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Perspective

An energetic framework for gut microbiome-mediated obesity induced by early-life exposure to antibiotics

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SUMMARY

Early-life antibiotic (ELA) exposure has garnered attention for its potential role in modulating obesity risk, although outcomes from mouse experiments and human epidemiological studies often vary based on dosage and sex. Low-dose (subtherapeutic) antibiotics can enhance energy availability through moderate alterations in gut microbiome profile, while high-dose (therapeutic) antibiotics substantially deplete the gut microbiota, thereby contributing to short-term negative energy balance. In this perspective, we propose a framework to understand how these distinct impacts of antibiotics on the gut microbiome during critical developmental windows shape long-term obesity risk through their influence on host energy balance. Using this framework, we then propose several hypotheses to explain variation in ELA-induced obesity outcomes across males and females. We conclude by discussing the evolutionary implications of ELAs, positing that the response of the gut microbiome to ELAs may signal energy availability and environmental volatility, influencing metabolic programming and adaptive traits across generations.

CURRENT UNDERSTANDING OF EARLY-LIFE ANTIBIOTIC-INDUCED ADIPOSITY

Antibiotics have been used to promote growth in agricultural animals since the middle of the 20th century. Antibiotic exposure starting in early life has been shown to promote weight gain in animals as diverse as chickens, cattle, and pigs.[1,2] Weight gain driven by exposure to early-life antibiotics (ELAs) in these animals is associated with increased feed efficiency (weight gain per unit of food consumed) and changes to both the composition of the gut microbiome and gut physiology.[1] Due in large part to concerns about antimicrobial resistance and the potential harm to consumers of residual antibiotics in meat, the use of antibiotics for growth promotion is now banned in the EU and the US. However, this has given rise to explorations into non-antibiotic compounds as growth promoters, including probiotics, prebiotics, and various plant extracts or phytochemicals that may have effects analogous to those of antibiotics.[3–5]

Despite the large body of research linking ELAs and obesity-like outcomes across species, the specific associations and their underlying mechanisms have remained unclear. It has generally been assumed that a gut microbiome is necessary to develop ELA-induced adiposity, stemming largely from a study in 1963 showing that germ-free chicks were resistant to potentiated growth in body weight with ELAs.[6] While antibiotics indeed target microbes, antibiotics can also have direct effects on the behavior of host tissues.[7] Tetracyclines, for instance, have been shown to impair mitochondrial function in plants, worms, flies, and mice, causing greater levels of disruption and reduced oxygen consumption with higher doses.[8] Additionally, phenotypes in agricultural animals can differ from those in humans and model organisms such as mice For example, the germ-free chicks in the 1963 study were larger than conventional animals,[6] whereas it has been well established in mice that germ-free animals are smaller and leaner than their conventional counterparts.[9]

Critically, the intensities and types of antibiotic exposure have also varied enormously across lines of evidence supporting ELA-induced adiposity. ELA-associated obesity in humans is typically linked to broad-spectrum antibiotic exposures involving a variety of different antibiotic classes, namely β-lactams and macrolides, as those are the antibiotics most commonly prescribed to infants and young children.[10,11] Most murine studies have used the β-lactam penicillin, but some have included macrolides, tetracyclines, and vancomycin (a glycopeptide) (Table 1). Additionally, although studies of ELAs in humans typically focus on high (therapeutic) doses of antibiotics, nearly all agricultural and mouse studies that have causally linked ELAs with later-life adiposity used low (subtherapeutic) doses that are 1–3 orders of magnitude lower, even after scaling doses isometrically across species using body surface area (Table 1).

The durations of antibiotic administration and the ages and biological sexes of treated subjects have also varied across studies (Table 1). Nevertheless, studies in humans and mice have documented critical windows for ELA-associated obesity, with the strongest increased risk of obesity for exposures within the first 6–12 months in humans[10] and from gestation through 4 weeks of age in mice.[13] Additionally, variation in the emergent phenotypes has complicated interpretation. Intra- and interspecific variations in observed phenotypic outcomes can manifest

Table 1. Mouse studies of early-life antibiotic-induced adiposity

Antibiotic dose	Exposure timing	Growth and body composition outcomes	Sex differences in body size and composition	Mechanistic evidence	Effects on gut microbiome	Diet
Cho et al.[12]						
6.7 mg/L (low-dose) penicillin, vancomycin, chlortetracycline, or penicillin + vancomycin	4 weeks to end (11 weeks)	fat mass: ↑ fat %: ↑ lean mass: no sig. diff.	unknown (only F tested)	cecal SCFA ↑	no change in density; altered composition	NC
Cox et al.[13]						
6.7 mg/L (low-dose) penicillin	weaning (4 weeks) to end (20 weeks)	fat mass: only M ↑	M-only adiposity	loss of key early-life taxa and subsequent impairment of immune development; altered hepatic and ileal gene expression; food intake in F ↑, and PYY ↓	no change in density; altered composition during treatment	NC
6.7 mg/L (low-dose) penicillin	birth to end (20 weeks)	week 3–4 growth rate: only M ↑ body mass: M and F ↑ fat mass: only M ↑	M-only adiposity			NC
6.7 mg/L (low-dose) penicillin	gestation to end (30 weeks)	fat %: M and F ↑ body mass, lean mass, fat mass: n.r.	M-biased adiposity (also earlier significant ↑ % fat in M)			NC
6.7 mg/L (low-dose) penicillin	gestation to end (30 weeks)	body mass: only M ↑ lean mass: only M ↑ fat mass: M ↑ (trend), F ↓ at 20 weeks only	M-biased adiposity (but also ↑ lean mass in M)			NC
6.7 mg/L (low-dose) penicillin	gestation to end (30 weeks)	body mass: M and F ↑ lean mass: only F ↑ fat mass: M and F ↑	no detectable bias in adiposity (but F trend of ↑ lean mass)			HFD after 17 weeks
6.7 mg/L (low-dose) penicillin	gestation to 4, 8, or 28 weeks	body mass: only F ↑ lean mass: 8-week M and all F ↑ fat mass: only F ↑	F-biased ↑ body mass			HFD after 8 weeks
Nobel et al.[14]						
333 mg/L (high-dose) tylosin	pulses from 10–15, 28–31, and 37–40 days of age	body mass: ↑ lean mass: ↑ (trend, significant only at 7 weeks) fat mass: no sig. diff.	unknown (only F tested)	altered hepatic gene expression	compositional change; delayed maturation; α-diversity ↓; absolute abundance of Bacteroidetes and Firmicutes ↓ (tylosin only)	HFD after 6 weeks
167 mg/L (high-dose) amoxicillin	pulses from 10–15, 28–31, and 37–40 days of age	body mass: ↑ from 3–5 weeks, ↓ from 6–14 weeks lean mass: ↑ (trend, significant only at 7 weeks) fat mass: no sig. diff.	unknown (only F tested)			HFD after 6 weeks

(*Continued on next page*)

