ORIGINAL ARTICLE

Antibiotic and acid-suppression medications during early childhood are associated with obesity

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ABSTRACT

Objective Gut microbiota alterations are associated with obesity. Early exposure to medications, including acid suppressants and antibiotics, can alter gut biota and may increase the likelihood of developing obesity. We investigated the association of antibiotic, histamine-2 receptor antagonist (H2RA) and proton pump inhibitor (PPI) prescriptions during early childhood with a diagnosis of obesity.

Design We performed a cohort study of US Department of Defense TRICARE beneficiaries born from October 2006 to September 2013. Exposures were defined as having any dispensed prescription for antibiotic, H2RA or PPI medications in the first 2 years of life. A single event analysis of obesity was performed using Cox proportional hazards regression.

Results 333 353 children met inclusion criteria, with 241 502 (72.4%) children prescribed an antibiotic, 39 488 (11.8%) an H2RA and 11 089 (3.3%) a PPI. Antibiotic prescriptions were associated with obesity (HR 1.26; 95% CI 1.23 to 1.28). This association persisted regardless of antibiotic class and strengthened with each additional class of antibiotic prescribed. H2RA and PPI prescriptions were also associated with obesity, with a stronger association for each 30-day supply prescribed. The HR increased commensurately with exposure to each additional medication group prescribed.

Conclusions Antibiotics, acid suppressants and the combination of multiple medications in the first 2 years of life are associated with a diagnosis of childhood obesity. Microbiota-altering medications administered in early childhood may influence weight gain.

Significance of this study

What is already known on this subject?
- Obesity has been linked to variations in the native gut microbiota.
- Several commonly prescribed paediatric medications are known to cause alterations in the native gut microbiota.
- There is conflicting evidence about the role of exposure to microbiota-altering medications and the development of childhood obesity.

What are the new findings?
- Prescriptions for antibiotics and acid-suppressing medications are associated with the development of obesity, with a stronger association noted after prolonged courses or with prescriptions to multiple antibiotic classes.
- Combinations of multiple microbiota-altering medication groups are associated with a commensurate increase in obesity.

How might it impact on clinical practice in the foreseeable future?
- These results further quantify the potential long-term risk of obesity associated with early exposure to acid-suppressing medications and antibiotics.
- The findings offer a framework for prospective research on inpatient and outpatient medication exposures and the subsequent development of obesity in paediatric patients. The recognition of modifiable risk factors for obesity is an essential step towards reducing the incidence and burden of the disease.

INTRODUCTION

The childhood obesity epidemic is a public health crisis in the USA. Obesity-associated health problems, including hypertension, diabetes and hyperlipidaemia, are becoming worryingly common in children.[1] An imbalance between energy intake and expenditure, typified by poor diet and physical inactivity, is the largest contributor to the emergence of childhood obesity, but many other factors define populations at risk of developing obesity.[2] Identifying modifiable risk factors through large population studies is essential to determine targets for public health interventions that combat obesity.

The human microbiome is immense, diverse and increasingly recognised to play an important role in health. Resident microbiota of the human body exist in a fluid symbiotic homeostasis, and disease can arise from dysbiosis.[3] Prenatal, perinatal and postnatal factors affect intestinal microbiota colonisation.[4] The intestinal microbial ecosystem is seeded at birth and quickly becomes more taxonomically diverse, until converging into a characteristic adult profile in the first few years of life.[5 6] A complex interaction of internal and external factors, including environmental exposures, birth mode and diet, influence the establishment and maturation of the gut microbiome.[7] Once established, there is relative stability in this ecosystem, but it may be intermittently punctuated by periods of acute or chronic perturbation with certain disease states or new exposures.[8] Many commonly prescribed medications have microbiota-altering effects via selectively promoting or inhibiting the growth of specific bacterial species.[9] Gastric acid secretion-inhibiting medications and antibiotics can affect the

gut microbiota by shifting the native GI tract acid milieu or by acting directly in a bactericidal or bacteriostatic manner.[10–13] Medication-induced gut microbiota alterations may persist indefinitely.[14]

Altering the paediatric intestinal microbiome may have significant longitudinal health consequences. Several maternal variables, such as caesarean section delivery, are associated with an increased risk of obesity in childhood and are thought to act through a mechanism of infant gut microbiota alterations.[15 16] Gut microbiota variations are associated with weight gain and increased adiposity through complex alterations in host metabolism.[17 18] American farmers commonly exploit this finding by using antibiotics as growth-promoting feed additives for livestock. These growth benefits are more profound if animals are exposed to antibiotics early in life.[19] In vivo animal studies show that altering the intestinal microbiota with medications during its critical developmental window influences host metabolism and adiposity.[20] Furthermore, transferring the altered microbiota of these animals to exposure-naive animals transfers the growth-promotion phenotype, supporting bacteria as a causative agent.[21] Importantly, human studies also support an association between antibiotic exposure and weight gain, but the strength of this association is unclear and conflicting findings exist.[22–24] There are no studies specifically investigating the effects of acid suppression medications and the development of childhood obesity, but these medications are known to cause significant dysbiosis.[25] Antibiotics and acid suppressants are among the most frequently prescribed medications for young children, necessitating close evaluation of potential long-term adverse health outcomes associated with exposure.[26]

