Neonatal and Early Childhood Outcomes Following Maternal Anaesthesia for Caesarean Section; a Population-based Cohort Study

Rachel J. Kearns, MD,[1*] Martin Shaw, PhD,[2*] Piotr S. Gromski, PhD,[1] Stamatina Iliodromiti, PhD,[3] Jill P. Pell, PhD,[4] Deborah A. Lawlor, PhD,[5**] Scott M. Nelson, PhD[1**]

[1] *School of Medicine, University of Glasgow, UK*

[2] *Department of Medical Physics, NHS Greater Glasgow and Clyde, UK*

[3] *Centre for Women's Health, Institute of Population Health Sciences, Queen Mary University, London, UK*

[4] *Institute of Health and Wellbeing, University of Glasgow, UK*

[5] *MRC Integrative Epidemiology Unit, University of Bristol, UK*

Corresponding author:

Dr Rachel J Kearns, School of Medicine, University of Glasgow, 2nd Floor, Lister Building, Glasgow Royal Infirmary, 10-16, Alexandra Parade, Glasgow, G31 2ER, United Kingdom.

Email: rachel.kearns@glasgow.ac.uk

Tel: 0141 2013870

https://orcid.org/0000-0001-6156-6858

*Denotes joint first author ** Denotes joint senior author

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Abbreviations

Adj	Adjusted
AR	Absolute risk
CI	Confidence interval
GA	General anaesthesia
NHS	National Health Service
FDA	The United States Food and Drug Administration
RR	Relative risk
US	United States of America

Abstract

Background

The fetus is vulnerable to maternal drug exposure. We determined associations of exposure to spinal, epidural, or general anaesthesia on neonatal and childhood development outcomes during the first 1000-days of life.

Methods

Population-based study of all singleton, caesarean livebirths of 24+0 to 43+6 weeks gestation between January 2007-December 2016 in Scotland, stratified by urgency with follow-up to age two-years. Models were adjusted for; maternal age, weight, ethnicity, socioeconomic status, smoking, drug-use, induction, parity, previous caesarean or abortion, pre-eclampsia, gestation, birthweight, and sex.

Results

140,866 mothers underwent caesarean section (41.2% [57,971/140,866] elective, 58.8% [82,895/140,866] emergency) with general anaesthesia used in 3.2% (1877/57,971) elective and 9.8% (8158/82,895) of emergency cases. In elective cases, general anaesthesia versus spinal was associated with: neonatal resuscitation (crude event rate 16.2% vs 1.9% [adjusted RR 8.20, 95% CI 7.20,9.33], Apgar <7 at 5-minutes (4.6% vs 0.4% [adjRR 11.44, 95%CI 8.88,14.75]), and neonatal admission (8.6% vs 4.9% [adjRR 1.65, 95%CI 1.40,1.94]). Associations were similar in emergencies; resuscitation (32.2% vs 12.3% [adjRR 2.40, 95% CI 2.30,2.50]), Apgar <7 (12.6% vs 2.8% [adjRR 3.87, 95% CI 3.56,4.20), and admission (31.6% vs 19.9% [adjRR 1.20, 95%CI 1.15,1.25). There was a weak association between general anaesthesia in emergency cases and having ≥1 concern noted in developmental assessment at two-years (21.0% vs 16.5% [adjRR 1.08, 95% CI 1.01,1.16]).

Conclusions

General anaesthesia for caesarean section, irrespective of urgency, is associated with neonatal resuscitation, low Apgar, and neonatal unit admission. Associations were strongest in non-urgent cases and at term. Further evaluation of long-term outcomes is warranted.

Trial registration: nil

Introduction

The United States Food and Drug Administration (FDA) has warned that exposure to general anaesthesia (GA) in children under three years, or during the third trimester of pregnancy, may adversely affect childhood neurological development.[1] Several studies (N=310 to 997) provide reassurance that a single, short exposure to GA in childhood does not have negative effects on learning or behaviour.[2–4] Data regarding short and longer-term effects of anaesthesia on the fetus are scarce,[5,6] with trials of maternal anaesthesia primarily focusing on maternal and immediate neonatal outcomes.[7,8]

Caesarean section is the most commonly performed surgery worldwide, accounting for one in fourteen surgeries with ~29·7 million performed annually.[9] International guidelines recommend regional anaesthetic techniques such as spinal or epidural rather than GA as they are associated with lower maternal morbidity.[10,11] Whilst maternal benefits of regional anaesthesia are widely accepted, the optimal mode of anaesthesia for fetal wellbeing remains less clear.[7,8] GA remains necessary where spinal or epidural anaesthesia is contraindicated, and is traditionally used to expedite delivery where there is maternal or fetal compromise. Women may choose to receive GA for elective delivery even when not clinically indicated,[12] and in low-income settings, GA is administered in 20% of caesarean sections, often due to lack of training in regional anaesthesia.[13]

The United Nations Sustainable Development Goals highlight the “First 1000-days” after birth as a critical phase of development during which foundations for lifelong health are laid.[14] With the global rise in caesarean sections, information on short and longer-term childhood outcomes after fetal exposure to anaesthesia is critical to inform decision-making. We sought to determine associations of exposure to spinal, epidural or GA on neonatal and childhood development outcomes in both elective and emergency cases during the first 1000-days of life.