Table 1. *Continued*

Antibiotic dose	Exposure timing	Growth and body composition outcomes	Sex differences in body size and composition	Mechanistic evidence	Effects on gut microbiome	Diet
Mahana et al.[15]						
6.8 mg/L (low-dose) penicillin	gestation to end (32 weeks)	body mass: M and F ↑ (detected earlier in M [4 weeks]) fat mass: M and F ↑ lean mass: M and F ↑	no significant sex differences (but adiposity detected earlier in M)	food consumption ↑ in F; no difference in fecal caloric density	altered composition	HFD after 13 weeks
Schulfer et al.[16]						
6.7 mg/L (low-dose) penicillin	gestation to 4 weeks	body mass: M ↑ (trend only), F ↑ body composition: n.r.	F-biased ↑ body mass	antibiotic-affected gut microbes (cohousing experiment)	altered composition	HFD after 16 weeks
Chen et al.[17]						
2.5 mg/L (low-dose) tylosin	gestation to end (17 weeks)	body mass: ↑ (HFD, transient for NC) fat %: ↑ (HFD, transient for NC) lean %: ↓ (HFD only, NC: n.r.)	unknown (only M tested)	altered bile acid metabolism (primary bile acids ↑, secondary bile acids ↓)	altered composition; α-diversity at 3 weeks ↑	either HFD or NC
0.31 mg/L (low-dose) tylosin	gestation to end (17 weeks)	body mass: ↑ (HFD, transient for NC) fat %: ↑ (HFD, transient for NC) lean %: ↓ (HFD only, NC: n.r.)	unknown (only M tested)		altered composition	either HFD or NC
0.31 mg/L (low-dose) tylosin	gestation to 3 weeks or end (20 weeks)	body mass: ↑ (both dose durations) fat %: ↑ (both dose durations)	unknown (only M tested)		altered composition during treatment	HFD after 3 weeks
Shelton et al.[18]						
6.7 mg/L (low-dose) penicillin	3 weeks to end (8 weeks)	body mass: no sig. diff. fat mass (abdominal): no sig. diff. lean mass: n.r.	unknown (only M tested)	intestinal lipoprotein secretion ↑, mediated by loss of *Lactobacillus* → phenyllactic acid → PPAR-γ signaling (only for mice on HFD)	altered composition, notably *Lactobacillus* ↓	NC
6.7 mg/L (low-dose) penicillin	3 weeks to end (8 weeks)	body mass: ↑ fat mass (abdominal): ↑ lean mass: n.r.	unknown (only M tested)			HFD
6.7 mg/L (low-dose) penicillin	3 weeks to 8 weeks	body mass: ↑ fat mass (abdominal): ↑ lean mass: n.r.	unknown (only M tested)			HFD
167 mg/L (high-dose) penicillin	pulses (5 days each) at 3, 5, and 7 weeks	body mass: ↑ fat mass (abdominal): ↑ lean mass: n.r.	unknown (only M tested)			HFD

For studies with multiple experiments or treatment conditions, each row represents a separate experiment or treatment. Antibiotic dose represents the concentration given in drinking water. Dosages reported relative to mouse body mass were converted using an assumed water intake of 15 mL water per kg body mass per day. All studies were performed using C57BL/6 mice. M, males; F, females; HFD, high-fat diet; NC, normal chow; SCFAs, short-chain fatty acids; PPAR-γ, peroxisome proliferator-activated receptor-γ; n.r., not reported.

as increases in fat mass only, lean mass only, or simply overall body mass, with differences in the reporting of absolute versus relative body composition making direct comparisons challenging. Studies have also routinely reported sex differences in growth and body composition, with evidence of male bias in ELA-associated obesity or overweight for humans[10] but more variable reports of sex differences in mice (Table 1).

Numerous mechanisms have been proposed to explain ELA-induced adiposity. Putative proximate mechanisms from mouse studies have focused on the impact of antibiotics on the gut microbiome, including the loss of keystone taxa within critical developmental windows[13] and subsequent changes in intestinal fat metabolism,[18] altered bile acid signaling pathways,[17] and increased microbial production of short-chain fatty acids (SCFAs).[12] There are also myriad other molecular pathways through which the gut microbiome can manipulate host energy balance.[19,20] For instance, germ-free status, antibiotic-induced microbiome depletion, or impairments to microbiome-driven SCFA production or embryonic SCFA receptors during gestation have been shown to promote later-life obesity in mice through SCFA-dependent alterations in metabolic development.[21]

Here, we synthesize knowledge of ELA effects on host energy metabolism. We then propose a general framework for understanding ELA-induced adiposity that is rooted in the role of early-life energy availability in the risk of obesity and the effects of antibiotics on microbial contributions to host energy balance. Given expected differences in the mechanisms underpinning the obesogenic effects of subtherapeutic and therapeutic ELA dosing regimens, we use here a dichotomy of “low-dose” versus “high-dose” to describe levels of antibiotic exposures, where low-dose refers to any dose set purposefully below standard therapeutic doses that has no measurable effect on absolute gut microbial abundance, while high-dose refers to therapeutic doses and above. These distinctions are by no means a precise classification but reflect the wide range of dosing in laboratory studies of ELA-induced obesity (Table 1) and allow us to better understand their varying impact on gut microbiota composition and function (see Energetic effects of early-life antibiotics across the dose spectrum). We use the term “host energy balance” throughout this piece to refer to relative energy availability, where positive energy balance occurs when an individual takes in more energy than they expend, thus gaining weight in the long term. Negative host energy balance entails the opposite, where individuals have high energy expenditure relative to intake, placing them in a state of weight loss or growth stunting.

ENERGETIC AND NON-ENERGETIC FACTORS IN THE DEVELOPMENTAL ORIGINS OF OBESITY

The environment during gestation and infancy can profoundly influence development, with lasting effects on adult phenotype. A broad literature on the developmental origins of health and disease spanning birds, rodents, and primates has shown that resource-poor, volatile, or otherwise stressful early-life environments can induce lasting changes in behavior,[22] neurophysiology,[23] and metabolism.[24,25] These physiological effects are often mediated by epigenetic modifications and contribute to shaping life history and the incidence of disease in adults, including obesity and other metabolic pathologies.

A classic illustration of the lasting impact of early-life environment on adult metabolic health in humans comes from humanitarian tragedies such as the Dutch famine of 1944–1945. The intense nutrient deprivation during this time disproportionately affected children *in utero*, increasing the risk of obesity and type 2 diabetes (T2D) when these children reached adulthood—effects that persisted even in the subsequent generation.[25,26] Similarly, *in utero* exposure to the Holodomor famine of 1932–1933 was recently found to correlate with T2D cases diagnosed from 2000 to 2008 in a large sample of >10 million Ukrainian males and females.[27] Adult T2D risk rose with the severity of famine exposure in a dose-response manner, with individuals exposed to peak famine in early gestation being more than twice as likely to have T2D compared with unexposed controls.[27] In the Dutch famine and others, prenatal famine exposure and subsequent metabolic phenotypes were linked to epigenetic modifications, particularly concerning genes related to growth and metabolism.[28]

The thrifty phenotype hypothesis characterizes increased risk of metabolic disease after early-life nutritional stress in terms of adaptations for metabolic frugality.[29,30] Under this hypothesis, predisposition toward metabolic diseases occurs because signals of an adverse environment that is resource-poor or volatile fall within critical development windows, resulting in the development of a “thrifty” phenotype in the form of a smaller, less metabolically costly body. Later in life, when the environment may not be as resource-poor or as volatile, there is considerably less phenotypic plasticity, so the thrifty phenotype persists, creating a greater vulnerability to mismatch diseases in conditions of excess energy availability.[31] Other studies have cited associations between low birth weight, smaller organs, faster post-natal growth, and adult disease to suggest that metabolic disease in adults could result from faster “catch-up” growth during childhood or else from overloading the lower metabolic capacity of relatively small organs in later-life resource-rich environments.[32]

