**Title:** Gastroschisis in Europe – a case-malformed control study of medication and maternal illness during pregnancy as risk factors

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# **Abstract**

Background: Gastroschisis, a congenital anomaly of the abdomen, is associated with young maternal age and has increased in prevalence in many countries. Maternal illness and medication exposure are among environmental risk factors implicated in its aetiology.

Methods: A population-based case-malformed control study was conducted using data from 18 European congenital anomaly registries, with information on first trimester medication use, covering 8 million births 1995-2012. 1,577 gastroschisis cases (of which 4% stillbirths, 11% terminations of pregnancy) were compared to 153,357 non-chromosomal/monogenic controls. Literature review identified previous associations concerning maternal illness and medication exposure to be tested as signals. Logistic regression adjusted for maternal age group, registry and time period was used to evaluate associations.

Results: Comparing gastroschisis to other congenital anomalies, the data supported signals concerning maternal depression [aOR 2.52, 95% CI 1.45, 4.39], antidepressant use [aOR 2.03, 95% CI 1.22, 3.38], postnatal depression/psychosis following a previous pregnancy [aOR 8.32, 95% CI 2.56, 27.01], sexually transmitted infections [aOR 2.85, 95% CI 1.13, 7.24], topical antivirals [aOR 5.31, 95% CI 1.63, 17.33] and continuation of oral contraceptives in early pregnancy [aOR 2.17, 95% CI 1.13, 4.18]. Exploratory analyses suggested associations with a wider range of maternal infections and medications, including tonsillitis and the expectorant bromhexine.

Conclusions: While it is difficult to disentangle the effects of the medication and underlying indication, our results add to the evidence base on preventable risk factors for gastroschisis. These risk factors may contribute to the higher risk among young mothers, and geographical and temporal variation in prevalence.

# **Gastroschisis in Europe– A Case-malformed Control Study of Medication and Maternal Illness During Pregnancy as Risk Factors**

Introduction

Gastroschisis is a congenital anomaly where the small intestine, part of the large intestine and occasionally other abdominal organs protrude through a lateral defect in the ventral abdomen.1,2 The majority of cases are isolated anomalies.3 The pathogenesis of gastroschisis is uncertain but it is thought to occur between the third and eighth gestational weeks. Historically a vascular disruption mechanism was proposed but recent hypotheses focus on abnormalities in the process of body wall4 or umbilical ring1 development.

Young maternal age has consistently been associated with an increased risk of gastroschisis.5,6 Links have also been found with nulliparity,7 white, Hispanic and indigenous Australian ethnic groups,7,8 smoking,9 alcohol,10 illicit drug use,11 medication exposure,9,12 maternal illness13 and low pre-pregnancy body mass index.14 None of these factors have been found to explain the geographical variation in prevalence in Europe,5 or the increase in prevalence seen since the 1970s.7,15

EUROmediCAT is a population based reproductive pharmacovigilance system, based on the European Surveillance of Congenital Anomalies (EUROCAT) network, and provides an opportunity to undertake research on medication exposure and maternal illness.16,17 This study aimed to use the EUROmediCAT database to test signals from the literature concerning first trimester medication exposure and maternal illness as risk factors for gastroschisis.

# Methods

A case-malformed control study was conducted using the EUROmediCAT database. Cases of gastroschisis were compared to controls with other non-chromosomal/monogenic congenital anomalies. The case-malformed control methodology was initially proposed for birth defect epidemiology as a method of controlling for maternal recall bias.18,19 It is used in EUROmediCAT to control for the source of exposure data and because data on non-malformed controls are not available.20

## Study population and data

EUROCAT registries record all cases of major congenital anomalies among live births, fetal deaths ≥20 weeks’ gestation and termination of pregnancy for fetal anomaly (TOPFA), in their populations using International Classification of Diseases (ICD)-9/ICD-10-British Paediatric Association (BPA) codes.16 The EUROmediCAT database includes data, from 1995, from those EUROCAT registries that record first trimester medication exposure either directly or through linkage with healthcare databases.21 Eighteen EUROmediCAT registries, across 14 countries 1995-2012 covering 8,096,594 births, participated in this study (Table 1).

**Table 1. Total births in population, number of Gastroschisis cases, number of malfromed controls, and total prevalence of Gastroschisis per 10,000 births by EUROCAT Registry, 1995-2012**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Country** | **Registry** | **Time period** | **Total births in population** | **Gastroschisis cases**a | **Malformed controls** | **Total prevalence of gastroschisis per 10,000 births [95% Confidence Interval]** |
| Belgium | Antwerp | 1997-2012 | 308,067 | 43 | 6,510 | 1.4 [1.0, 1.9] |
| Croatia | Zagreb | 1995-2012 | 120,403 | 21 | 1,858 | 1.7 [1.1, 2.7] |
| Denmark | Odense | 1995-2012 | 96,816 | 22 | 2,167 | 2.3 [1.4, 3.4] |
| France | Isle de Reunion | 2002-2012 | 161,071 | 37 | 3,530 | 2.3 [1.6, 3.2] |
| France | Paris | 2001-2012 | 319,636 | 51 | 7,608 | 1.6 [1.2, 2.1] |
| Germany | Mainz | 1996-2012 | 55,436 | 33 | 2,246 | 6.0 [4.1, 8.4] |
| Germany | Saxony Anhalt | 1995-2012 | 274,845 | 104 | 7,939 | 3.8 [3.1, 4.6] |
| Ireland | South East Ireland | 1997-2012 | 108,730 | 14 | 1,657 | 1.3 [0.7, 2.2] |
| Italy | Emilia Romagna | 1995-2012 | 595,214 | 52 | 9,923 | 0.9 [0.7, 1.1] |
| Italy | Tuscany | 1995-2012 | 505,101 | 34 | 9,277 | 0.7 [0.5, 0.9] |
| Netherlands | Northern Netherlands | 1995-2012 | 340,310 | 38 | 7,373 | 1.1 [0.8, 1.5] |
| Norway | Norway | 2005-2010 | 364,160 | 116 | 9,249 | 3.2 [2.6, 3.8] |
| Poland | Poland | 1999-2010 | 3,228,380 | 532 | 43,750 | 1.6 [1.5, 1.8] |
| Poland | Wielkopolska | 1999-2010 | 440,096 | 71 | 10,683 | 1.6 [1.3, 2.0] |
| Spain | Valencia Region | 2007-2012 | 314,704 | 37 | 5,939 | 1.2 [0.8, 1.6] |
| Switzerland | Vaud | 1997-2012 | 120,397 | 18 | 3,729 | 1.5 [0.9, 2.4] |
| Ukraine | Ukraine | 2005-2012 | 241,508 | 86 | 5,219 | 3.6 [2.8, 4.4] |
| United Kingdom | Wales | 1998-2012 | 501,720 | 278 | 16,220 | 5.5 [4.9, 6.2] |
| **Total** | **1995-2012** | **8,096,594** | **1,587**b | **154,877** | **2.0 [1.9, 2.1]** |

a Total cases = (Live births + stillbirths+ terminations of pregnancy). Excludes those with a chromosomal/monogenic syndrome

b Ten gastroschisis cases were excluded from the case-malformed control analysis as they were also recorded as having omphalocele, non-specific abdominal wall anomalies, limb-body-wall complex or body stalk anomalies.

## Cases and controls

Gastroschisis cases were those with an ICD-9 with BPA extension code 75671 or ICD-10 code Q793. Malformed controls consisted of those with a diagnosis of a major congenital anomaly not including gastroschisis. Those with codes for omphalocele (ICD-9-BPA 75670 or ICD-10 code Q792), non-specific abdominal wall anomalies (ICD-9-BPA 75679), limb-body-wall complex (ICD-10 Q795) or body stalk anomalies were excluded from both cases and controls.16 Chromosomal/monogenic conditions were excluded from cases and controls. Cases and controls were classified as isolated or potentially multiply malformed using the EUROCAT algorithm.22

## Exposure

First trimester maternal medication exposures were mostly obtained by registries from prospectively recorded maternity records. Additional data sources included the medical records of the infant, general practitioner records, maternity passports, and maternal interviews before or after birth.17 Norway medication exposures were based on first trimester prescription redemption records. Emilia Romagna did not have medication information for TOPFA. All first trimester medication exposures were recorded using the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system. This is a hierarchical system which categorizes substances according to the organ or system on which they act (1st level) and their therapeutic (2nd level), pharmacological (3rd level) and chemical properties (4th and 5th level). First trimester was defined as the period from the first day of the last menstrual period to the end of gestational week 12. Medications taken in the second or third trimester or where the timing was unknown were excluded.

Maternal illnesses before pregnancy, which may affect fetal development, and illnesses occurring during the first 20 weeks of pregnancy were recorded, mostly prospectively from maternity records, using ICD-9/ICD-10 codes.16 Registries not recording maternal illness were excluded from this analysis. In Norway, data were limited to maternal pregestational diabetes, asthma, epilepsy and pre-eclampsia so data from this registry were excluded from all other maternal illness analyses. See Supporting Figure 1 for the number of fetuses involved at each stage.

## Literature review to identify signals

A literature review was conducted to identify all first trimester medication exposures or maternal illnesses that were previously reported to be associated with gastroschisis. Medline, Embase and PubMed were searched, with no date or language limits. The search, detailed in Supporting Appendix 1 and Supporting Figures 2 and 3, was last updated on the 13/11/2015. Supporting Tables 1 and 2 report the positive associations, or signals, identified by individual studies.

Seventeen case-control studies and one cohort study reported associations between gastroschisis and 20 medications/medication groups. Seven case-control and 2 cohort studies reported associations between gastroschisis and 19 maternal illnesses/groups of illnesses. A number of reported associations were not explored due to insufficient exposures in the dataset.

## Statistical analysis

All analyses were conducted in Stata/SE 12.1 (StataCorp LP, USA). Prevalence rates, per 10,000 births were calculated as the (number of cases (Live Births + Still Births + TOPFA)/the number of births (Live Births + Still Births)) x 10,000.

