



# Prenatal and Early Childhood Exposure to Proton Pump Inhibitors and Antibiotics and the Risk of Childhood Cancer: A Nationwide Population-Based Cohort Study

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## Abstract

**Background** Our microbiome is established during infancy, a time important for later health and long-term effects. Proton pump inhibitors and antibiotics are regularly prescribed during pregnancy. Both drugs cause microbiome disturbance and have been associated with increased cancer risk in adults, but effects of these drugs on the growing foetus and infant remain understudied.

**Aim** The aim of this study is to study the association between prenatal and early life proton pump inhibitor and antibiotics exposure and the risk of childhood cancer.

**Methods** This study is a retrospective population-based cohort design, using registry data on all births ( $n = 722,372$ ) in Sweden between 2006 and 2016, according to the STROBE checklist. For women who had multiple children in the timeframe of the study, only the first child during the time period was included in the cohort. Exposure was defined as either  $\geq 1$  proton pump inhibitor or antibiotics prescription during pregnancy, or during the first 2 years of life. Outcome was defined as cancer at any time during the follow-up or cancer after the age of 2 years for early life exposure. Multivariable Cox proportional hazard models were used to calculate hazard ratios.

**Results** In total, 1091 (0.2%) children were diagnosed with malignant cancer during the follow-up. Prenatal exposure to proton pump inhibitors and antibiotics were not associated with an increased risk of cancer. Regarding early life exposure, proton pump inhibitors were associated with an increased risk of cancer at age two or older (adjusted hazard ratio [aHR] 3.68, 95% confidence interval [CI] 2.24–6.06).

**Conclusions** We did not find evidence that prenatal proton pump inhibitors and antibiotics were associated with overall childhood cancer. However, proton pump inhibitors during early life were associated with an increased risk of childhood cancer, but indication on drug use was not available and confounding by indication may be present.

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## Graphical Abstract

# Drug Safety

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## Prenatal and early childhood exposure to proton pump inhibitors and antibiotics and the risk of childhood cancer: A nationwide population-based cohort study

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### Background and Aim

Microbiome modulating drugs such as antibiotics and proton pump inhibitors have been associated with an increased cancer risk in adults.

Our aim was to study the association between prenatal and early life (< 2 years) exposure and the risk of cancer.

### Materials and Methods



All pregnancies in Sweden 2006-2016  
(n=722,372)



Registry based drug exposure and diagnoses codes

Multivariable Cox proportional hazard ratios

### Results



1,091 children diagnosed with malignant cancer

Prenatal exposure not associated with an increased risk of childhood cancer

Early life exposure to proton pump inhibitors was associated with an increased risk of cancer after the age of two (aHR 3.68, 95%CI 2.24-6.06)

Confounding by indication could not be controlled for.



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### Key Points

Increasing evidence shows that microbiome modulating drugs increase cancer risk in adults, while no studies have investigated this risk in children.

Prenatal exposure to proton pump inhibitors and antibiotics showed no association with cancer risk. On the other hand, exposure to proton pump inhibitors before the age of two was associated with an increased cancer risk, but confounding by indication could not be controlled for.

## 1 Introduction

Prescribed drug use is common during pregnancy, although little is known about long-term effects for mother and child [1–3]. Antibiotics and proton pump inhibitors (PPIs) can alter the gut microbiome [4–10], which may lead to health consequences, including cancer [6–8, 11–18]. During infancy there is a critical period when the gut microbiome is easily influenced, possibly with lasting health effects [19, 20], thus warranting the question how prenatal or early life PPIs and antibiotics affect the child's health.

It is estimated that 25% of women globally use antibiotics during pregnancy [16, 21, 22]. The most common use is to combat suspected bacterial infections such as urinary tract and upper respiratory tract infections [16]. However, antibiotic use is not without risk. Antibiotics have been associated with negative effects, such as congenital abnormalities, preterm birth, low Apgar score and negative changes in the gut microbiome [15–17, 21, 23].

Gastrointestinal symptoms, such as heartburn, are common pregnancy symptoms [24, 25] and can often be relieved by lifestyle alterations or PPIs. Approximately 1.7% of pregnant women use PPIs in Sweden during the first trimester [26], and they are generally regarded as safe [27]. However, our previous Swedish registry study and our meta-analysis suggested an increased risk for various pregnancy events and congenital malformations in pregnancies exposed to PPIs [28, 29]. Outside pregnancy, PPI was associated with increased all-cause and cause-specific mortality in a Swedish population study [30] and other specific populations [31–33], with various other adverse events ranging from gastro-intestinal infections to osteoporosis and kidney failure [34]. Yet, as we investigate a young population (pregnant women and infants), the probability of multi-morbidity is more limited. Additionally, off-label prescriptions of PPIs to infants has increased in the last decades [9, 35], while the efficacy of PPI treatment

on infant for gastroesophageal reflux disease (GERD) has not been shown [35].

Broad-spectrum antibiotics have been found to increase the risk of colorectal and breast cancer according to previous meta-analyses [36, 37]. As for PPIs, Swedish and other cohorts show that long-term PPI use may increase the risk of biliary tract, pancreatic, gastric and oesophageal cancer [30, 38–43], where the increased risk of gastric cancer is supported further in several meta-analyses [44–48].

Yet, to our knowledge, there is limited evidence on a potential association between antibiotics or PPIs and childhood cancer. There are few identified risk factors for childhood cancer, with the best-known being genetic predispositions, air pollution and chronic infections [49, 50]. However, most cases have an unknown cause [50]. Regarding in utero drug exposure and microbiome dysbiosis, current studies are inconsistent. A few studies have found associations between antibiotics during pregnancy (or certain trimesters) and several childhood cancer types including colorectal cancer, acute lymphoid leukaemia, acute myeloid leukaemia and Burkitt lymphoma [3, 51–53], while other studies do not [54–57].

The aim of this study is to investigate if there is an association between the exposure to PPIs and antibiotics prenatally and during early life (before the age of 2 years) and the risk of childhood cancer, using Swedish registers.

## 2 Materials and Methods

### 2.1 Study Design and Period

In this nationwide population-based cohort study, we extracted data on all liveborn singleton births in Sweden between July 2006 and December 2016 from high quality national registers: the Medical Birth Register [58], the Swedish Patient Register [59], the Swedish Cause of Death Register [60] and the Swedish Prescribed Drug Register [61]. Data were linked using Swedish personal identity numbers, assigned to all Swedish residents. For women that had multiple children in the timeframe of the study, only the first child during the time period was included in the cohort. Children were followed up until date of first cancer (day of admission or date of specialist outpatient visit), death or end of study (December 2017), whichever came first, or age 2 years for subgroup analyses addressing cancer during the first 2 years of life. This study was performed in accordance with the Declaration of Helsinki, approved by the Regional Ethics Committee of Stockholm (2017/2423-31). Informed consent was not required. The study was conducted according to the STROBE checklist [62].

## 2.2 Exposure

The study exposures were defined as prescription of systemic antibiotics, PPIs or histamine-2 receptor antagonist (H2RA) during pregnancy or early life (up to 2 years of age) during the period 2006–2016. H2RAs were included, as they are prescribed for similar indications as PPIs but have different mechanisms. As so few individuals (0.1%) got H2RA prescription, they were not used in further analysis.

Anatomical Therapeutic Chemical (ATC) classifications were included: antibacterials for systemic use (J01) and its ten classes (J01A, J01C, J01D, J01E, J01F, J01G, J01M and J01X merged with P01AB01) [63], and drugs for gastric-acid related disorders (A02BC proton pump inhibitors and A02BA H2-receptor antagonists).

Number of prescriptions and accumulated defined daily doses (DDD) were collected and categorized as quartiles. Information on over-the-counter drugs was not available for PPIs and H2RA (available over the counter in Sweden at a higher price).

