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Editorial

Is Early-Life Antibiotic Exposure Associated With Obesity in Children?

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Interest in the microbiome and its role in the developmental origins of obesity has increased substantially in the past decade, prompting multiple studies on early-life antibiotic exposures and childhood obesity. In addition to 20 previous studies on this topic, reviewed recently by Baron et al,[1] there are 2 new reports using prescription records to assess antibiotic exposures in New Zealand: a prospective cohort study of 5128 children by Chelimo et al[2] and a retrospective national study of 284 211 mothers and children by Leong et al.[3] Both studies found dose-dependent associations between early antibiotic exposure (prenatally or during the first 1-2 years of life) and body mass index or obesity at age 4 to 5 years. However, when Leong et al[3] restricted their analysis to siblings and twins, they found no significant association, suggesting that the association between antibiotics and obesity may be due to unmeasured confounding factors that are shared within families.

Although sibling comparisons have become popular in observational epidemiology for studying associations that are likely confounded by familial factors (eg, genetics, socioeconomic factors, home environment, and family lifestyle), they remain subject to bias from nonshared confounders and measurement error.[4] In this case, as Leong et al[3] acknowledge, it is possible that transmission of the unexposed sibling's microbiome could have "repaired" the antibiotic-induced dysbiosis in the exposed sibling. Bias can also occur in sibling studies through carry-over or contagion effects, whereby the exposure or outcome of 1 sibling affects the exposure or outcome of the other.[5] This is possible if an infection requiring antibiotic treatment (or an obesogenic microbiome) is transmitted between siblings. These potential biases should be considered alongside the authors' interpretation that the antibiotic-obesity association is entirely explained by unmeasured familial confounders.

It is noteworthy that although the cohort study by Chelimo et al[2] was smaller than that by Leong et al,[3] the authors were able to control for many familial, lifestyle, and socioeconomic factors that were not available in the larger database study by Leong et al.[3] These factors included diet, sleep, and television watching and maternal weight, education, and relationship status. Furthermore, 2 factors known to disrupt the infant microbiome—cesarean delivery and short breastfeeding duration—were assessed and found to be associated with higher body mass index later in childhood, supporting a role for the early microbiome in obesity development.

It is also important to acknowledge that childhood obesity results from multifactorial influences; thus, antibiotic exposure is neither necessary nor sufficient as a cause. However, its potential role cannot be ignored given the mounting evidence from livestock farming, animal experiments, and human studies[6] showing that antibiotics may cause changes in the gut microbiome that are associated with metabolism and weight gain. These 2 studies[2,3] contribute new data and highlight potential limitations to a growing body of evidence suggesting that antibiotics (among multiple other factors) may contribute to the development of childhood obesity, particularly when repeated exposures occur during the first year of life, a critical time for metabolic programming.

From a public health perspective, antibiotic stewardship is an urgent priority,[7] regardless of its potential role in obesity prevention. It remains unclear whether antibiotics causally influence obesity development in humans and whether particular antibiotic types or time windows of exposure are especially detrimental. These nuances are important to understand because, although the associations appear to be modest, they could be meaningful at the population level. However, further observational studies are unlikely to definitively answer these questions. It would be unethical to randomly assign infants to receive antibiotics; however, it should be feasible, as Chelimo et al[2] suggest, to study whether randomized interventions to reduce overprescribing of antibiotics

have an additional benefit of reducing the incidence of childhood obesity. Meanwhile, both antibiotic stewardship programs and childhood obesity prevention programs are clearly needed, although it remains to be seen whether and how these initiatives might converge.

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