Odds Ratios (ORs) were calculated for each of the medication exposure and maternal illness signals described in the literature where there were at least 3 observed, or 3 expected, gastroschisis cases in the EUROmediCAT database. If the signal was at the higher level, component groups were considered ‘signal components’ and are indicated as such in the tables e.g. depression was considered a component of the ‘any mental disorder’ signal. In addition, all medication exposures at the 5th and 4th ATC level and maternal illness, before or during pregnancy, with at least 3 observed, or 3 expected, gastroschisis cases were included in an exploratory signal generating analysis. If the same number of gastroschisis cases were exposed at the 4th and 5th level, the 4th level exposure was not investigated.

Logistic regression was used to calculate crude and adjusted ORs, and 95% CIs, for each exposure. Adjustment was made for maternal age group (<20, 20-24, 25-29 and 30+), registry and time period (1995-2000, 2001-2006 and 2007-2012). Likelihood ratio tests were used to assess interactions between maternal age and exposure variables.

For the medication exposures, sensitivity analyses were conducted 1) excluding those with pregestational or gestational diabetes, antidiabetic or anti-epileptic medication 2) excluding those whose medication exposure status was ‘unknown’ 3) excluding those not exposed to any medication (vitamin/mineral were not considered medications).

If a medication or maternal illness was known to be associated with a congenital anomaly subgroup included among the controls, a sensitivity analysis was conducted excluding the relevant congenital anomaly subgroup from the controls.

In recognition of the potential for multiple testing to generate significant results by chance, the need to avoid overreliance on significance testing23,24 and the low power of analyses of rare exposures, we pre-specified criteria for interpretation of the results. We considered a signal from the literature to be ‘supported’ if the aOR ≥1.5 and the CI excluded 1. If the aOR was ≥1.5 and the CIs did not exclude 1 the signal was ‘weakly supported’. New signals generated in the exploratory analysis were only considered if the aOR was ≥1.5 with CI excluding 1. Where the lower 95% CI of a new signal was not ≥1.5, generated signals were considered weak. We did not consider aORs <1.5 for signal evaluation or generation due to the small number of gastroschisis cases and the greater potential for confounding.

All medication and maternal illness exposures found to be associated with gastroschisis were validated by confirming the gastroschisis diagnosis, medication/illness exposure and timing of the exposure with the registries. The ratio of gastroschisis cases isolated/potentially multiply malformed was explored for associations with 10 or more exposures to identify any large disproportion.

## Ethics

Ethical approval was provided by the University of Ulster Nursing Research Governance Filter Committee.

# Results

Gastroschisis population

Excluding those with chromosomal/monogenic syndromes there were 1,587 gastroschisis cases across the 18 EUROmediCAT registries (1995-2012), for a total prevalence of 2.0 [95% CI 1.9, 2.1] gastroschisis cases per 10,000 births. The prevalence of gastroschisis varied across the registries (Table 1).

After exclusions, 1,577 gastroschisis cases, 83.0% of which were isolated, were compared to 153,357 non-chromosomal/monogenic controls. Of the gastroschisis cases 85% were live births, 4% stillbirths and 11% TOPFAs. 69% of cases were prenatally diagnosed (including TOPFA). Excluding TOPFAs 60% of cases were preterm (<37 gestational weeks) and 63% low birthweight (<2500g). Adjusting for registry and time period, cases were more likely to have been born to young mothers [<20, aOR 5.76, 95% CI 4.93, 6.72; 20-24, aOR 2.76, 95% CI 2.42-3.15] and less likely to have been born to older mothers [30+, aOR 0.44, 95% CI 0.38-0.53], compared to mothers aged 25-29.

Medication exposures: Signal evaluation

The signal for antidepressants was supported (Table 2). The majority of antidepressant exposures were to selective serotonin reuptake inhibitors (SSRIs) with fluoxetine, citalopram and sertraline all associated with gastroschisis (Table 2). After excluding congenital heart disease controls due to their putative association with SSRIs,12,25 the OR was essentially unchanged (aOR 2.40, 95% CI 1.36, 4.27). Antidepressant, and SSRI exposure, were twice as prevalent among mothers 30+ years old than among those <20, but there was no evidence of an interaction between maternal age and antidepressant exposure in their effect on gastroschisis risk (Likelihood-ratio test χ2 (3df) 2.77, P=0.43) or between maternal age and SSRI exposure (Likelihood-ratio test χ2 (3df) 1.58, P=0.66).

The signal for oral contraceptives was supported (Table 2) with 8 of the 10 gastroschisis cases exposed to the combined oral contraceptive levonorgestrel and ethinylestradiol. Exposure to an oral contraceptive was twice as prevalent among mothers <20 than among those 30+, but there was no evidence of an interaction between maternal age and oral contraceptive exposure (Likelihood-ratio test χ2 (2df) 0.85, P=0.66).

The signal for topical antivirals was supported (Table 2) but there were insufficient exposures to test the antiherpetic medication signal.

Signals relating to the analgesics paracetamol, nonsteroidal anti-inflammatory drugs, diclofenac, ibuprofen, opioid analgesics and codeine combinations excluding psycholeptics were weakly supported (Table 2). There was no support for the aspirin or salicylate signals.26,27

There was no support for the signals for asthma medications, either all asthma medications, inhaled β2 agonists28, bronchodilators,29 or salbutamol and gastroschisis (Table 2). Excluding from controls anomalies previously associated with asthma medication28 produced the same results.