We hypothesised that young children exposed to microbiota-altering medications in the first 2 years of life are more likely to develop obesity. We used a large electronic medical record database to evaluate this association. We also sought to evaluate a potential dose effect, measured by the length of medication exposure and the effect of exposure to multiple different microbiota-altering medications on the development of obesity.

METHODS

We conducted a retrospective cohort study including infants born into the US Military Health System (MHS) database from October 2006 to September 2013, who were followed in the database past 2 years of age and who had at least one set of vital signs with weight and height recorded during the period of October 2008–September 2015. The MHS consists of each of the components within the Office of the Assistant Secretary of Defense for Health Affairs, which includes the medical departments of the US Army, Navy and Air Force, and providers at civilian facilities. The MHS database includes all outpatient and inpatient billing records and prescriptions for all eligible military dependents in both military and civilian facilities. The MHS database was queried for all children eligible for TRICARE healthcare starting at birth.

Similar to previous studies evaluating medication exposure and the development of obesity, this study excluded low birth weight (<2500 g), premature infants and infants with an initial hospital stay greater than 7 days.[27–30] These exclusions were intended to eliminate potential confounding data related to premature infant growth patterns and hospital course exposures that may undermine generalisation. Children not followed past 2 years of age and those with no height and/or weight recorded during the study period were also excluded. When determining cohort continuations in the MHS, wherein families frequently translocate within its provider network, we included patients who were out of the network for less than 2 months as continuous members. Patients who were out of the provider network for longer than 2 months were excluded to prevent missed medication exposures.

Exposures were defined as days supplied for histamine-2-receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), and antibiotic classes. All study medications were prescribed in the first 2 years of life. American Hospital Formulary Service therapeutic classification codes were used to define antibiotics and acid-suppressing medications.[31] Caesarean section, birth weight and premature status were defined using associated hospital billing codes (online supplementary table 1). Sponsor rank was collected from outpatient medical records and was categorised based on pay grades into groupings of junior enlisted, senior enlisted, junior officer and senior officer ranks. The outcome of obesity was defined, using the US Centers for Disease Control and Prevention (CDC) growth parameters, as the first body mass index (BMI) measurement from a clinical encounter that was greater than or equal to the 95th percentile for age and sex.[32] Obesity, rather than overweight (BMI 85th to less than 95th percentile), was chosen as the primary outcome because previous studies have indicated that obesity is a better measure of long-term health risk.[33] To limit the inclusion of erroneous electronic medical record BMI measurements, height and weight data were screened using a standardised CDC programme to exclude patients flagged as 'biologically implausible'.[34] Patients were censored at last BMI measurement in the database. We summarised continuous data with medians and 25th–75th percentiles (P25–P27) and categorical data with numbers and percentages. Because the medication class exposure groups were not mutually exclusive, the demographics and other variables for infants who received antibiotics, PPIs, H2RAs or no medications were compared using repeated measure methods. The CDC recommends that healthcare providers use the CDC growth charts for children aged 2 years and older in the USA, so we used a single event survival analysis using Cox proportional hazards regression with time starting at age 2 years. HRs were reported with 95% CIs.

Statistical models included ordinal variables representing acid medication exposure and the binary variables for antibiotic classes in the first 2 years of life, sex, caesarean section birth and sponsor service member rank. Two-way interaction terms were evaluated for all variables with known, suspected or biologically plausible relationships, including the study medications and demographics. Significant interactions ($p<0.05$) were retained in the adjusted model. There was a significant two-way interaction noted between sex and H2RA prescriptions and sex and antibiotic prescriptions. No significant interactions were found between the three medication groups. A stratified Cox model analysis was performed by sex to account for the interaction of sex with H2RA and sex with antibiotics.[35] The proportional hazards assumption was verified by visual inspection for parallelism of the log–log survival curves for each variable in the models, as well as evaluating correlation of the Schoenfeld residuals with time.[36] Sponsor service member rank did not meet the proportional hazards assumption, so an adjustment was made by adding an interaction with time.[37]

Univariate analysis of the days supplied of acid suppression medications revealed that the majority of the prescriptions were in 30-day increments, likely as a result of provider prescribing habits (online supplementary figure 1). We therefore created an ordinal variable representing 30-day increases in prescription days. These levels were: no exposure, 1–30 days supply, 31–60

