25, 0.34)	
Maternal exposure								*0.601*
Unexposed	3438	17.0 (17.0, 17.1)	17.1 (17.0, 17.2)	16.9 (16.8, 17.1)	Ref	Ref	Ref	
Fetal exposed	2460	16.8 (16.7, 16.9)*	16.9 (16.7, 17.0)*	16.8 (16.6, 16.9)	-0.08 (-0.25, 0.09)	-0.13 (-0.35, 0.10)	-0.04 (-0.29, 0.22)	
Childhood exposed	2541	16.8 (16.7, 16.9)*	16.8 (16.7, 16.9)*	16.8 (16.6, 16.9)	0.06 (-0.16, 0.28)	0.02 (-0.28, 0.33)	0.09 (-0.23, 0.41)	
Parental exposure status[a]								*0.682*
P0M0	1930	17.0 (16.9, 17.1)	17.1 (17.0, 17.2)	16.9 (16.7, 17.0)	Ref	Ref	Ref	
P0M1	373	17.2 (16.9, 17.4)	17.3 (17.0, 17.6)	17.1 (16.7, 17.4)	0.17 (-0.15, 0.49)	0.24 (-0.18, 0.67)	0.05 (-0.44, 0.54)	
P1M0	1211	16.9 (16.8, 17.0)	17.0 (16.8, 17.2)	16.9 (16.7, 17.1)	-0.02 (-0.23, 0.19)	-0.06 (-0.35, 0.22)	0.02 (-0.29, 0.33)	
P1M1	3429	16.7 (16.6, 16.8)*	16.8 (16.6, 16.9)*	16.7 (16.6, 16.8)	-0.17 (-0.33, 0.00)	-0.24 (-0.46, -0.02)	-0.10 (-0.34, 0.14)	
Parental exposure timing[b]								*0.352*
p0m0	1930	17.0 (16.9, 17.1)	17.1 (17.0, 17.2)	16.9 (16.7, 17.0)	Ref	Ref	Ref	
p0m1	373	17.2 (16.9, 17.4)	17.3 (17.0, 17.6)	17.1 (16.7, 17.4)	0.17 (-0.15, 0.49)	0.25 (-0.18, 0.67)	0.05 (-0.44, 0.54)	
p1m0	951	17.0 (16.9, 17.2)	17.1 (16.9, 17.3)	17.0 (16.7, 17.2)	0.05 (-0.18, 0.27)	0.02 (-0.29, 0.32)	0.08 (-0.25, 0.42)	
p1m1	1052	16.7 (16.5, 16.8)*	16.8 (16.6, 17.0)*	16.6 (16.4, 16.8)*	-0.23 (-0.45, -0.02)	-0.26 (-0.56, 0.03)	-0.21 (-0.54, 0.11)	
p1m2	151	17.2 (16.8, 17.6)	17.6 (17.1, 18.1)	16.8 (16.2, 17.3)	0.34 (-0.12, 0.80)	0.68 (0.06, 1.30)	-0.12 (-0.80, 0.56)	
p2m0	260	16.4 (16.2, 16.7)*	16.4 (16.0, 16.8)*	16.5 (16.1, 16.9)	-0.29 (-0.67, 0.09)	-0.40 (-0.94, 0.14)	-0.21 (-0.74, 0.33)	
p2m1	853	16.8 (16.6, 16.9)*	16.8 (16.5, 17.0)*	16.7 (16.5, 17.0)	-0.13 (-0.36, 0.10)	-0.23 (-0.54, 0.09)	-0.05 (-0.39, 0.28)	
p2m2	1373	16.7 (16.5, 16.8)*	16.6 (16.4, 16.8)*	16.7 (16.5, 16.9)	-0.19 (-0.39, 0.01)	-0.33 (-0.61, -0.06)	-0.06 (-0.35, 0.23)	

Abbreviations: BMI - body mass index; CI - confidence Interval.

[†] Mean (95% CI) estimated using linear regression models adjusting for age at measurement.