**Table 2. The association between Gastroschisis and medications with signals in the literature: number of exposures, number of Gastroschisis cases exposed, crude and maternal age, registry and time adjusted Odds Ratios for main and sensitivity analyses**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Exposed in dataset** | **Gastro-schisis cases exposed** | **Main Analysis** | **Sensitivity analyses** |
| **Complete dataset** | **Excluding unknown medication exposures** | **Only medication exposed** | **Excluding diabetes and Anti-Epileptic medication exposed** |
| **Crude OR** **[95% CI]** | **Adjusted OR** **[95% CI]** | **Crude OR** **[95% CI]** | **Adjusted OR** **[95% CI]** | **Crude OR** **[95% CI]** | **Adjusted OR** **[95% CI]** | **Exposed in dataset** | **Gastro-schisis exposed** | **Crude OR****[95% CI]** | **Adjusted OR** **[95% CI]** |
| Aspirin | 577 | 2 | 0.34 [0.08, 1.36] | 0.59 [0.15, 2.37] | 0.30 [0.08, 1.22] | 0.52 [0.13, 2.11] | 0.31 [0.08, 1.25] | 0.51 [0.12, 2.08] | 536 | 2 | 0.36 [0.09, 1.45] | 0.62 [0.15, 2.48] |
| Aspirin or Ibuprofen | 825 | 6 | 0.72 [0.32, 1.60] | 1.00 [0.44, 2.25] | 0.64 [0.29, 1.44] | 0.91 [0.40, 2.05] | 0.66 [0.29, 1.48] | 0.86 [0.37, 1.95] | 775 | 6 | 0.75 [0.34, 1.68] | 1.03 [0.46, 2.31] |
| Ibuprofen | 249 | 4 | 1.60 [0.60, 4.30] | 1.54 [0.56, 4.20] | 1.44 [0.53, 3.87] | 1.44 [0.53, 3.96] | 1.49 [0.55, 4.05] | 1.30 [0.47, 3.60] | 240 | 4 | 1.64 [0.61, 4.40] | 1.55 [0.57, 4.24] |
| NSAIDs | 595 | 10 | 1.68 [0.90, 3.14] | 1.81 [0.95, 3.43] | 1.51 [0.80, 2.83] | 1.71 [0.89, 3.27] | 1.58 [0.83, 3.00] | 1.56 [0.81, 3.02] | 573 | 10 | 1.72 [0.92, 3.22] | 1.84 [0.97, 3.49] |
| Diclofenaca | 150 | 4 | 2.69 [0.99, 7.27] | 2.70 [0.98, 7.45] | 2.41 [0.89, 6.53] | 2.77 [1.00, 7.72] | 2.52 [0.92, 6.86] | 2.46 [0.87, 6.92] | 143 | 4 | 2.78 [1.03, 7.53] | 2.74 [0.99, 7.57] |
| Salicylates | 626 | 3 | 0.47 [0.15, 1.46] | 0.77 [0.25, 2.42] | 0.42 [0.14, 1.31] | 0.69 [0.22, 2.17] | 0.43 [0.14, 1.35] | 0.60 [0.19, 1.92] | 585 | 3 | 0.50 [0.16, 1.55] | 0.80 [0.26, 2.51] |
| Paracetamol | 1,064 | 15 | 1.40 [0.84, 2.34] | 1.66 [0.99, 2.81] | 1.26 [0.75, 2.11] | 1.43 [0.84, 2.42] | 1.32 [0.78, 2.24] | 1.27 [0.73, 2.19] | 1,038 | 15 | 1.42 [0.85, 2.37] | 1.69 [1.00, 2.85] |
| Opioid analgesics | 292 | 7 | 2.76 [1.36, 5.58] | 1.98 [0.97, 4.07] | 2.48 [1.22, 5.03] | 1.77 [0.86, 3.68] | 2.61 [1.28, 5.35] | 1.56 [0.74, 3.28] | 280 | 8 | 2.85 [1.41, 5.76] | 2.05 [1.00, 4.22] |
| Codeine, combinations excluding psycholepticsa | 181 | 5 | 2.79 [1.14, 6.79] | 1.84 [0.74, 4.57] | 2.51 [1.03, 6.11] | 1.68 [0.67, 4.21] | 2.62 [1.07, 6.44] | 1.47 [0.58, 3.72] | 174 | 5 | 2.86 [1.17, 6.97] | 1.93 [0.78, 4.78] |
| Anti-depressants | 777 | 16 | 2.07 [1.26, 3.41] | 2.03 [1.22, 3.38] | 1.86 [1.13, 3.07] | 1.73 [1.04, 2.90] | 1.99 [1.19, 3.32] | 1.64 [0.96, 2.81] | 709 | 16 | 2.24 [1.36, 3.69] | 2.14 [1.28, 3.56] |
| SSRIsa | 506 | 13 | 2.60 [1.49, 4.51] | 2.45 [1.39, 4.33] | 2.34 [1.34, 4.07] | 2.12 [1.20, 3.75] | 2.49 [1.41, 4.39] | 2.03 [1.12, 3.68] | 471 | 13 | 2.75 [1.58, 4.79] | 2.55 [1.44, 4.49] |
| Fluoxetinea | 113 | 4 | 3.60 [1.33, 9.78] | 3.03 [1.09, 8.45] | 3.24 [1.19, 8.80] | 2.53 [0.90, 7.08] | 3.38 [1.23, 9.25] | 2.20 [0.77, 6.25] | 104 | 4 | 3.87 [1.42, 10.52] | 3.15 [1.13, 8.79] |
| Citaloprama | 144 | 5 | 3.53 [1.44, 8.63] | 3.06 [1.23, 7.61] | 3.17 [1.30, 7.77] | 2.44 [0.97, 6.10] | 3.32 [1.35, 8.20] | 2.29 [0.89, 5.88] | 136 | 5 | 3.69 [1.51, 9.03] | 3.11 [1.25, 7.74] |
| Sertralinea | 74 | 3 | 4.14 [1.30, 13.17] | 4.19 [1.27, 13.76] | 3.72 [1.17, 11.84] | 3.74 [1.14, 12.31] | 3.88 [1.21, 12.42] | 3.86 [1.15, 12.94] | 68 | 3 | 4.46 [1.40, 14.21] | 4.35 [1.32, 14.33] |
| Topical antiviralsa | 82 | 3 | 3.72 [1.17, 11.81] | 5.31 [1.63, 17.33] | 3.35 [1.05, 10.62] | 5.47 [1.65, 18.15] | 3.49 [1.09, 11.13] | 5.13 [1.53, 17.22] | 79 | 3 | 3.81 [1.20, 12.10] | 5.40 [1.65, 17.64] |
| All Asthma Medications | 1,455 | 23 | 1.58 [1.04, 2.40] | 1.30 [0.85, 1.99] | 1.42 [0.94, 2.16] | 1.10 [0.71, 1.69] | 1.52 [0.98, 2.35] | 0.93 [0.58, 1.48] | 1,385 | 23 | 1.64 [1.08, 2.48] | 1.35 [0.88, 2.06] |
| Inhaled β2 agonists | 888 | 16 | 1.81 [1.10, 2.97] | 1.29 [0.77, 2.14] | 1.62 [0.99, 2.68] | 1.08 [0.65, 1.80] | 1.72 [1.03, 2.88] | 0.90 [0.52, 1.55] | 844 | 16 | 1.87 [1.14, 3.08] | 1.33 [0.80, 2.21] |
| Bronchodilatorsb | 820 | 16 | 1.96 [1.19, 3.22] | 1.44 [0.87, 2.40] | 1.76 [1.07, 2.91] | 1.21 [0.72, 2.02] | 1.88 [1.12, 3.14] | 1.01 [0.58, 1.75] | 776 | 16 | 2.04 [1.24, 3.36] | 1.50 [0.90, 2.49] |
| Salbutamola | 782 | 14 | 1.79 [1.05, 3.05] | 1.29 [0.75, 2.21] | 1.61 [0.95, 2.75] | 1.07 [0.62, 1.84] | 1.70 [0.99, 2.94] | 0.88 [0.49, 1.57] | 740 | 14 | 1.87 [1.10, 3.18] | 1.33 [0.78, 2.30] |
| Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergicsa | 214 | 3 | 1.39 [0.45, 4.36] | 1.35 [0.43, 4.30] | 1.25 [0.40, 3.92] | 1.23 [0.39, 3.95] | 1.30 [0.41, 4.08] | 1.11 [0.34, 3.61] | 207 | 3 | 1.42 [0.45, 4.44] | 1.36 [0.43, 4.34] |
| Glucocorticoidsa | 530 | 4 | 0.74 [0.28, 1.99] | 0.69 [0.26, 1.87] | 0.67 [0.25, 1.79] | 0.57 [0.21, 1.55] | 0.68 [0.25, 1.85] | 0.49 [0.18, 1.34] | 505 | 4 |  |  |
| Beclometasonea | 296 | 1 | 0.33 [0.05, 2.36] | 0.30 [0.04, 2.17] | 0.30 [0.04, 2.12] | 0.24 [0.03, 1.73] | 0.30 [0.04, 2.18] | 0.20 [0.03, 1.46] | 283 | 1 | 0.34 [0.05, 2.44] | 0.32 [0.04, 2.27] |
| Oral Contraceptives | 363 | 10 | 2.79 [1.48, 5.23] | 2.17 [1.13, 4.18] | 2.51 [1.33, 4.72] | 2.24 [1.15, 4.37] | 2.65 [1.39, 5.05] | 2.08 [1.05, 4.12] | 348 | 10 | 2.87 [1.53, 5.39] | 2.25 [1.17, 4.33] |
| Progestogens and estrogens, fixed combinationsa | 270 | 8 | 3.00 [1.48, 6.08] | 2.22 [1.07, 4.60] | 2.70 [1.33, 5.47] | 2.20 [1.05, 4.62] | 2.85 [1.39, 5.83] | 2.02 [0.95, 4.29] | 261 | 8 | 3.06 [1.51, 6.20] | 2.29 [1.10, 4.74] |
| Levonorgestrel and Ethinylestradiola | 163 | 8 | 5.08 [2.49, 10.35] | 4.02 [1.90, 8.50] | 4.57 [2.24, 9.33] | 4.07 [1.90, 8.72] | 4.84 [2.34, 9.98] | 3.71 [1.70, 8.12] | 161 | 8 | 5.07 [2.48, 10.33] | 4.06 [1.92, 8.60] |

It was not possible to test a number of signal medications due to insufficient numbers of exposed gastroschisis cases [n]: dihydrocodeine [n=0], paroxetine [n=0], venlafaxine [n=1], antiherpetics [n=2], diphenhydramine [n=0], phenylpropanolamine [n=0], pseudoephedrine [n=0], oral decongestants [n=0].

a Medication or medication group which is a component of a medication signal and had more than 3, or 3 expected, exposures at the 4th or 5th ATC level

b Salbutamol, salmeterol, pirbuterol, ipratropium bromide, ephedrine, epinephrine, theophylline

Maternal Illness: Signal Evaluation

Cases were less likely than controls to have had maternal exposure to ‘any (pregestational or gestational) diabetes’ and pregestational diabetes (Table 3 and Supporting Table 4). Excluding from controls anomalies previously associated with diabetes30 somewhat decreased the size of the negative association [aOR 0.41, 95% CI 0.17, 0.99 and aOR 0.20, 95% CI 0.03, 1.45 respectively].

There was weak support for an association with ‘any mental disorder’, depression and ‘mental and behavioral disorders associated with the puerperium’ (Table 3). Half of the gastroschisis cases with depression and a third of those with ‘mental and behavioral disorders associated with the puerperium’ were exposed to an antidepressant in the first trimester. The prevalence of these mental disorders varied little across maternal age groups.

Signals for sexually transmitted infections (STIs) excluding and including yeast/vaginal infections were supported but there was no evidence for an association with urinary tract infection.13,31 STIs including yeast/vaginal infections were six times as prevalent among mothers <20 than among mothers 30+ but there was no evidence of an interaction (Likelihood-ratio test χ2 (2df) 2.97, P=0.23). The STI diagnosis includes genital herpes but there were not enough exposures to genital herpes to explore this exposure directly.

**Table 3. The association between Gastroschisis and maternal illness: ICD 9 and ICD 10 code/s, number of exposures in the dataset, number of Gastroschisis cases exposed, crude and adjusted ORs**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Maternal illness signal** | **ICD-9** | **ICD-10** | **Exposures in dataset** | **Gastroschisis cases exposed** | **Crude OR [95% Confidence Interval]** | **Adjusteda OR [95% Confidence Interval]** |
| Any (pregestational or gestational) diabetes | 250, 648.0, 648.8 | E10-14, O24 | 2378 | 5 | 0.22 [0.09, 0.52] | 0.31 [0.13, 0.75] |
| Pregestational diabetesbc | 250 | E10-14 | 882 | 1 | 0.11 [0.02, 0.82] | 0.13 [0.02, 0.92] |
| Gestational diabetes c  | 648.8 | O244 | 1150 | 4 | 0.36 [0.14, 0.97] | 0.65 [0.24, 1.76] |
| Any mental disorder (psychoses, neurotic disorders, personality disorders, other nonpsychotic mental disorders, and mental retardation) | 290-9, 300-3, 305-9,310-9 | F00-F99 | 1113 | 20 | 1.94 [1.24, 3.04] | 1.55 [0.98, 2.44] |
| Depressionc | 300.4, 311 | F32-3 | 559 | 13 | 2.52 [1.45, 4.39] | 2.52 [1.45, 4.39] |
| Mental and behavioral disorders associated with the puerperium, not elsewhere classified (postnatal/postpartum depression and puerperal psychosis)c  | d | F53 | 41 | 3 | 8.32 [2.56, 27.01] | 8.32 [2.56, 27.01] |
| Urinary tract infection (UTI) | 646.6 | O23 | 1211 | 13 | 1.14 [0.66, 1.98] | 0.95 [0.54, 1.66] |
| Sexually transmitted infections (STIs) | 090-097, 054.1, 131, 647.0-2 | A50-A64, O98.1-3, M02.3 | 86 | 5 | 6.52 [2.64, 16.13] | 2.85 [1.13, 7.24] |
| STIs including yeast/vaginal infections (vaginal candida)  | 090-097, 054.1, 131, 647.0-2, 112.1 | A50-A64, O98.1-3, M02.3, B37.3 | 150 | 6 | 4.40 [1.94, 9.99] | 2.52 [1.09, 5.85] |
| UTI or STIs | 646.6, 090-097, 054.1, 131, 647.0-2 | O23, A50-A64, O98.1-3, M02.3 | 1298 | 18 | 1.49 [0.93, 2.38] | 1.17 [0.73, 1.89] |
| UTI or STIs including yeast/vaginal infections | 646.6, 090-097, 054.1, 131, 647.0-2, 112.1 | O23, A50-A64, O98.1-3, M02.3, B37.3 | 1355 | 18 | 1.42 [0.89, 2.28] | 1.13 [0.70, 1.83] |
| a Adjusted for maternal age, registry and time period.b Analysis includes data from Norway registry.c Illness which is a component of an illness signal.d ICD-9 and ICD-10 codes not comparable for this diagnosis so analysis was restricted to the ICD-9/10 code which produced the original signal. |

Medication and maternal illness: Exploratory analyses

Thirty-nine non-signal ATC codes were tested for an association with gastroschisis in the exploratory analysis (Supporting Table 3). There were signals for vitamin E [aOR 5.74, 95% CI 1.68, 19.59, n=3] and bromhexine [aOR 29.48, 95% CI 8.24, 105.50, n=3], and weak signals for hydrocortisone [aOR 3.94, 95% CI 1.19, 13.01, n=3] and drotaverine [aOR 2.31, 95% CI 1.08, 4.97, n=7]. Caution should be used when interpreting the drotaverine and vitamin E signals. The drotaverine signal was not robust in the sensitivity analysis and two of the three cases involved in the vitamin E signal were also exposed to drotaverine.

