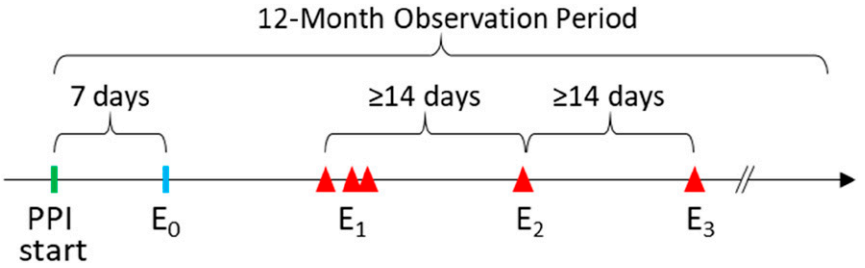
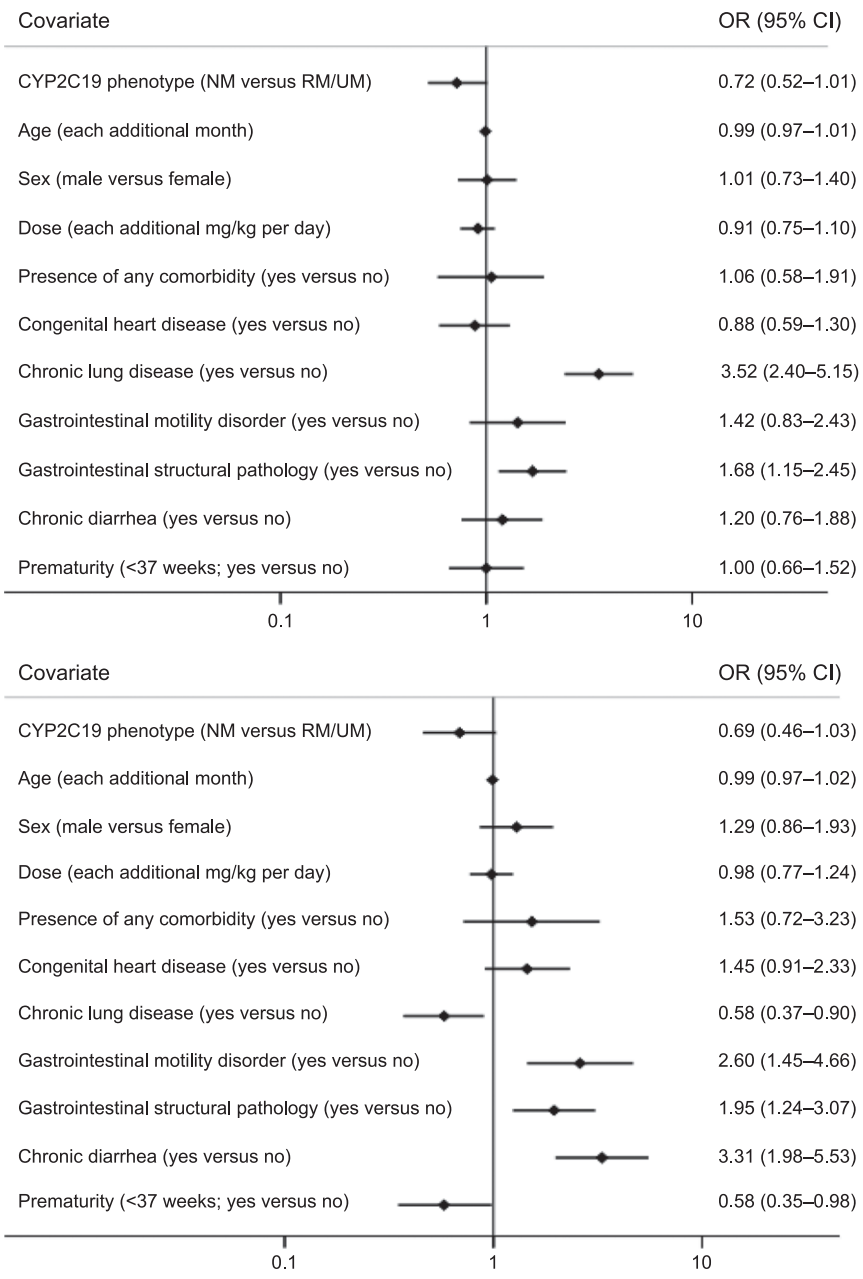
Supplemental Information