[‡] Difference in BMI (β, 95% CI) estimated using linear mixed effect models with fractional polynomials for age adjusting for sex and residence area (urban or rural) of offspring, parental educational level, BMI of both parents at the interview closest to the birth of their F2 offspring, and for birth year of mothers (in the analysis for paternal exposure) or birth year of fathers (in the analysis for maternal exposure).

[a]P0M0: neither parent exposed to famine; P1M0: paternal exposure only; P0M1: maternal exposure only; P1M1: both parents exposed to famine. [b]p0m1: unexposed father and fetal-exposed mother; p1m0: fetal-exposed father and unexposed mother; p1m1: both parents fetal-exposed to famine; p1m2: fetal-exposed father and childhood-exposed mother; p2m0: childhood-exposed father and unexposed mother; p2m1: childhood-exposed father and fetal-exposed mother; p2m2: both parents childhood-exposed to famine.

*$p < 0.05$ compared with the unexposed group.

Table 3 Association of parental famine exposure with BMI and risk of overweight in offspring of both parents born in 1955-1966

	No. of observations	Differences in BMI (kg/m^2, β with 95%CI)			Risk of overweight (OR with 95%CI)		
		All offspring	Boys	Girls	All offspring	Boys	Girls
Paternal exposure							
Unexposed	2303	Ref	Ref	Ref	Ref	Ref	Ref
Fetal exposed	2154	-0.08 (-0.27, 0.10)	-0.12 (-0.36, 0.13)	-0.04 (-0.32, 0.23)	1.02 (0.81, 1.29)	0.90 (0.66, 1.25)	1.19 (0.85, 1.66)
Childhood exposed	2486	-0.22 (-0.44, 0.00)	-0.40 (-0.71, -0.09)	-0.03 (-0.36, 0.30)	0.83 (0.62, 1.12)	0.63 (0.41, 0.97)	1.08 (0.72, 1.63)
Maternal exposure							
Unexposed	3141	Ref	Ref	Ref	Ref	Ref	Ref
Fetal exposed	2278	-0.04 (-0.22, 0.14)	0.00 (-0.24, 0.24)	-0.10 (-0.37, 0.16)	0.96 (0.76, 1.20)	0.96 (0.70, 1.33)	0.95 (0.69, 1.32)
Childhood exposed	1524	0.03 (-0.21, 0.28)	0.11 (-0.23, 0.45)	-0.06 (-0.40, 0.29)	0.89 (0.64, 1.23)	0.97 (0.59, 1.57)	0.82 (0.52, 1.29)
p for interaction*		*0.024*	*0.016*	*0.534*	*0.339*	*0.054*	*0.569*

Abbreviations: BMI - body mass index; OR - odds ratio; CI - confidence Interval.
β (95%CI) and OR (95%CI) derived from generalized linear mixed effect models with fractional polynomials for age adjusting for sex and residence area (urban or rural) of offspring, parental educational level, BMI of both parents at the interview closest to the birth of their F2 offspring, and for birth year of mothers (in the analysis for paternal exposure) or birth year of fathers (in the analysis for maternal exposure).
**p* for interaction between paternal and maternal famine exposures.

Table 4 Associations of famine exposures of parents with BMI in offspring by parental education level

