BMJ Open

Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: Cohort study of 151,141 singleton pregnancies

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048092
Article Type:	Original research
Date Submitted by the Author:	29-Dec-2020
Complete List of Authors:	Zafeiri, Aikaterini; University of Aberdeen, School of Medicine, Medical Sciences and Nutrition Hay, David ; University of Edinburgh Fowler, Paul ; University of Aberdeen Raja, Edwin Amalraj; University of Aberdeen, Medical Statistics Team Mitchell, Rod; The University of Edinburgh Bhattacharya, Sohinee; University of Aberdeen
Keywords:	Epidemiology < INFECTIOUS DISEASES, OBSTETRICS, CLINICAL PHARMACOLOGY

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Title: Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: Cohort study of 151,141 singleton pregnancies

Authors: [1]Aikaterini ZAFEIRI, MSci, Ms, [2]Edwin A. RAJA, PhD, [3]Rod T. MITCHELL, MBChB, PhD, [4]David C. HAY, PhD, [5]Sohinee BHATTACHARYA, MBBS, PhD, [1]Paul A. FOWLER, FRSB, PhD

[1]Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, [2]Medical Statistics Team, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, [3]MRC Centre for Reproductive Health, The Queen's Medical Research Institute, University of Edinburgh,47 Little France Crescent, Edinburgh, EH16 4JT, UK, [4]MRC Centre for Regenerative Medicine, 5 Little France Drive, Edinburgh, UK, [5]Aberdeen Centre for Women's Health Research, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom,

Corresponding Author: Aikaterini Zafeiri, Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, cell phone number: (+44)7713837285, email: r01az17@abdn.ac.uk

Running Title: Maternal over-the-counter analgesia and offspring outcomes

Abstract

OBJECTIVES

To identify any associations between *in utero* exposure to five over-the-counter (non-prescription) analgesics (paracetamol, ibuprofen, aspirin, diclofenac, naproxen) and adverse neonatal outcomes.

DESIGN

Retrospective cohort study using the Aberdeen Maternity and Neonatal Databank.

PARTICIPANTS

151,141 singleton pregnancies between 1985 and 2015.

MAIN OUTCOME MEASURES

Premature delivery (<37 weeks), stillbirth, neonatal death, birthweight, standardised birthweight score, neonatal unit admission, APGAR score at 1 and 5 minutes, neural tube and amniotic band defects, gastroschisis and, in males, cryptorchidism, and hypospadias.

RESULTS

83.7% of women taking over-the-counter analgesics reported first trimester use when specifically asked about use at their first antenatal clinic visit. Pregnancies exposed to at least one of the five analgesics were significantly independently associated with increased risks for premature delivery <37 weeks (aOR=1.50, 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), neonatal death (aOR=1.56, 95%CI 1.27-1.93), birthweight <2,500g (aOR=1.28, 95%CI 1.20-1.37), birthweight >4,000g (aOR=1.09, 95%CI 1.05-1.13), admission to neonatal unit

(aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at 1 minute (aOR=1.18, 95%CI 1.13-1.23) and 5 minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54 males only). The overall prevalence of over-the-counter analgesics use during pregnancy was 29.1%, however it rapidly increased over the 30-year study period, to include over 60% of women in the last seven years of the study. This makes our findings highly relevant to the wider pregnant population.

CONCLUSIONS

Over-the-counter (non-prescription) analgesics consumption during pregnancy was associated with a substantially higher risk for adverse perinatal health outcomes in the offspring. The use of paracetamol in combination with other non-steroidal anti-inflammatory drugs conferred the highest risk. The increased risks of adverse neonatal outcomes associated with non-prescribed, over-the-counter, analgesics use during pregnancy indicate that healthcare guidance for pregnant women regarding analgesic use need urgent updating.

Strengths and limitations of this study

- This is one of the largest and most comprehensive studies of this type. It includes consumption of five different analgesics during pregnancy in a large cohort of singleton pregnancies. It examines associations with an extensive range of offspring perinatal outcomes, while adjusting for important confounding factors
- Anlagesic consumption was analysed both as use of a single compound and in combinations of the five drugs considered in this study

- Details of the exact dose and timing of consumption during pregnancy was not available within our dataset
- Follow-up of the offspring health later in life was not available at this time

Funding Biotechnology and Biological Sciences Research council (BBSRC) funding under the EASTBIO doctoral training programme (grant number 1942576) to AZ and EU Horizon 2020 project FREIA (Grant Number 825100) to PAF. RTM is supported by MRC Centre for Reproductive Health Grant MR/N022556/1.

Key words acetaminophen, aspirin, diclofenac, ibuprofen, *in utero* exposure, naproxen, offspring outcomes, over-the-counter analgesics, offspring outcomes, paracetamol, pregnancy

Introduction

Globally 23-85% of women use one or more types of prescribed medications during pregnancy [1,2]. A similarly high proportion of expectant mothers self-medicate using non-prescription, "over-the-counter" (OTC) medicines [3,4] and use during pregnancy is becoming increasingly prevalent, especially in Western countries [5]. While some analgesics e.g. paracetamol are considered safe to consume throughout pregnancy, use of non-steroidal anti-inflammatory drugs (NSAIDs) is not recommended in pregnancy unless on the advice of a medical specialist and should be avoided beyond gestational week 30 because of the risk of premature closure of the ductus arteriosus. However, current evidence is largely conflicting regarding the safety of gestational analgesic use both for the pregnancy and offspring health [6]. Several studies have reported increased risks for multiple adverse outcomes including hypospadias, cryptorchidism, amniotic band defects and neural tube defects [7–11], whilst others have not found significant associations [12–17]. Taken overall, this has led to significant concern that postnatal health is adversely affected by maternal analgesic use during pregnancy [18].

The use of small cohorts in the current epidemiological studies makes it difficult to draw firm conclusions and definite recommendations[12,17,19,20]. There are other aspects of analgesic use that have to be taken into account. Firstly, due to their abundance, it is not always feasible to determine exact consumption rates and dosage. Secondly, even though the mechanisms of action for most of these compounds is not fully understood, most over-the-counter analgesics can diffuse through the placenta and reach the developing fetus [21]. Thirdly, maternal pharmacokinetics during pregnancy are altered and there are limited pregnancy safety data for these compounds.

Given the diversity in study population, methodology, sample size and findings in the published studies, we conclude that more extensive data from larger cohorts are essential in order to understand the risks over-the-counter analgesic use during pregnancy pose to neonatal health and function. Here we address many limitations of previous studies by analysing one of the largest cohorts, widest range of health data and, pregnancy use of five over-the-counter analgesics consumed in combination or separately. We report on the prevalence of maternal consumption of five different over-the-counter analgesics during pregnancy and their associations with offspring neonatal outcomes using a large cohort of 151,141 singleton pregnancies spanning three decades of population-based data from a single maternity hospital serving the entire population of Aberdeenshire in the North East of Scotland.

Materials and Methods

This retrospective cohort study utilised data collected in the Aberdeen Maternity and Neonatal Databank (AMND) in Aberdeen, UK on 151,141 pregnancies over a 30 year period (1985-2015). Details about AMND have been previously published [22]. Data were collected from medical notes of women retrospectively after delivery. Women were specifically asked about their use of over-the-counter (non-prescription) analgesics at their first antenatal clinic. Data were entered by dedicated coding staff into a computerised database. Data validity was ensured via checking completeness of data entry against NHS (UK National Health Service) returns monthly and constant data cleaning and validation against case notes reported quarterly by the Data Management team to the AMND Steering Committee. A research protocol was submitted and approved by the AMND Steering Committee before data extraction. Approval was received on 6 June 2018. The dataset was fully anonymised, therefore there was no requirement for NHS ethics committee approval. There was no involvement of patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

The main analysis considered consumption during pregnancy of at least one out of five different analgesics: paracetamol (no; yes), ibuprofen (no; yes), naproxen (no; yes), diclofenac (no; yes) or aspirin (no; yes) as the exposure group against no analgesic consumption as the unexposed group. Then, three sub-group analyses against the control group were performed using only paracetamol, only diclofenac, or at least one analgesic from aspirin/naproxen/ibuprofen as exposure groups, excluding pregnancies exposed to multiple analgesics at the same time. As 98.3% of pregnancies using diclofenac were between 2005 and 2015, diclofenac sub-group

analysis only considered pregnancies during that time frame in order to rule out any temporal effect.

The offspring outcomes compared between control and exposed groups were: gestation at delivery (preterm <37 gestation weeks, term ≥37 gestation weeks), pregnancy outcome (livebirth, stillbirth, neonatal death), baby weight (low birth weight (LBW) ≤2,499 g, high birth weight (HBW) ≥4,000 g, normal birth weight (NBW) 2,500g-3,999 g), standardised birthweight score was considered as a continuous variable as previously described by Campbell and colleagues[23], baby admission to neonatal unit (no; yes), APGAR score at one and five minutes (<7, ≥7), cryptorchidism (no; yes) (ICD-10 code Q53), neural tube defects (no; yes) (ICD-10 code Q00-07), amniotic band defects (no; yes) (ICD-10 codes Q70-74), hypospadias (no; yes) (ICD-10 code Q54), gastroschisis (no; yes) (ICD-10 code Q79.3). A composite outcome (presence of at least one congenital anomaly (no; yes)) was created using the variables neural tube defects, amniotic band defects, and gastroschisis and, in males, cryptorchidism and hypospadias.

The baseline characteristics compared between exposed and unexposed pregnancies were (reference category first): year of delivery (1985-1994, 1995-2004, 2005-2015), maternal age at delivery (20-25, <20, 26-35, >35 years), previous pregnancy (no; yes), maternal body mass index (BMI) (normal weight 18.5-24.9 kg/m^2, underweight <18.5 kg/m^2, overweight 25-29.9 kg/m^2, obese <30 kg/m^2), maternal first antenatal visit (1st, 2nd, 3rd trimester), maternal smoking status (non-smoker, smoker, ex-smoker), Scottish Index of Multiple Deprivation (SIMD) decile (1-6, 7-10, decreasing deprivation with increasing score), maternal hypertensive disorders (no disorder, gestational hypertension, preeclampsia, eclampsia), maternal antepartum haemorrhage (no haemorrhage, abruption, placental previa), type of

labour (spontaneous, elective caesarean section, induced), type of delivery (spontaneous vaginal delivery, instrumental, caesarean section), analgesia during labour (no; yes), baby presentation at delivery (occiput anterior, occiput posterior), baby sex (female; male).

Patient and Public Involvement

This was a retrospective analysis of data on singleton pregnancies over a 30-year period. Therefore, there was no involvement of patients or the public in the design, conduct, reporting or any other aspect of the study.

Statistical Analysis

Baseline characteristics were compared between exposed and unexposed pregnancies to any analgesic using χ^2 test for categorical variables and t-test for normally distributed continuous variables as appropriate. Relationships between exposures and outcomes were examined by binary logistic regression for binary outcome variables, multinomial logistic regression for nominal categorical outcome variables, and multiple linear regression for continuous variables. The strength of association was reported as odds ratios (ORs) with 95% confidence intervals (CI). The socio-demographic characteristics that were likely to confound our exposure-to-outcome path were identified using a directed acyclic graph (DAG) (Figure S1)[24]. Factors that were associated with consumption of over-the-counter analgesics during pregnancy at 10% level of significance and deemed clinically relevant, were included in the model as confounders. All outcomes were adjusted for year of delivery, maternal age at delivery, SIMD and maternal first antenatal visit. In addition to these confounders, individual outcomes were adjusted for relevant cofactors. Gestation at

delivery and pregnancy outcome were both additionally adjusted for maternal hypertensive disorders and antepartum haemorrhage. Weight of the baby, neonatal unit admission, cryptorchidism, neural tube defects, amniotic band defects, hypospadias and gastroschisis variables were also adjusted for gestation at delivery. APGAR score at one and five minutes were adjusted for type of delivery. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using IBM SPSS Statistics version 25.0 (Released 2017. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). R version 3.6.2 was used to generate Figure 2.

Results

83.7% of women taking over-the-counter analgesics reported first trimester use when specifically asked about use at their first antenatal clinic. Overall, from the total 151,141 pregnancies across 30 years in 107,143 (70.9%) pregnancies, no over-the-counter analgesic consumption was reported. At least one over-the-counter analgesic was consumed in 43,998 (29.1%) pregnancies, whereas paracetamol use alone was reported in 24,099 (18.4%) pregnancies. Diclofenac use was observed in 20.0% of pregnancies in the 10-year period when diclofenac was available over-the-counter (without prescription). Finally, at least one out of three analgesics (naproxen, ibuprofen, aspirin) was consumed in 762 (0.7%) pregnancies (Figure 1).

Prevalence of use for all five analgesics increased dramatically over the 30-year study period (1985-2015) (Figure 2). Percentage of pregnancies with consumption of at least one analgesic increased from 1.8% in 1985 to 70.6% in 2015. Paracetamol was consumed in 1.3% of pregnancies in 1985 and it continuously increased reaching 42.2% in 2015. Naproxen, ibuprofen or aspirin consumption during pregnancy was less prevalent, however it also increased during the 30-year study period, starting at 0.5% in 1985 and reaching 1.9% in 2015. Diclofenac was consumed in very few pregnancies between 1985 (<0.01%) and 2005 (0.2%). Percentage of consumption, however, dramatically increased during the next decade following deregulation of diclofenac, reaching 25.0% in just one year (2006) and 45.6% of all pregnancies in 2015.

Table 1 compares the baseline characteristics between the unexposed group of pregnancies where no analgesic was consumed and each of the exposure groups. In most, but not all, comparisons across all four analyses, there was a statistically

significant difference (p<0.001) for most variables. In the paracetamol sub-group analysis, baby presentation at delivery (p=0.525) and sex of the baby (p=0.861) were not significantly different between the groups. In the analysis considering consumption of at least one analgesic from aspirin/naproxen/ibuprofen, again the variables for baby presentation at delivery (p=0.093) and sex of the baby (p=0.732), together with maternal smoking status (p=0.132) and maternal antepartum haemorrhage (p=0.434) were not statistically different compared to the unexposed group. All variables were statistically different between unexposed and exposed groups for the main analysis and diclofenac sub-group analysis.

Table 2 summarises the comparison of neonatal outcomes between the unexposed group (no analgesic at all) and the exposed groups of at least one analgesic, only paracetamol and at least one out of aspirin/naproxen/ibuprofen. Comparison of outcomes for the diclofenac sub-group analysis is shown in Table 3.

All analgesics and neonatal outcomes

As shown in Table 2, compared to unexposed pregnancies in which women did not use any analgesic, pregnancies with consumption of at least one analgesic (paracetamol, diclofenac, aspirin, naproxen, ibuprofen) were independently associated with significantly higher odds for premature delivery (aOR=1.50, 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI1.15-1.54), LBW (aOR=1.28, 95%CI 1.20-1.37), HBW (aOR=1.09, 95%CI 1.05-1.13), baby admission to neonatal unit (aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at five minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54) in adjusted analyses. Significantly decreased odds for

APGAR score <7 at one minute were found in the crude analysis (cOR=0.96, 95%CI 0.92-0.99), however when adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking and type of delivery, the significance changed direction showing significantly increased odds (aOR=1.18, 95%CI 1.13-1.23). A significantly lower standardised birthweight score (aOR=0.046. 95%CI 0.032-0.059) was found for the exposure group compared to no analgesic at all. Cryptorchidism (aOR=0.92, 95%CI 0.77-1.11), amniotic band defects (aOR=1.02, 95%CI 0.71-1.47), gastroschisis (aOR=1.10, 95%CI 0.56-2.20) and the composite outcome variable (aOR=1.12, 95%CI 0.99-1.26), were all associated with increased odds in the exposure group compared to not exposed, however the association was not significant in the adjusted model. There was no significant association between neonatal death and exposure to at least one analgesic in the crude analysis (cOR=1.19, 95%CI 0.99-1.42), however there were significantly higher odds of neonatal death in the adjusted analysis (aOR=1.56, 95%CI 1.27-1.93) in the exposed group compared to control.

Paracetamol and neonatal outcomes

In the sub-group analysis considering only paracetamol consumption during pregnancy as our exposure group, most of the associations reported in the main analysis remained significant with the same direction of significance (Table 2). The differences were: maternal paracetamol consumption during pregnancy was associated with significantly decreased odds for offspring HBW (cOR=0.94, 95%CI 0.90-0.99) in the crude analysis however significance was lost in the adjusted model (aOR=0.98, 95%CI 0.93-1.02), and there were no significant associations in the

adjusted models for neural tube defects (aOR=1.21, 95%CI 0.71-2.06) and hypospadias (aOR=1.07, 95%CI 0.84-1.37).

Aspirin/naproxen/ibuprofen and neonatal outcomes

Consumption of at least one analgesic from aspirin, naproxen or ibuprofen during pregnancy was compared against the same control group of pregnancies where no analgesic was used (Table 2). Again, when comparing associations between groups in this sub-group analysis and main analysis, fewer outcome variants showed similar significance pattern. The only shared significant associations were for increased odds for premature delivery (aOR=1.42, 95%CI 1.08-1.86), stillbirth (aOR=2.34, 95%CI 1.29-4.25) and baby admission to neonatal unit (aOR=1.54, 95%CI 1.22-1.94) in the adjusted regression analyses.

Diclofenac and neonatal outcomes

In the sub-group analysis of pregnancies coinciding with non-prescription, over-the-counter, availability of diclofenac (years 2005-2015) were considered, and outcomes compared between the diclofenac group and no analgesic consumption group (Table 3). Compared to the main analysis, diclofenac consumption during pregnancy was not significantly associated with premature delivery (aOR=1.10, 95%CI 0.99-1.22), neonatal death (aOR=1.26, 95%CI 0.73-2.15) and APGAR score <7 in one minute (aOR=0.93, 95%CI 0.83-1.04) in the adjusted models. Associations with APGAR score <7 in five minutes (aOR=0.94, 95%CI 0.72-1.23), cryptorchidism (aOR=1.05, 95%CI 0.78-1.42), amniotic band defects (aOR=0.81, 95%CI 0.41-1.58) and gastroschisis (aOR=2.93, 95%CI 0.97-8.88) were no longer significant in both crude

and adjusted analyses. Maternal consumption of diclofenac was independently associated with a significant decrease in stillbirth (aOR=0.59, 95%CI 0.41-0.87). It is also interesting to note that diclofenac was the only sub-group analysis agreeing with the main analysis (exposure to at least one analgesic) on the significance of exposure association with increased incidence of neural tube defects (aOR=3.62, 95%CI 1.95-6.74) and hypospadias (aOR=1.49, 95%CI 1.09-2.03) compared to unexposed pregnancies in adjusted models.

Discussion

Main Findings

Consumption of paracetamol, ibuprofen, aspirin and naproxen during pregnancy, either in combination or separately, was significantly associated with increased premature delivery, stillbirth, neonatal death, LBW, abnormal standardised birthweight score and more frequent admission to neonatal unit. Consumption of paracetamol alone was further associated with higher odds for APGAR score <7 at one and five minutes both in crude and adjusted analyses. There was a dramatic increase in the frequency of over-the-counter (non-prescription) analgesic use in pregnancies between 1985 and 2015, reaching 70.5% of women in the final decade of our study. This means that our findings are applicable far beyond the percentage (between 14% and 38%) [25] of pregnant women with underlying health deficits related to the adverse outcomes we report here.

Diclofenac use increased steeply from 2005 (Figure 2A), which reflects the change in Scottish legislation, leading to diclofenac becoming available without prescription in that year. Diclofenac use was associated with fewer adverse outcomes but showed increased risk of neural tube defects and hypospadias in male neonates. Furthermore, and surprisingly, exposure to diclofenac only was associated with significant decrease in the incidence of stillbirth. The reasons for such differences between the changes in neonatal outcomes following diclofenac consumption compared with those following use of the other NSAIDS are not clear. The proportion of women using diclofenac, especially in the last 7 years of our study makes it highly unlikely to be due to an underlying maternal condition and/or other compounds used

in combination (e.g. prescriptions) by women taking diclofenac. It is possible that the drug could act directly on fetal development then this difference could also be due to structural and/or mechanistic differences of the compound compared to the other drugs. However, not enough is known about the specific mechanisms of action of the different analgesics studied to conclude further. Overall, comparing our main analysis with all three sub-analyses, it is evident that the most significant differences were observed when paracetamol was taken with at least one other analgesic. This is mostly due to the high number of pregnancies where paracetamol was used, comprising almost 55% of the exposed cases in the main analysis.

Strengths and Limitations

A major strength of the present study is the large cohort of 151,141 pregnancies over a 30-year study period from 1985 until 2015, using a robust data source AMND. This is one of the largest cohorts used in studies examining the effects of analgesic use during pregnancy. The dataset contains high quality and consistent data from the geographically defined area of Aberdeen and surrounding district, in the North East of Scotland, UK. In addition, as Aberdeen Maternity Hospital is the only maternity hospital serving the area, over 95% of pregnancies in the area are included in the dataset, considerably minimizing the risk for selection bias. We were able to analyse maternal consumption data of the five most commonly used analgesics available over-the-counter in the UK and most countries, which is not matched in the current literature. The nature of our data allowed for the analysis of analgesics consumed alone or in combination, unlike most existing studies, and this gives our study the added strength of better reflecting real-life consumption patterns [26,27]. We were able

to adjust for important confounding factors, relevant to each analysed outcome. Adjustment for maternal deprivation also allowed us to further account for potential unmeasured factors that can influence maternal and neonatal health, which is a major strength of our analysis compared to most studies.

A potential concern was that women were probably using analgesics to treat some inherent medical condition which in turn could have been the mediating factor for adverse outcomes. However, since these medications are widely available without prescription, this is unlikely to be a factor that affects the findings of this study. This is especially the case during the “diclofenac analysis” covering 2005-2015, where this study presents results on multiple neonatal outcomes for the given cohort. In this way we offer a comprehensive approach to the exploration of associations with *in utero* analgesic exposure rather than only focusing on a single outcome of interest. Our data were based on medical notes; however, over-the-counter consumption is self-reported, and details on the timing, dosage, product type (single-ingredient vs combination) and administration type were not available in the database. Complete case analyses were performed ignoring pregnancies with missing data in the covariates, however due to the low number of missing data there is little chance that this might have affected the validity of our results. Compared to our cohort size, there were, overall, very few cases of cryptorchidism, neural tube defects, amniotic band defects, hypospadias and gastroschisis, resulting in potentially underpowered statistical analyses to detect a difference for these outcomes. Our study only considered neonatal health outcomes and follow-up of the offspring was not available at this time.

Interpretation

Previous literature has considered fewer outcomes with fewer analgesic combinations compared to our study. Consistent with our results, increased risk of preterm birth and miscarriage has been associated with analgesic consumption during pregnancy [28–31], while others reported no associations with miscarriage, stillbirth or preterm delivery [20,28,29,32]. Similarly, increased risk for offspring cryptorchidism, hypospadias, neural tube defects, amniotic band defects and gastroschisis have been shown by many studies [7–9,33–40], although, again, a lack of associations with major birth defects have been reported [13–17,41,42]. Compared to our analysis, all these studies used a smaller cohort, considered a shorter study time and there was frequent disagreement with respect to the choices of adjusted confounding factors. Another difference is that maternal questionnaires/interviews were frequently the method of choice to evaluate maternal consumption. Some of the studies reported increased risks for specific pregnancy trimesters which is something our study could not evaluate. Differences in study design and adjustment for different confounders might also account for the disagreement of our results that provide a more accurate assessment. Our study is one of the largest in terms of cohort size, duration, number of analgesics and range of outcomes included which might also contribute to differences compared to other studies.

The literature currently reports conflicting evidence, limiting our ability for definite decision-making. Over-the-counter analgesics are recommended to women by healthcare professionals in order to deal with pregnancy symptoms and other conditions. Policy-makers have taken a stand on the topic, either being reassuring about over-the-counter use during pregnancy or recommending caution when consumption is necessary [43–46]. Different compounds can affect the mother and the

fetus in a different way, and their combined use might worsen the risk for offspring ill health. This study demonstrates the need for additional research, before the field can be confidently directed towards one direction or the other.

Whether the associations we report result from flu, fever, rheumatological or inflammatory conditions, and/or combination with other prescribed medications or solely related to over-the-counter analgesics consumption is a matter of further research. Underlying health conditions could well influence the outcomes we see in this study, however, as these could be very different conditions it is biologically unlikely that they are responsible for the effects we observe here. Our study demonstrates an association of maternal over-the-counter analgesic consumption during pregnancy with adverse neonatal offspring outcomes. Future collaborative approaches such as an individual patient data meta-analysis that includes follow-up data on long-term outcomes during childhood and adulthood would significantly inform decision making. Going forward, uncovering the mechanisms of action and off target effects will also provide a solid foundation for the development of pregnancy-safe compounds. Finally, the findings present here suggest that diclofenac is associated with fewer changes in risk for the more frequent adverse outcomes although it is associated more with rarer, but severe, negative outcomes, including neural tube defects. Diclofenac may have a lower risk for the main adverse neonatal outcomes reported for paracetamol. However, it should be noted that our study is not designed to specifically test differences in level of risk between the analgesics included. Therefore, it should be emphasised that this does not mean that the authors are stating that diclofenac is preferable to paracetamol.

Conclusions

Pain control is currently a therapeutic priority during pregnancy. Our findings of increased risk of adverse health outcomes for the offspring following at least first trimester maternal use of readily available over-the-counter analgesics are crucial to information for the management of pain during pregnancy.

Acknowledgements: N/A

Disclosure of interests: Professor David Hay is a founder, director and shareholder in Stemnovate Limited. The remaining authors have no interests to disclose.

Contribution to Authorship: AZ, SB and PAF contributed to the conception, design and coordination of the research. EAR provided critical input in the design and planning of statistical analysis. AZ conducted the statistical analysis and prepared the manuscript, figures and tables. AZ, SB, PAF, RTM and DCH substantially contributed to the analysis and interpretation of the work. All authors contributed to critical discussion of intellectual content, development and review/approval of the final manuscript version.

Funding: This work is supported by the Biotechnology and Biological Sciences Research council (BBSRC) funding the lead author under the EASTBIO doctoral training programme and to PAF, the EU Horizon 2020 project FREIA (Grant Number 825100). RTM is supported by MRC Centre for Reproductive Health Grant MR/N022556/1. The funders had no role in study design, data collection, data analysis, decision to publish, or manuscript preparation.

Ethics Statement: The AMND dataset used in this study was fully anonymised, therefore there was no requirement for ethical approval. The North of Scotland Research Ethics Service has devolved Caldicott approval to the Chair of the AMND steering committee. Approval to access and analyse data was obtained from the AMND steering Committee (AMND 004/2018).

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Table 1. Comparison of baseline characteristics between exposed (use of analgesics) and unexposed (no analgesic use) groups of pregnancies (P values <0.05 shown in bold).

