Infant feeding and adiposity: scientific challenges in life-course epidemiology\textsuperscript{1,2}

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INTRODUCTION

The article by Durmuş et al (1) published in this issue of the Journal is yet another important contribution from the Generation R Study in Rotterdam and shows the value of birth cohort studies in life-course epidemiology. The focus of this article is the relation between infant feeding (the duration and exclusivity of breastfeeding and the age at introduction of solid foods) and adiposity at 6 y of age. The major value of the study is its use of dual-energy X-ray absorptiometry and abdominal ultrasound to estimate percentage body fat and its distribution, ie, abdominal compared with general body fat. Because a great deal of information was collected during pregnancy and infancy, many important potentially confounding factors were measured and controlled for statistically. These features, along with a large sample size ($n = 5063$), improve the validity and precision of estimates of the associations between infant feeding and later general and abdominal adiposity, which are risk factors for later type 2 diabetes, hypertension, and coronary heart disease in adulthood. The results show that crude associations in the expected direction (lesser adiposity with more prolonged breastfeeding and later introduction of solids) attenuate and become nonsignificant after adjustment for key confounding variables.

Along with these strengths come several minor weaknesses. Although 30% of the cohort provided no information on breastfeeding, it seems unlikely that those losses led to an important selection bias. Another potential problem, which we discuss in greater detail below, relates to the authors’ adjustment for the child’s height at the time of the adiposity measurements. First, however, we discuss why confounding by factors that influence both infant feeding and later adiposity is so likely to bias studies of the effects of the former on the latter.

ASSOCIATION OR CAUSATION? THE POTENTIAL FOR CONFOUNDOING

In most Western industrialized countries, both child and adult obesity are strongly patterned by socioeconomic status (SES) (2–4). Moreover, energy-dense (“junk”) food intake is higher and whole-grain bread, fruit, and vegetable intakes are lower among lower-SES children from those settings (5, 6). Infant feeding patterns are also strongly patterned by SES. In high-income countries, mothers who breastfeed, and particularly those who breastfeed exclusively and for a prolonged duration, are more likely to be well educated and from high-income families (7–9). In addition to SES, other important potential confounding factors include maternal smoking and high maternal BMI, both of which have been robustly associated with formula feeding and with shorter durations of breastfeeding, on the one hand, and later adiposity, on the other (10).

The systematic review by Owen et al (10) published in the Journal in 2005 [the first reference cited by Durmuş et al (1)] is extremely instructive in this regard. The authors systematically reviewed the evidence bearing on breast compared with formula feeding and mean BMI, with follow-up ranging from infancy to late adulthood. Only 11 of the studies located by the systematic review controlled for the 3 key confounders mentioned above: SES, maternal BMI, and maternal smoking during pregnancy. In those 11 studies, no association was found between breastfeeding and mean BMI, and the CI around the pooled estimate excluded a clinically important effect [weighted mean difference in BMI (in kg/m$^2$): −0.01; 95% CI: −0.05 to +0.03].

Another instructive study is the Promotion of Breastfeeding Intervention Trial, our cluster-randomized trial of a breastfeeding promotion intervention in the Republic of Belarus (11). Our follow-up results at 6.5 y are cited by the authors (their reference 43), but not our more recently reported follow-up at 11.5 y (12). In addition to the anthropometric measurements (including skinfold thicknesses and waist and hip circumferences) we reported at age 6.5 y, we also obtained bioelectrical impedance estimates of percentage body fat at 11.5 y. No differences were observed in our intention-to-treat analyses between the experimental group (who were exposed to a breastfeeding promotion intervention modeled on the Baby-Friendly Hospital Initiative) and the control group (standard care) in any of these measures at 11.5 y of age. Unlike studies from many Western settings, no

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associations were seen in observational analyses [i.e., as fed, rather than as randomized (intention-to-treat)] either at age 6.5 or 11.5 y. Our negative findings in the observational analyses show how different settings can help minimize the potential for residual confounding. Similarly negative observational findings have been reported from Brazil (13–15).

The most important point, however, is that when confounding is adequately controlled, the association between infant feeding (including age at introduction of solid foods) is attenuated toward the null.

CONTROLLING FOR THE FUTURE: NOT ALL COVARIATES ARE CONFUNDERS

One of the issues mentioned in the Introduction is that even the authors’ base models, which control for the child’s sex and age at follow-up, include height at follow-up. Height is also included in the expanded multivariable regression results shown in their Table 3 (1). Controlling for height at the same age when analyzing adiposity at age 6 means that the outcome analyzed is no longer adiposity, but rather adiposity for height. If infant feeding affects subsequent height, then including height in the regression is not an “adjustment” in the sense of controlling for a confounder, because height itself may be influenced by infant feeding (16). This type of practice is quite common in life-course epidemiology but remains highly problematic (17–19). In fact, many studies examining the relations between early-life events (not just infant feeding, but also fetal and early infant growth) and later adiposity (20–24) “adjust” for the subject’s later BMI.

In the authors’ Table 1 (for never breastfed compared with ever breastfed) and Table S1 in the Supplemental data in the online issue (for duration of breastfeeding), no relation is observed between height and breastfeeding in the Generation R cohort (1). Adjustment for height in this study therefore has little or no impact. But in other studies, and particularly those that “adjust” for weight or BMI at the time of follow-up, relations between early-life exposures and later obesity and chronic disease outcomes will be biased, because adjusting for other body measurements that may be affected by exposure at the same age as the adiposity outcomes are measured will create a selection bias and result in incorrect estimates of association between the study exposures and outcomes (25, 26).

Causal modeling, e.g., through the use of direct acyclic graphs, requires a distinction between covariates that are true confounders (in the sense of underlying causes of, and therefore temporally precedent to, exposure and outcome) before proceeding to statistical analysis. Because modern, user-friendly statistical software programs permit rapid outputs, even for large sample sizes, multivariable linear, logistic, Poisson, and other regression models can be implemented easily without requiring the user to differentiate between true confounders and causal intermediates.

Humans are smarter than computers. The latter should not be relied on to yield accurate causal inferences, at least not without important input from a human mind and a biologically based understanding of potential causal pathways and temporal relations between the variables studied.

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REFERENCES