	BMI (kg/m^2, mean with 95% CI)[†]		Difference in BMI (kg/m^2, β with 95% CI)[‡]		*p* for interaction
	Low education	High education	Low education	High education	
Paternal exposure					*0.006*
No. of observations	5423	3040			
Unexposed	16.9(16.8, 17.0)	17.4(17.3, 17.6)	Ref	Ref	
Fetal exposed	17.0(16.8, 17.1)	16.8(16.7, 16.9)*	0.08(-0.14, 0.30)	-0.30(-0.57, -0.02)	
Childhood exposed	16.6(16.5, 16.7)*	16.7(16.6, 16.9)*	-0.23(-0.48, 0.02)	-0.11(-0.47, 0.26)	
Maternal exposure					*0.003*
No. of observations	5373	3066			
Unexposed	16.9(16.8, 17.0)	17.2(17.1,17.4)	Ref	Ref	
Fetal exposed	16.9(16.8, 17.1)	16.7(16.6, 16.8)*	0.16(-0.06, 0.37)	-0.38(-0.64, -0.11)	
Childhood exposed	16.7(16.6, 16.8)*	16.9(16.8, 17.1)*	0.12(-0.15, 0.39)	-0.01(-0.39, 0.36)	
Parental exposure status[a]					*0.032*
No. of observations	4239	2704			
P0M0	16.8(16.7, 17.0)	17.4(17.2, 17.6)	Ref	Ref	
P0M1	17.2(16.9, 17.5)*	17.1(16.7, 17.5)	0.28(-0.12, 0.69)	-0.08(-0.60, 0.44)	
P1M0	16.9(16.7, 17.1)	16.9(16.7, 17.1)*	0.10(-0.16, 0.37)	-0.26(-0.60, 0.08)	
P1M1	16.7(16.6, 16.9)	16.7(16.5, 16.8)*	0.02(-0.18, 0.22)	-0.49(-0.77, -0.22)	
Parental exposure timing[b]					*0.042*
p0m0	16.8(16.7, 17.0)	17.4(17.2, 17.6)	Ref	Ref	
p0m1	17.2(16.9, 17.5)*	17.1(16.7, 17.5)	0.28(-0.12, 0.69)	-0.08(-0.60, 0.44)	
p1m0	17.1(16.9, 17.3)	17.0(16.7, 17.2)*	0.22(-0.07, 0.51)	-0.23(-0.59, 0.12)	
p1m1	16.9(16.6, 17.1)	16.5(16.3, 16.7)*	0.15(-0.15, 0.45)	-0.69(-1.02, -0.37)	
p1m2	17.3(16.9, 17.8)	17.0(16.4, 17.7)	0.52(-0.05, 1.09)	0.00(-0.76, 0.77)	
p2m0	16.4(16.1, 16.8)*	16.5(16.0, 17.0)*	-0.25(-0.70, 0.21)	-0.39(-1.05, 0.28)	
p2m1	16.7(16.5, 16.9)	16.8(16.5, 17.0)*	0.01(-0.28, 0.30)	-0.39(-0.76, -0.02)	
p2m2	16.6(16.5, 16.8)*	16.7(16.5, 16.9)*	-0.09(-0.33, 0.15)	-0.39(-0.73, -0.05)	

Abbreviations: BMI - body mass index; CI - confidence Interval; Low education - both parents completed junior high school or below; High education - at least one parent completed high school or above; *p* for interaction: *p* values for interactions between parental exposure to famine and parental educational level.

[†] Mean (95% CI) estimated using linear regression models adjusting for sex and age at measurement.

[‡] Difference in BMI (β, 95%CI) estimated using linear mixed effect models with fractional polynomials for age adjusting for sex and residence area (urban/rural) of offspring, BMI of both parents at the interview closest to the birth of F2 offspring, and for birth year of mothers (in analysis for paternal exposure) or for birth year of fathers (in analysis for maternal exposure).

[a]P0M0: neither parent exposed to famine; P1M0: paternal exposure only; P0M1: maternal exposure only; P1M1: both parents exposed to famine. [b]p0m1: unexposed father and fetal-exposed mother; p1m0: fetal-exposed father and unexposed mother; p1m1: both parents fetal-exposed to famine; p1m2: fetal-exposed father and childhood-exposed mother; p2m0: childhood-exposed father and unexposed mother; p2m1: childhood-exposed father and fetal-exposed mother; p2m2: both parents childhood-exposed to famine.

*$p < 0.05$ compared with the unexposed group.