Maternal exposure was defined as first trimester (last menstrual period [LMP] 0–97), second trimester (LMP 98–202) and third trimester (LMP 203 to delivery). The LMP date was calculated by extracting the gestational age (as dated at ultrasound, from embryo transfer or last menstrual period) from the date of birth.

## 2.3 Outcomes

The main outcome was first diagnosis of childhood cancer (up to age 11 years) using the in- and out-patient registers with ICD-10 codes C00–C96 (malignant tumour) [64]. The most common subtypes of paediatric cancer (at least 40 cases) were categorized by anatomical location (Supplementary Table S1) [65].

Outcome was recorded at any time during the follow up period for prenatal exposure (2006–2017, age 0–11 years) and after the age of 2 years for early life exposure (2008–2017, age 2–11 years) (Supplementary Fig. 1).

## 2.4 Covariates

From the registry data, information on the following covariates were extracted: (1) maternal factors (age at childbirth (< 25, 25–29, 30–34, 35–39 and  $\geq 40$  years), country of birth of mother (Nordic or non-Nordic), body mass index (BMI, < 20.0, 20.0–24.9, 25.0–29.9 and  $\geq 30.0$  kg/m<sup>2</sup>), parity (nulliparous or parous), use of artificial reproductive technologies (ART, yes/no), delivery mode (vaginal, acute or elective caesarean section [c-section]), preterm status (birth before/after 37 completed weeks of gestation or not); (2) lifestyle factors (tobacco consumption during pregnancy [smoking

and smokeless tobacco]); (3) common maternal chronic comorbidities (hypertension, diabetes, hypo- and hyperthyroidism); and (4) child related factors (sex of the child, being small/large for gestational age at birth, Apgar score at 5 min (higher or lower than 7), use of nonsteroidal anti-inflammatory drugs (NSAIDs) before the age of 2 years and diagnosis of either gastro-oesophageal reflux disease (ICD-10: K21) or newborn oesophageal reflux (ICD-10: P78.83) before the age of 2 years. As the date of birth was provided in year/month format due to privacy regulations, it was set as the 15th of each month [21, 66].

## 2.5 Statistical Analysis

The risk of cancer after prenatal use of antibiotics or PPIs was estimated using multivariable Cox proportional hazard models presented as hazard ratios (HR) and 95% confidence intervals (CI) for four comparisons: (1) prenatal exposure and childhood cancer, (2) prenatal exposure and cancer before the age of 2 years, (3) prenatal exposure and cancer diagnosis after the age of 2 years and (4) early life (before the age of 2 years) exposure and cancer diagnosis after the age of two (Supplementary Fig 1).

For these models on cancer above age 2 years, follow-up started at the second birthday as, by definition, this outcome could not have occurred earlier. For the analysis of cancer before the age of 2 years, follow-up ended at the latest at their second birthday.

All models were adjusted for potential confounders (if  $p < 0.10$  in univariable analyses), as well as preselected variables: maternal age, maternal BMI, sex of child, gestational age at birth (preterm birth or not) and delivery mode.

Different interactions were assessed using log likelihood ratio tests: prenatal exposure to PPIs and antibiotics, early life exposure to PPIs and antibiotics, prenatal and early life PPIs and prenatal and early life antibiotics.

Stratified analyses were performed by delivery mode as this could be a mediator for microbiome related cancer [67], where exposed children born vaginally, via elective c-section or acute c-section were compared with unexposed children born the same way. Based on the strong multivariable results on mode of delivery, we also assessed if there was an interaction between prenatal or early life PPI use and c-section.

Stratified subanalyses were done if feasible, by antibiotic subclass, pregnancy trimester of maternal medication intake, preterm/term status and type of cancer.

Dose–response analyses were performed using DDD and number of prescriptions for prenatal antibiotics and PPIs.

Complete case analyses were used for all analyses, and absence of reporting of the respective ICD codes for exposures, listed above, was considered absence of the disease/disorder. For BMI, 7% of individuals did not have any data,

so a dummy variable was created to keep them in the models. A sensitivity analysis of the overall results was done excluding those 7% with missing values.

RStudio (version 1.3.1093) was used for all statistical analyses and to create figures.

### 3 Results

In total, 722,372 mother–child dyads were identified. Most mothers were 30–34 years old (31.7%), normal weight (49.0%) and nulliparous (66.9%) (Table 1).

Altogether, 23,910 (3.3%) women received a PPI prescription at any time during pregnancy, with 11,732 (1.6%) during the first, 10,251 (1.4%) the second and 9117 (1.3%) during the third trimester. For PPI-users, the mean DDD was 86 (interquartile range [IQR] 28–100) and the average number of prescriptions per individual was 1.6 (IQR 1–2).

Overall, 160,703 mothers (22.2%) were prescribed antibiotics at any time during pregnancy, with 63,374 (8.8%) during the first, 69,125 (9.6%) the second and 60,597 (8.4%) in the third trimester. For users, the mean DDD was 10.0 (IQR 6.3–16.0), and the average number of prescriptions per individual was 1.5 (IQR 1–2).

The number of H2RA prescriptions during pregnancy ( $n = 1080$ , 0.1%) did not allow for any statistical analyses, and therefore, only PPIs and antibiotics were investigated.

A total of 636,224 children reached at least age 2 years in the cohort and were used in early life exposure analysis. In total, when only considering early life exposure, 3903 (0.6%) got PPIs, 218,998 (34.4%) got antibiotics and 2193 (0.3%) got H2RAs before the age of 2 years (Table 2).

More children of nulliparous women got early life PPIs or antibiotics compared with those that did not (70.9% versus 64.4%), while children of multiparous women had higher prevalence of antibiotics exposure (43.1% versus 31.7%) (Table 2).

Children exposed to PPIs in early life (before second birthday) had higher prevalence of being delivered via acute c-section (19.9% versus 10.4% of unexposed) and having a reflux diagnosis before the age of two (35.8% versus 0.2%) (Table 2).

Follow-up time accumulated to 4,145,681 person-years, with mean follow-up of 6 years (IQR 3–8). Follow-up for children exposed to PPIs in early life was IQR 2–7, compared with IQR 3–8 of unexposed children. Children exposed to antibiotics in early life had follow-up with IQR 4–9, compared with IQR 3–8 of unexposed children. No subgroup analyses were performed regarding early life exposure to PPIs due to insufficient power.

### 3.1 Cancer Diagnoses

In total, 1091 (0.15%) children were diagnosed with malignant cancer during the follow-up (Table 1), with an incidence rate of 151 cases per 100,000 individuals.

Out of those exposed to PPIs prenatally, 0.1% got diagnosed with cancer and 0.2% of those exposed prenatally to antibiotics (Table 1). Regarding early life exposure, 0.1% of those with antibiotics prescription got cancer after the age of 2 years and 0.4% of those with PPI prescription (Table 2).

Considering cancer subtype, ‘eye, brain and other parts of central nervous system (CNS)’ were the most common ( $n = 271$ , 24.8%), followed by lymphoid leukaemia ( $n = 235$ , 21.5%). The age distribution for all subtypes of cancers was similar (Fig. 1).

### 3.2 Prenatal Exposure and Overall Risk of Cancer

Parity (HR 0.88, 95% CI 0.78–1.00), delivery mode (elective c-section HR 1.35, 95% CI 1.09–1.67), being born preterm (HR 1.36, 95% CI 1.08–1.72) and being large for gestational age (HR 1.48, 95% CI 1.11–1.99) were associated with a higher risk of cancer, ( $p < 0.10$  in a univariable model, Supplementary Table S2) and were, therefore, included in the multivariable model.