Baseline Characteristics	No analgesic (n=107,143) n (%)	At least one analgesic (n=43,998) n (%)	P value†	Paracetamol (n=24,099) n (%)	P value†	Ibuprofen/ Aspirin/ Naproxen (n=762) n (%)	P value†	No analgesic 2005-2015 (n=20,544) n (%)	Diclofenac 2005-2015 (n=10,291) n (%)	P value‡
Year of delivery										
1985-1994	50,152 (46.8)	5,737 (13.0)	**<0.001**	5,390 (22.4)	**<0.001**	213 (28.0)	**<0.001**	n/a	n/a	**<0.001**
1995-2004	36,447 (34.0)	7,263 (16.5)		6,571 (27.3)		321 (42.1)		n/a	n/a	
2005-2015 / 2005-2009 *	20,544 (19.2) n/a	30,998 (70.5) n/a		12,138 (50.4) n/a		228 (29.9) n/a		n/a 11,105 (54.1)	n/a 4,021 (39.1)	
2010-2015 *	n/a	n/a		n/a		n/a		9,439 (45.9)	6,270 (60.9)	
Maternal age at delivery										
Younger than 20	9,236 (8.6)	3,834 (8.7)	**<0.001**	2,936 (12.2)	**<0.001**	34 (4.5)	**<0.001**	1,286 (6.3)	311 (3.0)	**<0.001**
20-25	24,249 (22.6)	8,700 (19.8)		5,932 (24.6)		113 (14.8)		3,436 (16.7)	1,152 (11.2)	
26-35	63,499 (59.3)	25,367 (57.7)		12,896 (53.5)		464 (60.9)		12,664 (61.1)	6,628 (64.4)	
Older than 35	10,159 (9.5)	6,097 (13.9)		2,335 (9.7)		151 (19.8)		3,158 (15.4)	2,200 (21.4)	
Previous Parity										
Nulliparity (0)	48,684 (45.4)	23,353 (53.1)	**<0.001**	12,510 (51.9)	**<0.001**	300 (39.4)	**0.004**	8,336 (40.6)	5,004 (48.6)	**<0.001**
Multiparity (1-11)	58,457 (54.6)	20,639 (46.9)		11,587 (48.1)		462 (60.6)		12,206 (59.4)	5,284 (51.4)	
Missing	2 (<0.1)**§**	6 (<0.1)**§**		2 (<0.1)**§**		0 (0.0)**§**		2 (<0.1)**§**	3 (<0.1)**§**	
Maternal BMI										
Underweight (<18.5)	1,998 (2.4)	869 (2.2)	**<0.001**	545 (2.6)	**<0.001**	10 (1.5)	**0.007**	492 (2.7)	174 (1.9)	**<0.001**
Normal weight (18.5-24.9)	50,127 (60.8)	18,958 (48.8)		10,486 (50.5)		361 (55.)		10,239 (55.2)	4,671 (50.0)	
Overweight (25.0-29.9)	20,500 (24.9)	10,960 (28.2)		5,733 (27.6)		192 (29.5)		4,930 (26.6)	2,630 (28.1)	
Obese (≤ 30.0)	9,773 (11.9)	8,046 (20.7)		3,995 (19.2)		88 (13.5)		2,881 (15.5)	1,871 (20.0)	
Missing data	24,745 (23.1)**§**	5,165 (11.7)**§**		3,340 (13.9)**§**		111 (14.6)**§**		2,002 (9.7)**§**	945 (9.2)**§**	

Gestation weeks at earliest antenatal visit										
1st Trimester	69,896 (65.4)	36,789 (83.7)	**<0.001**	19,075 (79.2)	**<0.001**	569 (75.0)	**<0.001**	18,155 (88.4)	9,185 (89.4)	**0.036**
2nd Trimester	29,269 (27.4)	5,791 (13.2)		4,117 (17.1)		166 (21.9)		1,770 (8.6)	829 (8.1)	
3rd Trimester	7,741 (7.2)	1,376 (3.1)		890 (3.7)		24 (3.2)		605 (2.9)	264 (2.6)	
Missing	237 (0.2)**§**	42 (0.1)**§**		17 (0.1)**§**		3 (0.4)**§**		14 (0.1)**§**	13 (0.1)**§**	
Maternal smoking Status										
Unknown	6,505 (6.1)**§**	819 (1.9)**§**	**<0.001**	500 (2.1)**§**	**<0.001**	32 (4.2)**§**	0.132	448 (2.2)**§**	155 (1.5)**§**	**<0.001**
Ex-smoker	5,952 (5.6)	3,363 (7.6)		1,923 (8.1)		35 (4.8)		1,427 (7.1)	660 (6.5)	
Non-smoker	70,319 (69.9)	31,421 (72.8)		15,755 (66.8)		534 (73.2)		15,525 (77.3)	8,368 (82.6)	
Smoker	24,367 (24.2)	8,395 (19.4)		5,921 (25.1)		161 (22.2)		3,144 (15.6)	1,108 (10.9)	
Maternal SIMD Decile										
Least Deprived (7-10)	65,227 (61.8)	25,192 (57.9)	**<0.001**	12,807 (53.8)	**<0.001**	501 (66.3)	**0.012**	12,806 (62.9)	6,714 (66.1)	**<0.001**
Most Deprived (1-6)	40,321 (38.2)	18,289 (42.1)		11,017 (46.2)		255 (33.7)		7,564 (37.1)	3,442 (33.9)	
Missing	1,595 (1.5)**§**	517 (1.2)**§**		275 (1.1)**§**		6 (0.8)**§**		174 (0.8)**§**	135 (1.3)**§**	
Maternal hypertensive disorders										
None	91,276 (85.2)	35,529 (80.8)	**<0.001**	18,635 (77.3)	**<0.001**	636 (83.5)	**0.001**	18,851 (91.8)	9,273 (90.1)	**<0.001**
Gestational Hypertension	13,029 (12.2)	5,501 (12.5)		3,584 (14.9)		88 (11.5)		1,165 (5.7)	690 (6.7)	
Preeclampsia	2,780 (2.6)	2,941 (6.7)		1,861 (7.7)		38 (5.0)		523 (2.5)	324 (3.1)	
Eclampsia	58 (0.1)	27 (0.1)		19 (0.1)		0 (0.0)		5 (<0.1)	4 (<0.1)	
Maternal antepartum haemorrhage										
No haemorrhage	97,527 (91.0)	37,673 (85.6)	**<0.001**	20,306 (84.3)	**<0.001**	684 (89.8)	0.434	18,549 (90.3)	9,244 (89.8)	<0.001
Abruption	697 (0.7)	468 (1.1)		221 (0.9)		8 (1.0)		103 (0.5)	106 (1.0)	
Placenta previa	308 (0.3)	368 (0.8)		152 (0.6)		2 (0.3)		23 (0.1)	114 (1.1)	
Unspecified	8,611 (8.0)	5,489 (12.5)		3,420 (14.2)		68 (8.9)		1,869 (9.1)	827 (8.0)	
Type of labour										
Elective Caesarean Section	5,967 (5.6)	6,925 (15.7)	**<0.001**	1,384 (5.7)	**<0.001**	67 (8.8)	**<0.001**	616 (3.0)	3,843 (37.3)	**<0.001**
Induced	24,120 (22.5)	16,276 (37.0)		10,067 (41.8)		228 (29.9)		3,895 (19.0)	1,998 (19.4)	
Spontaneous	77,056 (71.9)	20,797 (47.3)		12,648 (52.5)		467 (61.3)		16,033 (78.0)	4,450 (43.2)	

Type of delivery										
Spontaneous vaginal delivery (SVD)	75,027 (70.1)	19,287 (43.8)	**<0.001**	15,983 (66.3)	**<0.001**	496 (65.2)	**0.003**	16,398 (79.8)	1,403 (13.6)	**<0.001**
Instrumental	15,409 (14.4)	8,107 (18.4)		4,043 (16.8)		120 (15.8)		2,546 (12.4)	1,927 (18.7)	
Caesarean Section	15,566 (14.5)	16,351 (37.2)		3,879 (16.1)		141 (18.5)		1,509 (7.3)	6,937 (67.4)	
Other	1,096 (1.0)	247 (0.6)		191 (0.8)		4 (0.5)		89 (0.4)	24 (0.2)	
Missing	45 (<0.1)**§**	6 (<0.1)**§**		3 (<0.1)**§**		1 (0.1)**§**		2 (<0.1)**§**	0 (0.0)**§**	
Analgesia during labour										
No	105,176 (98.2)	36,117 (82.1)	**<0.001**	20,974 (87.0)	**<0.001**	729 (95.7)	**<0.001**	19,915 (96.9)	8,235 (80.0)	**<0.001**
Yes	1,967 (1.8)	7,881 (17.9)		3,125 (13.0)		33 (4.3)		629 (3.1)	2,056 (20.0)	
Baby presentation at delivery										
Occiput anterior	11,571 (10.8)	8,152 (18.6)	**<0.001**	2,636 (11.0)	0.525	68 (8.9)	0.093	1,401 (6.8)	2,967 (28.9)	**<0.001**
Occiput posterior	95,352 (89.2)	35,745 (81.4)		21,409 (89.0)		694 (91.1)		19,100 (93.2)	7,306 (71.1)	
Missing	220 (0.2)**§**	101 (0.2)**§**		54 (0.2)**§**		0 (0.0)**§**		43 (0.2)**§**	18 (0.2)**§**	
Sex of baby										
Female	52,265 (48.8)	21,139 (48.0)	**0.010**	11,739 (48.7)	0.861	367 (48.2)	0.732	10,124 (49.3)	4,907 (47.7)	**0.008**
Male	54,866 (51.2)	22,852 (51.9)		12,354 (51.3)		395 (51.8)		10,417 (50.7)	5,384 (52.3)	
Missing	12 (<0.1)**§**	7 (<0.1)**§**		6 (<0.1)**§**		0 (0.0)**§**		3 (<0.1)**§**	0 (0.0)**§**	

n/a, not applicable; n, number of pregnancies

*****Only applicable to Diclofenac 2005-2015 analysis

†p value in comparison to the first ("No analgesic") column

‡p value in comparison to "No analgesic 2005-2015" control column

§Percentage of missing data on total, not included in the analysis

Table 2. Regression analysis of offspring outcomes between control (no analgesic) and groups exposed to at least one analgesic, only paracetamol, and at least one from ibuprofen, aspirin, naproxen.

Outcomes	No analgesic (n=107,143) n (%)	At least one analgesic (n=43,998) n (%)	Crude OR (CI 95%)	Adjusted OR (95% CI)	Paracetamol (n=24,099) n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Ibu/Asp/Napr (n=762) n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Gestation at delivery (weeks)										
>=37	100,879 (94.2)	39,838 (90.5)	1.00	1.00	21,589 (89.6)	1.00	1.00	697 (91.5)	1.00	1.00
<37	6,264 (5.8)	4,160 (9.5)	**1.68 (1.61-1.75)**	**1.50 (1.43-1.58)** [a]	2,510 (10.4)	**1.87 (1.78-1.97)**	**1.56 (1.48-1.65)** [a]	65 (8.5)	**1.50 (1.16-1.94)**	**1.42 (1.08-1.86)** [a]
Pregnancy outcome										
Livebirth	105,949 (98.9)	43,407 (98.7)	1.00	1.00	23,704 (98.4)	1.00	1.00	747 (98.0)	1.00	1.00
Stillbirth	803 (0.7)	405 (0.9)	**1.23 (1.09-1.39)**	**1.33 (1.15-1.54)** [a]	275 (1.1)	**1.53 (1.33-1.76)**	**1.52 (1.30-1.77)** [a]	13 (1.7)	**2.30 (1.32-3.99)**	**2.34 (1.29-4.25)** [a]
Neonatal Death	373 (0.3)	182 (0.4)	1.19 (0.99-1.42)	**1.56 (1.27-1.93)** [a]	117 (0.5)	**1.40 (1.14-1.73)**	**1.56 (1.24-1.96)** [a]	2 (0.3)	0.76 (0.19-3.06)	0.93 (0.23-3.74) [a]
Missing	18 (<0.1)	4 (<0.1)	n/a	n/a	3 (<0.1)	n/a	n/a	0 (0.0)	n/a	n/a
Weight of baby (grams)										
NBW	87,966 (82.1)	34,555 (78.6)	1.00	1.00	19,163 (79.5)	1.00	1.00	605 (79.5)	1.00	1.00
LBW	5,910 (5.5)	3,571 (8.1)	**1.54 (1.47-1.61)**	**1.28 (1.20-1.37)** [b]	2,213 (9.2)	**1.72 (1.63-1.81)**	**1.60 (1.51-1.69)** [b]	59 (7.7)	**1.45 (1.11-1.90)**	1.29 (0.91-1.83) [b]
HBW	13,233 (12.4)	5,863 (13.3)	**1.13 (1.09-1.17)**	**1.09 (1.05-1.13)** [b]	2,720 (11.3)	**0.94 (0.90-0.99)**	0.98 (0.93-1.02) [b]	97 (12.7)	1.07 (0.86-1.32)	0.99 (0.80-1.24) [b]
Missing	34 (<0.1)	9 (<0.1)	n/a	n/a	3 (<0.1)	n/a	n/a	1 (0.1)	n/a	n/a
Standardised Birthweight Score										
Mean (SD)	0.001 (0.003)	-0.002 (0.065)	**0.03 (0.02-0.04)**	**0.046 (0.032-0.059)** [c]	0.001 (0.991)	**-0.04 (-0.058- -0.029)**	**-0.014 (-0.029-0.001)** [c]	0.046 (0.038)	**0.045 (-0.029-0.119)**	**0.049 (-0.025-0.123)** [c]
Admitted to neonatal unit										
No	62,378 (58.2)	32,391 (73.6)	1.00	1.00	16,342 (67.8)	1.00	1.00	480 (63.0)	1.00	1.00
Yes	11,011 (10.3)	7,448 (16.9)	**1.30 (1.26-1.35)**	**1.57 (1.51-1.64)** [b]	3,956 (16.4)	**1.37 (1.32-1.43)**	**1.45 (1.38-1.53)** [b]	117 (15.4)	**1.38 (1.13-1.69)**	**1.54 (1.22-1.94)** [b]
Missing	33,754 (31.5)	4,159 (9.5)	n/a	n/a	3,801 (15.8)	n/a	n/a	762 (21.7)	n/a	n/a
APGAR score at 1 min										
Normal	92,217 (86.1)	38,224 (86.9)	1.00	1.00	20,593 (85.5)	1.00	1.00	659 (86.5)	1.00	1.00
<7	14,335 (13.4)	5,674 (12.9)	**0.96 (0.92-0.99)**	**1.18 (1.13-1.23)** [d]	3,437(14.3)	**1.07 (1.03-1.12)**	**1.23 (1.18-1.28)** [d]	101 (13.3)	0.99 (0.80-1.22)	1.07 (0.86-1.32) [d]
Missing	591 (0.6)	100 (0.2)		n/a	69 (0.3)	n/a	n/a	2 (0.3)	n/a	n/a
APGAR score at 5 min										
Normal	104,292 (97.3)	42,730 (97.1)	1.00	1.00	23,334 (96.8)	1.00	1.00	738 (96.9)	1.00	1.00
<7	2,216 (2.1)	1,163 (2.6)	**1.28 (1.19-1.38)**	**1.48 (1.35-1.62)** [d]	690 (2.9)	**1.39 (1.28-1.52)**	**1.53 (1.40-1.68)** [d]	21 (2.8)	1.34 (0.87-2.07)	1.52 (0.97-2.36) [d]
Missing	635 (0.6)	105 (0.2)	n/a	n/a	75 (0.3)	n/a	n/a	3 (0.4)	n/a	n/a
Cryptorchidism (only males included)										
No	54,509 (99.3)	22,616 (99.0)	1.00	1.00	12,247 (99.1)	1.00	1.00	394 (99.4)	1.00	1.00
Yes	357 (0.7)	236 (1.0)	**1.59 (1.35-1.88)**	0.92 (0.77-1.11) [b]	107 (0.9)	**1.33 (1.07-1.66)**	0.87 (0.69-1.09) [b]	1 (0.3)	0.39 (0.05-2.77)	0.28 (0.04-1.98) [b]
Neural Tube Defects										

No	107,093 (99.9)	43,928 (99.8)	1.00	1.00	24,077 (99.9)	1.00	1.00	762 (100)	1.00	1.00
Yes	50 (0.1)	70 (0.2)	**3.41 (2.37-4.91)**	**1.64 (1.08-2.47)** [b]	22 (0.1)	**1.96 (1.19-3.23)**	1.21 (0.71-2.06) [b]	0 (0.0)	n/a	n/a
Amniotic Band Defects										
No	107,053 (99.9)	43,936 (99.9)	1.00	1.00	24,070 (99.9)	1.00	1.00	760 (99.7)	1.00	1.00
Yes	90 (0.1)	62 (0.1)	**1.68 (1.21-2.32)**	1.02 (0.71-1.47) [b]	29 (0.1)	1.43 (0.94-2.18)	0.98 (0.63-1.52) [b]	2 (0.3)	3.13 (0.77-12.73)	2.29 (0.56-9.37) [b]
Hypospadias (only males included)										
No	54,607 (99.5)	22,600 (98.9)	1.00	1.00	12,258 (99.2)	1.00	1.00	390 (98.7)	1.00	1.00
Yes	259 (0.3)	252 (1.1)	**2.35 (1.98-2.80)**	**1.27 (1.05-1.54)** [b]	96 (0.8)	**1.65 (1.31-2.09)**	1.07 (0.84-1.37) [b]	5 (1.3)	**2.70 (1.11-6.59)**	1.91 (0.78-4.68) [b]
Gastroschisis										
No	107,120 (99.9)	43,979 (99.9)	1.00	1.00	24,089 (99.9)	1.00	1.00	762(100)	1.00	1.00
Yes	23 (0.1)	19 (0.1)	**2.01 (1.10-3.70)**	1.10 (0.56-2.20) [b]	10 (0.1)	1.93 (0.92-4.06)	0.99 (0.45-2.21) [b]	0 (0.0)	n/a	n/a
At least one outcome*										
No	106,367 (99.3%)	43,363 (98.6%)	1.00	1.00	23,835 (98.9%)	1.00	1.00	754 (99.0%)	1.00	1.00
Yes	776 (0.7%)	635 (1.4%)	**2.01 (1.81-2.23)**	1.12 (0.99-1.26) [b]	264 (1.1%)	**1.52 (1.32-1.75)**	0.97 (0.84-1.13) [b]	8 (1.0%)	1.45 (0.72-2.93)	1.11 (0.55-2.23) [b]

592 n/a, not applicable; n, number of pregnancies

593 [a] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, maternal hypertensive disorders, maternal antepartum

594 haemorrhage

595 [b] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at delivery

596 [c] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking

597 [d] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of delivery

598 *Including cryptorchidism, neural tube defects, amniotic band defects, hypospadias, gastroschisis

Table 3. Sub-group regression analysis between control pregnancies and exposed to diclofenac.

Outcomes	No analgesic (n=20,544) n (%)	Diclofenac 2005-2015 (n=10,291) n (%)	Crude OR (CI 95%)	Adjusted OR (CI 95%)
Gestation at delivery (weeks)				
>=37	19,407 (94.5%)	9,640 (93.7%)	1.00	1.00
<37	1,137 (5.5%)	651 (6.3%)	**1.15 (1.04, 1.27)**	1.10 (0.99, 1.22) [a]
Pregnancy outcome				
Livebirth	20,393 (99.3%)	10,227 (99.4%)	1.00	1.00
Stillbirth	116 (0.5%)	39 (0.4%)	**0.67 (0.47, 0.96)**	**0.59 (0.41, 0.87)** [a]
Neonatal Death	35 (0.2%)	25 (0.2%)	1.42 (0.85, 2.38)	1.26 (0.73, 2.15) [a]
Weight of baby (grams)				
NBW	16,869 (82.1%)	8,116 (78.9%)	1.00	1.00
LBW	965 (4.7%)	572 (5.6%)	**1.23 (1.11, 1.37)**	**1.22 (1.07, 1.40)** [b]
HBW	2,707 (13.2%)	1,600 (15.5%)	**1.23 (1.15, 1.31)**	**1.21 (1.13, 1.29)** [b]
Missing	3 (0.0%)	3 (0.0%)		
Standardised Birthweight Score				
	-0.039 (0.959)	0.132 (1.036)	**0.171 (0.145, 0.197)**	**0.167 (0.141, 0.193)** [c]
Admitted to neonatal unit				
No	18,224 (88.7%)	8,747 (85.0%)	1.00	1.00
Yes	2,175 (10.6%)	1,492 (14.5%)	**1.43 (1.33, 1.53)**	**1.46 (1.35, 1.58)** [b]
Missing	145 (0.7%)	52 (0.5%)		
APGAR score at 1 min				
Normal	18,709 (91.1%)	9,350 (90.9%)	1.00	1.00
<7	1,658 (8.1%)	924 (9.0%)	**1.12 (1.03, 1.21)**	0.93 (0.83, 1.04) [d]
Missing	177 (0.9%)	17 (0.2%)		
APGAR score at 5 min				
Normal	20,065 (97.7%)	10,096 (98.1%)	1.00	1.00
<7	302 (1.5%)	177 (1.7%)	0.86 (0.71, 1.04)	0.94 (0.72, 1.23) [d]
Missing	177 (0.9%)	18 (0.2%)		
Cryptorchidism (only males included)				
No	10,284 (98.7%)	5,314 (98.7%)	1.00	1.00
Yes	133 (1.3%)	70 (1.3%)	1.02 (0.76, 1.36)	1.05 (0.78, 1.42) [b]
Neural Tube Defects				
No	20,527 (99.9%)	10,263 (99.7%)	1.00	1.00
Yes	17 (0.1%)	28 (0.3%)	**3.29 (1.80, 6.02)**	**3.62 (1.95, 6.74)** [b]
Amniotic Band Defects				
No	20,514 (99.9%)	10,277 (99.9%)	1.00	1.00
Yes	30 (0.1%)	14 (0.1%)	0.93 (0.49, 1.76)	0.81 (0.41, 1.58) [b]
Hypospadias (only males included)				
No	10,317 (99.0%)	5,308 (98.6%)	1.00	1.00
Yes	100 (1.0%)	76 (1.4%)	**1.48 (1.09, 1.99)**	**1.49 (1.09, 2.03)** [b]
Gastroschisis				
No	20,538 (99.9%)	10,284 (99.9%)	1.00	1.00
Yes	6 (0.1%)	7 (0.1%)	2.33 (0.78, 6.94)	2.93 (0.97, 8.88) [b]
At least one outcome*				
No	20,258 (98.6%)	10,097 (98.1%)	1.00	1.00
Yes	286 (1.4%)	194 (1.9%)	**1.36 (1.13, 1.64)**	**1.38 (1.15, 1.67)** [b]

n/a, not applicable; n, number of pregnancies

[a] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at delivery, maternal hypertensive disorders, maternal antepartum haemorrhage

[b] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at delivery

[c] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking

[d] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of delivery

*Including cryptorchidism, neural tube defects, amniotic band defects, hypospadias, gastroschisis

Figure 1: Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis.*98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

Figure 2: Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. In 2005 there was a change in legislation making diclofenac available without prescription.

Figure S1: Directed acyclic graph (DAG) of exposure to outcome path and relevant measured and unmeasured biasing factors in our analysis.

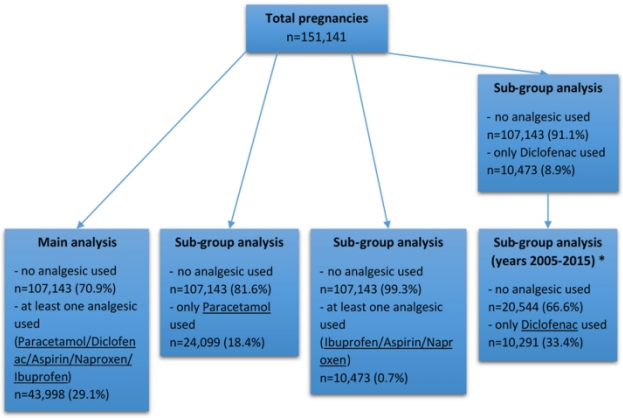


Figure 1: Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis.*98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

254x190mm (300 x 300 DPI)

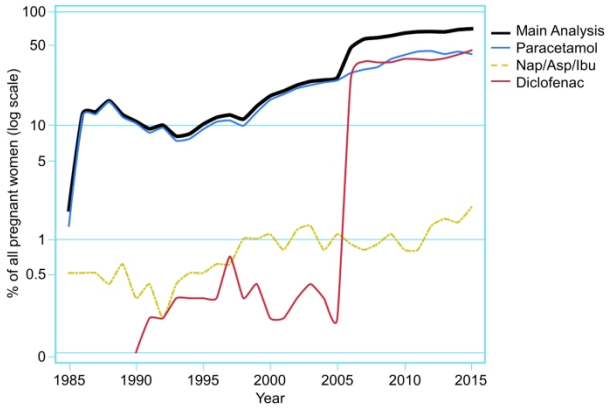
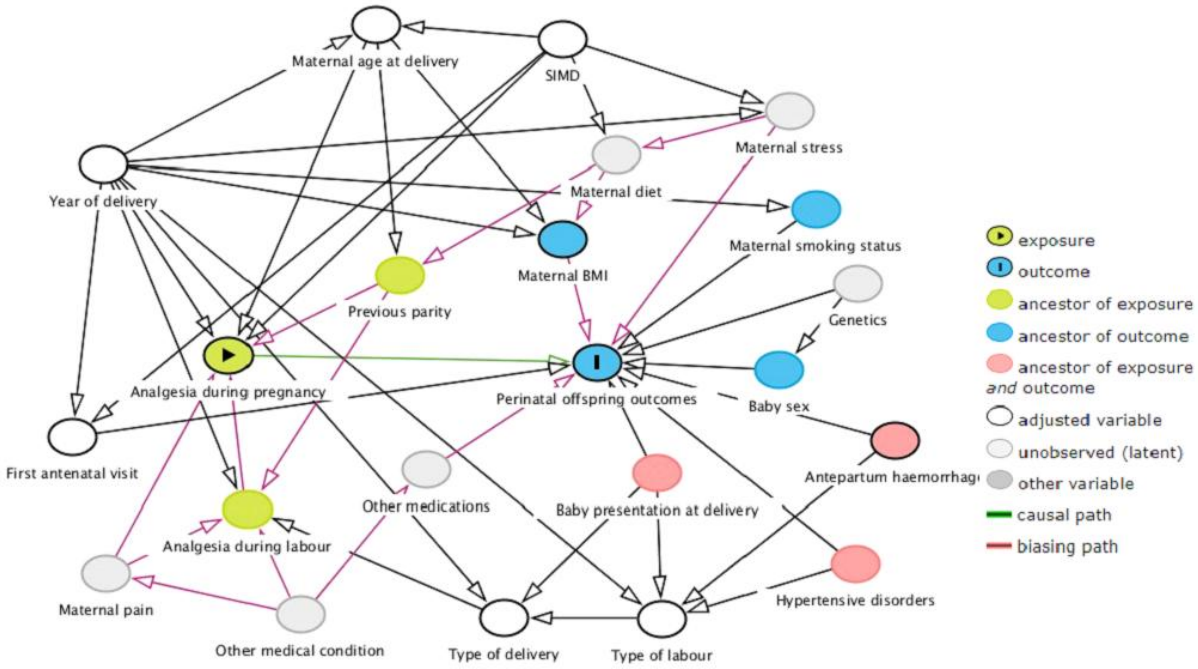


Figure 2: Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. In 2005 there was a change in legislation making diclofenac available without prescription.

254x190mm (300 x 300 DPI)


Maternal age at delivery
SIMD
Maternal stress
Year of delivery
Maternal diet
Maternal smoking status
Maternal BMI
Previous parity
Genetics
Analgesia during pregnancy
Perinatal offspring outcomes
Baby sex
First antenatal visit
Antepartum haemorrhage
Other medications
Baby presentation at delivery
Analgesia during labour
Maternal pain
Hypertensive disorders
Other medical condition
Type of delivery
Type of labour
exposure
outcome
ancestor of exposure
ancestor of outcome
ancestor of exposure and outcome
adjusted variable
unobserved (latent)
other variable
causal path
biasing path

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

	Item No	Recommendation	Paragraph #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**Title & Abstract Pages 1-3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**Abstract Pages 2-3**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**Introduction Page 5**
Objectives	3	State specific objectives, including any prespecified hypotheses	**Introduction Page 5**
Methods			
Study design	4	Present key elements of study design early in the paper	**Methods Page 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**Methods Page 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**Methods Pages 7-8**
		(*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	**Methods Pages 8-9**
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	**Methods Pages 8-9**
Bias	9	Describe any efforts to address potential sources of bias	**Methods Pages 7-8**
Study size	10	Explain how the study size was arrived at	**Methods Page 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**Methods Pages 8-9**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**Statistical Analysis paragraph pages 9-10**
		(*b*) Describe any methods used to examine subgroups and interactions	**Statistical Analysis paragraph pages 9-10**
		(*c*) Explain how missing data were addressed	**Statistical Analysis paragraph pages 9-10**
		(*d*) If applicable, explain how loss to follow-up was addressed	**n/a**
		(*e*) Describe any sensitivity analyses	**n/a**

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	**Figure 1**
		(b) Give reasons for non-participation at each stage	**Results Page 11**
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Table 1 Pages 29-31**
		(b) Indicate number of participants with missing data for each variable of interest	**Table 1 Pages 29-31**
		(c) Summarise follow-up time (eg, average and total amount)	**n/a**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**Tables 2 and 3 Pages 32-35**
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	**Tables 2 and 3 Pages 32-35**
		(*b*) Report category boundaries when continuous variables were categorized	**Table 1 Pages 29-31**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**Tables 2 and 3 Pages 32-35**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**n/a**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**Discussion Pages 16-17**
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	**Discussion Pages 16-18**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**Discussion Pages 19-21**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**Discussion Pages 20-21**
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	**Manuscript pages 4 and 21**

*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.