Fourteen non-signal maternal illnesses were tested for an association with gastroschisis in the exploratory analysis (Supporting Table 4). Further maternal infections were associated with gastroschisis, producing a signal for acute tonsillitis [aOR 8.40, 95% CI 2.41, 29.31, n=3] and weak signals for ‘acute upper respiratory infections of multiple or unspecified sites’ [aOR 2.65, 95% CI 1.46, 4.81, n=13] and ‘bacterial infection of unspecified site’ [aOR 3.56, 95% CI 1.06, 11.98, n=3]. There were also weak signals for hemorrhage in early pregnancy [aOR 1.52, 95% CI 1.01, 2.31, n=27] and ‘gastritis and duodenitis’ [aOR 3.12, 95% CI 1.11, 8.75, n=4].

 There was no disproportion in the ratio of isolated to potentially multiply malformed gastroschisis cases for any of the medication or maternal illness signals with more than 10 exposed cases.

# Comments

Gastroschisis is a rare anomaly, occurring on average in one in every 5,000 births in Europe. We have added to a growing evidence base that the maternofetal environment is important in the causation of gastroschisis, specifically in respect to maternal illness and medication, pointing to the need for greater understanding of causal pathways. Among teenage mothers, one in every 870 births was affected by gastroschisis, either due to their greater vulnerability to, or more frequent exposure to these and other unmeasured factors acting singly or in combination.

Mental illness is common among women of reproductive age with an estimated 7-11% of pregnant women affected by depression in their first trimester.32 Antidepressants are also increasingly being used during pregnancy, with SSRIs the most frequently prescribed.33,34 Our study confirmed that first trimester exposure to antidepressants, specifically SSRIs,12,25 and mental disorders,31 including depression, were associated with gastroschisis. As antidepressant use is more prevalent among older mothers this relationship is contrary to the known association between gastroschisis and young maternal age. A recent multi-country population based cohort study found a low and non-significant OR for SSRIs, particularly with sibling controls,35 but was much smaller and did not include stillbirths and TOPFAs. We could not effectively control for confounding by indication due to incomplete ascertainment of both medication and illness exposures. We had no information on lifestyle factors, such as smoking,9 alcohol consumption10 or illicit drug use11 which could confound the association with mental health. Whatever the causal pathway, mothers with depression should be considered a high-risk group for gastroschisis.

First trimester exposure to oral contraceptives, mainly levonorgestrel and ethinylestradiol, was confirmed to be associated with gastroschisis.36 Estrogen related thrombosis has been proposed as one of the pathogenic mechanisms behind gastroschisis.37 High estrogen levels are typical for young women in the early gestational stages when anomalies develop6 and this hormonal mechanism may contribute to the high risk for young women. Alternatively, oral contraceptive exposure may be acting as a marker for an unplanned pregnancy with a suboptimal periconceptional environment.

Infections repeatedly showed associations with gastroschisis in our data, adding to the existing literature.13,31,38 Maternal STI was associated with a 2½-3 times increased risk of gastroschisis. Further supporting evidence is provided by studies which found biological markers of recent chlamydia infection39 and reactivation of previous herpes simplex virus type 2 infection40 to be associated with gastroschisis. STIs may be one of the factors explaining the high risk of gastroschisis in young mothers. Both a direct effect and indirect effect of STI exposure, through immune and inflammatory responses, have been suggested.13,39 While the association found for topical antivirals may be confounded by indication there is also the potential for medications used in the treatment of STIs to be contributing to the increased risk of gastroschisis. Interestingly, we found no supporting evidence for an association with urinary tract infections, contrary to some other studies.13,31 There was new evidence in our data relating to acute tonsillitis and to a lesser degree respiratory infections, bacterial infections, and gastritis/duodenitis (which can be caused by helicobacter pylori infection). Maternal infection as indication may have confounded the signals we found for bromhexine, an expectorant, and drotaverine, an antispasmodic.

A number of analgesics were weakly associated with gastroschisis. We found weak evidence to support the signal for paracetamol and there is contradictory evidence relating to this association in the literature.10,26,41 While we found a weak association with nonsteroidal anti-inflammatory drugs generally, and ibuprofen and diclofenac specifically, both our study and another recent study42 found no evidence to support the signals previously published for aspirin or salicylates.26,43 There is known under ascertainment for over the counter medications in the EUROmediCAT database17 and this will have reduced our power to detect an increased risk associated with these analgesics. If these analgesics were used during maternal infections, there is again the potential for confounding by indication.

Pregestational diabetes is a strong risk factor for a range of anomalies.30 The signal for an increased risk of gastroschisis in those with (pregestational or gestational) diabetes arose in a study with unreliable diabetes ascertainment.44 We found no evidence for an increased risk of gastroschisis among those with either any (pregestational or gestational) diabetes or pregestational diabetes. Instead, in agreement with another study which was able to control for maternal body mass index,31 we found evidence for a protective effect of diabetes. While the magnitude of the effect decreased, it persisted after correcting for the fact that our malformed controls contained anomalies associated with pregestational diabetes. Further evidence to support this apparent protective effect should be sought but it does fit with the known negative association between gastroschisis and high maternal body mass index.45

No association was found between asthma medications, either all asthma medications, inhaled β2 agonists or bronchodilators, and gastroschisis. This signal arose in a study of bronchodilators,29 but previous evidence from EUROmediCAT data has been inconsistent.28,46

In a previous study,5 we established that the geographical variation within Europe persisted independently of maternal age differences between populations. We have shown here that many of the exposures conferring risk are more common among young mothers. Our ability to shed light on the extent to which maternal illness or medication contribute to maternal age and geographic variation in prevalence is limited due to incomplete ascertainment of both these exposures in cases and controls, and variation in ascertainment between registries.

## Strengths and weaknesses

EUROmediCAT’s international population based database covers a very large population suitable for studying a rare condition such as gastroschisis, contains detailed coding of all congenital anomalies16 and includes TOPFA which constituted more than 11% of gastroschisis cases and 5% of controls. The data are standardized across the registries, although registers differ in their exposure ascertainment methodology.16 Gastroschisis cases identified prenatally were confirmed after live/stillbirth. Practice following TOPFA varies but usually either an external or full post-mortem take place. Less than 1% of gastroschisis cases occurred in very early TOPFA (before 13 gestational weeks) where diagnostic accuracy may be less certain. Although the distinction between gastroschisis and omphalocele was a concern in early studies4 the data analysed here started in 1995 when diagnostic accuracy was good. Use of the BPA extension to ICD-9 ensured that gastroschisis and omphalocele were recorded separately and we excluded all of those with poorly specified abdominal wall diagnoses from both cases and controls.

There is no information on confounders such as smoking or alcohol, and limited ability to control for confounding by indication. It was therefore not possible to disentangle the relative contributions of maternal ill health and the medications used in its treatment. As maternal illness during pregnancy is recorded up to the 20th gestational week acute illnesses, such as infections, may have occurred outside the first trimester, in both cases and controls. This will be less of a concern for chronic illnesses such as depression.

Teratogen non-specificity bias, where the exposure in question is associated with both cases and controls, may have diluted ORs20. However, when the control group was restricted to address this issue the ORs changed very little suggesting that the wide variety of anomalies within our control group negated this problem.

There is known under ascertainment of medication exposure in the EUROmediCAT database, particularly for over the counter medications.17,47 This will have reduced the power of our analysis but should not have introduced bias as cases and controls had equal probability of having their exposure recorded.20

Due to multiple testing of many exposures, some chance positive associations are likely, but we found more positive associations than expected by chance. We mitigated this by clearly specifying our prior hypotheses, to be tested as signals from the literature, examining patterns of exposures (e.g. mental health or infection related) and pre-specifying criteria for interpretation of the strength of the evidence.

## Conclusion

Our study adds strong evidence that antidepressants and/or mental health disorders, a variety of maternal infections, particularly STIs, and continuation of oral contraceptives in early pregnancy are associated with gastroschisis. Better understanding of these risk factors, in particular the complex of risk factors more prevalent among young mothers, who are at higher risk of gastroschisis, should help target supportive services reducing the prevalence of gastroschisis and improving maternal and fetal health more generally.

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**Supporting Information**

## **Supporting Appendix 1. Literature Review to Identify ‘Signals’ to be Tested.**

Medline, Embase and PubMed were searched, with no date or language limits. For medication exposures the search term ‘gastroschisis’ was combined with ‘drug’, ‘medication’, ‘drug exposure’, ‘drug use’ or ‘prenatal drug exposure’. For maternal illnesses ‘gastroschisis’ was combined with ‘disease’, ‘acute disease’, ‘chronic disease’, ‘maternal disease’, ‘diseases’, ‘maternal illness’, ‘acute illness’ or ‘chronic illness’. The search was last updated on the 13/11/2015. Only full text articles of original studies exploring the risk of gastroschisis in humans were included. Where “drug” referred to illicit drugs, the information has not been used in this paper.