Table 1 Demographic data for children prescribed antibiotics, histamine-2 receptor antagonists (H2RAs) or proton pump inhibitors (PPIs)

	Total population	H2RA	PPI	Antibiotics	Any medications	No medications
Number (%)	333 353	39 488 (11.8)	11 089 (3.3)	241 502 (72.4)	249 071 (74.7)	84 282 (25.3)
Age at last measured BMI, years, median (P25–P75), n (%)	4.00 (2.70–5.50)	3.86 (2.65–5.28)	4.05 (2.89–5.52)	4.03 (2.80–5.60)	4.03 (2.79–5.58)	3.71 (2.46–5.27)
Female, n (%)	161 344 (48.4)	17 671 (44.8)	4718 (42.6)	113 391 (47.0)	117 071 (47.0)	44 273 (52.5)
Caesarean section	87 196 (26.2)	11 544 (29.2)	3401 (30.7)	64 955 (26.9)	66 977 (26.9)	20 219 (24.0)
Military rank						
Junior enlisted	62 359 (18.7)	6954 (17.6)	1739 (15.7)	45 684 (18.9)	46 991 (18.9)	15 368 (18.2)
Senior enlisted	196 482 (58.9)	23 034 (58.3)	6330 (57.1)	143 188 (59.3)	147 399 (59.2)	49 083 (58.2)
Junior officer	66 406 (19.9)	8539 (21.6)	2722 (24.6)	47 154 (19.5)	48 984 (19.7)	17 422 (20.7)
Senior officer	7364 (2.2)	881 (2.2)	276 (2.5)	4958 (2.0)	5161 (2.1)	2203 (2.6)
Other	742 (0.2)	80 (0.2)	22 (0.2)	518 (0.2)	536 (0.2)	206 (0.2)

Percentages are calculated from number of infants exposed or unexposed within group.
Other includes civilian or government employees with TRICARE insurance coverage.
BMI, body mass index.

days supply, 61–90 days supply, 91–120 days supply, 121–150 days supply, 151–180 days supply and >180 days supply. The variable for both H2RA and PPI with the 30-day levels of exposure were then treated as an ordinal variable in the analyses. Additional analyses were performed to evaluate the effect of prolonged or repeated courses and the potential additive effect of the three investigated medications. Antibiotic-exposed patients were divided into subgroups of patients with prescriptions for one, two, three or greater than three antibiotic classes. A separate model was developed comparing children who were exposed to one, two, three or none of the medication groups (antibiotic, H2RA or PPI), and estimated survival curves of these results based on the Cox proportional hazard model were constructed for visualisation purposes. Additionally, comparisons were made between patients prescribed one or multiple different classes of antibiotics. Individual classes of antibiotics, including penicillins, beta-lactam penicillins, cephalosporins, sulfonamides and macrolides, were also evaluated. A significant two-way interaction was noted between sex and sulfonamide antibiotic prescriptions, so a stratified Cox model analysis was performed by sex. Statistical analyses were performed using SAS V.9.4. This study was reviewed and approved by the Uniformed Services University of the Health Science institutional review board.

RESULTS

This study included a total of 745 555 eligible patients. A total of 333 353 patients met the study inclusion criteria. There was a median (P25–P75) of 4 (2–7) provider visits with measured BMIs after 2 years of age among all patients, with a median of 3 (2–6) visits prior to censorship. The patient population was evaluated to determine the median age, sex, number birthed via caesarean section and sponsor service member rank (table 1, online supplementary table 2). Infants were followed to the same median age across all medication exposure groups. A total (%) of 39 488 (11.8) were prescribed H2RAs, 11 089 (3.3) PPIs and 241 502 (72.4) antibiotics (figure 1). A significant number of patients were prescribed multiple study medications: 3700 received antibiotics and PPIs, 26 695 antibiotics and H2RAs, 877 PPIs and H2RAs and 5868 were prescribed all three medications. There were 46 993 (14.1) children who developed obesity. The median age (P25–P75) in years of first measurement of obesity among all patients was 3.03 (2.27–4.07). There were 9268 (11.0) children

