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

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

3
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19 **Running Title:** Maternal over-the-counter analgesia and offspring outcomes

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2
3 20 **Abstract**
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5
6 21 OBJECTIVES
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9 22 To identify any associations between *in utero* exposure to five over-the-counter (non-
10
11 23 prescription) analgesics (paracetamol, ibuprofen, aspirin, diclofenac, naproxen) and
12
13 24 adverse neonatal outcomes.
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16 25 DESIGN
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19 26 Retrospective cohort study using the Aberdeen Maternity and Neonatal Databank.
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22 27 PARTICIPANTS
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25 28 151,141 singleton pregnancies between 1985 and 2015.
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28 29 MAIN OUTCOME MEASURES
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31 30 Premature delivery (<37 weeks), stillbirth, neonatal death, birthweight, standardised
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33 31 birthweight score, neonatal unit admission, APGAR score at 1 and 5 minutes, neural
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35 32 tube and amniotic band defects, gastroschisis and, in males, cryptorchidism, and
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37 33 hypospadias.
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41 34 RESULTS
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43
44 35 83.7% of women taking over-the-counter analgesics reported first trimester use
45
46 36 when specifically asked about use at their first antenatal clinic visit. Pregnancies
47
48 37 exposed to at least one of the five analgesics were significantly independently
49
50 38 associated with increased risks for premature delivery <37 weeks (aOR=1.50,
51
52 39 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), neonatal death
53
54 40 (aOR=1.56, 95%CI 1.27-1.93), birthweight <2,500g (aOR=1.28, 95%CI 1.20-1.37),
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56 41 birthweight >4,000g (aOR=1.09, 95%CI 1.05-1.13), admission to neonatal unit
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3 42 (aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at 1 minute (aOR=1.18, 95%CI
4
5 43 1.13-1.23) and 5 minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects
6
7 44 (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54 males
8
9 45 only). The overall prevalence of over-the-counter analgesics use during pregnancy
10
11 46 was 29.1%, however it rapidly increased over the 30-year study period, to include
12
13 47 over 60% of women in the last seven years of the study. This makes our findings
14
15 48 highly relevant to the wider pregnant population.
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20 49 CONCLUSIONS

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22
23 50 Over-the-counter (non-prescription) analgesics consumption during pregnancy was
24
25 51 associated with a substantially higher risk for adverse perinatal health outcomes in
26
27 52 the offspring. The use of paracetamol in combination with other non-steroidal anti-
28
29 53 inflammatory drugs conferred the highest risk. The increased risks of adverse
30
31 54 neonatal outcomes associated with non-prescribed, over-the-counter, analgesics use
32
33 55 during pregnancy indicate that healthcare guidance for pregnant women regarding
34
35 56 analgesic use need urgent updating.
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40 57 **Strengths and limitations of this study**

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43 58 • This is one of the largest and most comprehensive studies of this type. It
44
45 59 includes consumption of five different analgesics during pregnancy in a large
46
47 60 cohort of singleton pregnancies. It examines associations with an extensive
48
49 61 range of offspring perinatal outcomes, while adjusting for important
50
51 62 confounding factors
52
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54 63 • Analgesic consumption was analysed both as use of a single compound and
55
56 64 in combinations of the five drugs considered in this study
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3 65 • Details of the exact dose and timing of consumption during pregnancy was
4
5 66 not available within our dataset

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7
8 67 • Follow-up of the offspring health later in life was not available at this time
9

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13
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17
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19
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23
24 73 **Key words** acetaminophen, aspirin, diclofenac, ibuprofen, *in utero* exposure,
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26 74 naproxen, offspring outcomes, over-the-counter analgesics, offspring outcomes,
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28 75 paracetamol, pregnancy
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77 Introduction

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

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

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3 102 Given the diversity in study population, methodology, sample size and findings in the
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5 103 published studies, we conclude that more extensive data from larger cohorts are
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7 104 essential in order to understand the risks over-the-counter analgesic use during
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9 105 pregnancy pose to neonatal health and function. Here we address many limitations
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11 106 of previous studies by analysing one of the largest cohorts, widest range of health
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13 107 data and, pregnancy use of five over-the-counter analgesics consumed in
14
15 108 combination or separately. We report on the prevalence of maternal consumption of
16
17 109 five different over-the-counter analgesics during pregnancy and their associations
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19 110 with offspring neonatal outcomes using a large cohort of 151,141 singleton
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21 111 pregnancies spanning three decades of population-based data from a single
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23 112 maternity hospital serving the entire population of Aberdeenshire in the North East of
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25 113 Scotland.
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114 **Materials and Methods**

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

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

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3 138 analysis only considered pregnancies during that time frame in order to rule out any
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5 139 temporal effect.
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8 140 The offspring outcomes compared between control and exposed groups were:
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10 141 gestation at delivery (preterm <37 gestation weeks, term \geq 37 gestation weeks),
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12 142 pregnancy outcome (livebirth, stillbirth, neonatal death), baby weight (low birth
13
14 143 weight (LBW) \leq 2,499 g, high birth weight (HBW) \geq 4,000 g, normal birth weight
15
16 144 (NBW) 2,500g-3,999 g), standardised birthweight score was considered as a
17
18 145 continuous variable as previously described by Campbell and colleagues²³, baby
19
20 146 admission to neonatal unit (no; yes), APGAR score at one and five minutes (<7, \geq 7),
21
22 147 cryptorchidism (no; yes) (ICD-10 code Q53), neural tube defects (no; yes) (ICD-10
23
24 148 code Q00-07), amniotic band defects (no; yes) (ICD-10 codes Q70-74), hypospadias
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26 149 (no; yes) (ICD-10 code Q54), gastroschisis (no; yes) (ICD-10 code Q79.3). A
27
28 150 composite outcome (presence of at least one congenital anomaly (no; yes)) was
29
30 151 created using the variables neural tube defects, amniotic band defects, and
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32 152 gastroschisis and, in males, cryptorchidism and hypospadias.
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39 153 The baseline characteristics compared between exposed and unexposed
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41 154 pregnancies were (reference category first): year of delivery (1985-1994, 1995-2004,
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43 155 2005-2015), maternal age at delivery (20-25, <20, 26-35, >35 years), previous
44
45 156 pregnancy (no; yes), maternal body mass index (BMI) (normal weight 18.5-24.9
46
47 157 kg/m², underweight <18.5 kg/m², overweight 25-29.9 kg/m², obese \geq 30 kg/m²),
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49 158 maternal first antenatal visit (1st, 2nd, 3rd trimester), maternal smoking status (non-
50
51 159 smoker, smoker, ex-smoker), Scottish Index of Multiple Deprivation (SIMD) decile (1-
52
53 160 6, 7-10, decreasing deprivation with increasing score), maternal hypertensive
54
55 161 disorders (no disorder, gestational hypertension, preeclampsia, eclampsia), maternal
56
57 162 antepartum haemorrhage (no haemorrhage, abruption, placental previa), type of
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3 163 labour (spontaneous, elective caesarean section, induced), type of delivery
4
5 164 (spontaneous vaginal delivery, instrumental, caesarean section), analgesia during
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7 165 labour (no; yes), baby presentation at delivery (occiput anterior, occiput posterior),
8
9 166 baby sex (female; male).

13 167 **Patient and Public Involvement**

16 168 This was a retrospective analysis of data on singleton pregnancies over a 30-year
17
18 169 period. Therefore, there was no involvement of patients or the public in the design,
19
20 170 conduct, reporting or any other aspect of the study.

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26 172 **Statistical Analysis**

29 173 Baseline characteristics were compared between exposed and unexposed
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31 174 pregnancies to any analgesic using χ^2 test for categorical variables and t-test for
32
33 175 normally distributed continuous variables as appropriate. Relationships between
34
35 176 exposures and outcomes were examined by binary logistic regression for binary
36
37 177 outcome variables, multinomial logistic regression for nominal categorical outcome
38
39 178 variables, and multiple linear regression for continuous variables. The strength of
40
41 179 association was reported as odds ratios (ORs) with 95% confidence intervals (CI).
42
43 180 The socio-demographic characteristics that were likely to confound our exposure-to-
44
45 181 outcome path were identified using a directed acyclic graph (DAG) (Figure S1)²⁴.
46
47 182 Factors that were associated with consumption of over-the-counter analgesics during
48
49 183 pregnancy at 10% level of significance and deemed clinically relevant, were included
50
51 184 in the model as confounders. All outcomes were adjusted for year of delivery,
52
53 185 maternal age at delivery, SIMD and maternal first antenatal visit. In addition to these
54
55 186 confounders, individual outcomes were adjusted for relevant cofactors. Gestation at

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3 187 delivery and pregnancy outcome were both additionally adjusted for maternal
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5 188 hypertensive disorders and antepartum haemorrhage. Weight of the baby, neonatal
6
7 189 unit admission, cryptorchidism, neural tube defects, amniotic band defects,
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10 190 hypospadias and gastroschisis variables were also adjusted for gestation at delivery.
11
12 191 APGAR score at one and five minutes were adjusted for type of delivery. A p-value
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14 192 of less than 0.05 was considered statistically significant. All statistical analyses were
15
16 193 carried out using IBM SPSS Statistics version 25.0 (Released 2017. IBM SPSS
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18 194 Statistics for Windows, Armonk, NY: IBM Corp.). R version 3.6.2 was used to
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21 195 generate Figure 2.
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196 Results

197 83.7% of women taking over-the-counter analgesics reported first trimester use
198 when specifically asked about use at their first antenatal clinic. Overall, from the total
199 151,141 pregnancies across 30 years in 107,143 (70.9%) pregnancies, no over-the-
200 counter analgesic consumption was reported. At least one over-the-counter
201 analgesic was consumed in 43,998 (29.1%) pregnancies, whereas paracetamol use
202 alone was reported in 24,099 (18.4%) pregnancies. Diclofenac use was observed in
203 20.0% of pregnancies in the 10-year period when diclofenac was available over-the-
204 counter (without prescription). Finally, at least one out of three analgesics (naproxen,
205 ibuprofen, aspirin) was consumed in 762 (0.7%) pregnancies (Figure 1).

206 Prevalence of use for all five analgesics increased dramatically over the 30-year
207 study period (1985-2015) (Figure 2). Percentage of pregnancies with consumption of
208 at least one analgesic increased from 1.8% in 1985 to 70.6% in 2015. Paracetamol
209 was consumed in 1.3% of pregnancies in 1985 and it continuously increased
210 reaching 42.2% in 2015. Naproxen, ibuprofen or aspirin consumption during
211 pregnancy was less prevalent, however it also increased during the 30-year study
212 period, starting at 0.5% in 1985 and reaching 1.9% in 2015. Diclofenac was
213 consumed in very few pregnancies between 1985 (<0.01%) and 2005 (0.2%).
214 Percentage of consumption, however, dramatically increased during the next decade
215 following deregulation of diclofenac, reaching 25.0% in just one year (2006) and
216 45.6% of all pregnancies in 2015.

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

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3 220 significant difference ($p < 0.001$) for most variables. In the paracetamol sub-group
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5 221 analysis, baby presentation at delivery ($p = 0.525$) and sex of the baby ($p = 0.861$) were
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7 222 not significantly different between the groups. In the analysis considering
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9 223 consumption of at least one analgesic from aspirin/naproxen/ibuprofen, again the
10 224 variables for baby presentation at delivery ($p = 0.093$) and sex of the baby ($p = 0.732$),
11
12 225 together with maternal smoking status ($p = 0.132$) and maternal antepartum
13
14 226 haemorrhage ($p = 0.434$) were not statistically different compared to the unexposed
15
16 227 group. All variables were statistically different between unexposed and exposed
17
18 228 groups for the main analysis and diclofenac sub-group analysis.
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24 229 Table 2 summarises the comparison of neonatal outcomes between the unexposed
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26 230 group (no analgesic at all) and the exposed groups of at least one analgesic, only
27
28 231 paracetamol and at least one out of aspirin/naproxen/ibuprofen. Comparison of
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30 232 outcomes for the diclofenac sub-group analysis is shown in Table 3.
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37 234 **All analgesics and neonatal outcomes**

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40 235 As shown in Table 2, compared to unexposed pregnancies in which women did not
41
42 236 use any analgesic, pregnancies with consumption of at least one analgesic
43
44 237 (paracetamol, diclofenac, aspirin, naproxen, ibuprofen) were independently
45
46 238 associated with significantly higher odds for premature delivery (aOR=1.50, 95%CI
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48 239 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), LBW (aOR=1.28, 95%CI 1.20-
49
50 240 1.37), HBW (aOR=1.09, 95%CI 1.05-1.13), baby admission to neonatal unit
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52 241 (aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at five minutes (aOR=1.48, 95%CI
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54 242 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias
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56 243 (aOR=1.27, 95%CI 1.05-1.54) in adjusted analyses. Significantly decreased odds for
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3 244 APGAR score <7 at one minute were found in the crude analysis (cOR=0.96, 95%CI
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5 245 0.92-0.99), however when adjusted for year of delivery, maternal age at delivery,
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7 246 SIMD, first gestational booking and type of delivery, the significance changed
8
9 247 direction showing significantly increased odds (aOR=1.18, 95%CI 1.13-1.23). A
10
11 248 significantly lower standardised birthweight score (aOR=0.046, 95%CI 0.032-0.059)
12
13 249 was found for the exposure group compared to no analgesic at all. Cryptorchidism
14
15 250 (aOR=0.92, 95%CI 0.77-1.11), amniotic band defects (aOR=1.02, 95%CI 0.71-1.47),
16
17 251 gastroschisis (aOR=1.10, 95%CI 0.56-2.20) and the composite outcome variable
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19 252 (aOR=1.12, 95%CI 0.99-1.26), were all associated with increased odds in the
20
21 253 exposure group compared to not exposed, however the association was not
22
23 254 significant in the adjusted model. There was no significant association between
24
25 255 neonatal death and exposure to at least one analgesic in the crude analysis
26
27 256 (cOR=1.19, 95%CI 0.99-1.42), however there were significantly higher odds of
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29 257 neonatal death in the adjusted analysis (aOR=1.56, 95%CI 1.27-1.93) in the
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31 258 exposed group compared to control.
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41 260 **Paracetamol and neonatal outcomes**

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44 261 In the sub-group analysis considering only paracetamol consumption during
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46 262 pregnancy as our exposure group, most of the associations reported in the main
47
48 263 analysis remained significant with the same direction of significance (Table 2). The
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50 264 differences were: maternal paracetamol consumption during pregnancy was
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52 265 associated with significantly decreased odds for offspring HBW (cOR=0.94, 95%CI
53
54 266 0.90-0.99) in the crude analysis however significance was lost in the adjusted model
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56 267 (aOR=0.98, 95%CI 0.93-1.02), and there were no significant associations in the
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3 268 adjusted models for neural tube defects (aOR=1.21, 95%CI 0.71-2.06) and
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5 269 hypospadias (aOR=1.07, 95%CI 0.84-1.37).
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11 271 **Aspirin/naproxen/ibuprofen and neonatal outcomes**

14 272 Consumption of at least one analgesic from aspirin, naproxen or ibuprofen during
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16 273 pregnancy was compared against the same control group of pregnancies where no
17
18 274 analgesic was used (Table 2). Again, when comparing associations between groups
19
20 275 in this sub-group analysis and main analysis, fewer outcome variants showed similar
21
22 276 significance pattern. The only shared significant associations were for increased
23
24 277 odds for premature delivery (aOR=1.42, 95%CI 1.08-1.86), stillbirth (aOR=2.34,
25
26 278 95%CI 1.29-4.25) and baby admission to neonatal unit (aOR=1.54, 95%CI 1.22-
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28 279 1.94) in the adjusted regression analyses.
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36 281 **Diclofenac and neonatal outcomes**

39 282 In the sub-group analysis of pregnancies coinciding with non-prescription, over-the-
40
41 283 counter, availability of diclofenac (years 2005-2015) were considered, and outcomes
42
43 284 compared between the diclofenac group and no analgesic consumption group (Table
44
45 285 3). Compared to the main analysis, diclofenac consumption during pregnancy was
46
47 286 not significantly associated with premature delivery (aOR=1.10, 95%CI 0.99-1.22),
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49 287 neonatal death (aOR=1.26, 95%CI 0.73-2.15) and APGAR score <7 in one minute
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51 288 (aOR=0.93, 95%CI 0.83-1.04) in the adjusted models. Associations with APGAR
52
53 289 score <7 in five minutes (aOR=0.94, 95%CI 0.72-1.23), cryptorchidism (aOR=1.05,
54
55 290 95%CI 0.78-1.42), amniotic band defects (aOR=0.81, 95%CI 0.41-1.58) and
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57 291 gastroschisis (aOR=2.93, 95%CI 0.97-8.88) were no longer significant in both crude
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3 292 and adjusted analyses. Maternal consumption of diclofenac was independently
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5 293 associated with a significant decrease in stillbirth (aOR=0.59, 95%CI 0.41-0.87). It is
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7
8 294 also interesting to note that diclofenac was the only sub-group analysis agreeing with
9
10 295 the main analysis (exposure to at least one analgesic) on the significance of
11
12 296 exposure association with increased incidence of neural tube defects (aOR=3.62,
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14 297 95%CI 1.95-6.74) and hypospadias (aOR=1.49, 95%CI 1.09-2.03) compared to
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17 298 unexposed pregnancies in adjusted models.
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300 Discussion

301 Main Findings

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

313

314 Diclofenac use increased steeply from 2005 (Figure 2A), which reflects the change in
315 Scottish legislation, leading to diclofenac becoming available without prescription in
316 that year. Diclofenac use was associated with fewer adverse outcomes but showed
317 increased risk of neural tube defects and hypospadias in male neonates.

