Early life incidence of gastrointestinal and respiratory infections in children with gastroschisis: a cohort study

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Abstract

Objectives: Survival in infants with gastroschisis is increasing although little is known about early childhood morbidity. In the context of a hypothesised link between the gastrointestinal (GI) tract and immune function, this study explores rates of GI and respiratory infections in children with gastroschisis.

Methods: We conducted a population-based retrospective cohort study using data from the Health Improvement Network (THIN), a large database of UK primary care medical records. We identified children born from 1990 to 2013, and extracted follow-up data to their fifth birthday. We calculate incidence rates (IR) of GI and respiratory tract infections, overall and stratified by age, sex, socioeconomic status and gestational age at birth, and compared these between children with and without gastroschisis by calculating adjusted incidence rate ratios (aIRR).

Results: Children with gastroschisis had a 65% higher IR of GI infection compared to children without (aIRR 1.65, 95% CI 1.37-1.99, $p<0.001$). Children with gastroschisis had a 27% higher IR of all respiratory tract infections (aIRR 1.27, 95% CI 1.12-1.44, $p<0.001$) and more than 2-fold increase in lower respiratory tract infections compared to children without the condition (aIRR 2.15, 95% CI 1.69-2.74, $p<0.001$).

Conclusions: Children born with gastroschisis have a significantly higher incidence of GI and respiratory tract infections compared to children without gastroschisis. This association requires further investigations but could be related to the neonatal care they receive such as delayed eneteral feeding or frequent antibiotic courses altering the gut microbiome and developing immune system.

Key words

e-health data research; The Health Improvement Network (THIN); observational study; child immune dysfunction

What is known?

- The short-term consequences of gastroschisis and persistence of longer-term functional gastrointestinal (GI) symptoms are well documented.
- The GI tract is an integral component of the developing immune system.
- Little is known about longer-term impacts of gastroschisis on immune function.

What is new?

- In early childhood, children with gastroschisis have higher incidence rates of GI and respiratory infections recorded in primary care than children without gastroschisis.
- These findings persist even after adjusting for gestation at birth, sex and socioeconomic status.

Introduction

Gastroschisis is a congenital defect of the anterior abdominal wall with an incidence of 1 in 2,500 births[1] equating to approximately 300 babies per year in the United Kingdom (UK). Survival rates for infants with gastroschisis now exceed 95%, largely due to advances in neonatal care and surgical management[2].

Short-term neonatal complications of gastroschisis are well-documented[3]. After undergoing corrective surgery nearly all children require total parenteral nutrition (TPN), until the establishment of enteral feeds, which brings attendant risks of catheter related sepsis[4]. These infants can remain in the neonatal unit for many weeks or months and often require multiple courses of antibiotics[5], potentially altering their gut microbial flora and long-term immune function[6].

Long-term outcomes in children with gastroschisis have focused on recurring abdominal pain or functional gastrointestinal (GI) symptoms, such as indigestion, chronic diarrhoea and constipation[7–13]. However, the majority of these studies are small, based on single centres, and many have pooled children born with gastroschisis with children born with omphalocele, despite their different embryological origins and clinical courses[7,10–13].

Here we report results from a UK population-based cohort study comparing the incidence of recorded common childhood GI and respiratory infections in children with and without gastroschisis, from the point of registration with a general practitioner (GP) to their fifth birthday.

Methods

Dataset and study population

Data were derived from The Health Improvement Network (THIN) database of anonymised patient primary care records from UK general practices[14]. We used the version of THIN comprising data to January 2013 and including 11,764,660 patient records collected from 570 UK practices. The THIN database is representative of the UK population in terms of patient age and sex, though slightly over represents patients from less socioeconomically deprived areas[15].

All children in THIN who were born between January 1990 and January 2013 and registered with a GP within the first six months after birth were included in the study. Children with any major congenital anomaly (based on the European Surveillance of Congenital Anomalies definition[16]) other than gastroschisis were excluded. Children were followed up from the date they were registered with the GP until the day before their fifth birthday, or the date they died, transferred to another practice or the date of last data collection.