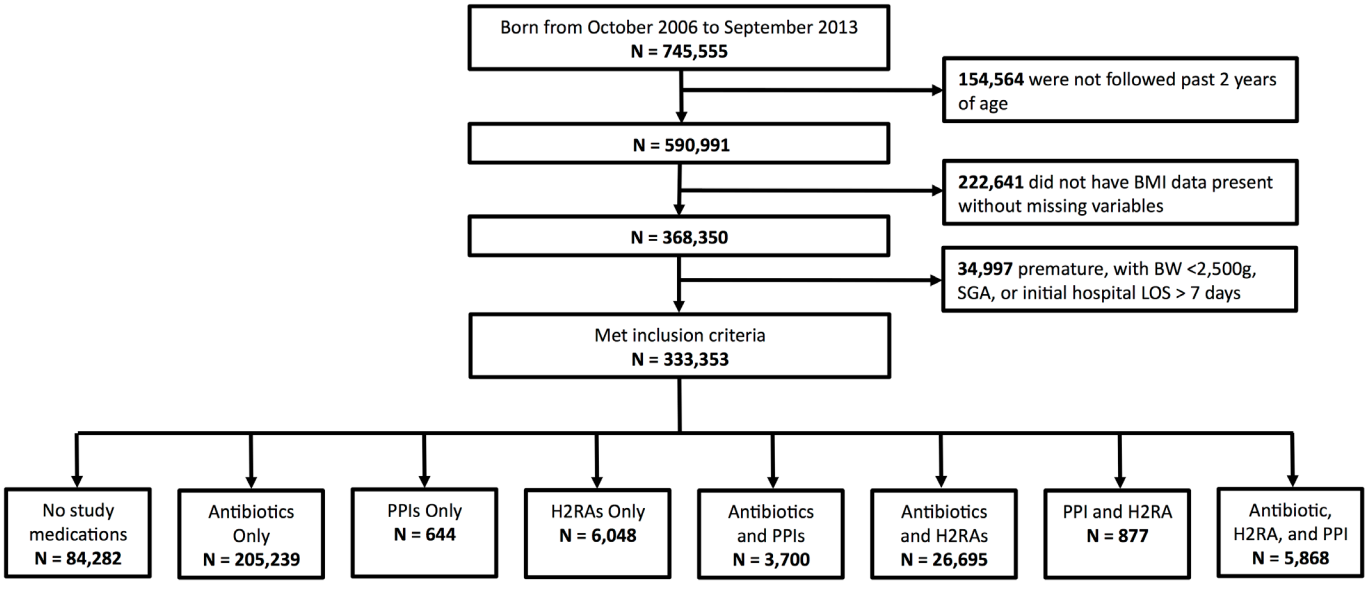

Figure 1 Patients included in study population divided into groups based on their medication prescription history.

Table 2 Total obese, incidence density, unadjusted and adjusted HRs of obesity for sex, caesarean section, military rank and those prescribed histamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs) and antibiotics

	Number of obese (%)	Incidence density (per 100 person-years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
PPI prescription	1841 (16.6)	3.85	1.04 (1.03 to 1.05)	1.02 (1.01 to 1.03)
H2RA prescription	5955 (15.1)	3.64	1.03 (1.02 to 1.03)	1.01 (1.004 to 1.02)
Antibiotic class prescriptions	36 899 (15.3)	3.54	1.26 (1.23 to 1.28)	–
0	10 094 (11.0)	2.71	Ref	Ref
1	13 852 (13.3)	3.17	1.14 (1.11 to 1.17)	1.12 (1.09 to 1.15)
2	10 882 (15.4)	3.56	1.26 (1.23 to 1.30)	1.23 (1.20 to 1.26)
3	7457 (17.4)	3.93	1.38 (1.34 to 1.42)	1.33 (1.29 to 1.37)
4+	4708 (19.4)	4.27	1.48 (1.43 to 1.53)	1.42 (1.37 to 1.46)
Caesarean section birth	14 571 (16.7)	3.95	1.28 (1.26 to 1.31)	1.26 (1.24 to 1.29)
Sex (M vs F)	26 748 (15.6)	3.68	1.26 (1.24 to 1.28)	–
Military rank				
Junior enlisted	8976 (14.4)	3.70	1.39 (1.33 to 1.45)	1.40 (1.34 to 1.46)
Senior enlisted	28 870 (14.7)	3.43	1.24 (1.20 to 1.27)	1.23 (1.20 to 1.27)
Junior officer	8136 (12.2)	2.76	Ref	Ref
Senior officer	893 (12.1)	2.65	0.96 (0.90 to 1.03)	0.96 (0.90 to 1.03)
Other	118 (15.9)	3.71	1.30 (1.08 to 1.57)	1.28 (1.06 to 1.54)

A significant interaction was found between sex and prescriptions for antibiotics and H2RAs. The effect of sex was adjusted through stratified Cox proportional hazards models and is presented in table 3. HRs for PPIs and H2RAs represent a unit increase in exposure level. Exposure levels were defined as 0 days, 1–30 days supply, 31–60 days supply, 61–90 days supply, 91–120 days supply, 121–150 days supply, 151–180 days supply and >180 days supply.
F, female; M, male.

that developed obesity who were not exposed to any of the study medications. The median age in years of first measurement of obesity was 3.0 years in all unexposed and medication exposed groups.