318 Furthermore, and surprisingly, exposure to diclofenac only was associated with
319 significant decrease in the incidence of stillbirth. The reasons for such differences
320 between the changes in neonatal outcomes following diclofenac consumption
321 compared with those following use of the other NSAIDS are not clear. The proportion
322 of women using diclofenac, especially in the last 7 years of our study makes it highly
323 unlikely to be due to an underlying maternal condition and/or other compounds used

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3 324 in combination (e.g. prescriptions) by women taking diclofenac. It is possible that the
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5 325 drug could act directly on fetal development then this difference could also be due to
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7 326 structural and/or mechanistic differences of the compound compared to the other
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10 327 drugs. However, not enough is known about the specific mechanisms of action of the
11
12 328 different analgesics studied to conclude further. Overall, comparing our main
13
14 329 analysis with all three sub-analyses, it is evident that the most significant differences
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16 330 were observed when paracetamol was taken with at least one other analgesic. This
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18 331 is mostly due to the high number of pregnancies where paracetamol was used,
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20 332 comprising almost 55% of the exposed cases in the main analysis.
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334 **Strengths and Limitations**

30 335 A major strength of the present study is the large cohort of 151,141 pregnancies over
31
32 336 a 30-year study period from 1985 until 2015, using a robust data source AMND. This
33
34 337 is one of the largest cohorts used in studies examining the effects of analgesic use
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36 338 during pregnancy. The dataset contains high quality and consistent data from the
37
38 339 geographically defined area of Aberdeen and surrounding district, in the North East
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40 340 of Scotland, UK. In addition, as Aberdeen Maternity Hospital is the only maternity
41
42 341 hospital serving the area, over 95% of pregnancies in the area are included in the
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44 342 dataset, considerably minimizing the risk for selection bias. We were able to analyse
45
46 343 maternal consumption data of the five most commonly used analgesics available
47
48 344 over-the-counter in the UK and most countries, which is not matched in the current
49
50 345 literature. The nature of our data allowed for the analysis of analgesics consumed
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52 346 alone or in combination, unlike most existing studies, and this gives our study the
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54 347 added strength of better reflecting real-life consumption patterns^{26,27}. We were able
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3 348 to adjust for important confounding factors, relevant to each analysed outcome.
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5 349 Adjustment for maternal deprivation also allowed us to further account for potential
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8 350 unmeasured factors that can influence maternal and neonatal health, which is a
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10 351 major strength of our analysis compared to most studies.
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13 352 A potential concern was that women were probably using analgesics to treat some
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15 353 inherent medical condition which in turn could have been the mediating factor for
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17 354 adverse outcomes. However, since these medications are widely available without
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20 355 prescription, this is unlikely to be a factor that affects the findings of this study. This
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22 356 is especially the case during the “diclofenac analysis” covering 2005-2015, where
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24
25 357 this study presents results on multiple neonatal outcomes for the given cohort. In this
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27 358 way we offer a comprehensive approach to the exploration of associations with *in*
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29 359 *utero* analgesic exposure rather than only focusing on a single outcome of interest.
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32 360 Our data were based on medical notes; however, over-the-counter consumption is
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34 361 self-reported, and details on the timing, dosage, product type (single-ingredient vs
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36 362 combination) and administration type were not available in the database. Complete
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38 363 case analyses were performed ignoring pregnancies with missing data in the
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41 364 covariates, however due to the low number of missing data there is little chance that
42
43 365 this might have affected the validity of our results. Compared to our cohort size,
44
45 366 there were, overall, very few cases of cryptorchidism, neural tube defects, amniotic
46
47 367 band defects, hypospadias and gastroschisis, resulting in potentially underpowered
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50 368 statistical analyses to detect a difference for these outcomes. Our study only
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52 369 considered neonatal health outcomes and follow-up of the offspring was not
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54 370 available at this time.
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372 Interpretation

373 Previous literature has considered fewer outcomes with fewer analgesic
374 combinations compared to our study. Consistent with our results, increased risk of
375 preterm birth and miscarriage has been associated with analgesic consumption
376 during pregnancy²⁸⁻³¹, while others reported no associations with miscarriage,
377 stillbirth or preterm delivery^{20,28,29,32}. Similarly, increased risk for offspring
378 cryptorchidism, hypospadias, neural tube defects, amniotic band defects and
379 gastroschisis have been shown by many studies^{7-9,33-40}, although, again, a lack of
380 associations with major birth defects have been reported^{13-17,41,42}. Compared to our
381 analysis, all these studies used a smaller cohort, considered a shorter study time
382 and there was frequent disagreement with respect to the choices of adjusted
383 confounding factors. Another difference is that maternal questionnaires/interviews
384 were frequently the method of choice to evaluate maternal consumption. Some of
385 the studies reported increased risks for specific pregnancy trimesters which is
386 something our study could not evaluate. Differences in study design and adjustment
387 for different confounders might also account for the disagreement of our results that
388 provide a more accurate assessment. Our study is one of the largest in terms of
389 cohort size, duration, number of analgesics and range of outcomes included which
390 might also contribute to differences compared to other studies.

391 The literature currently reports conflicting evidence, limiting our ability for definite
392 decision-making. Over-the-counter analgesics are recommended to women by
393 healthcare professionals in order to deal with pregnancy symptoms and other
394 conditions. Policy-makers have taken a stand on the topic, either being reassuring
395 about over-the-counter use during pregnancy or recommending caution when
396 consumption is necessary⁴³⁻⁴⁶. Different compounds can affect the mother and the

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3 397 fetus in a different way, and their combined use might worsen the risk for offspring ill
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5 398 health. This study demonstrates the need for additional research, before the field can
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8 399 be confidently directed towards one direction or the other.
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10 400 Whether the associations we report result from flu, fever, rheumatological or
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12 401 inflammatory conditions, and/or combination with other prescribed medications or
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14 402 solely related to over-the-counter analgesics consumption is a matter of further
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16 403 research. Underlying health conditions could well influence the outcomes we see in
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18 404 this study, however, as these could be very different conditions it is biologically
19
20 405 unlikely that they are responsible for the effects we observe here. Our study
21
22 406 demonstrates an association of maternal over-the-counter analgesic consumption
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24 407 during pregnancy with adverse neonatal offspring outcomes. Future collaborative
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26 408 approaches such as an individual patient data meta-analysis that includes follow-up
27
28 409 data on long-term outcomes during childhood and adulthood would significantly
29
30 410 inform decision making. Going forward, uncovering the mechanisms of action and off
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32 411 target effects will also provide a solid foundation for the development of pregnancy-
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34 412 safe compounds. Finally, the findings present here suggest that diclofenac is
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36 413 associated with fewer changes in risk for the more frequent adverse outcomes
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38 414 although it is associated more with rarer, but severe, negative outcomes, including
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40 415 neural tube defects. Diclofenac may have a lower risk for the main adverse neonatal
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42 416 outcomes reported for paracetamol. However, it should be noted that our study is not
43
44 417 designed to specifically test differences in level of risk between the analgesics
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46 418 included. Therefore, it should be emphasised that this does not mean that the
47
48 419 authors are stating that diclofenac is preferable to paracetamol.
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3 421 **Conclusions**
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6 422 Pain control is currently a therapeutic priority during pregnancy. Our findings of
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8 423 increased risk of adverse health outcomes for the offspring following at least first
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10 424 trimester maternal use of readily available over-the-counter analgesics are crucial to
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13 425 information for the management of pain during pregnancy.
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23
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25
26

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28
29 431 and coordination of the research. EAR provided critical input in the design and
30
31
32 432 planning of statistical analysis. AZ conducted the statistical analysis and prepared
33
34 433 the manuscript, figures and tables. AZ, SB, PAF, RTM and DCH substantially
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36 434 contributed to the analysis and interpretation of the work. All authors contributed to
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38
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3 443 **Ethics Statement:** The AMND dataset used in this study was fully anonymised,
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5 444 therefore there was no requirement for ethical approval. The North of Scotland
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7 445 Research Ethics Service has devolved Caldicott approval to the Chair of the AMND
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9 446 steering committee. Approval to access and analyse data was obtained from the
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11 447 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)	30,998 (70.5)		12,138 (50.4)		228 (29.9)		n/a	n/a	
2010-2015 *	n/a	n/a		n/a		n/a		11,105 (54.1)	4,021 (39.1)	
	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										
1 st 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
2 nd Trimester	29,269 (27.4)	5,791 (13.2)		4,117 (17.1)		166 (21.9)		1,770 (8.6)	829 (8.1)	
3 rd 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)§	

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

588 *Only applicable to Diclofenac 2005-2015 analysis

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

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

591 §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/Na pr (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	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

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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3 647 **Figure 1:** Flowchart of cohort selection and sub-group analyses. n=number of
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5 648 pregnancies in each analysis. *98.3% of pregnancies using only diclofenac occurred
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7 649 during 2005-2015, therefore analysis was performed only on data from that decade
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9 650 to rule out any temporal effect.
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14 652 **Figure 2:** Prevalence of use during pregnancy for each analgesic sub-group over
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17 653 our 30-year study period. In 2005 there was a change in legislation making
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19 654 diclofenac available without prescription.
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21 655

23 656 **Figure S1:** Directed acyclic graph (DAG) of exposure to outcome path and relevant
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26 657 measured and unmeasured biasing factors in our analysis.
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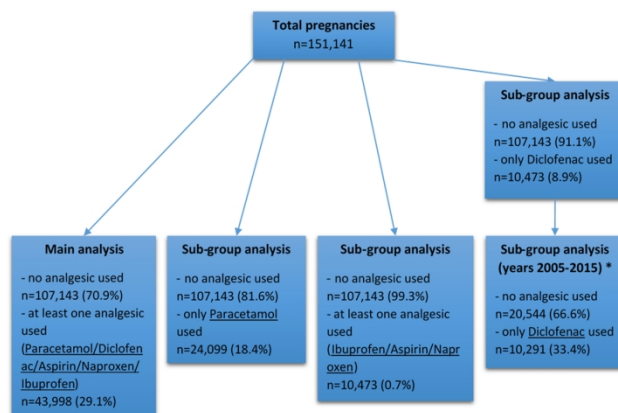


Figure 1: Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis. *98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

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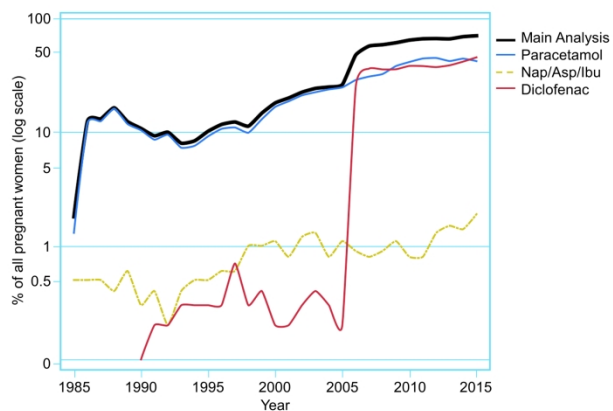
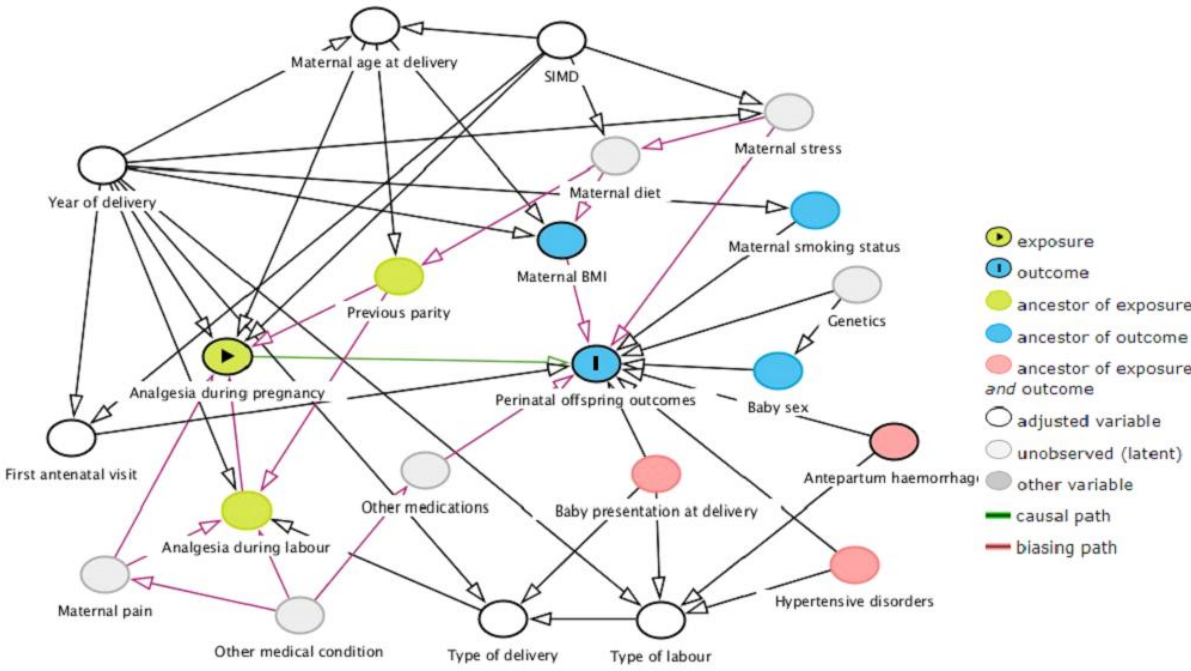


Figure 2: Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. In 2005 there was a change in legislation making diclofenac available without prescription.