Methods

This study was approved by the National Health Service (NHS) Greater Glasgow and Clyde Research and Development department (GN18AN131) and NHS Scotland Public Benefit and Privacy Panel for Health and Social Care (eDRIS_1617-0330). Data were de-identified by the electronic Data Research and Innovation Service of NHS Scotland. Participant-level consent was not required. Results were analysed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15]

Study population

We linked six national Scotland-wide databases of routinely collected administrative data; the Scottish Morbidity Record 02 (SMR02); the Scottish Birth Record (SBR), the National Records for Scotland (NRS); the Scottish Stillbirth and Infant Death Survey, The Scottish Morbidity Record 01 (SMR01) and the Child Health Surveillance System Programme Pre-School. SMR02 records information on all women discharged from Scottish maternity hospitals, and was >90% complete at last audit.[16]

We obtained data for all births delivered in Scotland from the linked dataset between 1st January 2007 and 31st December 2016 inclusive. Analyses were restricted to singleton livebirths born by caesarean section with gestational age at delivery of 24^{+0} to 43^{+6} weeks. Exclusions were; stillbirth prior to delivery, no recorded mode of delivery, known congenital anomaly, or vaginal delivery. Caesarean section was classified as elective where there was no acute fetal compromise, no trial of labour, and when scheduled at a time to suit the woman/healthcare team.[17] Emergency caesarean was defined as any non-elective caesarean section. The Scottish Index for Multiple Deprivation (SIMD), with decile one representing the most deprived, was used to control for socioeconomic status.[18] Ethnicity was classified with 2011 census categories (NHS Scotland).[19] Smoking status at booking was defined as current, former or never. Gestational age at birth was defined as completed weeks of gestation based on estimated date of delivery from sonography. Pre-eclampsia was defined according to ICD-10 classifications.

Anaesthesia type

Anaesthetic interventions were; spinal, epidural, or GA. In all analyses, spinal was used as the reference category, as this was the most frequently used mode of anaesthesia for caesarean section.

Outcomes

Neonatal resuscitation was defined by the use of bag-mask ventilation or intubation/ventilation with or without drugs. Transient facial oxygen was classified as not having resuscitation. Apgar score at 5-minutes was reported as low (0-6) or not low (7-10). Data for 1- and 10-minute Apgar scores were not available. Neonatal unit admission was dichotomised (yes/no). Childhood healthcare utilisation was reported as hospital length of stay, and number of clinical conditions recorded at in- or out-patient attendance, over the first 1000-days of life. Childhood development was assessed by health visitors using standardised proformas as part of the Child Health Programme in Scotland (data was 87% complete for all domains when last assessed).[20] Assessments were performed during 2007-2014 at “2-years of age” and from 2012 to present, at 27-30 months. There were two years of transitional period where assessment could have been at either time-point. From here onwards, we refer to this as “2-year” child health surveillance assessment. Development was assessed in; gross motor, fine motor, social and communication, with results scored as “concern” or “no concern”. The child’s age, corrected for gestation at birth, was used for all assessments. We also report a composite outcome of any concern noted in one or more of the four developmental assessments.

Covariates and statistical analyses

Results are presented separately for elective and emergency caesarean sections as the reasons for doing a caesarean section might indicate the presence of (or cause) an adverse developmental outcome, and the distribution of these reasons will differ by elective or emergency; and any change in policy around the use of GA would be easier to implement in elective cases. We used Poisson regression modelling with cluster robust errors (to account for more than one delivery in some women) to determine adjusted absolute and relative risks for anaesthetic technique and outcomes. A robust sandwich estimator was used under the generalised estimation equation framework to correct the inflated variance found from the standard Poisson model.[21] The robust Poisson modelling was chosen over the more common log-binomial model for the calculation of relative-risks to avoid convergence problems and to partially mitigate against any potential estimation bias due to uncontrolled confounding.[21] Multivariate Poisson regression was used for childhood development assessments to take into account the linked nature of the assessments (e.g. a child with a concern in social functioning may be more likely to have concern in communication). Robust Poisson regression with non-linear splines were fit to model associations of anaesthetic type in emergency cases over the continuous spectrum of gestational ages. Standard Poisson regression modelling was utilised to estimate the incidence rate ratios for the number of days in hospital and number of unique conditions.

Results are presented as absolute or relative risk with 95% confidence intervals referent to spinal anaesthesia. Models were adjusted for factors identified *a priori* as having an association with outcomes, but that could not be on a causal path from anaesthesia to outcome. These were; maternal age, weight, ethnicity, socioeconomic status, smoking history, illicit drug-use, induction of labour (emergency cases), parity, previous caesarean, previous spontaneous/therapeutic abortion, pre-eclampsia, gestation, birthweight, and sex.

All missing data were imputed using multiple imputation via chained equations (MICE) to form ten imputed datasets using a classification and regression trees (CART) methodology.[22] Ten iterations provided optimal data output stability, and ten imputations ensured accuracy of the pooled variable effect estimates given the amount of missing data. Missingness ranged from 0% (maternal age, gestation, sex, pre-eclampsia) to 37.4% (ethnicity) in the elective cohort, and 0% to 41.2% for the same outcomes in the emergency cohort (Table 1, Supplementary Table 1). Missing data in confounders were dealt with using a robust imputation method, and distributions of characteristics were similar in non-imputed and imputed datasets (Table 1, Supplementary Table 1).