Patients with prescriptions to H2RAs, PPIs and antibiotics had increased incidence densities and HR of developing obesity (table 2). The HR for PPIs and H2RAs represent an increase for each 30-day exposure level, with exposure levels defined as 0 days supply, 1–30 days supply, 31–60 days supply, 61–90 days supply, 91–120 days supply, 121–150 days supply, 151–180 days supply and >180 days supply. An interaction was found between sex and prescriptions for antibiotics and H2RAs. The effect of sex was adjusted through stratified Cox proportional hazards models (table 3). Males and those born via caesarean section had an increased HR of developing obesity. Patients who were born to families of junior and senior enlisted service members, as compared with officers, also had an increased HR of developing obesity.

The HR of developing obesity was significantly increased among young children prescribed any of the individual antibiotic classes studied (table 4). A significant interaction was identified between sex and sulfonamide prescriptions. The effect of sex was adjusted through a stratified Cox proportional hazards model. The HR of developing childhood obesity increased commensurately with each additional antibiotic class added. Children exposed to multiple classes of medications (H2RA, PPI or antibiotics) had increasing risk of obesity with each additional class of medication prescribed (table 5; figure 2).

Table 3 Adjusted HRs for those prescribed histamine-2 receptor antagonists (H2RA) and antibiotics stratified by sex

	Adjusted HR (95% CI)	
	Male	Female
H2RA prescription	1.02 (1.01 to 1.03)	1.00 (0.98 to1.01)
Antibiotic class prescriptions		
0	Ref	Ref
1	1.13 (1.09 to 1.17)	1.12 (1.07 to 1.16)
2	1.22 (1.18 to 1.27)	1.24 (1.19 to 1.29)
3	1.31 (1.26 to 1.36)	1.36 (1.30 to 1.42)
4+	1.36 (1.30 to 1.43)	1.50 (1.42 to 1.58)

DISCUSSION

Here we present a large retrospective cohort study of children within the US MHS. We found that outpatient prescriptions for antibiotics and acid-suppressing medications within the first 2 years of life are associated with the development of early childhood obesity. This association became stronger with prescriptions for more than one type of microbiota-altering medication. Prescriptions for all commonly prescribed antibiotic classes were associated with childhood obesity. Additionally, we found that prescriptions for multiple classes of antibiotics increases the risk of obesity. Our study represents the single largest cohort of paediatric patients evaluated for exposure to antibiotics and development of obesity. This is the first study to specifically evaluate multiple acid-suppressant medications and subsequent development of obesity in paediatric patients. H2RAs and prolonged courses of PPIs were weakly associated with an increased hazard of obesity. This study follows infants past their initial exposure period, with some infants followed up to 8 years of age.

The association between antibiotic exposure and childhood obesity has been noted previously. An observational study of 28 354 mother–child dyads by Ajslev *et al*[28] found that antibiotic use during the first 6 months of life led to increased risk of being overweight among children with normal weight mothers (OR 1.54; 95% CI 1.09 to 2.17) but not overweight (OR 0.54; 95% CI 0.30 to 0.98) or obese (OR 0.85; 95% CI 0.41 to 1.76) mothers. This study adjusted for maternal factors including age, socioeconomic status, prepregnancy BMI, smoking status and breastfeeding status but did not distinguish between antibiotic classes.[28] An observational study of 11 532 infants by Trasande *et al*[29] found that exposure to antibiotics during the first 6 months of life, but not between 6–14 months and 15–23 months, was

Table 4 Analysis of antibiotic class exposures and hazard of developing obesity

		Unadjusted		Adjusted	
	Total exposed	HR	95% CI	HR	95% CI
Beta-lactam penicillin	72 809	1.17	1.15 to 1.19	1.07	1.04 to 1.09
Penicillin	201 293	1.20	1.18 to 1.22	1.11	1.09 to 1.13
Cephalosporin	83 207	1.15	1.13 to 1.17	1.03	1.01 to 1.06
Sulfonamides*	27 305	1.21	1.18 to 1.25	M: 1.05 F: 1.19	M: 1.01 to 1.10 F: 1.14 to 1.24
Macrolides	84 578	1.21	1.19 to 1.24	1.12	1.10 to 1.15
Other	6052	1.38	1.31 to 1.47	1.24	1.17 to 1.32

Adjusted for caesarean section, sex and other medication exposures.
Other antibiotics category includes fluoroquinolones, lincosamides, doxycycline, vancomycin and linezolid.
*A significant interaction was found between sex and sulfonamide prescriptions. The effect of sex was adjusted through a stratified Cox proportional hazards model.
F, female; M, male.