254x190mm (300 x 300 DPI)

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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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1 Results Page 11 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

1 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
2 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
3 available at <http://www.strobe-statement.org>.
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BMJ Open

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

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Primary Subject Heading:	Epidemiology
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Keywords:	Epidemiology < INFECTIOUS DISEASES, OBSTETRICS, CLINICAL PHARMACOLOGY

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

3
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19 **Running Title:** Maternal over-the-counter analgesia and offspring outcomes

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2
3 20 **Abstract**
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5
6 21 OBJECTIVES
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9 22 To identify any associations between *in utero* exposure to five over-the-counter (non-
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11 23 prescription) analgesics (paracetamol, ibuprofen, aspirin, diclofenac, naproxen) and
12
13 24 adverse neonatal outcomes.
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16 25 DESIGN
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18
19 26 Retrospective cohort study using the Aberdeen Maternity and Neonatal Databank.
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22 27 PARTICIPANTS
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25 28 151,141 singleton pregnancies between 1985 and 2015.
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28 29 MAIN OUTCOME MEASURES
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31 30 Premature delivery (<37 weeks), stillbirth, neonatal death, birthweight, standardised
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33 31 birthweight score, neonatal unit admission, APGAR score at 1 and 5 minutes, neural
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35 32 tube and amniotic band defects, gastroschisis and, in males, cryptorchidism, and
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37 33 hypospadias.
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40 41 RESULTS
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43
44 35 83.7% of women taking over-the-counter analgesics reported first trimester use
45
46 36 when specifically asked about use at their first antenatal clinic visit. Pregnancies
47
48 37 exposed to at least one of the five analgesics were significantly independently
49
50 38 associated with increased risks for premature delivery <37 weeks (aOR=1.50,
51
52 39 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), neonatal death
53
54 40 (aOR=1.56, 95%CI 1.27-1.93), birthweight <2,500g (aOR=1.28, 95%CI 1.20-1.37),
55
56 41 birthweight >4,000g (aOR=1.09, 95%CI 1.05-1.13), admission to neonatal unit
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3 42 (aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at 1 minute (aOR=1.18, 95%CI
4
5 43 1.13-1.23) and 5 minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects
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7 44 (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54 males
8
9 45 only). The overall prevalence of over-the-counter analgesics use during pregnancy
10
11 46 was 29.1%, however it rapidly increased over the 30-year study period, to include
12
13 47 over 60% of women in the last seven years of the study. This makes our findings
14
15 48 highly relevant to the wider pregnant population.
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20 49 CONCLUSIONS

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23 50 Over-the-counter (non-prescription) analgesics consumption during pregnancy was
24
25 51 associated with a substantially higher risk for adverse perinatal health outcomes in
26
27 52 the offspring. The use of paracetamol in combination with other non-steroidal anti-
28
29 53 inflammatory drugs conferred the highest risk. The increased risks of adverse
30
31 54 neonatal outcomes associated with non-prescribed, over-the-counter, analgesics use
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33 55 during pregnancy indicate that healthcare guidance for pregnant women regarding
34
35 56 analgesic use need urgent updating.
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43 58 **Funding** Biotechnology and Biological Sciences Research council (BBSRC) funding
44
45 59 under the EASTBIO doctoral training programme (grant number 1942576) to AZ and
46
47 60 EU Horizon 2020 project FREIA (Grant Number 825100) to PAF. RTM is supported
48
49 61 by MRC Centre for Reproductive Health Grant MR/N022556/1.
50
51

52 62 **Key words** acetaminophen, aspirin, diclofenac, ibuprofen, *in utero* exposure,
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54 63 naproxen, offspring outcomes, over-the-counter analgesics, offspring outcomes,
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56 64 paracetamol, pregnancy
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66 Introduction

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

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

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3 91 Given the diversity in study population, methodology, sample size and findings in the
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5 92 published studies, we conclude that more extensive data from larger cohorts are
6
7 93 essential in order to understand the risks over-the-counter analgesic use during
8
9 94 pregnancy pose to neonatal health and function. Here we address many limitations
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11 95 of previous studies by analysing one of the largest cohorts, widest range of health
12
13 96 data and, pregnancy use of five over-the-counter analgesics consumed in
14
15 97 combination or separately. We report on the prevalence of maternal consumption of
16
17 98 five different over-the-counter analgesics during pregnancy and their associations
18
19 99 with offspring neonatal outcomes using a large cohort of 151,141 singleton
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21 100 pregnancies spanning three decades of population-based data from a single
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23 101 maternity hospital serving the entire population of Aberdeenshire in the North East of
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25 102 Scotland.
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103 **Materials and Methods**

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

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

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3 128 rule out any temporal effect. Analgesic consumption was not further assessed
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5 129 analytically.
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8 130 The offspring outcomes compared between control and exposed groups were:
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10 131 gestation at delivery (preterm <37 gestation weeks, term \geq 37 gestation weeks),
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12 132 pregnancy outcome (livebirth, stillbirth, neonatal death), baby weight (low birth
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14 133 weight (LBW) \leq 2,499 g, high birth weight (HBW) \geq 4,000 g, normal birth weight
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16 134 (NBW) 2,500g-3,999 g), standardised birthweight score was considered as a
17
18 135 continuous variable as previously described by Campbell and colleagues²³, baby
19
20 136 admission to neonatal unit (no; yes), APGAR score at one and five minutes (<7, \geq 7),
21
22 137 cryptorchidism (no; yes) (ICD-10 code Q53), neural tube defects (no; yes) (ICD-10
23
24 138 code Q00-07), amniotic band defects (no; yes) (ICD-10 codes Q70-74), hypospadias
25
26 139 (no; yes) (ICD-10 code Q54), gastroschisis (no; yes) (ICD-10 code Q79.3). A
27
28 140 composite outcome (presence of at least one congenital anomaly (no; yes)) was
29
30 141 created using the variables neural tube defects, amniotic band defects, and
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32 142 gastroschisis and, in males, cryptorchidism and hypospadias.
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39 143 The baseline characteristics compared between exposed and unexposed
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41 144 pregnancies were (reference category first): year of delivery (1985-1994, 1995-2004,
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43 145 2005-2015), maternal age at delivery (20-25, <20, 26-35, >35 years), previous
44
45 146 pregnancy (no; yes), maternal body mass index (BMI) (normal weight 18.5-24.9
46
47 147 kg/m², underweight <18.5 kg/m², overweight 25-29.9 kg/m², obese >30 kg/m²),
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49 148 maternal first antenatal visit (1st, 2nd, 3rd trimester), maternal smoking status (non-
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51 149 smoker, smoker, ex-smoker), Scottish Index of Multiple Deprivation (SIMD) decile (1-
52
53 150 6, 7-10, decreasing deprivation with increasing score), maternal hypertensive
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55 151 disorders (no disorder, gestational hypertension, preeclampsia, eclampsia), maternal
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57 152 antepartum haemorrhage (no haemorrhage, abruption, placental previa), type of
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3 153 labour (spontaneous, elective caesarean section, induced), type of delivery
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5 154 (spontaneous vaginal delivery, instrumental, caesarean section), analgesia during
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7 155 labour (no; yes), baby presentation at delivery (occiput anterior, occiput posterior),
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9 156 baby sex (female; male).
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13 157 **Patient and Public Involvement**

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16 158 This was a retrospective analysis of data on singleton pregnancies over a 30-year
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18 159 period. Therefore, there was no involvement of patients or the public in the design,
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20 160 conduct, reporting or any other aspect of the study.
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26 162 **Statistical Analysis**

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29 163 Baseline characteristics were compared between exposed and unexposed
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31 164 pregnancies to any analgesic using χ^2 test for categorical variables and t-test for
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33 165 normally distributed continuous variables as appropriate. Relationships between
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35 166 exposures and outcomes were examined by binary logistic regression for binary
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37 167 outcome variables, multinomial logistic regression for nominal categorical outcome
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39 168 variables, and multiple linear regression for continuous variables. The strength of
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41 169 association was reported as odds ratios (ORs) with 95% confidence intervals (CI).
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43 170 The socio-demographic characteristics that were likely to confound our exposure-to-
44
45 171 outcome path were identified using a directed acyclic graph (DAG) (Figure S1)²⁴.
46
47 172 Factors that were associated with consumption of over-the-counter analgesics during
48
49 173 pregnancy at 10% level of significance and deemed clinically relevant, were included
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51 174 in the model as confounders. All outcomes were adjusted for year of delivery,
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53 175 maternal age at delivery, SIMD and maternal first antenatal visit. In addition to these
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55 176 confounders, individual outcomes were adjusted for relevant cofactors. Gestation at
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3 177 delivery and pregnancy outcome were both additionally adjusted for maternal
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5 178 hypertensive disorders and antepartum haemorrhage. Weight of the baby, neonatal
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7 179 unit admission, cryptorchidism, neural tube defects, amniotic band defects,
8
9
10 180 hypospadias and gastroschisis variables were also adjusted for gestation at delivery.
11
12 181 APGAR score at one and five minutes were adjusted for type of delivery. A p-value
13
14 182 of less than 0.05 was considered statistically significant. All statistical analyses were
15
16 183 carried out using IBM SPSS Statistics version 25.0 (Released 2017. IBM SPSS
17
18 184 Statistics for Windows, Armonk, NY: IBM Corp.). R version 3.6.2 was used to
19
20 185 generate Figure 2. Numbers needed to harm (NNH) were also calculated for each
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22 186 outcome and are provided in Supplementary Tables 1 and 2.
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187 Results

188 83.7% of women taking over-the-counter analgesics reported first trimester use
189 when specifically asked about use at their first antenatal clinic. Overall, from the total
190 151,141 pregnancies across 30 years in 107,143 (70.9%) pregnancies, no over-the-
191 counter analgesic consumption was reported. At least one over-the-counter
192 analgesic was consumed in 43,998 (29.1%) pregnancies, whereas paracetamol use
193 alone was reported in 24,099 (18.4%) pregnancies. Diclofenac use was observed in
194 20.0% of pregnancies in the 10-year period when diclofenac was available over-the-
195 counter (without prescription). Finally, at least one out of three analgesics (naproxen,
196 ibuprofen, aspirin) was consumed in 762 (0.7%) pregnancies (Figure 1).

197 Prevalence of use for all five analgesics increased dramatically over the 30-year
198 study period (1985-2015) (Figure 2). Pregnancies with consumption of at least one
199 analgesic increased from 1.8% in 1985 to 70.6% in 2015. Pregnancies reporting
200 paracetamol use were 1.3% in 1985 and it continuously increased reaching 42.2%
201 in 2015. Naproxen, ibuprofen or aspirin consumption during pregnancy was less
202 prevalent (Figure 2A), however it also increased during the 30-year study period,
203 starting at 0.5% in 1985 and reaching 1.9% in 2015 (Figure 2B). Diclofenac was
204 consumed in very few pregnancies between 1985 (<0.01%) and 2005 (0.2%).
205 Percentage of consumption, however, dramatically increased during the next decade
206 following deregulation of diclofenac, reaching 25.0% in just one year (2006) and
207 45.6% of all pregnancies in 2015.

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

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3 211 significant difference ($p < 0.001$) for most variables. In the paracetamol sub-group
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5 212 analysis, baby presentation at delivery ($p = 0.525$) and sex of the baby ($p = 0.861$) were
6
7 213 not significantly different between the groups. In the analysis considering
8
9 214 consumption of at least one analgesic from aspirin/naproxen/ibuprofen, again the
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11 215 variables for baby presentation at delivery ($p = 0.093$) and sex of the baby ($p = 0.732$),
12
13 216 together with maternal smoking status ($p = 0.132$) and maternal antepartum
14
15 217 haemorrhage ($p = 0.434$) were not statistically different compared to the unexposed
16
17 218 group. All variables were statistically different between unexposed and exposed
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19 219 groups for the main analysis and diclofenac sub-group analysis.
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24 220 Table 2 summarises the comparison of neonatal outcomes between the unexposed
25
26 221 group (no analgesic at all) and the exposed groups of at least one analgesic, only
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28 222 paracetamol and at least one out of aspirin/naproxen/ibuprofen. Comparison of
29
30 223 outcomes for the diclofenac sub-group analysis is shown in Table 3.
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37 225 **All analgesics and neonatal outcomes**

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40 226 As shown in Table 2, compared to unexposed pregnancies in which women did not
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42 227 use any analgesic, pregnancies with consumption of at least one analgesic
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44 228 (paracetamol, diclofenac, aspirin, naproxen, ibuprofen) were independently
45
46 229 associated with significantly higher odds for premature delivery (aOR=1.50, 95%CI
47
48 230 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), LBW (aOR=1.28, 95%CI 1.20-
49
50 231 1.37), HBW (aOR=1.09, 95%CI 1.05-1.13), baby admission to neonatal unit
51
52 232 (aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at five minutes (aOR=1.48, 95%CI
53
54 233 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias
55
56 234 (aOR=1.27, 95%CI 1.05-1.54) in adjusted analyses. Significantly decreased odds for
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3 235 APGAR score <7 at one minute were found in the crude analysis (cOR=0.96, 95%CI
4
5 236 0.92-0.99), however when adjusted for year of delivery, maternal age at delivery,
6
7 237 SIMD, first gestational booking and type of delivery, the significance changed
8
9 238 direction showing significantly increased odds (aOR=1.18, 95%CI 1.13-1.23). A
10
11 239 significantly lower standardised birthweight score (p=0.046, 95%CI 0.032-0.059) was
12
13 240 found for the exposure group compared to no analgesic at all. Cryptorchidism
14
15 241 (aOR=0.92, 95%CI 0.77-1.11), amniotic band defects (aOR=1.02, 95%CI 0.71-1.47),
16
17 242 gastroschisis (aOR=1.10, 95%CI 0.56-2.20) and the composite outcome variable
18
19 243 (aOR=1.12, 95%CI 0.99-1.26), were all associated with increased odds in the
20
21 244 exposure group compared to not exposed, however the association was not
22
23 245 significant in the adjusted model. There was no significant association between
24
25 246 neonatal death and exposure to at least one analgesic in the crude analysis
26
27 247 (cOR=1.19, 95%CI 0.99-1.42), however there were significantly higher odds of
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29 248 neonatal death in the adjusted analysis (aOR=1.56, 95%CI 1.27-1.93) in the
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31 249 exposed group compared to control.
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41 251 **Paracetamol and neonatal outcomes**

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44 252 In the sub-group analysis considering only paracetamol consumption during
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46 253 pregnancy as our exposure group, most of the associations reported in the main
47
48 254 analysis remained significant with the same direction of significance (Table 2). The
49
50 255 differences were: maternal paracetamol consumption during pregnancy was
51
52 256 associated with significantly decreased odds for offspring HBW (cOR=0.94, 95%CI
53
54 257 0.90-0.99) in the crude analysis however significance was lost in the adjusted model
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56 258 (aOR=0.98, 95%CI 0.93-1.02), and there were no significant associations in the
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259 adjusted models for neural tube defects (aOR=1.21, 95%CI 0.71-2.06) and
260 hypospadias (aOR=1.07, 95%CI 0.84-1.37).

261

262 **Aspirin/naproxen/ibuprofen and neonatal outcomes**

263 Consumption of at least one analgesic from aspirin, naproxen or ibuprofen during
264 pregnancy was compared against the same control group of pregnancies where no
265 analgesic was used (Table 2). Again, when comparing associations between groups
266 in this sub-group analysis and main analysis, fewer outcome variants showed similar
267 significance pattern. The only shared significant associations were for increased
268 odds for premature delivery (aOR=1.42, 95%CI 1.08-1.86), stillbirth (aOR=2.34,
269 95%CI 1.29-4.25) and baby admission to neonatal unit (aOR=1.54, 95%CI 1.22-
270 1.94) in the adjusted regression analyses.

271

272 **Diclofenac and neonatal outcomes**

273 In the sub-group analysis of pregnancies coinciding with non-prescription, over-the-
274 counter, availability of diclofenac (years 2005-2015) were considered, and outcomes
275 compared between the diclofenac group and no analgesic consumption group (Table
276 3). Compared to the main analysis, diclofenac consumption during pregnancy was
277 not significantly associated with premature delivery (aOR=1.10, 95%CI 0.99-1.22),
278 neonatal death (aOR=1.26, 95%CI 0.73-2.15) and APGAR score <7 in one minute
279 (aOR=0.93, 95%CI 0.83-1.04) in the adjusted models. Associations with APGAR
280 score <7 in five minutes (aOR=0.94, 95%CI 0.72-1.23), cryptorchidism (aOR=1.05,
281 95%CI 0.78-1.42), amniotic band defects (aOR=0.81, 95%CI 0.41-1.58) and
282 gastroschisis (aOR=2.93, 95%CI 0.97-8.88) were no longer significant in both crude

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3 283 and adjusted analyses. Maternal consumption of diclofenac was independently
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5 284 associated with a significant decrease in stillbirth (aOR=0.59, 95%CI 0.41-0.87). It is
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7
8 285 also interesting to note that diclofenac was the only sub-group analysis agreeing with
9
10 286 the main analysis (exposure to at least one analgesic) on the significance of
11
12 287 exposure association with increased incidence of neural tube defects (aOR=3.62,
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14 288 95%CI 1.95-6.74) and hypospadias (aOR=1.49, 95%CI 1.09-2.03) compared to
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17 289 unexposed pregnancies in adjusted models. As most of the outcomes studied were
18
19 290 relatively rare the numbers needed to harm were mostly more than 100. Preterm
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21 291 birth, low birthweight and admission to the neonatal unit were exceptions with NNH
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24 292 ranging from 15 to 38. (Tables S1 and S2).
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293 Discussion

294 Main Findings

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

306

307 Diclofenac use increased steeply from 2005 (Figure 2A), which reflects the change in
308 Scottish legislation, leading to diclofenac becoming available without prescription in
309 that year. Diclofenac use was associated with fewer adverse outcomes but showed
310 increased risk of neural tube defects and hypospadias in male neonates.