SUPPLEMENTAL FIGURE 2

Definition of infection events. Infection events were determined for each individual beginning 7 days after the start of PPI therapy (E_0) and ending 1 year after PPI start. Billing codes for all RTIs and GTIs were obtained from EHR data. Infection events (E_1, E_2, E_3, etc) were required to be separated by at least 14 days to avoid overcounting of multiple visits for single-infection events.



SUPPLEMENTAL FIGURE 3

Multivariable analyses of RTI events (top) and GTI events (bottom) in CYP2C19 NMs versus RM/UMs. Shown are the ORs (diamonds) and the 95% CIs (horizontal lines) for each of the variables included in the ordinal regression model for association to infection events in the 670 children treated with PPIs. ORs are for CYP2C19 phenotype (NM versus RM/UM), age (each additional month), sex (male versus female), and dose (each additional mg/kg per day) and 7 additional dichotomous variables (presence of comorbidity, congenital heart disease, chronic lung disease, gastrointestinal motility disorder, gastrointestinal structural pathology, chronic diarrhea, and prematurity, all yes versus no). Point estimates for the ORs and 95% CIs are listed to the right of each plot.

SUPPLEMENTAL TABLE 3 ICD Codes Used To Define Respiratory and Gastrointestinal Infection Events

ICD Code	ICD 9	ICD 10	Frequency, %[a]
RTI			
Diagnosis			
Nasopharyngitis	460*	J00*	0.1
Acute sinusitis	461*	J01*	0.2
Viral pharyngitis	462*	J02.9	0.6
Acute tonsillitis	463*	J03.90	0
Croup, laryngitis, or tracheitis	464*	J04.0, J04.10, J04.11, J04.2, J05.0	10.0
Upper RTI	465*	J06	19.5
Bronchiolitis	466*	J20.9, J21.0, J21.8	9.2
Pneumonia	480*–486*	J12–15, J18	15.1
Influenza	487*	J11.0, J12.9, J10.1, J11.1, J11.2, J11.81, J11.89	2.1
	488*		
Cough	786.2	R05	29.2
Streptococcal pharyngitis	034.0	J03.00	0
Viral infection (unspecified)	079.89	B33.8, B34.8, B97.89	3.4
	079.99		
GTI			
Diagnosis			
Acute gastroenteritis	558.9	A02*, A03*, A04*, A08*, A09	7.6
	009*		
	008*		
Clostridium difficile colitis	008.45	A04*	1.5
Diarrhea	787.91	R19.7, K52.89	18.0

[a] Sum of frequencies exceeds 100% because of infection events with multiple codes.