BMJ Open

Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: Cohort study of 151,141 singleton pregnancies

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048092.R1
Article Type:	Original research
Date Submitted by the Author:	12-Sep-2021
Complete List of Authors:	Zafeiri, Aikaterini; University of Aberdeen, School of Medicine, Medical Sciences and Nutrition Raja, Edwin Amalraj; University of Aberdeen, Medical Statistics Team Mitchell, Rod; The University of Edinburgh Hay, David ; University of Edinburgh Bhattacharya, Sohinee; University of Aberdeen Fowler, Paul ; University of Aberdeen
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Epidemiology < INFECTIOUS DISEASES, OBSTETRICS, CLINICAL PHARMACOLOGY

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Title: Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: Cohort study of 151,141 singleton pregnancies

Authors: [1]Aikaterini ZAFEIRI, MSci, Ms, [2]Edwin A. RAJA, PhD, [3]Rod T. MITCHELL, MBChB, PhD, [4]David C. HAY, PhD, [5]Sohinee BHATTACHARYA, MBBS, PhD, [1]Paul A. FOWLER, FRSB, PhD

[1]Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, [2]Medical Statistics Team, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, [3]MRC Centre for Reproductive Health, The Queen's Medical Research Institute, University of Edinburgh,47 Little France Crescent, Edinburgh, EH16 4JT, UK, [4]MRC Centre for Regenerative Medicine, 5 Little France Drive, Edinburgh, UK, [5]Aberdeen Centre for Women's Health Research, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom,

Corresponding Author: Aikaterini Zafeiri, Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, cell phone number: (+44)7713837285, email: r01az17@abdn.ac.uk

Running Title: Maternal over-the-counter analgesia and offspring outcomes

Abstract

OBJECTIVES

To identify any associations between *in utero* exposure to five over-the-counter (non-prescription) analgesics (paracetamol, ibuprofen, aspirin, diclofenac, naproxen) and adverse neonatal outcomes.

DESIGN

Retrospective cohort study using the Aberdeen Maternity and Neonatal Databank.

PARTICIPANTS

151,141 singleton pregnancies between 1985 and 2015.

MAIN OUTCOME MEASURES

Premature delivery (<37 weeks), stillbirth, neonatal death, birthweight, standardised birthweight score, neonatal unit admission, APGAR score at 1 and 5 minutes, neural tube and amniotic band defects, gastroschisis and, in males, cryptorchidism, and hypospadias.

RESULTS

83.7% of women taking over-the-counter analgesics reported first trimester use when specifically asked about use at their first antenatal clinic visit. Pregnancies exposed to at least one of the five analgesics were significantly independently associated with increased risks for premature delivery <37 weeks (aOR=1.50, 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), neonatal death (aOR=1.56, 95%CI 1.27-1.93), birthweight <2,500g (aOR=1.28, 95%CI 1.20-1.37), birthweight >4,000g (aOR=1.09, 95%CI 1.05-1.13), admission to neonatal unit

(aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at 1 minute (aOR=1.18, 95%CI 1.13-1.23) and 5 minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54 males only). The overall prevalence of over-the-counter analgesics use during pregnancy was 29.1%, however it rapidly increased over the 30-year study period, to include over 60% of women in the last seven years of the study. This makes our findings highly relevant to the wider pregnant population.

CONCLUSIONS

Over-the-counter (non-prescription) analgesics consumption during pregnancy was associated with a substantially higher risk for adverse perinatal health outcomes in the offspring. The use of paracetamol in combination with other non-steroidal anti-inflammatory drugs conferred the highest risk. The increased risks of adverse neonatal outcomes associated with non-prescribed, over-the-counter, analgesics use during pregnancy indicate that healthcare guidance for pregnant women regarding analgesic use need urgent updating.

Funding Biotechnology and Biological Sciences Research council (BBSRC) funding under the EASTBIO doctoral training programme (grant number 1942576) to AZ and EU Horizon 2020 project FREIA (Grant Number 825100) to PAF. RTM is supported by MRC Centre for Reproductive Health Grant MR/N022556/1.

Key words acetaminophen, aspirin, diclofenac, ibuprofen, *in utero* exposure, naproxen, offspring outcomes, over-the-counter analgesics, offspring outcomes, paracetamol, pregnancy

Introduction

Globally 23-85% of women use one or more types of prescribed medications during pregnancy [1,2]. A similarly high proportion of expectant mothers self-medicate using non-prescription, "over-the-counter" (OTC) medicines [3,4] and use during pregnancy is becoming increasingly prevalent, especially in Western countries [5]. While some analgesics e.g. paracetamol (acetaminophen) are considered safe to consume throughout pregnancy, use of non-steroidal anti-inflammatory drugs (NSAIDs) is not recommended in pregnancy unless on the advice of a medical specialist and should be avoided beyond gestational week 30 because of the risk of premature closure of the ductus arteriosus. However, current evidence is largely conflicting regarding the safety of gestational analgesic use both for the pregnancy and offspring health [6]. Several studies have reported increased risks for multiple adverse outcomes including hypospadias, cryptorchidism, amniotic band defects and neural tube defects [7–11], whilst others have not found significant associations [12–17]. Taken overall, this has led to significant concern that postnatal health is adversely affected by maternal analgesic use during pregnancy [18].

The use of small cohorts in the current epidemiological studies makes it difficult to draw firm conclusions and definite recommendations[12,17,19,20]. There are other aspects of analgesic use that have to be taken into account. Firstly, due to their abundance, it is not always feasible to determine exact consumption rates and dosage. Secondly, even though the mechanisms of action for most of these compounds is not fully understood, most over-the-counter analgesics can diffuse through the placenta and reach the developing fetus [21]. Thirdly, maternal pharmacokinetics during pregnancy are altered and there are limited pregnancy safety data for these compounds.

Given the diversity in study population, methodology, sample size and findings in the published studies, we conclude that more extensive data from larger cohorts are essential in order to understand the risks over-the-counter analgesic use during pregnancy pose to neonatal health and function. Here we address many limitations of previous studies by analysing one of the largest cohorts, widest range of health data and, pregnancy use of five over-the-counter analgesics consumed in combination or separately. We report on the prevalence of maternal consumption of five different over-the-counter analgesics during pregnancy and their associations with offspring neonatal outcomes using a large cohort of 151,141 singleton pregnancies spanning three decades of population-based data from a single maternity hospital serving the entire population of Aberdeenshire in the North East of Scotland.

Materials and Methods

This retrospective cohort study utilised data collected in the Aberdeen Maternity and Neonatal Databank (AMND) in Aberdeen, UK on 151,141 pregnancies over a 30 year period (1985-2015). Details about AMND have been previously published [22]. Data were collected from medical notes of women retrospectively after delivery. Women were specifically asked about their use of over-the-counter (non-prescription) analgesics at their first antenatal clinic. Data were entered by dedicated coding staff into a computerised database. Data validity was ensured via checking completeness of data entry against NHS (UK National Health Service) returns monthly and constant data cleaning and validation against case notes reported quarterly by the Data Management team to the AMND Steering Committee. A research protocol was submitted and approved by the AMND Steering Committee before data extraction. Approval was received on 6 June 2018. The dataset was fully anonymised, therefore there was no requirement for NHS ethics committee approval. There was no involvement of patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

The main analysis considered consumption during pregnancy of at least one out of five different analgesics: paracetamol (no; yes), ibuprofen (no; yes), naproxen (no; yes), diclofenac (no; yes) or aspirin (no; yes) as the exposure group against no analgesic consumption as the unexposed group. Then, three sub-group analyses against the control group were performed using only paracetamol, only diclofenac, or at least one analgesic from aspirin/naproxen/ibuprofen as exposure groups, excluding pregnancies exposed to multiple analgesics at the same time (Figure 1). As 98.3% of pregnancies using diclofenac were between 2005 and 2015, diclofenac sub-group analysis only considered pregnancies during that time frame in order to

rule out any temporal effect. Analgesic consumption was not further assessed analytically.

The offspring outcomes compared between control and exposed groups were: gestation at delivery (preterm <37 gestation weeks, term ≥37 gestation weeks), pregnancy outcome (livebirth, stillbirth, neonatal death), baby weight (low birth weight (LBW) ≤2,499 g, high birth weight (HBW) ≥4,000 g, normal birth weight (NBW) 2,500g-3,999 g), standardised birthweight score was considered as a continuous variable as previously described by Campbell and colleagues[23], baby admission to neonatal unit (no; yes), APGAR score at one and five minutes (<7, ≥7), cryptorchidism (no; yes) (ICD-10 code Q53), neural tube defects (no; yes) (ICD-10 code Q00-07), amniotic band defects (no; yes) (ICD-10 codes Q70-74), hypospadias (no; yes) (ICD-10 code Q54), gastroschisis (no; yes) (ICD-10 code Q79.3). A composite outcome (presence of at least one congenital anomaly (no; yes)) was created using the variables neural tube defects, amniotic band defects, and gastroschisis and, in males, cryptorchidism and hypospadias.

The baseline characteristics compared between exposed and unexposed pregnancies were (reference category first): year of delivery (1985-1994, 1995-2004, 2005-2015), maternal age at delivery (20-25, <20, 26-35, >35 years), previous pregnancy (no; yes), maternal body mass index (BMI) (normal weight 18.5-24.9 kg/m^2, underweight <18.5 kg/m^2, overweight 25-29.9 kg/m^2, obese >30 kg/m^2), maternal first antenatal visit (1st, 2nd, 3rd trimester), maternal smoking status (non-smoker, smoker, ex-smoker), Scottish Index of Multiple Deprivation (SIMD) decile (1-6, 7-10, decreasing deprivation with increasing score), maternal hypertensive disorders (no disorder, gestational hypertension, preeclampsia, eclampsia), maternal antepartum haemorrhage (no haemorrhage, abruption, placental previa), type of

labour (spontaneous, elective caesarean section, induced), type of delivery (spontaneous vaginal delivery, instrumental, caesarean section), analgesia during labour (no; yes), baby presentation at delivery (occiput anterior, occiput posterior), baby sex (female; male).

Patient and Public Involvement

This was a retrospective analysis of data on singleton pregnancies over a 30-year period. Therefore, there was no involvement of patients or the public in the design, conduct, reporting or any other aspect of the study.

Statistical Analysis

Baseline characteristics were compared between exposed and unexposed pregnancies to any analgesic using χ^2 test for categorical variables and t-test for normally distributed continuous variables as appropriate. Relationships between exposures and outcomes were examined by binary logistic regression for binary outcome variables, multinomial logistic regression for nominal categorical outcome variables, and multiple linear regression for continuous variables. The strength of association was reported as odds ratios (ORs) with 95% confidence intervals (CI). The socio-demographic characteristics that were likely to confound our exposure-to-outcome path were identified using a directed acyclic graph (DAG) (Figure S1)[24]. Factors that were associated with consumption of over-the-counter analgesics during pregnancy at 10% level of significance and deemed clinically relevant, were included in the model as confounders. All outcomes were adjusted for year of delivery, maternal age at delivery, SIMD and maternal first antenatal visit. In addition to these confounders, individual outcomes were adjusted for relevant cofactors. Gestation at

delivery and pregnancy outcome were both additionally adjusted for maternal hypertensive disorders and antepartum haemorrhage. Weight of the baby, neonatal unit admission, cryptorchidism, neural tube defects, amniotic band defects, hypospadias and gastroschisis variables were also adjusted for gestation at delivery. APGAR score at one and five minutes were adjusted for type of delivery. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using IBM SPSS Statistics version 25.0 (Released 2017. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). R version 3.6.2 was used to generate Figure 2. Numbers needed to harm (NNH) were also calculated for each outcome and are provided in Supplementary Tables 1 and 2.

Results

83.7% of women taking over-the-counter analgesics reported first trimester use when specifically asked about use at their first antenatal clinic. Overall, from the total 151,141 pregnancies across 30 years in 107,143 (70.9%) pregnancies, no over-the-counter analgesic consumption was reported. At least one over-the-counter analgesic was consumed in 43,998 (29.1%) pregnancies, whereas paracetamol use alone was reported in 24,099 (18.4%) pregnancies. Diclofenac use was observed in 20.0% of pregnancies in the 10-year period when diclofenac was available over-the-counter (without prescription). Finally, at least one out of three analgesics (naproxen, ibuprofen, aspirin) was consumed in 762 (0.7%) pregnancies (Figure 1).

Prevalence of use for all five analgesics increased dramatically over the 30-year study period (1985-2015) (Figure 2). Pregnancies with consumption of at least one analgesic increased from 1.8% in 1985 to 70.6% in 2015. Pregnancies reporting paracetamol use were 1.3% in 1985 and it continuously increased reaching 42.2% in 2015. Naproxen, ibuprofen or aspirin consumption during pregnancy was less prevalent (Figure 2A), however it also increased during the 30-year study period, starting at 0.5% in 1985 and reaching 1.9% in 2015 (Figure 2B). Diclofenac was consumed in very few pregnancies between 1985 (<0.01%) and 2005 (0.2%). Percentage of consumption, however, dramatically increased during the next decade following deregulation of diclofenac, reaching 25.0% in just one year (2006) and 45.6% of all pregnancies in 2015.

Table 1 compares the baseline characteristics between the unexposed group of pregnancies where no analgesic was consumed and each of the exposure groups. In most, but not all, comparisons across all four analyses, there was a statistically

significant difference (p<0.001) for most variables. In the paracetamol sub-group analysis, baby presentation at delivery (p=0.525) and sex of the baby (p=0.861) were not significantly different between the groups. In the analysis considering consumption of at least one analgesic from aspirin/naproxen/ibuprofen, again the variables for baby presentation at delivery (p=0.093) and sex of the baby (p=0.732), together with maternal smoking status (p=0.132) and maternal antepartum haemorrhage (p=0.434) were not statistically different compared to the unexposed group. All variables were statistically different between unexposed and exposed groups for the main analysis and diclofenac sub-group analysis.

Table 2 summarises the comparison of neonatal outcomes between the unexposed group (no analgesic at all) and the exposed groups of at least one analgesic, only paracetamol and at least one out of aspirin/naproxen/ibuprofen. Comparison of outcomes for the diclofenac sub-group analysis is shown in Table 3.

All analgesics and neonatal outcomes

As shown in Table 2, compared to unexposed pregnancies in which women did not use any analgesic, pregnancies with consumption of at least one analgesic (paracetamol, diclofenac, aspirin, naproxen, ibuprofen) were independently associated with significantly higher odds for premature delivery (aOR=1.50, 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI1.15-1.54), LBW (aOR=1.28, 95%CI 1.20-1.37), HBW (aOR=1.09, 95%CI 1.05-1.13), baby admission to neonatal unit (aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at five minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54) in adjusted analyses. Significantly decreased odds for

APGAR score <7 at one minute were found in the crude analysis (cOR=0.96, 95%CI 0.92-0.99), however when adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking and type of delivery, the significance changed direction showing significantly increased odds (aOR=1.18, 95%CI 1.13-1.23). A significantly lower standardised birthweight score (p=0.046, 95%CI 0.032-0.059) was found for the exposure group compared to no analgesic at all. Cryptorchidism (aOR=0.92, 95%CI 0.77-1.11), amniotic band defects (aOR=1.02, 95%CI 0.71-1.47), gastroschisis (aOR=1.10, 95%CI 0.56-2.20) and the composite outcome variable (aOR=1.12, 95%CI 0.99-1.26), were all associated with increased odds in the exposure group compared to not exposed, however the association was not significant in the adjusted model. There was no significant association between neonatal death and exposure to at least one analgesic in the crude analysis (cOR=1.19, 95%CI 0.99-1.42), however there were significantly higher odds of neonatal death in the adjusted analysis (aOR=1.56, 95%CI 1.27-1.93) in the exposed group compared to control.

Paracetamol and neonatal outcomes

In the sub-group analysis considering only paracetamol consumption during pregnancy as our exposure group, most of the associations reported in the main analysis remained significant with the same direction of significance (Table 2). The differences were: maternal paracetamol consumption during pregnancy was associated with significantly decreased odds for offspring HBW (cOR=0.94, 95%CI 0.90-0.99) in the crude analysis however significance was lost in the adjusted model (aOR=0.98, 95%CI 0.93-1.02), and there were no significant associations in the

adjusted models for neural tube defects (aOR=1.21, 95%CI 0.71-2.06) and hypospadias (aOR=1.07, 95%CI 0.84-1.37).

Aspirin/naproxen/ibuprofen and neonatal outcomes

Consumption of at least one analgesic from aspirin, naproxen or ibuprofen during pregnancy was compared against the same control group of pregnancies where no analgesic was used (Table 2). Again, when comparing associations between groups in this sub-group analysis and main analysis, fewer outcome variants showed similar significance pattern. The only shared significant associations were for increased odds for premature delivery (aOR=1.42, 95%CI 1.08-1.86), stillbirth (aOR=2.34, 95%CI 1.29-4.25) and baby admission to neonatal unit (aOR=1.54, 95%CI 1.22-1.94) in the adjusted regression analyses.

Diclofenac and neonatal outcomes

In the sub-group analysis of pregnancies coinciding with non-prescription, over-the-counter, availability of diclofenac (years 2005-2015) were considered, and outcomes compared between the diclofenac group and no analgesic consumption group (Table 3). Compared to the main analysis, diclofenac consumption during pregnancy was not significantly associated with premature delivery (aOR=1.10, 95%CI 0.99-1.22), neonatal death (aOR=1.26, 95%CI 0.73-2.15) and APGAR score <7 in one minute (aOR=0.93, 95%CI 0.83-1.04) in the adjusted models. Associations with APGAR score <7 in five minutes (aOR=0.94, 95%CI 0.72-1.23), cryptorchidism (aOR=1.05, 95%CI 0.78-1.42), amniotic band defects (aOR=0.81, 95%CI 0.41-1.58) and gastroschisis (aOR=2.93, 95%CI 0.97-8.88) were no longer significant in both crude

and adjusted analyses. Maternal consumption of diclofenac was independently associated with a significant decrease in stillbirth (aOR=0.59, 95%CI 0.41-0.87). It is also interesting to note that diclofenac was the only sub-group analysis agreeing with the main analysis (exposure to at least one analgesic) on the significance of exposure association with increased incidence of neural tube defects (aOR=3.62, 95%CI 1.95-6.74) and hypospadias (aOR=1.49, 95%CI 1.09-2.03) compared to unexposed pregnancies in adjusted models. As most of the outcomes studied were relatively rare the numbers needed to harm were mostly more than 100. Preterm birth, low birthweight and admission to the neonatal unit were exceptions with NNH ranging from 15 to 38. (Tables S1 and S2).

Discussion

Main Findings

Consumption of paracetamol, ibuprofen, aspirin and naproxen during pregnancy, either in combination or separately, was significantly associated with increased premature delivery, stillbirth, neonatal death, LBW, abnormal standardised birthweight score and more frequent admission to neonatal unit. Consumption of paracetamol alone was further associated with higher odds for APGAR score <7 at one and five minutes both in crude and adjusted analyses. There was a dramatic increase in the frequency of over-the-counter (non-prescription) analgesic use in pregnancies between 1985 and 2015, reaching 70.5% of women using those compounds in the final decade of our study. This means that our findings are applicable far beyond the percentage (between 14% and 38%) [25] of pregnant women with underlying health deficits related to the adverse outcomes we report here.

Diclofenac use increased steeply from 2005 (Figure 2A), which reflects the change in Scottish legislation, leading to diclofenac becoming available without prescription in that year. Diclofenac use was associated with fewer adverse outcomes but showed increased risk of neural tube defects and hypospadias in male neonates. Furthermore, and surprisingly, exposure to diclofenac only was associated with significant decrease in the incidence of stillbirth. The reasons for such differences between the changes in neonatal outcomes following diclofenac consumption compared with those following use of the other NSAIDS are not clear. The proportion of women using diclofenac, especially in the last 7 years of our study makes it highly unlikely to be due to an underlying maternal condition and/or other compounds used

in combination (e.g. prescriptions) by women taking diclofenac. It is possible that the drug could act directly on fetal development then this difference could also be due to structural and/or mechanistic differences of the compound compared to the other drugs. However, not enough is known about the specific mechanisms of action of the different analgesics studied to conclude further. Overall, comparing our main analysis with all three sub-analyses, it is evident that the most significant differences were observed when paracetamol was taken with at least one other analgesic. This is mostly due to the high number of pregnancies where paracetamol was used, comprising almost 55% of the exposed cases in the main analysis. Most numbers needed to harm for our outcomes (Tables S1 and S2) ranged between 1000 and 100, apart from preterm birth, low birth weight and baby admission to neonatal unit, which were 27, 38 and 15 respectively for our main analysis further strengthening observed associations.

Strengths and Limitations

A major strength of the present study is the large cohort of 151,141 pregnancies over a 30-year study period from 1985 until 2015, using a robust data source AMND. This is one of the largest cohorts used in studies examining the effects of analgesic use during pregnancy. The dataset contains high quality and consistent data from the geographically defined area of Aberdeen and surrounding district, in the North East of Scotland, UK. In addition, as Aberdeen Maternity Hospital is the only maternity hospital serving the area, over 95% of pregnancies in the area are included in the dataset, considerably minimizing the risk for selection bias. We were able to analyse maternal consumption data of the five most commonly used analgesics available

over-the-counter in the UK and most countries, which is not matched in the current literature. The nature of our data allowed for the analysis of analgesics consumed alone or in combination, unlike most existing studies, and this gives our study the added strength of better reflecting real-life consumption patterns [26,27]. We were able to adjust for important confounding factors, relevant to each analysed outcome. Adjustment for maternal deprivation also allowed us to further account for potential unmeasured factors that can influence maternal and neonatal health, which is a major strength of our analysis compared to most studies.

A potential concern was that women were probably using analgesics to treat some inherent medical condition which in turn could have been the mediating factor for adverse outcomes. However, since these medications are widely available without prescription, this is unlikely to be a factor that affects the findings of this study. This is especially the case during the “diclofenac analysis” covering 2005-2015, where this study presents results on multiple neonatal outcomes for the given cohort. In this way we offer a comprehensive approach to the exploration of associations with *in utero* analgesic exposure rather than only focusing on a single outcome of interest. Our data were based on medical notes; however, over-the-counter consumption is self-reported, and details on the timing, duration, dosage, product type (single-ingredient vs combination) and administration type were not available in the database. In addition, the group of pregnancies with aspirin consumption might include use of low-dose aspirin which is recommended to help reduce risk of some pregnancy complications and outcomes related to placental function. Most women had their first antenatal clinic visit during the 1st pregnancy trimester, which might imply our results were affected by primarily 1st trimester exposure, although analgesic use in first trimester is most likely replicated in the rest of pregnancy.

Complete case analyses were performed ignoring pregnancies with missing data in the covariates, however due to the low number of missing data there is little chance that this might have affected the validity of our results. Compared to our cohort size, there were, overall, very few cases of cryptorchidism, neural tube defects, amniotic band defects, hypospadias and gastroschisis, resulting in potentially underpowered statistical analyses to detect a difference for these outcomes. Our study only considered neonatal health outcomes and follow-up of the offspring was not available at this time.

Interpretation

Previous literature has considered fewer outcomes with fewer analgesic combinations compared to our study. Consistent with our results, increased risk of preterm birth and miscarriage has been associated with analgesic consumption during pregnancy [28–31], while others reported no associations with miscarriage, stillbirth or preterm delivery [20,28,29,32]. Similarly, increased risk for offspring cryptorchidism, hypospadias, neural tube defects, amniotic band defects and gastroschisis have been shown by many studies [7–9,33–40], although, again, a lack of associations with major birth defects have been reported [13–17,41,42]. Compared to our analysis, all these studies used a smaller cohort, considered a shorter study time and there was frequent disagreement with respect to the choices of adjusted confounding factors. Another difference is that maternal questionnaires/interviews were frequently the method of choice to evaluate maternal consumption. Some of the studies reported increased risks for specific pregnancy trimesters which is something our study could not evaluate. Differences in study design and adjustment

for different confounders might also account for the disagreement of our results that provide a more accurate assessment. Our study is one of the largest in terms of cohort size, duration, number of analgesics and range of outcomes included which might also contribute to differences compared to other studies.

The literature currently reports conflicting evidence, limiting our ability for definite decision-making. Over-the-counter analgesics are recommended to women by healthcare professionals in order to deal with pregnancy symptoms and other conditions. Policy-makers have taken a stand on the topic, either being reassuring about over-the-counter use during pregnancy or recommending caution when consumption is necessary [43–46]. Different compounds can affect the mother and the fetus in a different way, and their combined use might worsen the risk for offspring ill health. This study demonstrates the need for additional research, before the field can be confidently directed towards one direction or the other.

Whether the associations we report result from flu, fever, rheumatological or inflammatory conditions, and/or combination with other prescribed medications or solely related to over-the-counter analgesics consumption is a matter of further research. Underlying health conditions could well influence the outcomes we see in this study, however, as these could be very different conditions it is biologically unlikely that they are responsible for the effects we observe here. Our study demonstrates an association of maternal over-the-counter analgesic consumption during pregnancy with adverse neonatal offspring outcomes. Future collaborative approaches such as an individual patient data meta-analysis that includes follow-up data on long-term outcomes during childhood and adulthood would significantly inform decision making. Going forward, uncovering the mechanisms of action and off target effects will also provide a solid foundation for the development of pregnancy-

safe compounds. Finally, the findings present here suggest that diclofenac is associated with fewer changes in risk for the more frequent adverse outcomes although it is associated more with rarer, but severe, negative outcomes, including neural tube defects. Diclofenac may have a lower risk for the main adverse neonatal outcomes reported for paracetamol. However, it should be noted that our study is not designed to specifically test differences in level of risk between the analgesics included. Therefore, it should be emphasised that this does not mean that the authors are stating that diclofenac is preferable to paracetamol.

Conclusions

Pain control is currently a therapeutic priority during pregnancy. Our findings of increased risk of adverse health outcomes for the offspring following at least first trimester maternal use of readily available over-the-counter analgesics are crucial to information for the management of pain during pregnancy.

Acknowledgements: N/A

Disclosure of interests: Professor David Hay is a founder, director and shareholder in Stemnovate Limited. The remaining authors have no interests to disclose.

Contribution to Authorship: AZ, SB and PAF contributed to the conception, design and coordination of the research. EAR provided critical input in the design and planning of statistical analysis. AZ conducted the statistical analysis and prepared the manuscript, figures and tables. AZ, SB, PAF, RTM and DCH substantially contributed to the analysis and interpretation of the work. All authors contributed to

critical discussion of intellectual content, development and review/approval of the final manuscript version.

Funding: This work is supported by the Biotechnology and Biological Sciences Research council (BBSRC) funding the lead author under the EASTBIO doctoral training programme and to PAF, the EU Horizon 2020 project FREIA (Grant Number 825100). RTM is supported by MRC Centre for Reproductive Health Grant MR/N022556/1. The funders had no role in study design, data collection, data analysis, decision to publish, or manuscript preparation.

Ethics Statement: The AMND dataset used in this study was fully anonymised, therefore there was no requirement for ethical approval. The North of Scotland Research Ethics Service has devolved Caldicott approval to the Chair of the AMND steering committee. Approval to access and analyse data was obtained from the AMND steering Committee (AMND 004/2018).

Data Availability Statement: No additional data available.

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Table 2. Comparison of offspring outcomes between control (no analgesic) and groups exposed to at least one analgesic, only paracetamol, and at least one from ibuprofen, aspirin, naproxen.

