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Antibiotics, infections, and childhood obesity

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The so-called antibiotic growth effect in animals has been well understood for the past 70 years. Antibiotics given to farm animals increase their weight. The effect is more pronounced for broad-spectrum antibiotics, and it is attenuated when animals are raised in sanitary conditions.[1] Burgeoning empirical evidence suggests that antibiotics also affect human growth. As early as 1955, Haight and Pierce[2] reported that in a randomized controlled trial of Navy recruits, a 7 week course of antibiotics led to significantly greater weight gain in the treated group compared with placebo. Although the mechanisms by which antibiotics affect growth are still being elucidated, most research points to the metabolic consequences of antimicrobial-mediated changes to the intestinal microbiota.

Because early life is a time when the intestinal micro-biome is being established and metabolic processes are developing, several investigators have done epidemiological studies to investigate the effects of antibiotics given to children and animals during infancy and subsequent development of obesity. Cox and colleagues[3] showed that antibiotics given to young mice before they wean lead to long-term increases in weight. Using electronic health record data from 64,000 children, our research team identified an exposure-response association between the number of antibiotic treatment episodes during the first 2 years of life and development of obesity in later childhood, an effect that was most pronounced for broad-spectrum antibiotics.[4] Results from several other studies[5,6] have similarly shown a positive effect of antibiotics on childhood obesity.

In their study in this issue of The Lancet Diabetes & Endocrinology, De-Kun Li and colleagues[7] challenge the notion that an antibiotic growth effect exists in human beings by investigating whether the antibiotic effect is confounded by the indications for which antibiotics are used, i.e., infections. They studied a large birth cohort of children who received care from Kaiser Permanente Northern California, a staff-model health maintenance organization in the USA. The investigators used data from electronic health records to group children into three categories according to infections and antibiotic use during the first 12 months of life: those with no infections (44 250 [17%] of 260,556 participants), those with infections but no antibiotics (77,889 [30%] participants), and those with infections who were given antibiotics (138,417 [53%] participants). Similar to other studies, they report that if they had simply compared infants given antibiotics with those

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who were not (including those with and without infections), they would have seen that antibiotics given during infancy were associated with an increased risk of childhood obesity. However, when they contrasted the risk of obesity between the antibiotic group and the infections but no antibiotic group, they identified no difference in obesity risk adjusted odds ratio [OR] 1·01, 95% CI 0·98–1·04). Moreover, they reported a significant increase in risk in the untreated infection group compared with the no infection group (OR 1.25, 95% CI 1.20–1.29) with an exposure-response association between number of infections and risk of obesity (p<0·0001). These findings led the authors to conclude that exposure to infections, and not antibiotics, increases the risk of childhood obesity, a provocative and interesting finding that merits attention.

Perhaps the first question to ask about this study is the biological plausibility of the effect of infections on bodyweight: how do infections during infancy affect long-term growth? When infants have an infection, they lose weight acutely because of increased metabolic demands and, with gastrointestinal illnesses, increased fluid loss. A tantalizing thread of evidence suggests that infections, even with respiratory viruses, could affect the intestinal microbiome through the release of interferons and other cytokines.[8] From an evolutionary perspective, this effect could be seen as adaptive; infants who have repeated infections and lose weight with each one might have had a survival advantage if their metabolic pathways were altered in ways that lead to greater weight gain in the future. This effect could be regarded as a predictive adaptive plastic response that buffers children from potentially dangerous weight loss associated with repeated infections.[9] However, this notion is speculative, and more research, particularly in animal studies, is needed to identify the potentially causal pathways between infection and weight gain.

In any observational study, special attention must be given to the potential of selection bias to explain the findings. Li and colleagues did an impressive job of measuring a large number of potential confounders, including maternal factors that might confound the association under investigation. Nonetheless, the three exposure groups were not equivalent. Because data were obtained from records of health-care service use, group assignment reflected patient care-seeking and physician practice patterns. All infants have multiple infections over the course of their first year of life, and most infant infections are not brought to medical attention. Physicians vary widely in their propensity to prescribe antibiotics.[10] Could the findings be interpreted as showing that infants whose families are more likely to seek care for infections are more likely to develop obesity in the future? The no infection group actually had sociodemographic and clinical characteristics that made it less likely that these participants would develop obesity in childhood and adolescence, including higher proportions of individuals of Asian ethnic origin, higher parental educational levels, lower maternal BMI, and lower rates of low birthweight. Although the statistical models controlled for these differences, unmeasured effects, such as stronger measures of socioeconomic status, could explain the findings. The issue of unmeasured confounding is especially important when the biological plausibility of a finding is unclear, which is the case for the linkages between infections and children’s growth.

In several other studies, the antibiotic growth effect was not limited to exposure to antibiotics during the first 12 months of life. Even the Navy recruits,[2] who were aged on

average 18 years, showed increased weight gain after antibiotic use. Future studies should attempt to replicate Li and colleagues' findings and assess a longer period of antibiotic exposure, with special emphasis on repeated use of antibiotics.[4] Establishing the reproducibility of these findings is essential before the claim can be accepted that infections, rather than antibiotics, affect children's growth. We are involved in an ongoing study of the effects of antibiotics on growth, which is being done in PCORnet, a national patient-centered outcomes research network in the US, and can attempt to replicate and further extend Li and colleagues' findings. With growing public concern about the presence of antibiotics in the food supply and their effects on human health,[11] the outcome of this work and other research on this topic, which might affect how antibiotics are used in children, will have important implications for public health policy and clinical practice.

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