Definitions of exposure and outcomes

We used Read codes[17] (available on request) recorded in THIN to identify individuals with gastroschisis and the outcomes of interest. The exposed group was defined as children with gastroschisis and the non-exposed group comprised all other children.

In line with previously-published work[18], our primary outcomes were episodes of GI infection and respiratory tract infection (RTI) diagnosed by a general practitioner. Children were defined as having a GI infection if they had at least one clinical diagnosis of a relevant infection (e.g. infectious colitis or gastroenteritis) or an infection-related symptom (e.g. vomiting or diarrhoea) recorded in their primary care records during the follow-up period. Symptom codes were included, in line with other work[19], as most cases of GI infection which present to a GP will not be confirmed by laboratory testing. The 15th day after the initial diagnosis of an infection

was defined as the date of recovery. If a subsequent diagnosis was recorded prior to the recovery date, this was considered to be part of the same infection episode and the recovery date was extended to the 8th day after this recording (only if later than the original recovery date), to ensure each episode lasted at least 14 days. Any additional recordings prior to the recovery date were treated similarly. Recordings after the date of recovery were treated as a new episode of illness. Similar procedures were used to identify and classify episodes of RTI if children had at least one recorded clinical diagnosis of RTI (e.g. common cold, tonsillitis, bronchitis) or an infection-related symptom (e.g. sore throat).

Other co-variables

Where available, data were also extracted on co-variables which were potentially associated with changes in infection rates. These included sex, socioeconomic status measured using Townsend quintile of deprivation, and gestational age at birth (classified as <32, 32-36, and 37+ completed weeks). Children's follow-up time was split into five age groups: 0-1, 1-2, 2-3, 3-4 and 4-5 years.

Data analysis

All data management and analyses were carried out using STATA v14 (Stata Corp, College Station, TX). The characteristics of children with and without gastroschisis were described, including sex, Townsend quintile of deprivation, gestational age at birth, age of child at start of follow-up and length of follow-up. Univariable analyses (chi-squared test, t-test or Wilcoxon rank sum test, as appropriate) were carried out to identify significant differences in the characteristics between children with and without gastroschisis. Missing data for Townsend quintile of deprivation and gestational age at birth were included in separate categories.

The number of episodes of GI and respiratory infection and the absolute rate per 10 person years with 95% confidence intervals (95% CIs) were calculated, both overall and separately for each co-variable for both children with and without gastroschisis. Absolute rate differences with 95% CIs comparing children with and without gastroschisis were calculated. Incidence rate ratios (IRRs) were calculated overall and separately for each co-variable using negative binomial regression with a logarithmic link function (as the assumptions of the Poisson distribution were not met, based on the Pearson's goodness-of-fit statistic) with adjustment for co-variables.

Sensitivity analysis

We conducted two sensitivity analyses to minimise ascertainment bias and assess whether the incidence of more severe infection differed between groups. Symptomatic Read codes were included in the case definitions of GI infection described above, as GPs may use such codes alongside specific diagnostic codes for childhood infections in their routine practice. However, this approach could result in the inclusion of some non-infectious conditions. Therefore, we examined only the recording of specific GI infections, excluding symptomatic codes. We also examined the occurrence of lower respiratory tract infections (LRTI), i.e. influenza, pneumonia, bronchitis or bronchiolitis, excluding upper RTIs and symptom codes. The incidence rates of specific GI infection and LRTI were calculated and compared between children with and without gastroschisis.

Our primary analyses used data from all children born from January 1990 onwards who registered with a GP within six months of birth. However, this is likely to have introduced some selection bias as sicker children who did not survive to discharge were excluded, a particular problem in the early years of the study period when mortality rates from gastroschisis were higher. To address this bias we conducted a sensitivity analysis calculating adjusted incidence

rate ratios for all GI and respiratory infections in a subset of children born from January 2000 only.

Ethical approval

The providers of the THIN data received ethical approval for the collection of data from GP practices from the South East Multicentre Research Ethics Committee (SE-MREC). Individual studies using THIN data do not require further separate ethical approval if only anonymised THIN data are used. The protocol for this project was approved by the THIN Scientific Review Committee (reference 15THIN066).