While the thrifty phenotype hypothesis focuses on the metabolic effects of early-life undernutrition, there are also strong links between adult metabolic disease and characteristics of early-life overnutrition, such as maternal obesity/overweight,[33] maternal high-fat diet[34] or consumption of ultra-processed foods,[35] and high birth weight.[36] For instance, a large meta-analysis reported that high birth weight (defined as >4 kg) nearly doubled the risk of obesity compared with lower birth weights.[36]

Finally, in addition to energetic deficiency or excess, environmental factors with no clear energetic contribution can also promote later-life obesity, such as maternal smoking,[37] short sleep duration,[38] and a range of psychological stressors, including parental abuse/neglect, unstable home environments, and witnessing violence.[39] In these cases of early-life adversity—whether involving energetic restriction, energetic excess, or non-energetic adversity—the risk of developing adult obesity is compounded by other obesity risk factors, such as consumption of a processed diet high in fat and sugar. Even in mouse studies of ELA-induced obesity, researchers have observed that high-fat diet feeding greatly exacerbates the obesogenic effects of ELA exposure.[13] Overall, developmental risk factors for obesity are therefore closely tied, but not limited to, variations in early-life energy availability (Figure 1A).

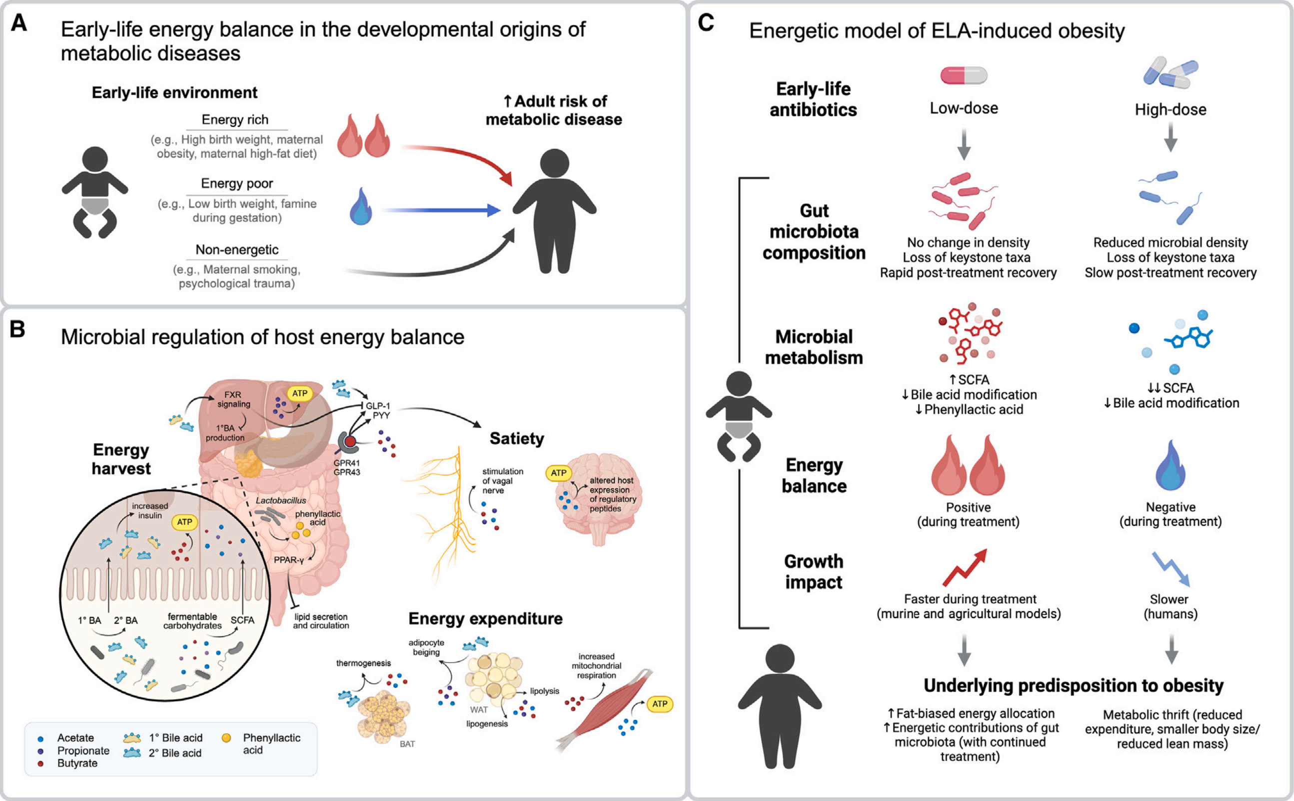

Figure 1. Proposed energetic and developmental framework underlying ELA-induced obesity

(A) Conventional understanding of developmental contributors to adult risk of metabolic diseases includes characteristics associated with energetic excess and energetic limitation in addition to those unrelated to energy availability.

(B) The gut microbiota contributes to host energy balance through a variety of mechanisms. Highlighted here are the pleiotropic effects of short-chain fatty acids (SCFAs), primary and secondary bile acids (1°BA and 2°BA), and phenyllactic acid on pathways involved in energy harvest, energy expenditure, and satiety. Abbreviations are as follows: brown adipose tissue, BAT; white adipose tissue, WAT; farnesoid X receptor, FXR; glucagon-like peptide-1, GLP-1; peptide YY, PYY; G-protein coupled receptor, GPR; adenosine triphosphate, ATP.

(C) Early-life exposure to low-dose or high-dose antibiotics affects the gut microbiota and microbial metabolism, resulting in changes to host energy balance, growth patterns, and ultimately increased risk of obesity.

Figure 1 was created with BioRender.com.

GUT MICROBIOME IN HOST ENERGY BALANCE

The gut microbiome plays an essential role in host energy balance, modulating mechanisms of energy gain, energy expenditure, and energy storage, as well as impacting the risk and onset of metabolic diseases[20] (Figure 1B). The presence of microbes in the gut dramatically increases energy gain. A seminal study demonstrated that when germ-free mice were inoculated with a typical murine gut microbiota, their body fat increased by 57%, despite a 29% reduction in food intake and 27% higher energy expenditure compared with mice that remained germ free.[9] Conversely, when obese or diabetic mice had their gut microbiota largely ablated through heavy treatment with antibiotics, they returned to normal or near-normal levels of body fat and insulin sensitivity.[40–42]

Critically, variation in gut microbiome profiles contributes to variation in energy metabolism. Metabolic-disease-associated gut microbiome profiles have been shown to contribute causally to disease phenotypes, as evidenced by gnotobiotic transplant experiments in which germ-free mice colonized with the gut microbiota of individuals with or without obesity or glucose intolerance recapitulate the metabolic phenotypes of their donors.[40,43] Social transmission of gut microbes between individuals, such as when mice are housed together in a cage, can also partially transfer the metabolic phenotype between individuals,[16,43] raising the possibility that classically "non-communicable" metabolic conditions could have a communicable degree of risk or protection mediated by the social transmission of risk-modulating microbes.[44]

