News and Views

The Lasting Impact of Early-Life Antibiotic Exposure

A new study published April 16, 2025 in *The Journal of Infectious Diseases* found that children who received multiple antibiotic courses before age 2 are at a higher risk of developing asthma, food allergies, allergic rhinitis, and intellectual disability[1]. The risk was greater with 5 or more antibiotic courses.

The retrospective cohort study investigated the associations between antibiotic exposure in early childhood and the development of asthma and allergic conditions, autoimmune disorders, and neurodevelopmental or psychiatric conditions. Data was sourced from the electronic health records from the United Kingdom from 1987 to 2020. The primary exposure was defined as antibiotic prescriptions received from birth to 2 years of age. Over half of the study population was female. The study outcomes were diagnoses of chronic pediatric conditions, specifically asthma and other allergic diseases, autoimmune disorders, and neurodevelopmental or psychiatric conditions. A diagnosis of forearm fracture was included as a negative control outcome.

Among the 1,091,449 children included in the study, 685,665 had early-childhood antibiotic exposure while 405,784 did not. Antibiotic exposure before the age of 2 was associated with an increased risk of developing asthma with hazard ratio (HR) of 1.24, food allergy (HR 1.33), and allergic rhinitis (HR 1.06) compared to those without early-childhood exposure. The associations were stronger among children who received multiple courses of antibiotics. Similar results were observed in sibling-matched analyses.

Early childhood antibiotic exposure was also associated with an increased risk of intellectual disability in a dose-dependent manner, with children receiving 5 or more courses having a higher risk compared to those with 1 to 2 courses (HR 1.73). This association was even stronger in sibling-matched analyses (HR 2.79).

No significant associations were observed between antibiotic exposure and autoimmune diseases like celiac disease, inflammatory bowel disease, juvenile idiopathic arthritis, psoriasis, type 1 diabetes, or neurodevelopmental conditions, such as attention-deficit/hyperactivity disorder, autism spectrum disorders, or anxiety. The findings in sibling-matched analyses, along with negative control outcomes, suggested minimal confounding bias.

This study adds to the growing evidence of long-term adverse outcomes from early-life antibiotic exposure, and calls for judicious use of antibiotics in infancy and early childhood to not only curb antibiotic resistance, but also help lower the risk of chronic conditions later in life. When feasible, adopting a strategy of watchful waiting and monitoring may be more appropriate before initiating antibiotic treatment.

Reference

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Nontraditional Risk Factors in Young Adults with Unexplained Stroke

Nontraditional risk factors, especially migraine with aura, significantly contribute to the risk of cryptogenic ischemic stroke in adults under 50 years of age rather than traditional risks such as high blood pressure, according to research published in the journal *Stroke*[1].

The Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Triggers, Causes, and Outcome (SECRETO) study, which was conducted across 19 centers in Europe between November 2013 and January 2022. Researchers enrolled 523 patients, aged 18 to 49 years, who had recently suffered a cryptogenic ischemic. A total of 523 age- and sex-matched stroke-free individuals were also included in the study as controls. Women comprised nearly half of the study group.

A clinically significant patent foramen ovale (PFO), defined by the presence of high-risk features such as an atrial septal aneurysm or a large right-to-left shunt, was identified in 37.5% of participants. Researchers examined 12 traditional, 10 nontraditional (such as venous thromboembolism, migraine with aura, chronic kidney disease, chronic liver disease, or cancer), and 5 female-specific risk factors (such as gestational diabetes, gestational hypertension, various pregnancy complications, estrogen use, current pregnancy or puerperium), as stratified by PFO status. More than one-third of the participants (37.5%) had a clinically relevant PFO.

Stroke patients without PFO had a higher number of traditional risk factors. In these patients, the probability of cryptogenic ischemic stroke increased with each

additional traditional risk factor (odds ratio [OR] 1.42), nontraditional risk factor (OR 1.70), and female sex-specific risk factor (OR 1.70).

In patients with a PFO, each additional traditional risk factor modestly increased stroke risk (OR 1.18), but only nontraditional risk factors and female sex-specific risk factors remained significant in fully adjusted models with ORs of 2.66 and 1.94, respectively.

Population-attributable risk analysis showed that in patients without a PFO, traditional risk factors accounted for 64.7% of cryptogenic ischemic stroke cases, nontraditional factors for 26.5%, and female-specific factors for 18.9%. Among patients with a PFO, traditional factors contributed to 33.8% of cases, nontraditional factors to 49.4%, and female-specific factors to 21.8%, highlighting the greater impact of nontraditional factors in this group.

Migraine with aura had the highest individual population-attributable risk for cryptogenic stroke in both groups, 45.8% in patients with a PFO and 22.7% in those without, which the authors note aligns with previous research linking migraine to cryptogenic stroke.

PFOs can raise the risk of stroke. These findings show that traditional risk factors were more strongly associated with cryptogenic ischemic stroke in patients without a PFO, whereas nontraditional factors played a greater role in those with a PFO. Migraine with aura was a significant factor in the development of young-onset cryptogenic ischemic stroke, especially in women. Hence, due to the overlap of symptoms, patients with migraine with aura should be vigilant about stroke signs and seek medical attention immediately if they experience any sudden neurological changes.