Figure 1

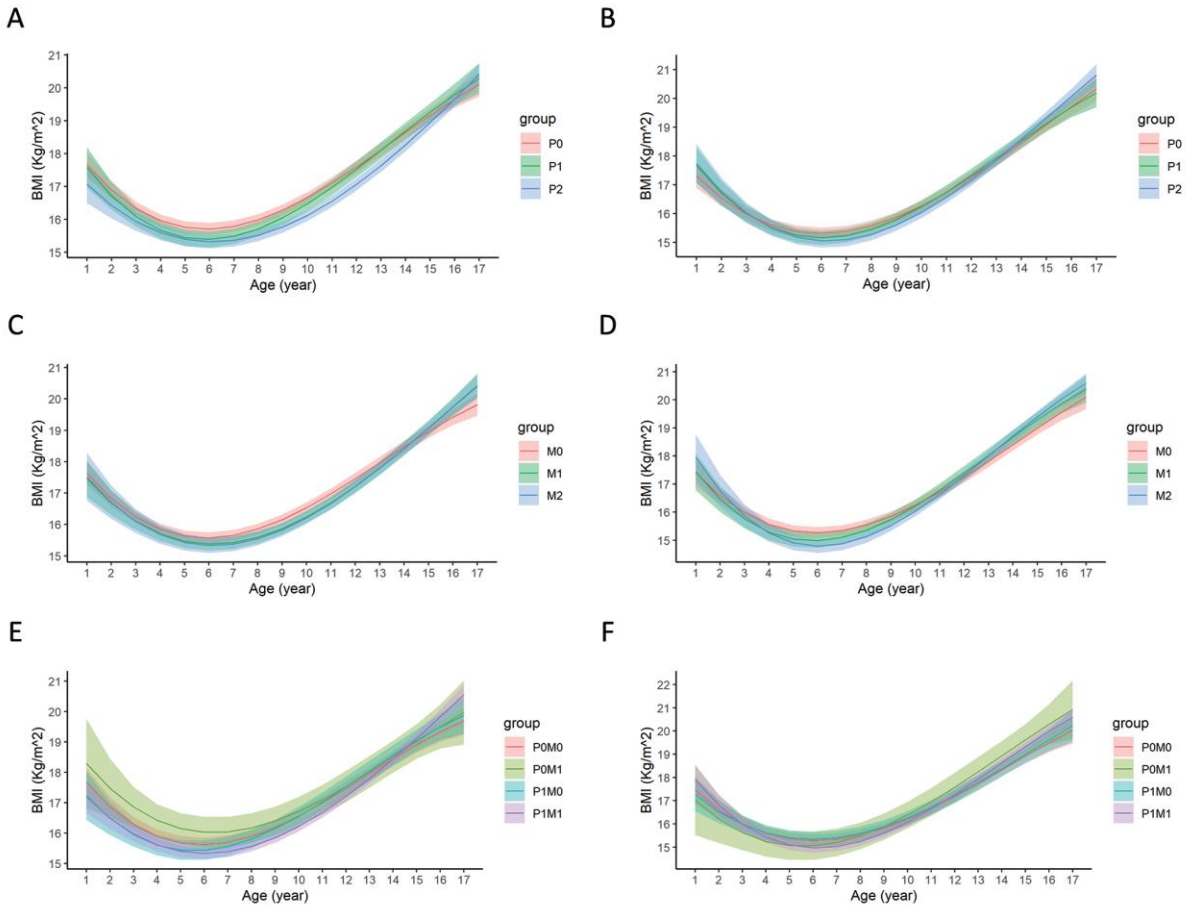

A
B
C
D
E
F
BMI (Kg/m^2)
Age (year)
group
P0
P1
P2
M0
M1
M2
P0M0
P0M1
P1M0
P1M1

Figure 2

Paternal exposure	No. of observations	Prevalence of Overweight (n, %)			Risk of Overweight (OR, 95% CI)			*p* for interaction with sex
		All offspring	Boys	Girls	All offspring	Boys	Girls	
Unexposed	3356	493 (14.7)	277 (15.1)	216 (14.2)	Ref	Ref	Ref	*0.055*
Fetal exposed	2264	312 (13.8)	155 (12.7)	157 (15.0)	0.99 (0.81, 1.22)	0.83 (0.62, 1.11)	1.20 (0.89, 1.62)	
Childhood exposed	2843	270 (9.5)	117 (8.3)	153 (10.7)	0.80 (0.61, 1.04)	0.59 (0.40, 0.87)	1.06 (0.73, 1.53)	
Maternal exposure								
Unexposed	3438	475 (13.8)	266 (14.1)	209 (13.5)	Ref	Ref	Ref	*0.244*
Fetal exposed	2460	305 (12.4)	150 (11.3)	155 (13.7)	0.95 (0.76, 1.18)	0.83 (0.61, 1.13)	1.09 (0.79, 1.49)	
Childhood exposed	2541	224 (8.8)	102 (7.8)	122 (9.8)	0.89 (0.66, 1.21)	0.84 (0.54, 1.30)	0.96 (0.63, 1.46)	
Parental exposure status[a]								
P0M0	1930	263 (13.6)	158 (14.5)	105 (12.5)	Ref	Ref	Ref	*0.363*