Such effects of the gut microbiome on energy metabolism at least partly derive from the colonic microbial fermentation of carbohydrates that escape digestion in the host small intestine into SCFAs. SCFAs can be absorbed by the host for direct use as energy substrates and indirect use in many signaling pathways, including those for appetite, fat storage, thermogenesis, and immune regulation.[45,46] Some studies have implicated increases in SCFA-mediated colonic energy harvest as a contributor to host body fat.[45,47] Additionally, loss of acetate (the most abundant SCFA in the gut) has been implicated in the beiging of white adipose tissue and brown fat thermogenesis, a mechanism through which heavy antibiotic treatment is thought to reverse diet-induced obesity in mice.[41,48] However, pleiotropic effects of

SCFAs mean that they do not always contribute to positive host energy balance.[20] For instance, increased intestinal SCFA production is a commonly cited mechanism for the protective effects of a high-fiber diet against chronic inflammation and obesity. In particular, providing the gut microbiota with fermentable substrates generates butyrate, a primary metabolic fuel for the gut epithelium, and thereby an important contributor to gut barrier integrity.[45,49] Additionally, the SCFA compounds butyrate and propionate can regulate hunger by stimulating the production of GLP-1 and peptide YY (PYY) by intestinal L cells via interactions with GPR41 and GPR43 receptors.[45]

The gut microbiome also produces or modifies many other metabolites with significant effects on host energy metabolism, such as bile acids that can confer protection against obesity and T2D[50] (Figure 1B). Upon the release of liver-derived primary bile acids into the gut lumen, the microbiomes of the small and large intestine deconjugate and dehydroxylate primary bile acids, generating secondary forms.[51] Once absorbed, both primary and secondary bile acids act on multiple different tissues to modulate the further hepatic production of primary bile acids, increase GLP-1 production in enteroendocrine cells, or increase insulin sensitivity and energy expenditure in muscle and brown adipose tissue.[46,50]

The effects of the gut microbiome on host energy balance are complex, multifaceted, and challenging to predict.[20] Overall, however, germ-free status or robust depletions of the gut microbiota typically promote negative energy balance, whereas more modest perturbations of the gut microbiome shift the relative abundance of microbial taxa and metabolites, eliciting more varied downstream consequences for host energy metabolism.

LOW-DOSE ELAs: NEUTRAL-TO-POSITIVE EFFECTS ON HOST ENERGY BALANCE

Most murine and agricultural studies linking ELA exposure to adiposity or faster weight gain have used low (subtherapeutic) doses, typically ~2% of a standard therapeutic dose[52] (Table 1). A landmark study of low-dose ELAs in mice found that adult obesity could be induced by early-life treatment with subtherapeutic doses of various antibiotics, including penicillin, vancomycin, chlortetracycline, or all three in combination.[12] While this study and prior agricultural studies used continuous, life-long antibiotic administration, later studies established that exposures prior to weaning were sufficient to induce the later-life adiposity phenotype.[13] Indeed, continued low-dose antibiotic exposures later in life seem to have little additive effect, with similar adult outcomes observed among mice with life-long treatment versus treatment stopped at weaning.[13] These mouse studies of low-dose ELAs also found faster growth rates in young ELA-treated mice, concurring with agricultural evidence that low-dose ELAs may increase the amount of energy available to the host.[13]

Low-dose ELA exposure has relatively moderate effects on the gut microbiota compared with therapeutic exposures. Whereas therapeutic exposures typically elicit dramatic changes in both the relative and absolute abundances of gut microbes, low doses of antibiotics have been shown to consistently alter gut microbiome composition without detectable reductions in gut microbial community density.[12,13] When treatment stops, gut microbiome composition tends to recover quickly to resemble that of untreated controls.[13] However, the extent to which there may be persistent transcriptional or metabolomic differences in gut microbiomes with a history of low-dose antibiotic exposure remains largely undetermined. Despite the apparently moderate effects of low-dose ELAs on the gut microbiome, these microbiome changes are nevertheless consequential for adiposity, with transplantation of the gut microbiota from mice treated with low-dose ELAs shown to promote obesity in murine gnotobiotic recipients.[13,17]

Two murine studies of low-dose ELAs have shown that the gut microbiota associated with ELA-induced adiposity can transfer the phenotype of greater adiposity to germ-free mice.[13,17] In the first, Cox et al.[13] used the cecal microbiota of 18-week-old female controls and those treated continuously with low-dose penicillin from mid-gestation to inoculate 3-week-old germ-free female mice. After 5 weeks, recipients of ELA donor microbiota gained significantly more body fat than recipients of control microbiota. In a second gnotobiotic experiment, Chen et al. transplanted the fecal microbiota of adult male controls or males treated continuously with low-dose tylosin from mid-gestation into 8-week-old germ-free males.[17] Here as well, recipients of ELA donor microbiota gained slightly more weight and body fat over the subsequent 12 weeks post-inoculation.

However, interpretation of these outcomes should be approached with caution for two main reasons. First, in these transplant studies, obesity in recipients may have been driven by the transplant of obesity-associated gut microbiota rather than the effects of antibiotic treatment per se. Studies of obesity in humans and mouse models of genetic or diet-induced obesity have consistently found that the obesity-associated microbiome promotes increased adiposity.[43] As these gnotobiotic transplant studies of low-dose ELA-induced obesity derived their inocula from adult mice that were already obese,[13,17] we cannot distinguish whether the recipients of ELA-exposed microbiota recapitulated donor phenotypes because of the effects of ELAs or, alternatively, because of the effects of obesity on the microbiota of ELA-exposed donors. A more robust test of whether low-dose antibiotics increase gut microbial contributions to host energy balance would be to transplant using the same donors exposed to ELAs but using microbiome samples collected early in life, prior to the onset of obesity or other metabolic differences from controls.

Second, while the first of these studies colonized 3-week-old germ-free mice,[13] the second used 8-week-old germ-free mice as transplant recipients,[17] meaning that they were well past the previously proposed murine critical window for ELA-induced adiposity (gestation through 4 weeks of age).[13] This use of older mice is an understandable choice given the practical difficulty of directly inoculating very young germ-free mice, a procedure typically involving oral gavage. If anything, using these older mice as recipients likely dampened the impacts of inoculation with an ELA-exposed microbiota. However, such evidence reopens the question of how important the critical window of antibiotic exposure actually is for the development of low-dose ELA-induced adiposity. One alternative explanation could be that gut microbiomes during treatment with low-dose antibiotics are slightly obesogenic, regardless of host age. In this case, increased host adiposity may be more evident with earlier ELA treatment simply because of the longer duration of exposure or else due to the additional impact of early-life overnutrition on metabolic development. Colonization of younger mice, for instance by cross-fostering newborn pups with treated mothers or performing transplant experiments involving age-matched donors and recipients at varying stages of donor development, would better isolate the direct impact of an ELA-altered gut microbiota on metabolic development.