Outcomes	No analgesic (n=107,143) n (%)	At least one analgesic (n=43,998) n (%)	Crude OR (CI 95%)	Adjusted OR (95% CI)	Paracetamol (n=24,099) n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Ibu/Asp/Napr (n=762) n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Gestation at delivery (weeks)										
>=37	100,879 (94.2)	39,838 (90.5)	1.00	1.00	21,589 (89.6)	1.00	1.00	697 (91.5)	1.00	1.00
<37	6,264 (5.8)	4,160 (9.5)	**1.68 (1.61-1.75)**	**1.50 (1.43-1.58)** [a]	2,510 (10.4)	**1.87 (1.78-1.97)**	**1.56 (1.48-1.65)** [a]	65 (8.5)	**1.50 (1.16-1.94)**	**1.42 (1.08-1.86)** [a]
Pregnancy outcome										
Livebirth	105,949 (98.9)	43,407 (98.7)	1.00	1.00	23,704 (98.4)	1.00	1.00	747 (98.0)	1.00	1.00
Stillbirth	803 (0.7)	405 (0.9)	**1.23 (1.09-1.39)**	**1.33 (1.15-1.54)** [a]	275 (1.1)	**1.53 (1.33-1.76)**	**1.52 (1.30-1.77)** [a]	13 (1.7)	**2.30 (1.32-3.99)**	**2.34 (1.29-4.25)** [a]
Neonatal Death	373 (0.3)	182 (0.4)	1.19 (0.99-1.42)	**1.56 (1.27-1.93)** [a]	117 (0.5)	**1.40 (1.14-1.73)**	**1.56 (1.24-1.96)** [a]	2 (0.3)	0.76 (0.19-3.06)	0.93 (0.23-3.74) [a]
Missing	18 (<0.1)	4 (<0.1)	n/a	n/a	3 (<0.1)	n/a	n/a	0 (0.0)	n/a	n/a
Weight of baby (grams)										
NBW	87,966 (82.1)	34,555 (78.6)	1.00	1.00	19,163 (79.5)	1.00	1.00	605 (79.5)	1.00	1.00
LBW	5,910 (5.5)	3,571 (8.1)	**1.54 (1.47-1.61)**	**1.28 (1.20-1.37)** [b]	2,213 (9.2)	**1.72 (1.63-1.81)**	**1.60 (1.51-1.69)** [b]	59 (7.7)	**1.45 (1.11-1.90)**	1.29 (0.91-1.83) [b]
HBW	13,233 (12.4)	5,863 (13.3)	**1.13 (1.09-1.17)**	**1.09 (1.05-1.13)** [b]	2,720 (11.3)	**0.94 (0.90-0.99)**	0.98 (0.93-1.02) [b]	97 (12.7)	1.07 (0.86-1.32)	0.99 (0.80-1.24) [b]
Missing	34 (<0.1)	9 (<0.1)	n/a	n/a	3 (<0.1)	n/a	n/a	1 (0.1)	n/a	n/a
Standardised Birthweight Score§										
Mean (SD)	0.001 (0.003)	-0.002 (0.065)	**0.03 (0.02-0.04)**	**0.046 (0.032-0.059)** [c]	0.001 (0.991)	**-0.04 (-0.058- -0.029)**	**-0.014 (-0.029-0.001)** [c]	0.046 (0.038)	**0.045 (-0.029-0.119)**	**0.049 (-0.025-0.123)** [c]
Admitted to neonatal unit										
No	62,378 (58.2)	32,391 (73.6)	1.00	1.00	16,342 (67.8)	1.00	1.00	480 (63.0)	1.00	1.00
Yes	11,011 (10.3)	7,448 (16.9)	**1.30 (1.26-1.35)**	**1.57 (1.51-1.64)** [b]	3,956 (16.4)	**1.37 (1.32-1.43)**	**1.45 (1.38-1.53)** [b]	117 (15.4)	**1.38 (1.13-1.69)**	**1.54 (1.22-1.94)** [b]
Missing	33,754 (31.5)	4,159 (9.5)	n/a	n/a	3,801 (15.8)	n/a	n/a	762 (21.7)	n/a	n/a
APGAR score at 1 min										
Normal	92,217 (86.1)	38,224 (86.9)	1.00	1.00	20,593 (85.5)	1.00	1.00	659 (86.5)	1.00	1.00
<7	14,335 (13.4)	5,674 (12.9)	**0.96 (0.92-0.99)**	**1.18 (1.13-1.23)** [d]	3,437(14.3)	**1.07 (1.03-1.12)**	**1.23 (1.18-1.28)** [d]	101 (13.3)	0.99 (0.80-1.22)	1.07 (0.86-1.32) [d]
Missing	591 (0.6)	100 (0.2)		n/a	69 (0.3)	n/a	n/a	2 (0.3)	n/a	n/a
APGAR score at 5 min										
Normal	104,292 (97.3)	42,730 (97.1)	1.00	1.00	23,334 (96.8)	1.00	1.00	738 (96.9)	1.00	1.00
<7	2,216 (2.1)	1,163 (2.6)	**1.28 (1.19-1.38)**	**1.48 (1.35-1.62)** [d]	690 (2.9)	**1.39 (1.28-1.52)**	**1.53 (1.40-1.68)** [d]	21 (2.8)	1.34 (0.87-2.07)	1.52 (0.97-2.36) [d]
Missing	635 (0.6)	105 (0.2)	n/a	n/a	75 (0.3)	n/a	n/a	3 (0.4)	n/a	n/a
Cryptorchidism (only males included)										
No	54,509 (99.3)	22,616 (99.0)	1.00	1.00	12,247 (99.1)	1.00	1.00	394 (99.4)	1.00	1.00
Yes	357 (0.7)	236 (1.0)	**1.59 (1.35-1.88)**	0.92 (0.77-1.11) [b]	107 (0.9)	**1.33 (1.07-1.66)**	0.87 (0.69-1.09) [b]	1 (0.3)	0.39 (0.05-2.77)	0.28 (0.04-1.98) [b]
Neural Tube Defects										

No	107,093 (99.9)	43,928 (99.8)	1.00	1.00	24,077 (99.9)	1.00	1.00	762 (100)	1.00	1.00
Yes	50 (0.1)	70 (0.2)	**3.41 (2.37-4.91)**	**1.64 (1.08-2.47)** [b]	22 (0.1)	**1.96 (1.19-3.23)**	1.21 (0.71-2.06) [b]	0 (0.0)	n/a	n/a
Amniotic Band Defects										
No	107,053 (99.9)	43,936 (99.9)	1.00	1.00	24,070 (99.9)	1.00	1.00	760 (99.7)	1.00	1.00
Yes	90 (0.1)	62 (0.1)	**1.68 (1.21-2.32)**	1.02 (0.71-1.47) [b]	29 (0.1)	1.43 (0.94-2.18)	0.98 (0.63-1.52) [b]	2 (0.3)	3.13 (0.77-12.73)	2.29 (0.56-9.37) [b]
Hypospadias (only males included)										
No	54,607 (99.5)	22,600 (98.9)	1.00	1.00	12,258 (99.2)	1.00	1.00	390 (98.7)	1.00	1.00
Yes	259 (0.3)	252 (1.1)	**2.35 (1.98-2.80)**	**1.27 (1.05-1.54)** [b]	96 (0.8)	**1.65 (1.31-2.09)**	1.07 (0.84-1.37) [b]	5 (1.3)	**2.70 (1.11-6.59)**	1.91 (0.78-4.68) [b]
Gastroschisis										
No	107,120 (99.9)	43,979 (99.9)	1.00	1.00	24,089 (99.9)	1.00	1.00	762(100)	1.00	1.00
Yes	23 (0.1)	19 (0.1)	**2.01 (1.10-3.70)**	1.10 (0.56-2.20) [b]	10 (0.1)	1.93 (0.92-4.06)	0.99 (0.45-2.21) [b]	0 (0.0)	n/a	n/a
At least one outcome*										
No	106,367 (99.3%)	43,363 (98.6%)	1.00	1.00	23,835 (98.9%)	1.00	1.00	754 (99.0%)	1.00	1.00
Yes	776 (0.7%)	635 (1.4%)	**2.01 (1.81-2.23)**	1.12 (0.99-1.26) [b]	264 (1.1%)	**1.52 (1.32-1.75)**	0.97 (0.84-1.13) [b]	8 (1.0%)	1.45 (0.72-2.93)	1.11 (0.55-2.23) [b]

n/a, not applicable; n, number of pregnancies

[a] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, maternal hypertensive disorders, maternal antepartum haemorrhage

[b] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at delivery

[c] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking

[d] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of delivery

§ Linear regression analysis reporting differences with 95% CI

*Including cryptorchidism, neural tube defects, amniotic band defects, hypospadias, gastroschisis

Table 3. Sub-group regression analysis comparing pregnancies unexposed to any analgesic and those exposed to diclofenac (years 2005-2015).

Outcomes	No analgesic (n=20,544) n (%)	Diclofenac 2005-2015 (n=10,291) n (%)	Crude OR (CI 95%)	Adjusted OR (CI 95%)
Gestation at delivery (weeks)				
>=37	19,407 (94.5%)	9,640 (93.7%)	1.00	1.00
<37	1,137 (5.5%)	651 (6.3%)	**1.15 (1.04, 1.27)**	1.10 (0.99, 1.22) [a]
Pregnancy outcome				
Livebirth	20,393 (99.3%)	10,227 (99.4%)	1.00	1.00
Stillbirth	116 (0.5%)	39 (0.4%)	**0.67 (0.47, 0.96)**	**0.59 (0.41, 0.87)** [a]
Neonatal Death	35 (0.2%)	25 (0.2%)	1.42 (0.85, 2.38)	1.26 (0.73, 2.15) [a]
Weight of baby (grams)				
NBW	16,869 (82.1%)	8,116 (78.9%)	1.00	1.00
LBW	965 (4.7%)	572 (5.6%)	**1.23 (1.11, 1.37)**	**1.22 (1.07, 1.40)** [b]
HBW	2,707 (13.2%)	1,600 (15.5%)	**1.23 (1.15, 1.31)**	**1.21 (1.13, 1.29)** [b]
Missing	3 (0.0%)	3 (0.0%)		
Standardised Birthweight Score §				
	-0.039 (0.959)	0.132 (1.036)	**0.171 (0.145, 0.197)**	**0.167 (0.141, 0.193)** [c]
Admitted to neonatal unit				
No	18,224 (88.7%)	8,747 (85.0%)	1.00	1.00
Yes	2,175 (10.6%)	1,492 (14.5%)	**1.43 (1.33, 1.53)**	**1.46 (1.35, 1.58)** [b]
Missing	145 (0.7%)	52 (0.5%)		
APGAR score at 1 min				
Normal	18,709 (91.1%)	9,350 (90.9%)	1.00	1.00
<7	1,658 (8.1%)	924 (9.0%)	**1.12 (1.03, 1.21)**	0.93 (0.83, 1.04) [d]
Missing	177 (0.9%)	17 (0.2%)		
APGAR score at 5 min				
Normal	20,065 (97.7%)	10,096 (98.1%)	1.00	1.00
<7	302 (1.5%)	177 (1.7%)	0.86 (0.71, 1.04)	0.94 (0.72, 1.23) [d]
Missing	177 (0.9%)	18 (0.2%)		
Cryptorchidism (only males included)				
No	10,284 (98.7%)	5,314 (98.7%)	1.00	1.00
Yes	133 (1.3%)	70 (1.3%)	1.02 (0.76, 1.36)	1.05 (0.78, 1.42) [b]
Neural Tube Defects				
No	20,527 (99.9%)	10,263 (99.7%)	1.00	1.00
Yes	17 (0.1%)	28 (0.3%)	**3.29 (1.80, 6.02)**	**3.62 (1.95, 6.74)** [b]
Amniotic Band Defects				
No	20,514 (99.9%)	10,277 (99.9%)	1.00	1.00
Yes	30 (0.1%)	14 (0.1%)	0.93 (0.49, 1.76)	0.81 (0.41, 1.58) [b]
Hypospadias (only males included)				
No	10,317 (99.0%)	5,308 (98.6%)	1.00	1.00
Yes	100 (1.0%)	76 (1.4%)	**1.48 (1.09, 1.99)**	**1.49 (1.09, 2.03)** [b]
Gastroschisis				
No	20,538 (99.9%)	10,284 (99.9%)	1.00	1.00
Yes	6 (0.1%)	7 (0.1%)	2.33 (0.78, 6.94)	2.93 (0.97, 8.88) [b]
At least one outcome*				
No	20,258 (98.6%)	10,097 (98.1%)	1.00	1.00
Yes	286 (1.4%)	194 (1.9%)	**1.36 (1.13, 1.64)**	**1.38 (1.15, 1.67)** [b]

n/a, not applicable; n, number of pregnancies

[a] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, maternal hypertensive disorders, maternal antepartum haemorrhage

[b] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at delivery

[c] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking

[d] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of delivery

§ Linear regression analysis reporting differences with 95% CI

*Including cryptorchidism, neural tube defects, amniotic band defects, hypospadias, gastroschisis

Figure 1. Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis.*98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

Figure 2. Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. (**A**) Merge graph showing percentage of pregnancies using each analgesic group during pregnancy. (**B**) Percentage of use for at least one analgesic out of ibuprofen, aspirin, naproxen. *In 2005 there was a change in legislation making diclofenac available without prescription.

Figure S1. Directed acyclic graph (DAG) of exposure to outcome path and relevant measured and unmeasured biasing factors in our analysis.

Table 1. Comparison of baseline characteristics between exposed (use of analgesics) and unexposed (no analgesic use) groups of pregnancies (P values <0.05 shown in bold).

Baseline Characteristics	No analgesic (n=107,143) n (%)	At least one analgesic (n=43,998) n (%)	P value†	Paracetamol (n=24,099) n (%)	P value†	Ibuprofen/ Aspirin/ Naproxen (n=762) n (%)	P value†	No analgesic 2005-2015 (n=20,544) n (%)	Diclofenac 2005-2015 (n=10,291) n (%)	P value‡
Year of delivery										
1985-1994	50,152 (46.8)	5,737 (13.0)	**<0.001**	5,390 (22.4)	**<0.001**	213 (28.0)	**<0.001**	n/a	n/a	**<0.001**
1995-2004	36,447 (34.0)	7,263 (16.5)		6,571 (27.3)		321 (42.1)		n/a	n/a	
2005-2015 /	20,544 (19.2)	30,998 (70.5)		12,138 (50.4)		228 (29.9)		n/a	n/a	
2005-2009 *	n/a	n/a		n/a		n/a		11,105 (54.1)	4,021 (39.1)	
2010-2015 *	n/a	n/a		n/a		n/a		9,439 (45.9)	6,270 (60.9)	
Maternal age at delivery										
Younger than 20	9,236 (8.6)	3,834 (8.7)	**<0.001**	2,936 (12.2)	**<0.001**	34 (4.5)	**<0.001**	1,286 (6.3)	311 (3.0)	**<0.001**
20-25	24,249 (22.6)	8,700 (19.8)		5,932 (24.6)		113 (14.8)		3,436 (16.7)	1,152 (11.2)	
26-35	63,499 (59.3)	25,367 (57.7)		12,896 (53.5)		464 (60.9)		12,664 (61.1)	6,628 (64.4)	
Older than 35	10,159 (9.5)	6,097 (13.9)		2,335 (9.7)		151 (19.8)		3,158 (15.4)	2,200 (21.4)	
Previous Parity										
Nulliparity (0)	48,684 (45.4)	23,353 (53.1)	**<0.001**	12,510 (51.9)	**<0.001**	300 (39.4)	**0.004**	8,336 (40.6)	5,004 (48.6)	**<0.001**
Multiparity (1-11)	58,457 (54.6)	20,639 (46.9)		11,587 (48.1)		462 (60.6)		12,206 (59.4)	5,284 (51.4)	
Missing	2 (<0.1)**§**	6 (<0.1)**§**		2 (<0.1)**§**		0 (0.0)**§**		2 (<0.1)**§**	3 (<0.1)**§**	
Maternal BMI										
Underweight (<18.5)	1,998 (2.4)	869 (2.2)	**<0.001**	545 (2.6)	**<0.001**	10 (1.5)	**0.007**	492 (2.7)	174 (1.9)	**<0.001**
Normal weight (18.5-24.9)	50,127 (60.8)	18,958 (48.8)		10,486 (50.5)		361 (55.)		10,239 (55.2)	4,671 (50.0)	
Overweight (25.0-29.9)	20,500 (24.9)	10,960 (28.2)		5,733 (27.6)		192 (29.5)		4,930 (26.6)	2,630 (28.1)	
Obese (≥ 30.0)	9,773 (11.9)	8,046 (20.7)		3,995 (19.2)		88 (13.5)		2,881 (15.5)	1,871 (20.0)	
Missing data	24,745 (23.1)**§**	5,165 (11.7)**§**		3,340 (13.9)**§**		111 (14.6)**§**		2,002 (9.7)**§**	945 (9.2)**§**	

Gestation weeks at earliest antenatal visit										
1st Trimester	69,896 (65.4)	36,789 (83.7)	**<0.001**	19,075 (79.2)	**<0.001**	569 (75.0)	**<0.001**	18,155 (88.4)	9,185 (89.4)	**0.036**
2nd Trimester	29,269 (27.4)	5,791 (13.2)		4,117 (17.1)		166 (21.9)		1,770 (8.6)	829 (8.1)	
3rd Trimester	7,741 (7.2)	1,376 (3.1)		890 (3.7)		24 (3.2)		605 (2.9)	264 (2.6)	
Missing	237 (0.2)**§**	42 (0.1)**§**		17 (0.1)**§**		3 (0.4)**§**		14 (0.1)**§**	13 (0.1)**§**	
Maternal smoking Status										
Unknown	6,505 (6.1)**§**	819 (1.9)**§**	**<0.001**	500 (2.1)**§**	**<0.001**	32 (4.2)**§**	0.132	448 (2.2)**§**	155 (1.5)**§**	**<0.001**
Ex-smoker	5,952 (5.6)	3,363 (7.6)		1,923 (8.1)		35 (4.8)		1,427 (7.1)	660 (6.5)	
Non-smoker	70,319 (69.9)	31,421 (72.8)		15,755 (66.8)		534 (73.2)		15,525 (77.3)	8,368 (82.6)	
Smoker	24,367 (24.2)	8,395 (19.4)		5,921 (25.1)		161 (22.2)		3,144 (15.6)	1,108 (10.9)	
Maternal SIMD Decile										
Least Deprived (7-10)	65,227 (61.8)	25,192 (57.9)	**<0.001**	12,807 (53.8)	**<0.001**	501 (66.3)	**0.012**	12,806 (62.9)	6,714 (66.1)	**<0.001**
Most Deprived (1-6)	40,321 (38.2)	18,289 (42.1)		11,017 (46.2)		255 (33.7)		7,564 (37.1)	3,442 (33.9)	
Missing	1,595 (1.5)**§**	517 (1.2)**§**		275 (1.1)**§**		6 (0.8)**§**		174 (0.8)**§**	135 (1.3)**§**	
Maternal hypertensive disorders										
None	91,276 (85.2)	35,529 (80.8)	**<0.001**	18,635 (77.3)	**<0.001**	636 (83.5)	**0.001**	18,851 (91.8)	9,273 (90.1)	**<0.001**
Gestational Hypertension	13,029 (12.2)	5,501 (12.5)		3,584 (14.9)		88 (11.5)		1,165 (5.7)	690 (6.7)	
Preeclampsia	2,780 (2.6)	2,941 (6.7)		1,861 (7.7)		38 (5.0)		523 (2.5)	324 (3.1)	
Eclampsia	58 (0.1)	27 (0.1)		19 (0.1)		0 (0.0)		5 (<0.1)	4 (<0.1)	
Maternal antepartum haemorrhage										
No haemorrhage	97,527 (91.0)	37,673 (85.6)	**<0.001**	20,306 (84.3)	**<0.001**	684 (89.8)	0.434	18,549 (90.3)	9,244 (89.8)	<0.001
Abruption	697 (0.7)	468 (1.1)		221 (0.9)		8 (1.0)		103 (0.5)	106 (1.0)	
Placenta previa	308 (0.3)	368 (0.8)		152 (0.6)		2 (0.3)		23 (0.1)	114 (1.1)	
Unspecified	8,611 (8.0)	5,489 (12.5)		3,420 (14.2)		68 (8.9)		1,869 (9.1)	827 (8.0)	
Type of labour										
Elective Caesarean Section	5,967 (5.6)	6,925 (15.7)	**<0.001**	1,384 (5.7)	**<0.001**	67 (8.8)	**<0.001**	616 (3.0)	3,843 (37.3)	**<0.001**
Induced	24,120 (22.5)	16,276 (37.0)		10,067 (41.8)		228 (29.9)		3,895 (19.0)	1,998 (19.4)	
Spontaneous	77,056 (71.9)	20,797 (47.3)		12,648 (52.5)		467 (61.3)		16,033 (78.0)	4,450 (43.2)	

Type of delivery										
Spontaneous vaginal delivery (SVD)	75,027 (70.1)	19,287 (43.8)	**<0.001**	15,983 (66.3)	**<0.001**	496 (65.2)	**0.003**	16,398 (79.8)	1,403 (13.6)	**<0.001**
Instrumental	15,409 (14.4)	8,107 (18.4)		4,043 (16.8)		120 (15.8)		2,546 (12.4)	1,927 (18.7)	
Caesarean Section	15,566 (14.5)	16,351 (37.2)		3,879 (16.1)		141 (18.5)		1,509 (7.3)	6,937 (67.4)	
Other	1,096 (1.0)	247 (0.6)		191 (0.8)		4 (0.5)		89 (0.4)	24 (0.2)	
Missing	45 (<0.1)**§**	6 (<0.1)**§**		3 (<0.1)**§**		1 (0.1)**§**		2 (<0.1)**§**	0 (0.0)**§**	
Analgesia during labour										
No	105,176 (98.2)	36,117 (82.1)	**<0.001**	20,974 (87.0)	**<0.001**	729 (95.7)	**<0.001**	19,915 (96.9)	8,235 (80.0)	**<0.001**
Yes	1,967 (1.8)	7,881 (17.9)		3,125 (13.0)		33 (4.3)		629 (3.1)	2,056 (20.0)	
Baby presentation at delivery										
Occiput anterior	11,571 (10.8)	8,152 (18.6)	**<0.001**	2,636 (11.0)	0.525	68 (8.9)	0.093	1,401 (6.8)	2,967 (28.9)	**<0.001**
Occiput posterior	95,352 (89.2)	35,745 (81.4)		21,409 (89.0)		694 (91.1)		19,100 (93.2)	7,306 (71.1)	
Missing	220 (0.2)**§**	101 (0.2)**§**		54 (0.2)**§**		0 (0.0)**§**		43 (0.2)**§**	18 (0.2)**§**	
Sex of baby										
Female	52,265 (48.8)	21,139 (48.0)	**0.010**	11,739 (48.7)	0.861	367 (48.2)	0.732	10,124 (49.3)	4,907 (47.7)	**0.008**
Male	54,866 (51.2)	22,852 (51.9)		12,354 (51.3)		395 (51.8)		10,417 (50.7)	5,384 (52.3)	
Missing	12 (<0.1)**§**	7 (<0.1)**§**		6 (<0.1)**§**		0 (0.0)**§**		3 (<0.1)**§**	0 (0.0)**§**	

n/a, not applicable; n, number of pregnancies

*****Only applicable to Diclofenac 2005-2015 analysis

†p value in comparison to the first ("No analgesic") column

‡p value in comparison to "No analgesic 2005-2015" control column

§Percentage of missing data on total, not included in the analysis

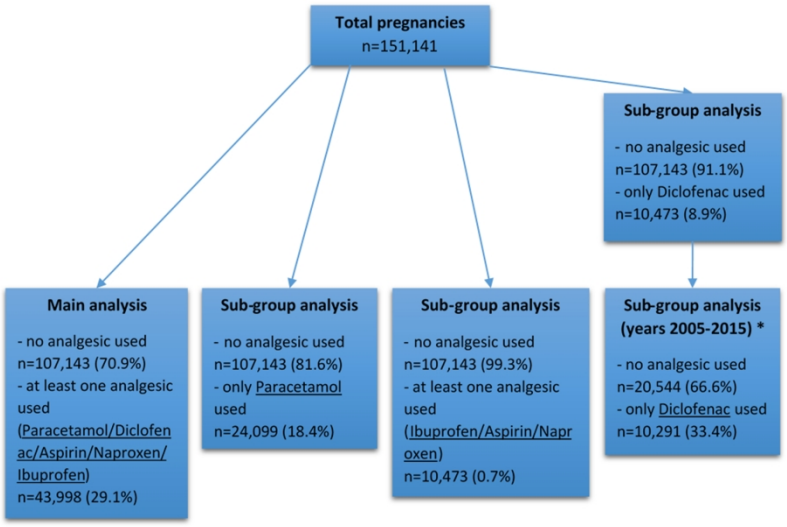

Figure 1. Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis.*98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

338x190mm (300 x 300 DPI)

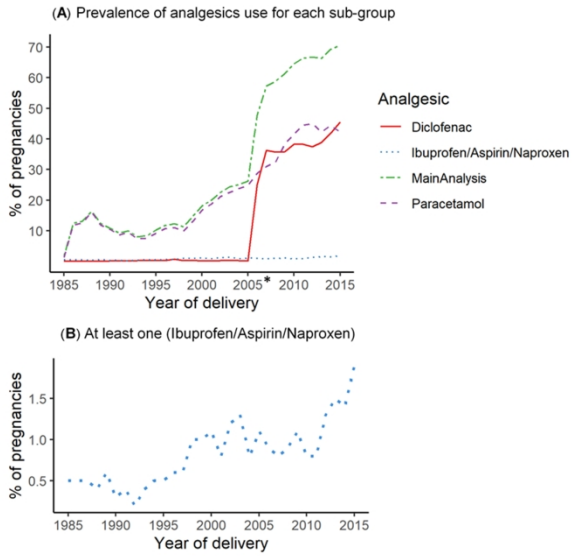

Figure 2. Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. (A) Merge graph showing percentage of pregnancies using each analgesic group during pregnancy. (B) Percentage of use for at least one analgesic out of ibuprofen, aspirin, naproxen. *In 2005 there was a change in legislation making diclofenac available without prescription.

338x190mm (300 x 300 DPI)

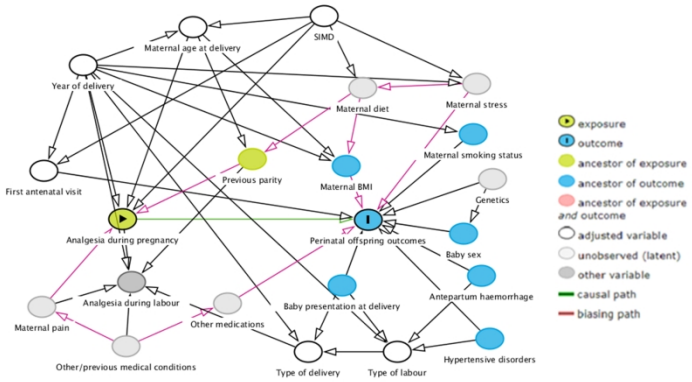

Figure S1. Directed acyclic graph (DAG) of exposure to outcome path and relevant measured and unmeasured biasing factors in our analysis.

338x190mm (300 x 300 DPI)

Table S1. Numbers needed to harm (NNH) calculations

Outcomes	No analgesic (n=107,143) n (%)	At least one analgesic (n=43,998) n (%)	NNH	Paracetamol (n=24,099) n (%)	NNH	Ibu/Asp/Napr (n=762) n (%)	NNH
Gestation at delivery (weeks)							
>=37	100,879 (94.2)	39,838 (90.5)		21,589 (89.6)		697 (91.5)	
<37	6,264 (5.8)	4,160 (9.5)	27	2,510 (10.4)	22	65 (8.5)	37
Pregnancy outcome							
Livebirth	105,949 (98.9)	43,407 (98.7)		23,704 (98.4)		747 (98.0)	
Stillbirth	803 (0.7)	405 (0.9)	500	275 (1.1)	250	13 (1.7)	100
Neonatal Death	373 (0.3)	182 (0.4)	1000	117 (0.5)	500	2 (0.3)	**n/a**
Missing	18 (<0.1)	4 (<0.1)	**n/a**	3 (<0.1)	**n/a**	0 (0.0)	**n/a**
Weight of baby (grams)							
NBW	87,966 (82.1)	34,555 (78.6)		19,163 (79.5)		605 (79.5)	
LBW	5,910 (5.5)	3,571 (8.1)	38	2,213 (9.2)	39	59 (7.7)	46
HBW	13,233 (12.4)	5,863 (13.3)	111	2,720 (11.3)	**n/a**	97 (12.7)	333
Missing	34 (<0.1)	9 (<0.1)	**n/a**	3 (<0.1)	**n/a**	1 (0.1)	**n/a**
Admitted to neonatal unit							
No	62,378 (58.2)	32,391 (73.6)		16,342 (67.8)		480 (63.0)	
Yes	11,011 (10.3)	7,448 (16.9)	15	3,956 (16.4)	16	117 (15.4)	20
Missing	33,754 (31.5)	4,159 (9.5)	**n/a**	3,801 (15.8)	**n/a**	762 (21.7)	**n/a**
APGAR score at 1 min							
Normal	92,217 (86.1)	38,224 (86.9)		20,593 (85.5)		659 (86.5)	
<7	14,335 (13.4)	5,674 (12.9)	**n/a**	3,437(14.3)	111	101 (13.3)	**n/a**
Missing	591 (0.6)	100 (0.2)		69 (0.3)	**n/a**	2 (0.3)	**n/a**
APGAR score at 5 min							
Normal	104,292 (97.3)	42,730 (97.1)		23,334 (96.8)		738 (96.9)	
<7	2,216 (2.1)	1,163 (2.6)	200	690 (2.9)	125	21 (2.8)	143
Missing	635 (0.6)	105 (0.2)	**n/a**	75 (0.3)	**n/a**	3 (0.4)	**n/a**
Cryptorchidism (only males included)							
No	54,509 (99.3)	22,616 (99.0)		12,247 (99.1)		394 (99.4)	
Yes	357 (0.7)	236 (1.0)	333	107 (0.9)	500	1 (0.3)	**n/a**
Neural Tube Defects							
No	107,093 (99.9)	43,928 (99.8)		24,077 (99.9)		762 (100)	
Yes	50 (0.1)	70 (0.2)	1000	22 (0.1)	**n/a**	0 (0.0)	**n/a**
Amniotic Band Defects							
No	107,053 (99.9)	43,936 (99.9)		24,070 (99.9)		760 (99.7)	
Yes	90 (0.1)	62 (0.1)	**n/a**	29 (0.1)	**n/a**	2 (0.3)	500
Hypospadias (only males included)							
No	54,607 (99.5)	22,600 (98.9)		12,258 (99.2)		390 (98.7)	
Yes	259 (0.3)	252 (1.1)	125	96 (0.8)	200	5 (1.3)	100
Gastroschisis							
No	107,120 (99.9)	43,979 (99.9)		24,089 (99.9)		762(100)	
Yes	23 (0.1)	19 (0.1)	**n/a**	10 (0.1)	**n/a**	0 (0.0)	**n/a**
At least one outcome*							
No	106,367 (99.3%)	43,363 (98.6%)		23,835 (98.9%)		754 (99.0%)	
Yes	776 (0.7%)	635 (1.4%)	142	264 (1.1%)	250	8 (1.0%)	333

n/a, not applicable

Table S2. Numbers needed to harm (NNH) for exposure to diclofenac (years 2005-2015).

