Substantial intergenerational increases in body mass index are not explained by the fetal overnutrition hypothesis: the Cardiovascular Risk in Young Finns Study[1–3]

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ABSTRACT

Background: According to the fetal overnutrition hypothesis, intrauterine influences of maternal obesity increased lifelong obesity risk in the offspring. If the hypothesis is true, then the association between maternal body mass index (BMI; in kg/m^2) and offspring BMI should be stronger than the association between paternal BMI and offspring BMI, because only the mother directly influences the fetal environment.

Objectives: We prospectively examined intergenerational change in BMI and tested the fetal overnutrition hypothesis.

Design: Data on offspring weight were obtained from mothers. BMI was assessed from 2980 complete parent-offspring trios when the offspring were 3 to 18 y of age. The assessment of offspring BMI was repeated 21 y later at age 24–39 y.

Results: Adult BMI of the offspring was 1.21 units higher than the BMI of their parents at the same age, which indicates an increase in obesity levels across generations ($P < 0.0001$). Maternal BMI was more strongly associated with offspring birth weight than was paternal BMI ($P = 0.0009$). However, there were no such differences in parent-offspring associations for BMI at later developmental stages when offspring were aged 3-39 y ($P > 0.35$). The results did not materially change in a sensitivity analysis for 1% to 15% nonpaternity.

Conclusions: Because offspring share all genes with their parents, the observed substantially higher adult BMI for offspring than for parents is likely explained by environmental influences. No support was found for any specific influence from fetal environment on this intergenerational increase in adult obesity. The findings were consistent with the fetal overnutrition hypothesis only in relation to birth weight. *Am J Clin Nutr* 2007;86:1509–14.

KEY WORDS Body mass index, obesity, fetal overnutrition hypothesis, cardiovascular disease risk, Finns

INTRODUCTION

During the past decades, the prevalence of overweight and obesity has increased to epidemic proportions (1). The growing imbalance of energy intake to energy expenditure is an obvious proximal determinant for this growing trend (2), but other mechanisms may also be important (3–5). According to the fetal overnutrition hypothesis (3, 4, 6–9), greater maternal obesity during pregnancy leads to higher plasma concentrations of glucose and free fatty acids and thus to greater placental transfer of nutrients during embryonic and fetal development. This is thought to cause permanent changes in appetite, energy metabolism, and the neuroendocrine function of offspring and, as a consequence, to result in a greater risk of obesity in later life in the offspring. This hypothesis has important implications at a population level, because such fetal influence of maternal body composition on offspring body composition is likely to create a feed-forward process that accelerates the increase in obesity levels across generations (2). Indeed, there is a clear increasing trend in adult obesity over time (10).

Studies in animal models provide some support for the existence of the fetal overnutrition hypothesis (4, 5, 7). However, a key to human research in this field involves expected consequences arising from this hypothesis (8, 9). If maternal obesity affects offspring obesity through fetal influences, the association between maternal body mass index (BMI; in kg/m^2) and offspring BMI should be stronger than that between paternal BMI and offspring BMI (8, 9). This is because both father and mother contribute to the fetal genome and influence socioeconomic and behavioral factors that are important determinants of obesity in their offspring (eg, diet and physical activity), but the mother additionally directly influences the fetal environment, including fetal nutrition. To date, relatively few studies have compared the

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maternal-offspring association with the paternal-offspring association, with these showing conflicting results and mostly being based on small sample sizes (11–24). The 2 largest studies report inconsistent findings and do not include assessment of offspring BMI after adolescence (8, 9).

In the present study, we examined associations of maternal and paternal BMI estimated from parental reported weight and height with offspring birth weight and BMI in childhood, adolescence, and adulthood in a large cohort of Finns. Whereas offspring BMI was measured objectively, maternal and paternal BMIs were self-reported.