Results

The study cohort consisted of 942,810 children who met the inclusion criteria, 212 with gastroschisis and 942,598 without (an incidence of 0.56 cases per 2,500 children included). The median duration of follow-up in the dataset was 4.8 years (interquartile range 2.0-4.9 years) and 52.9% of children had data to the age of five. There were no significant differences between the sexes of the children in the two groups, though children with gastroschisis were more likely to be from more deprived areas and to have been born prematurely (Table 1).

GI infections

The overall incidence rate of GI infection per 10 person years (hereafter referred to as incidence rate) in children born with gastroschisis was 2.64 per 10 person years (95% CI 2.27-3.06), higher than the rate of 1.61 (95% CI 1.61-1.62) in children without gastroschisis (Table 2). The unadjusted IRR was marginally attenuated after adjustment for age, sex, socioeconomic status and gestational age at birth (adjusted IRR 1.65, 95% CI 1.37-1.99, $p<0.001$). GI infection rates

were generally higher in children born with gastroschisis compared to children without across all categories of co-variables (Table 2).

Respiratory infections

The overall incidence rate of RTI in children born with gastroschisis was 7.94 (95% CI 7.28-8.67), higher than the rate of 6.11 (95% CI 6.10-6.12) observed in children born without gastroschisis (Table 3). The unadjusted rate ratio was only marginally attenuated after adjustment for age, sex, socioeconomic status and gestational age at birth (adjusted IRR 1.27, 95% CI 1.12-1.44, $p<0.001$).

After adjusting for other variables, incidence rates increased in children with gastroschisis of both sexes and in all age groups (though only reached statistical significance in the 1-2 years age group). Rates were also higher in children with gastroschisis than children without gastroschisis in all deprivation groups (Table 3). Comparison of incidence by gestational age was limited by the small number of infection episodes in children born at <32 completed weeks' gestation, though for children born at term there was some evidence of an increased rate of RTI in children with gastroschisis compared to those without, though the effect estimate was marginally non-significant.

Sensitivity analyses

After excluding GI infections identified using symptomatic Read codes, there were very few episodes of GI infection in children born with gastroschisis (11 events), which precluded assessment of rates by subgroup. The overall adjusted IRR of GI infection was not statistically significant (adjusted IRR 0.69, 95% CI 0.38-1.25, $p=0.218$).

Overall the number of LRTI episodes were lower than RTI episodes (Table 4). The rate of LRTI was higher in children with gastroschisis than children without and the adjusted IRR was 2.15 (95% CI 1.69-2.74, p<0.001) which was higher than that for RTI. The pattern in the IRRs across categories of age, sex, socioeconomic status and gestational age at birth were broadly similar for LRTIs compared to RTIs, though generally the magnitude of the effect estimates were higher (Table 4).

The incidence of gastroschisis in the subset of children born from January 2000 onwards was 0.71 cases per 2,500 registered children. Overall adjusted IRRs for the primary outcomes were similar in the subset of children born from 2000 onwards compared to the full dataset (adjusted IRR for GI infection 1.46, 95% CI 1.19-1.78, p<0.001; adjusted IRR for RTI 1.23, 95% CI 1.08-1.40, p=0.002).

Discussion

To our knowledge, this is the largest population-based cohort study of children with gastroschisis. We identify significantly higher incidence rates of GI and respiratory infections in children born with gastroschisis, compared to children without, over the first five years of life following hospital discharge after birth. Particularly, we found a 2-fold increased incidence rate of LRTIs in children with gastroschisis, as diagnosed by their general practitioner, compared to children without, after adjusting for age, sex, socioeconomic status and gestational age at birth.

Previous studies have noted a relatively high number of babies with gastroschisis admitted to neonatal intensive care units developed viral respiratory tract infections [20,21]. However, none of these studies have been able to examine the risk of common infections after children are discharged from the hospital. Our findings from this exploratory study support the hypothesis

that children with gastroschisis may have a dysfunctional immune system and so be more likely to develop GI and respiratory infections in early life.