Outcomes	No analgesic (n=20,544) n (%)	Diclofenac 2005-2015 (n=10,291) n (%)	NNH
Gestation at delivery (weeks)			
>=37	19,407 (94.5%)	9,640 (93.7%)	
<37	1,137 (5.5%)	651 (6.3%)	125
Pregnancy outcome			
Livebirth	20,393 (99.3%)	10,227 (99.4%)	
Stillbirth	116 (0.5%)	39 (0.4%)	**n/a**
Neonatal Death	35 (0.2%)	25 (0.2%)	**n/a**
Weight of baby (grams)			
NBW	16,869 (82.1%)	8,116 (78.9%)	
LBW	965 (4.7%)	572 (5.6%)	111
HBW	2,707 (13.2%)	1,600 (15.5%)	44
Missing	3 (0.0%)	3 (0.0%)	
Admitted to neonatal unit			
No	18,224 (88.7%)	8,747 (85.0%)	
Yes	2,175 (10.6%)	1,492 (14.5%)	26
Missing	145 (0.7%)	52 (0.5%)	
APGAR score at 1 min			
Normal	18,709 (91.1%)	9,350 (90.9%)	
<7	1,658 (8.1%)	924 (9.0%)	111
Missing	177 (0.9%)	17 (0.2%)	
APGAR score at 5 min			
Normal	20,065 (97.7%)	10,096 (98.1%)	
<7	302 (1.5%)	177 (1.7%)	500
Missing	177 (0.9%)	18 (0.2%)	
Cryptorchidism (only males included)			
No	10,284 (98.7%)	5,314 (98.7%)	
Yes	133 (1.3%)	70 (1.3%)	**n/a**
Neural Tube Defects			
No	20,527 (99.9%)	10,263 (99.7%)	
Yes	17 (0.1%)	28 (0.3%)	500
Amniotic Band Defects			
No	20,514 (99.9%)	10,277 (99.9%)	
Yes	30 (0.1%)	14 (0.1%)	**n/a**
Hypospadias (only males included)			
No	10,317 (99.0%)	5,308 (98.6%)	
Yes	100 (1.0%)	76 (1.4%)	250
Gastroschisis			
No	20,538 (99.9%)	10,284 (99.9%)	
Yes	6 (0.1%)	7 (0.1%)	**n/a**
At least one outcome*			
No	20,258 (98.6%)	10,097 (98.1%)	
Yes	286 (1.4%)	194 (1.9%)	200

n/a, not applicable

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

	Item No	Recommendation	Paragraph #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**Title & Abstract Pages 1-3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**Abstract Pages 2-3**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**Introduction Page 5**
Objectives	3	State specific objectives, including any prespecified hypotheses	**Introduction Page 5**
Methods			
Study design	4	Present key elements of study design early in the paper	**Methods Page 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**Methods Page 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**Methods Pages 7-8**
		(*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	**Methods Pages 8-9**
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	**Methods Pages 8-9**
Bias	9	Describe any efforts to address potential sources of bias	**Methods Pages 7-8**
Study size	10	Explain how the study size was arrived at	**Methods Page 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**Methods Pages 8-9**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**Statistical Analysis paragraph pages 9-10**
		(*b*) Describe any methods used to examine subgroups and interactions	**Statistical Analysis paragraph pages 9-10**
		(*c*) Explain how missing data were addressed	**Statistical Analysis paragraph pages 9-10**
		(*d*) If applicable, explain how loss to follow-up was addressed	**n/a**
		(*e*) Describe any sensitivity analyses	**n/a**

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	**Figure 1**
		(b) Give reasons for non-participation at each stage	**Results Page 11**
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Table 1 Pages 29-31**
		(b) Indicate number of participants with missing data for each variable of interest	**Table 1 Pages 29-31**
		(c) Summarise follow-up time (eg, average and total amount)	**n/a**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**Tables 2 and 3 Pages 32-35**
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	**Tables 2 and 3 Pages 32-35**
		(*b*) Report category boundaries when continuous variables were categorized	**Table 1 Pages 29-31**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**Tables 2 and 3 Pages 32-35**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**n/a**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**Discussion Pages 16-17**
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	**Discussion Pages 16-18**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**Discussion Pages 19-21**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**Discussion Pages 20-21**
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	**Manuscript pages 4 and 21**

*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.

BMJ Open

Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: Cohort study of 151,141 singleton pregnancies

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048092.R2
Article Type:	Original research
Date Submitted by the Author:	07-Mar-2022
Complete List of Authors:	Zafeiri, Aikaterini; University of Aberdeen, School of Medicine, Medical Sciences and Nutrition Raja, Edwin Amalraj; University of Aberdeen, Medical Statistics Team Mitchell, Rod; The University of Edinburgh Hay, David ; University of Edinburgh Bhattacharya, Sohinee; University of Aberdeen Fowler, Paul ; University of Aberdeen
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	OBSTETRICS, CLINICAL PHARMACOLOGY, EPIDEMIOLOGY

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Title: Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: Cohort study of 151,141 singleton pregnancies

Authors: [1]Aikaterini ZAFEIRI, MSci, Ms, [2]Edwin A. RAJA, PhD, [3]Rod T. MITCHELL, MBChB, PhD, [4]David C. HAY, PhD, [5]Sohinee BHATTACHARYA, MBBS, PhD, [1]Paul A. FOWLER, FRSB, PhD

[1]Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, [2]Medical Statistics Team, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, [3]MRC Centre for Reproductive Health, The Queen's Medical Research Institute, University of Edinburgh,47 Little France Crescent, Edinburgh, EH16 4JT, UK, [4]MRC Centre for Regenerative Medicine, 5 Little France Drive, Edinburgh, UK, [5]Aberdeen Centre for Women's Health Research, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom,

Corresponding Author: Aikaterini Zafeiri, Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, cell phone number: (+44)7713837285, email: r01az17@abdn.ac.uk

Running Title: Maternal over-the-counter analgesia and offspring outcomes

Abstract

OBJECTIVES

To identify any associations between *in utero* exposure to five over-the-counter (non-prescription) analgesics (paracetamol, ibuprofen, aspirin, diclofenac, naproxen) and adverse neonatal outcomes.

DESIGN

Retrospective cohort study using the Aberdeen Maternity and Neonatal Databank.

PARTICIPANTS

151,141 singleton pregnancies between 1985 and 2015.

MAIN OUTCOME MEASURES

Premature delivery (<37 weeks), stillbirth, neonatal death, birthweight, standardised birthweight score, neonatal unit admission, APGAR score at 1 and 5 minutes, neural tube and amniotic band defects, gastroschisis and, in males, cryptorchidism, and hypospadias.

RESULTS

83.7% of women taking over-the-counter analgesics reported first trimester use when specifically asked about use at their first antenatal clinic visit. Pregnancies exposed to at least one of the five analgesics were significantly independently associated with increased risks for premature delivery <37 weeks (aOR=1.50, 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), neonatal death (aOR=1.56, 95%CI 1.27-1.93), birthweight <2,500g (aOR=1.28, 95%CI 1.20-1.37), birthweight >4,000g (aOR=1.09, 95%CI 1.05-1.13), admission to neonatal unit

(aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at 1 minute (aOR=1.18, 95%CI 1.13-1.23) and 5 minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54 males only). The overall prevalence of over-the-counter analgesics use during pregnancy was 29.1%, however it rapidly increased over the 30-year study period, to include over 60% of women in the last seven years of the study. This makes our findings highly relevant to the wider pregnant population.

CONCLUSIONS

Over-the-counter (non-prescription) analgesics consumption during pregnancy was associated with a substantially higher risk for adverse perinatal health outcomes in the offspring. The use of paracetamol in combination with other non-steroidal anti-inflammatory drugs conferred the highest risk. The increased risks of adverse neonatal outcomes associated with non-prescribed, over-the-counter, analgesics use during pregnancy indicate that healthcare guidance for pregnant women regarding analgesic use need urgent updating.

Strengths and limitations of this study

- This is one of the largest and most comprehensive studies of this type. It includes consumption of five different analgesics during pregnancy in a large cohort of singleton pregnancies. It examines associations with extensive range of offspring perinatal outcomes, while adjusting for important confounding factors.
- Analgesic consumption was analysed both as use of a single compound and in combinations of the five drugs considered in this study.

- Details of the exact dose and timing of consumption during pregnancy were not available within our dataset.
- Follow-up of the offspring health later in life was not available at this time.

Funding Biotechnology and Biological Sciences Research council (BBSRC) funding under the EASTBIO doctoral training programme (grant number 1942576) to AZ and EU Horizon 2020 project FREIA (Grant Number 825100) to PAF. RTM is supported by MRC Centre for Reproductive Health Grant MR/N022556/1.

Key words acetaminophen, aspirin, diclofenac, ibuprofen, *in utero* exposure, naproxen, offspring outcomes, over-the-counter analgesics, offspring outcomes, paracetamol, pregnancy

Introduction

Globally 23-85% of women use one or more types of prescribed medications during pregnancy [1,2]. A similarly high proportion of expectant mothers self-medicate using non-prescription, "over-the-counter" (OTC) medicines [3,4] and use during pregnancy is becoming increasingly prevalent, especially in Western countries [5]. While some analgesics e.g. paracetamol (acetaminophen) are considered safe to consume throughout pregnancy, use of non-steroidal anti-inflammatory drugs (NSAIDs) is not recommended in pregnancy unless on the advice of a medical specialist and should be avoided beyond gestational week 30 because of the risk of premature closure of the ductus arteriosus. However, current evidence is largely conflicting regarding the safety of gestational analgesic use both for the pregnancy and offspring health [6]. Several studies have reported increased risks for multiple adverse outcomes including hypospadias, cryptorchidism, amniotic band defects and neural tube defects [7–11], whilst others have not found significant associations [12–17]. Taken overall, this has led to significant concern that postnatal health is adversely affected by maternal analgesic use during pregnancy [18].

The use of small cohorts in the current epidemiological studies makes it difficult to draw firm conclusions and definite recommendations[12,17,19,20]. There are other aspects of analgesic use that must be considered. Firstly, due to their abundance, it is not always feasible to determine exact consumption rates and dosage. Secondly, even though the mechanisms of action for most of these compounds is not fully understood, most over-the-counter analgesics can diffuse through the placenta and reach the developing fetus [21]. Thirdly, maternal pharmacokinetics during pregnancy are altered and there are limited pregnancy safety data for these compounds.

Given the diversity in study population, methodology, sample size and findings in the published studies, we conclude that more extensive data from larger cohorts are essential in order to understand the risks over-the-counter analgesic use during pregnancy pose to neonatal health and function. Here we address many limitations - however, not all[22] - of previous studies by analysing one of the largest cohorts, widest range of health data and, pregnancy use of five over-the-counter analgesics consumed in combination or separately. We report on the prevalence of maternal consumption of five different over-the-counter analgesics during pregnancy and their associations with offspring neonatal outcomes using a large cohort of 151,141 singleton pregnancies spanning three decades of population-based data from a single maternity hospital serving the entire population of Aberdeenshire in the Northeast of Scotland.

Materials and Methods

This retrospective cohort study utilised data collected in the Aberdeen Maternity and Neonatal Databank (AMND) in Aberdeen, UK on 151,141 pregnancies over a 30-year period (1985-2015). Details about AMND have been previously published [23]. Data were collected from medical notes of women retrospectively after delivery. Women were specifically asked about their use of over-the-counter (non-prescription) analgesics at their first antenatal clinic. Data were entered by dedicated coding staff into a computerised database. Data validity was ensured via checking completeness of data entry against NHS (UK National Health Service) returns monthly and constant data cleaning and validation against case notes reported quarterly by the Data Management team to the AMND Steering Committee. A research protocol was submitted and approved by the AMND Steering Committee before data extraction. Approval was received on 6 June 2018. The dataset was fully anonymised, therefore there was no requirement for NHS ethics committee approval. There was no involvement of patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

The main analysis considered consumption during pregnancy of at least one out of five different analgesics: paracetamol (no; yes), ibuprofen (no; yes), naproxen (no; yes), diclofenac (no; yes) or aspirin (no; yes) as the exposure group against no analgesic consumption as the unexposed group. Then, three sub-group analyses against the control group were performed using only paracetamol, only diclofenac, or at least one analgesic from aspirin/naproxen/ibuprofen as exposure groups, excluding pregnancies exposed to multiple analgesics at the same time (Figure 1). As 98.3% of pregnancies using diclofenac were between 2005 and 2015, diclofenac sub-group analysis only considered pregnancies during that time frame in order to

rule out any temporal effect. Analgesic consumption was not further assessed analytically.

The offspring outcomes compared between control and exposed groups were: gestation at delivery (preterm <37 gestation weeks, term ≥37 gestation weeks), pregnancy outcome (livebirth, stillbirth, neonatal death), baby weight (low birth weight (LBW) ≤2,499 g, high birth weight (HBW) ≥4,000 g, normal birth weight (NBW) 2,500g-3,999 g), standardised birthweight score was considered as a continuous variable as previously described by Campbell and colleagues[24], baby admission to neonatal unit (no; yes), APGAR score at one and five minutes (<7, ≥7), cryptorchidism (no; yes) (ICD-10 code Q53), neural tube defects (no; yes) (ICD-10 code Q00-07), amniotic band defects (no; yes) (ICD-10 codes Q70-74), hypospadias (no; yes) (ICD-10 code Q54), gastroschisis (no; yes) (ICD-10 code Q79.3). A composite outcome (presence of at least one congenital anomaly (no; yes)) was created using the variables neural tube defects, amniotic band defects, and gastroschisis and, in males, cryptorchidism and hypospadias.

The baseline characteristics compared between exposed and unexposed pregnancies were (reference category first): year of delivery (1985-1994, 1995-2004, 2005-2015), maternal age at delivery (20-25, <20, 26-35, >35 years), previous pregnancy (no; yes), maternal body mass index (BMI) (normal weight 18.5-24.9 kg/m^2, underweight <18.5 kg/m^2, overweight 25-29.9 kg/m^2, obese >30 kg/m^2), maternal first antenatal visit (1st, 2nd, 3rd trimester), maternal smoking status (non-smoker, smoker, ex-smoker), Scottish Index of Multiple Deprivation (SIMD) decile (1-6, 7-10, decreasing deprivation with increasing score), maternal hypertensive disorders (no disorder, gestational hypertension, preeclampsia, eclampsia), maternal antepartum haemorrhage (no haemorrhage, abruption, placental previa), type of

labour (spontaneous, elective caesarean section, induced), type of delivery (spontaneous vaginal delivery, instrumental, caesarean section), analgesia during labour (no; yes), baby presentation at delivery (occiput anterior, occiput posterior), baby sex (female; male).

Patient and Public Involvement

This was a retrospective analysis of data on singleton pregnancies over a 30-year period. Therefore, there was no involvement of patients or the public in the design, conduct, reporting or any other aspect of the study.

Statistical Analysis

Baseline characteristics were compared between exposed and unexposed pregnancies to any analgesic using χ^2 test for categorical variables and t-test for normally distributed continuous variables as appropriate. Relationships between exposures and outcomes were examined by binary logistic regression for binary outcome variables, multinomial logistic regression for nominal categorical outcome variables, and multiple linear regression for continuous variables. The strength of association was reported as odds ratios (ORs) with 95% confidence intervals (CI). The socio-demographic characteristics that were likely to confound our exposure-to-outcome path were identified using directed acyclic graphs (DAG) (Supplementary figures S1-11)[25]. Factors that were associated with consumption of over-the-counter analgesics during pregnancy at 10% level of significance and deemed clinically relevant, were included in the model as confounders. All outcomes were adjusted for year of delivery, maternal age at delivery, SIMD and maternal first antenatal visit. In addition to these confounders, individual outcomes were adjusted for relevant

cofactors. Gestation at delivery and pregnancy outcome were both additionally adjusted for maternal hypertensive disorders and antepartum haemorrhage. Weight of the baby, neonatal unit admission, cryptorchidism, neural tube defects, amniotic band defects, hypospadias and gastroschisis variables were also adjusted for gestation at delivery. APGAR score at one and five minutes were adjusted for type of delivery. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using IBM SPSS Statistics version 25.0 (Released 2017. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). R version 3.6.2 was used to generate Figure 2. Numbers needed to harm (NNH) were also calculated for each outcome and are provided in Supplementary Tables 1 and 2.

Results

Overall, from the total 151,141 pregnancies across 30 years in 107,143 (70.9%) pregnancies, no over-the-counter analgesic consumption was reported. At least one over-the-counter analgesic was consumed in 43,998 (29.1%) pregnancies, whereas paracetamol use alone was reported in 24,099 (18.4%) pregnancies. Diclofenac use was observed in 20.0% of pregnancies in the 10-year period when diclofenac was available over-the-counter (without prescription). Finally, at least one out of three analgesics (naproxen, ibuprofen, aspirin) was consumed in 762 (0.7%) pregnancies (Figure 1). At their first antenatal clinic visit, 83.7% of women taking over-the-counter analgesics reported use in the first trimester of pregnancy.

Prevalence of use for all five analgesics increased dramatically over the 30-year study period (1985-2015) (Figure 2). Pregnancies with consumption of at least one analgesic increased from 1.8% in 1985 to 70.6% in 2015. Pregnancies reporting paracetamol use were 1.3% in 1985 and it continuously increased reaching 42.2% in 2015. Naproxen, ibuprofen or aspirin consumption during pregnancy was less prevalent (Figure 2A), however it also increased during the 30-year study period, starting at 0.5% in 1985 and reaching 1.9% in 2015 (Figure 2B). Diclofenac was consumed in very few pregnancies between 1985 (<0.01%) and 2005 (0.2%). Percentage of consumption, however, dramatically increased during the next decade following deregulation of diclofenac, reaching 25.0% in just one year (2006) and 45.6% of all pregnancies in 2015.

Table 1 compares the baseline characteristics between the unexposed group of pregnancies where no analgesic was consumed and each of the exposure groups. In most, but not all, comparisons across all four analyses, there was a statistically

significant difference (p<0.001) for most variables. In the paracetamol sub-group analysis, baby presentation at delivery (p=0.525) and sex of the baby (p=0.861) were not significantly different between the groups. In the analysis considering consumption of at least one analgesic from aspirin/naproxen/ibuprofen, again the variables for baby presentation at delivery (p=0.093) and sex of the baby (p=0.732), together with maternal smoking status (p=0.132) and maternal antepartum haemorrhage (p=0.434) were not statistically different compared to the unexposed group. All variables were statistically different between unexposed and exposed groups for the main analysis and diclofenac sub-group analysis.

Table 2 summarises the comparison of neonatal outcomes between the unexposed group (no analgesic at all) and the exposed groups of at least one analgesic, only paracetamol and at least one out of aspirin/naproxen/ibuprofen. Comparison of outcomes for the diclofenac sub-group analysis is shown in Table 3.

All analgesics and neonatal outcomes

As shown in Table 2, compared to unexposed pregnancies in which women did not use any analgesic, pregnancies with consumption of at least one analgesic (paracetamol, diclofenac, aspirin, naproxen, ibuprofen) were independently associated with significantly higher odds for premature delivery (aOR=1.50, 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI1.15-1.54), LBW (aOR=1.28, 95%CI 1.20-1.37), HBW (aOR=1.09, 95%CI 1.05-1.13), baby admission to neonatal unit (aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at five minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54) in adjusted analyses. Significantly decreased odds for

APGAR score <7 at one minute were found in the crude analysis (cOR=0.96, 95%CI 0.92-0.99), however when adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking and type of delivery, the significance changed direction showing significantly increased odds (aOR=1.18, 95%CI 1.13-1.23). A significantly lower standardised birthweight score (p=0.046, 95%CI 0.032-0.059) was found for the exposure group compared to no analgesic at all. Cryptorchidism (aOR=0.92, 95%CI 0.77-1.11), amniotic band defects (aOR=1.02, 95%CI 0.71-1.47), gastroschisis (aOR=1.10, 95%CI 0.56-2.20) and the composite outcome variable (aOR=1.12, 95%CI 0.99-1.26), were all associated with increased odds in the exposure group compared to not exposed, however the association was not significant in the adjusted model. There was no significant association between neonatal death and exposure to at least one analgesic in the crude analysis (cOR=1.19, 95%CI 0.99-1.42), however there were significantly higher odds of neonatal death in the adjusted analysis (aOR=1.56, 95%CI 1.27-1.93) in the exposed group compared to control.

Paracetamol and neonatal outcomes

In the sub-group analysis considering only paracetamol consumption during pregnancy as our exposure group, most of the associations reported in the main analysis remained significant with the same direction of significance (Table 2). The differences were: maternal paracetamol consumption during pregnancy was associated with significantly decreased odds for offspring HBW (cOR=0.94, 95%CI 0.90-0.99) in the crude analysis however significance was lost in the adjusted model (aOR=0.98, 95%CI 0.93-1.02), and there were no significant associations in the

adjusted models for neural tube defects (aOR=1.21, 95%CI 0.71-2.06) and hypospadias (aOR=1.07, 95%CI 0.84-1.37).

Aspirin/naproxen/ibuprofen and neonatal outcomes

Consumption of at least one analgesic from aspirin, naproxen or ibuprofen during pregnancy was compared against the same control group of pregnancies where no analgesic was used (Table 2). Again, when comparing associations between groups in this sub-group analysis and main analysis, fewer outcome variants showed similar significance pattern. The only shared significant associations were for increased odds for premature delivery (aOR=1.42, 95%CI 1.08-1.86), stillbirth (aOR=2.34, 95%CI 1.29-4.25) and baby admission to neonatal unit (aOR=1.54, 95%CI 1.22-1.94) in the adjusted regression analyses.

Diclofenac and neonatal outcomes

In the sub-group analysis of pregnancies coinciding with non-prescription, over-the-counter, availability of diclofenac (years 2005-2015) were considered, and outcomes compared between the diclofenac group and no analgesic consumption group (Table 3). Compared to the main analysis, diclofenac consumption during pregnancy was not significantly associated with premature delivery (aOR=1.10, 95%CI 0.99-1.22), neonatal death (aOR=1.26, 95%CI 0.73-2.15) and APGAR score <7 in one minute (aOR=0.93, 95%CI 0.83-1.04) in the adjusted models. Associations with APGAR score <7 in five minutes (aOR=0.94, 95%CI 0.72-1.23), cryptorchidism (aOR=1.05, 95%CI 0.78-1.42), amniotic band defects (aOR=0.81, 95%CI 0.41-1.58) and gastroschisis (aOR=2.93, 95%CI 0.97-8.88) were no longer significant in both crude

and adjusted analyses. Maternal consumption of diclofenac was independently associated with a significant decrease in stillbirth (aOR=0.59, 95%CI 0.41-0.87). It is also interesting to note that diclofenac was the only sub-group analysis agreeing with the main analysis (exposure to at least one analgesic) on the significance of exposure association with increased incidence of neural tube defects (aOR=3.62, 95%CI 1.95-6.74) and hypospadias (aOR=1.49, 95%CI 1.09-2.03) compared to unexposed pregnancies in adjusted models. As most of the outcomes studied were relatively rare the numbers needed to harm were mostly more than 100. Preterm birth, low birthweight and admission to the neonatal unit were exceptions with NNH ranging from 15 to 38. (Tables S1 and S2).

Discussion

Main Findings

Consumption of paracetamol, ibuprofen, aspirin and naproxen during pregnancy, either in combination or separately, was significantly associated with increased premature delivery, stillbirth, neonatal death, LBW, abnormal standardised birthweight score and more frequent admission to neonatal unit. Consumption of paracetamol alone was further associated with higher odds for APGAR score <7 at one and five minutes both in crude and adjusted analyses. There was a dramatic increase in the frequency of over-the-counter (non-prescription) analgesic use in pregnancies between 1985 and 2015, starting from only 10.3% of women using one or more of the compounds between 1985 and 1994, climbing to60.1% of women in the final decade of our study. This means that our findings are applicable far beyond the percentage (between 14% and 38%) [26] of pregnant women with underlying health deficits related to the adverse outcomes we report here.

Diclofenac use increased steeply from 2005 (Figure 2A), which reflects the change in Scottish legislation, leading to diclofenac becoming available without prescription in that year. Diclofenac use was associated with fewer adverse outcomes but showed increased risk of neural tube defects and hypospadias in male neonates. Furthermore, and surprisingly, exposure to diclofenac only was associated with significant decrease in the incidence of stillbirth. The reasons for such differences between the changes in neonatal outcomes following diclofenac consumption compared with those following use of the other NSAIDs are not clear. The proportion of women using diclofenac, especially in the last 7 years of our study makes it highly

unlikely to be due to an underlying maternal condition and/or other compounds used in combination (e.g. prescriptions) by women taking diclofenac. It is possible that the drug could act directly on fetal development then this difference could also be due to structural and/or mechanistic differences of the compound compared to the other drugs. However, not enough is known about the specific mechanisms of action of the different analgesics studied to conclude further. Overall, comparing our main analysis with all three sub-analyses, it is evident that the most significant differences were observed when paracetamol was taken with at least one other analgesic. This is mostly due to the high number of pregnancies where paracetamol was used, comprising almost 55% of the exposed cases in the main analysis. Most numbers needed to harm for our outcomes (Tables S1 and S2) ranged between 1000 and 100, apart from preterm birth, low birth weight and baby admission to neonatal unit, which were 27, 38 and 15 respectively for our main analysis further strengthening observed associations.

Strengths and Limitations

A major strength of the present study is the large cohort of 151,141 pregnancies over a 30-year study period from 1985 until 2015, using a robust data source AMND. This is one of the largest cohorts used in studies examining the effects of analgesic use during pregnancy. The dataset contains high quality and consistent data from the geographically defined area of Aberdeen and surrounding district, in the North East of Scotland, UK. In addition, as Aberdeen Maternity Hospital is the only maternity hospital serving the area, over 95% of pregnancies in the area are included in the dataset, considerably minimizing the risk for selection bias. We were able to analyse

maternal consumption data of the five most commonly used analgesics available over-the-counter in the UK and most countries, which is not matched in the current literature. The nature of our data allowed for the analysis of analgesics consumed alone or in combination, unlike most existing studies, and this gives our study the added strength of better reflecting real-life consumption patterns [27,28]. We were able to adjust for important confounding factors, relevant to each analysed outcome. Adjustment for maternal deprivation also allowed us to further account for potential unmeasured factors that can influence maternal and neonatal health, which is a major strength of our analysis compared to most studies.

A potential concern was that women were probably using analgesics to treat some inherent medical condition which in turn could have been the mediating factor for adverse outcomes. Data on indication for use were not available in the database. However, since these medications are widely available without prescription, this is unlikely to be a factor that affects the findings of this study. This is especially the case during the “diclofenac analysis” covering 2005-2015, where

this study presents results on multiple neonatal outcomes for the given cohort. In this way we offer a comprehensive approach to the exploration of associations with *in utero* analgesic exposure rather than only focusing on a single outcome of interest. Our data were based on medical notes; however, over-the-counter consumption is self-reported, and details on the timing, duration, dosage, product type (single-ingredient vs combination) and administration type were not available in the database. In addition, the group of pregnancies with aspirin consumption might include use of low-dose aspirin which is recommended to help reduce risk of some pregnancy complications and outcomes related to placental function. Genetic factors potentially relating to the emergence of offspring health outcomes was an

unmeasured variable in our analysis. This study does not include a quantitative bias analysis to identify potential distort of results presented here. Most women had their first antenatal clinic visit during the 1st pregnancy trimester, which might imply our results were affected by primarily 1st trimester exposure, although analgesic use in first trimester is most likely replicated in the rest of pregnancy. Complete case analyses were performed ignoring pregnancies with missing data in the covariates, however due to the low number of missing data there is little chance that this might have affected the validity of our results. Compared to our cohort size, there were, overall, very few cases of cryptorchidism, neural tube defects, amniotic band defects, hypospadias and gastroschisis, resulting in potentially underpowered statistical analyses to detect a difference for these outcomes. Our study only considered neonatal health outcomes and follow-up of the offspring was not available at this time.