In the Cox proportional hazard model (adjusted for pre-selected variables: maternal age, maternal BMI, sex of child and the variables mentioned above) prenatal PPIs (adjusted hazard ratio [aHR] 1.11, 95% CI 0.79–1.56) and antibiotics (aHR 0.95, 95% CI 0.83–1.11) were not associated with the risk of cancer (Table 3). A sensitivity analysis showed that the missing BMI values did not influence the analysis (results not shown).

Likelihood ratio tests showed that prenatal exposure to PPIs and antibiotics showed no interaction ( $p = 0.94$ ).

Furthermore, there was no interaction between prenatal PPIs and delivery mode ( $p = 0.69$ ).

Cumulative incidence curve can be seen in Supplementary Material (Supplementary Fig. 2).

Estimation of the proportional hazard assumption for the adjusted model showed that all predictors met that assumption ( $p = 0.57$ ).

#### 3.2.1 Subgroup Analysis

Subgroup analyses on antibiotic classes and cancer locations (insufficient power for PPIs) did not show any statistically significant associations (Supplementary Tables S3 and S4).

No association was observed for PPIs and antibiotics for any trimester (Table 4). Furthermore, no association

**Table 1** Descriptive statistics for the cohort, stratified by prenatal exposure to proton pump inhibitors (PPIs) or antibiotics

	Total ( <i>N</i> = 722372)	Prenatal PPI <sup>‡</sup> exposure ( <i>N</i> = 23910)	No prenatal PPI <sup>‡</sup> exposure ( <i>N</i> = 698462)	Prenatal antibiotics exposure ( <i>N</i> = 160703)	No prenatal antibiotics exposure ( <i>N</i> = 561669)
<b>Maternal age</b>					
< 25	125,030 (17.3%)	4145 (17.3%)	120,885 (17.3%)	31,724 (19.7%)	93306 (16.6%)
25–29	223,796 (31.0%)	6758 (28.3%)	217,038 (31.1%)	46,458 (28.9%)	17,7338 (31.6%)
30–34	228,993 (31.7%)	7079 (29.6%)	221,914 (31.8%)	49,021 (30.5%)	17,9972 (32.0%)
> 34	144,553 (20.0%)	5928 (24.8%)	138,625 (19.8%)	33,500 (20.8%)	11,1053 (19.8%)
<b>Maternal BMI*</b>					
Underweight	72,200 (10.0%)	2249 (9.4%)	69,951 (10.0%)	15,930 (9.9%)	56,270 (10.0%)
Normal weight	353,848 (49.0%)	9688 (40.5%)	344,160 (49.3%)	74,756 (46.5%)	279,092 (49.7%)
Overweight	164,450 (22.8%)	6161 (25.8%)	158,289 (22.7%)	37,330 (23.2%)	127,120 (22.6%)
Obese	79,498 (11.0%)	4069 (17.0%)	75,429 (10.8%)	20,642 (12.8%)	58,856 (10.5%)
Missing	52,376 (7.3%)	1743 (7.3%)	50,633 (7.2%)	12,045 (7.5%)	40,331 (7.2%)
<b>Parity</b>					
Multiparous	238,893 (33.1%)	8231 (34.4%)	230,662 (33.0%)	61,758 (38.4%)	177,135 (31.5%)
Nulliparous	483,479 (66.9%)	15,679 (65.6%)	467,800 (67.0%)	98,945 (61.6%)	384,534 (68.5%)
Maternal Nordic birth country	549,640 (76.1%)	15,119 (63.2%)	53,4521 (76.5%)	122,043 (75.9%)	427,597 (76.1%)
<b>Cohabitation</b>					
Cohabiting with father	636,317 (88.1%)	20,209 (84.5%)	616,108 (88.2%)	138,610 (86.3%)	497,707 (88.6%)
Single	15,757 (2.2%)	918 (3.8%)	148,39 (2.1%)	4383 (2.7%)	11,374 (2.0%)
Other	37,414 (5.2%)	1678 (7.0%)	35,736 (5.1%)	10,196 (6.3%)	27,218 (4.8%)
Assisted conception	26,147 (3.6%)	1087 (4.5%)	25,060 (3.6%)	5633 (3.5%)	20,514 (3.7%)
Tobacco use	52,952 (7.3%)	2072 (8.7%)	50,880 (7.3%)	15,432 (9.6%)	37,520 (6.7%)
Maternal hypertension	3479 (0.5%)	214 (0.9%)	3265 (0.5%)	944 (0.6%)	2535 (0.5%)
Maternal diabetes mellitus	6086 (0.8%)	450 (1.9%)	5636 (0.8%)	2089 (1.3%)	3997 (0.7%)
Maternal hypothyroidism	19,809 (2.7%)	1199 (5.0%)	18610 (2.7%)	5342 (3.3%)	14467 (2.6%)
Maternal hyperthyroidism	3925 (0.5%)	191 (0.8%)	3734 (0.5%)	1004 (0.6%)	2921 (0.5%)
<b>Delivery mode</b>					
Vaginal	597,852 (82.8%)	18,429 (77.1%)	579,423 (83.0%)	129,539 (80.6%)	468,313 (83.4%)
Elective c-section	46,852 (6.5%)	2224 (9.3%)	44,628 (6.4%)	12,257 (7.6%)	34,595 (6.2%)
Acute c-section	77,668 (10.8%)	3257 (13.6%)	74,411 (10.7%)	18,907 (11.8%)	58,761 (10.5%)
<b>Sex of child</b>					
Boy	371,899 (51.5%)	12,274 (51.3%)	359,625 (51.5%)	83,015 (51.7%)	288,884 (51.4%)
Girl	350,473 (48.5%)	11,636 (48.7%)	338,837 (48.5%)	77,688 (48.3%)	272,785 (48.6%)
Preterm	38,167 (5.3%)	1596 (6.7%)	36,571 (5.2%)	9357 (5.8%)	28,810 (5.1%)
Small for gestational age	20,251 (2.8%)	952 (4.0%)	19,299 (2.8%)	4438 (2.8%)	15,813 (2.8%)
Large for gestational age	19,996 (2.8%)	733 (3.1%)	19,263 (2.8%)	5345 (3.3%)	14,651 (2.6%)
Apgar score < 7 at 5 min	9914 (1.4%)	427 (1.8%)	9487 (1.4%)	2460 (1.5%)	7454 (1.3%)
NSAID** prescription before age 2	5676 (0.8%)	358 (1.5%)	5318 (0.8%)	1599 (1.0%)	4077 (0.7%)
Reflux diagnosis before age 2	3488 (0.5%)	264 (1.1%)	3224 (0.5%)	1099 (0.7%)	2389 (0.4%)
Cancer diagnosis	1091 (0.2%)	35 (0.1%)	1056 (0.2%)	243 (0.2%)	848 (0.2%)
Cancer diagnosis after age of 2	781 (0.1%)	27 (0.1%)	754 (0.1%)	169 (0.1%)	612 (0.1%)

\*Body mass index (BMI)

\*\*Nonsteroidal anti-inflammatory drugs (NSIAD)

‡Proton pump inhibitors (PPIs)