311 Furthermore, and surprisingly, exposure to diclofenac only was associated with
312 significant decrease in the incidence of stillbirth. The reasons for such differences
313 between the changes in neonatal outcomes following diclofenac consumption
314 compared with those following use of the other NSAIDS are not clear. The proportion
315 of women using diclofenac, especially in the last 7 years of our study makes it highly
316 unlikely to be due to an underlying maternal condition and/or other compounds used

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3 317 in combination (e.g. prescriptions) by women taking diclofenac. It is possible that the
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5 318 drug could act directly on fetal development then this difference could also be due to
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8 319 structural and/or mechanistic differences of the compound compared to the other
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10 320 drugs. However, not enough is known about the specific mechanisms of action of the
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12 321 different analgesics studied to conclude further. Overall, comparing our main
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14 322 analysis with all three sub-analyses, it is evident that the most significant differences
15
16 323 were observed when paracetamol was taken with at least one other analgesic. This
17
18 324 is mostly due to the high number of pregnancies where paracetamol was used,
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20 325 comprising almost 55% of the exposed cases in the main analysis. Most numbers
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22 326 needed to harm for our outcomes (Tables S1 and S2) ranged between 1000 and
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24 327 100, apart from preterm birth, low birth weight and baby admission to neonatal unit,
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26 328 which were 27, 38 and 15 respectively for our main analysis further strengthening
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28 329 observed associations.
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331 **Strengths and Limitations**

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

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3 341 over-the-counter in the UK and most countries, which is not matched in the current
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5 342 literature. The nature of our data allowed for the analysis of analgesics consumed
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8 343 alone or in combination, unlike most existing studies, and this gives our study the
9
10 344 added strength of better reflecting real-life consumption patterns^{26,27}. We were able
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12 345 to adjust for important confounding factors, relevant to each analysed outcome.
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14 346 Adjustment for maternal deprivation also allowed us to further account for potential
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16 347 unmeasured factors that can influence maternal and neonatal health, which is a
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19 348 major strength of our analysis compared to most studies.

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22 349 A potential concern was that women were probably using analgesics to treat some
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24 350 inherent medical condition which in turn could have been the mediating factor for
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27 351 adverse outcomes. However, since these medications are widely available without
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29 352 prescription, this is unlikely to be a factor that affects the findings of this study. This
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31 353 is especially the case during the “diclofenac analysis” covering 2005-2015, where
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33
34 354 this study presents results on multiple neonatal outcomes for the given cohort. In this
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36 355 way we offer a comprehensive approach to the exploration of associations with *in*
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38 356 *utero* analgesic exposure rather than only focusing on a single outcome of interest.
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41 357 Our data were based on medical notes; however, over-the-counter consumption is
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43 358 self-reported, and details on the timing, duration, dosage, product type (single-
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45 359 ingredient vs combination) and administration type were not available in the
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48 360 database. In addition, the group of pregnancies with aspirin consumption might
49
50 361 include use of low-dose aspirin which is recommended to help reduce risk of some
51
52 362 pregnancy complications and outcomes related to placental function. Most women
53
54 363 had their first antenatal clinic visit during the 1st pregnancy trimester, which might
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57 364 imply our results were affected by primarily 1st trimester exposure, although
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59 365 analgesic use in first trimester is most likely replicated in the rest of pregnancy.

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3 366 Complete case analyses were performed ignoring pregnancies with missing data in
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5 367 the covariates, however due to the low number of missing data there is little chance
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7 368 that this might have affected the validity of our results. Compared to our cohort size,
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9 369 there were, overall, very few cases of cryptorchidism, neural tube defects, amniotic
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11 370 band defects, hypospadias and gastroschisis, resulting in potentially underpowered
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13 371 statistical analyses to detect a difference for these outcomes. Our study only
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15 372 considered neonatal health outcomes and follow-up of the offspring was not
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17 373 available at this time.
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25 375 **Interpretation**

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28 376 Previous literature has considered fewer outcomes with fewer analgesic
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30 377 combinations compared to our study. Consistent with our results, increased risk of
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32 378 preterm birth and miscarriage has been associated with analgesic consumption
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34 379 during pregnancy²⁸⁻³¹, while others reported no associations with miscarriage,
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36 380 stillbirth or preterm delivery^{20,28,29,32}. Similarly, increased risk for offspring
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38 381 cryptorchidism, hypospadias, neural tube defects, amniotic band defects and
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40 382 gastroschisis have been shown by many studies^{7-9,33-40}, although, again, a lack of
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42 383 associations with major birth defects have been reported^{13-17,41,42}. Compared to our
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44 384 analysis, all these studies used a smaller cohort, considered a shorter study time
45
46 385 and there was frequent disagreement with respect to the choices of adjusted
47
48 386 confounding factors. Another difference is that maternal questionnaires/interviews
49
50 387 were frequently the method of choice to evaluate maternal consumption. Some of
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52 388 the studies reported increased risks for specific pregnancy trimesters which is
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54 389 something our study could not evaluate. Differences in study design and adjustment
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3 390 for different confounders might also account for the disagreement of our results that
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5 391 provide a more accurate assessment. Our study is one of the largest in terms of
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8 392 cohort size, duration, number of analgesics and range of outcomes included which
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10 393 might also contribute to differences compared to other studies.

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12
13 394 The literature currently reports conflicting evidence, limiting our ability for definite
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15 395 decision-making. Over-the-counter analgesics are recommended to women by
16
17 396 healthcare professionals in order to deal with pregnancy symptoms and other
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19 397 conditions. Policy-makers have taken a stand on the topic, either being reassuring
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21 398 about over-the-counter use during pregnancy or recommending caution when
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23 399 consumption is necessary^{43–46}. Different compounds can affect the mother and the
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25 400 fetus in a different way, and their combined use might worsen the risk for offspring ill
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27 401 health. This study demonstrates the need for additional research, before the field can
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29 402 be confidently directed towards one direction or the other.

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34 403 Whether the associations we report result from flu, fever, rheumatological or
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36 404 inflammatory conditions, and/or combination with other prescribed medications or
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38 405 solely related to over-the-counter analgesics consumption is a matter of further
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40 406 research. Underlying health conditions could well influence the outcomes we see in
41
42 407 this study, however, as these could be very different conditions it is biologically
43
44 408 unlikely that they are responsible for the effects we observe here. Our study
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46 409 demonstrates an association of maternal over-the-counter analgesic consumption
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48 410 during pregnancy with adverse neonatal offspring outcomes. Future collaborative
49
50 411 approaches such as an individual patient data meta-analysis that includes follow-up
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52 412 data on long-term outcomes during childhood and adulthood would significantly
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54 413 inform decision making. Going forward, uncovering the mechanisms of action and off
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56 414 target effects will also provide a solid foundation for the development of pregnancy-

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3 415 safe compounds. Finally, the findings present here suggest that diclofenac is
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5 416 associated with fewer changes in risk for the more frequent adverse outcomes
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7 417 although it is associated more with rarer, but severe, negative outcomes, including
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9 418 neural tube defects. Diclofenac may have a lower risk for the main adverse neonatal
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11 419 outcomes reported for paracetamol. However, it should be noted that our study is not
12
13 420 designed to specifically test differences in level of risk between the analgesics
14
15 421 included. Therefore, it should be emphasised that this does not mean that the
16
17 422 authors are stating that diclofenac is preferable to paracetamol.
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423

424 **Conclusions**

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

429

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1
2
3 438 critical discussion of intellectual content, development and review/approval of the
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6 439 final manuscript version.
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18
19 445 analysis, decision to publish, or manuscript preparation.
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24
25 447 therefore there was no requirement for ethical approval. The North of Scotland
26
27 448 Research Ethics Service has devolved Caldicott approval to the Chair of the AMND
28
29 449 steering committee. Approval to access and analyse data was obtained from the
30
31 450 AMND steering Committee (AMND 004/2018).
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35 451 **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/Na pr (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	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										

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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

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

592 ^a Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, maternal hypertensive disorders, maternal antepartum

593 haemorrhage

594 ^b Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at delivery

595 ^c Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking

596 ^d Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of delivery

597 § Linear regression analysis reporting differences with 95% CI

598 *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

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

600 ^a Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, maternal
601 hypertensive disorders, maternal antepartum haemorrhage

602 ^b Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at
603 delivery

604 ^c Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking

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605 ^dAdjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of
606 delivery
607 [§] Linear regression analysis reporting differences with 95% CI
608 *Including cryptorchidism, neural tube defects, amniotic band defects, hypospadias, gastroschisis

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3 609 **Figure 1.** Flowchart of cohort selection and sub-group analyses. n=number of
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5 610 pregnancies in each analysis. *98.3% of pregnancies using only diclofenac occurred
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7 611 during 2005-2015, therefore analysis was performed only on data from that decade
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9 612 to rule out any temporal effect.
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3 614 **Figure 2.** Prevalence of use during pregnancy for each analgesic sub-group over our
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5 615 30-year study period. **(A)** Merge graph showing percentage of pregnancies using
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7 616 each analgesic group during pregnancy. **(B)** Percentage of use for at least one
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9 617 analgesic out of ibuprofen, aspirin, naproxen. *In 2005 there was a change in
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11 618 legislation making diclofenac available without prescription.
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3 620 **Figure S1.** Directed acyclic graph (DAG) of exposure to outcome path and relevant
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5 621 measured and unmeasured biasing factors in our analysis.
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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)	30,998 (70.5)		12,138 (50.4)		228 (29.9)		n/a	11,105 (54.1)		4,021 (39.1)
2010-2015 *	n/a	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										
1 st 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
2 nd Trimester	29,269 (27.4)	5,791 (13.2)		4,117 (17.1)		166 (21.9)		1,770 (8.6)	829 (8.1)	
3 rd 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

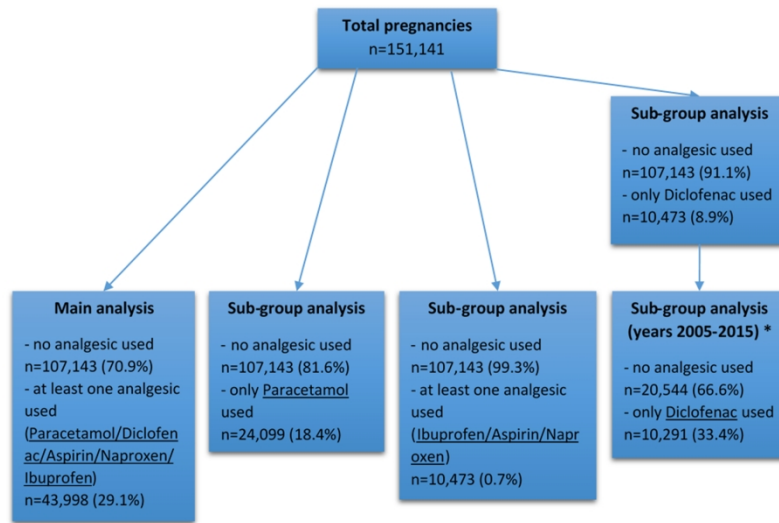


Figure 1. Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis.*98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

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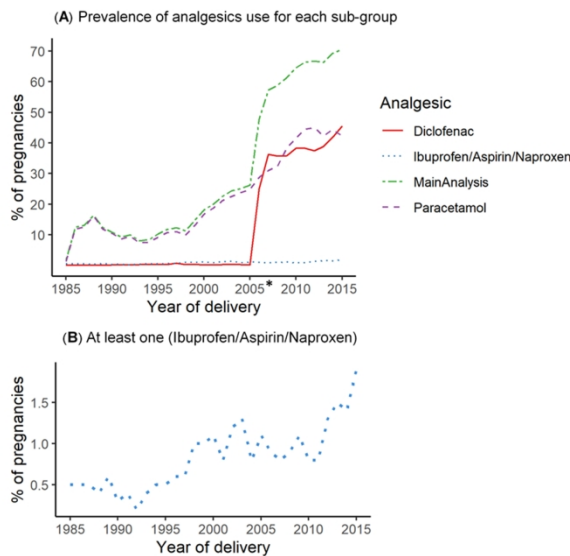


Figure 2. Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. (A) Merge graph showing percentage of pregnancies using each analgesic group during pregnancy. (B) Percentage of use for at least one analgesic out of ibuprofen, aspirin, naproxen. *In 2005 there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

338x190mm (300 x 300 DPI)

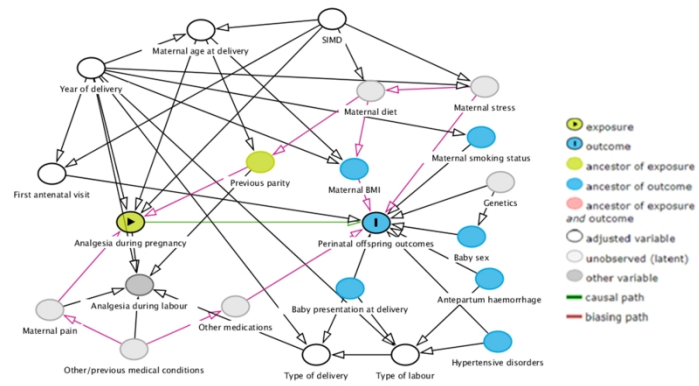


Figure S1. Directed acyclic graph (DAG) of exposure to outcome path and relevant measured and unmeasured biasing factors in our analysis.

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

1 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1 Results Page 11 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

1 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
2 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
3 available at <http://www.strobe-statement.org>.
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BMJ Open

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

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Keywords:	OBSTETRICS, CLINICAL PHARMACOLOGY, EPIDEMIOLOGY

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

3
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19 **Running Title:** Maternal over-the-counter analgesia and offspring outcomes

1
2
3 20 **Abstract**
4

5
6 21 OBJECTIVES
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8
9 22 To identify any associations between *in utero* exposure to five over-the-counter (non-
10
11 23 prescription) analgesics (paracetamol, ibuprofen, aspirin, diclofenac, naproxen) and
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13 24 adverse neonatal outcomes.
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16 25 DESIGN
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19 26 Retrospective cohort study using the Aberdeen Maternity and Neonatal Databank.
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22 27 PARTICIPANTS
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25 28 151,141 singleton pregnancies between 1985 and 2015.
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28 29 MAIN OUTCOME MEASURES
29

30
31 30 Premature delivery (<37 weeks), stillbirth, neonatal death, birthweight, standardised
32
33 31 birthweight score, neonatal unit admission, APGAR score at 1 and 5 minutes, neural
34
35 32 tube and amniotic band defects, gastroschisis and, in males, cryptorchidism, and
36
37 33 hypospadias.
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40 41 RESULTS
42

43
44 35 83.7% of women taking over-the-counter analgesics reported first trimester use
45
46 36 when specifically asked about use at their first antenatal clinic visit. Pregnancies
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48 37 exposed to at least one of the five analgesics were significantly independently
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50 38 associated with increased risks for premature delivery <37 weeks (aOR=1.50,
51
52 39 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), neonatal death
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54 40 (aOR=1.56, 95%CI 1.27-1.93), birthweight <2,500g (aOR=1.28, 95%CI 1.20-1.37),
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56 41 birthweight >4,000g (aOR=1.09, 95%CI 1.05-1.13), admission to neonatal unit
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3 42 (aOR=1.57, 95%CI 1.51-1.64), APGAR score <7 at 1 minute (aOR=1.18, 95%CI
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5 43 1.13-1.23) and 5 minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects
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7 44 (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54 males
8
9 45 only). The overall prevalence of over-the-counter analgesics use during pregnancy
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11 46 was 29.1%, however it rapidly increased over the 30-year study period, to include
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13 47 over 60% of women in the last seven years of the study. This makes our findings
14
15 48 highly relevant to the wider pregnant population.
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20 49 CONCLUSIONS

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23 50 Over-the-counter (non-prescription) analgesics consumption during pregnancy was
24
25 51 associated with a substantially higher risk for adverse perinatal health outcomes in
26
27 52 the offspring. The use of paracetamol in combination with other non-steroidal anti-
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29 53 inflammatory drugs conferred the highest risk. The increased risks of adverse
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31 54 neonatal outcomes associated with non-prescribed, over-the-counter, analgesics use
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33 55 during pregnancy indicate that healthcare guidance for pregnant women regarding
34
35 56 analgesic use need urgent updating.
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40 57 **Strengths and limitations of this study**

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43 58 • This is one of the largest and most comprehensive studies of this type. It
44
45 59 includes consumption of five different analgesics during pregnancy in a large
46
47 60 cohort of singleton pregnancies. It examines associations with extensive
48
49 61 range of offspring perinatal outcomes, while adjusting for important
50
51 62 confounding factors.
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54 63 • Analgesic consumption was analysed both as use of a single compound and
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56 64 in combinations of the five drugs considered in this study.
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3 65 • Details of the exact dose and timing of consumption during pregnancy were
4
5 66 not available within our dataset.
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8 67 • Follow-up of the offspring health later in life was not available at this time.
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14 69 **Funding** Biotechnology and Biological Sciences Research council (BBSRC) funding
15
16 70 under the EASTBIO doctoral training programme (grant number 1942576) to AZ and
17
18 71 EU Horizon 2020 project FREIA (Grant Number 825100) to PAF. RTM is supported
19
20 72 by MRC Centre for Reproductive Health Grant MR/N022556/1.
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23 73 **Key words** acetaminophen, aspirin, diclofenac, ibuprofen, *in utero* exposure,
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25 74 naproxen, offspring outcomes, over-the-counter analgesics, offspring outcomes,
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27 75 paracetamol, pregnancy
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77 Introduction

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

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

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3 101 Given the diversity in study population, methodology, sample size and findings in the
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5 102 published studies, we conclude that more extensive data from larger cohorts are
6
7 103 essential in order to understand the risks over-the-counter analgesic use during
8
9 104 pregnancy pose to neonatal health and function. Here we address many limitations -
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11 105 however, not all²² - of previous studies by analysing one of the largest cohorts,
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13 106 widest range of health data and, pregnancy use of five over-the-counter analgesics
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15 107 consumed in combination or separately. We report on the prevalence of maternal
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17 108 consumption of five different over-the-counter analgesics during pregnancy and their
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19 109 associations with offspring neonatal outcomes using a large cohort of 151,141
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21 110 singleton pregnancies spanning three decades of population-based data from a
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23 111 single maternity hospital serving the entire population of Aberdeenshire in the
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25 112 Northeast of Scotland.
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113 **Materials and Methods**

114 This retrospective cohort study utilised data collected in the Aberdeen Maternity and
115 Neonatal Databank (AMND) in Aberdeen, UK on 151,141 pregnancies over a 30-
116 year period (1985-2015). Details about AMND have been previously published²³.