Interpretation

Previous literature has considered fewer outcomes with fewer analgesic combinations compared to our study. Consistent with our results, increased risk of preterm birth and miscarriage has been associated with analgesic consumption during pregnancy [29–32], while others reported no associations with miscarriage, stillbirth or preterm delivery [20,29,30,33]. Similarly, increased risk for offspring cryptorchidism, hypospadias, neural tube defects, amniotic band defects and gastroschisis have been shown by many studies [7,8,9,34–41], although, again, a lack of associations with major birth defects have been reported [13–17,42,43]. Compared to our analysis, all these studies used a smaller cohort, considered a shorter study time

and there was frequent disagreement with respect to the choices of adjusted confounding factors. Another difference is that maternal questionnaires/interviews were frequently the method of choice to evaluate maternal consumption. Some of the studies reported increased risks for specific pregnancy trimesters which is something our study could not evaluate. Differences in study design and adjustment for different confounders might also account for the disagreement of our results that provide a more accurate assessment. Our study is one of the largest in terms of cohort size, duration, number of analgesics and range of outcomes included which might also contribute to differences compared to other studies. Another study with a large sample size (98,190 pregnancies) and a 7 year study time from Rebordosa and colleagues[29], also reported an increased risk of preterm birth following paracetamol use during pregnancy, which was increased in mothers with pre-eclampsia. Our results showed a significant association of the adjusted ORs following adjustment for maternal hypertensive disorders. In addition, they did not find a significant association with stillbirth, or low birth weight as we report here. This disagreement could be due to dataset differences including the information about use in each pregnancy trimester, but also methodological differences such as the use of questionnaires versus medical notes or adjustment for different confounders.

The literature currently reports conflicting evidence, limiting our ability for definite decision-making. Over-the-counter analgesics are recommended to women by healthcare professionals in order to deal with pregnancy symptoms and other conditions. Policy-makers have taken a stand on the topic, either being reassuring about over-the-counter use during pregnancy or recommending caution when consumption is necessary [44–47]. Different compounds can affect the mother and the fetus in a different way, and their combined use might worsen the risk for offspring ill

health. This study demonstrates the need for additional research before the field can be confidently directed towards one direction or the other.

Whether the associations we report result from flu, fever, rheumatological or inflammatory conditions, and/or combination with other prescribed medications or solely related to over-the-counter analgesics consumption is a matter of further research. Underlying health conditions could well influence the outcomes we see in this study, however, as these could be very different conditions it is biologically unlikely that they are responsible for the effects we observe here. Our study demonstrates an association of maternal over-the-counter analgesic consumption during pregnancy with adverse neonatal offspring outcomes. Future collaborative approaches such as an individual patient data meta-analysis that includes follow-up data on long-term outcomes during childhood and adulthood would significantly inform decision making. Going forward, uncovering the mechanisms of action and off target effects will also provide a solid foundation for the development of pregnancy-safe compounds. Finally, the findings present here suggest that diclofenac is associated with fewer changes in risk for the more frequent adverse outcomes although it is associated more with rarer, but severe, negative outcomes, including neural tube defects. Diclofenac may have a lower risk for the main adverse neonatal outcomes reported for paracetamol. However, it should be noted that our study is not designed to specifically test differences in level of risk between the analgesics included. Therefore, it should be emphasised that this does not mean that the authors are stating that diclofenac is preferable to paracetamol.

Conclusions

Pain control is currently a therapeutic priority during pregnancy. Our findings of increased risk of adverse health outcomes for the offspring following at least first trimester maternal use of readily available over-the-counter analgesics are crucial to information for the management of pain during pregnancy.

Acknowledgements: N/A

Disclosure of interests: Professor David Hay is a founder, director and shareholder in Stemnovate Limited. The remaining authors have no interests to disclose.

Contribution to Authorship: AZ, SB and PAF contributed to the conception, design and coordination of the research. EAR provided critical input in the design and planning of statistical analysis. AZ conducted the statistical analysis and prepared the manuscript, figures and tables. AZ, SB, PAF, RTM and DCH substantially contributed to the analysis and interpretation of the work. All authors contributed to critical discussion of intellectual content, development and review/approval of the final manuscript version.

Funding: This work is supported by the Biotechnology and Biological Sciences Research council (BBSRC) funding the lead author under the EASTBIO doctoral training programme and to PAF, the EU Horizon 2020 project FREIA (Grant Number 825100). RTM is supported by MRC Centre for Reproductive Health Grant MR/N022556/1. The funders had no role in study design, data collection, data analysis, decision to publish, or manuscript preparation.

Ethics Statement: The AMND dataset used in this study was fully anonymised, therefore there was no requirement for ethical approval. The North of Scotland Research Ethics Service has devolved Caldicott approval to the Chair of the AMND

steering committee. Approval to access and analyse data was obtained from the AMND steering Committee (AMND 004/2018).

Data Availability Statement: No additional data available.

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Table 1. Comparison of baseline characteristics between exposed (use of analgesics) and unexposed (no analgesic use) groups of pregnancies (P values <0.05 shown in bold).

Baseline Characteristics	No analgesic (n=107,143) n (%)	At least one analgesic (n=43,998) n (%)	P value†	Paracetamol only (n=24,099) n (%)	P value†	Ibuprofen/ Aspirin/ Naproxen (n=762) n (%)	P value†	No analgesic 2005-2015 (n=20,544) n (%)	Diclofenac only 2005-2015 (n=10,291) n (%)	P value‡
Year of delivery										
1985-1994	50,152 (46.8)	5,737 (13.0)	**<0.001**	5,390 (22.4)	**<0.001**	213 (28.0)	**<0.001**	n/a	n/a	**<0.001**
1995-2004	36,447 (34.0)	7,263 (16.5)		6,571 (27.3)		321 (42.1)		n/a	n/a	
2005-2015 / 2005-2009 *	20,544 (19.2) n/a	30,998 (70.5) n/a		12,138 (50.4) n/a		228 (29.9) n/a		n/a 11,105 (54.1)	n/a 4,021 (39.1)	
2010-2015 *	n/a	n/a		n/a		n/a		9,439 (45.9)	6,270 (60.9)	
Maternal age at delivery										
Younger than 20	9,236 (8.6)	3,834 (8.7)	**<0.001**	2,936 (12.2)	**<0.001**	34 (4.5)	**<0.001**	1,286 (6.3)	311 (3.0)	**<0.001**
20-25	24,249 (22.6)	8,700 (19.8)		5,932 (24.6)		113 (14.8)		3,436 (16.7)	1,152 (11.2)	
26-35	63,499 (59.3)	25,367 (57.7)		12,896 (53.5)		464 (60.9)		12,664 (61.1)	6,628 (64.4)	
Older than 35	10,159 (9.5)	6,097 (13.9)		2,335 (9.7)		151 (19.8)		3,158 (15.4)	2,200 (21.4)	
Previous Parity										
Nulliparity (0)	48,684 (45.4)	23,353 (53.1)	**<0.001**	12,510 (51.9)	**<0.001**	300 (39.4)	**0.004**	8,336 (40.6)	5,004 (48.6)	**<0.001**
Multiparity (1-11)	58,457 (54.6)	20,639 (46.9)		11,587 (48.1)		462 (60.6)		12,206 (59.4)	5,284 (51.4)	
Missing	2 (<0.1)**§**	6 (<0.1)**§**		2 (<0.1)**§**		0 (0.0)**§**		2 (<0.1)**§**	3 (<0.1)**§**	
Maternal BMI										
Underweight (<18.5)	1,998 (2.4)	869 (2.2)	**<0.001**	545 (2.6)	**<0.001**	10 (1.5)	**0.007**	492 (2.7)	174 (1.9)	**<0.001**
Normal weight (18.5-24.9)	50,127 (60.8)	18,958 (48.8)		10,486 (50.5)		361 (55.)		10,239 (55.2)	4,671 (50.0)	
Overweight (25.0-29.9)	20,500 (24.9)	10,960 (28.2)		5,733 (27.6)		192 (29.5)		4,930 (26.6)	2,630 (28.1)	
Obese (≥ 30.0)	9,773 (11.9)	8,046 (20.7)		3,995 (19.2)		88 (13.5)		2,881 (15.5)	1,871 (20.0)	
Missing data	24,745 (23.1)**§**	5,165 (11.7)**§**		3,340 (13.9)**§**		111 (14.6)**§**		2,002 (9.7)**§**	945 (9.2)**§**	

Gestation weeks at earliest antenatal visit										
1st Trimester	69,896 (65.4)	36,789 (83.7)	**<0.001**	19,075 (79.2)	**<0.001**	569 (75.0)	**<0.001**	18,155 (88.4)	9,185 (89.4)	**0.036**
2nd Trimester	29,269 (27.4)	5,791 (13.2)		4,117 (17.1)		166 (21.9)		1,770 (8.6)	829 (8.1)	
3rd Trimester	7,741 (7.2)	1,376 (3.1)		890 (3.7)		24 (3.2)		605 (2.9)	264 (2.6)	
Missing	237 (0.2)**§**	42 (0.1)**§**		17 (0.1)**§**		3 (0.4)**§**		14 (0.1)**§**	13 (0.1)**§**	
Maternal smoking Status										
Unknown	6,505 (6.1)**§**	819 (1.9)**§**	**<0.001**	500 (2.1)**§**	**<0.001**	32 (4.2)**§**	0.132	448 (2.2)**§**	155 (1.5)**§**	**<0.001**
Ex-smoker	5,952 (5.6)	3,363 (7.6)		1,923 (8.1)		35 (4.8)		1,427 (7.1)	660 (6.5)	
Non-smoker	70,319 (69.9)	31,421 (72.8)		15,755 (66.8)		534 (73.2)		15,525 (77.3)	8,368 (82.6)	
Smoker	24,367 (24.2)	8,395 (19.4)		5,921 (25.1)		161 (22.2)		3,144 (15.6)	1,108 (10.9)	
Maternal SIMD Decile										
Least Deprived (7-10)	65,227 (61.8)	25,192 (57.9)	**<0.001**	12,807 (53.8)	**<0.001**	501 (66.3)	**0.012**	12,806 (62.9)	6,714 (66.1)	**<0.001**
Most Deprived (1-6)	40,321 (38.2)	18,289 (42.1)		11,017 (46.2)		255 (33.7)		7,564 (37.1)	3,442 (33.9)	
Missing	1,595 (1.5)**§**	517 (1.2)**§**		275 (1.1)**§**		6 (0.8)**§**		174 (0.8)**§**	135 (1.3)**§**	
Maternal hypertensive disorders										
None	91,276 (85.2)	35,529 (80.8)	**<0.001**	18,635 (77.3)	**<0.001**	636 (83.5)	**0.001**	18,851 (91.8)	9,273 (90.1)	**<0.001**
Gestational Hypertension	13,029 (12.2)	5,501 (12.5)		3,584 (14.9)		88 (11.5)		1,165 (5.7)	690 (6.7)	
Preeclampsia	2,780 (2.6)	2,941 (6.7)		1,861 (7.7)		38 (5.0)		523 (2.5)	324 (3.1)	
Eclampsia	58 (0.1)	27 (0.1)		19 (0.1)		0 (0.0)		5 (<0.1)	4 (<0.1)	
Maternal antepartum haemorrhage										
No haemorrhage	97,527 (91.0)	37,673 (85.6)	**<0.001**	20,306 (84.3)	**<0.001**	684 (89.8)	0.434	18,549 (90.3)	9,244 (89.8)	<0.001
Abruption	697 (0.7)	468 (1.1)		221 (0.9)		8 (1.0)		103 (0.5)	106 (1.0)	
Placenta previa	308 (0.3)	368 (0.8)		152 (0.6)		2 (0.3)		23 (0.1)	114 (1.1)	
Unspecified	8,611 (8.0)	5,489 (12.5)		3,420 (14.2)		68 (8.9)		1,869 (9.1)	827 (8.0)	
Type of labour										
Elective Caesarean Section	5,967 (5.6)	6,925 (15.7)	**<0.001**	1,384 (5.7)	**<0.001**	67 (8.8)	**<0.001**	616 (3.0)	3,843 (37.3)	**<0.001**
Induced	24,120 (22.5)	16,276 (37.0)		10,067 (41.8)		228 (29.9)		3,895 (19.0)	1,998 (19.4)	
Spontaneous	77,056 (71.9)	20,797 (47.3)		12,648 (52.5)		467 (61.3)		16,033 (78.0)	4,450 (43.2)	

Type of delivery										
Spontaneous vaginal delivery (SVD)	75,027 (70.1)	19,287 (43.8)	**<0.001**	15,983 (66.3)	**<0.001**	496 (65.2)	**0.003**	16,398 (79.8)	1,403 (13.6)	**<0.001**
Instrumental	15,409 (14.4)	8,107 (18.4)		4,043 (16.8)		120 (15.8)		2,546 (12.4)	1,927 (18.7)	
Caesarean Section	15,566 (14.5)	16,351 (37.2)		3,879 (16.1)		141 (18.5)		1,509 (7.3)	6,937 (67.4)	
Other	1,096 (1.0)	247 (0.6)		191 (0.8)		4 (0.5)		89 (0.4)	24 (0.2)	
Missing	45 (<0.1)**§**	6 (<0.1)**§**		3 (<0.1)**§**		1 (0.1)**§**		2 (<0.1)**§**	0 (0.0)**§**	
Analgesia during labour										
No	105,176 (98.2)	36,117 (82.1)	**<0.001**	20,974 (87.0)	**<0.001**	729 (95.7)	**<0.001**	19,915 (96.9)	8,235 (80.0)	**<0.001**
Yes	1,967 (1.8)	7,881 (17.9)		3,125 (13.0)		33 (4.3)		629 (3.1)	2,056 (20.0)	
Baby presentation at delivery										
Occiput posterior	11,571 (10.8)	8,152 (18.6)	**<0.001**	2,636 (11.0)	0.525	68 (8.9)	0.093	1,401 (6.8)	2,967 (28.9)	**<0.001**
Occiput anterior	95,352 (89.2)	35,745 (81.4)		21,409 (89.0)		694 (91.1)		19,100 (93.2)	7,306 (71.1)	
Missing	220 (0.2)**§**	101 (0.2)**§**		54 (0.2)**§**		0 (0.0)**§**		43 (0.2)**§**	18 (0.2)**§**	
Sex of baby										
Female	52,265 (48.8)	21,139 (48.0)	**0.010**	11,739 (48.7)	0.861	367 (48.2)	0.732	10,124 (49.3)	4,907 (47.7)	**0.008**
Male	54,866 (51.2)	22,852 (51.9)		12,354 (51.3)		395 (51.8)		10,417 (50.7)	5,384 (52.3)	
Missing	12 (<0.1)**§**	7 (<0.1)**§**		6 (<0.1)**§**		0 (0.0)**§**		3 (<0.1)**§**	0 (0.0)**§**	

n/a, not applicable; n, number of pregnancies

***Only applicable to Diclofenac 2005-2015 analysis

†p value in comparison to the first ("No analgesic") column

‡p value in comparison to "No analgesic 2005-2015" control column

§Percentage of missing data on total, not included in the analysis

Table 2. Regression analysis of offspring outcomes between control (no analgesic) and groups exposed to at least one analgesic, only paracetamol, and at least one from ibuprofen, aspirin, naproxen.

Outcomes	No analgesic (n=107,143) n (%)	At least one analgesic (n=43,998) n (%)	Crude OR (CI 95%)	Adjusted OR (95% CI)	Paracetamol only (n=24,099) n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Ibu/Asp/Napr (n=762) n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Gestation at delivery (weeks)										
>=37	100,879 (94.2)	39,838 (90.5)	1.00	1.00	21,589 (89.6)	1.00	1.00	697 (91.5)	1.00	1.00
<37	6,264 (5.8)	4,160 (9.5)	**1.68 (1.61-1.75)**	**1.50 (1.43-1.58)** [a]	2,510 (10.4)	**1.87 (1.78-1.97)**	**1.56 (1.48-1.65)** [a]	65 (8.5)	**1.50 (1.16-1.94)**	**1.42 (1.08-1.86)** [a]
Pregnancy outcome										
Livebirth	105,949 (98.9)	43,407 (98.7)	1.00	1.00	23,704 (98.4)	1.00	1.00	747 (98.0)	1.00	1.00
Stillbirth	803 (0.7)	405 (0.9)	**1.23 (1.09-1.39)**	**1.33 (1.15-1.54)** [a]	275 (1.1)	**1.53 (1.33-1.76)**	**1.52 (1.30-1.77)** [a]	13 (1.7)	**2.30 (1.32-3.99)**	**2.34 (1.29-4.25)** [a]
Neonatal Death	373 (0.3)	182 (0.4)	1.19 (0.99-1.42)	**1.56 (1.27-1.93)** [a]	117 (0.5)	**1.40 (1.14-1.73)**	**1.56 (1.24-1.96)** [a]	2 (0.3)	0.76 (0.19-3.06)	0.93 (0.23-3.74) [a]
Missing	18 (<0.1)	4 (<0.1)	n/a	n/a	3 (<0.1)	n/a	n/a	0 (0.0)	n/a	n/a
Weight of baby (grams)										
NBW	87,966 (82.1)	34,555 (78.6)	1.00	1.00	19,163 (79.5)	1.00	1.00	605 (79.5)	1.00	1.00
LBW	5,910 (5.5)	3,571 (8.1)	**1.54 (1.47-1.61)**	**1.28 (1.20-1.37)** [b]	2,213 (9.2)	**1.72 (1.63-1.81)**	**1.60 (1.51-1.69)** [b]	59 (7.7)	**1.45 (1.11-1.90)**	1.29 (0.91-1.83) [b]
HBW	13,233 (12.4)	5,863 (13.3)	**1.13 (1.09-1.17)**	**1.09 (1.05-1.13)** [b]	2,720 (11.3)	**0.94 (0.90-0.99)**	0.98 (0.93-1.02) [b]	97 (12.7)	1.07 (0.86-1.32)	0.99 (0.80-1.24) [b]
Missing	34 (<0.1)	9 (<0.1)	n/a	n/a	3 (<0.1)	n/a	n/a	1 (0.1)	n/a	n/a
Standardised Birthweight Score										
Mean (SD)	0.001 (0.003)	-0.002 (0.065)	**0.03 (0.02-0.04)**	**0.046 (0.032-0.059)** [c]	0.001 (0.991)	**-0.04 (-0.058- -0.029)**	**-0.014 (-0.029-0.001)** [c]	0.046 (0.038)	**0.045 (-0.029-0.119)**	**0.049 (-0.025-0.123)** [c]
Admitted to neonatal unit										
No	62,378 (58.2)	32,391 (73.6)	1.00	1.00	16,342 (67.8)	1.00	1.00	480 (63.0)	1.00	1.00
Yes	11,011 (10.3)	7,448 (16.9)	**1.30 (1.26-1.35)**	**1.57 (1.51-1.64)** [b]	3,956 (16.4)	**1.37 (1.32-1.43)**	**1.45 (1.38-1.53)** [b]	117 (15.4)	**1.38 (1.13-1.69)**	**1.54 (1.22-1.94)** [b]
Missing	33,754 (31.5)	4,159 (9.5)	n/a	n/a	3,801 (15.8)	n/a	n/a	762 (21.7)	n/a	n/a
APGAR score at 1 min										
Normal	92,217 (86.1)	38,224 (86.9)	1.00	1.00	20,593 (85.5)	1.00	1.00	659 (86.5)	1.00	1.00
<7	14,335 (13.4)	5,674 (12.9)	**0.96 (0.92-0.99)**	**1.18 (1.13-1.23)** [d]	3,437(14.3)	**1.07 (1.03-1.12)**	**1.23 (1.18-1.28)** [d]	101 (13.3)	0.99 (0.80-1.22)	1.07 (0.86-1.32) [d]
Missing	591 (0.6)	100 (0.2)		n/a	69 (0.3)	n/a	n/a	2 (0.3)	n/a	n/a
APGAR score at 5 min										
Normal	104,292 (97.3)	42,730 (97.1)	1.00	1.00	23,334 (96.8)	1.00	1.00	738 (96.9)	1.00	1.00
<7	2,216 (2.1)	1,163 (2.6)	**1.28 (1.19-1.38)**	**1.48 (1.35-1.62)** [d]	690 (2.9)	**1.39 (1.28-1.52)**	**1.53 (1.40-1.68)** [d]	21 (2.8)	1.34 (0.87-2.07)	1.52 (0.97-2.36) [d]
Missing	635 (0.6)	105 (0.2)	n/a	n/a	75 (0.3)	n/a	n/a	3 (0.4)	n/a	n/a
Cryptorchidism (only males included)										
No	54,509 (99.3)	22,616 (99.0)	1.00	1.00	12,247 (99.1)	1.00	1.00	394 (99.4)	1.00	1.00
Yes	357 (0.7)	236 (1.0)	**1.59 (1.35-1.88)**	0.92 (0.77-1.11) [b]	107 (0.9)	**1.33 (1.07-1.66)**	0.87 (0.69-1.09) [b]	1 (0.3)	0.39 (0.05-2.77)	0.28 (0.04-1.98) [b]
Neural Tube Defects										

No	107,093 (99.9)	43,928 (99.8)	1.00	1.00	24,077 (99.9)	1.00	1.00	762 (100)	1.00	1.00
Yes	50 (0.1)	70 (0.2)	**3.41 (2.37-4.91)**	**1.64 (1.08-2.47)** [b]	22 (0.1)	**1.96 (1.19-3.23)**	1.21 (0.71-2.06) [b]	0 (0.0)	n/a	n/a
Amniotic Band Defects										
No	107,053 (99.9)	43,936 (99.9)	1.00	1.00	24,070 (99.9)	1.00	1.00	760 (99.7)	1.00	1.00
Yes	90 (0.1)	62 (0.1)	**1.68 (1.21-2.32)**	1.02 (0.71-1.47) [b]	29 (0.1)	1.43 (0.94-2.18)	0.98 (0.63-1.52) [b]	2 (0.3)	3.13 (0.77-12.73)	2.29 (0.56-9.37) [b]
Hypospadias (only males included)										
No	54,607 (99.5)	22,600 (98.9)	1.00	1.00	12,258 (99.2)	1.00	1.00	390 (98.7)	1.00	1.00
Yes	259 (0.3)	252 (1.1)	**2.35 (1.98-2.80)**	**1.27 (1.05-1.54)** [b]	96 (0.8)	**1.65 (1.31-2.09)**	1.07 (0.84-1.37) [b]	5 (1.3)	**2.70 (1.11-6.59)**	1.91 (0.78-4.68) [b]
Gastroschisis										
No	107,120 (99.9)	43,979 (99.9)	1.00	1.00	24,089 (99.9)	1.00	1.00	762(100)	1.00	1.00
Yes	23 (0.1)	19 (0.1)	**2.01 (1.10-3.70)**	1.10 (0.56-2.20) [b]	10 (0.1)	1.93 (0.92-4.06)	0.99 (0.45-2.21) [b]	0 (0.0)	n/a	n/a
At least one outcome*										
No	106,367 (99.3%)	43,363 (98.6%)	1.00	1.00	23,835 (98.9%)	1.00	1.00	754 (99.0%)	1.00	1.00
Yes	776 (0.7%)	635 (1.4%)	**2.01 (1.81-2.23)**	1.12 (0.99-1.26) [b]	264 (1.1%)	**1.52 (1.32-1.75)**	0.97 (0.84-1.13) [b]	8 (1.0%)	1.45 (0.72-2.93)	1.11 (0.55-2.23) [b]

n/a, not applicable; n, number of pregnancies

[a] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, maternal hypertensive disorders, maternal antepartum haemorrhage

[b] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at delivery

[c] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking

[d] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of delivery

*Including cryptorchidism, neural tube defects, amniotic band defects, hypospadias, gastroschisis

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Table 3. Sub-group regression analysis between control pregnancies and exposed to diclofenac.

Outcomes	No analgesic (n=20,544) n (%)	Diclofenac only 2005-2015 (n=10,291) n (%)	Crude OR (CI 95%)	Adjusted OR (CI 95%)
Gestation at delivery (weeks)				
>=37	19,407 (94.5%)	9,640 (93.7%)	1.00	1.00
<37	1,137 (5.5%)	651 (6.3%)	**1.15 (1.04, 1.27)**	1.10 (0.99, 1.22) [a]
Pregnancy outcome				
Livebirth	20,393 (99.3%)	10,227 (99.4%)	1.00	1.00
Stillbirth	116 (0.5%)	39 (0.4%)	**0.67 (0.47, 0.96)**	**0.59 (0.41, 0.87)** [a]
Neonatal Death	35 (0.2%)	25 (0.2%)	1.42 (0.85, 2.38)	1.26 (0.73, 2.15) [a]
Weight of baby (grams)				
NBW	16,869 (82.1%)	8,116 (78.9%)	1.00	1.00
LBW	965 (4.7%)	572 (5.6%)	**1.23 (1.11, 1.37)**	**1.22 (1.07, 1.40)** [b]
HBW	2,707 (13.2%)	1,600 (15.5%)	**1.23 (1.15, 1.31)**	**1.21 (1.13, 1.29)** [b]
Missing	3 (0.0%)	3 (0.0%)		
Standardised Birthweight Score				
	-0.039 (0.959)	0.132 (1.036)	**0.171 (0.145, 0.197)**	**0.167 (0.141, 0.193)** [c]
Admitted to neonatal unit				
No	18,224 (88.7%)	8,747 (85.0%)	1.00	1.00
Yes	2,175 (10.6%)	1,492 (14.5%)	**1.43 (1.33, 1.53)**	**1.46 (1.35, 1.58)** [b]
Missing	145 (0.7%)	52 (0.5%)		
APGAR score at 1 min				
Normal	18,709 (91.1%)	9,350 (90.9%)	1.00	1.00
<7	1,658 (8.1%)	924 (9.0%)	**1.12 (1.03, 1.21)**	0.93 (0.83, 1.04) [d]
Missing	177 (0.9%)	17 (0.2%)		
APGAR score at 5 min				
Normal	20,065 (97.7%)	10,096 (98.1%)	1.00	1.00
<7	302 (1.5%)	177 (1.7%)	0.86 (0.71, 1.04)	0.94 (0.72, 1.23) [d]
Missing	177 (0.9%)	18 (0.2%)		
Cryptorchidism (only males included)				
No	10,284 (98.7%)	5,314 (98.7%)	1.00	1.00
Yes	133 (1.3%)	70 (1.3%)	1.02 (0.76, 1.36)	1.05 (0.78, 1.42) [b]
Neural Tube Defects				
No	20,527 (99.9%)	10,263 (99.7%)	1.00	1.00
Yes	17 (0.1%)	28 (0.3%)	**3.29 (1.80, 6.02)**	**3.62 (1.95, 6.74)** [b]
Amniotic Band Defects				
No	20,514 (99.9%)	10,277 (99.9%)	1.00	1.00
Yes	30 (0.1%)	14 (0.1%)	0.93 (0.49, 1.76)	0.81 (0.41, 1.58) [b]
Hypospadias (only males included)				
No	10,317 (99.0%)	5,308 (98.6%)	1.00	1.00
Yes	100 (1.0%)	76 (1.4%)	**1.48 (1.09, 1.99)**	**1.49 (1.09, 2.03)** [b]
Gastroschisis				
No	20,538 (99.9%)	10,284 (99.9%)	1.00	1.00
Yes	6 (0.1%)	7 (0.1%)	2.33 (0.78, 6.94)	2.93 (0.97, 8.88) [b]
At least one outcome*				
No	20,258 (98.6%)	10,097 (98.1%)	1.00	1.00
Yes	286 (1.4%)	194 (1.9%)	**1.36 (1.13, 1.64)**	**1.38 (1.15, 1.67)** [b]

[a] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, maternal hypertensive disorders, maternal antepartum haemorrhage

[b] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at delivery

[c] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking

[d] Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of delivery

*Including cryptorchidism, neural tube defects, amniotic band defects, hypospadias, gastroschisis

Figure 1. Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis.*98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

Figure 2. Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. (**A**) Merge graph showing percentage of pregnancies using each analgesic group during pregnancy. (**B**) Percentage of use for at least one analgesic out of ibuprofen, aspirin, naproxen. *In 2005 there was a change in legislation making diclofenac available without prescription.