We performed a sub-group analysis for 14,808 patients where further information on caesarean section urgency was available. In this sub-group, emergency caesareans were further categorised as; category-1 indicating immediate threat to maternal/fetal life, category-2 indicating maternal/fetal distress which was not life-threatening, and category-3 indicating need for early delivery but with no maternal/fetal compromise.[17] Analyses were validated to ensure distributional assumptions were met and were undertaken using R (version 3.6.2), R Foundation for Statistical Computing.

Results

Between January 1^{st} 2007, and December 31^{st} 2016, after exclusions, 510,803 livebirths between 24^{+0} and 43^{+6} weeks gestation were recorded in Scotland, of which 28% (140,866/510,803) were delivered by caesarean section. Of these, 41·2% (57,971/140,866) were undertaken electively and 58.8% (82,895/140,866) as emergencies, with 3·2% (1,877/57,971) and 9·8% (8,158/82,895) performed under GA in each group respectively (unadjusted crude event rates, Figure 1). Irrespective of urgency, mothers receiving GA were more likely to have; lower socioeconomic status, history of smoking, pre-eclampsia, be delivering preterm, and have an infant of lower birthweight than those receiving spinal/epidural (Table 1, Supplementary Table 1).

Adverse outcomes were generally more common after emergency compared with elective caesarean sections (Table 2, Figure 2). In both elective and emergency cases, GA was associated with increased risk of; neonatal resuscitation, 5-minute Apgar score <7, and neonatal admission, compared with spinal or epidural anaesthesia (Tables 2 and 3).
The difference in risk for neonatal outcomes between spinal and GA increased with greater gestational age reaching maximal divergence around term (Figure 3). Relative risks of GA compared with spinal for neonatal outcomes were higher in elective than emergency cases (Table 3).

In the sub-group analysis of 14,808 emergency cases, the strongest associations were observed in the least urgent deliveries. Neonatal resuscitation; category-1 (adjusted RR 2.36, 95% CI 1.31,4.26), category-2 (adjRR 3.26, 95% CI 1.26,8.48), and category-3 (adjRR 7.75, 95% 2.21,27.18 CI), and neonatal admission: category 1 (adjRR 1.39, 95% CI 0.79,2.43), category 2 (adjRR 1.60, 95% CI 0.63,4.09), and category-3 (adjRR 2.43, 95% CI 0.77,7.70).

Maternal, and perinatal characteristics of this sub-group were similar to the overall cohort, though confidence intervals were wide in the category-3 group and may reflect that the subgroup analysis was not adequately powered for the outcomes. There was no strong evidence of difference in any outcomes between epidural and spinal anaesthesia (Table 3).

We had developmental assessment data for 28,888 elective and 42,293 emergency mother-infant pairs. There was an association between GA and fine motor concern in elective cases compared with spinal/epidural (4.1 vs 2.1%, adj RR 1.57 [95% CI 1.07,2.29]). In emergency cases, GA had weak associations with communication concern (18.2% vs 14.6%, adj RR 1.08 [95% CI 1.00,1.17]), and with having a concern in ≥1 developmental domains (21% vs 14%, adj RR1.08 [95% CI 1.01,1.16] - Table 3, Figure 2). Associations did not diverge as gestation increased (Figure 3). Mothers and offspring with developmental data were similar to those without follow-up (Supplementary Table 9). Results were similar across complete case, imputed, unadjusted and adjusted analyses (Supplementary Tables 2-5).

Discussion

This study demonstrates an association between fetuses exposed to maternal GA (compared with spinal/epidural anaesthesia) and; neonatal resuscitation, Apgar score <7 at 5-minutes, and neonatal unit admission in both elective and emergency cases. Associations with developmental concerns at two-years were weak and should be interpreted with caution. Our findings do not appear to be driven by increased healthcare utilisation which might result in increased monitoring or reflect other underlying health conditions.

Our study confirms that the risk of neonatal resuscitation/admission or Apgar <7 at 5-minutes is higher in emergency compared with elective cases, and further increases with increasing prematurity. That the mode of anaesthesia appears to make least difference to neonatal outcomes in the most urgent deliveries, may reflect the presence of other more influential factors in such cases. Conversely, associations are strongest in elective deliveries, and at term gestation where babies are less likely to have pre-existing compromise. These findings support that there is some aspect of GA, or the decision to perform GA (even for a term infant with no urgency for delivery), that results in an increased risk of these neonatal outcomes. As GA is strongly associated with both neonatal resuscitation and admission, appropriate neonatal support should be available for all women being delivered under GA. We found no strong evidence of difference in outcomes between epidural and spinal anaesthesia.