There is no universal set of features that characterizes a low-dose ELA-treated gut microbiome, but there have also been few attempts to compare the effects of low-dose ELAs on microbiome composition across studies. It is possible that interstudy differences in factors such as antibiotic class, dose, intervention timing, and the species, source, and sex of subjects would preclude the detection of any consistent gut microbial signature associated with the effects of low-dose ELA treatment. In one effort, Cox et al.[13] performed and compared the results of four separate low-dose ELA experiments in mice. They highlighted certain microbial taxa, normally present at high levels in the fecal microbiota of young mice, that were consistently reduced by low-dose ELA treatment.[13] Loss of these "keystone" taxa (*Lactobacillus*, *Allobaculum*, Rikenellaceae, and segmented filamentous bacteria) was proposed to impair proper metabolic and immune development, with low-dose ELAs promoting later-life adiposity and immune dysfunction by targeting them.[13] More recently, low-dose ELA-induced reductions in *Lactobacillus* were shown to causally contribute to adiposity by reducing small intestinal phenyllactic acid, a *Lactobacillus*-derived metabolite that limits fat accumulation via the regulation of peroxisome proliferator-activated receptor-γ (PPAR-γ) expression in small intestinal epithelial cells.[18]

There are numerous additional proposed mechanisms by which low-dose ELA-mediated disruption of the gut microbiome may elicit host adiposity, none of which are necessarily mutually exclusive. Some studies have identified increased SCFA production by the low-dose antibiotic-treated microbiome,[12] which could directly contribute to increased colonic energy harvest for the host or else play a role in developmental signaling, with cascading downstream effects on metabolic development.[21] Another proposed mechanism implicates altered bile acid metabolism by the gut microbiome, as increasing the proportion of primary versus secondary bile acids can subsequently impact energy balance through farnesoid X receptor (FXR) pathway signaling.[17] Last, impaired immune development with low-dose ELAs is well documented and could potentially contribute to adiposity by lowering energetic investments in immune function.[13] The immune system is energetically costly,[53] such that reduced investment in immune function could result in a reduced resting metabolic rate, ultimately promoting adiposity. However, the potential net impact of this mechanism remains unclear, as impaired intestinal immunity could also allow for greater infiltration of microbial products such as lipopolysaccharide (LPS) into host tissues, promoting chronic low-grade inflammation and ultimately greater visceral fat storage.[42]

Ultimately, multiple mechanisms—including the loss of keystone taxa, higher SCFAs, PPAR-γ signaling, reduced bile acid metabolism, reduced small intestinal phenyllactic acid, and impaired immune development—may bias the host toward fat storage and contribute to positive or neutral energy balance under low-dose ELA treatment. Future research on low-dose ELA-induced obesity would benefit from gnotobiotic studies using gut microbiota transplanted from very young (rather than adult) mice, age-matching of gut microbiota donors and recipients, or cross-fostering newborns to distinguish the effects of ELAs from those of current obesity status on gut microbial contributions to host phenotype. Additionally, analyses or meta-analyses of low-dose ELA microbiomes should leverage transcriptomic and/or metabolomic data that provide insight into functional consequences in addition to taxonomic signatures of low-dose ELA exposure. Such studies could also establish the extent to which the many proposed molecular mechanisms of low-dose ELAs are reproducible or consistent across studies. Lastly, human epidemiological studies of ELA-associated obesity have focused exclusively on high-dose ELAs, but evidence of low-dose ELA-associated obesity in humans remains elusive. This is likely due to the difficulty of identifying low-dose antibiotic exposures in humans, as they would not come from documented therapeutic use but rather from less easily traced sources such as naturally occurring,[54] added,[5] or residual[55] antimicrobial compounds in food that would require direct quantification of residues in infants. Further studies in this area will be vital to help link the wealth of low-dose ELA research in animals to human health outcomes.

HIGH-DOSE ELAs: EARLY-LIFE CONSTRICTION OF AVAILABLE ENERGY

Human exposure to antibiotics is typically in the form of high-dose (therapeutic) antibiotics administered in pulses. Pulsed high-dose antibiotic exposure has been shown to elicit both striking changes in gut microbial composition and multiple-order-of-magnitude reductions in the density of gut microbes,[14,56,57] including local microbial extinctions and long-term increases in the abundance and expression of antibiotic resistance genes.[58,59] In mouse models, these effects of high-dose antibiotic treatment are typically associated with immediate negative consequences for host energy balance. High-dose antibiotic ablation of the gut microbiome in adult mice has been repeatedly shown to reverse or attenuate obesity, improve glucose tolerance and insulin sensitivity, and promote more negative energy balance by increasing brown fat thermogenesis.[40–42] For instance, lean, obese leptin-deficient (*ob/ob*), and high-fat diet-fed mice all exhibited improved glucose homeostasis and smaller visceral and subcutaneous fat deposits after treatment with a high-dose antibiotic cocktail.[41] These effects have been ascribed to altered patterns of energy storage, thermogenic browning of white adipose tissue, and loss of fermentative energy salvage in the absence of a functioning gut microbiota.[9,41,60] High doses of antibiotics can also alter bile acid profiles by disrupting microbial bile acid metabolism,[61] with subsequent consequences for host energy balance (Figure 1B).

However, if mice are exposed to high-dose antibiotics in early life, then negative energy balance and the loss of microbiome-mediated signaling can trigger developmental changes that then promote adiposity in adulthood. For example, ablation of the maternal microbiome and the resultant loss of circulating SCFAs have been shown to promote adult adiposity and impaired glucose homeostasis in offspring via reduced SCFA signaling through GPR41- and GPR43-mediated developmental pathways.[21] These two pathways modulate adult metabolism due to their effects on the development of the sympathetic nervous system (GPR41), resulting in slower heart rate and lower body temperature, as well as the impaired development of pancreatic β-cells and GLP-1-producing enteroendocrine cells (GPR43), resulting in impaired glucose homeostasis.[21] Thus, offspring lacking sufficient SCFA exposure *in utero* exhibited impaired organ development and higher susceptibility to diet-induced obesity as adults, whereas offspring exposed *in utero* to SCFAs developed normally and were protected. Importantly, mice in both the SCFA-exposed and -unexposed groups were surgically delivered and cross-fostered, indicating that the developmental programming mediated by these gut microbial metabolites occurred during gestation and was not the outcome of perinatal vertical transmission or post-natal horizontal transmission of risk-modulating microbes.

Evidence from pulsed high-dose ELAs in mice suggests that among the high, therapeutic doses administered, those resulting in stronger disruption of the gut microbiome lead to greater changes in the host. In one study, repeated pulsed exposure to tylosin (a macrolide) induced stronger and more lasting changes in gut microbiome composition and abundance, as well as greater increases in body mass and more extensive changes in hepatic gene expression patterns, compared with amoxycillin (a β-lactam).[14] While increases in body mass were largely attributable to lean mass with no significant increase in fat mass, this study only used females, so the lack of adult adiposity in ELA-exposed animals may have been due to the lack of males in the study.