117 Data were collected from medical notes of women retrospectively after delivery.

118 Women were specifically asked about their use of over-the-counter (non-
119 prescription) analgesics at their first antenatal clinic. Data were entered by dedicated
120 coding staff into a computerised database. Data validity was ensured via checking
121 completeness of data entry against NHS (UK National Health Service) returns
122 monthly and constant data cleaning and validation against case notes reported
123 quarterly by the Data Management team to the AMND Steering Committee. A
124 research protocol was submitted and approved by the AMND Steering Committee
125 before data extraction. Approval was received on 6 June 2018. The dataset was fully
126 anonymised, therefore there was no requirement for NHS ethics committee approval.
127 There was no involvement of patients or the public in the design, or conduct, or
128 reporting, or dissemination plans of our research.

129 The main analysis considered consumption during pregnancy of at least one out of
130 five different analgesics: paracetamol (no; yes), ibuprofen (no; yes), naproxen (no;
131 yes), diclofenac (no; yes) or aspirin (no; yes) as the exposure group against no
132 analgesic consumption as the unexposed group. Then, three sub-group analyses
133 against the control group were performed using only paracetamol, only diclofenac, or
134 at least one analgesic from aspirin/naproxen/ibuprofen as exposure groups,
135 excluding pregnancies exposed to multiple analgesics at the same time (Figure 1).

136 As 98.3% of pregnancies using diclofenac were between 2005 and 2015, diclofenac
137 sub-group analysis only considered pregnancies during that time frame in order to

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3 138 rule out any temporal effect. Analgesic consumption was not further assessed
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5 139 analytically.
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8 140 The offspring outcomes compared between control and exposed groups were:
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10 141 gestation at delivery (preterm <37 gestation weeks, term \geq 37 gestation weeks),
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12 142 pregnancy outcome (livebirth, stillbirth, neonatal death), baby weight (low birth
13
14 143 weight (LBW) \leq 2,499 g, high birth weight (HBW) \geq 4,000 g, normal birth weight
15
16 144 (NBW) 2,500g-3,999 g), standardised birthweight score was considered as a
17
18 145 continuous variable as previously described by Campbell and colleagues²⁴, baby
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20 146 admission to neonatal unit (no; yes), APGAR score at one and five minutes (<7, \geq 7),
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22 147 cryptorchidism (no; yes) (ICD-10 code Q53), neural tube defects (no; yes) (ICD-10
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24 148 code Q00-07), amniotic band defects (no; yes) (ICD-10 codes Q70-74), hypospadias
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26 149 (no; yes) (ICD-10 code Q54), gastroschisis (no; yes) (ICD-10 code Q79.3). A
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28 150 composite outcome (presence of at least one congenital anomaly (no; yes)) was
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30 151 created using the variables neural tube defects, amniotic band defects, and
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32 152 gastroschisis and, in males, cryptorchidism and hypospadias.
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39 153 The baseline characteristics compared between exposed and unexposed
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41 154 pregnancies were (reference category first): year of delivery (1985-1994, 1995-2004,
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43 155 2005-2015), maternal age at delivery (20-25, <20, 26-35, >35 years), previous
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45 156 pregnancy (no; yes), maternal body mass index (BMI) (normal weight 18.5-24.9
46
47 157 kg/m², underweight <18.5 kg/m², overweight 25-29.9 kg/m², obese >30 kg/m²),
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49 158 maternal first antenatal visit (1st, 2nd, 3rd trimester), maternal smoking status (non-
50
51 159 smoker, smoker, ex-smoker), Scottish Index of Multiple Deprivation (SIMD) decile (1-
52
53 160 6, 7-10, decreasing deprivation with increasing score), maternal hypertensive
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55 161 disorders (no disorder, gestational hypertension, preeclampsia, eclampsia), maternal
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57 162 antepartum haemorrhage (no haemorrhage, abruption, placental previa), type of
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3 163 labour (spontaneous, elective caesarean section, induced), type of delivery
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5 164 (spontaneous vaginal delivery, instrumental, caesarean section), analgesia during
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7 165 labour (no; yes), baby presentation at delivery (occiput anterior, occiput posterior),
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9 166 baby sex (female; male).

13 167 **Patient and Public Involvement**

16 168 This was a retrospective analysis of data on singleton pregnancies over a 30-year
17
18 169 period. Therefore, there was no involvement of patients or the public in the design,
19
20 170 conduct, reporting or any other aspect of the study.

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26 172 **Statistical Analysis**

29 173 Baseline characteristics were compared between exposed and unexposed
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31 174 pregnancies to any analgesic using χ^2 test for categorical variables and t-test for
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33 175 normally distributed continuous variables as appropriate. Relationships between
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35 176 exposures and outcomes were examined by binary logistic regression for binary
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37 177 outcome variables, multinomial logistic regression for nominal categorical outcome
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39 178 variables, and multiple linear regression for continuous variables. The strength of
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41 179 association was reported as odds ratios (ORs) with 95% confidence intervals (CI).
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43 180 The socio-demographic characteristics that were likely to confound our exposure-to-
44
45 181 outcome path were identified using directed acyclic graphs (DAG) (Supplementary
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47 182 figures S1-11)²⁵. Factors that were associated with consumption of over-the-counter
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49 183 analgesics during pregnancy at 10% level of significance and deemed clinically
50
51 184 relevant, were included in the model as confounders. All outcomes were adjusted for
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53 185 year of delivery, maternal age at delivery, SIMD and maternal first antenatal visit. In
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55 186 addition to these confounders, individual outcomes were adjusted for relevant
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3 187 cofactors. Gestation at delivery and pregnancy outcome were both additionally
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5 188 adjusted for maternal hypertensive disorders and antepartum haemorrhage. Weight
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7 189 of the baby, neonatal unit admission, cryptorchidism, neural tube defects, amniotic
8
9 190 band defects, hypospadias and gastroschisis variables were also adjusted for
10
11 191 gestation at delivery. APGAR score at one and five minutes were adjusted for type of
12
13 192 delivery. A p-value of less than 0.05 was considered statistically significant. All
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15 193 statistical analyses were carried out using IBM SPSS Statistics version 25.0
16
17 194 (Released 2017. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). R
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19 195 version 3.6.2 was used to generate Figure 2. Numbers needed to harm (NNH) were
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21 196 also calculated for each outcome and are provided in Supplementary Tables 1 and
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198 **Results**

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

208 Prevalence of use for all five analgesics increased dramatically over the 30-year
209 study period (1985-2015) (Figure 2). Pregnancies with consumption of at least one
210 analgesic increased from 1.8% in 1985 to 70.6% in 2015. Pregnancies reporting
211 paracetamol use were 1.3% in 1985 and it continuously increased reaching 42.2% in
212 2015. Naproxen, ibuprofen or aspirin consumption during pregnancy was less
213 prevalent (Figure 2A), however it also increased during the 30-year study period,
214 starting at 0.5% in 1985 and reaching 1.9% in 2015 (Figure 2B). Diclofenac was
215 consumed in very few pregnancies between 1985 (<0.01%) and 2005 (0.2%).
216 Percentage of consumption, however, dramatically increased during the next decade
217 following deregulation of diclofenac, reaching 25.0% in just one year (2006) and
218 45.6% of all pregnancies in 2015.

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

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3 222 significant difference ($p < 0.001$) for most variables. In the paracetamol sub-group
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5 223 analysis, baby presentation at delivery ($p = 0.525$) and sex of the baby ($p = 0.861$) were
6
7 224 not significantly different between the groups. In the analysis considering
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9 225 consumption of at least one analgesic from aspirin/naproxen/ibuprofen, again the
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11 226 variables for baby presentation at delivery ($p = 0.093$) and sex of the baby ($p = 0.732$),
12
13 227 together with maternal smoking status ($p = 0.132$) and maternal antepartum
14
15 228 haemorrhage ($p = 0.434$) were not statistically different compared to the unexposed
16
17 229 group. All variables were statistically different between unexposed and exposed
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19 230 groups for the main analysis and diclofenac sub-group analysis.
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24 231 Table 2 summarises the comparison of neonatal outcomes between the unexposed
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26 232 group (no analgesic at all) and the exposed groups of at least one analgesic, only
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28 233 paracetamol and at least one out of aspirin/naproxen/ibuprofen. Comparison of
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30 234 outcomes for the diclofenac sub-group analysis is shown in Table 3.
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37 236 **All analgesics and neonatal outcomes**

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40 237 As shown in Table 2, compared to unexposed pregnancies in which women did not
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42 238 use any analgesic, pregnancies with consumption of at least one analgesic
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44 239 (paracetamol, diclofenac, aspirin, naproxen, ibuprofen) were independently
45
46 240 associated with significantly higher odds for premature delivery (aOR=1.50, 95%CI
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48 241 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), LBW (aOR=1.28, 95%CI 1.20-
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50 242 1.37), HBW (aOR=1.09, 95%CI 1.05-1.13), baby admission to neonatal unit
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52 243 (aOR=1.57, 95%CI 1.51-1.64), APGAR score < 7 at five minutes (aOR=1.48, 95%CI
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54 244 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias
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56 245 (aOR=1.27, 95%CI 1.05-1.54) in adjusted analyses. Significantly decreased odds for
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3 246 APGAR score <7 at one minute were found in the crude analysis (cOR=0.96, 95%CI
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5 247 0.92-0.99), however when adjusted for year of delivery, maternal age at delivery,
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7 248 SIMD, first gestational booking and type of delivery, the significance changed
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9 249 direction showing significantly increased odds (aOR=1.18, 95%CI 1.13-1.23). A
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11 250 significantly lower standardised birthweight score (p=0.046, 95%CI 0.032-0.059) was
12
13 251 found for the exposure group compared to no analgesic at all. Cryptorchidism
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15 252 (aOR=0.92, 95%CI 0.77-1.11), amniotic band defects (aOR=1.02, 95%CI 0.71-1.47),
16
17 253 gastroschisis (aOR=1.10, 95%CI 0.56-2.20) and the composite outcome variable
18
19 254 (aOR=1.12, 95%CI 0.99-1.26), were all associated with increased odds in the
20
21 255 exposure group compared to not exposed, however the association was not
22
23 256 significant in the adjusted model. There was no significant association between
24
25 257 neonatal death and exposure to at least one analgesic in the crude analysis
26
27 258 (cOR=1.19, 95%CI 0.99-1.42), however there were significantly higher odds of
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29 259 neonatal death in the adjusted analysis (aOR=1.56, 95%CI 1.27-1.93) in the
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31 260 exposed group compared to control.
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262 **Paracetamol and neonatal outcomes**

263 In the sub-group analysis considering only paracetamol consumption during
264 pregnancy as our exposure group, most of the associations reported in the main
265 analysis remained significant with the same direction of significance (Table 2). The
266 differences were: maternal paracetamol consumption during pregnancy was
267 associated with significantly decreased odds for offspring HBW (cOR=0.94, 95%CI
268 0.90-0.99) in the crude analysis however significance was lost in the adjusted model
269 (aOR=0.98, 95%CI 0.93-1.02), and there were no significant associations in the
270

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

272

273 **Aspirin/naproxen/ibuprofen and neonatal outcomes**

274 Consumption of at least one analgesic from aspirin, naproxen or ibuprofen during
275 pregnancy was compared against the same control group of pregnancies where no
276 analgesic was used (Table 2). Again, when comparing associations between groups
277 in this sub-group analysis and main analysis, fewer outcome variants showed similar
278 significance pattern. The only shared significant associations were for increased
279 odds for premature delivery (aOR=1.42, 95%CI 1.08-1.86), stillbirth (aOR=2.34,
280 95%CI 1.29-4.25) and baby admission to neonatal unit (aOR=1.54, 95%CI 1.22-
281 1.94) in the adjusted regression analyses.

282

283 **Diclofenac and neonatal outcomes**

284 In the sub-group analysis of pregnancies coinciding with non-prescription, over-the-
285 counter, availability of diclofenac (years 2005-2015) were considered, and outcomes
286 compared between the diclofenac group and no analgesic consumption group (Table
287 3). Compared to the main analysis, diclofenac consumption during pregnancy was
288 not significantly associated with premature delivery (aOR=1.10, 95%CI 0.99-1.22),
289 neonatal death (aOR=1.26, 95%CI 0.73-2.15) and APGAR score <7 in one minute
290 (aOR=0.93, 95%CI 0.83-1.04) in the adjusted models. Associations with APGAR
291 score <7 in five minutes (aOR=0.94, 95%CI 0.72-1.23), cryptorchidism (aOR=1.05,
292 95%CI 0.78-1.42), amniotic band defects (aOR=0.81, 95%CI 0.41-1.58) and
293 gastroschisis (aOR=2.93, 95%CI 0.97-8.88) were no longer significant in both crude

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3 294 and adjusted analyses. Maternal consumption of diclofenac was independently
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5 295 associated with a significant decrease in stillbirth (aOR=0.59, 95%CI 0.41-0.87). It is
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8 296 also interesting to note that diclofenac was the only sub-group analysis agreeing with
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10 297 the main analysis (exposure to at least one analgesic) on the significance of
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12 298 exposure association with increased incidence of neural tube defects (aOR=3.62,
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14 299 95%CI 1.95-6.74) and hypospadias (aOR=1.49, 95%CI 1.09-2.03) compared to
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16
17 300 unexposed pregnancies in adjusted models. As most of the outcomes studied were
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19 301 relatively rare the numbers needed to harm were mostly more than 100. Preterm
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21 302 birth, low birthweight and admission to the neonatal unit were exceptions with NNH
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24 303 ranging from 15 to 38. (Tables S1 and S2).
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304 Discussion

305 Main Findings

306 Consumption of paracetamol, ibuprofen, aspirin and naproxen during pregnancy,
307 either in combination or separately, was significantly associated with increased
308 premature delivery, stillbirth, neonatal death, LBW, abnormal standardised
309 birthweight score and more frequent admission to neonatal unit. Consumption of
310 paracetamol alone was further associated with higher odds for APGAR score <7 at
311 one and five minutes both in crude and adjusted analyses. There was a dramatic
312 increase in the frequency of over-the-counter (non-prescription) analgesic use in
313 pregnancies between 1985 and 2015, starting from only 10.3% of women using one
314 or more of the compounds between 1985 and 1994, climbing to 60.1% of women in
315 the final decade of our study. This means that our findings are applicable far beyond
316 the percentage (between 14% and 38%)²⁶ of pregnant women with underlying
317 health deficits related to the adverse outcomes we report here.

318

319 Diclofenac use increased steeply from 2005 (Figure 2A), which reflects the change in
320 Scottish legislation, leading to diclofenac becoming available without prescription in
321 that year. Diclofenac use was associated with fewer adverse outcomes but showed
322 increased risk of neural tube defects and hypospadias in male neonates.

