



Published in final edited form as:

*Am J Epidemiol.* 2007 July 1; 166(1): 14–18.

## Invited Commentary: Antecedents of Obesity—Analysis, Interpretation, and Use of Longitudinal Data

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### Abstract

The obesity epidemic causes misery and death. Most epidemiologists accept the hypothesis that characteristics of the early stages of human development have lifelong influences on obesity-related health outcomes. Unfortunately, there is a dearth of data of sufficient scope and individual history to help unravel the associations of prenatal, postnatal, and childhood factors with adult obesity and health outcomes. Here the authors discuss analytic methods, the interpretation of models, and the use to which such rare and valuable data may be put in developing interventions to combat the epidemic. For example, analytic methods such as quantile and multinomial logistic regression can describe the effects on body mass index range rather than just its mean; structural equation models may allow comparison of the contributions of different factors at different periods in the life course. Interpretation of the data and model construction is complex, and it requires careful consideration of the biologic plausibility and statistical interpretation of putative causal factors. The goals of discovering modifiable determinants of obesity during the prenatal, postnatal, and childhood periods must be kept in sight, and analyses should be built to facilitate them. Ultimately, interventions in these factors may help prevent obesity-related adverse health outcomes for future generations.

### Keywords

birth weight; body mass index; body size; growth; obesity; overweight

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In the United States, obesity is epidemic and causes misery and death. By now most epidemiologists accept that factors operating in early stages of human development can have lifelong influences on obesity-related health consequences (1,2). Two paradigms that address these issues are now converging. The first, dubbed the life-course approach to chronic disease (3), posits that ultimate health outcomes result from a myriad of factors—ranging from the macro level (e.g., the built environment) to the micro level (e.g., epigenetics)—interacting dynamically from conception through adulthood. The second, the developmental origins hypothesis of health and disease (4), emphasizes the primacy of the prenatal and early postnatal periods.

No matter which paradigm you recognize, studies that have longitudinal data for the entire period ranging from before birth to adulthood are extremely valuable. Few studies can boast this design; but owing to research-quality data collected more than four decades ago from pregnant women and their children through 7 years of age, the National Collaborative Perinatal Project (NCPP) provides an example in which adult follow-up makes it possible to examine

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Conflict of interest: none declared.

the long-term effects of these early-life exposures. In this issue of the *Journal*, Terry et al. (5) have followed a subset of female NCPP children through the age of 40 years.

In their approach to studying early-life influences on adult body mass, Terry et al. have provided two valuable services. The first is their analytic approach. Outcomes of most previous studies of obesity have been mean body mass index (BMI) or the proportion of participants whose BMI exceeds a single cutpoint (e.g., 25 kg/m<sup>2</sup> or 30 kg/m<sup>2</sup>). These approaches do not account for effects on other parts of the BMI distribution. Quantile regression is a flexible technique that allowed Terry et al. to examine the effects of exposures at many different points in the adult BMI distribution. This technique is analogous to the familiar ordinary least squares regression, which estimates the effects of exposures on the mean of the outcome distribution. In contrast, quantile regression can estimate the effects on the median of the distribution and on the 10th and 90th percentiles (as in Terry et al.'s table 2 (5)), or any other percentile, or indeed over the whole range of BMIs (6). The figures presented by Terry et al. (5) are based on quantile regressions performed for numerous percentiles, enough to produce an apparently continuous curve showing the predicted value of BMI for each quantile. The figures are a useful way to present the results in terms of actual BMI values rather than the somewhat abstract parameter estimates that the authors show for selected quantiles in their tables. In their figure 1 (5), for example, they illustrate that larger amounts of gestational weight gain had a greater impact on the upper end of the adult BMI distribution than they had on the lower end.

The second service the authors provide is more subtle but perhaps even more important. Given the strengths of the NCPP design, Terry et al. were able to examine combinations of pre- and postnatal influences in the same analysis. The first generation of life-course studies showed that the combination of lower birth weight and higher adult BMI confers the highest risk of cardiometabolic consequences of obesity (7–9). A next generation of studies, incorporating postnatal growth measures, has implicated excess weight gain throughout childhood as a determinant of adverse obesity-related outcomes in adults (10,11). While Terry et al.'s study outcome was limited to a measure of obesity itself (not its cardiometabolic consequences), the authors took another step on the exposure side of the equation by incorporating data on prenatal weight-related factors, as well as birth size and childhood weight gain. Examining prenatal factors themselves, rather than relying on birth size as a proxy, is key to understanding the relation of early developmental influences to factors operating during later periods of the life course.

The article by Terry et al. (5) raises more questions than it answers. Accordingly, some comments on methods, interpretation, and implications are warranted. Consider the quantile regression method. Other methods for examining the entire BMI distribution exist. One of them is multinomial logistic regression (12,13). Under that approach, one would examine associations with preset categories of the outcome (e.g., BMI <18.5, 18.5–<25, 25–<30, and ≥30 kg/m<sup>2</sup>). Its advantage is simplicity of interpretation, but it assumes that the categories are meaningful. Given the continuous nature of most associations between adult BMI and health outcomes, these categories of BMI are somewhat arbitrary for etiologic work. In contrast, Terry et al.'s quantile regression approach does not make assumptions about categories. For public health or clinical decision-making, however, categorical information is often more compelling, and the above BMI categories are in widespread use. Thus, no single approach is best. Tailoring an analytic strategy to a conceptual model, the available data, and the utility of the findings, as well as a combination of approaches within and across studies, will probably yield the most robust results.