High-dose antibiotics also affect host growth in early life. In humans, therapeutic antibiotic exposures within the first year of life are associated with slower childhood gain in height, but not weight, for males.[62] Phenotypic differences observed among male children with or without high-dose ELA exposure were recapitulated in murine gnotobiotic recipients of gut microbiota transplanted from these children, suggesting a microbiome-mediated mechanism.[62] Reduced gain in height but not weight as a result of ELAs is consistent with adiposity-focused studies of ELAs in humans that find increases (often biased toward male children) in total or relative body fat using metrics such as BMI, overweight and obesity, or waist circumference during early to late childhood.[10,11] It is also possible that high doses of antibiotics may affect early-life growth independent of the gut microbiome through effects on mitochondrial function. High doses of tetracyclines have been shown to disrupt mitochondrial function in adult mice, with additional evidence for the stunting of growth in similarly treated nematodes and fruit flies,[8] although it remains unknown whether such growth stunting would continue to present in the absence of a gut microbial community.

Together, observations of consistently negative energy balance in adult mice treated with high-dose antibiotics and altered growth rates in humans exposed to therapeutic ELAs suggest that high-dose ELAs have negative effects on host energy balance during treatment. We argue that the resultant reduced energy budget of the host—mother or offspring, depending on the developmental period—then constrains birth weight and/or early-life growth, which ultimately increases the risk of obesity in an energy-rich adult environment (Figure 1C). In addition to examining these early-life markers of growth, future high-dose ELA studies would benefit from directly quantifying energy balance during and after treatment, including measurements of overall caloric absorption from food, gut microbial SCFA production, and energy expenditure. Additionally, studies in mice and other model organisms should test the extent to which some of the many molecular mechanisms promoting obesity in low-dose ELA models apply to high-dose ELA-induced obesity.

PROPOSED ENERGETIC FRAMEWORK FOR EARLY-LIFE ANTIBIOTIC-INDUCED OBESITY

Differing doses of antibiotics have divergent effects on the gut microbiota and host energy balance. Limited perturbation of the gut microbiota is coupled to neutral-to-positive impacts on energy balance, while gut microbiota ablation by high doses is coupled to negative energy balance. However, both low-dose ELAs and high-dose ELAs ultimately promote obesity in adulthood. How can the divergent energetic consequences of low-dose ELAs and high-dose ELAs lead to the convergent phenotype of adult adiposity? We propose that the short-term impact of differing doses of ELAs on gut microbial regulation of host energy balance is ultimately responsible for programming the long-term predisposition toward obesity.

Metabolic development in early life is highly sensitive to environmental inputs, especially energy availability. Undernutrition, overnutrition, and certain non-energetic environmental exposures in early life can all promote adult metabolic disease, sometimes with differences by host sex (Figure 1A). Moreover, the gut microbiome is an important regulator of host energy balance, mediating energy intake, expenditure, and storage through diverse pathways of influence (Figure 1B). Collectively, these dynamics suggest that any disruption of the gut microbiome that affects host energy balance during critical windows of metabolic development is expected to have long-term impacts on host energy metabolism. Because different antibiotic dosages and types can have markedly different impacts on gut microbiome density, composition, and function with downstream positive or negative effects on host energy balance, we reason that ELAs may promote adult obesity via developmental effects associated with perturbations of the gut microbial regulation of host energy balance in early life (Figure 1C).

Under this model, variable links between ELAs and adult obesity can be traced to the nature of ELA-based disruption of host-microbiome interactions in energy metabolism and subsequent effects on metabolic development (Figure 1). There are, of course, some similarities in the effects of low-dose and high-dose ELAs, as both can deplete keystone microbial taxa during treatment and impair immune development, often promoting chronic inflammation that may bias the host toward fat deposition.[13,63] However, the immediate energetic impacts of low-dose and high-dose ELAs differ markedly. In our energetic framework, low-dose ELAs may promote increased gut microbial contributions to host energy balance during and after treatment through various mechanisms, including slightly increased SCFA production, reduced bile acid modification, and reduced phenyllactic acid-mediated inhibition of fat accumulation, resulting in downstream effects on important signaling pathways (GPR41 and GPR43, FXR, and PPAR-γ). Such changes ultimately promote obesity through excess energy provided by the gut microbiome and by biasing host energy allocation toward fat storage in early life and adulthood.

Conversely, high-dose ELAs induce a period of energy restriction during treatment, including reductions in SCFA production

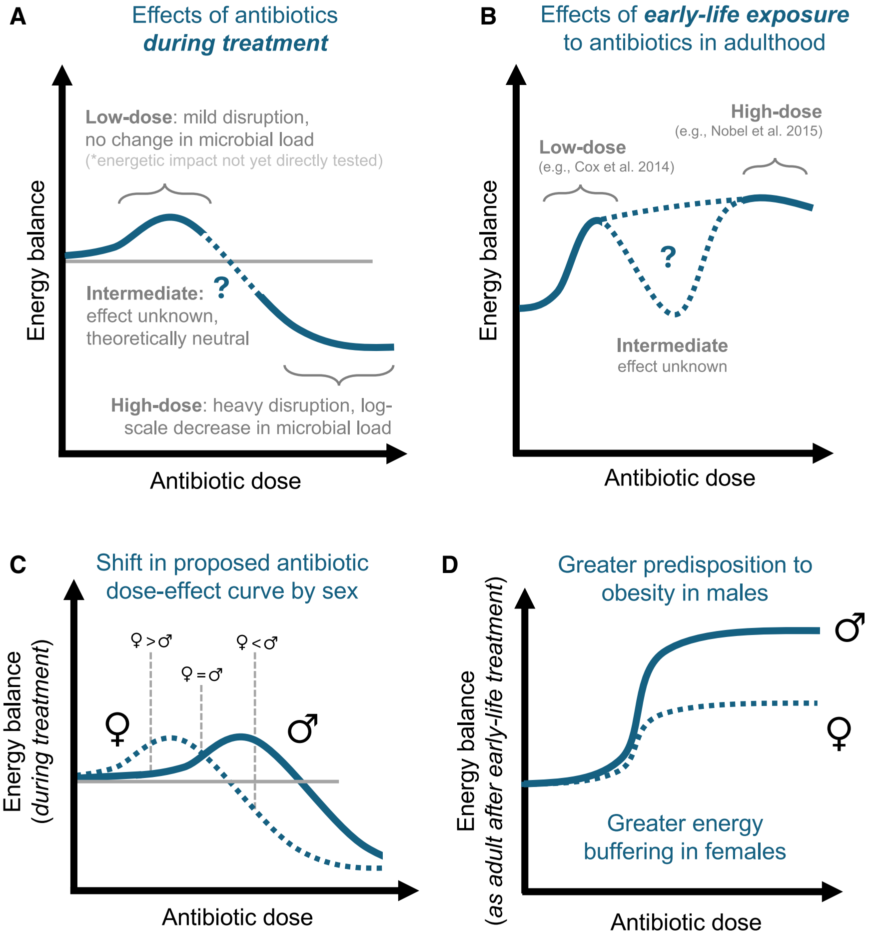

Figure 2. Energetic effects of ELAs over short-term and long-term timescales and potential avenues of sex differences in ELA-induced obesity

(A) During treatment, low doses of antibiotics can have positive or neutral impacts on host energy balance and do not reduce total microbial load, despite some changes to community composition. By contrast, higher doses of antibiotics greatly reduce microbial load with a longer-lasting and stronger disruption of gut microbial community composition, promoting short-term negative energy balance. Effects of intermediate doses are unknown (dotted line) but potentially energetically neutral.