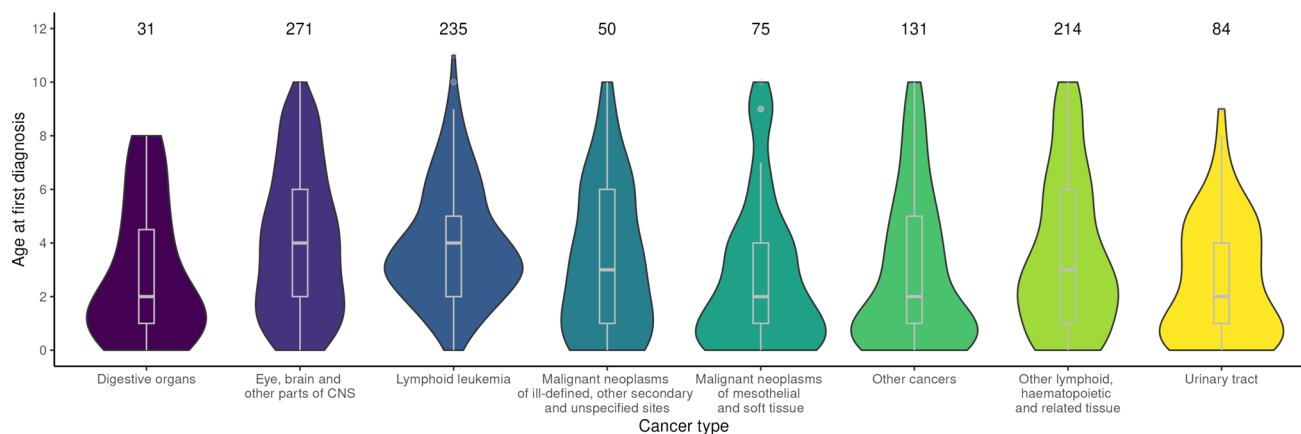
**Table 2** Descriptive statistics for the cohort, stratified by early life (before age 2 years) exposure to proton pump inhibitors (PPIs) or antibiotics

	Total children at least 2 years old ( <i>N</i> = 636224)	Early life PPI <sup>‡</sup> exposure ( <i>N</i> = 3903)	No early life PPI <sup>‡</sup> exposure ( <i>N</i> = 632321)	Early life antibiotics exposure ( <i>N</i> = 218998)	No early life antibiotics exposure ( <i>N</i> = 417226)
<b>Maternal age</b>					
< 25	108,971 (17.1%)	591 (15.1%)	108,380 (17.1%)	38,092 (17.4%)	70,879 (17.0%)
25–29	192,654 (30.3%)	1105 (28.3%)	191,549 (30.3%)	65,596 (30.0%)	127,058 (30.5%)
30–34	204,290 (32.1%)	1335 (34.2%)	202,955 (32.1%)	70,862 (32.4%)	133,428 (32.0%)
> 34	130,309 (20.5%)	872 (22.3%)	129,437 (20.5%)	44,448 (20.3%)	85,861 (20.6%)
<b>Maternal BMI*</b>					
Underweight	63,207 (9.9%)	391 (10.0%)	62,816 (9.9%)	20,298 (9.3%)	42,909 (10.3%)
Normal weight	312,377 (49.1%)	1885 (48.3%)	310,492 (49.1%)	103,999 (47.5%)	20,8378 (49.9%)
Overweight	144,291 (22.7%)	814 (20.9%)	143,477 (22.7%)	51,561 (23.5%)	92,730 (22.2%)
Obese	69,496 (10.9%)	449 (11.5%)	69,047 (10.9%)	26,249 (12.0%)	43,247 (10.4%)
Missing	46,853 (7.4%)	364 (9.3%)	46,489 (7.4%)	16,891 (7.7%)	29,962 (7.2%)
<b>Parity</b>					
Multiparous	226,352 (35.6%)	1134 (29.1%)	225,218 (35.6%)	94,293 (43.1%)	132,059 (31.7%)
Nulliparous	409,872 (64.4%)	2769 (70.9%)	407,103 (64.4%)	124,705 (56.9%)	285,167 (68.3%)
Maternal Nordic birth country	488,885 (76.8%)	3054 (78.2%)	485,831 (76.8%)	164,421 (75.1%)	324,464 (77.8%)
<b>Cohabitation</b>					
Cohabiting with father	561,826 (88.3%)	3349 (85.8%)	558,477 (88.3%)	192,603 (87.9%)	369,223 (88.5%)
Single	13,717 (2.2%)	123 (3.2%)	13,594 (2.1%)	5185 (2.4%)	8532 (2.0%)
Other	32,350 (5.1%)	182 (4.7%)	32,168 (5.1%)	11,131 (5.1%)	21,219 (5.1%)
Assisted conception	21,790 (3.4%)	208 (5.3%)	21,582 (3.4%)	6895 (3.1%)	14,895 (3.6%)
Tobacco use	47,994 (7.5%)	272 (7.0%)	47,722 (7.5%)	18,760 (8.6%)	29,234 (7.0%)
Maternal hypertension	3166 (0.5%)	23 (0.6%)	3143 (0.5%)	1182 (0.5%)	1984 (0.5%)
Maternal diabetes mellitus	5291 (0.8%)	52 (1.3%)	5239 (0.8%)	1991 (0.9%)	3300 (0.8%)
Maternal hypothyroidism	16,159 (2.5%)	185 (4.7%)	15,974 (2.5%)	5731 (2.6%)	10,428 (2.5%)
Maternal hyperthyroidism	3398 (0.5%)	27 (0.7%)	3371 (0.5%)	1262 (0.6%)	2136 (0.5%)
<b>Delivery mode</b>					
Vaginal	528,124 (83.0%)	2704 (69.3%)	525,420 (83.1%)	179,931 (82.2%)	348,193 (83.5%)
Elective c-section	41,600 (6.5%)	424 (10.9%)	41,176 (6.5%)	15,909 (7.3%)	25,691 (6.2%)
Acute c-section	66,500 (10.5%)	775 (19.9%)	65,725 (10.4%)	23,158 (10.6%)	43,342 (10.4%)
<b>Sex of child</b>					
Boy	327,358 (51.5%)	2256 (57.8%)	325,102 (51.4%)	120,284 (54.9%)	207,074 (49.6%)
Girl	308,866 (48.5%)	1647 (42.2%)	307,219 (48.6%)	98714 (45.1%)	210,152 (50.4%)
Preterm	32,885 (5.2%)	718 (18.4%)	32,167 (5.1%)	11,707 (5.3%)	21,178 (5.1%)
Small for gestational age	17,131 (2.7%)	335 (8.6%)	16,796 (2.7%)	5773 (2.6%)	11,358 (2.7%)
Large for gestational age	18,101 (2.8%)	121 (3.1%)	17,980 (2.8%)	7047 (3.2%)	11,054 (2.6%)
Apgar score < 7 at 5 min	7770 (1.2%)	248 (6.4%)	7522 (1.2%)	2817 (1.3%)	4953 (1.2%)
NSAID** prescription before age 2	4918 (0.8%)	82 (2.1%)	4836 (0.8%)	3595 (1.6%)	1323 (0.3%)
Reflux diagnosis before age 2	2896 (0.5%)	1396 (35.8%)	1500 (0.2%)	1408 (0.6%)	1488 (0.4%)
Cancer diagnosis	789 (0.1%)	16 (0.4%)	773 (0.1%)	299 (0.1%)	490 (0.1%)
Cancer diagnosis after age of 2	781 (0.1%)	15 (0.4%)	766 (0.1%)	293 (0.1%)	488 (0.1%)

\*Body mass index (BMI)

\*\*Nonsteroidal anti-inflammatory drugs (NSIAD)

‡Proton pump inhibitors (PPIs)



**Fig. 1** Distribution of age at first diagnosis by cancer type

**Table 3** Prenatal exposure to proton pump inhibitors (PPIs) and antibiotics and the risk of overall cancer, and risk of cancer before and after the age of two

	No of events	Overall		No of events	Diagnosis under 2		No of events	Diagnosis over 2	
		HR (95% CI)	aHR (95% CI)		HR (95% CI)	aHR (95% CI)		HR (95% CI)	aHR (95% CI)
PPI during pregnancy	35	1.11 (0.79–1.56)	1.11 (0.79–1.55)	8	0.54 (0.27–1.09)	0.56 (0.28–1.13)	27	1.26 (0.86–1.85)	1.26 (0.86–1.85)
Any antibiotics during pregnancy	243	0.95 (0.83–1.10)	0.96 (0.83–1.11)	74	<b>1.31 (1.01–1.71)</b>	1.28 (0.98–1.67)	169	0.90 (0.76–1.07)	0.91 (0.77–1.08)
PPI early life		NA	NA		NA	NA	15	<b>3.89 (2.37–6.39)</b>	<b>3.68 (2.24–6.06)</b>
Any antibiotics early life		NA	NA		NA	NA	293	1.02 (0.89–1.18)	1.04 (0.90–1.21)

Early life exposure (before the age of two) to PPIs and antibiotics and the risk of cancer after the age of two. Hazard ratios (HR) with 95% confidence intervals (CI), and adjusted Hazard ratios (aHR). Overall model adjusted for maternal age, BMI, sex of child, parity, delivery mode, preterm status and being large for gestational age. Model for cancer before 2 adjusted for maternal age, BMI, sex of child, maternal Nordic birth country, tobacco use, delivery mode and preterm status. Model after two adjusted for maternal age, BMI, sex of child, parity, tobacco use, delivery mode, preterm status and being large for gestational age

Significant results ( $p < 0.05$ ) are highlighted in bold

‡Proton pump inhibitors (PPIs)

was seen when the cohort was divided by delivery mode or preterm status (Table 4).