Another issue is the meaning of BMI itself. BMI is a useful proxy for adiposity in clinical and public health applications, because even clinicians can cheaply and accurately measure weight and height, at least after the age of 2 or 3 years (14). In addition, BMI is a good predictor of

major health outcomes through at least middle age (15). For these reasons, epidemiologists use BMI as a surrogate outcome. Like most surrogate outcomes, however, BMI has limitations, primarily because it measures lean body mass as well as fat mass. Indeed, birth weight may be more strongly related to lean mass than to fat mass in adulthood (16). Studies of the life-course approach to adult obesity can benefit from having direct measures of adiposity, body fat distribution, and the physiologic and metabolic sequelae of adiposity.

Next consider the exposures, from both an analytic and an interpretive perspective. In their tables (5), Terry et al. show the impact of childhood weight gain per increment of 10 percentile points. This approach is intuitive, but interpretation is murky. The biggest issue is that over the 90th percentile, an increase of 10 percentile points is impossible. Similarly impossible is a decrease of 10 points below the 10th percentile. Therefore, it is usually preferable to express differences in childhood BMI with  $z$  scores. Another concern is the authors' contention, based on the data depicted in figure 2 (5), that the highest risk of adult overweight was present among persons with lower birth weights who gained weight rapidly during childhood. The difficulty is that Terry et al. did not show data for another group that may have had even higher risk—babies born *large* who gained rapidly. Understanding the interplay between birth size and subsequent weight gain is essential for pediatric clinicians, who regularly face questions about optimal growth of their youngest patients.

Terry et al. take a traditional approach to modeling the exposures. In their table 2 (5), they show how the estimates change as they enter groups of variables—maternal, birth, childhood—into the model. This approach is very useful for examining the extent to which each later group “mediates” the effects of earlier groups. However, it may not account for the complex interdependencies of particular variables on each other. For example, within the childhood group, it is plausible that weight gain from birth to age 4 months biologically entrains weight gain from ages 4 months to 12 months. In other words, through hormonal or other influences, excess weight gain in the earlier period may cause excess weight gain in the next. Including both variables in the model at the same time might cause one to underestimate the overall contribution of the earlier period. In life-course analyses, some investigators have recommended pathway analyses using structural equation modeling to overcome these difficulties (17). Whether that approach leads to greater biologic understanding or better targeting of interventions is an open question.

Ultimately, one hopes that analyses like those of Terry et al. will lead to effective, developmentally appropriate interventions for preventing adult obesity and its consequences. This public health perspective requires consideration of a number of issues beyond ranking of exposures based on relative deviance, the authors' modeling counterpart to the  $R^2$  statistic. One issue is the biologic meaning of each exposure. For example, maternal BMI may influence offspring BMI through inherited genes, fetal environment, or postnatal environment. Any particular intervention designed to change maternal BMI may have no effect on offspring BMI if the intervention does not target a relevant etiologic pathway. For example, a drug taken to reduce maternal body weight before or after pregnancy might not affect any pathway that leads to offspring adiposity. Birth weight is another variable that can represent many different etiologic pathways. On the other hand, gestational weight gain almost surely has its greatest impact through the fetal environment. Gestational weight gain is thus closer to what we might call a causative risk factor than is maternal BMI (or birth weight). As a consequence, even though maternal BMI and gestational weight gain appeared to be fairly equivalent by virtue of their similar statistical rankings at the 75th and 90th percentiles of adult BMI (Terry et al.'s table 3 (5)), without more mechanistic information about the effects of maternal BMI, changing gestational weight gain might be more effective. A related issue is the practical ability to change any of these factors. Maternal prepregnancy BMI reflects a cumulative influence of many factors over a woman's entire lifetime—even before her own birth, as emphasized by Terry et

al. (5). In some ways, trying to influence this variable is tantamount to solving the entire puzzle of the obesity epidemic, a rather large challenge indeed. In comparison, affecting gestational weight gain or perhaps infant weight gain, while daunting, seems within reach in the foreseeable future. The implication is that while many of us are trying to address the obesity epidemic from multiple fronts, let us not forget to test more focused interventions that could have a substantial impact in the near future.

The question remains of how one might modify weight gain in pregnancy or early childhood. Investigators are still in “infancy” in terms of discovering the key modifiable determinants of weight gain during these periods and effective behavior-change strategies for altering these factors. Continuing to identify and quantify these factors will make effective and cost-effective interventions possible. The promise is that such interventions will help to prevent adverse obesity-related health consequences for generations to come.

### Acknowledgements

This article was supported by a grant from the National Institutes of Health (HL 68041), Harvard Medical School, and the Harvard Pilgrim Health Care Foundation.

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## Abbreviations

**BMI**

body mass index

**NCPP**

National Collaborative Perinatal Project