The GI tract is an integral component of the immune system[22]. In gastroschisis, however, GI tract development is altered both pre- and postnatally. The gut flora plays an important part in immune function[23] and there is a bi-directional relationship between GI motility and microbiota[24]. The colonisation of the GI tract in infants born with gastroschisis may be affected by delay in establishing enteral feeds and administration of antibiotics to prevent and treat sepsis, which may also affect the healthy balance of bacteria[6,25,26]. Infants with gastroschisis may also have dysmotility which has also been found to lead to overgrowth of bacteria in short bowel[24]. Alterations to the gut flora may have long-term immunological consequences. Indeed, as well as reports of increased susceptibility to viral respiratory tract infection[20,21], gastroschisis is associated with immune dysfunction including cow's milk protein allergy[27], hypogammaglobulinaemia[28], and secondary non-severe combined immunodeficiency (SCID) T-cell lymphopenia[29].

Our findings persist after adjustment for gestational age at birth, suggesting an association independent of the effect of the reduced immune function which has been shown to persist in preterm children in later life[30]. Similarly, our results also remain after adjustment for socioeconomic status, a variable which helps to account for any differences in healthcare seeking behaviour related to parental affluence.

A key strength of this work is the relatively large number of children with gastroschisis studied. Compared to the use of bespoke surveys, primary care data afford the opportunity to follow up substantial numbers of children with rare conditions with relative ease. Additionally, the data were nationally representative with a similar age and sex distribution to the general population in the UK[15]. The use of data recorded during the course of routine primary care practice reduces

the potential for recall bias, a limitation of some previous studies[8,9]. The large dataset also enabled analyses to be stratified by and adjusted for socio-demographic characteristics and gestational age at birth. However, power was limited in some subgroups, and by the absence of data on other important potential confounders such as birth weight and exposure to tobacco smoke during gestation and childhood which are incompletely recorded in THIN.

We identified children with gastroschisis based on clinical diagnosis recorded in primary care. The incidence of gastroschisis recorded in THIN, using a denominator of children registered with a GP, was however lower than the incidence among live births suggested by recent national registry data[1]. The present study only includes children who survived to discharge from hospital. With both the increase in incidence and better survival rates in recent years[5], it is probable the lower incidence in this study is a reflection of this. Indeed, our study data show increases in incidence from approximately the year 2000 onwards; the confidence interval for the incidence rate spans the value of 1 per 2,500 included children for nine of the years from 2000 onwards, compared to none beforehand. Our sensitivity analysis showed similar incidence rate ratios for GI and respiratory infection in the subset of children born from 2000 onwards compared to the full dataset, suggesting a minimal impact of selection bias on our primary results. The THIN database does marginally underrepresent more deprived areas of the UK[15], and as gastroschisis is associated with deprivation it may therefore miss some cases.

Our definitions of episodes of infection were necessarily broad, based on recorded diagnostic and symptom codes by the child's general practitioner. With the data available to us it was not possible to identify, for example, GI upset due to underlying disease (such as a persistent ileus) as opposed to infection. Less severe infections may not be recorded in primary care if a parent feels they do not warrant consultation with a GP, and conversely, more severe infections treated directly in hospital may also not be fully transcribed into GP records. A GP's propensity to

investigate a potential infection further, perhaps requesting microbiology tests, may be influenced by the presence of any underlying health conditions in a child, though this ascertainment bias may not apply with more severe infections. Our sensitivity analysis demonstrated increased LRTI rates in children with gastroschisis compared to children without gastroschisis, which helps to exclude the possibility of ascertainment bias affecting the primary analysis. In addition, based on our algorithm a child with gastroschisis reporting bowel dysfunction such as chronic diarrhoea may have been miscoded as having GI infection which could result in a higher recorded rate of GI infection in our study. Whilst this may also occur in the non-gastroschisis group, the misclassification is likely to be differential as studies have consistently identified GI tract dysfunction as an issue in gastroschisis[8,9,31]. Our sensitivity analysis excluding recordings of GI symptoms found a decreased GI infection rate in children with gastroschisis compared to children without. However, this result was not statistically significant and was based on only 11 infection episodes in children with gastroschisis; we therefore cannot rule out the potential for elevated GI infection rates in children with gastroschisis.