### 3.2.2 Dose–Response

No association was observed for prenatal PPI exposure as DDD or number of prescriptions with increased risk of childhood cancer. For prenatal antibiotics, the association with an increased risk of childhood cancer increased

with the number of prescriptions, being the highest for > 3 prescriptions (aHR 1.51, 95% CI 1.02–2.25) (Fig. 2).

### 3.3 The Risk of Cancer Before the Age of 2 Years

After univariable analysis, the multivariable model was adjusted for maternal age, BMI, parity, sex of child, maternal Nordic birth country, tobacco use, delivery mode and preterm status (Supplementary Table S2).

**Table 4** Prenatal exposure of proton pump inhibitors (PPIs) and antibiotics and the risk of overall cancer, stratified by delivery mode, trimester of exposure and preterm status

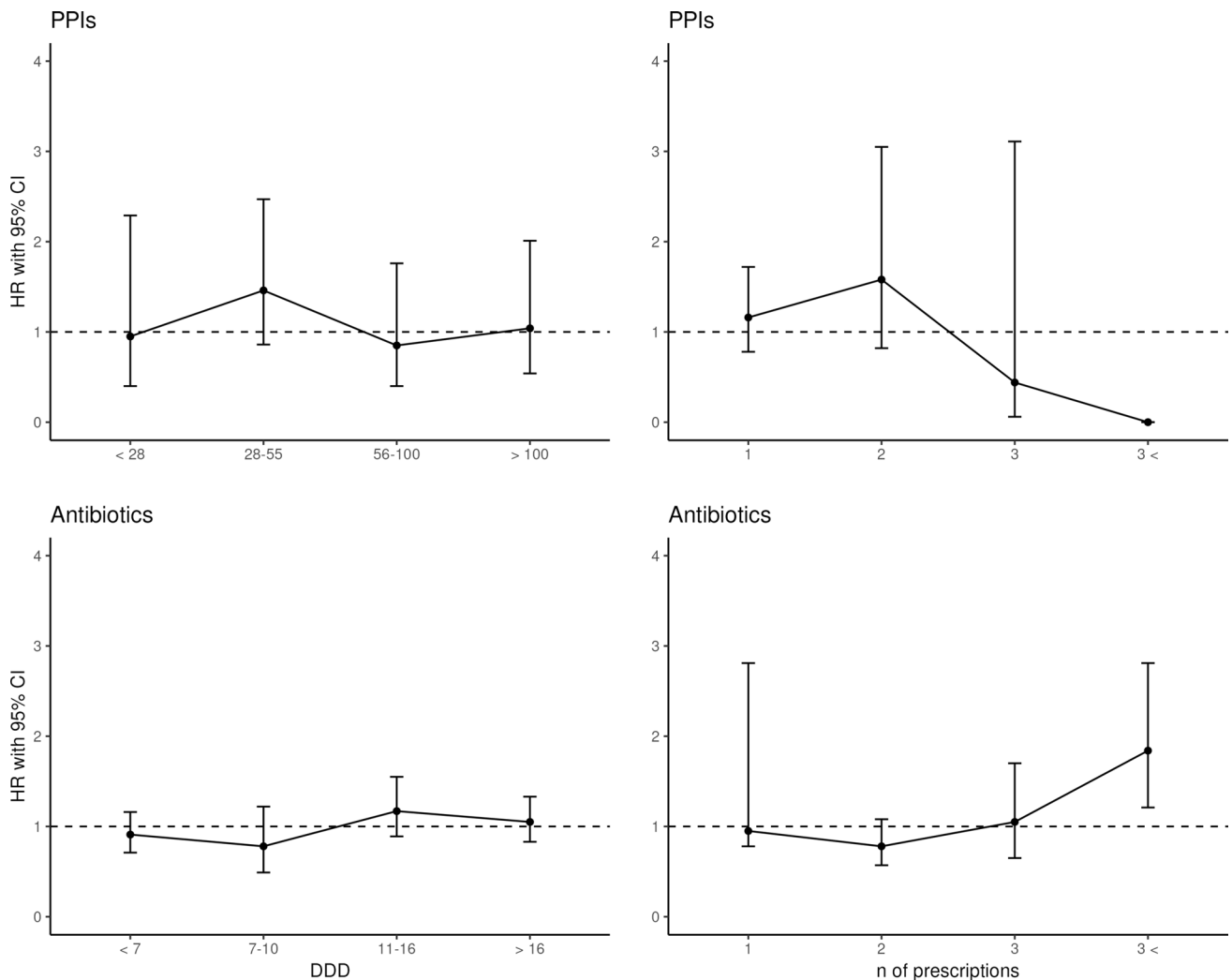
	PPI HR, 95%CI	Antibiotics HR, 95%CI
Vaginal	0.99 (0.65–1.49)	0.94 (0.80–1.11)
Elective c-section	1.08 (0.39–2.94)	0.85 (0.53–1.36)
Acute c-section	1.75 (0.81–1.75)	1.19 (0.81–1.75)
Trimester 1	1.42 (0.93–2.16)	1.01 (0.82–1.24)
Trimester 2	0.96 (0.55–1.66)	0.94 (0.77–1.16)
Trimester 3	0.74 (0.38–1.43)	0.98 (0.79–1.22)
Preterm	0.68 (0.17–1.66)	0.98 (0.58–1.66)
Term	1.15 (0.81–1.63)	0.96 (0.82–1.11)

Hazard ratios (aHR) with 95% confidence intervals (CI), adjusted for maternal age, BMI, sex of child, parity, delivery mode, preterm status and being large for gestational age

Neither prenatal PPIs (aHR 0.56, 95% CI 0.28–1.09) nor prenatal antibiotics (aHR 1.28, 95% CI 0.98–1.67) were associated with an increased risk of cancer before the age of 2 years (Table 3).

No interaction was found for prenatal exposure of both PPIs and antibiotics ( $p = 0.87$ ).

In subgroup analysis, those exposed to quinolone antibacterials (J01M) prenatally ( $n = 4$  cancer cases) were associated with increased risk of cancer before the age of 2 years (aHR 4.23, 95% CI 1.36–13.21) (Supplementary Table S3). No association was found for other antibiotics or cancer locations (Supplementary Table 4).



**Fig. 2** Dose–response analysis using multivariable Cox hazard models (aHR, 95%CI) adjusted for maternal age, BMI, sex of child, parity, delivery mode, preterm status and being large for gestational age, with no prescriptions as reference for all analyses. PPIs (top row) and

antibiotics (bottom row) regarding DDD as quartiles (left column) and number of prescriptions (right columns) and the overall risk of childhood cancer

### 3.4 The Risk of Cancer After the Age of 2 Years

After univariable analysis, the multivariable model was adjusted for maternal age, BMI, sex of child, parity, tobacco use, delivery mode, preterm status and being large for gestational age (Supplementary Table S2).