Figure S1. Directed acyclic graph (DAG) of analgesics use to amniotic band defects outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S2. Directed acyclic graph (DAG) of analgesics use to APGAR score outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S3. Directed acyclic graph (DAG) of analgesics use to cryptorchidism outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S4. Directed acyclic graph (DAG) of analgesics use to gastroschisis outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S5. Directed acyclic graph (DAG) of analgesics use to gestation at delivery outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S6. Directed acyclic graph (DAG) of analgesics use to hypospadias outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S7. Directed acyclic graph (DAG) of analgesics use to admission to neonatal unit outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S8. Directed acyclic graph (DAG) of analgesics use to neural tube defects outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S9. Directed acyclic graph (DAG) of analgesics use to pregnancy outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S10. Directed acyclic graph (DAG) of analgesics use to standardised birthweight score outcome path and relevant measured and unmeasured biasing factors in our analysis.

Figure S11. Directed acyclic graph (DAG) of analgesics use to weight of baby outcome path and relevant measured and unmeasured biasing factors in our analysis.

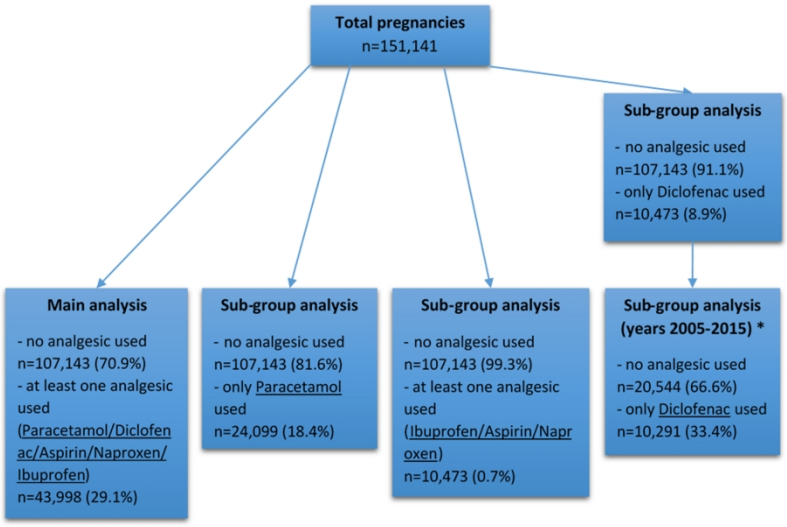

Figure 1. Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis.*98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

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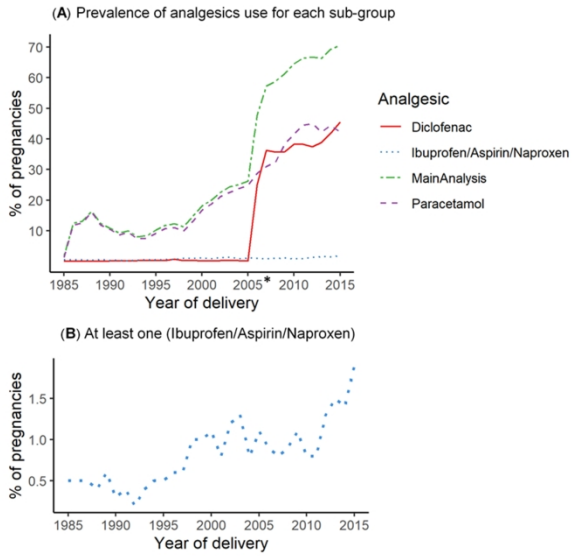

Figure 2. Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. (A) Merge graph showing percentage of pregnancies using each analgesic group during pregnancy. (B) Percentage of use for at least one analgesic out of ibuprofen, aspirin, naproxen. *In 2005 there was a change in legislation making diclofenac available without prescription.

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Table S1. Numbers needed to harm (NNH) calculations

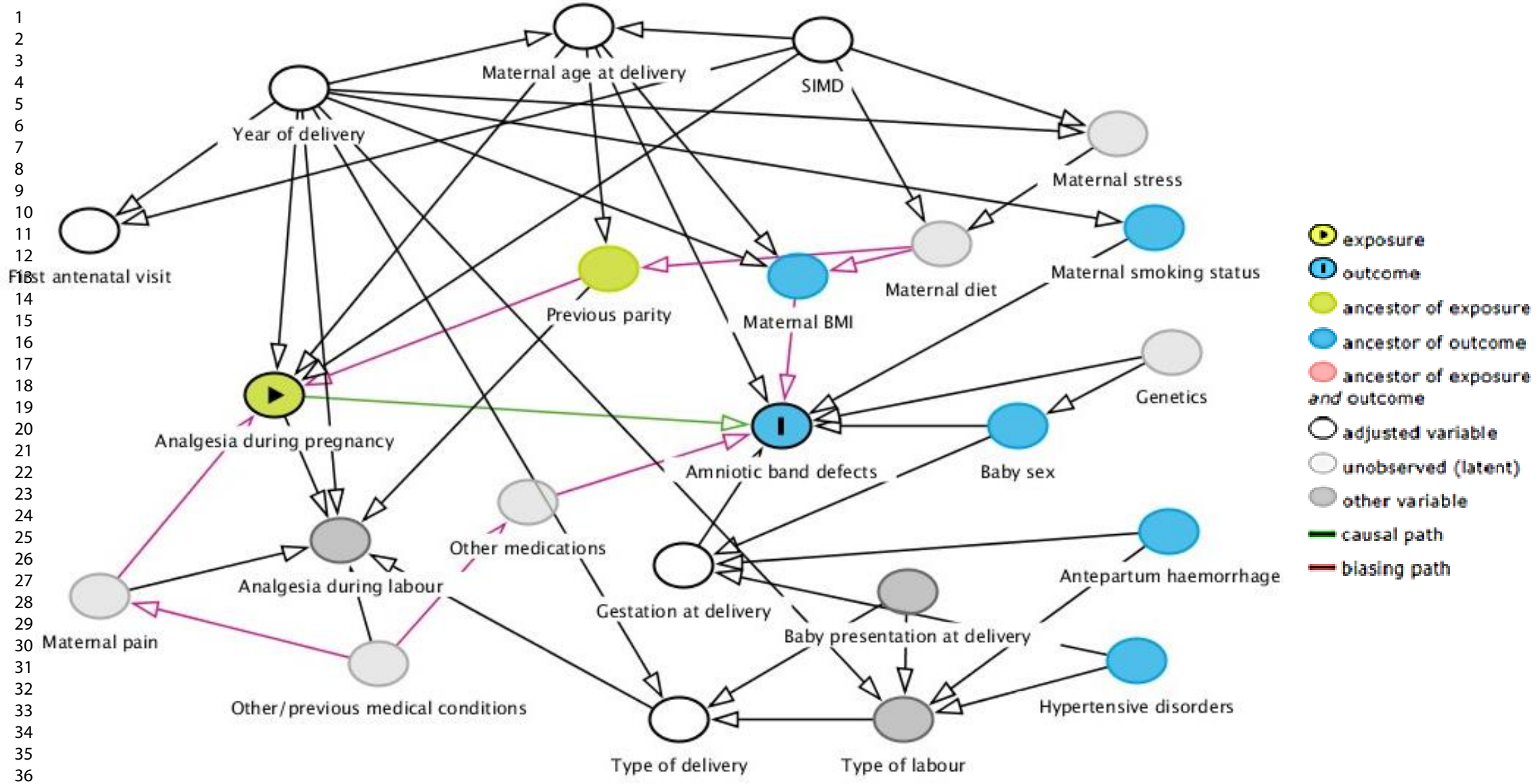
Outcomes	No analgesic (n=107,143) n (%)	At least one analgesic (n=43,998) n (%)	NNH	Paracetamol (n=24,099) n (%)	NNH	Ibu/Asp/Napr (n=762) n (%)	NNH
Gestation at delivery (weeks)							
>=37	100,879 (94.2)	39,838 (90.5)		21,589 (89.6)		697 (91.5)	
<37	6,264 (5.8)	4,160 (9.5)	27	2,510 (10.4)	22	65 (8.5)	37
Pregnancy outcome							
Livebirth	105,949 (98.9)	43,407 (98.7)		23,704 (98.4)		747 (98.0)	
Stillbirth	803 (0.7)	405 (0.9)	500	275 (1.1)	250	13 (1.7)	100
Neonatal Death	373 (0.3)	182 (0.4)	1000	117 (0.5)	500	2 (0.3)	**n/a**
Missing	18 (<0.1)	4 (<0.1)	**n/a**	3 (<0.1)	**n/a**	0 (0.0)	**n/a**
Weight of baby (grams)							
NBW	87,966 (82.1)	34,555 (78.6)		19,163 (79.5)		605 (79.5)	
LBW	5,910 (5.5)	3,571 (8.1)	38	2,213 (9.2)	39	59 (7.7)	46
HBW	13,233 (12.4)	5,863 (13.3)	111	2,720 (11.3)	**n/a**	97 (12.7)	333
Missing	34 (<0.1)	9 (<0.1)	**n/a**	3 (<0.1)	**n/a**	1 (0.1)	**n/a**
Admitted to neonatal unit							
No	62,378 (58.2)	32,391 (73.6)		16,342 (67.8)		480 (63.0)	
Yes	11,011 (10.3)	7,448 (16.9)	15	3,956 (16.4)	16	117 (15.4)	20
Missing	33,754 (31.5)	4,159 (9.5)	**n/a**	3,801 (15.8)	**n/a**	762 (21.7)	**n/a**
APGAR score at 1 min							
Normal	92,217 (86.1)	38,224 (86.9)		20,593 (85.5)		659 (86.5)	
<7	14,335 (13.4)	5,674 (12.9)	**n/a**	3,437(14.3)	111	101 (13.3)	**n/a**
Missing	591 (0.6)	100 (0.2)		69 (0.3)	**n/a**	2 (0.3)	**n/a**
APGAR score at 5 min							
Normal	104,292 (97.3)	42,730 (97.1)		23,334 (96.8)		738 (96.9)	
<7	2,216 (2.1)	1,163 (2.6)	200	690 (2.9)	125	21 (2.8)	143
Missing	635 (0.6)	105 (0.2)	**n/a**	75 (0.3)	**n/a**	3 (0.4)	**n/a**
Cryptorchidism (only males included)							
No	54,509 (99.3)	22,616 (99.0)		12,247 (99.1)		394 (99.4)	
Yes	357 (0.7)	236 (1.0)	333	107 (0.9)	500	1 (0.3)	**n/a**
Neural Tube Defects							
No	107,093 (99.9)	43,928 (99.8)		24,077 (99.9)		762 (100)	
Yes	50 (0.1)	70 (0.2)	1000	22 (0.1)	**n/a**	0 (0.0)	**n/a**
Amniotic Band Defects							
No	107,053 (99.9)	43,936 (99.9)		24,070 (99.9)		760 (99.7)	
Yes	90 (0.1)	62 (0.1)	**n/a**	29 (0.1)	**n/a**	2 (0.3)	500
Hypospadias (only males included)							
No	54,607 (99.5)	22,600 (98.9)		12,258 (99.2)		390 (98.7)	
Yes	259 (0.3)	252 (1.1)	125	96 (0.8)	200	5 (1.3)	100
Gastroschisis							
No	107,120 (99.9)	43,979 (99.9)		24,089 (99.9)		762(100)	
Yes	23 (0.1)	19 (0.1)	**n/a**	10 (0.1)	**n/a**	0 (0.0)	**n/a**
At least one outcome*							
No	106,367 (99.3%)	43,363 (98.6%)		23,835 (98.9%)		754 (99.0%)	
Yes	776 (0.7%)	635 (1.4%)	142	264 (1.1%)	250	8 (1.0%)	333

n/a, not applicable

Table S2. Numbers needed to harm (NNH) for exposure to diclofenac (years 2005-2015).

Outcomes	No analgesic (n=20,544) n (%)	Diclofenac 2005-2015 (n=10,291) n (%)	NNH
Gestation at delivery (weeks)			
>=37	19,407 (94.5%)	9,640 (93.7%)	
<37	1,137 (5.5%)	651 (6.3%)	125
Pregnancy outcome			
Livebirth	20,393 (99.3%)	10,227 (99.4%)	
Stillbirth	116 (0.5%)	39 (0.4%)	**n/a**
Neonatal Death	35 (0.2%)	25 (0.2%)	**n/a**
Weight of baby (grams)			
NBW	16,869 (82.1%)	8,116 (78.9%)	
LBW	965 (4.7%)	572 (5.6%)	111
HBW	2,707 (13.2%)	1,600 (15.5%)	44
Missing	3 (0.0%)	3 (0.0%)	
Admitted to neonatal unit			
No	18,224 (88.7%)	8,747 (85.0%)	
Yes	2,175 (10.6%)	1,492 (14.5%)	26
Missing	145 (0.7%)	52 (0.5%)	
APGAR score at 1 min			
Normal	18,709 (91.1%)	9,350 (90.9%)	
<7	1,658 (8.1%)	924 (9.0%)	111
Missing	177 (0.9%)	17 (0.2%)	
APGAR score at 5 min			
Normal	20,065 (97.7%)	10,096 (98.1%)	
<7	302 (1.5%)	177 (1.7%)	500
Missing	177 (0.9%)	18 (0.2%)	
Cryptorchidism (only males included)			
No	10,284 (98.7%)	5,314 (98.7%)	
Yes	133 (1.3%)	70 (1.3%)	**n/a**
Neural Tube Defects			
No	20,527 (99.9%)	10,263 (99.7%)	
Yes	17 (0.1%)	28 (0.3%)	500
Amniotic Band Defects			
No	20,514 (99.9%)	10,277 (99.9%)	
Yes	30 (0.1%)	14 (0.1%)	**n/a**
Hypospadias (only males included)			
No	10,317 (99.0%)	5,308 (98.6%)	
Yes	100 (1.0%)	76 (1.4%)	250
Gastroschisis			
No	20,538 (99.9%)	10,284 (99.9%)	
Yes	6 (0.1%)	7 (0.1%)	**n/a**
At least one outcome*			
No	20,258 (98.6%)	10,097 (98.1%)	
Yes	286 (1.4%)	194 (1.9%)	200

n/a, not applicable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SIMD
Year of delivery
Maternal stress
First antenatal visit
Maternal diet
Maternal smoking status
Previous parity
Maternal BMI
Genetics
Analgesia during pregnancy
Amniotic band defects
Baby sex
Other medications
Antepartum haemorrhage
Analgesia during labour
Gestation at delivery
Maternal pain
Baby presentation at delivery
Other/previous medical conditions
Hypertensive disorders
Type of delivery
Type of labour
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adjusted variable
unobserved (latent)
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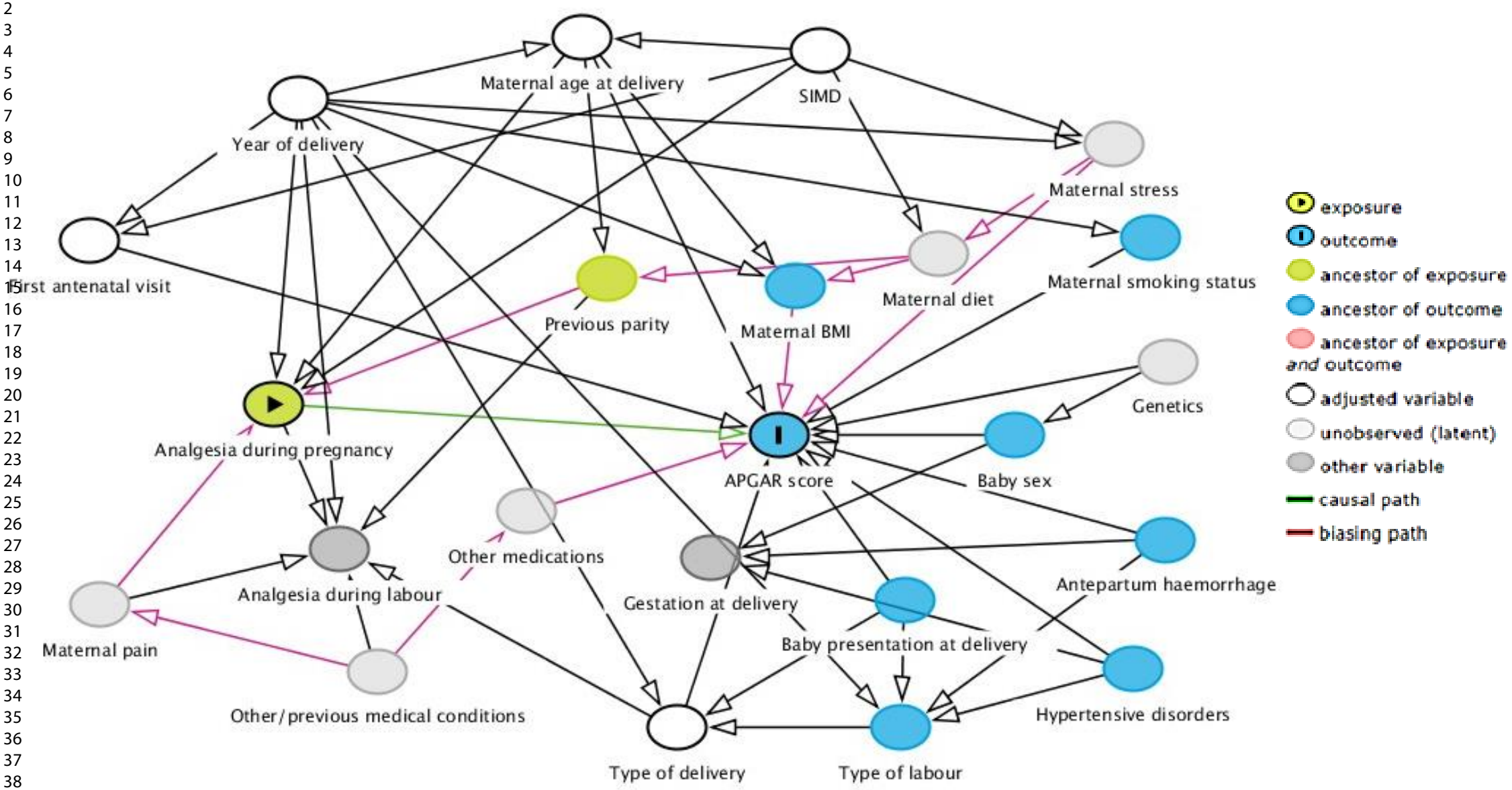
causal path
biasing path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Year of delivery
Maternal stress
First antenatal visit
Maternal smoking status
Previous parity
Maternal BMI
Maternal diet
Genetics
Analgesia during pregnancy
APGAR score
Baby sex
Other medications
Antepartum haemorrhage
Analgesia during labour
Gestation at delivery
Baby presentation at delivery
Maternal pain
Hypertensive disorders
Other/previous medical conditions
Type of delivery
Type of labour
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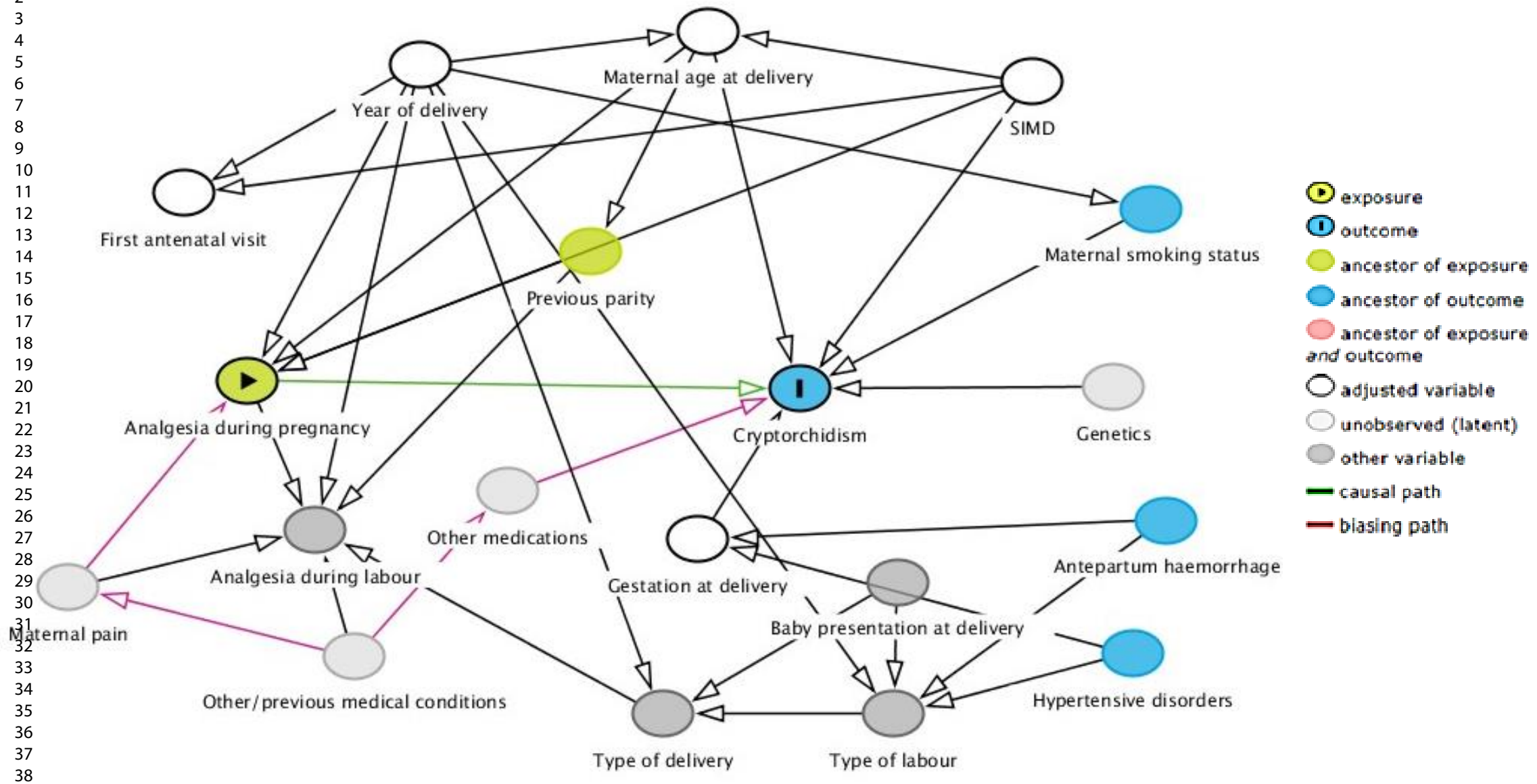
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Previous parity
Analgesia during pregnancy
Cryptorchidism
Genetics
Other medications
Analgesia during labour
Antepartum haemorrhage
Gestation at delivery
Maternal pain
Baby presentation at delivery
Other/previous medical conditions
Hypertensive disorders
Type of delivery
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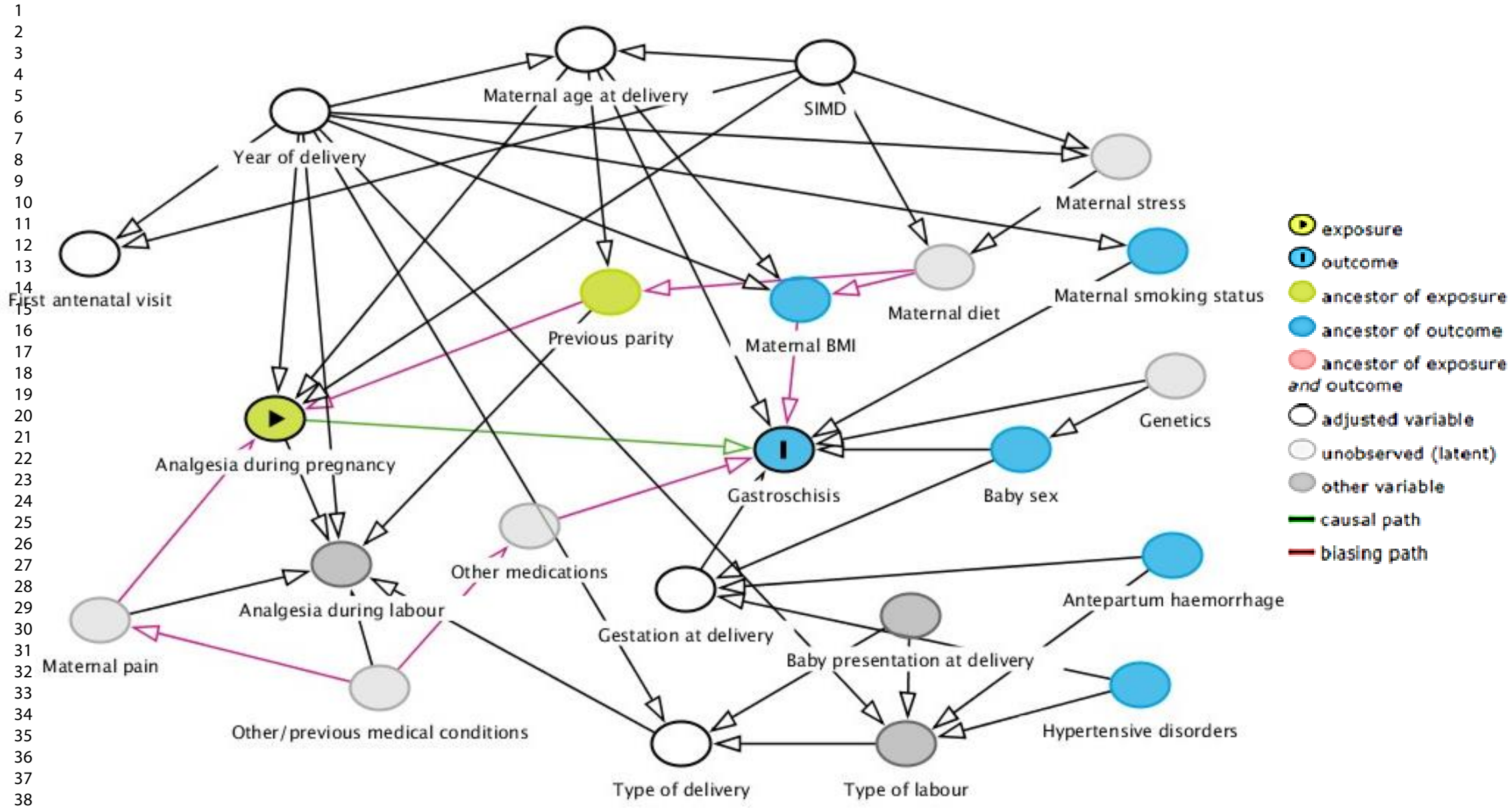
other variable
causal path
biasing path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Year of delivery
Maternal stress
First antenatal visit
Maternal smoking status
Previous parity
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Maternal BMI
Genetics
Analgesia during pregnancy
Gastroschisis
Baby sex
Other medications
Antepartum haemorrhage
Analgesia during labour
Gestation at delivery
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Baby presentation at delivery
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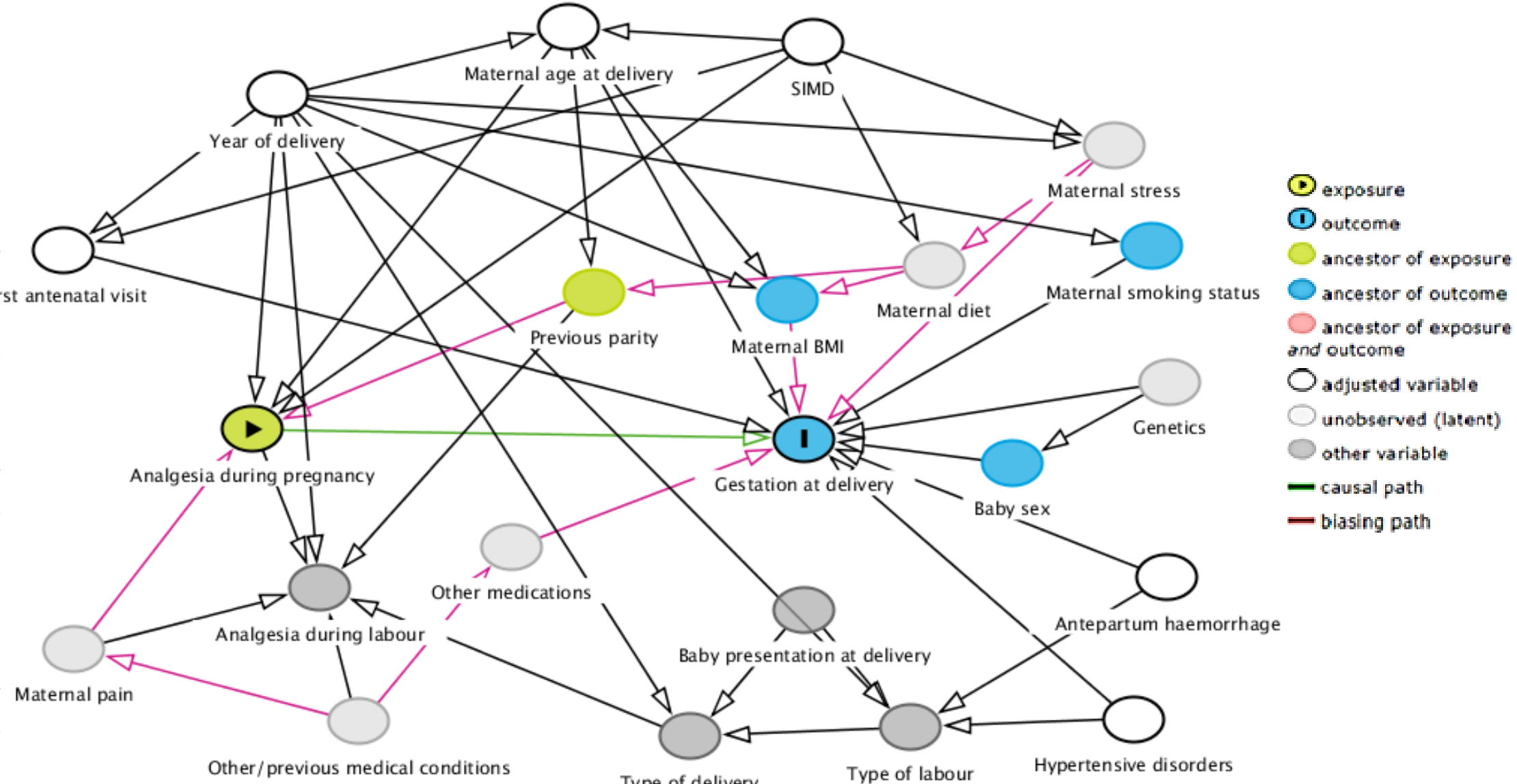
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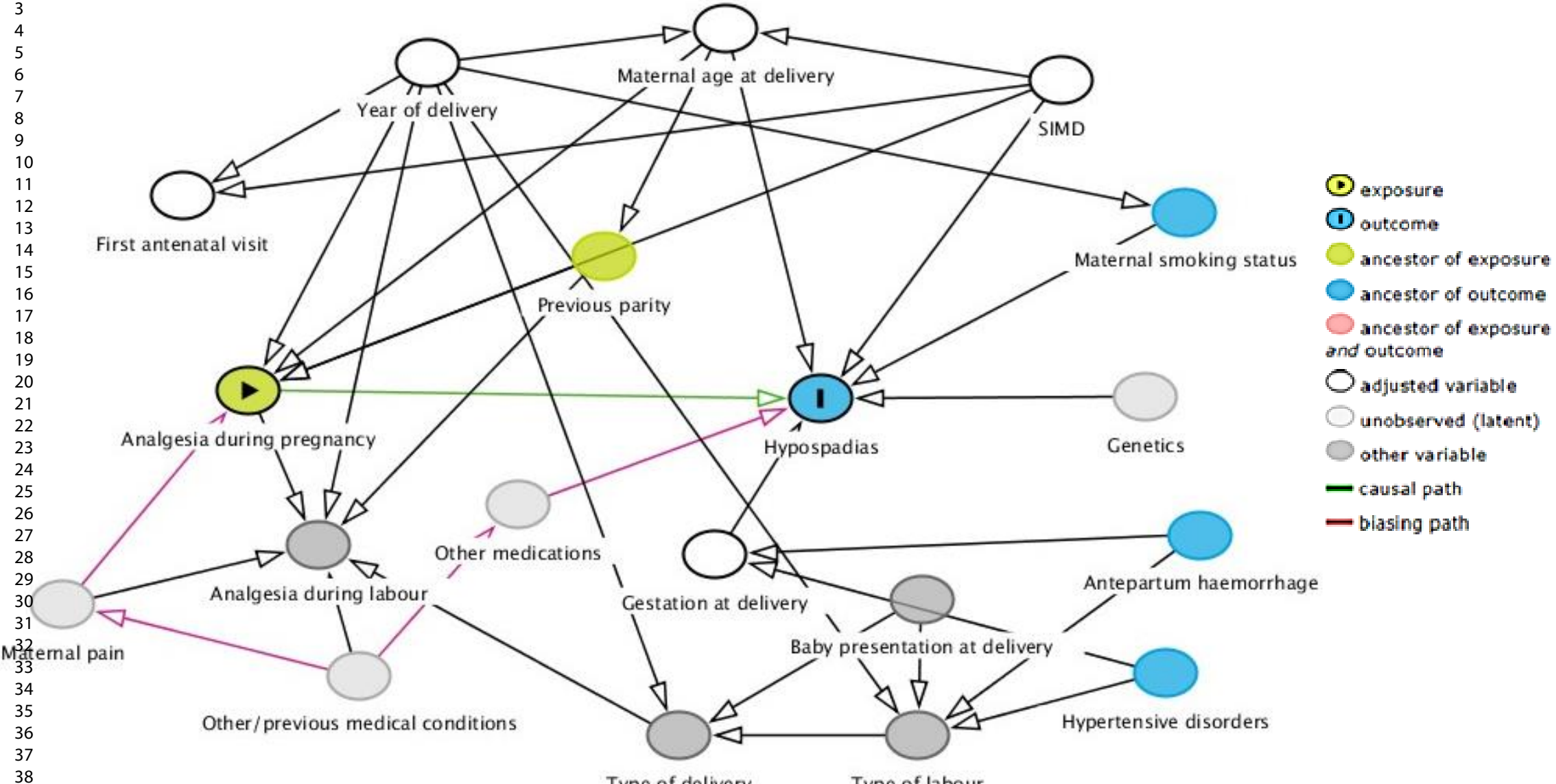
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Other medications
Analgesia during labour
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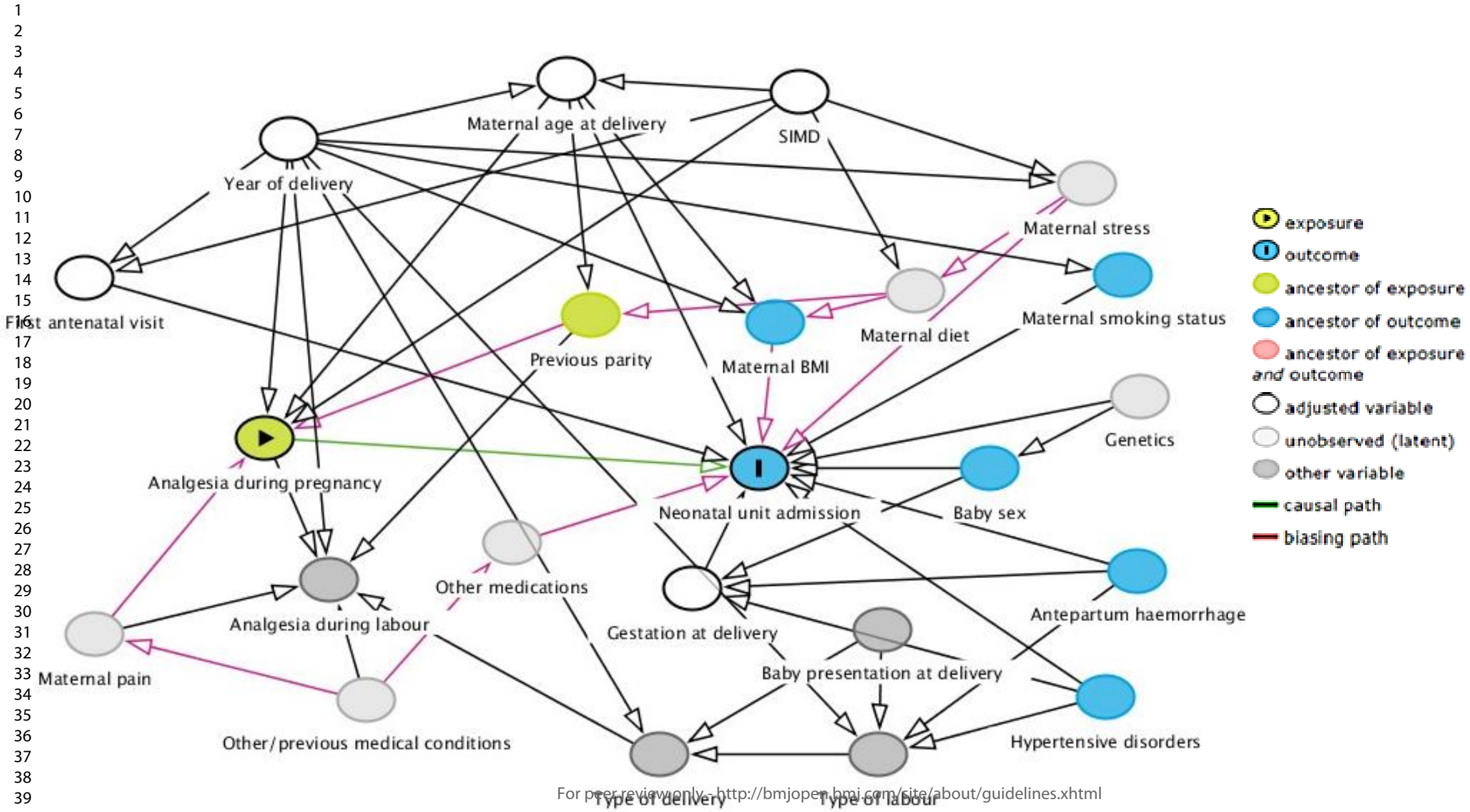