Future work could usefully consider differences between groups in treatment for infections, such as antibiotic prescribing, or investigate hospital admissions using linked secondary care data. This would help identify the most severe infections, but would exclude less severe, but more common, infections where a GP may recommend supportive care only. In addition, further work would be helpful to explore the impact of other potential confounders and effect modifiers, particularly where good quality data are only available from linked secondary care records; this could include the effects of maternal age and parity, more complete data on gestational age, birthweight, presence of other congenital anomalies, complexity of gastroschisis and frequency of consultation with a GP.

The absolute difference in the incidence of infection between children with and without gastroschisis is relatively small. However, understanding the later outcomes of gastroschisis is important to the growing number of survivors and their caregivers, and longer-term follow-up to assess whether increased infection rates persist would be useful. The results of this study could help to inform further research and prevention strategies and to ensure appropriate preventive and management advice is given to reduce the burden of infection. For example, if there is indeed an immune component at play, promotion of smoking cessation, improving breastfeeding rates and early use of probiotics[32] may be beneficial to provide extra immune protection or a more natural gut microbiota and potentially reduce infection incidence in children with gastroschisis.

Author contributions: LB, LS and DS designed the study, with clinical paediatric expertise provided by DS and ST. LF extracted the THIN data and undertook initial data management. LB built the final dataset for the study. JB conducted the data analysis with support from LB and LS. JB wrote the first draft of the manuscript, which was subsequently revised and approved by all authors.

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List of tables

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page no.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	7,8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	8, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2,3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9, Table 2,3
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10, Table 4

Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11,12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Table 1: Characteristics of children with and without gastroschisis

	Children with gastroschisis **n (%)**	**Children without gastroschisis** **n (%)**	***p*-value for difference**
Total	212 (0.02)	942,598 (99.98)	
Sex			
Female	107 (50.5)	459,141 (48.7)	0.608
Male	105 (49.5)	483,457 (51.3)	
Townsend deprivation quintile			
1 (least deprived)	23 (10.9)	202,499 (21.5)	<0.001
2	25 (11.8)	173,584 (18.4)	
3	42 (19.8)	184,802 (19.6)	
4	52 (24.5)	175,950 (18.7)	
5 (most deprived)	53 (25.0)	133,131 (14.1)	
Missing	17 (8.0)	72,632 (7.7)	
Gestational age at birth (completed weeks)			
37+	105 (49.5)	649,575 (68.9)	<0.001
32-36	42 (19.8)	35,464 (3.8)	
<32	4 (1.89)	6,456 (0.68)	
Missing	61 (28.8)	251,103 (26.6)	
Age of child at start of follow-up (days)			
Median (**IQR**)	43.5 (30.0-60.0)	30.0 (15.0-43.0)	<0.001
Length of follow-up (months)			
Median (**IQR**)	42.9 (15.7-59.1)	58.4 (24.3-59.8)	<0.001

IQR=interquartile range

Table 2: Incidence rates and rate ratios of gastrointestinal tract infection in children with and without gastroschisis