## **Supporting Table 1. Medications associated with gastroschisis in the literature, crude, and adjusted ORs and study details**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medication group** | **Medication/s** | **Exposed cases** | **Crude OR [95% Confidence Intervals]** | **Adjusted OR [95% Confidence Intervals]** | **Article** | **Country** | **Study** | **Years** | **Design** | **Maternal age adjustment** |
| Analgesics | Aspirin | 13 |  | 2.7a [1.2, 5.9] | Werler et al. 2002 1 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1995-1999 | Matched case-control (malformed and non-malformed) | Matched on maternal age |
| 7 |  | 20.4b [2.2, 191.5] | Draper et al. 2008 2 | UK | Trent, Northern, and West Midlands Regional Congenital Anomaly Registers | 2001-2003 | Matched case-control | Matched on maternal age |
| 7 | 4.7 [1.2, 18.1] |  | Torfs et al. 1996 3 | USA | California Birth Defects Monitoring Program | 1989-1990 | Matched case-control | Matched on maternal age |
| Aspirin or ibuprofen | 13 | 5.2 [1.9, 14.6] | 4.6c [1.4, 14.7] |
| Ibuprofen | 6 | 4.0 [1.0, 16.0] |  |
|  |  | 1.6d [1.2, 2.1] | Mac Bird et al. 2009 4 | USA | National Birth Defects Prevention Study | 1997-2003 | Case-control | Yes |
| NSAIDs | 151 |  | 1.4e [1.1, 1.7] | Werler et al. 2009 5 | USA | National Birth Defects Prevention Study | 1997-2003 | Matched case-control | Matched on maternal age |
| Salicylates | 5 | 3.3 [1.1, 9.8] | 3.5f No CI provided | Martínez-Frías et al. 1997 6 | Spain | Spanish Collaborative Study of Congenital Malformations | 1976-1996 | Case-Control | Yes |
| Paracetamol | 120 |  | 1.5)a [1.1, 2.2] | Werler et al. 2002 1 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1995-1999 | Matched case-control (malformed and non-malformed) | Matched on maternal age |
| Opioid analgesics | 26 |  | 1.8g [1.1, 2.9] | Broussard et al. 2011 7 | USA | National Birth Defects Prevention Study | 1997-2005 | Case-control | Yes |
| Dihydrocodeine | 15 | 3.3 [1.8, 6.1] |  |
| Anti-depressants | Antidepressants | 22 | 4.7 [2.6, 8.3] | 4.0h [1.4, 11.8] | Skarsgard et al. 2015 8 | Canada | Canadian Pediatric Surgery Network/ Canadian Community Health Survey | 2006-2012 | Cohort | Yes |
| The Paroxetine | 5 |  | 2.9i [1.0, 8.4] | Alwan et al. 2007 9 | USA | National Birth Defects Prevention Study | 1997-2002 | Case-Control | No |
| 13 |  | 2.5j [1.2, 4.8] | Reefhuis et al. 2015 10 | USA | National Birth Defects Prevention Study | 1997-2009 | Case-control | No |
| Venlafaxine | 6 | 3.8 [1.2, 10.5] | 5.7k [1.8, 15.9] | Polen et al. 2013 11 | USA | National Birth Defects Prevention Study | 1997-2007 | Case-control | Yes |
| Anti-herpetics | Antiherpetics (aciclovir, valaciclovir or famciclovir) | 4 | 3.6 [1.1, 11.5] | 4.7l [1.2, 19.0] | Ahrens et al. 2013 12 | USA | National Birth Defects Prevention Study | 1997-2007 | Case-control | Yes |
| Anti-histamines | Diphenhydramine | 16 |  | 2.0m [1.0, 3.9] | Gilboa et al. 2009 13 | USA | National Birth Defects Prevention Study | 1997-2003 | Case-control | Yes |
| Asthma medication | Any asthma medicationuv | 22 |  | 1.6o [1.0, 2.5] | Garne et al. 2015 14 | Europe | EUROmediCAT | 1995-2010 | Case- malformed control | Yes |
| Inhaled β2 agonistsv | 19 |  | 1.9p [1.1, 3.2] |
| Bronchodilators (Salbutamol, salmeterol, pirbuterol, ipratropium bromide, ephedrine, epinephrine, theophyline) | 17 | 1.9 [1.1, 3.3] | 2.1q [1.2, 3.6] | Lin et al. 2008 15 | USA | National Birth Defects Prevention Study | 1997-2002 | Case-control | Yes |
| Contracep-tives | Oral contraceptives | 40 |  | 1.8r [1.3, 2.7] | Waller et al. 2010 16 | USA | National Birth Defects Prevention Study | 1997-2003 | Case-control | Yes |
| Deconges-tants | Phenylpropan-olamine | 5 | 10.0 [1.2, 85.6] |  | Torfs et al. 1996 3 | USA | California Birth Defects Monitoring Program | 1989-1990 | Matched case-control | Matched on maternal age |
| Pseudoephedrine | 9 |  | Relative risk 3.2s [1.3, 7.7] | Werler et al. 1992 17 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1976-1990 | Case- malformed control | Yes |
| 35 |  | 1.8a [1.0, 3.2] | Werler et al. 2002 1 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1995-1999 | Matched case-control (malformed and non-malformed) | Matched on maternal age |
| Oral decongestants (pseudoephedrine, phenylephrine and phenylpropan-olamine) | 20 |  | 1.7t [1.0, 2.9] | Yau et al. 2013 18 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1993-2010 | Case-control | Yes |

1. Adjusted for education, income, medication use, illness, illicit drug use, and cigarette smoking. Control group consisted of both malformed and non-malformed infants
2. Adjusted for use of any recreational drug, use of a vasoactive recreational drug, BMI, marital status, homeowner status, history of gynaecologic infection/disease and cigarette smoking.
3. Adjusted for smoking status, prenatal care, mothers father absent during youth, family income and exposure to solvents, decongestants, x-rays and ‘cocaine and other drugs’.
4. Adjusted for race/ethnicity, plurality, family income, parity, maternal age, fever, infant sex, any maternal drinking, maternal smoking, maternal BMI, gestational diabetes, pre-existing diabetes, folic acid supplementation, study centre and exposure to pseudoephedrine, aspirin, paracetamol, naproxen, marijuana, and cocaine
5. Adjusted for maternal age at delivery and state of residence by stratification and for race/ethnicity, BMI, education, alcohol use, oral contraceptive use, folic acid supplementation
6. Adjusted for maternal age and smoking status
7. Adjusted for maternal age, race/ethnicity, education, presence or absence of pre-pregnancy obesity, presence or absence of periconceptional smoking, and study centre
8. Adjusted for area, maternal age, alcohol, tobacco, illicit drug use, pregestational/gestational diabetes and folic acid
9. Adjusted for maternal race or ethnic group, maternal obesity, maternal smoking and family income. Infants whose mothers had pregestational diabetes mellitus type 1 or 2 were excluded
10. Adjusted for maternal race/ethnicity, maternal education, obesity, and smoking
11. Adjusted for maternal age and race/ethnicity
12. Adjusted for maternal age at delivery and BMI before conception
13. Adjusted for maternal age, maternal race or ethnicity, maternal education, entry into prenatal care, parity, household income, and study centre, periconceptional folic acid use, smoking, and alcohol intake
14. Includes all medications starting with the ATC code R03. Note this dataset overlaps to some extent with that used in this study
15. Adjusted for registry and maternal age
16. Adjusted for registry, maternal age and use of corticosteroids
17. Adjusted for maternal age, ethnicity, educational level, smoking, folic acid, and any of the following vasoactive medications: aspirin, ibuprofen, acetaminophen, amoxicillin, pseudoephedrine, phenylpropanolamine, and methylenedioxymethamphetamine
18. Adjusted for maternal age
19. Adjusted for maternal age, years of education, parity, alcohol consumption, influenza in the first trimester, interview year, study centre and exposure to salicylates, paracetamol, ibuprofen, phenylpropanolamine, other oral decongestants, other nasal/ophthalmic decongestants, antihistamines, antibiotics and oral contraceptives
20. Adjusted for maternal age, pre-pregnancy weight, educational level, and smoking
21. Includes all medications starting with the ATC code R03
22. Note this dataset overlaps to some extent with that used in this study