SUPPLEMENTAL TABLE 4 ICD Codes Used To Define Assessed Comorbidities

Code	Description	Code	Description
	Congenital heart disease		Chronic lung disease
394	Mitral stenosis	31.29	Other permanent tracheostomy
394.2	Mitral stenosis with insufficiency	31.74	Revision of tracheostomy
394.9	Other and unspecified mitral valve diseases	277	Cystic fibrosis without mention of meconium ileus
396	Mitral valve stenosis and aortic valve stenosis	277	Cystic fibrosis
396.1	Mitral valve stenosis and aortic valve insufficiency	277.01	Cystic fibrosis with meconium ileus
396.2	Mitral valve insufficiency and aortic valve stenosis	277.02	Cystic fibrosis with pulmonary manifestations
396.3	Mitral valve insufficiency and aortic valve insufficiency	277.03	Cystic fibrosis with gastrointestinal manifestations
396.8	Multiple involvement of mitral and aortic valves	277.09	Cystic fibrosis with other manifestations
396.9	Mitral and aortic valve diseases, unspecified	416	Primary pulmonary hypertension
397	Diseases of tricuspid valve	416	Chronic pulmonary heart disease
397	Diseases of other endocardial structures	416.8	Other chronic pulmonary heart diseases
414.1	Aneurysm of heart (wall)	416.9	Chronic pulmonary heart disease, unspecified
414.11	Aneurysm of coronary vessels	493	Extrinsic asthma, unspecified
414.19	Other aneurysm of heart	493	Asthma
414.8	Other specified forms of chronic ischemic heart disease	493.01	Extrinsic asthma with status asthmaticus
417	Other diseases of pulmonary circulation	493.1	Intrinsic asthma, unspecified
417.1	Aneurysm of pulmonary artery	493.11	Intrinsic asthma with status asthmaticus
417.8	Other specified diseases of pulmonary circulation	493.12	Intrinsic asthma with (acute) exacerbation
417.9	Unspecified disease of pulmonary circulation	493.82	Cough variant asthma
424	Mitral valve disorders	493.9	Asthma, unspecified type, unspecified
424.1	Aortic valve disorders	493.9	Asthma, unspecified
424.2	Tricuspid valve disorders, specified as nonrheumatic	493.91	Asthma, unspecified type, with status asthmaticus
424.3	Pulmonary valve disorders	493.92	Asthma, unspecified type, with (acute) exacerbation
425.1	Hypertrophic cardiomyopathy	494	Bronchiectasis without acute exacerbation
425.11	Hypertrophic obstructive cardiomyopathy	494	Bronchiectasis
425.18	Other hypertrophic cardiomyopathy	494.1	Bronchiectasis with acute exacerbation
425.3	Endocardial fibroelastosis	496	Chronic airway obstruction, not elsewhere classified
425.4	Other primary cardiomyopathies	515	Postinflammatory pulmonary fibrosis
425.7	Nutritional and metabolic cardiomyopathy	516.61	Neuroendocrine cell hyperplasia of infancy
425.9	Secondary cardiomyopathy, unspecified	516.63	Surfactant mutations of the lung
429.89	Other ill-defined heart diseases	516.69	Other interstitial lung diseases of childhood
429.9	Heart disease, unspecified	516.8	Other specified alveolar and parietoalveolar pneumonopathies
514	Pulmonary congestion and hypostasis	518.1	Interstitial emphysema
745.1	Complete transposition of great vessels	748	Anomalies of respiratory system, congenital
745.1	Transposition of great vessels	748.4	Congenital cystic lung
745.11	Double outlet right ventricle	748.5	Agenesis, hypoplasia, and dysplasia of lung
745.12	Corrected transposition of great vessels	748.6	Anomaly of lung, unspecified
745.19	Other transposition of great vessels	748.61	Congenital bronchiectasis
745.2	Tetralogy of Fallot	748.69	Other congenital anomalies of lung
745.3	Common ventricle	770.7	Chronic respiratory disease arising in the perinatal period
745.4	Ventricular septal defect	E84.0	Cystic fibrosis with pulmonary manifestations
745.5	Ostium secundum type atrial septal defect	E84.19	Cystic fibrosis with other intestinal manifestations
745.6	Endocardial cushion defect, unspecified type	E84.8	Cystic fibrosis with other manifestations
745.6	Endocardial cushion defects	E84.9	Cystic fibrosis, unspecified
745.61	Ostium primum defect	I27.0	Primary pulmonary hypertension
745.69	Other endocardial cushion defects	I27.2	Other secondary pulmonary hypertension
745.7	Cor biloculare	I28.8	Other diseases of pulmonary vessels
745.8	Other bulbus cordis anomalies and anomalies of cardiac septal closure	J96.10	Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia
745.9	Unspecified defect of septal closure	J98.4	Other disorders of lung
746	Other congenital anomalies of heart	J98.8	Other specified respiratory disorders
746	Congenital pulmonary valve anomaly, unspecified	J98.9	Respiratory disorder, unspecified
746.01	Atresia of pulmonary valve, congenital	P27.1	Bronchopulmonary dysplasia originating in the perinatal period
746.02	Stenosis of pulmonary valve, congenital	Q32.2	Congenital bronchomalacia
746.09	Other congenital anomalies of pulmonary valve	Q32.4	Other congenital malformations of bronchus
746.1	Tricuspid atresia and stenosis, congenital	V13.66	Personal history of (corrected) congenital malformations of respiratory system
746.2	Ebstein anomaly	V44.0	Tracheostomy status
746.3	Congenital stenosis of aortic valve	V55.0	Attention to tracheostomy
746.4	Congenital insufficiency of aortic valve	Z93.0	Tracheostomy status