Prenatal exposure to PPIs (aHR 1.26, 95% CI 0.86–1.85) and antibiotics (aHR 0.91, 95% CI 0.77–1.08) did not show an association with increased risk of cancer after the age of 2 years (Table 3).

For early life exposure of PPIs, there was an association with an increased risk of cancer after the age of two (aHR 3.68, 95% CI 2.24–6.06). For early life antibiotics exposure, the association was not significant (aHR 1.04, 95% CI 0.90–1.21) (Table 3).

Neither prenatal exposure to PPIs and antibiotics ( $p = 0.92$ ) nor early life exposure to both drugs ( $p = 0.15$ ) showed an interaction.

When looking at interaction between prenatal and early life exposure to PPIs ( $p = 0.89$ ) and prenatal and early life exposure to antibiotics ( $p = 0.25$ ) showed no interaction.

No association was found with a specific cancer location (Supplementary Table S4).

Cumulative incidence curve can be seen in Supplementary Material (Supplementary Fig. 3).

Estimation of the proportional hazard assumption showed that all predictors met that assumption ( $p = 0.65$ ).

## 4 Discussion

### 4.1 Principal Findings

The use of PPIs and antibiotics during pregnancy was not associated with an increased risk of childhood cancer. However, early life use of PPIs (before the age of 2 years) was associated with over threefold increased risk of cancer after the age of 2 years, although confounding by indication could not be controlled for.

### 4.2 Comparison with Existing Evidence

Little research has been done on the long-term side effects of PPIs taken prenatally and the cancer risk of the child [68], and current research does not agree on cancer risk after prenatal antibiotics exposure [3, 51–57]. Microbiome modulating drugs could affect the infant in utero through immune responses, microbial metabolites across the placenta [20] or cause the infant to have a dysbiotic microbiome from birth. Although our results do not show increased risk of

overall cancer after prenatal exposure to PPIs and antibiotics, this does not imply (unwarranted) exposure to these drugs is without risk. Despite the large study base, childhood cancer is rare, and our subgroup analyses may have been underpowered.

Exposure to PPIs before the age of 2 years was associated with increased risk of cancer after the age of 2 years. However, it must be considered that the indication for PPI use was unknown and may explain the observed association. Further studies are needed to corroborate or refute the reported association. The association between PPIs and cancer has previously been shown in adult populations but not in children [30, 38–48]. It is possible that during infancy when the microbiome is immature, great disturbances such as PPIs have lasting effects [20, 69] which may create a pro-carcinogenic environment. To our knowledge, there is little evidence linking paediatric PPI indications to cancer [70], even in case of gastro-oesophageal reflux, an established risk factor for oesophageal cancer in adults [71]. Some reports warned for a potential increased risk of Barrett's oesophagus and oesophageal cancer after oesophageal atresia repair [72], but it is hard to distinguish the effects of indication and treatment, as PPI treatment for at least 1 year is the recommended treatment post-surgery, while efficacy is also questioned [10, 73]. There are few other indications requiring long-term PPI exposure, including other congenital malformations such as congenital diaphragmatic hernia, genetic syndromes or trauma resulting in swallowing difficulties or regurgitation [74]. Long-term PPI use in children has also been associated with increased risks of infections, bone fractures and allergy [74, 75] and, as said earlier, disruptions of the microbiome [10]. Taking into account that PPI use in children is usually off-label and often administered for unclear indications without sufficient proof of efficacy [76, 77], we plead for more caution in prescribing PPIs in young children and more research into short- and long-term safety and efficacy of drugs in young children [78].

It must be noted that (childhood) cancer is highly heterogeneous in terms of risk factors such as genetic predisposition, viral infections (including cytomegalovirus and Epstein–Barr virus), maternal health (including smoking and alcohol), environmental factors and pathophysiology [49, 50, 79]. Therefore, potential microbiome modulating drugs may affect the cancer risk differently, so further (mechanistic) studies with larger cohorts and are needed to investigate cancer subtypes in depth.

### 4.3 Clinical and Research Implications

Both antibiotic and PPI use outside of pregnancy have been associated with cancer risk in adults [37, 44]. Although causality cannot be established based on association studies, and the absolute effects may be limited, it is important to explore potential associations and underlying mechanisms—especially since the aetiology of cancer is still largely unknown. Clinical trials would be unethical and infeasible as follow-up time and power would need to be large.

Ideally, to limit all potential side-effects of PPIs, many lifestyle changes might relieve symptoms and should be considered on an individual basis [80]. Dose and duration should ideally be as minimal as possible, taking into account short- and long-term efficacy and safety.

Concerning early life exposure, PPIs are approved for children over 1 year for short-term use for certain conditions [74, 81, 82] but are not recommended for infants [83]. However, their use has increased worldwide in the last decades and has been associated with gut microbiome alterations in infants [10]. Chronic use has been associated with adverse outcomes such as gastrointestinal infections (including *Clostridium difficile*) and allergies in children [74, 75, 81, 82, 84]. This study further supports that the use of PPIs in young children needs further investigation to ensure its safety, ideally including the underlying cause for drug use and self-reporting of over-the-counter use. Of highest concern are paediatric indications for which long-term (> 1 year) PPIs are currently recommended [10, 85], including oesophageal atresia, and PPI exposure very early in life when the acquisition of the microbiome is initiated [86]. Furthermore, recent studies have highlighted the over-consumption of both antibiotics and PPIs in children [87–89] and off-label use of PPIs [76].

### 4.4 Strengths and Limitations

The major strengths of this study are the large population size and robust, high-quality nationwide registries used. Thereby, we can minimize recall-bias, loss to follow-up and volunteer bias.

Regarding both antibiotics and PPIs, a major limitation is that data on indication for drug prescription were not available in the Drug Registry, which makes it difficult to distinguish the independent effect of the drug and the underlying indication, which could be an important residual confounder for cancer risk. Other in- and out-patient drugs may also affect cancer development in children and should be explored in the future. Yet, large databases with sufficiently long follow-up will be required to obtain sufficient power for less common drugs and to assess interaction between co-administered drug classes.

For example, a recent studies have shown that hyperemesis gravidarum is associated with an increased risk of childhood cancer [90], respiratory morbidity [91] and cardiovascular abnormalities [92]. Furthermore, as we use non-users as reference groups in our model, they may be overall healthier than the group that uses the drugs studied.

Other confounders which were not included might be environmental (such as pollution levels) and hereditary risk of cancer. Additionally, the registries do not include in-hospital medication (including peri-partum antibiotics) or over-the-counter PPIs. However, we can assume that individuals who get prescribed PPIs are more severe cases, compared with others who purchase smaller quantities over-the-counter, at a higher price.

### 4.5 Conclusions

Our results show that prenatal exposure of PPIs and antibiotics was not associated with an increased risk of childhood cancer. However, we found that early-life PPI exposure was associated with an over threefold increased risk of childhood cancer after the age of 2 years. Our results may be affected by limited power, as childhood cancer is fortunately a rare outcome and confounding by indication.

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#### Declarations

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**Conflicts of Interest** The authors report no conflict of interest.

**Data Availability Statement** Data are located on an access-controlled server at Karolinska Institutet and is not openly available due to the sensitive personal nature of it.

**Ethics Approval** This study was approved by the Regional Ethics Committee of Stockholm (2017/2423-31) and was conducted according to the Declaration of Helsinki.