## **Supporting Table 2. Maternal illnesses associated with gastroschisis in the literature, crude, and adjusted ORs and study details**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Maternal illness**  | **Maternal disease** | **Exposed cases** | **Crude OR [95% Confidence Intervals]** | **Adjusted OR [95% Confidence Intervals]** | **Article** | **Country**  | **Study** | **Years** | **Design** | **Maternal age adjustment** |
| Low BMI | Low BMIa (<18.1) | 16 | 3.16 [1.38, 7.26] | 3.20b [1.38, 7.42] | Lam et al. 1999 19 | USA | California Birth Defects Monitoring Programme | 1988-1990 | Matched case-control | Matched on maternal age |
| Diabetes | Any (pregestational or gestational) diabetes | 19 | 2.34 [1.39, 3.98] | 2.81c [1.42, 5.57] | Skarsgard et al. 2015 8 | Canada | Canadian Pediatric Surgery Network/ Canadian Community Health Survey | 2006-2012 | Cohort | Yes |
| Other endocrine disorders | ‘Other endocrine disorder’ (pancreatic, parathyroid, pituitary, thymus, adrenal, ovarian, polyglandular, and other endocrine dysfunction.) | 6 | 1.5 [0.7, 3.4] | 3.2 for those 20-24d [1.2, 8.5] | Baer et al. 2015 20 | USA | California Office of Statewide Health Planning and Development Livebirth Cohort | 2005-2010 | Cohort study | Stratified by age group |
| Mental disorder | Mental disorder (psychoses, neurotic disorders, personality disorders, other nonpsychotic mental disorders, and mental retardation) | 75 | 1.8 [1.4, 2.3] | 2.1 for those >24e [1.4, 3.2] | Baer et al. 2015 20 | USA | California Office of Statewide Health Planning and Development Livebirth Cohort | 2005-2010 | Cohort study | Stratified by age group |
| Previous pregnancy loss | Previous pregnancy lossa |  |  | 2.34f (malformed controls) [1.37, 3.97]3.43 (non-malformed controls) [2.07, 5.66] | Rittler et al. 2015 21 | South America | Estudio Colaborativo Latino Americano de Malformaciones Congenitas | 1995-2010 | Case-controlp  | Only those <20 included in study |
| Infection | Chest cold | 5 | 16.8 [1.98, 150.3] |  | Elliott et al. 2009 22 | USA | 2 medical centres in Nevada | 2007-2008 | Matched case-control | Matched on maternal age |
| Sore throat | 5 | 12.7 [1.3, 122.5] |  |
| Viral infection ‘complicating pregnancy’ | 40 | 1.8 [1.3, 2.5] | 2.0 for those 20-24g[1.3, 3.3]2.1 for those >24h [1.3, 3.6] | Baer et al. 2015 20 | USA | California Office of Statewide Health Planning and Development Livebirth Cohort | 2005-2010 | Cohort study | Stratified by age group |
| Other specified infection complicating pregnancy (including tuberculosis, malaria, rubella, and other specified infectious and parasitic diseases) | 17 | 1.9 [1.2, 3.1] | 2.0 for those 20-24i [1.0, 3.8] | Baer et al. 2015 20 | USA | California Office of Statewide Health Planning and Development Livebirth Cohort | 2005-2010 | Cohort study | Stratified by age group |
| UTI | 60 | 1.9 [1.5, 2.6] | 1.4j [1.0, 2.0] | Feldkamp et al. 2008 23 | USA | National Birth Defects Prevention Study | 1997-2003 | Case-control | Yes |
| UTI  | 127 | 1.9 [1.6, 2.3] | 1.5 for those <20k [1.1, 1.9] | Baer et al. 2015 20 | USA | California Office of Statewide Health Planning and Development Livebirth Cohort | 2005-2010 | Cohort study | Stratified by age group |
| UTI | 33 | 3.6 [2.5, 5.4] | 2.3l [1.5, 3.5] | Yazdy et al. 2014 24 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1998-2010 | Case-control | Yes |
| Genital herpes (including those with use of Antiherpetic medication) | 6 | 3.2 [1.3, 8.1] | 4.7m [1.7, 13.3] | Ahrens et al. 2013 12 | USA | National Birth Defects Prevention Study | 1997-2007 | Case-control | Yes |
| Genital herpes (excluding those with use of Antiherpetic medication) | 16 | 2.6 [1.5, 4.6] | 3.0m [1.6, 5.7] |
| STI | 17 | 2.7 [1.7, 4.4] | 2.0 for those <20n[1.1, 3.6] | Baer et al. 2015 20 | USA | California Office of Statewide Health Planning and Development Livebirth Cohort | 2005-2010 | Cohort study | Stratified by age group |
| STI | 14 | 1.7 [1.0, 3.0] | 1.3h [0.7, 2.3] | Feldkamp et al. 2008 23 | USA | National Birth Defects Prevention Study | 1997-2003 | Case-control | Yes |
| STI including yeast/vaginal infections | 33 | 1.3 [1.1, 1.6] | 1.2j [1.0, 1.5] | Yazdy et al. 2014 24 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1998-2010 | Case-control | Yes |
| UTI or STI | 81 | 2.0 [1.6, 2.6] | 1.5h [1.1, 1.9] | Feldkamp et al. 2008 23 | USA | National Birth Defects Prevention Study | 1997-2003 | Case-control | Yes |
| UTI or STI including yeast/vaginal infections | 73 | 2.4 [1.8, 3.1] | 1.8j [1.3, 2.4] | Yazdy et al. 2014 24 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1998-2010 | Case-control | Yes |
| UTI & STI | 7 | 6.8 [2.6, 17.5] | 4.0h [1.4, 11.6] | Feldkamp et al. 2008 23 | USA | National Birth Defects Prevention Study | 1997-2003  | Case-control | Yes |
| UTI & STI including yeast/vaginal infections | 7 | 1.5 [1.1, 1.9] | 1.2j [0.9, 1.6] | Yazdy et al. 2014 24 | USA and Canada | Slone Epidemiology Center Birth Defects Study | 1998-2010 | Case-control | Yes |
| Prior history of gynaecologic infection or disease (recurrent UTI, chlamydia or abnormal smear prior to current pregnancy)a | 18 | 2.8 [1.4, 5.5] | 2.6o [1.2, 5.6] | Draper et al. 2008 2 | UK | Trent, Northern, and West Midlands Regional Congenital Anomaly Registers | 2001-2003 | Matched case-control | Matched on maternal age |

Not considered a maternal illness within the EUROCAT illness variable and therefore not analysed.

Adjusted for maternal age and ethnicity

Adjusted for area, maternal age, alcohol, tobacco, illicit drug use, depression medication and folic acid

Adjusted for race/ethnicity, type of health insurance, education, parity, mother’s country of birth, obesity, any diabetes, any gestational hypertension, viral infection and other specified infection

Adjusted for race/ethnicity, type of health insurance, education, parity, obesity, smoking, any gestational hypertension and viral infection

Adjusted for hospital, year of birth, young paternal age, maternal education, paternal education, paternal occupation, consanguinity, race/ethnicity, short inter-birth interval, change in paternity, parity, duration of cohabitation, prenatal control, medication, maternal illness, smoking, alcohol and illicit drugs

Adjusted for adjusted for race/ethnicity, type of health insurance, education, parity, mothers country of birth, obesity, any diabetes, any gestational hypertension, other specified infection and other endocrine disorder

Adjusted for race/ethnicity, type of health insurance, education, parity, obesity, smoking, any gestational hypertension and mental disorder

Adjusted for race/ethnicity, type of health insurance, education, parity, mother’s country of birth, obesity, any diabetes, any gestational hypertension, viral infection and other endocrine disorder

Adjusted for maternal age, BMI before conception, smoking, and Hispanic ethnicity

Adjusted for adjusted for race/ethnicity, obesity, smoking, any gestational hypertension, sexually transmitted infection and drug dependency

 Adjusted for maternal age

 Adjusted for maternal age at delivery and BMI before conception

Adjusted for race/ethnicity, obesity, smoking, any gestational hypertension, urinary tract infection and drug dependency

Adjusted for use of any recreational drug, use of a vasoactive recreational drug, use of aspirin, BMI, marital status, homeowner status and cigarette smoking

Malformed [omphalocele, spina bifida, hydrocephaly, cleft lip with or without cleft palate, and Down syndrome] and non-malformed controls

## **Supporting Table 3. Medication exploratory analysis results - crude and maternal age, registry and time adjusted ORs for main and sensitivity analyses**