Our results agree with previous meta-analyses. A Cochrane review of 21 RCTs (1768 participants) comparing GA with regional anaesthesia for caesarean section found no difference in Apgar scores nor need for neonatal resuscitation, though no studies reported longer-term childhood outcomes.[7] A network meta-analysis including 46 RCTs (3689 participants) showed GA was associated with marginally lower 5-minute Apgar scores compared with spinal or epidural (mean difference 0.24 (95% CI 0.07–0.41), however, additional important clinical outcomes such as neonatal resuscitation and admission were not examined.[8] Findings of both meta-analyses are limited by small study size, a mainly elective population, and high risk of bias, with allocation concealment and blinding not achieved in most studies.[7,8] Two Australasian observational studies including 50,806,[23] and 6,729 caesarean sections[24] reported increased neonatal intubation and low Apgar score with GA, but restricted analyses to births at term, and did not adjust for confounders such as maternal demographics and lifestyle factors.[23,24] A large prospective study (n=37,142) found a higher risk of low Apgar with GA but did not stratify by urgency nor control for confounding.[25] All three studies were performed before 2005 when caesarean rates were lower and may not reflect contemporary obstetric, neonatal and anaesthetic practice.[23–25] A WHO study of caesarean sections in low- and middle-income countries comparing GA and spinal/epidural found an association between GA and adverse neonatal outcomes.[26] That our findings for neonatal outcomes, from a country with free, accessible healthcare and advanced obstetric, anaesthetic and neonatal practice are broadly similar to those reported from low- and middle-income countries supports current guidance of using regional anaesthetic techniques where possible.[10,11]

Rates of GA for both elective and emergency caesarean were within best practice targets set by the Royal College of Anaesthetists (<5% in elective and <15% in emergencies).[27] We did not have data regarding GA indication and acknowledge that this may be influenced by maternal factors and could constitute residual confounding. The use of GA did not change with time, indicating that factors influencing its performance in Scotland have remained consistent. An American study found that 4·8% of GAs for caesarean were potentially avoidable.[28] In this study; younger age, ethnic minorities, Medicaid status, comorbidities, and non-elective admission were associated with GA, though other reasons such as operator/maternal choice were not examined.[28]

Until recently, thiopentone and suxamethonium have persisted as the most commonly used GA induction agents in UK obstetric practice.[29] Over the last eight years, the use of propofol has increased.[30,31] The period evaluated in our study ends in December 2016 and is likely to reflect a majority of GAs performed using thiopentone and suxamethonium, though propofol use may have been increasing. There is no evidence of a beneficial effect of propofol over thiopentone on fetal outcomes.[32] The use of opioids during induction of GA has become more common,[31] though any concerns relating to association with adverse neonatal outcomes are not supported by meta-analysis.[33] The use of pre-medication before caesarean section remains unusual in the UK. GA remains an important technique for the obstetric anaesthetist, and future research should concentrate on its optimisation for both maternal and neonatal outcomes.

Few studies have investigated longer-term outcomes after fetal anaesthesia exposure.[5] A cohort of 5320 children born between 1976-82 showed no difference in learning disabilities between babies born by caesarean under regional anaesthesia or GA compared with vaginal delivery.[6] This study was not designed to compare anaesthesia types for caesarean section and is further limited by its historical nature. A cohort of 40 children born to mothers with occupational anaesthetic exposure found lower gross motor scores and higher levels of inattention/hyperactivity in the exposed group.[34] The recent suggestion of higher rates of autism in babies born by caesarean section under GA has been criticised for lack of direct comparison between GA and regional anaesthesia, low numbers, and lack of adjustment for confounding including urgency of delivery.[35] Whether the usually short exposure of the fetus to GA during delivery is likely to influence longer-term development remains unclear and findings in healthy children exposed to GA of short duration are reassuring.[2-4] The associations with long-term development observed in our study are weak and are likely to be subject to unmeasured mediation over the two-year period. GA should continue to be utilised when clinically indicated and should not be avoided on the basis of these findings alone.

Our study has a number of strengths including an unselected, whole-population cohort, a recent ten-year period reflecting contemporary anaesthetic, obstetric and neonatal practice, separate analyses of elective and emergency cases, adjustment for a wide range of confounders, and prolonged follow-up over the first two years of life. However, we acknowledge limitations, including that caesarean section has inherent confounding by indication, and we cannot assume the associations are causal. Whilst we had data to further categorise caesarean urgency in a subgroup of 14,808 patients for two neonatal outcomes, we did not have this granularity for the whole cohort. Our inability to adjust for GA indication, agents, duration of exposure, use of multiple forms of anaesthesia, opioid administration, and intra-operative haemodynamics may confound our observations. Longer delay from GA induction to delivery is a potential hypothesis to explain the greater associations seen in the elective group. We acknowledge that there may be other unmeasured confounders. However, that our results were similar for both adjusted and unadjusted analyses, for elective and emergency cases, and were strengthened at term, would all support the observed associations. We did not have data on Apgar scores at other time points nor cord blood gas results, though Apgar at 5-minutes has greater predictive performance on outcomes than Apgar at 1-minute.[36,37] Reasons for lower patient numbers in analyses of developmental outcomes are unclear and may reflect change in timing of assessments, however characteristics of those with follow-up were similar to those without. We acknowledge that the subjective nature of the assessments, and large size of the dataset may have contributed to the associations observed, and that weaker associations seen with language than motor skills may reflect difficulties in assessing language at this age. Future studies with prolonged follow-up including educational outcomes would be useful, as we acknowledge that our findings may be by chance. We have used robust statistical imputation techniques to minimise potential selection bias and maximise statistical efficiency and show similar results when analysing only those with no missing data or when restricting imputation to confounding variables.

In conclusion, our data from a contemporary population of 57,971 elective and 82,895 emergency mother-infant pairs show that fetal exposure to maternal GA for caesarean section, irrespective of urgency, is associated with increased risk of neonatal resuscitation, Apgar <7 at 5-minutes and neonatal admission. Associations with longer-term childhood developmental concerns are weak and require further investigation. These findings support restricting GA to mothers where there is a clear clinical indication, provide further valuable information to inform consent processes and clinical decision making, and highlight the need to prioritise investment in obstetric anaesthesia on a global scale.