associated with an increase in BMI (OR 1.22; p=0.029). This study defined antibiotic exposure as a binary variable based on parental report and included covariates of social class, maternal BMI and breastfeeding status in its analysis.[29] Bailey *et al*,[27] in their cohort study of 64 580 children, found that repeated exposure to broad-spectrum antibiotics at 0–23 months was associated with the development of obesity. Broad-spectrum antibiotics were defined as second-line antibiotics for common childhood infections.[27] Their study notably included antireflux medications (PPIs and H2RAs) as a clinical covariate to evaluate for an effect of any medication use on risk of developing obesity but found no significant association with antireflux medication use and obesity (rate ratio 1.032; 95% CI 0.996 to 1.072). A 2015 population cohort study of 12 062 infants by Saari *et al*[30] found that males, but not females, exposed to any antibiotics before 6 months of age (adjusted OR (aOR) 1.34; 95% CI 1.06 to 1.66) or exposed to multiple courses of antibiotics during the first 2 years of life had greater odds of becoming overweight. Covariates for this study included maternal smoking, parental relationship, mode of delivery, birth weight and birth length. They noted that exposure to cephalosporins and macrolides had the strongest association with obesity. A 2016 retrospective study by Gerber *et al*,[24] which included 38 522 singleton children (5287 antibiotic exposed) and a small cohort of twins with discordant antibiotic exposure, failed to find any statistically significant childhood weight gain associated with antibiotic exposure in the first 6 months of life (p=0.07). Covariates included sex, Medicaid insurance status, race, household density and birth year. Their study found a significant difference in weight gain for children exposed to any antibiotics in the first 24 months of life (p=0.001) and presented evidence of a dose–response effect with more courses of antibiotics and increased weight. Azad *et al*[38] performed a nested case–control study of 616 children exposed to antibiotics during the first year of life and found that exposed infants were more likely to be overweight in later childhood (p=0.002). After adjusting for birth weight, breast feeding, maternal weight and other survey-derived covariates, the association persisted only in males (aOR 2.19; 95% CI 1.06 to 4.54 at age 9 years, and aOR OR 5.35; 95% CI 1.94 to 14.72 at age 12 years).[38] A retrospective cohort study of 21 714 children (14 870 antibiotic exposed) by Scott *et al*[39] found that antibiotic exposure before 2 years of age was associated with an increased risk of obesity at 4 years of age (OR 1.21; 95% CI 1.07 to 1.38). Exposure to three or more courses of antibiotics had a stronger association, providing further evidence of a possible dose–response relationship with multiple courses of antibiotics. Covariates within this study included sex, geographic location, socioeconomic status, maternal and sibling obesity and mode of delivery.[39] The first prospective study to evaluate for an association was recently performed by Edmonson and Eickhoff,[40] in which they performed secondary analysis of data from a randomised clinical trial of 607 children <2 years old with vesicoureteral reflux given daily prophylactic trimethoprim–sulfamethoxazole doses or placebo for the first 2 years of life. This study found no significant weight gain in the medication exposed groups at 6, 12 or 18 months old but did not follow infant growth patterns after the 2-year clinical trial period.[40]

Our study found that children prescribed H2RAs and PPIs were slightly more likely to develop obesity. Longer prescription length in days supply (either single or serially dispensed) of both H2RAs and PPIs were associated with obesity, although

Table 5 Adjusted hazard of developing obesity for those prescribed none, one, two or three antibiotics, histamine-2 receptor antagonists or proton pump inhibitor medication classes

	HR	95% CI
No medications	Ref	Ref
One medication	1.21	1.18 to 1.24
Two medications	1.31	1.26 to 1.35
Three medications	1.42	1.33 to 1.51

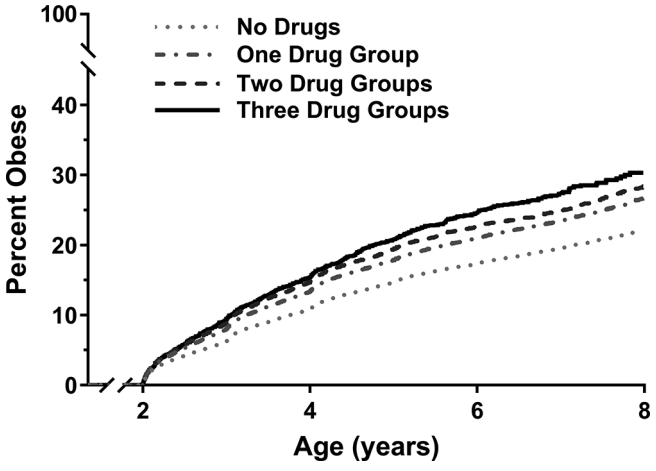

Figure 2 Estimated survival curve for patients prescribed medications prior to the age of 2 years of age who develop obesity after prescription to none, one or multiple medication groups (proton pump inhibitors, histamine-2 receptor antagonists and/or antibiotics).