SUPPLEMENTAL TABLE 4 Continued

Code	Description
746.5	Congenital mitral stenosis
746.6	Congenital mitral insufficiency
746.7	Hypoplastic left heart syndrome
746.8	Other specified congenital anomalies of heart
746.81	Subaortic stenosis
746.83	Infundibular pulmonic stenosis
746.84	Obstructive anomalies of heart, not elsewhere classified
746.85	Coronary artery anomaly
746.87	Malposition of heart and cardiac apex
746.89	Other specified congenital anomalies of heart
746.9	Unspecified congenital anomaly of heart
747.1	Coarctation of aorta (preductal, postductal)
747.11	Interruption of aortic arch
747.21	Anomalies of aortic arch
747.22	Atresia and stenosis of aorta
747.29	Other anomalies of aorta
747.3	Anomalies of pulmonary artery, congenital
747.31	Pulmonary artery coarctation and atresia
747.32	Pulmonary arteriovenous malformation
747.39	Other anomalies of pulmonary artery and pulmonary circulation
747.4	Anomaly of great veins, unspecified
747.41	Total anomalous pulmonary venous connection
747.42	Partial anomalous pulmonary venous connection
747.49	Other anomalies of great veins
I42.0	Dilated cardiomyopathy
I42.8	Other cardiomyopathies
I42.9	Cardiomyopathy, unspecified
Q21.0	Ventricular septal defect
Q21.1	Atrial septal defect
Q21.2	Atrioventricular septal defect
Q21.3	Tetralogy of Fallot
Q21.9	Congenital malformation of cardiac septum, unspecified
Q22.0	Pulmonary valve atresia
Q22.1	Congenital pulmonary valve stenosis
Q22.8	Other congenital malformations of tricuspid valve
Q23.1	Congenital insufficiency of aortic valve
Q23.3	Congenital mitral insufficiency
Q23.4	Hypoplastic left heart syndrome
Q24.3	Pulmonary infundibular stenosis
Q24.5	Malformation of coronary vessels
Q24.9	Congenital malformation of heart, unspecified
Q25.5	Atresia of pulmonary artery
Q25.6	Stenosis of pulmonary artery
Q25.79	Other congenital malformations of pulmonary artery
V13.65	Personal history of (corrected) congenital malformations of heart and circulatory system
	Gastrointestinal motility disorders
530.5	Dyskinesia of esophagus
536.3	Gastroparesis
560.1	Paralytic ileus
564.81	Neurogenic bowel
741	Spina bifida with hydrocephalus, unspecified region
741.01	Spina bifida with hydrocephalus, cervical region
741.03	Spina bifida with hydrocephalus, lumbar region
741.9	Spina bifida without mention of hydrocephalus, unspecified region
741.92	Spina bifida without mention of hydrocephalus, dorsal (thoracic) region
741.93	Spina bifida without mention of hydrocephalus, lumbar region