Competing interest Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support via grant funding form the Obstetric Association of Anaesthetists and Scottish Society of Anaesthetists for the submitted work. SMN has participated in Advisory Boards and received consultancy or speakers' fees from Access Fertility, Beckman Coulter, Ferring, Finox, Merck, MSD, Roche Diagnostics, and The Fertility Partnership. DAL has received grant funding for other studies, not related to this one, from government, charity and industry funders, including Roche Diagnostics and Medtronic. no other relationships or activities that could appear to have influenced the submitted work.

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Author contributions

RK, MS, SI and SMN designed the study. RK, PG, MS, and SMN wrote the analysis plan. SI facilitated data access. PG, MS and RK analysed the data. RK, SMN and DAL drafted the initial manuscript. All authors contributed to data interpretation, critical revision, and final approval of the submitted manuscript.

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Transparency statement

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination declaration

We plan to disseminate the results to patient organisations such as the James Lind Alliance to disseminate emerging findings with relevant couples and health care professionals.

Data sharing statement

The data analysed during this work are not permitted to be made publicly available and will be archived and destroyed in line with eDRIS protocols. We can make available the code used in cleaning the data and deriving the variables on request to ensure reproducibility of the research. As we are not data custodians, we are not permitted to pass the data to third parties under the terms of the access agreement. Any applications to access the data would have to be submitted directly to the data custodian.

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Figure and table legends

Figure 1 – **Definition of cohort for analysis**

Table 1 – Maternal and neonatal characteristics of patients delivered by elective and emergency caesarean section in relation to anaesthetic type. Data are no. (%) or median (IQR). [a]The degree of social deprivation was categorised using deciles according to the Scottish Index of Multiple Deprivation (SIMD) with deciles of 1 (most deprived) to 10 (least deprived).

Table 2 – Unadjusted crude event rates for all outcomes in relation to anaesthetic type and urgency of caesarean section. *Data are N (%) or median (range). §Days in hospital are counts of full days. Hospital stays are counted as 0 if less than 24 hours duration

Table 3 –Adjusted relative risks for outcomes in relation to anaesthetic type and urgency of caesarean section referent to spinal anaesthesia (RR = 1). Results are adjusted for maternal age, maternal weight, SIMD decile, ethnicity, smoking history, illicit drug use, induction of labour (in emergency cases), parity, previous CS, previous spontaneous or therapeutic abortion, pre-eclampsia, gestational age, birthweight, and sex of neonate

Figure 2 –Adjusted absolute risks + 95% CI for neonatal outcomes after birth and childhood development outcomes at 3 years in relation to anaesthetic type and urgency of caesarean section
(A) neonatal resuscitation, (B) Apgar score < 7 at 5 minutes, (C) admission to neonatal unit, (D) childhood development assessment - any concern**.** Emergency caesarean section is denoted in black and elective CS in grey. Results are adjusted for; maternal age, maternal weight, SIMD decile, ethnicity, smoking history, illicit drug use, induction of labour (in emergency cases), parity, previous CS, previous spontaneous or therapeutic abortion, pre-eclampsia, gestational age, birthweight, and sex of neonate.

Figure 3 –Time-varying absolute risks + 95% CI (ribbon) for each outcome in relation to gestation in weeks for each anaesthetic type in emergency caesarean section.
(A) neonatal resuscitation, (B) Apgar score < 7 at 5 minutes, (C) Neonatal unit admission, (D) childhood development assessment - any concern. Results are adjusted for; maternal age, maternal weight, SIMD decile,

ethnicity, smoking history, illicit drug use, induction of labour (in emergency cases), parity, previous CS, previous spontaneous or therapeutic abortion, pre-eclampsia, gestational age, birthweight, and sex of neonate