(B) In the long term, both low and high doses of ELAs can promote obesity. Again, the effects of intermediate doses of ELAs are unknown (dotted lines). All doses of ELAs may promote obesity (upper, straight dotted line), but our model suggests that energetically neutral doses should have no such effect (lower, dipped dotted line).

(C) In the short term, males and females may be differentially susceptible to the impacts of antibiotics on the gut microbiome.

(D) In the long term, sex differences in ELA outcomes may arise from a general predisposition of males toward obesity or else differential responses of each sex to early-life perturbations in energy balance.

at a scale sufficient to reduce colonic energy harvest and promote increased thermogenesis in host tissues. These short-term energy-limiting effects of high-dose ELAs therefore result in the developmental characteristics of early-life nutritional deprivation previously shown to lead to obesity: low birth weight, growth stunting followed by catch-up growth, and low metabolic rate in adulthood. The convergent long-term impacts of low-dose and high-dose ELAs on the risk of obesity can therefore be understood through their varying short-term impacts on the gut microbial regulation of host energy balance.

Additional research comparing the short-term and longer-term energetic impacts of low-dose and high-dose ELAs is necessary to directly test this model. We have hypothesized that the differing impacts of antibiotic dose on microbial processes such as SCFA production cause divergent changes in energy availability and growth rates, but these differences have yet to be established empirically.

ENERGETIC EFFECTS OF EARLY-LIFE ANTIBIOTICS ACROSS THE DOSE SPECTRUM

As outlined thus far, much of the evidence linking antibiotics to altered energy balance comes from the extreme ends of antibiotic dosing—either subtherapeutic doses that alter relative but not absolute abundance of gut microbes or high therapeutic doses that substantially deplete absolute microbial abundance. Hence, we have, to this point, described differing antibiotic exposures as either low dose or high dose. However, antibiotic dosage is continuous, raising the question of what happens at the theoretical inflection point between energy-increasing low doses and energy-decreasing high doses of antibiotics (Figure 2A). To our knowledge, neither the short-term nor long-term energetic impacts of ELAs have been investigated along a dosing gradient. Under the proposed energetic model, we would predict that an exposure at this theoretical energy-neutral inflection point should not meaningfully increase the risk of adult obesity because it does not affect the early-life energetic environment. This could also explain why some therapeutic doses of ELAs with limited effects on the gut microbiome have failed to promote adult adiposity, as they likely also have limited short-term energetic impacts.[14] If an energy-neutral dose of ELAs was nevertheless found to promote adult obesity, this would potentially indicate that antibiotic modulation of gut microbial signaling rather than net energetic impact is the main driver of ELA-induced obesity (Figure 2B).

Despite the common dichotomy drawn between low-dose and high-dose antibiotics, the actual impact of antibiotics on the gut microbiota is much more complex than that of dose alone,[64,65] even when described on a continuous scale. First, the prescribed “normal dose” of an antibiotic may differ based on the type or location of infection and may not be adjusted for variations in body size within pediatric cohorts or among adults. Even where body size adjustments are made, relative therapeutic doses do not scale linearly by body weight where there are large differences in body size—for instance, between mice and humans or between children and adults. Antibiotic classes themselves differ in the microbes they target and their downstream impacts on energy harvest. For instance, broad-spectrum antibiotics, particularly macrolides, have been found to promote later-life obesity more strongly than other antibiotic classes.[10] Individuals may also differ in the personal susceptibility of their gut microbiota to antibiotics. For instance, researchers have found that even in a tightly controlled laboratory setting with inbred mice, some individuals can exhibit rapid microbiome-wide resistance to antibiotic treatment, resulting in an antibiotic ‘‘non-responder’’ phenotype.[66] In addition to individual variation in gut microbial sensitivity to antibiotics, variation in the pharmacokinetics of different antibiotic classes, routes or frequency of administration, and even drug metabolism by gut microbes[67] could change the quantities of functional antibiotics that reach the gut microbiome. Recovery of the microbiome after antibiotic treatment is also highly variable and potentially linked to growth trajectories in high-dose ELA-treated mice.[14] Microbiome recovery generally depends on initial microbiome composition, diversity, and functional redundancy, combined with a microbiota-accessible post-antibiotic diet (e.g., high-fiber, prebiotic-rich, minimally processed) and exposure to exogenous microbes (e.g., via probiotics/transplantation, environmental reservoirs, or social transmission).[65]

Therefore, while antibiotic dose is a useful continuum through which to conceptualize the differing short- and long-term impacts of antibiotics on energy balance, the energetic impact of any given antibiotic dose may still vary greatly between individuals. Under our model, adult obesity is more closely tied to the energetic consequences of different antibiotic exposures rather than their dose. Achieving a better understanding of factors underlying the effects of antibiotic dose on short-term energy availability will require studies of antibiotic dose across a gradient of low to high doses, ideally linking quantifiable aspects of net energy balance (e.g., food intake, nutrient absorption, and energy expenditure) to functional properties of the gut microbiome (e.g., SCFA production, bile acid metabolism, and phenyllactic acid production).

SEX DIFFERENCES IN EARLY-LIFE ANTIBIOTIC-INDUCED OBESITY

One intriguing insight derived from our emerging model linking ELAs and adult obesity concerns the difference in phenotypic response between males and females. Meta-analyses of ELAs in humans report that the effect of ELA exposure on body fat, obesity, and related outcomes is exacerbated or present only in males.[10] Additionally, the epidemiological link between ELAs and slowed growth in children was also observed exclusively among males,[62] which is consistent with our hypothesis that high-dose ELAs induce obesity by promoting metabolic thrift via smaller, less energetically costly bodies. Studies in mice, all conducted with low-dose ELAs, have sometimes corroborated the trends observed in humans, finding exacerbated responses to ELAs in males (Table 1). However, others have found either no distinguishable difference between sexes or else reported greater responses in females, although these differences are sometimes reported only in terms of body mass and lean mass rather than fat mass (Table 1). Many studies used or reported results for only one sex in ELA experiments, precluding the identification of sex-specific responses. Therefore, to the best of our knowledge, high-dose ELA-associated obesity is male-biased in humans with an unknown sex bias in mice, while low-dose ELA-induced obesity is not consistently biased by sex in mice and remains largely unstudied in humans.

No explanation has yet been proposed for the inconsistent observations of sex differences in mouse models of low-dose ELA-induced adiposity. However, our framework of dose-dependent energetic effects of ELAs offers some potential solutions. We propose that variable sex differences in murine studies of ELA-induced obesity may arise in part because one sex is more sensitive to the short-term impact of antibiotics on the gut microbiome and energy balance. It is unclear why such differential sensitivity might exist beyond observations of sex differences in the microbiome that contribute to differential metabolic phenotypes.[68,69] However, dimorphic sensitivity to antibiotics could explain many of the conflicting observations of sex differences in ELA outcomes. Under our biphasic model for the impact of antibiotic dosages on short-term host energy balance (where low doses have neutral-to-positive effects and high doses have negative effects, Figure 2A), a shift of the curve for one sex could result in situations where a given dose impacts males more, females more, or else both sexes equally (Figure 2C). Thus, small differences in effective antibiotic dosing—whether due to different compounds, different dosages, different dosing schedules, or varying degrees of antimicrobial resistance in the gut microbiome— could result in highly variable outcomes by sex.