the adjusted model for H2RAs found that this increase is male specific. H2RAs and PPIs are commonly prescribed in paediatric populations to treat gastro-oesophageal reflux, and infants are typically exposed to these medications prior to antibiotics. Acid-suppressant medications are known to affect the gut microbiome by decreasing bacterial diversity and increasing the presence of potentially pathogenic bacteria.[41 42] This reduction of diversity could have implications for weight gain. H2RAs have not been studied specifically to determine their potential role in paediatric obesity. H2RA prescriptions were associated with an increased obesity risk in males but not females. The significance of this sex-related difference is unclear. One recent study found that faecal microbiota composition was associated with an increased fat-free mass index in males aged 2–3 years but not females.[43] Our study evaluated obesity in relation to BMI and did not evaluate differences between fat mass and fat-free mass in the exposed and unexposed populations. Further evaluation of sex-related differences in the gut microbiota and obesity risk factors are needed. The role of PPIs in weight gain has been evaluated previously in the context of outcomes of postgastric bypass patients. A study of adult patients that underwent laparoscopic Roux-en-Y gastric bypass found that PPI users 6 months postgastric bypass trended towards less weight loss.[44] This finding was postulated to be associated with PPI-induced changes in the gut microbiota. Bailey *et al*[27] evaluated the pooled effect of H2RAs and PPIs in a retrospective study of 65 480 patients and found no association between antireflux medications and obesity. H2RAs and PPIs are commonly prescribed to healthy infants to treat physiological reflux that resolves by late infancy.[27] The previous study had a significantly smaller population size, whereas the present study's large population size may have captured a small effect that would have otherwise been missed. The potential role of antiacid secretion medications and obesity may be confounded by the presence of underlying disease that could negatively impact growth. Additionally, established negative side effects of PPIs, including increased risk of respiratory and GI infections, may also lead to subsequent weight loss in paediatric patients prescribed PPIs.[45] Susceptibility to infection may be a possible uncontrolled confounder in our study.

Interestingly, we found that prescriptions to more than one of H2RA, PPI or antibiotic medication classes led to an increasing risk of obesity. Our survival analysis suggests the presence of an additive effect of antibiotics, PPI and H2RA prescriptions on the risk of obesity. Multiple or prolonged disruptions from microbiota-altering medications can augment the development of obesity. Further evaluation of longitudinal data and in vivo studies may help distinguish the nature of this effect. A similar thread between H2RA, PPI and antibiotic medications is their effects on GI microbiota, although their mechanism and efficiency in enacting this change varies greatly. Recent studies have provided evidence that antibiotics can cause gut micriobiota alterations after a relatively short period of exposure, whereas antiacid medications tend to require a more prolonged course to have clinically significant changes.[46 47] This agrees with our findings of an increasing association with the development of obesity in infants for each 30-day level of exposure to PPIs and H2RAs. Infants are frequently prescribed prolonged courses of H2RAs or PPIs for management of gastro-oesophageal reflux. Antibiotics alter the intestinal biota through direct bactericidal or bacteriostatic properties and are typically non-refillable and prescribed in shorter courses than acid secretion-inhibiting medications. The antimicrobial spectrum of an antibiotic, as determined by the antibiotic class, was therefore more relevant to evaluate than treatment length. Exposure to more than one class of antibiotics was observed to have a stronger association with the development of obesity, which may represent an increased effect in a dose–response manner. These findings should give pause to providers who may renew antiacid medication prescriptions without proven clinical benefit or prescribe an antibiotic course in the absence of a true medical indication.

Similar to previous studies, we found that caesarean section birth was associated with an increased risk of developing obesity in childhood. The mechanism of this finding is the source of significant debate, with some focusing on the role of microbiota alterations, while others consider confounders, such as greater birth spacing until the next child among caesarean-delivered children, as the main factor in this finding.[16 48] It is important to consider that the American College of Obstetricians and Gynecologists and standard practice at military treatment facilities is to provide antibiotic prophylaxis prior to all caesarean deliveries.[49] The role of perinatal medication exposure in caesarean-born infants and subsequent risk of obesity requires further study.

We found that male sex was associated with childhood obesity. This finding has been reported in several previous studies, but it is inconsistent, and there are possible geographic and ethnic confounders.[50] Delineating differences in vulnerability to obesogenic environments depending on gender requires further study.

Military rank was evaluated as a proxy for socioeconomic status, and we found that children of lower ranking enlisted service members were more likely to develop obesity. US service members and their dependents have access to universal healthcare with minimal or no copayments regardless of rank. Military salary is commensurate with rank, so lower ranking service members may, on average, have lower monthly income than higher ranking service members. Previous studies have found that lower income households in the USA are at increased risk of obesity.[51] Our findings suggests that incidence of obesity is greater even with equal access to healthcare. Socioeconomic status, healthcare disparities and paediatric obesity have a complex interaction that requires further research to delineate.