Figure 1 – Definition of cohort for analysis

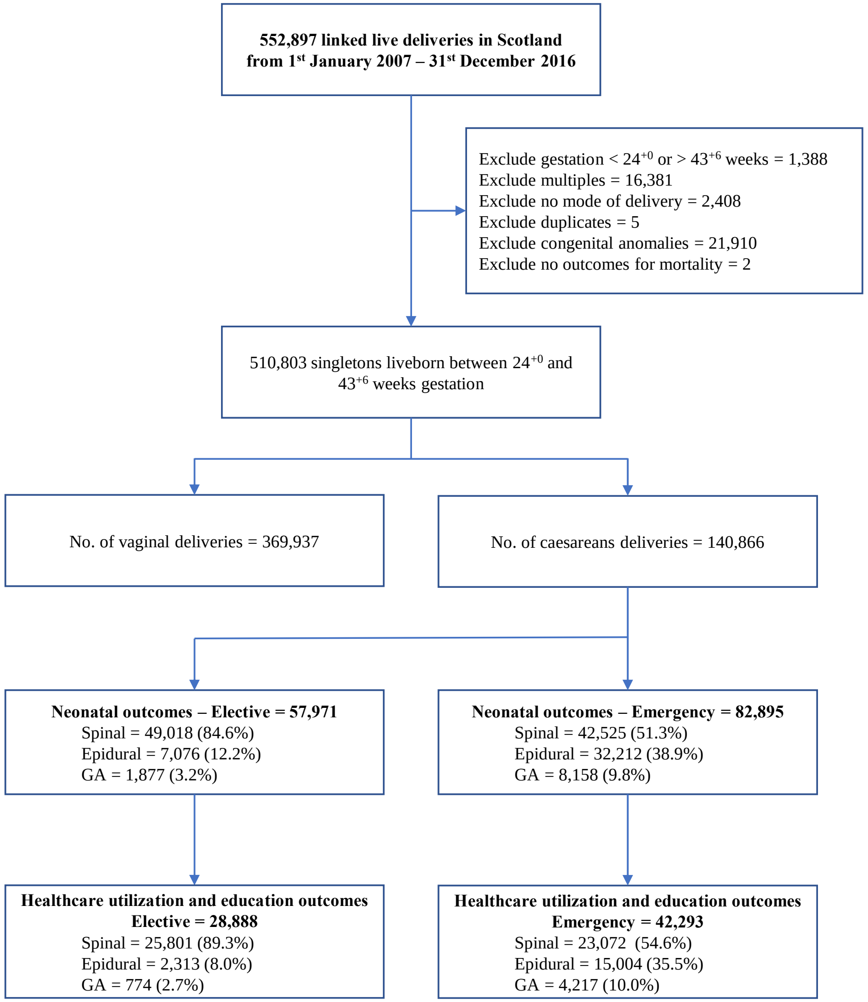

Table 1 – Maternal and neonatal characteristics of patients delivered by elective and emergency caesarean section in relation to anaesthetic type.

Total (n = 140,866)	Elective n = 57,971			Emergency n = 82,895		
	Spinal	Epidural	GA	Spinal	Epidural	GA
Anaesthetic type, n (%)	49018 (84.6)	7076 (12.2)	1877 (3.2)	42525 (51.3)	32212 (38.9)	8158 (9.8)
Age of mother, median (IQR)	32 (28–36)	32 (28–36)	32 (28–36)	30 (26–34)	30 (26–34)	29 (24–34)
Weight of mother, median (IQR)	71 (62–84)	70 (61–83)	72 (62–87)	70 (61–83)	69 (60–82)	68 (60–82)
Height of mother, median (IQR)	163 (159–168)	163 (159–168)	163 (159–168)	163 (159–168)	163 (158–167)	163 (158–167)
Ethnic group, n (%)						
Asian	1906 (3.9)	323 (4.6)	110 (5.9)	2050 (4.8)	1794 (5.6)	408 (5.0)
Black	949 (1.9)	143 (2.0)	45 (2.4)	1003 (2.4)	735 (2.3)	182 (2.2)
Mixed	254 (0.5)	36 (0.5)	15 (0.8)	211 (0.5)	142 (0.4)	24 (0.3)
Other	393 (0.8)	51 (0.7)	16 (0.9)	401 (0.9)	286 (0.9)	61 (0.7)
White	45516 (92.9)	6523 (92.2)	1691 (90.1)	38860 (91.4)	29255 (90.8)	7483 (91.7)
SIMD decile[a], n (%)						
1	6050 (12.3)	847 (12.0)	261 (13.9)	5878 (13.8)	4117 (12.8)	1270 (15.6)
2	5334 (10.9)	635 (9.0)	221 (11.8)	5231 (12.3)	3690 (11.5)	1119 (13.7)
3	5049 (10.3)	568 (8.0)	171 (9.1)	4739 (11.1)	3390 (10.5)	1000 (12.3)
4	4867 (9.9)	580 (8.2)	195 (10.4)	4562 (10.7)	3190 (9.9)	875 (10.7)
5	4742 (9.7)	588 (8.3)	151 (8.0)	4374 (10.3)	3008 (9.3)	783 (9.6)
6	4643 (9.5)	651 (9.2)	172 (9.2)	3999 (9.4)	2877 (8.9)	699 (8.6)
7	4623 (9.4)	609 (8.6)	150 (8.0)	3780 (8.9)	2925 (9.1)	617 (7.6)
8	4676 (9.5)	873 (12.3)	172 (9.2)	3693 (8.7)	3214 (10.0)	628 (7.7)
9	4739 (9.7)	878 (12.4)	149 (7.9)	3409 (8.0)	3019 (9.4)	625 (7.7)
10	4295 (8.8)	847 (12.0)	235 (12.5)	2860 (6.7)	2782 (8.6)	542 (6.6)
Smoker during pregnancy, n (%)						
Current	7003 (14.3)	1036 (14.6)	314 (16.7)	7395 (17.4)	4785 (14.9)	1979 (24.3)
Former	5931 (12.1)	607 (8.6)	187 (10.0)	5597 (13.2)	4660 (14.5)	1062 (13.0)
Never	36084 (73.6)	5433 (76.8)	1376 (73.3)	29533 (69.4)	22767 (70.7)	5117 (62.7)