A major takeaway from this study therefore is the necessity to recognize and consider the impact of nontraditional risk factors including female-specific factors, as they also significantly increase stroke risk. Careful assessment of both traditional and nontraditional risk factors is essential for developing effective prevention and evaluation strategies in young adults, including those who may appear to be at low risk for stroke[2].

References

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Emerging Role of Semaglutide in Metabolic Liver Disease

Semaglutide administered once-weekly at a dose of 2.4 mg resulted in significant improvements in liver histology in patients with metabolic dysfunction-associated steatohepatitis (MASH) and moderate to advanced fibrosis. Semaglutide treatment also led to substantial weight loss, according to results from a prespecified interim analysis of the ESSENCE trial at week 72 published April 30, 2025 in the *New England Journal of Medicine*[1].

In this ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled trial, 1,197 patients with biopsy-confirmed MASH and stage 2 or 3 liver fibrosis were randomly assigned to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for a total of 240 weeks in a 2:1 ratio. The co-primary endpoints for part 1 of the study were resolution of steatohepatitis without worsening of fibrosis, and improvement in liver fibrosis without worsening of steatohepatitis.

At week 72, resolution of steatohepatitis without worsening of fibrosis was achieved in nearly 63% of patients receiving semaglutide with no worsening of liver fibrosis, compared to 34.3% in the placebo group, yielding an estimated difference of 28.7 percentage points ($p < 0.001$). Improvement in liver fibrosis without worsening of steatohepatitis was observed in 36.8% of patients treated with semaglutide with no worsening of steatohepatitis compared to 22.4% in the placebo group, resulting in an estimated difference of 14.4% points ($p < 0.001$).

Combined resolution of steatohepatitis and improvement in liver fibrosis, a confirmatory secondary endpoint, was achieved in 32.7% of patients receiving semaglutide compared to 16.1% in the placebo group. This corresponded to an estimated difference of 16.5% points ($p < 0.001$).

Semaglutide treatment led to a significantly greater reduction in body weight compared to placebo, with a mean decrease of 10.5% versus 2.0%, respectively (estimated difference, –8.5% points; $p < 0.001$). However, there was no significant difference between the groups in mean changes in bodily pain scores.

Gastrointestinal adverse events occurred more frequently in patients treated with semaglutide. These included nausea (36.3% vs. 13.2%), diarrhea (26.9% vs. 12.2%), constipation (22.3% vs. 8.4%), and vomiting (18.6% vs. 5.6%).

This trial, based on data from the first 800 participants, demonstrates that once-weekly semaglutide significantly improved the major histological elements, which may reduce disease progression to cirrhosis and end-stage liver disease. The associated weight loss also contributes to the improvement of metabolic dysfunction-associated steatotic liver disease (MASLD). These findings therefore support the potential role of semaglutide as an effective therapeutic option for MASH, which addresses both hepatic pathology as well as metabolic risk factors.

Reference

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Improving Ketone Monitoring in Gestational Diabetes

Measuring blood ketone levels before breakfast, lunch, and dinner detects more episodes of ketosis compared to urinary ketone testing in women with gestational diabetes mellitus (GDM), according to results from the EVOKING study published on April 29, 2025, in the journal *Hormones*[1].

This single-center, prospective observational study from Italy enrolled 101 women with GDM who had negative fasting urinary ketone tests with the aim to evaluate whether intensive blood ketone monitoring could improve the detection of ketosis in women with GDM who test negative for urinary ketones. Their mean age was 34.7 years and they had a mean prepregnancy body mass index (BMI) of 28.2 kg/m^2. All participants were assessed between gestational weeks 30 and 32 and instructed to measure blood ketone levels before each main meal.

Ketosis was defined as having blood ketone levels exceeding 0.1 mmol/L in the fasting state on at least 25% of occasions or >0.2 mmol/L before lunch and dinner.

Blood ketones were detected in 37.6% of participants before breakfast, 13.9% before lunch, and 11.9% before dinner. Overall, 40.6% of the women showed at least one daily episode of elevated blood ketones despite negative urinary results. The presence of fasting blood ketones showed a strong correlation with detection of ketones before lunch (correlation coefficient [r] = 0.63, $p < 0.0001$) and before dinner ($r = 0.55$, $p < 0.0001$), as well as a moderate correlation with mean glucose levels one hour after breakfast ($r = 0.23$, $p = 0.02$).

The authors note that women with GDM are instructed to check their ketone levels by performing a urine test before breakfast.

However, there is often a poor correlation between fasting urine and serum ketone levels, as women with moderate to high urinary ketones may have normal serum levels. This discrepancy may be due to variable renal excretion of ketones, and dehydration where the more concentrated the urine, the higher the measured ketones. It has also been observed that since urine can remain in the bladder for many hours before excretion, the urinary ketone levels likely correspond to serum ketone levels from several hours earlier[2].

This study demonstrates that blood ketone monitoring identified more ketosis episodes than urine testing suggesting that current protocols may underestimate ketone presence. Routine monitoring of blood ketone levels before meals, particularly during fasting and postprandial states, may be recommended in women with GDM to gauge a more accurate assessment of metabolic status. This may help limit the potential risk of adverse fetal and maternal outcomes of ketosis.

References

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