P0M1	373	53 (14.2)	30 (14.0)	23 (14.6)	0.98 (0.65, 1.47)	0.92 (0.53, 1.60)	1.03 (0.56, 1.90)	
P1M0	1211	163 (13.5)	76 (12.1)	87 (14.9)	0.99 (0.77, 1.29)	0.84 (0.58, 1.21)	1.20 (0.83, 1.74)	
P1M1	3429	367 (10.7)	173 (9.9)	194 (11.6)	0.84 (0.68, 1.04)	0.71 (0.53, 0.95)	1.01 (0.74, 1.37)	
Parental exposure timing[b]								
p0m0	1930	263 (13.6)	158 (14.5)	105 (12.5)	Ref	Ref	Ref	*0.188*
p0m1	373	53 (14.2)	30 (14.0)	23 (14.6)	0.98 (0.65, 1.47)	0.93 (0.54, 1.61)	1.03 (0.56, 1.89)	
p1m0	951	141 (14.8)	67 (13.4)	74 (16.4)	1.08 (0.82, 1.43)	0.92 (0.62, 1.35)	1.31 (0.89, 1.95)	
p1m1	1052	132 (12.5)	65 (11.4)	67 (13.9)	0.90 (0.68, 1.19)	0.74 (0.50, 1.10)	1.11 (0.74, 1.67)	
p1m2	151	19 (12.6)	14 (17.3)	5 (7.1)	1.18 (0.65, 2.13)	1.83 (0.86, 3.86)	0.62 (0.22, 1.75)	
p2m0	260	22 (8.5)	9 (7.1)	13 (9.7)	0.66 (0.38, 1.13)	0.51 (0.22, 1.15)	0.82 (0.40, 1.70)	
p2m1	853	99 (11.6)	48 (11.0)	51 (12.3)	0.90 (0.66, 1.21)	0.77 (0.50, 1.18)	1.06 (0.69, 1.63)	
p2m2	1373	117 (8.5)	46 (6.9)	71 (10.1)	0.72 (0.54, 0.95)	0.52 (0.34, 0.79)	0.94 (0.64, 1.38)	