SUBJECTS AND METHODS

Study population

The parents and offspring were from the Cardiovascular Risk in Young Finns Study, an ongoing multicenter follow-up study of Finnish children and adolescents (25, 26). The original sample was 4320 children and adolescents aged 3, 6, 9, 12, 15, and 18 y who were randomly chosen in 5 areas of Finland from the national register. The baseline examination was conducted in 1980, and a follow-up was conducted in 2001 when the offspring reached 24 to 39 y of age. At baseline, the mean (±SD) age of fathers was 40.0 ± 8.4 y and that of mothers was 37.5 ± 7.6 y. The present study was conducted according to the guidelines of the Helsinki Declaration, and the study protocol was approved by local ethics committees.

Measurements

Parental BMI was determined at baseline when the children were aged 3-18 y. Mothers and fathers were asked to record their height and weight on a self-reported questionnaire (27). For pregnant women ($n = 85$), prepregnancy weight was requested. Offspring birth weight (g) and birth height (cm) were reported by the mothers, who were asked to bring with them the booklet from the well baby center in which the information is recorded. We calculated offspring ponderal index from the following formula: birth weight (kg)/[birth height (m)]^3. Offspring weight was measured at baseline (at age 3 to 18 y) and at follow-up (at age 24 to 39 y) with the offspring in light clothing without shoes to an accuracy of 0.1 kg, and height was measured by use of a wall-mounted stadiometer with 0.5-cm accuracy (28). BMI was calculated from the formula weight (kg)/[height (m)]^2.

Statistical analysis

Differences between the included and excluded individuals were assessed with the use of chi-square and *t* tests. Bivariate associations between continuous variables were assessed with Pearson's correlations. Differences in BMI, birth weight, and ponderal index between groups were tested with analysis of variance, and change in offspring BMI between baseline and follow-up was tested with repeated-measures analysis of variance. The effect of parental BMI on offspring BMI was assessed by using linear regression. The outcomes were offspring birth weight and ponderal index (total cohort), offspring BMI at age 3 to 9 y (baseline measurement for younger birth cohorts), offspring BMI at age 12 to 18 y (baseline measurement for older birth cohorts), and offspring BMI at age 24 to 39 y (follow-up measurement for the total cohort). We calculated sex-, age-, and parental age–adjusted models for maternal BMI and paternal BMI separately. A fully adjusted model included simultaneously maternal and paternal BMI in addition to sex, age, and parental age. We examined whether maternal BMI was more strongly associated with offspring birth weight, ponderal index, or BMI than was paternal BMI with the use of the one-tailed Wald test.

To examine the potential role of nonpaternity in generating attenuated paternal associations, given the nonbiological relation between some fathers and their apparent offspring, we conducted a sensitivity analysis modeling the effects of nonpaternity rates of between 1% and 15% by using the following equation (8, 9):

$$\Lambda = \begin{pmatrix} \sigma_{ff} & a\sigma_{fm} \\ a\sigma_{fm} & \sigma_{mm} \end{pmatrix}^{-1} \begin{bmatrix} (1-p)\sigma_{ff} & (1-p)\sigma_{fm} \\ \sigma_{fm} & \sigma_{mm} \end{bmatrix} \quad (1)$$

where σ_{ff} is the variance of reported father's BMI, σ_{mm} is the variance of the mother's BMI, σ_{fm} is the covariance of reported father's and mother's BMI, and p is the probability that the reported father is not the biological father. The a is used to indicate the possible covariances between the mother's and biological father's BMI; we assumed it to be equal to the covariance between the mother's and the reported father's BMI, and we used $a = 1$. The observed regression coefficients were multiplied by Λ^{-1} to obtain the corrected coefficients.

RESULTS

At baseline, full data on mothers, fathers, and their children's BMIs were obtained from 2980 parent-offspring trios (82.9% of the baseline cohort). At follow-up, data on offspring adult BMI were available for 1918 parent-offspring trios (52.2% of the baseline cohort). There were no large significant differences in age ($P = 0.77$), sex ($P = 0.08$), or BMI at baseline ($P = 0.09$) between those who were included and those who were lost to follow-up.