	Children with gastroschisis		Children without gastroschisis						
	Events	Rate per 10 person years (95% CI)	Events	Rate per 10 person years (95% CI)	Rate difference (95% CI)	Unadjusted IRR (95% CI)	*p*-value	Adjusted IRR[#] (95% CI)	*p*-value
Overall	171	2.64 (2.27-3.06)	538386	1.61 (1.61-1.62)	1.03 (0.63-1.42)	1.64 (1.40-1.90)	<0.001	1.65 (1.37-1.99)	<0.001
Age (years)									
0-1	68	4.14 (3.26-5.25)	232772	2.93 (2.92-2.94)	1.20 (0.22-2.19)	1.41 (1.12-1.78)	0.004	1.37 (1.06-1.75)	0.014
1-2	51	3.26 (2.48-4.29)	159612	2.10 (2.09-2.11)	1.17 (0.27-2.06)	1.56 (1.16-2.05)	0.002	1.78 (1.11-2.75)	0.009
2-3	30	2.30 (1.61-3.29)	74834	1.12 (1.11-1.13)	1.18 (0.36-2.00)	2.05 (1.38-2.93)	<0.001	2.41 (1.39-4.19)	0.002
3-4	19	1.75 (1.12-2.74)	42422	0.72 (0.71-0.72)	1.03 (0.24-1.82)	2.44 (1.47-3.81)	<0.001	3.00 (1.51-5.96)	0.002
4-5	3	0.34 (0.11-1.05)	28746	0.55 (0.54-0.55)	-0.21 (-0.59-0.18)	0.62 (0.13-1.81)	0.213	0.53 (0.15-1.86)	0.324
Sex									
Female	82	2.44 (1.97-3.03)	250741	1.54 (1.54-1.55)	0.90 (0.37-1.43)	1.58 (1.26-1.97)	<0.001	1.57 (1.20-2.04)	0.001
Male	89	2.85 (2.32-3.51)	287645	1.68 (1.67-1.69)	1.17 (0.58-1.76)	1.70 (1.36-2.09)	<0.001	1.74 (1.34-2.25)	<0.001
Townsend deprivation quintile									
1 (least deprived)	22	2.82 (1.86-4.29)	116910	1.50 (1.49-1.51)	1.32 (0.14-2.50)	1.88 (1.18-2.85)	0.003	1.80 (1.11-2.93)	0.017
2	31	3.87 (2.72-5.50)	95943	1.49 (1.48-1.50)	2.38 (1.02-3.74)	2.60 (1.76-3.68)	<0.001	2.86 (1.84-4.46)	<0.001
3	29	2.20 (1.53-3.16)	103527	1.58 (1.57-1.59)	0.61 (-0.19-1.41)	1.39 (0.93-1.99)	0.045	1.39 (0.90-2.15)	0.136
4	33	2.09 (1.49-2.95)	102061	1.70 (1.69-1.71)	0.40 (-0.32-1.11)	1.23 (0.85-1.73)	0.117	1.30 (0.85-1.99)	0.220
5 (most deprived)	40	2.55 (1.87-3.47)	82933	1.88 (1.87-1.90)	0.67 (-0.12-1.46)	1.35 (0.97-1.84)	0.033	1.48 (0.99-2.21)	0.056
Missing	16	3.66 (2.24-5.98)	37012	1.67 (1.65-1.69)	1.99 (0.20-3.79)	2.19 (1.25-3.56)	0.003	2.05 (1.09-3.86)	0.026
Gestational age at birth (complete weeks)									
37+	83	2.59 (2.08-3.21)	423247	1.83 (1.82-1.84)	0.76 (0.20-1.31)	1.41 (1.13-1.75)	0.001	1.36 (1.05-1.76)	0.018
32-36	42	3.02 (2.23-4.09)	25939	2.13 (2.11-2.16)	0.89 (-0.02-1.81)	1.42 (1.02-1.92)	0.015	1.60 (1.08-2.37)	0.018
<32	9	6.07 (3.16-11.67)	4766	2.13 (2.07-2.19)	3.94 (-0.03-7.90)	2.85 (1.30-5.41)	0.004	3.82 (1.43-10.21)	0.008
Missing	37	2.13 (1.54-2.94)	84434	0.96 (0.95-0.96)	1.17 (0.49-1.86)	2.23 (1.57-3.07)	<0.001	2.78 (1.75-4.42)	<0.001

[#] Adjusted for age, sex, Townsend deprivation quintile and gestational age at birth; CI=confidence interval; IRR=incidence rate ratio

Table 3: Incidence rates and rate ratios of respiratory tract infection in children with and without gastroschisis