**Consent to Participate** Informed consent was not required for this study.

**Consent to Publish** Not applicable.

**Code Availability** Code used for data analysis is available upon a reasonable request.

**Author Contributions** Conceptualization (U.G., E.F. and N.B.), methodology (U.G., G.L. and N.B.), software (U.G. and N.B.), validation (U.G. and N.B.), formal analysis (U.G. under supervision of N.B.),

investigation (U.G. and N.B.), resources (E.F., L.E. and N.B.), data curation (U.G. and N.B.), writing—original draft (U.G., E.F. and N.B.), writing—review and editing (U.G., E.F., G.L., A.W., E.V., L.E. and N.B.), visualization (U.G.), supervision (E.F. and N.B.), project administration (E.F., L.E. and N.B.) and funding acquisition (E.F., L.E. and N.B.). All authors read and approved the final version of the manuscript.

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## References

- Läkemedelsverket. Läkemedel vid graviditet och amning. 2022 December 5th 2019; Available from: <https://www.lakemedelsverket.se/sv/behandling-och-forskrivning/kopa-anvanda-och-hantera/anvanda-medicin/graviditet-och-amning#hmainbody1>.
- NIDA. Are prescription drugs safe to take when pregnant? 2020 June 2020; Available from: <https://nida.nih.gov/publications/research-reports/misuse-prescription-drugs/are-prescription-drugs-safe-to-take-when-pregnant>.
- Bonaventure A, et al. Prescription drug use during pregnancy and risk of childhood cancer—is there an association? *Cancer Epidemiol.* 2015;39(1):73–8.
- Falony G, et al. Population-level analysis of gut microbiome variation. *Science.* 2016;352(6285):560–4.
- Zhernakova A, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science.* 2016;352(6285):565–9.
- Macke L, et al. Systematic review: the effects of proton pump inhibitors on the microbiome of the digestive tract—evidence from next-generation sequencing studies. *Aliment Pharmacol Ther.* 2020;51(5):505–26.
- Konstantinidis T, et al. Effects of antibiotics upon the gut microbiome: a review of the literature. *Biomedicines.* 2020;8(11):502.
- Nel Van Zyl K, et al. Effect of antibiotics on the human microbiome: a systematic review. *Int J Antimicrob Agents.* 2022;59(2):106502.
- Levy EI, Hoang DM, Vandenplas Y. The effects of proton pump inhibitors on the microbiome in young children. *Acta Paediatr.* 2020;109(8):1531–8.
- Brusselsaers N, et al. Effect of proton pump inhibitors in infants with esophageal atresia on the gut microbiome: a pilot cohort. *Gut Pathog.* 2022;14(1):47.
- Sepich-Poore GD et al. The microbiome and human cancer. *Science* 2021;371(6536).
- Brusselsaers N. Prescribed drugs and the microbiome. *Gastroenterol Clin North Am.* 2019;48(3):331–42.
- Imhann F, et al. Proton pump inhibitors affect the gut microbiome. *Gut.* 2016;65(5):740–8.
- Imhann F, et al. The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. *Gut Microbes.* 2017;8(4):351–8.
- Qu W, Liu L, Miao L. Exposure to antibiotics during pregnancy alters offspring outcomes. *Expert Opin Drug Metab Toxicol.* 2021;17(10):1165–74.
- Bookstaver PB, et al. A review of antibiotic use in pregnancy. *Pharmacotherapy.* 2015;35(11):1052–62.
- Azad MB, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG.* 2016;123(6):983–93.
- Martins Lopes MS, et al. Antibiotics, cancer risk and oncologic treatment efficacy: a practical review of the literature. *Ecancermedicalscience.* 2020;14:1106.
- Ahearn-Ford S, Berrington JE, Stewart CJ. Development of the gut microbiome in early life. *Exp Physiol.* 2022;107(5):415–21.
- Dominguez-Bello MG, et al. Role of the microbiome in human development. *Gut.* 2019;68(6):1108–14.
- Nguyen MH, et al. Antibiotic use during pregnancy and the risk of preterm birth: a population-based Swedish cohort study. *J Antimicrob Chemother.* 2022;77(5):1461–7.
- Orwa SA, Gudnadottir U, Brusselsaers N. Global prevalence of antibiotic consumption during pregnancy: a systematic review and meta-analysis. *Under Rev.* 2023;89(2): 106189.
- Cantarutti A, et al. Use of antibiotic treatment in pregnancy and the risk of several neonatal outcomes: a population-based study. *Int J Environ Res Public Health.* 2021;18(23):12621.
- Koch KL. Gastrointestinal factors in nausea and vomiting of pregnancy. *Am J Obstet Gynecol.* 2002;186(5):S198–203.
- McParlin C, et al. Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review. *JAMA.* 2016;316(13):1392–401.
- Stephansson O, et al. Drug use during pregnancy in Sweden—assessed by the prescribed drug register and the medical birth register. *Clin Epidemiol.* 2011;3:43–50.
- Vanderhoff BT, Tahboub RM. Proton pump inhibitors: an update. *Am Fam Physician.* 2002;66(2):273–80.
- Li CM, et al. Systematic review with meta-analysis: the risks of proton pump inhibitors during pregnancy. *Aliment Pharmacol Ther.* 2020;51(4):410–20.
- Breddels EM, et al. Population-based cohort study: proton pump inhibitor use during pregnancy in Sweden and the risk of maternal and neonatal adverse events. *BMC Med.* 2022;20(1):492.
- Ngwenya S, Simin J and Brusselsaers N. Maintenance proton pump inhibitor use associated with increased all-cause and cause-specific mortality in Sweden. *Dig Dis Sci.* 2023.
- Xie Y, et al. Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. *BMJ.* 2019;365:11580.
- Baik SH, Fung KW, McDonald CJ. The mortality risk of proton pump inhibitors in 1.9 million US seniors: an extended Cox survival analysis. *Clin Gastroenterol Hepatol.* 2022;20(4):e671–81.
- Ben-Eltriki M, et al. Do proton pump inhibitors increase mortality? A systematic review and in-depth analysis of the evidence. *Pharmacol Res Perspect.* 2020;8(5): e00651.
- Thurber KM, Otto AO, Stricker SL. Proton pump inhibitors: understanding the associated risks and benefits of long-term use. *Am J Health Syst Pharm.* 2023;80(8):487–94.
- Ward RM, Kearns GL. Proton pump inhibitors in pediatrics: mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. *Paediatr Drugs.* 2013;15(2):119–31.
- Simin J, et al. Antibiotic use and risk of colorectal cancer: a systematic review and dose-response meta-analysis. *Br J Cancer.* 2020;123(12):1825–32.