Mean BMIs for parents and their offspring and birth weight and ponderal index at birth for offspring are shown in **Table 1**. Fathers had a BMI 1.5 higher than mothers, and there was a 1.1 difference between male and female offspring at age 24 to 39 y. Boys had a slightly higher birth weight than did girls, but sex differences were small in offspring ponderal index and BMI during childhood and adolescence. In linear regression models adjusted for age and sex, higher birth weight predicted higher BMI at ages 3 to 18 y ($B = 0.77$, SE = 0.08, $P < 0.0001$) and 24 to 39 y ($B = 0.48$, SE = 0.20, $P = 0.01$).

Effect of parental body mass index on offspring body mass index

Maternal and paternal BMIs were correlated ($r = 0.189$, $P < 0.0001$). The association of parental BMI with offspring ponderal index and birth weight is shown in **Table 2**. Irrespective of adjustments, maternal BMI was a stronger predictor of ponderal index and birth weight than was paternal BMI. Sex-specific analyses replicated these findings for both males and females (*see* Table 1 under "Supplemental Data" in the online issue). The sensitivity analyses that take into account nonpaternity strengthened the association between paternal BMI and offspring size at birth, but the effects of maternal BMI remained substantially stronger (**Table 3**).

Associations between parental BMI and offspring BMI by age group are shown in **Table 4**. The parental-offspring associations for BMI were weaker in childhood than in adulthood. However,

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TABLE 1
Parental BMI and offspring birth weight, ponderal index, and BMI in childhood, adolescence, and adulthood: the Cardiovascular Risk in Young Finns Study ($n = 2980$)

	Male participants		Female participants		
	n	$\bar{x} \pm$ SD	n	$\bar{x} \pm$ SD	P[1]
Maternal BMI (kg/m^2)	1442	23.9 ± 3.8	1538	24.1 ± 3.9	0.51
Paternal BMI (kg/m^2)	1442	25.4 ± 3.1	1538	25.6 ± 3.1	0.15
Birth weight (g)	1217	3594 ± 562	1334	3471 ± 512	<0.0001
Ponderal index (kg/m^3)	1169	27.4 ± 2.9	1289	27.6 ± 3.6	0.07
BMI at age 3–9 y (kg/m^2)[2,3]	771	16.0 ± 1.8	806	15.9 ± 1.9	0.14
BMI at age 12–18 y (kg/m^2)[2,3]	671	19.7 ± 3.0	732	19.8 ± 2.8	0.39
BMI at age 24–39 y (kg/m^2)[3]	866	25.6 ± 4.0	1052	24.4 ± 4.6	<0.0001

[1] Age-adjusted ANOVA.
[2] $P < 0.0001$ for differences between BMI at age 3–9 and 12–18 y (sex-adjusted ANOVA).
[3] $P < 0.0001$ for differences between BMI at age 3–18 and 24–39 y (age- and sex-adjusted repeated-measures ANOVA).

the association of maternal BMI with offspring BMI did not exceed that of paternal BMI in any of the age groups, and, thus, there was no strong evidence to suggest that maternal BMI is a stronger predictor of offspring BMI than is paternal BMI. These findings were replicated in sex-specific analyses for both males and females (*see* Table 2 under "Supplemental Data" in the online issue). In an analysis stratified by years between pregnancy and measurement of parental BMI, maternal BMI was not a stronger predictor of offspring BMI than was paternal BMI when parental BMI was measured 3 y (B coefficients 0.05 and 0.05, respectively), 6 y (0.04 and 0.15), or 9 y (0.15 and 0.15) after birth.

Higher parental height was associated with higher offspring birth weight (B for maternal height = 13.3, SE = 2.15, $P < 0.0001$; B for paternal height = 3.99, SE = 1.89, $P = 0.04$), but not with offspring BMI at later life stages ($P > 0.05$). Thus, adjustment for parental height had little effect on the association between parental BMI and offspring BMI.

