Intergenerational obesity involves both the father and the mother

Dear Sir:

Kivimäki et al (1) showed that, in a large Finnish cohort, offspring body mass index (BMI) after age 3 y is associated equally strongly with paternal and maternal BMI. It confirms a similar finding from the British 1958 cohort (2). The authors interpret the finding in light of the fetal overnutrition hypothesis (3) and conclude that maternal obesity operating prenatally cannot explain the intergenerational increase in obesity. Instead, they argue that the intergenerational increase must arise from the postnatal environment, where it is assumed that the 2 parents are equally influential.

The key assumption of the fetal overnutrition hypothesis is that “Only the mother directly influences the fetal environment” (1). If true, it would make the mother’s influence on offspring BMI greater than the father’s, which would contradict the observed equality of parental association. Hence, the authors argue that the fetal overnutrition hypothesis cannot explain the intergenerational increase in obesity.

At first sight, this conclusion seems reasonable. However, the same finding can be interpreted quite differently in a way that has important implications for the etiology of intergenerational obesity. The crux of the argument is the statement above rephrased as the question, “To what extent does the father influence the fetal environment?”

Traditionally, the answer to the question has been, “Not at all” (3), as “only the mother” has any fetal influence. But recent research suggests that this view is wrong; there is substantial literature on genomic imprinting, whereby certain fetal genes are identifiable in terms of their parent of origin (ie, mother or father), and they are differentially expressed (ie, switched on) or imprinted (ie, switched off) epigenetically. More than 50 such human genes have been identified to date, several of which relate to fetal growth (4).

A popular explanation for imprinting is the parental conflict theory of Moore and Haig (5), which states that the 2 parents of the fetus have, in evolutionary terms, different and conflicting aims for their child. The father’s fecundity is maximized by the fetus growing fast and being large at birth, whereas the mother’s fecundity is maximized if they are not so large, to avoid problems with delivery or breastfeeding. Thus, the mother and father disagree about how fast the fetus should grow. Imprinting effectively allows each parent to manipulate the other’s genes, so that growth-enhancing genes from the father and growth-suppressing genes from the mother are imprinted (4).

Thus, fetal growth depends on the expression of both maternal and paternal genes (4), and this contradicts the basis of the fetal overnutrition hypothesis that the father has no role to play in the process. Instead, both he and the mother influence the fetal environment, and both can contribute to the intergenerational increase in obesity.

Of course the mother, not the father, physically accommodates the pregnancy; therefore, one might expect her prenatal influence to be greater than his. However, we know that their combined prenatal and postnatal influences are equal, so the father would need to be more influential postnatally to compensate for the mother’s greater prenatal role.

Yet, it is hard to believe that the father has the greater influence on the child’s postnatal environment, for 2 reasons. First, his influence on offspring diet is likely if anything to be smaller than the mother’s, because she is usually the family food provider. Second, family-based interventions aimed at modification of diet or physical activity, although modestly successful (6), suggest that parental influences are too weak to explain the strong parent-child associations reported by Kivimäki et al (1) and elsewhere (2). The idea that the father’s postnatal influence is large enough to compensate for the mother’s greater prenatal influence is untested; however, we argue that this is highly unlikely.

We agree with Kivimäki et al that the postnatal influences of the mother and father may well be similar, which, given the equality of parental associations, implies similar prenatal influences as well. This leads to a surprising and counterintuitive conclusion: if the father has a fetal presence, as genomic imprinting strongly suggests, then his influence on programming the fetal environment must be similar to the mother’s.

How genomic imprinting might operate to equalize parental fetal influences is as yet a mystery, although the field is developing rapidly, and an explanation may soon emerge. We also do not yet know the relative size of the prenatal and postnatal parental contributions to intergenerational obesity, but we speculate that the influence of the prenatal component may be substantial. It is also possible that influences in the postnatal environment interact with the child’s susceptibility as programmed prenatally.