Code	Description
	Gastrointestinal structural disorders
42	Operations on esophagus
42.11	Cervical esophagostomy
42.41	Partial esophagectomy
42.51	Intrathoracic esophagoesophagostomy
42.54	Other intrathoracic esophagoenterostomy
42.55	Intrathoracic esophageal anastomosis with interposition of colon
42.61	Antesternal esophagoesophagostomy
42.89	Other repair of esophagus
43.11	Percutaneous (endoscopic) gastrostomy
43.19	Other gastrostomy
43.3	Pyloromyotomy
43.7	Partial gastrectomy with anastomosis to jejunum
44.29	Other pyloroplasty
44.39	Other gastroenterostomy without gastrectomy
44.66	Other procedures for creation of esophagogastric sphincteric competence
44.67	Laparoscopic procedures for creation of esophagogastric sphincteric competence
44.69	Other repair of stomach
45	Incision of intestine, not otherwise specified
45.02	Other incision of small intestine
45.61	Multiple segmental resection of small intestine
45.62	Other partial resection of small intestine
45.73	Open and other right hemicolectomy
45.74	Open and other resection of transverse colon
45.75	Open and other left hemicolectomy
45.76	Open and other sigmoidectomy
45.8	Total intraabdominal colectomy
45.82	Open total intraabdominal colectomy
45.91	Small-to-small intestinal anastomosis
45.93	Other small-to-large intestinal anastomosis
46.01	Exteriorization of small intestine
46.1	Colostomy, not otherwise specified
46.11	Temporary colostomy
46.13	Permanent colostomy
46.2	Ileostomy, not otherwise specified
46.21	Temporary ileostomy
46.23	Other permanent ileostomy
46.32	Percutaneous (endoscopic) jejunostomy
46.39	Other enterostomy
46.79	Other repair of intestine
47.01	Laparoscopic appendectomy
47.09	Other appendectomy
47.19	Other incidental appendectomy
48.41	Soave submucosal resection of rectum
48.42	Laparoscopic pull-through resection of rectum
48.43	Open pull-through resection of rectum
48.79	Other repair of rectum
51.32	Anastomosis of gallbladder to intestine
51.36	Choledochoenterostomy
51.37	Anastomosis of hepatic duct to gastrointestinal tract
54.71	Repair of gastroschisis
530.3	Stricture and stenosis of esophagus
530.84	Tracheoesophageal fistula
537	Acquired hypertrophic pyloric stenosis
560	Intussusception
560	Intestinal obstruction without mention of hernia