Another way in which antibiotic-mediated changes in the gut microbiome could induce sex-specific effects is through interactions with steroid hormones.[70] The presence of a gut microbiome affects circulating hormone levels, with germ-free mice showing deficits in estrogen, progesterone, and corticosterone compared to specific-pathogen-free animals that are partially recovered by colonization with a typical murine microbiome.[71] Moreover, the composition of the gut microbiome matters. For instance, circulating estrogen levels are enhanced by microbiome-mediated enterohepatic circulation, a process in which gut microbial β-glucuronidase enzymes deconjugate estrogens excreted into the gut lumen via bile, thereby returning estrogens to circulation. The loss of microbes with β-glucuronidases can therefore suppress total circulating estrogens, a phenomenon evident in humans given antibiotics.[72] Furthermore, the gut microbiota of male mice was shown to increase circulating testosterone levels when transplanted into young females.[69] Both estrogens and androgens play important roles in growth and development. Changes in circulating hormones as a result of ELA treatment might be expected to differentially impact males and females depending on their differing sensitivities to and baseline productions of the hormone in question.

In some ways, a general male bias in ELA-induced obesity is not surprising. Obesity and excess weight are more prevalent among males in both humans and mice. This effect is especially pronounced in C57BL/6 mice,[73] the strain used in nearly every study of ELA-induced adiposity (Table 1). Among humans, men exhibit higher rates of obesity and diabetes than do women, an outcome attributable to the protective effect of estrogen in reproductive-age women that is abrogated with the onset of menopause and subsequent reductions in circulating estrogen.[74] A male bias is also evident across many examples of early-life adversity compromising adult health in humans. For instance, low birth weight is associated with worse survival and health outcomes for males with remarkable consistency, even after controlling for other genetic, socioeconomic, environmental, and lifestyle factors.[75]

Importantly, evolutionary theory predicts on first principles that males and females might be differentially susceptible to alterations in energy allocation, as female fitness is more directly tied to the amount of energy available for reproduction. The trend of male-biased ELA-associated adiposity and growth effects in humans and some mouse studies might therefore result from an evolutionary trend of greater life-long energy buffering in females compared with males (Figure 2D). Numerous mechanisms exist through which metabolic traits may be inherited or arise due to gestational exposures in a sex-specific manner.[76] For instance, smaller placental size in male offspring has been proposed as a reason why males may be less able than females to buffer against fluctuations in energy availability *in utero*.[77] Critically, however, evolutionary theory also predicts that differential energy allocations represent trade-offs. For example, while females may be less susceptible to the later-life metabolic impacts of ELAs, they may instead be more susceptible to impairments in other areas of fitness, such as immunity or reproduction. The broader impacts of ELAs on energy allocation throughout the life course and their differential consequences for male and female health and fitness outcomes remain untested but ripe for study. Potentially most interesting would be a test of the hypothesis that antibiotic disruption of gut microbial hormone metabolism contributes to dimorphic outcomes of ELA-induced obesity, given the importance of estrogens and androgens in growth and development. One could also test the extent to which any known mechanism of sex bias in the developmental risk of metabolic diseases, such as differences in placenta size and function,[76] might apply to the particular case of ELA-induced obesity. Lastly, investigations into ultimate explanations of sex differences in ELA-induced obesity should consider potential trade-offs, namely the possibility that apparent resistance to ELA-induced obesity in females comes at the cost of other physiological processes like immunity or reproduction.

EARLY-LIFE ANTIBIOTICS IN ECOLOGICAL AND EVOLUTIONARY CONTEXTS

Therapeutic use of antibiotics is undoubtedly a modern phenomenon, but humans have been exposed to antimicrobial compounds throughout our history. First, most of the antibiotics used therapeutically today originated from compounds produced naturally by various organisms[78]—most famously penicillin from the bread mold *Penicillium*. Antibiotic resistance has been detected in ancient, protected sites,[79,80] suggesting that ancient human-associated bacteria may have been exposed to similar compounds. Additionally, while the high doses of antibiotics used in medicine are not naturally occurring outside of modern contexts, low doses of antibiotics produced by many bacteria are known to serve as signaling molecules and weapons for inter-microbe warfare, among other functions.[81,82] Furthermore, many plant foods synthesize antimicrobial compounds,[83] and research on evolutionarily important foods like starch-rich tubers has shown that these compounds, when ingested, can have antibiotic-like effects on the gut microbiome.[54] Humans and other hosts could therefore have been exposed throughout evolutionary history to a diverse array of antimicrobial compounds through endogenous production by gut bacteria or ingestion of plant foods with native antimicrobial properties. The two patterns of antibiotic-mediated disruption of the gut microbiota discussed here—chronic low doses or pulsed high doses—may therefore be equally relevant to human ecology: pulsed high-dose antibiotics more closely mirror contemporary patterns of intentional antibiotic exposure, while low doses of antibiotics may emulate a more ancient model of antibiotic exposure through bacteria or food.

Similarly, early-life gut microbiome disruption itself is an ancient phenomenon. For instance, bouts of diarrhea could induce rapid restructuring of the gut microbiome comparable to a high, therapeutic dose of antibiotics. Consumption of plant-derived xenobiotics[54] or traditional dietary preservatives[5] could induce changes in the gut microbiome comparable to low-dose antibiotics. The high day-to-day stochasticity and longer-term seasonality of dietary intake present in many recent or contemporary hunter-gatherer groups[84] likewise suggest substantial volatility in ancestral gut microbiome profiles.[85,86] It is therefore reasonable to expect that the human body may capitalize on signals of gut microbiome disruption to tune its development in order to maximize its fit with expected environmental conditions.

Assuming the main driver of ELA-induced developmental programming in the host is the gut microbial response to antibiotics rather than any direct effect of antibiotics on the host, it is reasonable to speculate that the gut microbial response to ELAs may signal energy availability, environmental volatility, or both. Literature on the developmental origins of health and disease contains abundant examples of fitness-enhancing developmental responses to variable energy availability across species.[87] Offspring of undernourished rodent mothers, for instance, demonstrate adaptations for metabolic thrift (e.g., reduced lean mass) along with lower satiety, greater preference for dietary fat, and faster sexual maturation—traits that would be expected to enhance survival and reproduction in an energy-limited environment.[87] In this manner, the biological response to ELAs can be contextualized within the broader canon of evidence showing that developmental plasticity in response to early-life adversity may be adaptive and that negative health consequences, such as obesity, may reflect mismatch diseases that arise because the adult environment differs from the one predicted during development.

CONCLUSION

We have used available evidence and interdisciplinary insights from evolutionary theory and the developmental origins of health and disease to focus a new lens on the gut microbial origins of ELA-induced obesity and observed variation by dose and sex. We propose that low-dose and high-dose ELAs have different impacts on gut microbial modulation of host energy balance in the short term, despite similar energetic outcomes for the host in the long term. Accounting for these dose-dependent short-term differences in gut microbial function could therefore help explain underlying physiological mechanisms of ELA-induced obesity and the variable sex differences in growth and adiposity outcomes observed for both humans and mice. Additionally, because evolutionary mechanisms of ELA-induced developmental programming overlap with those of environmental volatility more broadly, our framework may shed light on other early-life experiences that elicit long-term metabolic consequences due to interactions with the gut microbiome.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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