Injected illicit drugs – YES, n (%)	403 (0.8)	61 (0.9)	52 (2.8)	479 (1.1)	231 (0.7)	161 (2.0)
Spontaneous abortion ≥ 1, n (%)	13885 (28.3)	2064 (29.2)	524 (27.9)	10267 (24.1)	6974 (21.7)	1990 (24.4)
Therapeutic abortion ≥ 1, n (%)	3846 (7.8)	676 (9.6)	167 (8.9)	3275 (7.7)	2601 (8.1)	709 (8.7)
Parity, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0 (0–1)	0 (0–1)	0 (0–1)
Previous CS, median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
Induction, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	14194 (33.4)	15008 (46.6)	2532 (31.0)
Estimated gestation, n (%)	39 (38–39)	39 (38–39)	39 (38–39)	39 (37–40)	40 (39–41)	39 (36–40)
Premature (< 37 weeks) , n (%)	0 (0.0)	0 (0.0)	0 (0.0)	8557 (20.1)	1879 (5.8)	2056 (25.2)
Birthweight, median (IQR)	3490 (3180–3810)	3490 (3180–3810)	3410 (3100–3742)	3360 (2842–3780)	3600 (3230–3950)	3210 (2620–3670)
Male sex, n (%)	24502 (50.0)	3489 (49.3)	945 (50.3)	22829 (53.7)	17921 (55.6)	4552 (55.8)
Pre–eclampsia, n (%)	198 (0.4)	28 (0.4)	18 (1.0)	1526 (3.6)	883 (2.7)	396 (4.9)

a: the degree of social deprivation was categorised using deciles according to the Scottish Index of Multiple Deprivation (SIMD) with deciles of 1 (most deprived) to 10 (least deprived)

Table 2 – Unadjusted crude event rates for all outcomes in relation to anaesthetic type and urgency of caesarean section.

	Elective				Emergency			
	No. of events, all anaesthesia types (n=57,971)	Spinal (n=49,018)	Epidural (n=7,076)	GA (n=1,877)	No. of events, all anaesthesia types (n=82,895)	Spinal (n=42,525)	Epidural (32,212)	GA (n=8,158)
Neonatal resuscitation, n (%)	1391 (2.4)	952 (1.9)	134 (1.9)	305 (16.2)	11414 (13.8)	5226 (12.3)	3564 (11.1)	2624 (32.2)
Apgar score < 7 at 5 mins, n (%)	305 (0.5)	194 (0.4)	25 (0.4)	86 (4.6)	2889 (3.5)	1181 (2.8)	681 (2.1)	1027 (12.6)
Admitted to neonatal unit, n (%)	2895 (5.0)	2423 (4.9)	311 (4.4)	161 (8.6)	14409 (17.4)	8464 (19.9)	3367 (10.5)	2578 (31.6)

Long term outcomes

	No. of events, all anaesthesia types (n=28,888)	Spinal (n=25,801)	Epidural (n=2,313)	GA (n=774)	No. of events, all anaesthesia types (n=42,293)	Spinal (n=23,072)	Epidural (15,004)	GA (n=4,217)
Days in hospital [a,b]	–	0 (0–0)	0 (0–0)	0 (0–0)	–	0 (0–0)	0 (0–0)	0 (0–0)
No of unique conditions [a]	–	0 (0–1)	0 (0–1)	0 (0–1)	–	0 (0–1)	0 (0–1)	0 (0–1)
Gross motor concern, n (%)	616 (2.1)	539 (2.1)	53 (2.3)	24 (3.1)	1135 (2.7)	684 (3.0)	274 (1.8)	177 (4.2)
Fine motor concern, n (%)	645 (2.2)	552 (2.1)	61 (2.6)	32 (4.1)	1247 (2.9)	716 (3.1)	343 (2.3)	188 (4.5)
Communication concern, n (%)	3867 (13.4)	3406 (13.2)	328 (14.2)	133 (17.2)	6003 (14.2)	3369 (14.6)	1868 (12.5)	766 (18.2)
Social concern, n (%)	1234 (4.3)	1087 (4.2)	104 (4.5)	43 (5.6)	2133 (5.0)	1208 (5.2)	643 (4.3)	282 (6.7)
Any concern noted, n (%)	4426 (15.3)	3909 (15.2)	367 (15.9)	150 (19.4)	6962 (16.5)	3917 (17.0)	2158 (14.4)	887 (21.0)

a: median (range)
b: Days in hospital are counts of full days. Hospital stays are counted as 0 if less than 24 hours duration

Table 3 – Adjusted relative risks for outcomes in relation to anaesthetic type and urgency of caesarean section referent to spinal anaesthesia (RR = 1). Results are adjusted for maternal age, maternal weight, SIMD decile, ethnicity, smoking history, illicit drug use, induction of labour (in emergency cases), parity, previous CS, previous spontaneous or therapeutic abortion, pre-eclampsia, gestational age, birthweight, and sex of neonate.