323 Furthermore, and surprisingly, exposure to diclofenac only was associated with
324 significant decrease in the incidence of stillbirth. The reasons for such differences
325 between the changes in neonatal outcomes following diclofenac consumption
326 compared with those following use of the other NSAIDs are not clear. The proportion
327 of women using diclofenac, especially in the last 7 years of our study makes it highly

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3 328 unlikely to be due to an underlying maternal condition and/or other compounds used
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5 329 in combination (e.g. prescriptions) by women taking diclofenac. It is possible that the
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7 330 drug could act directly on fetal development then this difference could also be due to
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9 331 structural and/or mechanistic differences of the compound compared to the other
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11 332 drugs. However, not enough is known about the specific mechanisms of action of the
12
13 333 different analgesics studied to conclude further. Overall, comparing our main
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15 334 analysis with all three sub-analyses, it is evident that the most significant differences
16
17 335 were observed when paracetamol was taken with at least one other analgesic. This
18
19 336 is mostly due to the high number of pregnancies where paracetamol was used,
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21 337 comprising almost 55% of the exposed cases in the main analysis. Most numbers
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23 338 needed to harm for our outcomes (Tables S1 and S2) ranged between 1000 and
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25 339 100, apart from preterm birth, low birth weight and baby admission to neonatal unit,
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27 340 which were 27, 38 and 15 respectively for our main analysis further strengthening
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29 341 observed associations.
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39 **Strengths and Limitations**

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42 344 A major strength of the present study is the large cohort of 151,141 pregnancies over
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44 345 a 30-year study period from 1985 until 2015, using a robust data source AMND. This
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46 346 is one of the largest cohorts used in studies examining the effects of analgesic use
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48 347 during pregnancy. The dataset contains high quality and consistent data from the
49
50 348 geographically defined area of Aberdeen and surrounding district, in the North East
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52 349 of Scotland, UK. In addition, as Aberdeen Maternity Hospital is the only maternity
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54 350 hospital serving the area, over 95% of pregnancies in the area are included in the
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56 351 dataset, considerably minimizing the risk for selection bias. We were able to analyse
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3 352 maternal consumption data of the five most commonly used analgesics available
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5 353 over-the-counter in the UK and most countries, which is not matched in the current
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7 354 literature. The nature of our data allowed for the analysis of analgesics consumed
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9 355 alone or in combination, unlike most existing studies, and this gives our study the
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11 356 added strength of better reflecting real-life consumption patterns^{27,28}. We were able
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13 357 to adjust for important confounding factors, relevant to each analysed outcome.
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15 358 Adjustment for maternal deprivation also allowed us to further account for potential
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17 359 unmeasured factors that can influence maternal and neonatal health, which is a
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19 360 major strength of our analysis compared to most studies.

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24 361 A potential concern was that women were probably using analgesics to treat some
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26 362 inherent medical condition which in turn could have been the mediating factor for
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28 363 adverse outcomes. Data on indication for use were not available in the database.
29
30 364 However, since these medications are widely available without prescription, this is
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32 365 unlikely to be a factor that affects the findings of this study. This is especially the
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34 366 case during the “diclofenac analysis” covering 2005-2015, where
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38 367 this study presents results on multiple neonatal outcomes for the given cohort. In this
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40 368 way we offer a comprehensive approach to the exploration of associations with *in*
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42 369 *utero* analgesic exposure rather than only focusing on a single outcome of interest.
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44 370 Our data were based on medical notes; however, over-the-counter consumption is
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46 371 self-reported, and details on the timing, duration, dosage, product type (single-
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48 372 ingredient vs combination) and administration type were not available in the
49
50 373 database. In addition, the group of pregnancies with aspirin consumption might
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52 374 include use of low-dose aspirin which is recommended to help reduce risk of some
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54 375 pregnancy complications and outcomes related to placental function. Genetic factors
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56 376 potentially relating to the emergence of offspring health outcomes was an

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3 377 unmeasured variable in our analysis. This study does not include a quantitative bias
4
5 378 analysis to identify potential distort of results presented here. Most women had their
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7 379 first antenatal clinic visit during the 1st pregnancy trimester, which might imply our
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9 380 results were affected by primarily 1st trimester exposure, although analgesic use in
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11 381 first trimester is most likely replicated in the rest of pregnancy. Complete case
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13 382 analyses were performed ignoring pregnancies with missing data in the covariates,
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15 383 however due to the low number of missing data there is little chance that this might
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17 384 have affected the validity of our results. Compared to our cohort size, there were,
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19 385 overall, very few cases of cryptorchidism, neural tube defects, amniotic band defects,
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21 386 hypospadias and gastroschisis, resulting in potentially underpowered statistical
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23 387 analyses to detect a difference for these outcomes. Our study only considered
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25 388 neonatal health outcomes and follow-up of the offspring was not available at this
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27 389 time.
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37 **Interpretation**

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39 392 Previous literature has considered fewer outcomes with fewer analgesic
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41 393 combinations compared to our study. Consistent with our results, increased risk of
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43 394 preterm birth and miscarriage has been associated with analgesic consumption
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45 395 during pregnancy ^{29–32}, while others reported no associations with miscarriage,
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47 396 stillbirth or preterm delivery ^{20,29,30,33}. Similarly, increased risk for offspring
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49 397 cryptorchidism, hypospadias, neural tube defects, amniotic band defects and
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51 398 gastroschisis have been shown by many studies ^{7,8,9,34–41}, although, again, a lack of
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53 399 associations with major birth defects have been reported ^{13–17,42,43}. Compared to our
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55 400 analysis, all these studies used a smaller cohort, considered a shorter study time
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3 401 and there was frequent disagreement with respect to the choices of adjusted
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5 402 confounding factors. Another difference is that maternal questionnaires/interviews
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7 403 were frequently the method of choice to evaluate maternal consumption. Some of
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9 404 the studies reported increased risks for specific pregnancy trimesters which is
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11 405 something our study could not evaluate. Differences in study design and adjustment
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13 406 for different confounders might also account for the disagreement of our results that
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15 407 provide a more accurate assessment. Our study is one of the largest in terms of
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17 408 cohort size, duration, number of analgesics and range of outcomes included which
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19 409 might also contribute to differences compared to other studies. Another study with a
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21 410 large sample size (98,190 pregnancies) and a 7 year study time from Rebordosa and
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23 411 colleagues²⁹, also reported an increased risk of preterm birth following paracetamol
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25 412 use during pregnancy, which was increased in mothers with pre-eclampsia. Our
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27 413 results showed a significant association of the adjusted ORs following adjustment for
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29 414 maternal hypertensive disorders. In addition, they did not find a significant
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31 415 association with stillbirth, or low birth weight as we report here. This disagreement
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33 416 could be due to dataset differences including the information about use in each
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35 417 pregnancy trimester, but also methodological differences such as the use of
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37 418 questionnaires versus medical notes or adjustment for different confounders.
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45 419 The literature currently reports conflicting evidence, limiting our ability for definite
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47 420 decision-making. Over-the-counter analgesics are recommended to women by
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49 421 healthcare professionals in order to deal with pregnancy symptoms and other
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51 422 conditions. Policy-makers have taken a stand on the topic, either being reassuring
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53 423 about over-the-counter use during pregnancy or recommending caution when
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55 424 consumption is necessary ⁴⁴⁻⁴⁷. Different compounds can affect the mother and the
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57 425 fetus in a different way, and their combined use might worsen the risk for offspring ill
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3 426 health. This study demonstrates the need for additional research before the field can
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5 427 be confidently directed towards one direction or the other.
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8 428 Whether the associations we report result from flu, fever, rheumatological or
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10 429 inflammatory conditions, and/or combination with other prescribed medications or
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12 430 solely related to over-the-counter analgesics consumption is a matter of further
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14 431 research. Underlying health conditions could well influence the outcomes we see in
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16 432 this study, however, as these could be very different conditions it is biologically
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18 433 unlikely that they are responsible for the effects we observe here. Our study
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20 434 demonstrates an association of maternal over-the-counter analgesic consumption
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22 435 during pregnancy with adverse neonatal offspring outcomes. Future collaborative
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24 436 approaches such as an individual patient data meta-analysis that includes follow-up
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26 437 data on long-term outcomes during childhood and adulthood would significantly
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28 438 inform decision making. Going forward, uncovering the mechanisms of action and off
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30 439 target effects will also provide a solid foundation for the development of pregnancy-
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32 440 safe compounds. Finally, the findings present here suggest that diclofenac is
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34 441 associated with fewer changes in risk for the more frequent adverse outcomes
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36 442 although it is associated more with rarer, but severe, negative outcomes, including
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38 443 neural tube defects. Diclofenac may have a lower risk for the main adverse neonatal
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40 444 outcomes reported for paracetamol. However, it should be noted that our study is not
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42 445 designed to specifically test differences in level of risk between the analgesics
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44 446 included. Therefore, it should be emphasised that this does not mean that the
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46 447 authors are stating that diclofenac is preferable to paracetamol.
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58 449 **Conclusions**
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3 450 Pain control is currently a therapeutic priority during pregnancy. Our findings of
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5 451 increased risk of adverse health outcomes for the offspring following at least first
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7 452 trimester maternal use of readily available over-the-counter analgesics are crucial to
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9 453 information for the management of pain during pregnancy.
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20
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23

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25
26 459 and coordination of the research. EAR provided critical input in the design and
27
28 460 planning of statistical analysis. AZ conducted the statistical analysis and prepared
29
30 461 the manuscript, figures and tables. AZ, SB, PAF, RTM and DCH substantially
31
32 462 contributed to the analysis and interpretation of the work. All authors contributed to
33
34 463 critical discussion of intellectual content, development and review/approval of the
35
36 464 final manuscript version.
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51 470 analysis, decision to publish, or manuscript preparation.
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57 472 therefore there was no requirement for ethical approval. The North of Scotland
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59 473 Research Ethics Service has devolved Caldicott approval to the Chair of the AMND
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3 474 steering committee. Approval to access and analyse data was obtained from the
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5 475 AMND steering Committee (AMND 004/2018).
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8 476 **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)	30,998 (70.5)		12,138 (50.4)		228 (29.9)		n/a	n/a	
2010-2015 *	n/a	n/a		n/a		n/a		11,105 (54.1)	4,021 (39.1)	
	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										
1 st 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
2 nd Trimester	29,269 (27.4)	5,791 (13.2)		4,117 (17.1)		166 (21.9)		1,770 (8.6)	829 (8.1)	
3 rd 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)§	

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

644 *Only applicable to Diclofenac 2005-2015 analysis

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

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

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

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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. 35

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/Na pr (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	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										

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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

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

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3 651 ^a Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, maternal
4 652 hypertensive disorders, maternal antepartum haemorrhage
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6 653 ^b Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, gestation at
7 654 delivery
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9 655 ^c Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking
10 656 ^d Adjusted for year of delivery, maternal age at delivery, SIMD, first gestational booking, type of
11 657 delivery
12 658 *Including cryptorchidism, neural tube defects, amniotic band defects, hypospadias, gastroschisis
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3 659 **Figure 1.** Flowchart of cohort selection and sub-group analyses. n=number of
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5 660 pregnancies in each analysis. *98.3% of pregnancies using only diclofenac occurred
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7 661 during 2005-2015, therefore analysis was performed only on data from that decade
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9 662 to rule out any temporal effect.
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3 664 **Figure 2.** Prevalence of use during pregnancy for each analgesic sub-group over our
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5 665 30-year study period. **(A)** Merge graph showing percentage of pregnancies using
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7 666 each analgesic group during pregnancy. **(B)** Percentage of use for at least one
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9 667 analgesic out of ibuprofen, aspirin, naproxen. *In 2005 there was a change in
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11 668 legislation making diclofenac available without prescription.
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3 670 **Figure S1.** Directed acyclic graph (DAG) of analgesics use to amniotic band defects

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5 671 outcome path and relevant measured and unmeasured biasing factors in our

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7 672 analysis.

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3 674 **Figure S2.** Directed acyclic graph (DAG) of analgesics use to APGAR score
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5 675 outcome path and relevant measured and unmeasured biasing factors in our
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7 676 analysis.
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3 678 **Figure S3.** Directed acyclic graph (DAG) of analgesics use to cryptorchidism

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5 679 outcome path and relevant measured and unmeasured biasing factors in our

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

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3 685 **Figure S5.** Directed acyclic graph (DAG) of analgesics use to gestation at delivery

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5 686 outcome path and relevant measured and unmeasured biasing factors in our

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7 687 analysis.

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

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3 692 **Figure S7.** Directed acyclic graph (DAG) of analgesics use to admission to neonatal
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5 693 unit outcome path and relevant measured and unmeasured biasing factors in our
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7 694 analysis.
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696 **Figure S8.** Directed acyclic graph (DAG) of analgesics use to neural tube defects
697 outcome path and relevant measured and unmeasured biasing factors in our
698 analysis.

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3 700 **Figure S9.** Directed acyclic graph (DAG) of analgesics use to pregnancy outcome
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5 701 path and relevant measured and unmeasured biasing factors in our analysis.
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703 **Figure S10.** Directed acyclic graph (DAG) of analgesics use to standardised
704 birthweight score outcome path and relevant measured and unmeasured biasing
705 factors in our analysis.
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3 707 **Figure S11.** Directed acyclic graph (DAG) of analgesics use to weight of baby
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5 708 outcome path and relevant measured and unmeasured biasing factors in our
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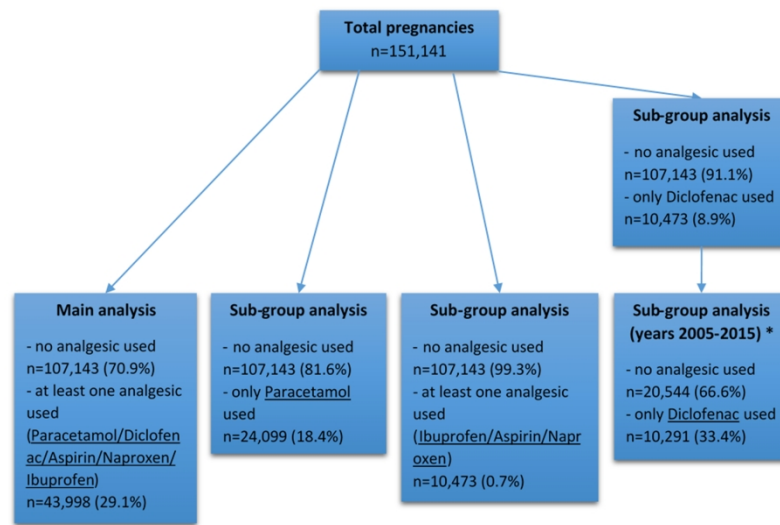


Figure 1. Flowchart of cohort selection and sub-group analyses. n=number of pregnancies in each analysis. *98.3% of pregnancies using only diclofenac occurred during 2005-2015, therefore analysis was performed only on data from that decade to rule out any temporal effect.

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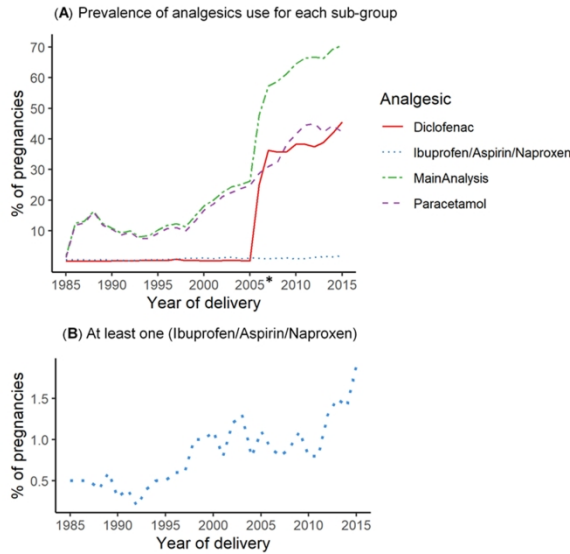


Figure 2. Prevalence of use during pregnancy for each analgesic sub-group over our 30-year study period. (A) Merge graph showing percentage of pregnancies using each analgesic group during pregnancy. (B) Percentage of use for at least one analgesic out of ibuprofen, aspirin, naproxen. *In 2005 there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