The fetal overnutrition hypothesis predicts that greater maternal obesity leads to a permanent change in offspring appetite (1). In light of the above, this can be restated as parental obesity up-regulating the child’s appetite, which in turn affects the child’s growth rate (7). This has important public health policy implications. It also explains the article’s other main finding, ie, that the equality of parental associations does not hold at the time of birth, when the mother’s BMI is far more predictive of offspring weight. If the child’s appetite drives their growth rate (as opposed to growth driving appetite), then the father’s influence on appetite ought to affect growth only postnatally, once enteral feeding has been established, and thus should have little effect on birth weight. Recent findings from the Millennium Cohort Study (8) support this idea, in that the mother’s influence on birth weight is greater than the father’s; however, both parents have a similar influence on weight gain from birth to 9 mo.

In conclusion, we argue that the fetal overnutrition hypothesis needs to be recast in a form that treats the 2 parents symmetrically, to reflect the reality of genomic imprinting. Revised in this way, the hypothesis provides a plausible explanation for the intergenerational increase in obesity.

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to increased intrauterine glucose concentrations) than in their siblings born before their mother’s diagnosis (ie, exposure to lower intrauterine glucose concentrations) (4, 7). In an elegant control it was shown that the same was not true with respect to whether the offspring were born before or after the diagnosis of diabetes in their fathers (7).

An extension of the fetal overnutrition hypothesis suggests that greater maternal adiposity might act through similar intrauterine mechanisms and might be an important driver of the obesity epidemic (8). Because greater maternal adiposity is associated with a greater risk of insulin resistance and glucose intolerance, mothers who are more obese at the time of their pregnancy will have higher concentrations of glucose and free fatty acids, and the offspring of these mothers would be expected to be programmed to become more obese themselves. The consequences of this hypothesis (if true) are important: “the obesity epidemic could accelerate through successive generations independent of further genetic or environmental factors” (8). In our recent article in the Journal (9) and in other recent articles (10–12), we have sought specifically to address this question, ie, whether via a specific intrauterine effect, greater maternal adiposity during pregnancy results in greater offspring adiposity.

A positive association between maternal BMI and offspring BMI could be explained by fetal overnutrition, but could also be explained by the simple inheritance by the fetus of their mother’s adiposity-related genes or by shared familial lifestyles related to adiposity. We argued that genetic inheritance and shared familial environment are mechanisms likely to act similarly with respect to mothers and fathers, whereas fetal overnutrition is by definition a maternal-specific effect (9–12). Thus, similar associations of maternal BMI with offspring BMI to that of paternal BMI with offspring BMI would support mechanisms likely to be similar for mothers and fathers (genetic inheritance and shared familial lifestyle/obesogenic environment).

The implication of Cole et al’s correspondence is that genomic imprinting could produce a paternally mediated prenatal effect that would closely match in size that of any maternal overnutrition effect. Although it is possible that male-line epigenetic factors exactly mimic a biological influence of maternal obesity and a consequent greater delivery of glucose, free fatty acids, and amino acids on the intrauterine environment to generate very similar associations, we feel this is unlikely. Informal or formal approaches to comparing explanatory models, which adopt the parsimony principle of Occam’s Razor (13), suggest that the likelihood of such perfectly mimicked effects, when they are produced by mechanistically completely distinct effects, is rather low.

Cole et al seem to only consider prenatal and postnatal environmental influences as explanations for the intergenerational association of BMI or obesity. It seems likely to us that genetic inheritance is one mechanism contributing to this association, although, as discussed in our article, germline genetic factors are clearly not an explanation for the increases in BMI and obesity prevalence across generations (9). In addition to examining the fetal overnutrition hypothesis in the Young Finns cohort, we have compared maternal to paternal BMI associations with offspring adiposity in 2 additional populations (10–12). In an Australian birth cohort there was a weak, but consistent, stronger association of maternal BMI with offspring BMI than of paternal BMI with offspring BMI (11). In the UK Avon Longitudinal Study of Parents and Children, associations were equivalent (as they were in the Young Finns cohort) when offspring BMI was the outcome of interest (10), but there was a consistently (though weak) stronger association of maternal BMI with offspring fat mass (12). Furthermore, in the latter study, in which we used maternal FTO genotype as an instrumental variable for her adiposity,