	Adjusted Relative Risk (95% CI)			
	Elective		Emergency	
	Epidural vs spinal	GA vs spinal	Epidural vs spinal	GA vs spinal
Neonatal resuscitation	0.96 (0.79, 1.17)	8.20 (7.20, 9.33)	1.04 (1.00, 1.09)	2.40 (2.30, 2.50)
Apgar Score < 7 at 5-mins	0.83 (0.53, 1.30)	11.44 (8.88, 14.75)	0.96 (0.87, 1.06)	3.87 (3.56, 4.20)
Neonatal unit admission	0.87 (0.77, 0.98)	1.65 (1.40, 1.94)	0.81 (0.78, 0.84)	1.20 (1.15, 1.25)
Long term outcomes				
Days in hospital[a]	0.96 (0.76, 1.23)	2.65 (1.01, 6.95)	1.13 (0.97, 1.32)	1.00 (0.84, 1.18)
No of conditions	0.91 (0.84, 0.99)	1.06 (0.92, 1.23)	0.96 (0.92, 1.00)	0.99 (0.93, 1.05)
Gross motor	1.13 (0.84, 1.51)	1.44 (0.94, 2.22)	0.87 (0.75, 1.01)	1.13 (0.95, 1.34)
Fine motor	1.17 (0.86, 1.59)	1.57 (1.07, 2.29)	0.97 (0.84, 1.12)	1.15 (0.97, 1.37)
Communication	1.07 (0.95, 1.20)	1.17 (0.98, 1.40)	0.96 (0.90, 1.02)	1.08 (1.00, 1.17)
Social	1.02 (0.82, 1.26)	1.24 (0.90, 1.70)	0.96 (0.87, 1.07)	1.08 (0.95, 1.24)
Any concern noted	1.04 (0.94, 1.15)	1.15 (0.99, 1.34)	0.96 (0.91, 1.01)	1.08 (1.01, 1.16)

Abbreviations: CI, 95% confidence intervals;
a: see Figure S4 and Table S1.

Figure 2 –Adjusted absolute risks + 95% CI for neonatal outcomes after birth and childhood development outcomes at 3 years in relation to anaesthetic type and urgency of caesarean section.

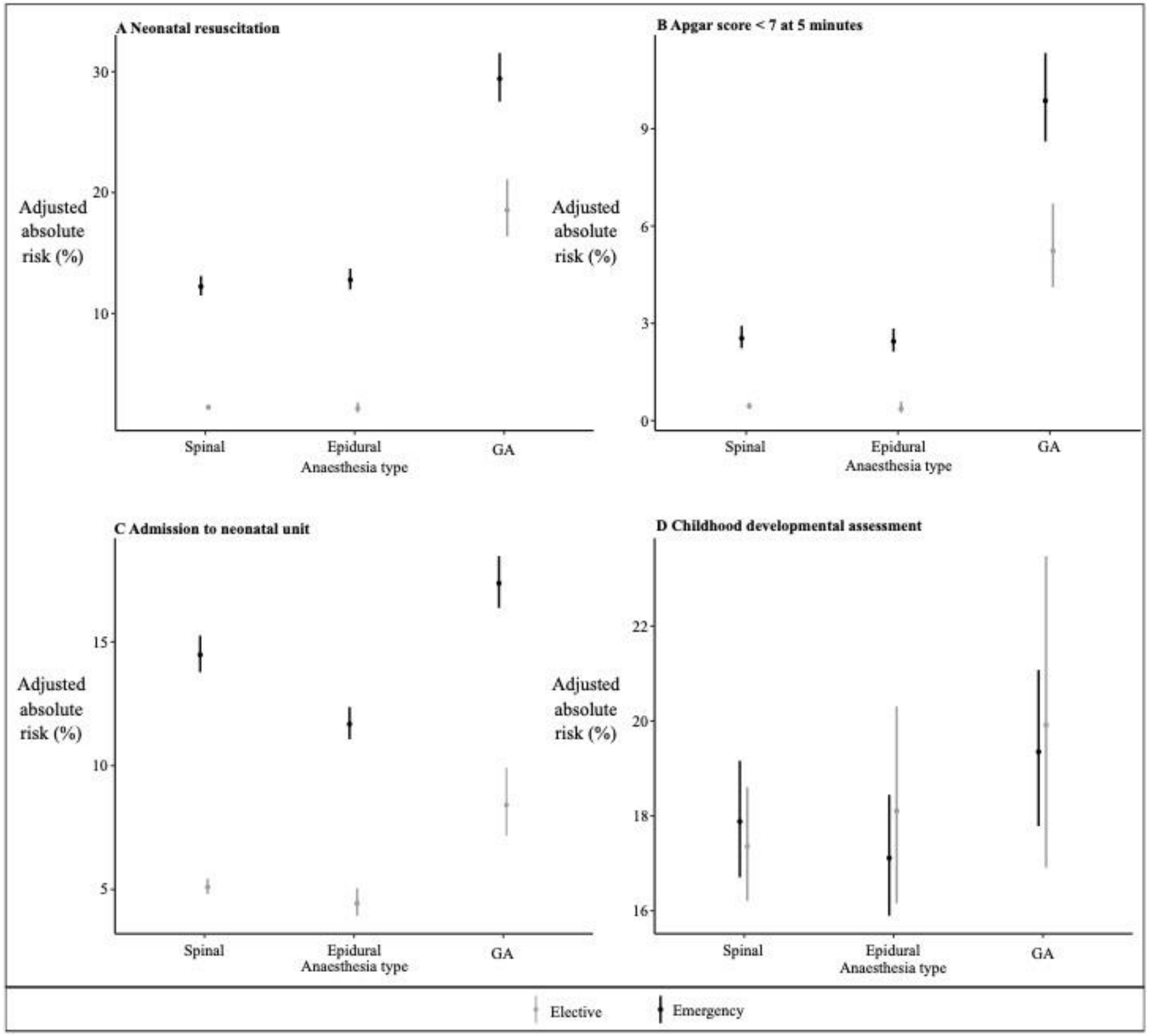

Figure 3 –Time-varying absolute risks + 95% CI (ribbon) for each outcome in relation to gestation in weeks for each anaesthetic type in emergency caesarean section.