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

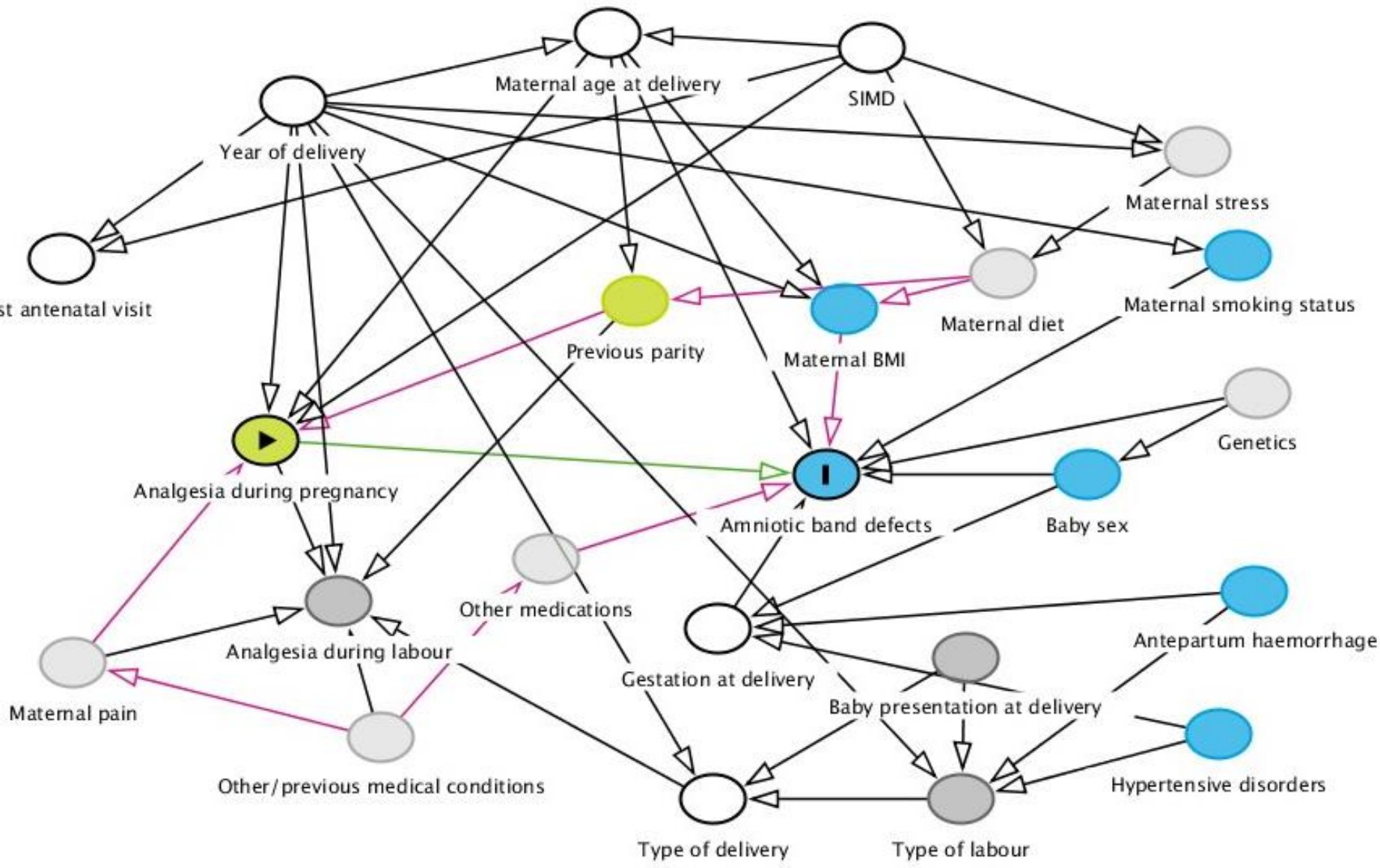
n/a, not applicable

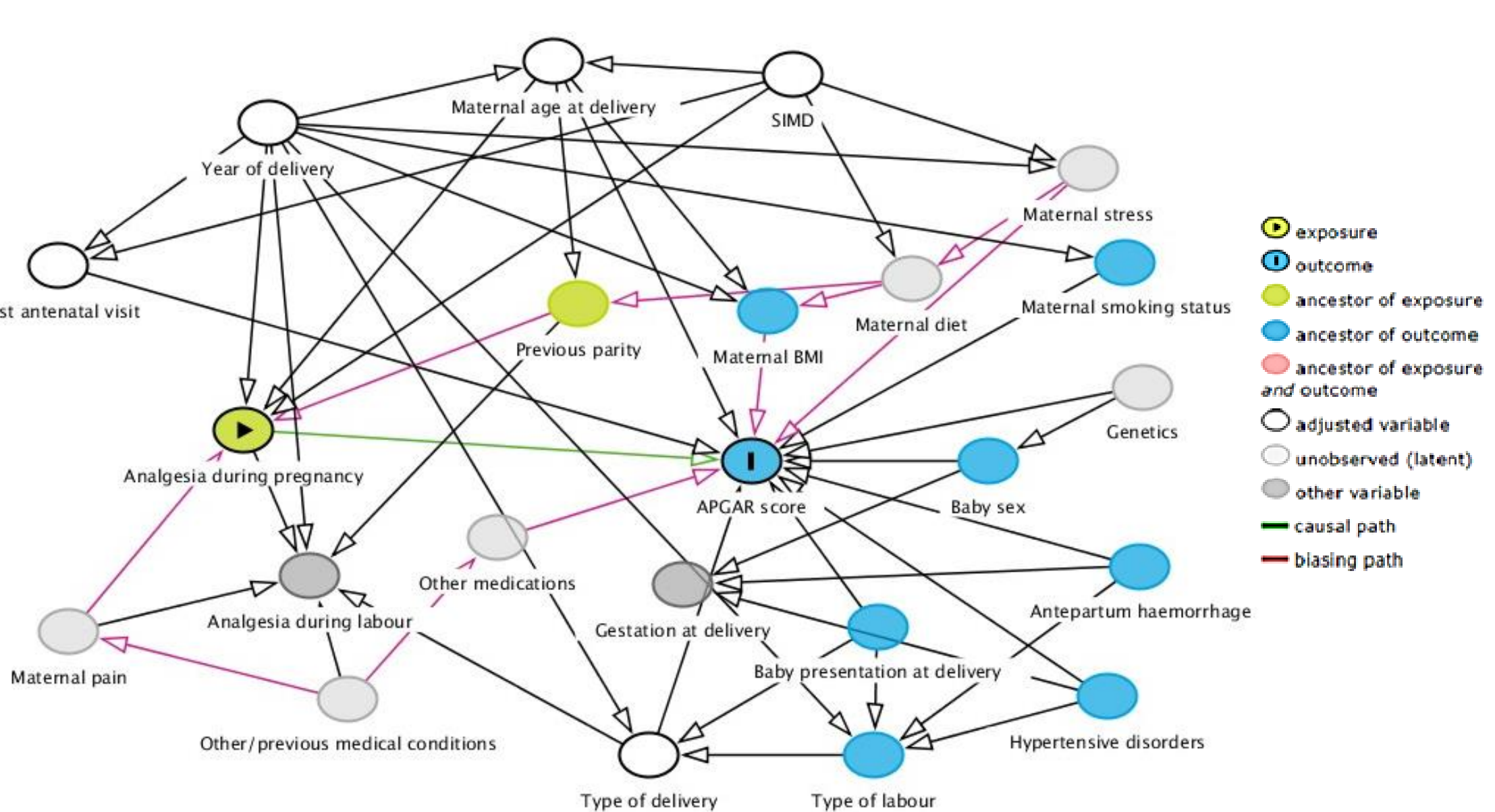
Table S2. Numbers needed to harm (NNH) for exposure to diclofenac (years 2005-2015).

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

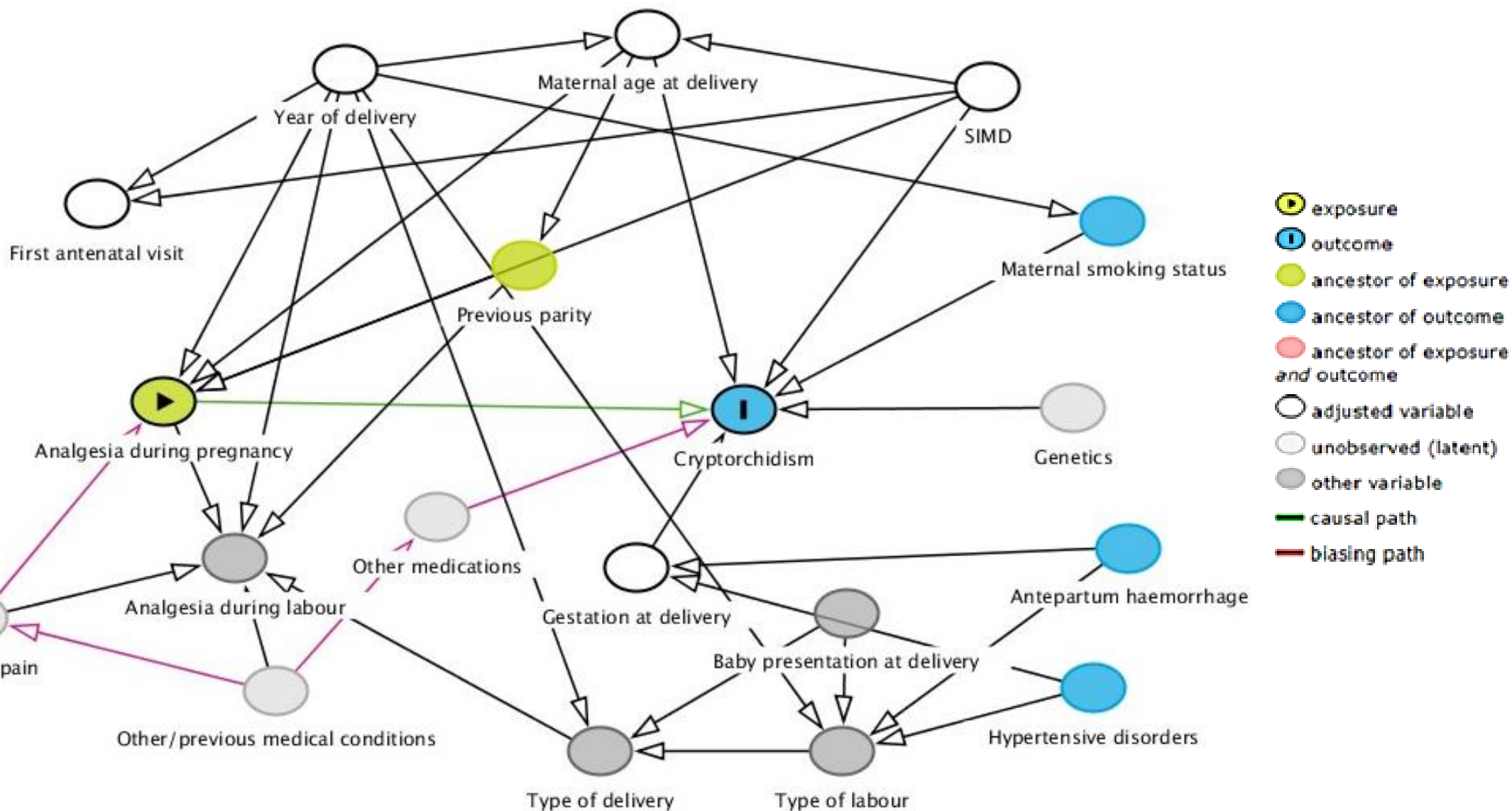
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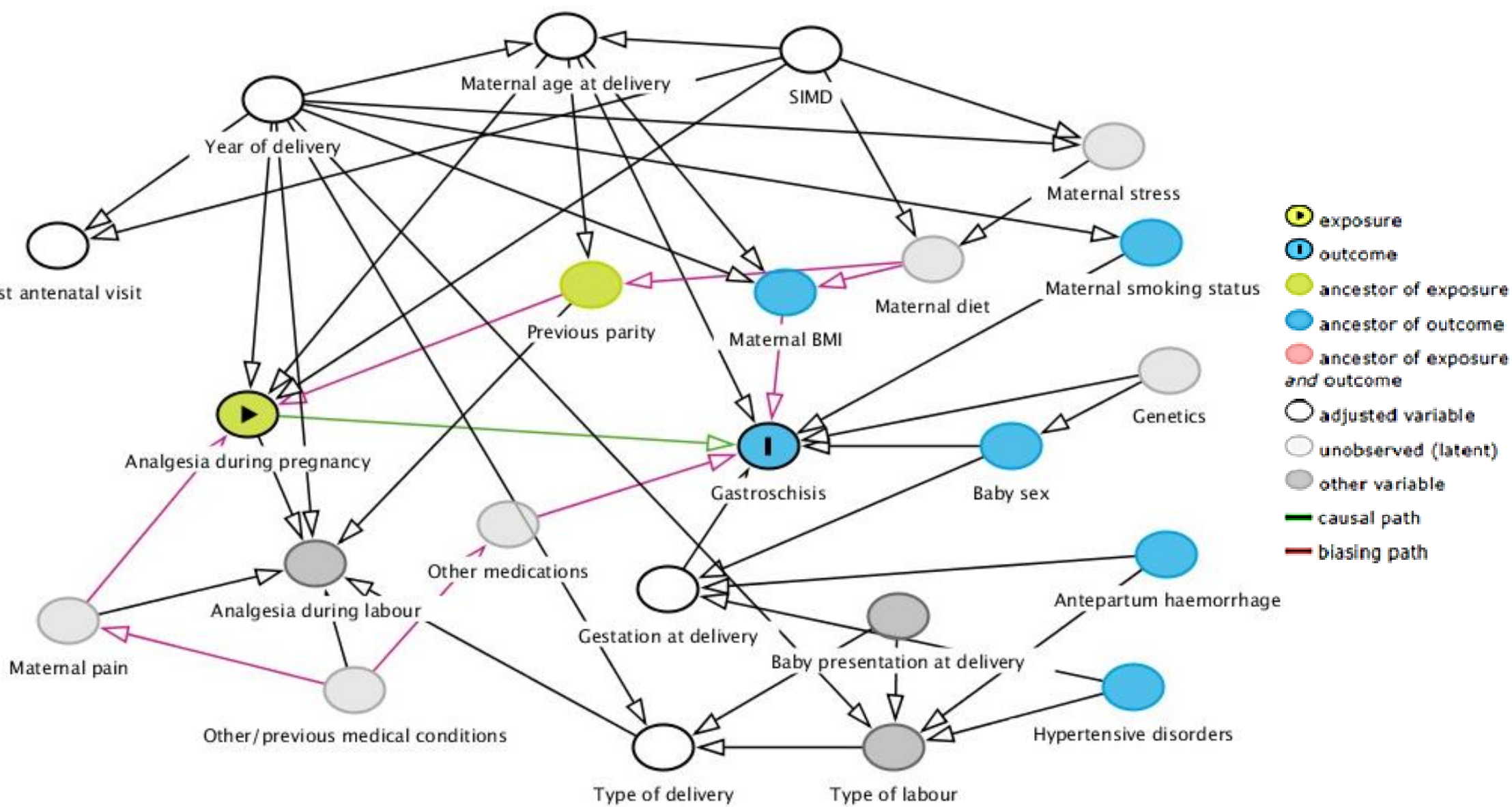