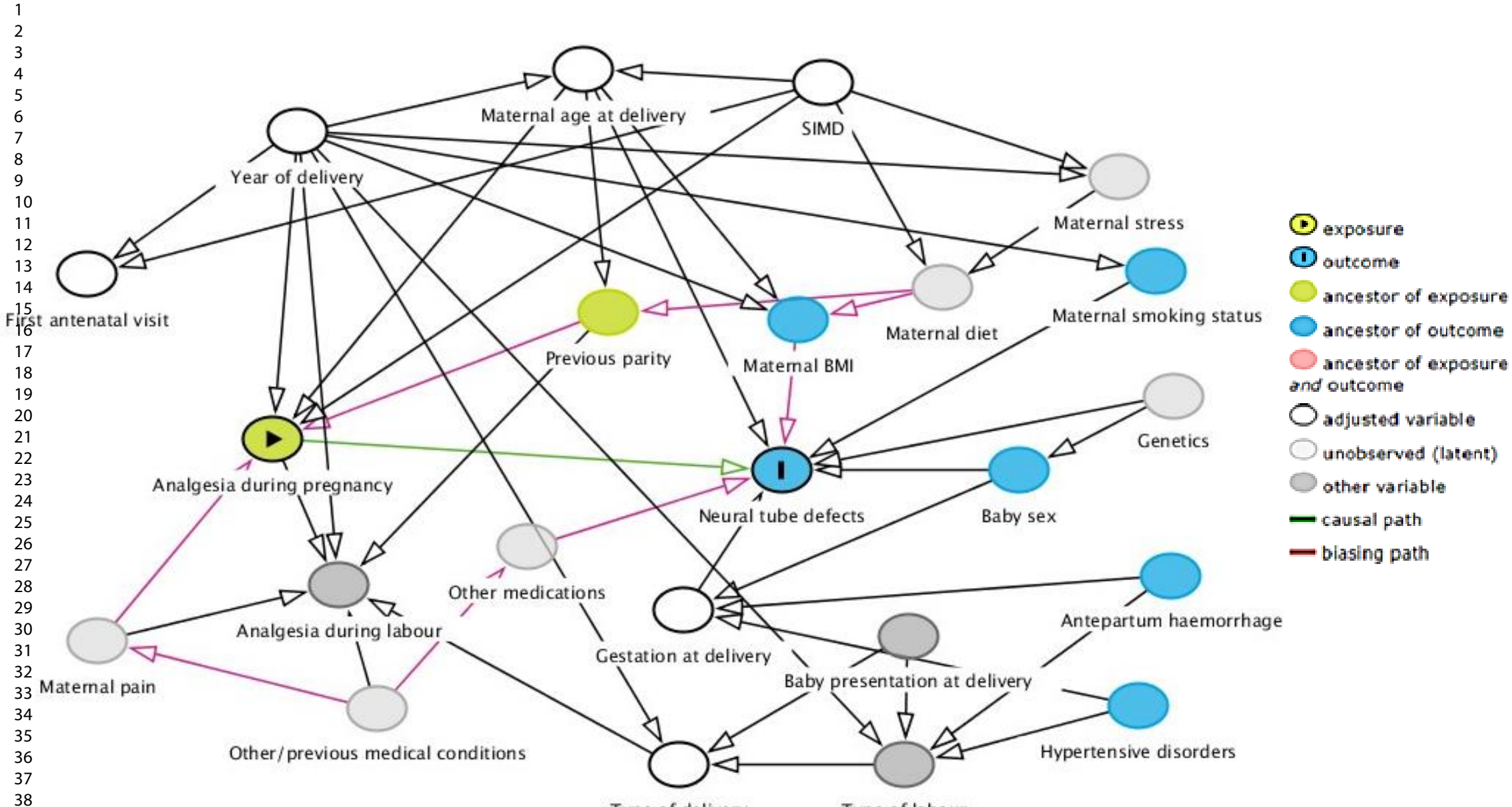

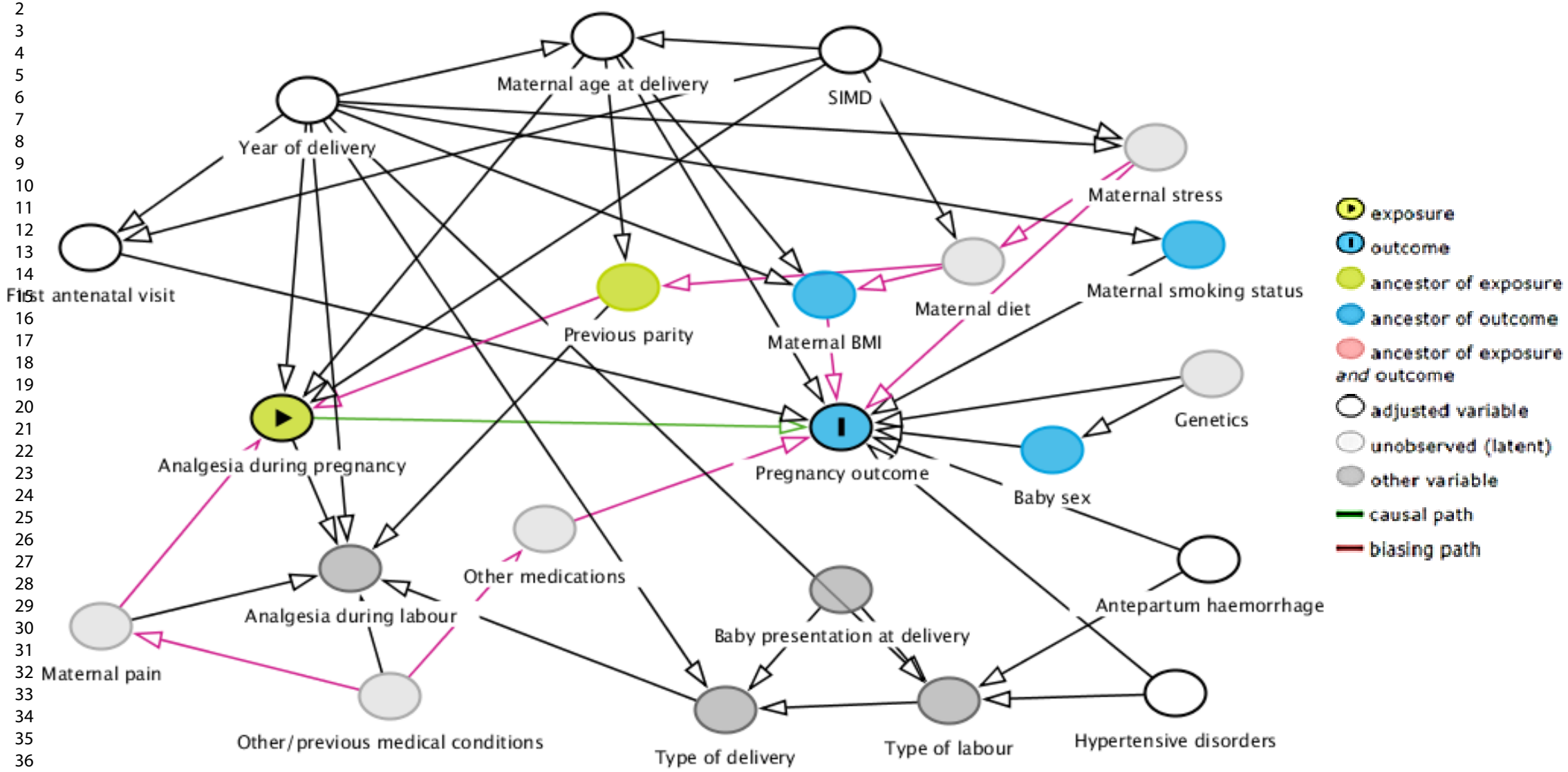
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Previous parity
Maternal BMI
Maternal diet
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Analgesia during pregnancy
Pregnancy outcome
Baby sex
Other medications
Antepartum haemorrhage
Analgesia during labour
Baby presentation at delivery
Maternal pain
Other/previous medical conditions
Type of delivery
Type of labour
Hypertensive disorders
exposure
outcome
ancestor of exposure
ancestor of outcome
ancestor of exposure and outcome
adjusted variable
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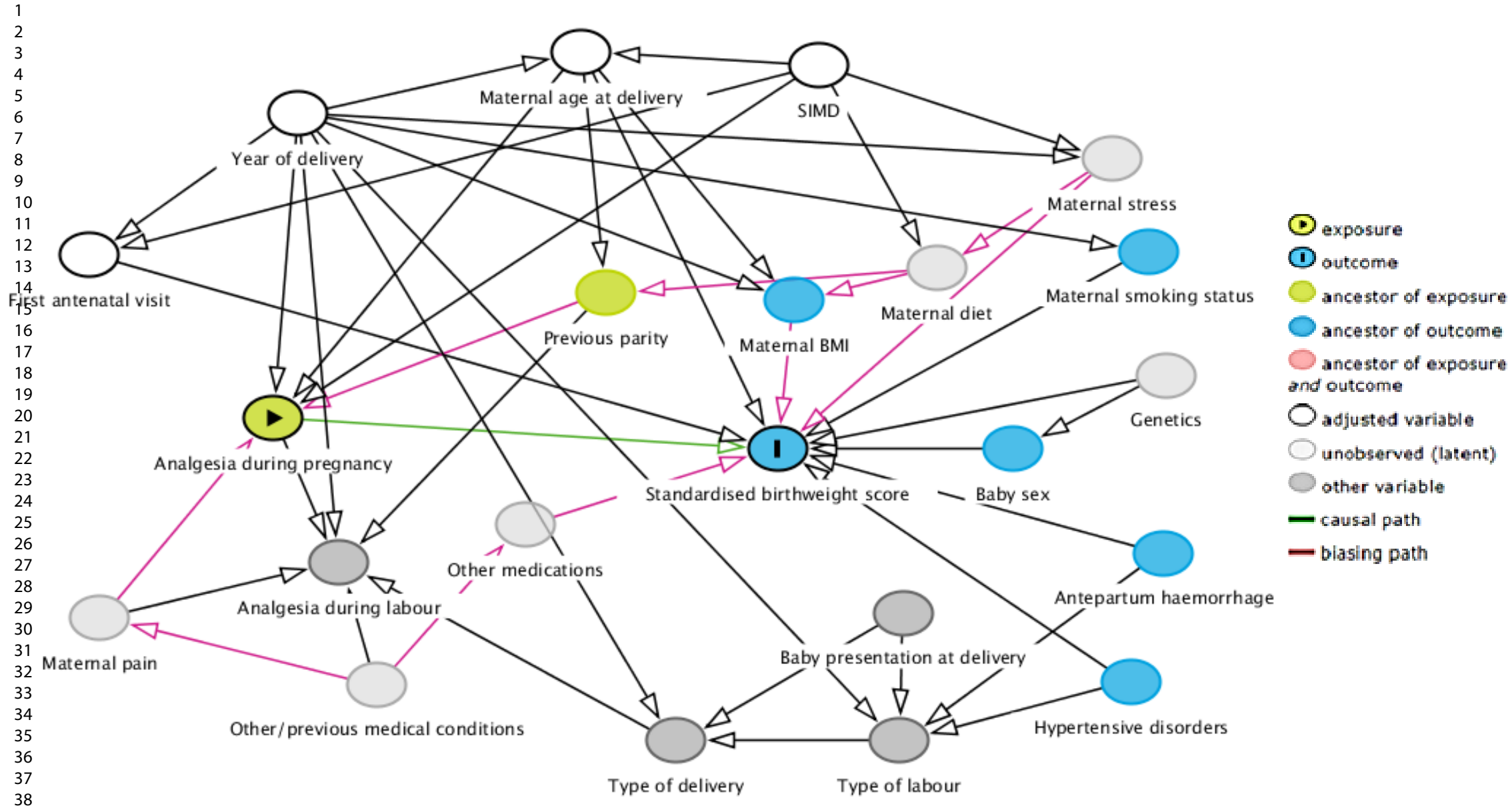
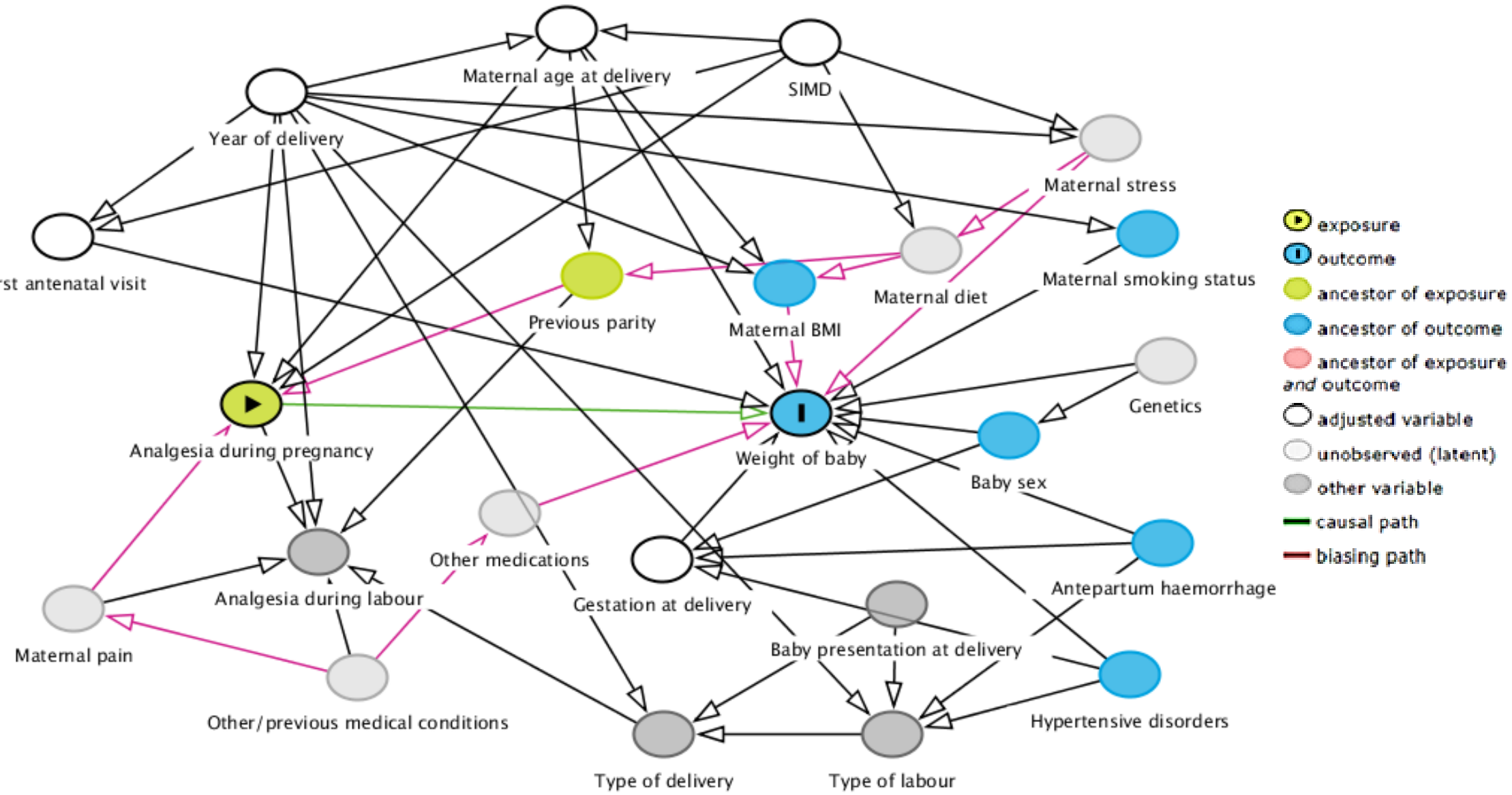
causal path
biasing path


Maternal age at delivery
SIMD
Year of delivery
Maternal stress
First antenatal visit
Maternal smoking status
Previous parity
Maternal diet
Maternal BMI
Genetics
Analgesia during pregnancy
Standardised birthweight score
Baby sex
Other medications
Antepartum haemorrhage
Analgesia during labour
Maternal pain
Baby presentation at delivery
Other/previous medical conditions
Hypertensive disorders
Type of delivery
Type of labour
exposure
outcome
ancestor of exposure
ancestor of outcome
ancestor of exposure and outcome
adjusted variable
unobserved (latent)
other variable
causal path
biasing path


Maternal age at delivery
SIMD
Year of delivery
Maternal stress
First antenatal visit
Maternal smoking status
Previous parity
Maternal BMI
Maternal diet
Genetics
Analgesia during pregnancy
Weight of baby
Baby sex
Other medications
Antepartum haemorrhage
Analgesia during labour
Gestation at delivery
Maternal pain
Baby presentation at delivery
Other/previous medical conditions
Hypertensive disorders
Type of delivery
Type of labour
exposure
outcome
ancestor of exposure
ancestor of outcome
ancestor of exposure and outcome
adjusted variable
unobserved (latent)
other variable
causal path
biasing path

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

	Item No	Recommendation	Paragraph #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**Title & Abstract Pages 1-3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**Abstract Pages 2-3**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**Introduction Page 5**
Objectives	3	State specific objectives, including any prespecified hypotheses	**Introduction Page 5**
Methods			
Study design	4	Present key elements of study design early in the paper	**Methods Page 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**Methods Page 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**Methods Pages 7-8**
		(*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	**Methods Pages 8-9**
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	**Methods Pages 8-9**
Bias	9	Describe any efforts to address potential sources of bias	**Methods Pages 7-8**
Study size	10	Explain how the study size was arrived at	**Methods Page 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**Methods Pages 8-9**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**Statistical Analysis paragraph pages 9-10**
		(*b*) Describe any methods used to examine subgroups and interactions	**Statistical Analysis paragraph pages 9-10**
		(*c*) Explain how missing data were addressed	**Statistical Analysis paragraph pages 9-10**
		(*d*) If applicable, explain how loss to follow-up was addressed	**n/a**
		(*e*) Describe any sensitivity analyses	**n/a**

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	**Figure 1**
		(b) Give reasons for non-participation at each stage	**Results Page 11**
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Table 1 Pages 29-31**
		(b) Indicate number of participants with missing data for each variable of interest	**Table 1 Pages 29-31**
		(c) Summarise follow-up time (eg, average and total amount)	**n/a**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**Tables 2 and 3 Pages 32-35**
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	**Tables 2 and 3 Pages 32-35**
		(*b*) Report category boundaries when continuous variables were categorized	**Table 1 Pages 29-31**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**Tables 2 and 3 Pages 32-35**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**n/a**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**Discussion Pages 16-17**
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	**Discussion Pages 16-18**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**Discussion Pages 19-21**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**Discussion Pages 20-21**
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	**Manuscript pages 4 and 21**

*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.