Changes in body mass index between generations

To estimate intergenerational increase in adult BMI, **Table 5** shows BMIs of parents and their offspring when both parents and offspring were of a similar age (24-39 y). The age-adjusted BMI of sons was 0.8 units higher than that of their fathers, and daughters had an age-adjusted BMI that was 1.5 units higher than that of their mothers ($P < 0.0001$ for both). The age- and sex-adjusted difference between offspring and parental BMI was 1.2 (95% CI: 1.0, 1.4).

DISCUSSION

Our findings suggest that maternal BMI is more strongly associated with offspring weight and ponderal index at birth than is paternal BMI, but that this difference in maternal and paternal effects disappears at later developmental stages. At 3 to 39 y of age, the association between maternal BMI and offspring BMI was not stronger than that between paternal BMI and offspring BMI. This result was seen in both male and female offspring. Our results further show an important intergenerational increase in BMI. At 24 to 39 y of age, sons' BMI was nearly one unit greater on average than was their fathers' BMI at the same age, and daughters' BMI was more than one unit greater on average than was their mothers' BMI at that age.

We directly measured weight and height to calculate BMI for the offspring; but for their parents, only self-reported information on weight and height was available. Despite underreporting

TABLE 2
Regression coefficients (B) for offspring ponderal index and birth weight on parental BMI: the Cardiovascular Risk in Young Finns Study ($n = 2458–2551$)

	B (95% CI)[1]			
Outcome	Age and sex adjusted	Age, sex, and parental age adjusted[2]	Fully adjusted[3]	P[4]
Ponderal index at birth				
Maternal BMI	0.07 (0.03, 0.10)	0.06 (0.02, 0.10)	0.06 (0.02, 0.10)	—
Paternal BMI	0.01 (−0.03, 0.06)	0.01 (−0.03, 0.05)	−0.00 (−0.05, 0.04)	0.048
Birth weight				
Maternal BMI	23.4 (17.8, 29.1)	22.0 (16.2, 27.7)	21.2 (15.3, 27.1)	—
Paternal BMI	9.4 (2.5, 16.3)	8.6 (1.8, 15.5)	4.7 (−2.2, 11.6)	0.0009

[1] Linear regression analysis ($n = 2458$ in all models for ponderal index and $n = 2551$ in all models for birth weight).
[2] Model with maternal BMI as an independent variable is adjusted for maternal age and participant's age at study entry. Model with paternal BMI as an independent variable is adjusted for paternal age and participant's age at study entry.
[3] Includes participant age, sex, maternal age, paternal age, maternal BMI, and paternal BMI as independent variables.
[4] Difference between the effects of maternal BMI and paternal BMI in the fully adjusted model based on one-tailed Wald test.

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TABLE 3
Regression coefficients for offspring birth weight on parental BMI, assuming various proportions of nonpaternity: the Cardiovascular Risk in Young Finns Study (n = 2551 parent-offspring trios)

Rate of nonpaternity	Paternal BMI	Maternal BMI	P[1]
0%	9.4	23.4	0.001
5%	10.0	23.3	0.002
10%	10.6	23.2	0.003
15%	11.4	23.1	0.006

[1] Difference between maternal-offspring and paternal-offspring associations based on one-tailed Wald test adjusted for participant's sex and age at study entry.