37. Simin J, et al. Antibiotic use and the risk of breast cancer: a systematic review and dose-response meta-analysis. *Pharmacol Res.* 2020;160: 105072.
38. Brusselaers N, Lagergren J, Engstrand L. Duration of use of proton pump inhibitors and the risk of gastric and oesophageal cancer. *Cancer Epidemiol.* 2019;62: 101585.
39. Brusselaers N, et al. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. *BMJ Open.* 2017;7(10): e017739.
40. Brusselaers N, Sadr-Azodi O, Engstrand L. Long-term proton pump inhibitor usage and the association with pancreatic cancer in Sweden. *J Gastroenterol.* 2020;55(4):453–61.
41. Kamal H, et al. Association between proton pump inhibitor use and biliary tract cancer risk: a Swedish population-based cohort study. *Hepatology.* 2021;74(4):2021–31.
42. Abrahami D, et al. Proton pump inhibitors and risk of gastric cancer: population-based cohort study. *Gut.* 2022;71(1):16–24.
43. Seo SI, et al. Association between proton pump inhibitor use and gastric cancer: a population-based cohort study using two different types of nationwide databases in Korea. *Gut.* 2021;70(11):2066–75.
44. Segna D, et al. Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review with meta-analysis. *Therap Adv Gastroenterol.* 2021;14:17562848211051464.
45. Ahn JS, et al. Acid suppressive drugs and gastric cancer: a meta-analysis of observational studies. *World J Gastroenterol.* 2013;19(16):2560–8.
46. Peng TR, Wu TW, Li CH. Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review and meta-analysis. *Int J Clin Oncol.* 2023;28(1):99–109.
47. Guo H, et al. Association of proton pump inhibitors with gastric and colorectal cancer risk: a systematic review and meta-analysis. *Front Pharmacol.* 2023;14:1129948.
48. Zeng R, et al. Comprehensive analysis of proton pump inhibitors and risk of digestive tract cancers. *Eur J Cancer.* 2021;156:190–201.
49. Buser JM, Lake K, Ginier E. Environmental risk factors for childhood cancer in an era of global climate change: a scoping review. *J Pediatr Health Care.* 2022;36(1):46–56.
50. (WHO), W.H.O. Childhood cancer. 2021; Available from: <https://www.who.int/news-room/fact-sheets/detail/cancer-in-children>.
51. Kaatsch P, Scheidemann-Wesp U, Schuz J. Maternal use of antibiotics and cancer in the offspring: results of a case-control study in Germany. *Cancer Causes Control.* 2010;21(8):1335–45.
52. Ye X, et al. Maternal use of antibiotics and cancer incidence risk in offspring: a population-based cohort study in Manitoba, Canada. *Cancer Med.* 2019;8(11):5367–72.
53. Murphy CC, et al. In-utero exposure to antibiotics and risk of colorectal cancer in a prospective cohort of 18,000 adult offspring. *Int J Epidemiol.* 2023;52(5):1448–58.
54. Stalberg K, et al. Prenatal exposure to medicines and the risk of childhood brain tumor. *Cancer Epidemiol.* 2010;34(4):400–4.
55. Hjorth S, et al. Prenatal exposure to nitrofurantoin and risk of childhood leukaemia: a registry-based cohort study in four Nordic countries. *Int J Epidemiol.* 2022;51(3):778–88.
56. Thapa PB, et al. Prenatal exposure to metronidazole and risk of childhood cancer: a retrospective cohort study of children younger than 5 years. *Cancer.* 1998;83(7):1461–8.
57. Momen NC, et al. Exposure to systemic antibacterial medications during pregnancy and risk of childhood cancer. *Pharmacoepidemiol Drug Saf.* 2015;24(8):821–9.
58. Epidemiology, C.f. The Swedish medical birth register, S.N.B.o.H.a. Welfare, Editor. 2003. Centre for Epidemiology
59. Socialstyrelsen. National Patient Register. 2022; Available from: <https://www.socialstyrelsen.se/en/statistics-and-data/register/national-patient-register/>.
60. Brooke HL, et al. The Swedish cause of death register. *Eur J Epidemiol.* 2017;32(9):765–73.
61. Wettermark B, et al. The new Swedish prescribed drug register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf.* 2007;16(7):726–35.
62. von Elm E, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;61(4):344–9.
63. Methodology, W.C.C.f.D.S. ATC/DDD Index 2022. 2021; Available from: [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/).
64. Socialstyrelsen, Klassifikation av sjukdomar och hälsoproblem 1997, Socialstyrelsen, Editor. 1996.
65. National Cancer Institute. ICCO recode third edition ICD-O-3/ IARC 2017.1. 2017; Available from: <https://seer.cancer.gov/icco/icco-iarc-2017.html>.
66. Fornes R, et al. Pregnancy, perinatal and childhood outcomes in women with and without polycystic ovary syndrome and metformin during pregnancy: a nationwide population-based study. *Reprod Biol Endocrinol.* 2022;20(1):30.
67. Jiang LL, et al. Cesarean section and risk of childhood leukemia: a systematic review and meta-analysis. *World J Pediatr.* 2020;16(5):471–9.
68. Akimoto N, et al. Rising incidence of early-onset colorectal cancer—a call to action. *Nat Rev Clin Oncol.* 2021;18(4):230–43.
69. Selma-Royo M, et al. Shaping microbiota during the first 1000 days of life. *Adv Exp Med Biol.* 2019;1125:3–24.
70. National Institute for Health and Care Excellence (NICE). Gastrooesophageal reflux disease in children and young people: diagnosis and management. 2015. <https://www.nice.org.uk/guidance/ng1>.
71. Wang S, et al. Causal analysis of gastroesophageal reflux disease and esophageal cancer. *Medicine (Baltimore).* 2024;103(11): e37433.
72. Krishnan U, et al. ESPGHAN-NASPGHAN guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with esophageal atresia-tracheoesophageal fistula. *J Pediatr Gastroenterol Nutr.* 2016;63(5):550–70.
73. Dimitrov G, et al. Proton pump inhibitors in esophageal atresia: a systematic review and meta-analysis. *J Pediatr Gastroenterol Nutr.* 2024;78(3):457–70.
74. Dipasquale V, et al. A narrative review on efficacy and safety of proton pump inhibitors in children. *Front Pharmacol.* 2022;13: 839972.
75. Lassalle M, Zureik M, Dray-Spira R. Proton pump inhibitor use and risk of serious infections in young children. *JAMA Pediatr.* 2023;177(10):1028–38.
76. van der Zanden TM, et al. Off-label, but on-evidence? A review of the level of evidence for pediatric pharmacotherapy. *Clin Pharmacol Ther.* 2022;112(6):1243–53.
77. Tafuri G, et al. Off-label use of medicines in children: can available evidence avoid useless paediatric trials? The case of proton pump inhibitors for the treatment of gastroesophageal reflux disease. *Eur J Clin Pharmacol.* 2009;65(2):209–16.
78. Brusselaers N, G U, Engstrand L, Lilja H E. Trends in proton pump inhibitor use in Sweden by sex and age - a drug utilisation study. *Drug Safety*, In revision, 2024.
79. Oh JK, Weiderpass E. Infection and cancer: global distribution and burden of diseases. *Ann Glob Health.* 2014;80(5):384–92.
80. Altuwajri M. Evidence-based treatment recommendations for gastroesophageal reflux disease during pregnancy: a review. *Medicine (Baltimore).* 2022;101(35): e30487.

81. Pasman EA, et al. Proton pump inhibitors in children: the good, the bad, and the ugly. *Curr Allergy Asthma Rep.* 2020;20(8):39.
82. De Bruyne P, Ito S. Toxicity of long-term use of proton pump inhibitors in children. *Arch Dis Child.* 2018;103(1):78–82.
83. Vandenplas Y, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49(4):498–547.
84. Lyamouri M, et al. Proton pump inhibitors for infants in three scandinavian countries increased from 2007 to 2020 despite international recommendations. *Acta Paediatr.* 2022;111(11):2222–8.
85. Wyllie T, et al. Prophylactic acid-suppression medication to prevent anastomotic strictures after oesophageal atresia surgery: a systematic review and meta-analysis. *J Pediatr Surg.* 2023;58(10):1954–62.
86. Human Microbiome Project, C. A framework for human microbiome research. *Nature.* 2012;486(7402):215–21.
87. Stocker M, et al. Less is more: antibiotics at the beginning of life. *Nat Commun.* 2023;14(1):2423.
88. Wolf ER, et al. Overuse of reflux medications in infants. *Pediatrics.* 2023. <https://doi.org/10.1542/peds.2022-058330>.
89. Arnoux A, et al. Proton pump inhibitors are still overprescribed for hospitalized children. *Arch Pediatr.* 2022;29(4):258–62.
90. Orimoloye HT, et al. Hyperemesis gravidarum and the risk of childhood cancer—a case-control study in Denmark. *Cancer Epidemiol.* 2023;87: 102472.
91. Hazan G, et al. The impact of maternal hyperemesis gravidarum on early childhood respiratory morbidity. *Pediatr Pulmonol.* 2024;59(3):707–14.
92. Fan J, Yin M. Offspring of women with hyperemesis gravidarum are more likely to have cardiovascular abnormalities. *BMC Pregnancy Childbirth.* 2024;24(1):119.