Our study is strengthened by its large, geographically diverse population, which has access to universal healthcare within the MHS through TRICARE. Armed Service members and their families have demographic diversity in line with the general US population.[52] TRICARE patients have access to medications with no or minimal copayments, reducing sampling bias. Socioeconomic status, as determined by sponsor pay-grade, was analysed and may be more accurate in this form than self-reported income data of previous studies. Additionally, this cohort may continue to be followed with future studies over time as the population ages.

Limitations of our study include possible misclassification bias of caesarean section or prematurity due to reliance on diagnostic and procedure codes. Information on maternal weight, smoking status and other comorbid health problems were not available for this study. This is a potentially significant limitation, as a strong maternal confounder could account for some of the differences that were seen in the exposed populations. Our data include only prescriptions that were filled by the patients, but we are unable to confirm whether the entire prescribed treatment course was completed. Prescriptions dispensed outside of the MHS, such as at an emergency department or urgent care clinic, were only included if TRICARE was used to purchase the medications. Inpatient medication exposures were not included in our study. Breastfeeding status, which is associated with lower childhood obesity rates, was not included in this study due to

lack of data availability.[53] Previous studies suggest that US Active Duty service members may have decreased breastfeeding rates compared with their civilian counterparts, although there are no previous studies to quantify breastfeeding trends among military dependents.[54] Our study does not account for child temperament, which is associated with maternal feeding behaviours that may promote obesity[55] or other social factors that may lead infants to be more frequently prescribed antibiotics. The design of our retrospective cohort study may be limited by the potential for immortal time bias. Immortal time bias refers to a span of time in the observation period of a cohort during which the outcome under study could not have occurred.[56] We sought to minimise the risk of immortal time bias through study design by temporally separating the exposure from the outcome. Within our study design, exposure must have occurred in the first 2 years of life and the observation period for measurement of obesity started at age 2 years. All patients included in the study could have a measurement of obesity during the observation period regardless of exposure status. Although BMI can be ≥95% for age prior to 2 years of age, the American Academy of Pediatrics recommends using BMI to evaluate for obesity beginning at 2 years of age.

The interaction between gut microbiota, obesity and PPIs is multifactorial and complex. Microbial diversity of the GI tract varies widely by anatomical location, diet and exposure history. PPIs increase gastric pH, which disrupts the native GI microecosystem.[12] PPI use has been previously associated with a decrease in lower GI tract microbial diversity; however, the clinical relevance of these findings is unclear.[57] A recent twin study comparing concordance of leanness or obesity found that obesity was associated with a significant reduction in overall GI tract bacterial diversity.[58] Apart from a general decrease in microbial diversity, PPI use is associated with a relative increase or decrease in multiple different bacterial phyla.[59] Actinobacter, Bacteroidetes, and Firmicutes have been identified as increased in prevalence with PPI users. A study of human stool samples found that Actinobacteria were present in greater proportions in obese individuals compared with lean, whereas Bacteroidetes were found in lower proportions.[58] The stool study found no significant difference in Firmicutes between obese and lean individuals. Another study of 12 obese individuals found decreased Bacteroides and increased Firmicutes in the distal gut when compared with lean individuals.[17] These findings highlight the complex obesogenic interactions with host metabolism and energy expenditure that expound the current difficulty of drawing clear conclusions about the interplay between exposure history, gut microbiota and propensity to develop obesity. Non-antimicrobial effects of antibiotics, such as the anti-inflammatory or promotility properties of macrolides, may also contribute to the observed findings. Infection, rather than antibiotic exposure, may also be a risk factor for obesity. Human adenovirus 36 infection has been previously associated with a diagnosis of obesity.[60] The role of infection and risk of obesity requires further evaluation.

There is an important therapeutic role for microbiota-altering medications. The long-term risks to health must be weighed against the short-term benefits. Overprescription is a significant problem for antibiotics and antiacid medications. One recent study found that almost one-third of all outpatient antibiotic prescriptions could be categorised as inappropriate.[61] Additionally, antiacid medications continue to be prescribed at high rates in children less than 1 year old, despite limited evidence to support any clinically significant benefits.[62] Medication overprescription and overmedicalisation of physiological symptoms persists, despite growing evidence of negative health consequences, especially related to alterations of the human microbiome. Specific comparisons among alterations in the GI microbial motif in H2RA-exposed, PPI-exposed and antibiotic-exposed infants have not been reported. This comparison would offer a valuable avenue to help determine which bacterial populations are selected in different body biomes. Clear documentation of the specific effects of these medications at the level of the microbiota would provide further justification for prevention of extraneous prescriptions and may further convince providers to adhere to strict clinical guidelines for prescriptions of these medications. Additionally, there is a need to evaluate factors, such as probiotic exposure, that may ameliorate negative effects of exposure to microbiota-altering medications. Although there is mounting evidence of unanticipated consequences associated with antibiotic and antiacid medication use, providers should practice appropriate stewardship as the first-line response to these findings.

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