TABLE 5
Parents' and their offspring's BMI at ages 24–39 y: the Cardiovascular Risk in Young Finns Study (n = 4063)[1]

	BMI	Age-adjusted mean difference (95% CI)	P[2]
	kg/m^2	kg/m^2	
Fathers (n = 975)	25.1 ± 3.1[3]	—	—
Sons (n = 867)	25.6 ± 4.0	0.8 (0.4, 1.2)	<0.0001
Mothers (n = 1169)	23.1 ± 3.6	—	—
Daughters (n = 1052)	24.4 ± 4.6	1.5 (1.2, 1.9)	<0.0001

[1] Includes participants and their parents.
[2] Age-adjusted ANOVA.
[3] $\bar{x}$ ± SD (all such values).

of weight and overreporting of height in some individuals (29, 30), validity studies suggest that self-reported weight and height are generally accurate, and there is no evidence of substantial sex differences in accuracy (31). In the present study, the correlation between measured and self-reported offspring BMI was 0.99 (P < 0.0001) in both men (n = 950) and women (n = 1173) at ages 24 to 39 y. If parents' self-reports were equally accurate, it is unlikely that self-reporting led to any major bias in the comparison of maternal and paternal effects on offspring weight and BMI.

To our knowledge, only 3 previous large-scale studies have directly compared the associations of mothers' and fathers' BMIs with their offspring's BMI. In the 1958 British birth cohort, maternal correlations were slightly stronger than were paternal correlations, but, according to the authors, this may have been "due to the poorer quality of the father's height and weight data" than that of the maternal data (15). A similar finding was obtained in the Mater-University Study of Pregnancy and Its Outcomes (8). That study requested maternal BMI soon after pregnancy was ascertained (ie, at the first antenatal clinic visit), which is a particular strength because the hypothesis is concerned with maternal adiposity during pregnancy, but the use of mothers' reports to obtain paternal BMI is a weakness and could have contributed to the weaker effects in fathers. Indeed, we are not aware of any studies confirming the accuracy of BMI obtained from partners' reports. In the Avon Longitudinal Study of Parents and Children (ALSPAC; 9), mothers and fathers reported their own weight and height, and the magnitude of the association between parental and offspring BMI did not differ between parents, which corresponds with the findings of the present study.

We assessed parents' BMI when their children were aged 3 to 18 y, and we adjusted the analyses for parental age. Ideally, the measurement of parental BMI would have been taken during the intrauterine period, because later, the mother, father, and offspring may learn similar dietary and exercise habits, potentially unifying the risk of obesity between the 3 over time. However, if this removes the differences between mother-offspring and father-offspring associations for BMI, then the comparisons that are based on parental BMI assessed long after pregnancy should be diluted to a greater extent than those based on parental BMI near the pregnancy. This was not the case in our study because the

TABLE 4
Regression coefficients (B) for offspring BMI at childhood, adolescence, and adulthood on parental BMI: the Cardiovascular Risk in Young Finns Study (n = 2980)

	B (95% CI) for offspring BMI[1]			
	Age and sex adjusted	Age, sex, and parental age adjusted[2]	Fully adjusted[3]	P[4]
Offspring at age 3–9 y (n = 1577)[5]				
Maternal BMI	0.10 (0.08, 0.13)	0.10 (0.08, 0.13)	0.09 (0.06, 0.11)	—
Paternal BMI	0.12 (0.10, 0.15)	0.12 (0.09, 0.15)	0.11 (0.08, 0.14)	0.85
Offspring at age 12–18 y (n = 1403)[5]				
Maternal BMI	0.16 (0.13, 0.20)	0.17 (0.13, 0.20)	0.15 (0.11, 0.18)	—
Paternal BMI	0.21 (0.16, 0.25)	0.21 (0.16, 0.25)	0.17 (0.13, 0.22)	0.82
Offspring at age 24–39 y (n = 1918)[5]				
Maternal BMI	0.32 (0.27, 0.37)	0.35 (0.30, 0.40)	0.31 (0.26, 0.36)	—
Paternal BMI	0.34 (0.28, 0.41)	0.34 (0.28, 0.41)	0.29 (0.23, 0.35)	0.36

[1] Linear regression analysis.
[2] Model with maternal BMI as an independent variable is adjusted for maternal age and participant's age at study entry. Model with paternal BMI as an independent variable is adjusted for paternal age and participant's age at study entry.
[3] Includes participant age, sex, maternal age, paternal age, maternal BMI, and paternal BMI as independent variables.
[4] Difference between the effects of maternal BMI and paternal BMI in the fully adjusted model based on one-tailed Wald test.
[5] The association between parental BMI and offspring BMI is stronger in older age groups: P for interaction at age 3–9 and 12–18 y with maternal BMI = 0.002 and with paternal BMI = 0.003 (linear regression analysis); P for interaction at age 3–18 and 24–39 y with maternal BMI and with paternal BMI <0.0001 (repeated-measures ANOVA).