	Children with gastroschisis		Children without gastroschisis						
	Events	Rate per 10 person years (95% CI)	Events	Rate per 10 person years (95% CI)	Rate difference (95% CI)	Unadjusted IRR (95% CI)	*p*-value	Adjusted IRR[#] (95% CI)	*p*-value
Overall	504	7.94 (7.28-8.67)	2003284	6.11 (6.10-6.12)	1.83 (1.14-2.53)	1.30 (1.19-1.42)	<0.001	1.27 (1.12-1.44)	<0.001
Age (years)									
0-1	177	11.06 (9.55-12.82)	702290	9.07 (9.05-9.09)	1.99 (0.35-3.62)	1.22 (1.05-1.41)	0.005	1.18 (0.98-1.43)	0.086
1-2	145	9.51 (8.09-11.20)	523199	7.01 (6.99-7.03)	2.50 (0.95-4.05)	1.36 (1.15-1.60)	<0.001	1.48 (1.15-1.92)	0.003
2-3	77	6.00 (4.80-7.50)	326150	4.96 (4.94-4.98)	1.04 (-0.30-2.38)	1.21 (0.95-1.51)	0.051	1.20 (0.86-1.68)	0.292
3-4	65	6.08 (4.77-7.76)	259172	4.45 (4.43-4.47)	1.63 (0.15-3.11)	1.37 (1.05-1.74)	0.008	1.33 (0.92-1.93)	0.133
4-5	40	4.60 (3.37-6.27)	192473	3.71 (3.69-7.23)	0.89 (-0.54-2.32)	1.24 (0.89-1.69)	0.091	1.19 (0.75-1.90)	0.458
Sex									
Female	260	7.91 (7.00-8.93)	931444	5.83 (5.82-5.84)	2.08 (1.12-3.04)	1.36 (1.20-1.53)	<0.001	1.33 (1.12-1.59)	0.001
Male	244	7.98 (7.04-9.05)	1071840	6.38 (6.37-6.39)	1.60 (0.60-2.60)	1.25 (1.10-1.42)	<0.001	1.20 (1.01-1.43)	0.042
Townsend deprivation quintile									
1 (least deprived)	52	6.78 (5.16-8.89)	448714	5.87 (5.85-5.89)	0.91 (-0.93-2.75)	1.15 (0.86-1.51)	0.150	1.08 (0.75-1.58)	0.671
2	81	10.38 (8.35-12.90)	362645	5.73 (5.71-5.75)	4.65 (2.39-6.91)	1.81 (1.44-2.25)	<0.001	1.84 (1.34-2.52)	<0.001
3	89	6.87 (5.58-8.46)	384703	5.99 (5.97-6.01)	0.88 (-0.55-2.30)	1.15 (0.92-1.41)	0.101	1.17 (0.88-1.57)	0.285
4	105	6.72 (5.55-8.15)	374861	6.36 (6.34-6.38)	0.37 (-0.92-1.66)	1.06 (0.86-1.28)	0.280	1.06 (0.81-1.39)	0.653
5 (most deprived)	145	9.51 (8.08-11.19)	301916	7.00 (6.98-7.03)	2.51 (0.96-4.05)	1.36 (1.15-1.60)	<0.001	1.35 (1.06-1.71)	0.013
Missing	33	7.68 (5.46-10.80)	130445	5.99 (5.96-6.02)	1.69 (-0.93-4.31)	1.28 (0.88-1.80)	0.082	1.24 (0.76-2.01)	0.386
Gestational age at birth (complete weeks)									
37+	260	8.29 (7.34-9.36)	1561444	6.89 (6.88-6.90)	1.39 (0.39-2.40)	1.20 (1.06-1.36)	0.002	1.18 (1.00-1.40)	0.053
32-36	129	9.54 (8.03-11.33)	95587	8.05 (8.00-8.10)	1.49 (-0.16-3.13)	1.18 (0.99-1.41)	0.030	1.22 (0.96-1.56)	0.102
<32	9	6.05 (3.15-11.63)	19266	8.87 (8.74-8.99)	-2.81 (-6.77-1.14)	0.68 (0.31-1.30)	0.123	0.60 (0.26-1.38)	0.229
Missing	106	6.21 (5.14-7.52)	326987	3.75 (3.74-3.76)	2.47 (1.28-3.65)	1.66 (1.36-2.01)	<0.001	1.62 (1.19-2.22)	0.003

[#] Adjusted for age, sex, Townsend deprivation quintile and gestational age at birth; CI=confidence interval; IRR=incidence rate ratio

Table 4: Incidence rates and rate ratios of lower respiratory tract infection in children with and without gastroschisis (sensitivity analysis)