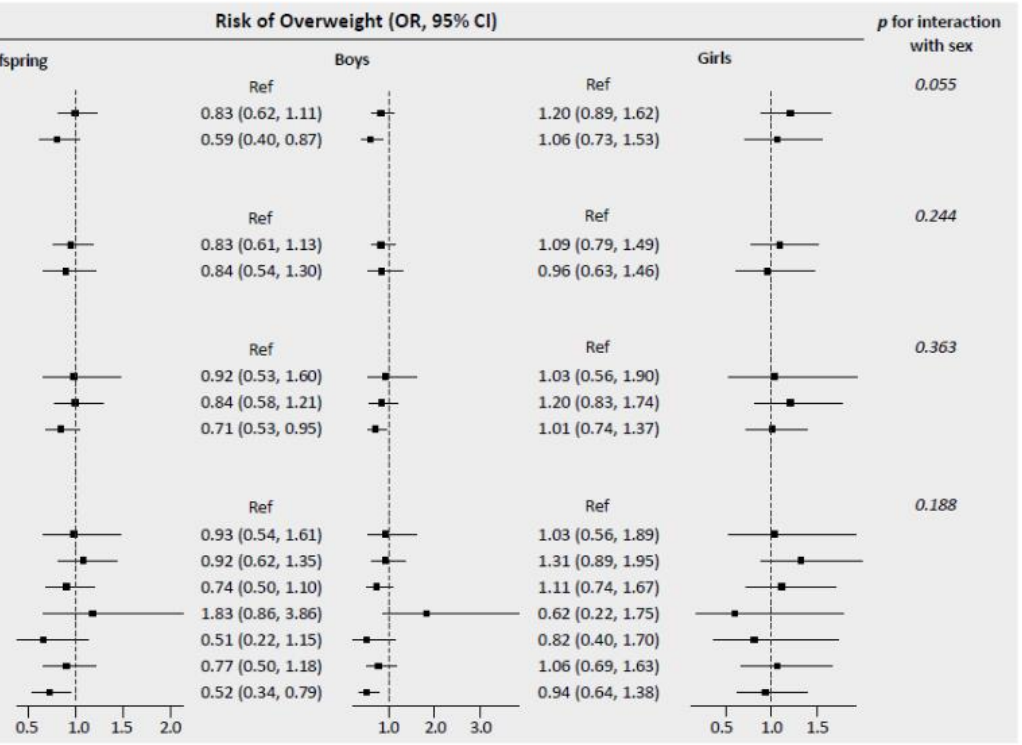
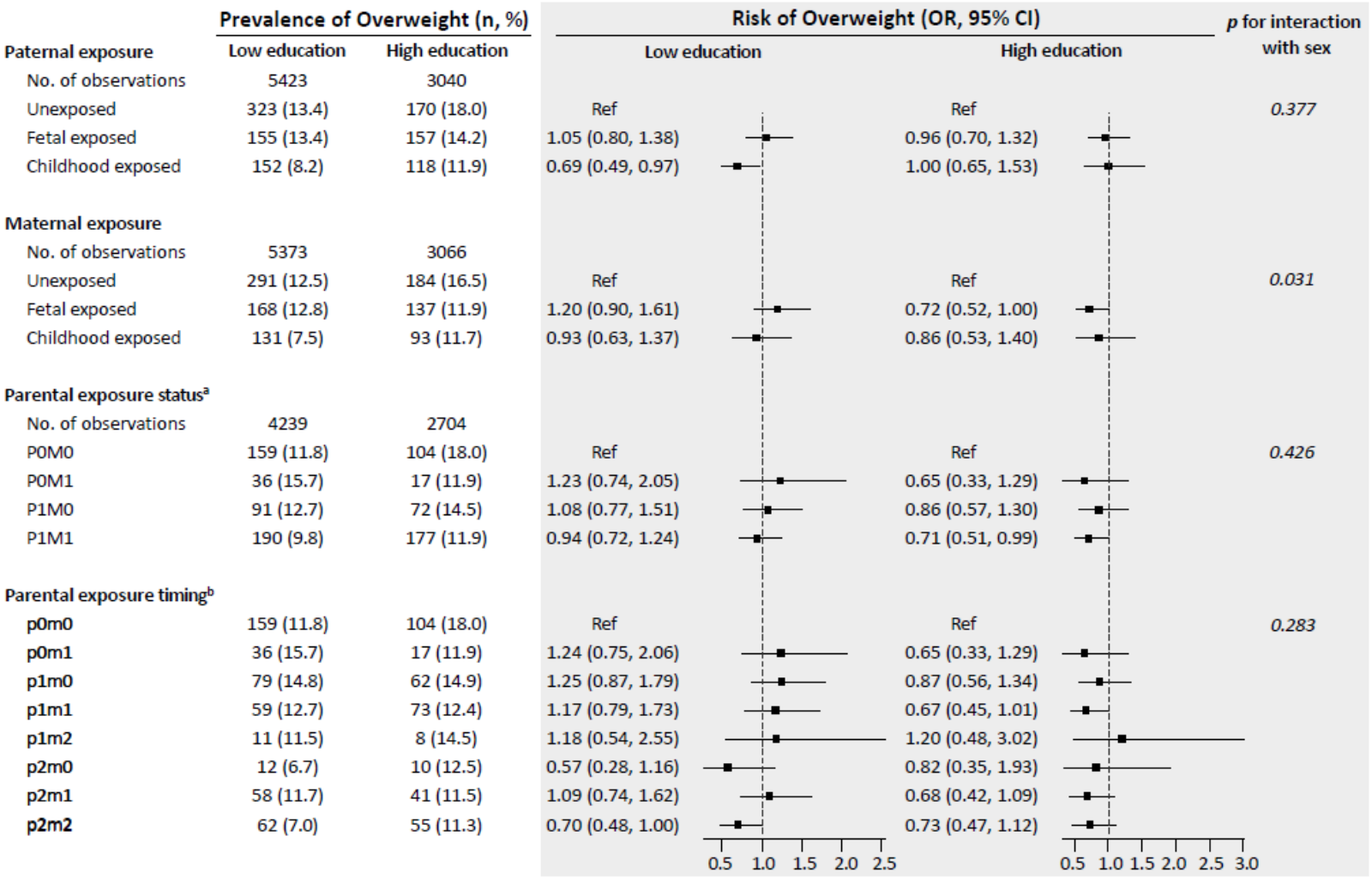