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lack of difference between mother-offspring and father-offspring associations for BMI was found in all assessments of mothers' BMI from 3 to 18 y after pregnancy. In the ALSPAC study, mothers' BMI was determined during pregnancy by requesting prepregnancy weight (9), and in that study, the strengths of the mother-offspring and father-offspring associations for BMI were in close agreement with those we obtained for offspring in childhood.

Maternal prenatal smoking has been associated with obesity in offspring (32–34), and because mothers who smoke also tend to be lighter, adjusting for this factor could have strengthened the effect of maternal BMI on offspring BMI. However, recent results suggest that the association between maternal prenatal smoking and offspring adiposity is not causal because an association of the same magnitude was also found for paternal smoking with offspring adiposity (33). There is no reason to think that maternal and paternal prenatal smoking would not also be associated with offspring BMI to the same extent in the present study, which means that lack of adjustment for maternal prenatal smoking would not substantially bias our parental comparisons.

There is some, although not consistent, evidence that greater absolute weight gain in pregnancy is associated with overnutrition of the developing fetus and later elevated adiposity in the offspring (35–38). Given that, in general, women who are lighter at the start of pregnancy will tend to gain more weight, it is possible that our findings of the effect of developmental nutrition are underestimated by the simple association of maternal BMI after pregnancy with offspring BMI. However, we found that maternal BMI was more strongly associated with offspring birth weight and ponderal index than was paternal BMI, although no difference in parental effects were seen at later stages of life. This suggests that major bias is unlikely because inaccurate measurement of maternal BMI would have diluted all comparisons between maternal and paternal effects.

The determination of offspring BMI at various stages of the offspring's life course is a particular strength of the present study. Associations between parental BMI and offspring BMI were weaker in childhood than in adulthood, which corresponds with findings in previous studies (15). This is probably because BMI in childhood changes substantially. According to a large multinational survey, the median BMI is 17 at age 1 y, decreases to 15.5 at age 6 y, and finally increases to 21 at age 20 y (39). Because of the variation in maturation pace between individuals, the shift from one stage of development to the next does not occur at the same age for everyone, which is a source of confounding in any associations between parental BMI and offspring BMI in childhood irrespective of adjustment for age and even when the assessment of offspring BMI has been at a fixed age. Such confounding may affect opportunities to detect differences in the strength between mother-offspring and father-offspring associations if the fetal effects of mothers' obesity involve programming of offspring's maturation pace. However, because there was no difference in maternal and paternal correlations with offspring BMI from across childhood, adolescence, and adulthood, our results suggest that fetal effects do not have a strong effect on future obesity risk.

The increasing trend in adult obesity was documented previously (10). Our findings are unique in showing this prospectively across 2 successive generations. Because offspring share all genes with their parents, any explanations attributing the intergenerational weight gain to genetic change are implausible. Thus, the more than one unit greater adult BMI in offspring than in their same-sex parent is likely to represent a consequence of changes in environmental factors between the successive generations.

In summary, we found higher adult BMI for offspring than for their parents, but we found no significant difference in the association of maternal BMI with later offspring BMI compared with that of paternal BMI with later offspring BMI, which suggests that shared familial characteristics such as socioeconomic position, diet, and physical activity may underlie these associations. Our findings do not support the hypothesis that fetal influences and related intergenerational acceleration mechanisms make an important contribution to the obesity epidemic in children and adults.

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