	Children with gastroschisis		Children without gastroschisis						
	Events	Rate per 10 person years (95% CI)	Events	Rate per 10 person years (95% CI)	Rate difference (95% CI)	Unadjusted IRR (95% CI)	*p*-value	Adjusted IRR[#] (95% CI)	*p*-value
Overall	135	2.08 (1.75-2.46)	350349	1.05 (1.04-1.05)	1.03 (0.71-1.41)	1.98 (1.68-2.35)	<0.001	2.15 (1.69-2.74)	<0.001
Age (years)									
0-1	58	3.52 (2.72-4.55)	136525	1.71 (1.70-1.72)	1.81 (0.90-2.71)	2.05 (1.56-2.66)	<0.001	2.18 (1.57-3.04)	<0.001
1-2	34	2.17 (1.55-3.03)	94044	1.23 (1.22-1.24)	0.93 (0.21-1.66)	1.76 (1.22-2.46)	0.001	1.96 (1.09-3.52)	0.024
2-3	22	1.68 (1.11-2.56)	54530	0.82 (0.81-0.82)	0.87 (0.16-1.57)	2.06 (1.29-3.12)	0.001	2.77 (1.35-5.71)	0.006
3-4	16	1.47 (0.90-2.40)	39078	0.66 (0.65-0.67)	0.81 (0.09-1.53)	2.23 (1.27-3.61)	0.002	2.58 (1.14-5.80)	0.022
4-5	5	0.57 (0.24-1.36)	26172	0.50 (0.49-0.50)	0.07 (-0.43-0.56)	1.14 (0.37-2.65)	0.365	1.06 (0.33-3.42)	0.923
Sex									
Female	60	1.78 (1.38-2.29)	153201	0.94 (0.93-0.94)	0.84 (0.39-1.29)	1.90 (1.45-2.44)	<0.001	1.95 (1.36-2.79)	<0.001
Male	75	2.40 (1.91-3.00)	197148	1.15 (1.14-1.15)	1.25 (0.71-1.79)	2.09 (1.64-2.62)	<0.001	2.34 (1.68-3.26)	<0.001
Townsend deprivation quintile									
1 (least deprived)	17	2.18 (1.35-3.50)	78660	1.01 (1.00-1.02)	1.27 (0.13-2.20)	2.16 (1.26-3.45)	0.002	1.91 (0.98-3.74)	0.059
2	23	2.86 (1.90-4.30)	63384	0.98 (0.97-0.99)	1.87 (0.71-3.04)	2.91 (1.84-4.37)	<0.001	3.03 (1.63-5.64)	<0.001
3	26	1.97 (1.34-2.89)	66273	1.01 (1.00-1.02)	0.96 (0.20-1.71)	1.94 (1.27-2.85)	0.001	2.35 (1.35-4.09)	0.003
4	30	1.90-1.33-2.72)	65528	1.09 (1.08-1.10)	0.82 (0.13-1.50)	1.75 (1.18-2.50)	0.002	2.15 (1.29-3.59)	0.003
5 (most deprived)	27	1.71 (1.18-2.50)	50962	1.15 (1.14-1.16)	0.56 (-0.09-1.21)	1.49 (0.98-2.16)	0.025	1.53 (0.91-2.59)	0.109
Missing	12	2.74 (1.55-4.82)	25542	1.15 (1.14-1.16)	1.59 (0.04-3.14)	2.38 (1.23-4.16)	0.004	2.88 (1.18-7.02)	0.020
Gestational age at birth (complete weeks)									
37+	74	2.30 (1.83-2.89)	268125	1.16 (1.15-1.16)	1.15 (0.62-1.67)	1.99 (1.56-2.50)	<0.001	2.51 (1.80-3.50)	<0.001
32-36	27	1.94 (1.33-2.82)	18476	1.51 (1.49-1.54)	0.42 (-0.31-1.15)	1.28 (0.84-1.86)	0.105	1.11 (0.68-1.84)	0.670
<32	3	1.98 (0.64-6.15)	4268	1.91 (1.85-1.97)	0.08 (-2.17-2.32)	1.04 (0.21-3.04)	0.439	0.98 (0.21-4.70)	0.984
Missing	31	1.78 (1.25-2.54)	59480	0.67 (0.67-0.68)	1.11 (0.48-1.74)	2.65 (1.80-3.76)	<0.001	3.30 (1.86-5.88)	<0.001

[#] Adjusted for age, sex, Townsend deprivation quintile and gestational age at birth; CI=confidence interval; IRR=incidence rate ratio