|  |  |  |
| --- | --- | --- |
| **Medication/medication group** | **Main analysis** | **Sensitivity analyses** |
| **Complete dataset** | **Excluding unknown drug exposures** | **Only drug exposed** | **Excluding diabetes and AEDs** |
| **Exposed in dataset** | **Gastroschisis exposed** | **Crude OR [95% CI]** | **Adjusted OR [95% CI]** | **Crude OR [95% CI]** | **Adjusted OR [95% CI]** | **Crude OR [95% CI]** | **Adjusted OR [95% CI]** | **Exposed in dataset** | **Gastroschisis exposed** | **Crude OR [95% CI]** | **Adjusted OR [95% CI]** |
| Hydrocortisone | 108 | 3 | 2.8 [0.9, 8.8] | 3.9 [1.2, 13] | 2.5 [0.8, 7.9] | 4.0 [1.2, 13.2] | 2.6 [0.8, 8.4] | 2.8 [0.9, 9.2] | 104 | 3 | 2.9 [0.9, 9.1] | 4.0 [1.2, 13.1] |
| Combinations and complexes of aluminium, calcium and magnesium compounds | 339 | 1 | 0.3 [0.0, 2.1] | 0.6 [0.1, 4.6] | 0.3 [0.0, 1.9] | 0.6 [0.1, 4.0] | 0.3 [0.0, 1.9] | 0.4 [0.1, 2.7] | 329 | 1 | 0.3 [0.0, 2.1] | 0.6 [0.1, 4.6] |
| Metoclopramide | 409 | 3 | 0.7 [0.2, 2.3] | 0.6 [0.2, 2.0] | 0.7 [0.2, 2.0] | 0.7 [0.2, 2.2] | 0.7 [0.2, 2.1] | 0.6 [0.2, 2.0] | 404 | 3 | 0.7 [0.2, 2.3] | 0.7 [0.2, 2.1] |
| Drotaverine | 249 | 7 | 2.8 [1.3, 6.0] | 2.3 [1.1, 5.0] | 2.6 [1.2, 5.4] | 2.4 [1.1, 5.2] | 2.7 [1.3, 5.8] | 1.8 [0.8, 3.9] | 245 | 7 | 2.9 [1.3, 6.1] | 2.3 [1.1, 5.0] |
| Propulsives | 442 | 3 | 0.7 [0.2, 2.1] | 0.6 [0.2, 1.9] | 0.6 [0.2, 1.9] | 0.6 [0.2, 2.1] | 0.6 [0.2, 1.9] | 0.6 [0.2, 1.9] | 436 | 3 | 0.7 [0.2, 2.1] | 0.6 [0.2, 2.0] |
| Insulins and analogues for injection, fast-acting | 312 | 2 | 0.6 [0.2, 2.5] | 0.6 [0.2, 2.4] | 0.6 [0.1, 2.3] | 0.5 [0.1, 2.2] | 0.6 [0.1, 2.4] | 0.6 [0.1, 2.3] |  |  |  |  |
| Multivitamins and minerals | 1,708 | 18 | 1.0 [0.7, 1.7] | 1.0 [0.6, 1.7] | 0.9 [0.6, 1.5] | 1.0 [0.6, 1.6] |  |  | 1,685 | 18 | 1.0 [0.7, 1.7] | 1.0 [0.7, 1.7] |
| Multivitamins and other minerals, incl. combinations | 1,612 | 16 | 1.0 [0.6, 1.6] | 1.0 [0.6, 1.6] | 0.9 [0.5, 1.4] | 0.9 [0.6, 1.6] |  |  | 1,590 | 16 | 1.0 [0.6, 1.6] | 1.0 [0.6, 1.6] |
| Tocopherol (vitamin E) | 42 | 3 | 7.6 [2.3, 24.5] | 5.7 [1.7, 19.6] | 6.8 [2.1, 22] | 6.0 [1.7, 21.5] |  |  | 41 | 3 | 7.6 [2.4, 24.8] | 5.8 [1.7, 19.9] |
| Magnesium | 552 | 9 | 1.6 [0.8, 3.2] | 1.4 [0.6, 3.0] | 1.5 [0.8, 2.8] | 1.4 [0.6, 3.0] |  |  | 512 | 9 | 1.7 [0.9, 3.4] | 1.4 [0.6, 3.0] |
| Enoxaparin | 227 | 3 | 1.3 [0.4, 4.1] | 1.6 [0.5, 5.2] | 1.2 [0.4, 3.7] | 1.4 [0.4, 4.3] | 1.2 [0.4, 3.9] | 1.6 [0.5, 5.2] | 214 | 3 | 1.4 [0.4, 4.3] | 1.8 [0.6, 5.5] |
| Iron bivalent, oral preparations | 1209 | 12 | 1.0 [0.6, 1.7] | 1.1 [0.6, 2.1] | 0.9 [0.5, 1.6] | 0.9 [0.5, 1.6] |  |  | 1,172 | 12 | 1.0 [0.6, 1.8] | 1.2 [0.6, 2.1] |
| Ferrous sulphate | 834 | 11 | 1.3 [0.7, 2.4] | 1.5 [0.8, 2.7] | 1.2 [0.7, 2.1] | 1.1 [0.6, 2.0] |  |  | 808 | 11 | 1.3 [0.7, 2.4] | 1.5 [0.8, 2.8] |
| Folic acid | 9,981 | 99 | 1.0 [0.8, 1.2] | 0.9 [0.7, 1.1] | 0.9 [0.7, 1.1] | 0.9 [0.7, 1.1] |  |  | 9,800 | 97 | 1.0 [0.8, 1.2] | 0.9 [0.7, 1.1] |
| Gynecological antibiotics | 234 | 3 | 1.3 [0.4, 4.0] | 1.5 [0.5, 4.9] | 1.1 [0.4, 3.6] | 1.1 [0.3, 3.6] | 1.2 [0.4, 3.7] | 1.2 [0.4, 3.9] | 219 | 3 | 1.3 [0.4, 4.2] | 1.6 [0.5, 5.1] |
| Imidazole derivatives | 377 | 3 | 0.8 [0.3, 2.5] | 1.0 [0.3, 3.1] | 0.7 [0.2, 2.2] | 0.9 [0.3, 2.9] | 0.7 [0.2, 2.3] | 0.7 [0.2, 2.2] | 366 | 3 | 0.8 [0.3, 2.5] | 1.0 [0.3, 3.1] |
| Isoxsuprine hydrochloride | 494 | 1 | 0.2 [0.0, 1.4] | 0.5 [0.1, 3.8] | 0.2 [0.0, 1.3] | 0.4 [0.1, 3.1] | 0.2 [0.0, 1.3] | 0.3 [0.0, 1.9] | 486 | 1 | 0.2 [0.0, 1.4] | 0.5 [0.1, 3.8] |
| Pregnen (4) derivatives | 1,315 | 7 | 0.5 [0.3, 1.1] | 0.8 [0.4, 1.7] | 0.5 [0.2, 1.0] | 0.8 [0.4, 1.7] | 0.5 [0.2, 1.0] | 0.7 [0.3, 1.4] | 1,260 | 7 | 0.5 [0.3, 1.1] | 0.8 [0.4, 1.8] |
| Progesterone | 1,160 | 6 | 0.5 [0.2, 1.1] | 0.8 [0.4, 1.8] | 0.5 [0.2, 1.0] | 0.8 [0.3, 1.7] | 0.5 [0.2, 1.0] | 0.7 [0.3, 1.5] | 1,113 | 6 | 0.5 [0.2, 1.2] | 0.8 [0.4, 1.8] |
| Dydrogesterone | 732 | 10 | 1.4 [0.7, 2.5] | 1.6 [0.8, 3.0] | 1.2 [0.7, 2.3] | 1.7 [0.9, 3.2] | 1.3 [0.7, 2.4] | 1.2 [0.6, 2.3] | 722 | 10 | 1.4 [0.7, 2.5] | 1.6 [0.9, 3.0] |
| Glucocorticoids | 565 | 2 | 0.4 [0.1, 1.4] | 0.6 [0.1, 2.3] | 0.3 [0.1, 1.3] | 0.4 [0.1, 1.6] | 0.3 [0.1, 1.3] | 0.4 [0.1, 1.6] | 525 | 2 | 0.4 [0.1, 1.5] | 0.6 [0.2, 2.4] |
| Levothyroxine sodium | 1,301 | 7 | 0.5 [0.3, 1.1] | 0.9 [0.4, 1.9] | 0.5 [0.2, 1.0] | 0.8 [0.4, 1.7] | 0.5 [0.2, 1.0] | 0.8 [0.4, 1.7] | 1,179 | 7 | 0.6 [0.3, 1.2] | 1.0 [0.5, 2.1] |
| Amoxicillin and clavulanic acid | 370 | 3 | 0.8 [0.3, 2.5] | 1.0 [0.3, 3.2] | 0.7 [0.2, 2.2] | 0.9 [0.3, 2.9] | 0.7 [0.2, 2.3] | 0.7 [0.2, 2.2] | 355 | 3 | 0.8 [0.3, 2.6] | 1.0 [0.3, 3.3] |
| Penicillins with extended spectrum | 1,395 | 18 | 1.3 [0.8, 2.1] | 1.3 [0.8, 2.1] | 1.2 [0.7, 1.8] | 1.2 [0.8, 2.0] | 1.2 [0.7, 2.0] | 1.1 [0.7, 1.8] | 1,360 | 17 | 1.2 [0.8, 2.0] | 1.2 [0.8, 2.0] |
| Amoxicillin | 816 | 8 | 1.0 [0.5, 2.0] | 1.0 [0.5, 2.1] | 0.9 [0.4, 1.8] | 1.0 [0.5, 2.0] | 0.9 [0.4, 1.8] | 0.8 [0.4, 1.6] | 799 | 8 | 1.0 [0.5, 2.0] | 1.0 [0.5, 2.1] |
| Pivmecillinam | 389 | 9 | 2.3 [1.2, 4.5] | 1.7 [0.8, 3.3] | 2.1 [1.1, 4.1] | 2.0 [0.9, 4.2] | 2.2 [1.1, 4.4] | 1.9 [0.9, 3.7] | 376 | 8 | 2.1 [1.0, 4.3] | 1.5 [0.7, 3.2] |
| Beta-lactamase sensitive penicillins | 339 | 7 | 2.1 [1.0, 4.4] | 1.8 [0.8, 3.8] | 1.9 [0.9, 3.9] | 1.9 [0.8, 4.1] | 2.0 [0.9, 4.2] | 1.8 [0.8, 3.9] | 328 | 7 | 2.1 [1.0, 4.5] | 1.9 [0.9, 4.0] |
| Phenoxymethyl-penicillin | 273 | 4 | 1.5 [0.5, 3.9] | 1.3 [0.5, 3.5] | 1.3 [0.5, 3.5] | 1.4 [0.5, 4.0] | 1.4 [0.5, 3.7] | 1.5 [0.5, 4.0] | 263 | 4 | 1.5 [0.6, 4.0] | 1.3 [0.5, 3.7] |
| Combinations of penicillins, incl. beta-lactamase inhibitors | 377 | 3 | 0.8 [0.3, 2.5] | 1.0 [0.3, 3.2] | 0.7 [0.2, 2.2] | 0.9 [0.3, 2.9] | 0.7 [0.2, 2.3] | 0.7 [0.2, 2.2] | 362 | 3 | 0.8 [0.3, 2.5] | 1.0 [0.3, 3.3] |
| Macrolides | 456 | 1 | 0.2 [0.0, 1.5] | 0.3 [0.0, 1.8] | 0.2 [0.0, 1.4] | 0.2 [0.0, 1.6] | 0.2 [0.0, 1.4] | 0.2 [0.0, 1.5] | 441 | 1 | 0.2 [0.0, 1.6] | 0.3 [0.0, 1.8] |
| Nitrofurantoin | 219 | 4 | 1.8 [0.7, 4.9] | 1.7 [0.6, 4.7] | 1.6 [0.6, 4.4] | 1.8 [0.6, 4.9] | 1.7 [0.6, 4.7] | 1.4 [0.5, 3.9] | 212 | 4 | 1.9 [0.7, 5.0] | 1.7 [0.6, 4.8] |
| Valproate | 263 | 4 | 1.5 [0.6, 4.1] | 1.5 [0.5, 3.9] | 1.4 [0.5, 3.7] | 1.4 [0.5, 3.8] | 1.4 [0.5, 3.8] | 1.1 [0.4, 3.0] |  |  |  |  |
| ‘Other’ antiepileptics | 188 | 3 | 1.6 [0.5, 5.0] | 1.2 [0.4, 3.9] | 1.4 [0.5, 4.5] | 1.1 [0.4, 3.6] | 1.5 [0.5, 4.7] | 1.1 [0.3, 3.4] |  |  |  |  |
| Benzodiazepine derivatives | 394 | 5 | 1.3 [0.5, 3.1] | 1.6 [0.7, 4.0] | 1.1 [0.5, 2.7] | 1.6 [0.7, 4.0] | 1.2 [0.5, 2.9] | 1.3 [0.5, 3.2] | 349 | 5 | 1.4 [0.6, 3.4] | 1.8 [0.7, 4.3] |
| Diazepam | 195 | 3 | 1.5 [0.5, 4.8] | 1.5 [0.5, 4.8] | 1.4 [0.4, 4.3] | 1.6 [0.5, 5.0] | 1.4 [0.5, 4.5] | 1.3 [0.4, 4.0] | 175 | 3 | 1.7 [0.5, 5.3] | 1.6 [0.5, 5.1] |
| Nasal corticosteroids for topical use | 255 | 3 | 1.2 [0.4, 3.6] | 1.4 [0.4, 4.5] | 1.1 [0.3, 3.3] | 1.4 [0.4, 4.5] | 1.1 [0.4, 3.4] | 1.4 [0.4, 4.4] | 244 | 3 | 1.2 [0.4, 3.8] | 1.5 [0.5, 4.7] |
| Betamethasone | 351 | 2 | 0.6 [0.1, 2.3] | 0.9 [0.2, 3.5] | 0.5 [0.1, 2.0] | 0.6 [0.1, 2.3] | 0.5 [0.1, 2.1] | 0.6 [0.2, 2.4] | 324 | 2 | 0.6 [0.2, 2.4] | 0.9 [0.2, 3.7] |
| Bromhexine | 23 | 3 | 14.7 [4.4, 49.6]  | 29.5 [8.2, 105.5] | 13.2 [3.9, 44.6] | 30.1 [8.3, 108.7] | 13.9 [4.1, 47.1] | 21.2 [5.9, 75.8] | 23 | 3 | 14.5 [4.3, 48.9] | 29.0 [8.1, 103.8] |
| Piperazine derivatives | 582 | 2 | 0.3 [0.1, 1.4] | 0.3 [0.1, 1.4] | 0.3 [0.1, 1.2] | 0.3 [0.1, 1.4] | 0.3 [0.1, 1.2] | 0.3 [0.1, 1.2] | 567 | 2 | 0.3 [0.1, 1.4] | 0.4 [0.1, 1.4] |