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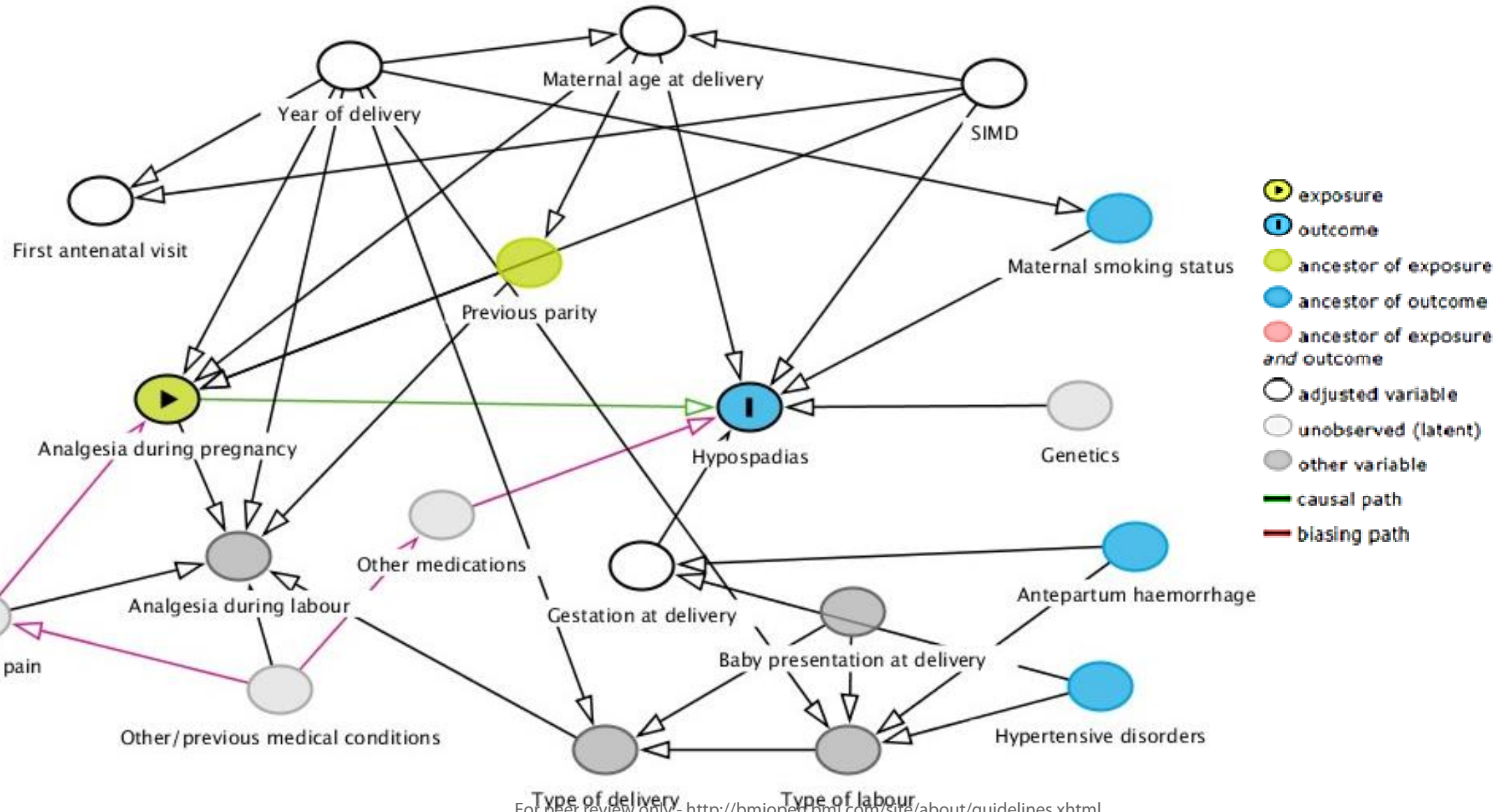
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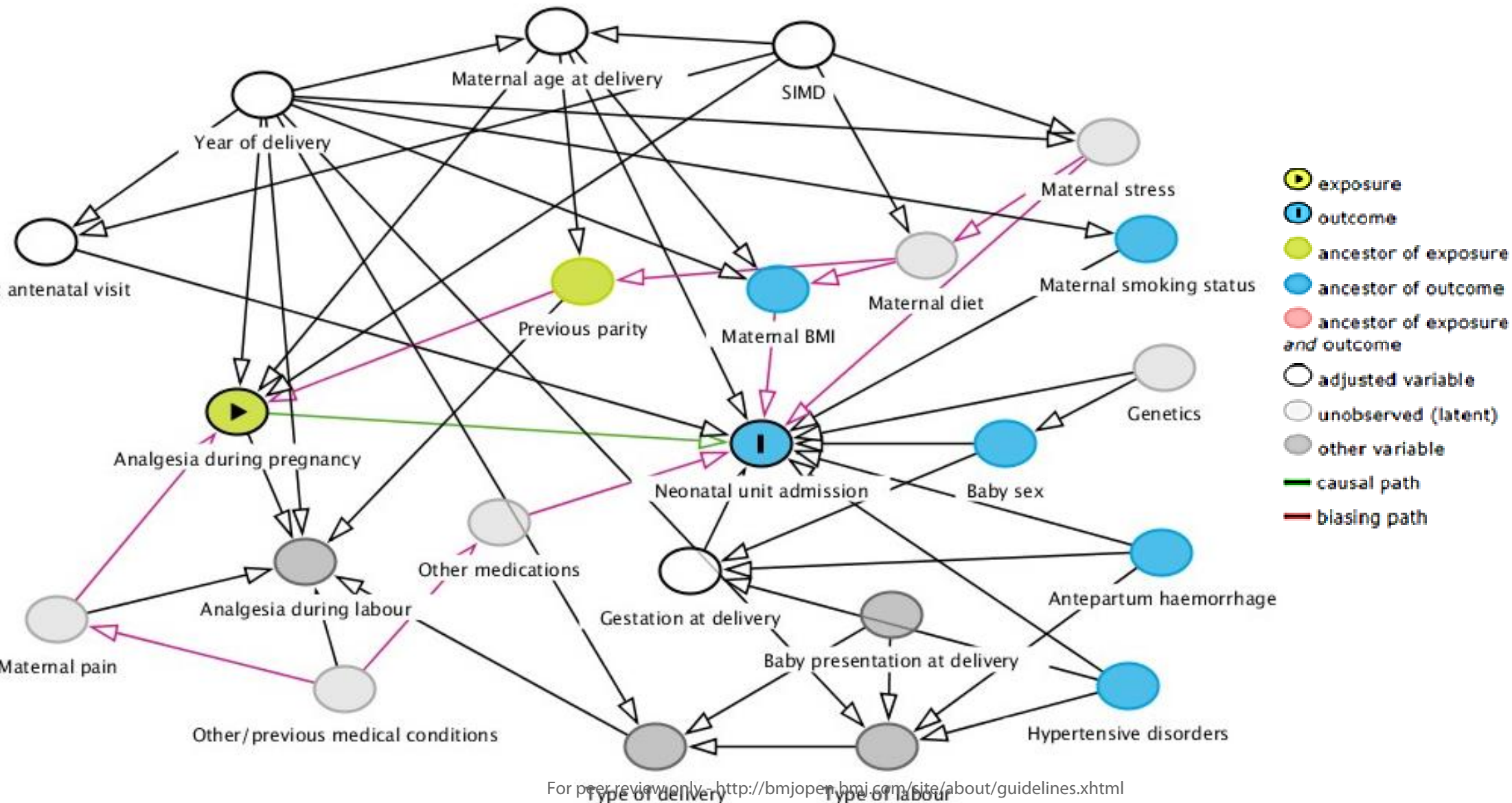
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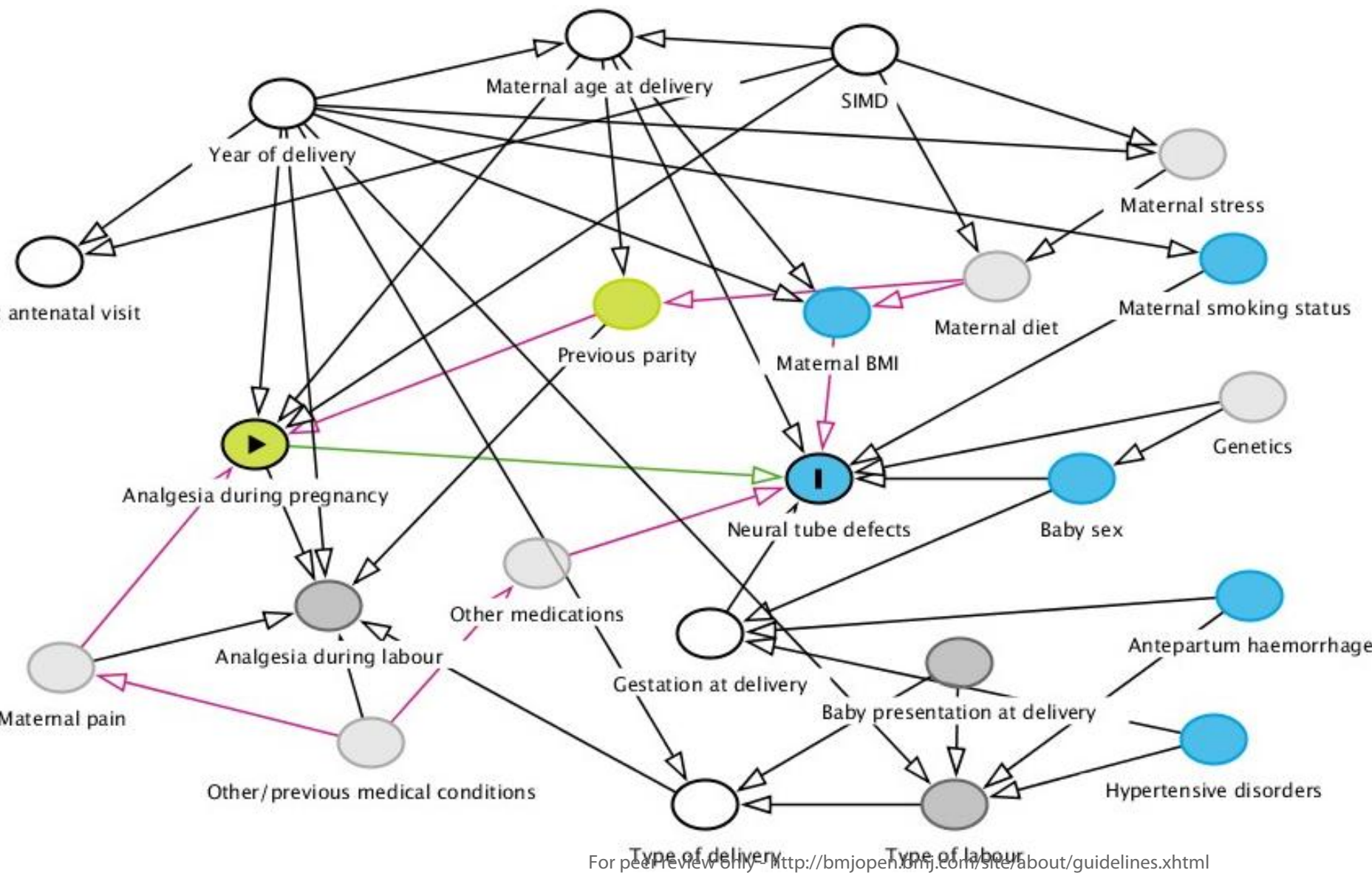
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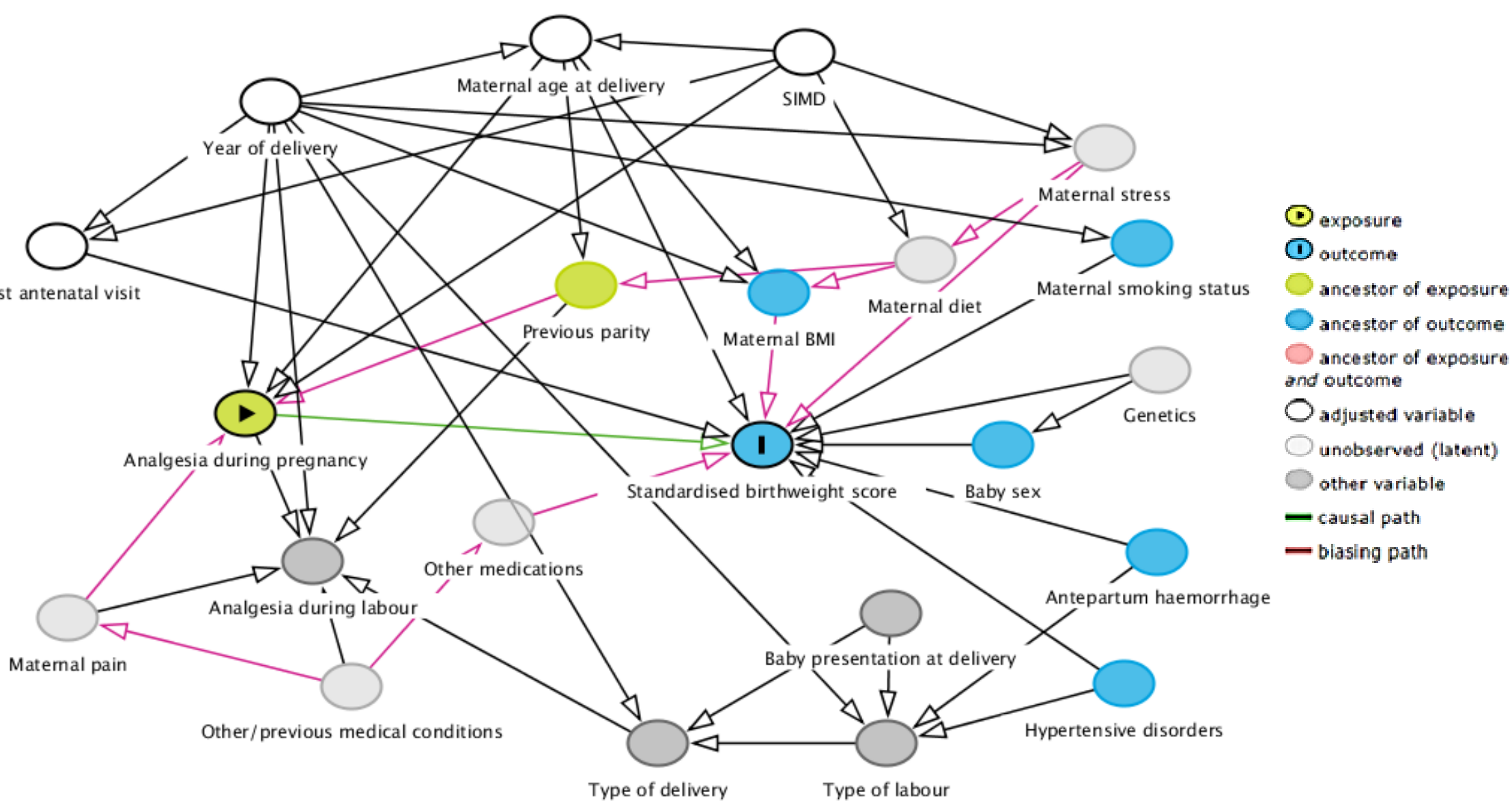


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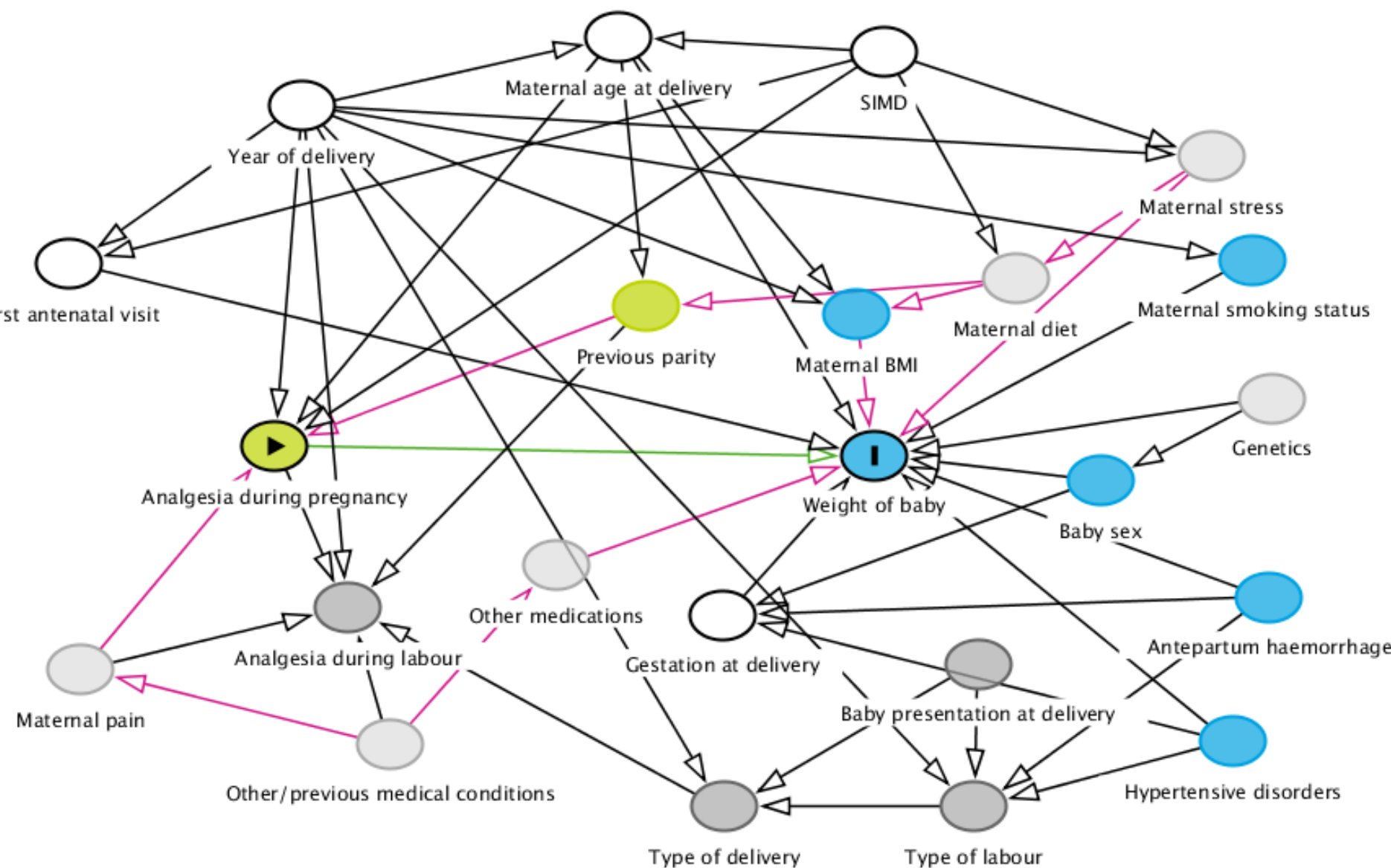


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- ancestor of exposure
- ancestor of outcome
- ancestor of exposure and outcome
- adjusted variable
- unobserved (latent)
- other variable
- causal path
- biasing path

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1 Results Page 11 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

1 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
2 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
3 available at <http://www.strobe-statement.org>.
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