Figure 3


Prevalence of Overweight (n, %)
Risk of Overweight (OR, 95% CI)
p for interaction with sex
Paternal exposure
Low education
High education
Low education
High education
No. of observations 5423 3040
Unexposed 323 (13.4) 170 (18.0) Ref Ref 0.377
Fetal exposed 155 (13.4) 157 (14.2) 1.05 (0.80, 1.38) 0.96 (0.70, 1.32)
Childhood exposed 152 (8.2) 118 (11.9) 0.69 (0.49, 0.97) 1.00 (0.65, 1.53)
Maternal exposure
No. of observations 5373 3066
Unexposed 291 (12.5) 184 (16.5) Ref Ref 0.031
Fetal exposed 168 (12.8) 137 (11.9) 1.20 (0.90, 1.61) 0.72 (0.52, 1.00)
Childhood exposed 131 (7.5) 93 (11.7) 0.93 (0.63, 1.37) 0.86 (0.53, 1.40)
Parental exposure status[a]
No. of observations 4239 2704
P0M0 159 (11.8) 104 (18.0) Ref Ref 0.426
P0M1 36 (15.7) 17 (11.9) 1.23 (0.74, 2.05) 0.65 (0.33, 1.29)
P1M0 91 (12.7) 72 (14.5) 1.08 (0.77, 1.51) 0.86 (0.57, 1.30)
P1M1 190 (9.8) 177 (11.9) 0.94 (0.72, 1.24) 0.71 (0.51, 0.99)
Parental exposure timing[b]
p0m0 159 (11.8) 104 (18.0) Ref Ref 0.283
p0m1 36 (15.7) 17 (11.9) 1.24 (0.75, 2.06) 0.65 (0.33, 1.29)
p1m0 79 (14.8) 62 (14.9) 1.25 (0.87, 1.79) 0.87 (0.56, 1.34)
p1m1 59 (12.7) 73 (12.4) 1.17 (0.79, 1.73) 0.67 (0.45, 1.01)
p1m2 11 (11.5) 8 (14.5) 1.18 (0.54, 2.55) 1.20 (0.48, 3.02)
p2m0 12 (6.7) 10 (12.5) 0.57 (0.28, 1.16) 0.82 (0.35, 1.93)
p2m1 58 (11.7) 41 (11.5) 1.09 (0.74, 1.62) 0.68 (0.42, 1.09)
p2m2 62 (7.0) 55 (11.3) 0.70 (0.48, 1.00) 0.73 (0.47, 1.12)
0.5 1.0 1.5 2.0 2.5
0.5 1.0 1.5 2.0 2.5 3.0