## **Supporting Table 4. Maternal illness signal analysis results - crude and maternal age, registry and time adjusted ORs**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **ICD-9** | **ICD-10** | **Exposed in dataset** | **Gastroschisis cases exposed** | **Crude OR [95% CI]** | **Adjusted OR [95% CI]** |
| All pregestational Diabetes Mellitusa  | 250 | E10-14 | 882 | 1 | 0.1 [0.0, 0.8] | 0.1 [0.0, 0.9] |
| All Diabetes Mellitus (pregestational and gestational)  | 250, 648.0, 648.8 | E10-14, O24 | 2378 | 5 | 0.2 [0.1, 0.5] | 0.3 [0.1, 0.8] |
| Gestational Diabetes Mellitus | 648.8 | O244 | 1150 | 4 | 0.4 [0.1, 1.0] | 0.7 [0.2, 1.8] |
| Other Endocrine disorders  | 251-9 | E15,E16, E2, E30-5,  | 223 | 1 |  |  |
| Mental Disorder | 290-9, 300-3, 305-9,310-9 | F00-F99 | 1113 | 20 | 1.9 [1.2, 3.0] | 1.6 [1.0, 2.4] |
| Depression | 300.4, 311 | F32-3 | 559 | 13 | 2.5 [1.5, 4.4] | 2.5 [1.5, 4.4] |
| Mental and behavioural disorders associated with the puerperium  |  | F53 | 41 | 3 | 8.3 [2.6, 27.0] | 8.3 [2.6, 27.0] |
| Chest Cold  | 466 | J20, J21 | 41 | 0 |  |  |
| Sore Throat  | 462, 472.1 | J02, J31.2 | 90 | 1 |  |  |
| Viral Infection Complicating Pregnancy  | 647.6, 042, 050-5, 057-079 |  | 3 | 0 |  |  |
| Other Specified Infections (as per Baer et al.20) | 647.3-5, 647.8, 010-018, 084, 056  |  | 8 | 0 |  |  |
| Urinary Tract Infection (UTI) | 646.6 | O23 | 1211 | 13 | 1.1 [0.7, 2.0] | 1.0 [0.5, 1.7] |
| Genital Herpes | 054.1 | A60.0 | 2 | 0 |  |  |
| Genital Herpes - excluding those taking antiherpetic medication | 054.1 | A60.0 | 2 | 0 |  |  |
| Sexually Transmitted Infection (STI) | 090-097, 054.1, 131, 647.0-2 | A50-A64, O98.1-3, M02.3 | 86 | 5 | 6.5 [2.6, 16.1] | 2.9 [1.1, 7.2] |
| STI (including thrush) | 090-097, 054.1, 131, 647.0-2, 112.1 | A50-A64, O98.1-3, M02.3, B37.3 | 150 | 6 | 4.4 [1.9, 10.0] | 2.5 [1.1, 5.9] |
| UTI or STI | 646.6, 090-097, 054.1, 131, 647.0-2 | O23, A50-A64, O98.1-3, M02.3 | 1298 | 18 | 1.5 [0.9, 2.4] | 1.2 [0.7, 1.9] |
| STI (including thrush) or UTI | 646.6, 090-097, 054.1, 131, 647.0-2, 112.1 | O23, A50-A64, O98.1-3, M02.3, B37.3 | 1355 | 18 | 1.4 [0.9, 2.3] | 1.1 [0.7, 1.8] |
| STI and UTI | 646.6 & 090-097, 054.1, 131, 647.0-2 | O23 & A50-A64, O98.1-3, M02.3 | 1 | 0 |  |  |
| STI (including thrush) and UTI | 646.6 & 090-097, 054.1, 131, 647.0-2, 112.1 | O23 & A50-A64, O98.1-3, M02.3, B37.3 | 6 | 1 |  |  |

a Includes Norway registry

## **Supporting Table 5. Maternal illness exploratory analysis results - crude and maternal age, registry and time adjusted ORs**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **ICD-9** | **ICD-10** | **Exposed in dataset** | **Gastroschisis cases exposed** | **Crude OR [95% CI]** | **Adjusted OR [95% CI]** |
| Asthmaa | 493 | J45 | 21,166 | 31 | 1.5 [1.1, 2.2] | 1.1 [0.8, 1.6] |
| Epilepsya | 345 | G40 | 974 | 7 | 1.1 [0.5, 2.3] | 1.0 [0.5, 2.1] |
| Pre-eclampsiaa | 642.5 | O14 | 817 | 5 | 0.6 [0.3, 1.5] | 0.5 [0.2, 1.2] |
| Gastritis and duodenitis | 535 | K29 | 101 | 4 | 4.4 [1.6, 11.9[ | 3.1 [1.1, 8.8] |
| Chronic Interstitial Nephritis | b | N11 | 159 | 3 | 2.0 [0.6, 6.4] | 1.2 [0.4, 3.8] |
| Hypothyroidism | 243, 244 | E00-E03, E89.0 | 1010 | 2 | 0.2 [0.1, 0.8] | 0.3 [0.1, 1.2] |
| Obesity | 278 | E66 | 1555 | 12 | 0.8 [0.5, 1.4] | 0.6 [0.3, 1.0] |
| Haemorrhage in early pregnancy | 640 | O20 | 2028 | 27 | 1.4 [1.0, 2.1] | 1.5 [1.0, 2.3] |
| Acute upper respiratory infections of multiple or unspecified sites | 465 | J06 | 360 | 13 | 4.0 [2.3, 7.0] | 2.7 [1.5, 4.8] |
| Premature rupture of the membranes | 658.1 | O42 | 276 | 5 | 1.9 [0.8, 4.7] | 1.2 [0.4, 3.3] |
| Influenza | 487, 488 | J09-J11 | 705 | 3 | 0.5 [0.1, 1.4] | 0.9 [0.3, 2.9] |
| Bacterial Infection of Unspecified Site | b | A49 | 47 | 3 | 7.2 [2.2, 23.2] | 3.6 [1.1, 12.0] |
| Hyperemesis | 643 | O21 | 371 | 4 | 1.2 [0.4, 3.1] | 1.0 [0.4, 2.7] |
| Tonsillitis | 463 | J03 | 37 | 3 | 9.3 [2.9, 30.3] | 8.4 [2.4, 29.3] |

a Includes Norway registry

b ICD-9 and ICD-10 codes not comparable for this diagnosis so analysis was restricted to the ICD-10 code.

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## Supporting Figure 1. Flowchart detailing number of congenital anomaly affected foetuses, excluding those with chromosomal/monogenic conditions, included at each stage of the analysis



A includes those with pregestational diabetes, gestational diabetes or exposure to an antidiabetic medication.

B includes only those exposed to a medication, exposed only to vitamin/minerals, or known not to be exposed to a medication.

C those exposed only to vitamins/minerals were not considered to be medication exposed.

## Supporting figure 2. Flowchart detailing the literature review for first trimester medication exposure signals.

Records identified through database searching
(n = 183)

Additional records identified through other sources
(n = 4)

Records after duplicates removed
(n = 138)

Records screened
(n = 138)

Records excluded
(n = 57)

Full-text articles assessed for drug exposure risk factors
(n = 81)

Full-text articles excluded- no drug exposure risk factors identified or review of other studies

(n = 63)

Original studies identifying medication exposure signals

(n = 18)

Medication/medication group signals identified (included in analysis)

(n = 20)

Illicit drug/drug group signals identified

(Not included in analysis)

(n = 5)

## Supporting figure 3. Flowchart detailing the literature review for first trimester maternal illness exposure signals

Records identified through database searching
(n = 176)

Additional records identified through other sources
(n = 5)

Records after duplicates removed
(n = 181)

Records screened
(n = 181)

Records excluded
(n = 141)

Full-text articles assessed for drug exposure risk factors
(n = 40)

Full-text articles excluded
(n = 31)

Original studies identifying maternal illness risk factors
(n = 9)

Individual/group of maternal illness diagnoses signals (included in analysis)
(n = 16)

Individual/group of maternal illness diagnoses signals (not included in analysis)
(n = 3)