SUPPLEMENTAL TABLE 4 Continued

Code	Description	Code	Description
K31.84	Gastroparesis	560.2	Volvulus
		560.81	Intestinal or peritoneal adhesions with obstruction (postoperative, postinfection)
	Gastrointestinal chronic diarrhea disorders	560.89	Other specified intestinal obstruction
271.3	Intestinal disaccharidase deficiencies and disaccharide malabsorption	560.9	Unspecified intestinal obstruction
558.3	Allergic gastroenteritis and colitis	750.3	Tracheoesophageal fistula, esophageal atresia and stenosis
558.41	Eosinophilic gastroenteritis	750.4	Other specified anomalies of esophagus
558.42	Eosinophilic colitis	750.5	Congenital hypertrophic pyloric stenosis
579	Celiac disease	750.6	Congenital hiatus hernia
579	Intestinal malabsorption	751.1	Atresia and stenosis of small intestine
579.4	Pancreatic steatorrhea	751.2	Atresia and stenosis of large intestine, rectum, and anal canal
579.8	Other specified intestinal malabsorption	751.3	Hirschsprung disease and other congenital functional disorders of colon
579.9	Unspecified intestinal malabsorption	751.4	Anomalies of intestinal fixation
K90.9	Intestinal malabsorption, unspecified	751.5	Other anomalies of intestine
		756.71	Prune belly syndrome
	Prematurity	756.72	Omphalocele
765	Extreme immaturity, unspecified wt	756.73	Gastroschisis
765.01	Extreme immaturity, $<$500 g	K56.2	Volvulus
765.02	Extreme immaturity, 500–749 g	K56.60	Unspecified intestinal obstruction
765.03	Extreme immaturity, 750–999 g	K56.69	Other intestinal obstruction
765.04	Extreme immaturity, 1000–1249 g	V13.67	Personal history of (corrected) congenital malformations of digestive system
765.05	Extreme immaturity, 1250–1499 g	V44.1	Gastrostomy status
765.06	Extreme immaturity, 1500–1749 g	V44.2	Ileostomy status
765.07	Extreme immaturity, 1750–1999 g	V44.3	Colostomy status
765.08	Extreme immaturity, 2000–2499 g	V44.4	Status of other artificial opening of gastrointestinal tract
765.09	Extreme immaturity, 2500 g and over	V45.72	Acquired absence of intestine (large, small)
765.1	Other preterm infants, unspecified wt	V45.75	Acquired absence of organ, stomach
765.1	Other preterm infants	V55.1	Attention to gastrostomy
765.12	Other preterm infants, 500–749 g	V55.2	Attention to ileostomy
765.13	Other preterm infants, 750–999 g	V55.3	Attention to colostomy
765.14	Other preterm infants, 1000–1249 g	V55.4	Attention to other artificial opening of digestive tract
765.15	Other preterm infants, 1250–1499 g	Z93.1	Gastrostomy status
765.16	Other preterm infants, 1500–1749 g		
765.17	Other preterm infants, 1750–1999 g		
765.18	Other preterm infants, 2000–2499 g		
765.19	Other preterm infants, 2500 g and more		
765.21	Less than 24 completed weeks' gestation		
765.22	24 completed weeks' gestation		
765.23	25–26 completed weeks' gestation		
765.24	27–28 completed weeks' gestation		
765.25	29–30 completed weeks' gestation		
765.26	31–32 completed weeks' gestation		
765.27	33–34 completed weeks' gestation		
765.28	35–36 completed weeks' gestation		
P07.24	Extreme immaturity of newborn, gestational age 25 completed weeks		
P07.30	Preterm newborn, unspecified weeks' gestation		
P07.31	Preterm newborn, gestational age 28 completed weeks		
P07.39	Preterm newborn, gestational age 36 completed weeks		

SUPPLEMENTAL TABLE 5 CYP2C19 Metabolizer Phenotypes

Diplotypes[a]	Genotype Description	Phenotype
*1/*n, *n/*n, *n/*17	Combination of loss-of-function alleles	PM/IM
*1/*1	Normal-function allele	NM
*1/*17, *17/*17	Gain-of-function allele ± normal-function allele	RM/UM

[a] "n" refers to any 1 of the no-function (*2, *3, *4, *8) or decreased-function (*9) alleles.

SUPPLEMENTAL TABLE 6 *CYP2C19* Allele Frequencies

CYP2C19 Haplotype	rsID	All Participants (*N* = 670)		Whites (*N* = 553)		African American (*N* = 76)		Asian American and/or Pacific Islanders (*N* = 11)		Other or Unknown (*N* = 30)	
		Total Minor Alleles	MAF	Total Minor Alleles	MAF	Total Minor Alleles	MAF	Total Minor Alleles	MAF	Total Minor Alleles	MAF
*2	rs4244285	195	0.1455	158	0.1429	25	0.1645	5	0.2273	7	0.1167
*3	rs4986893	1	0.0007	0	0.0000	0	0.0000	1	0.0455	0	0.0000
*4	rs28399504	2	0.0015	1	0.0009	0	0.0000	0	0.0000	1	0.0167
*8	rs41291556	4	0.0030	4	0.0036	0	0.0000	0	0.0000	0	0.0000
*9	rs17884712	0	0.0000	0	0.0000	0	0.0000	0	0.0000	0	0.0000
*17	rs12248560	304	0.2269	250	0.2260	42	0.2763	1	0.0455	11	0.1833

MAF - Minor Allele Frequency; rsID - Reference SNP cluster ID.