Obstetric anaesthesia and socio-economic disparity

Thesis by

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Abstract

Obstetric anaesthesia is one of the largest subspecialties of anaesthesia. Anaesthetists participate in over 60% of births in the UK, and this number is continuing to rise. Obstetric anaesthesia is concerned with the management of pain in labour, and of anaesthesia for caesarean birth, as well as the management of high-risk patients. Women of low socioeconomic position are at a higher risk during childbirth than the general population. They have higher rates of obesity and adverse health behaviours at baseline, and are at a greater risk of severe maternal morbidity and mortality. Maternity services in Scotland are run by the publicly funded National Health Service, which aims to provide equitable treatment that is free at the point of care.

A body of work on labour epidural analgesia and anaesthesia for caesarean birth is presented. The first part is concerned with labour epidural analgesia. A narrative review is undertaken in which all of current research relating to labour epidural analgesia is summarised. This is followed by a network meta-analysis of ultra-low, low and high concentration local anaesthetics for labour epidural analgesia. This demonstrated that ultra-low concentrations of local anaesthetic (<0.08% bupivacaine or equivalent) are associated with at least as good outcomes as low concentration local anaesthetics and may be associated with some improved outcomes, including reduced overall local anaesthetic consumption and reduced incidence of motor block, whilst maintaining analgesic efficacy. A survey into current epidural practice in Scotland is then presented. This demonstrates that within Scotland there is considerable variability in labour epidural analgesia initiation and management, including choice of local anaesthetic, drug delivery systems and initial management of low block.

The final two chapters are concerned with socio-economic position and how it is associated with the provision of obstetric anaesthesia in Scotland's National Health Service (NHS Scotland). Firstly I demonstrate that low socio-economic position is associated with reduced utilisation of labour epidural analgesia, and this disparity persists even in women who are identified as having a medical condition for which labour epidural analgesia is recommended. These results were similar in sensitivity

analyses of primiparous women, and of women giving birth in one Scottish city with 24-hour uniform access to obstetric and anaesthetic care. The relationship is compounded in women of non-white ethnicity. In contrast I found that low socio-economic position is associated with an increased utilisation of general anaesthesia for caesarean birth. To explore the robustness of these findings, I undertook a number of sensitivity analyses to investigate the observed discrepancy. These included, (1) the exclusion of women with relative contraindications to utilisation of neuraxial analgesia, (2) excluding women with previous caesarean birth, and (3) only include women delivering babies at term. The results of all of these sensitivity analyses were consistent with the main analysis, that low socio-economic position is associated with greater use of general anaesthesia at caesarean birth.

The aim of this body of work is to identify best possible practice in obstetric anaesthesia. This is achieved through a combination of narrative review, meta-analysis, survey and two population level analyses. I take advantage of the exponential growth in computational processing power of the last few years, by using specialised statistical computing software to analyse vast quantities of data relevant to obstetric anaesthesia and create graphics to communicate the results. These studies highlight areas for improvement to minimise harm and maximise benefits for all women in Scotland, and in particular those of low socio-economic position who are at a higher risk of adverse events during labour and delivery.

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Publications

1. Halliday L, Nelson SM, Kearns RJ. **Epidural analgesia in labor: A narrative review.** *International Journal of Gynaecology and Obstetrics* 2022; **159(2):** 356-364. doi: 10.1002/ijgo.14175.

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i. Dennis AT, Sheridan N. **Extreme inequity in analgesia and peri-operative management of pregnant patients**. Anaesthesia; 2024. doi:10.1111/anae.16237.

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Presentations

Comparison of ultra-low, low and high concentration local anaesthetic for labour epidural analgesia: March 2021
School of Medicine, Dentistry and Nursing Postgraduate Research Day

Comparison of ultra-low, low and high concentration local anaesthetic for labour epidural analgesia – April 2022
Gynaecological Visiting Society annual meeting

Socioeconomic deprivation and epidural analgesia – April 2022
Scottish Society of Anaesthetists **(1st prize oral presentation)**

Survey of current epidural practice in Scotland – May 2022
OAA annual meeting

LA limbo: How low should we go? - November 2022
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Socioeconomic disadvantage and uptake of epidural labour analgesia – March 2023
The Future of Reproductive Health

Socioeconomic disadvantage and uptake of epidural labour analgesia – May 2023
Obstetric Anaesthetists' Association annual meeting

Socioeconomic disparity in anaesthesia for caesarean birth – May 2023
OAA annual meeting
Poster category prize

Socioeconomic disadvantage and uptake of epidural labour analgesia – May 2023
St Mungo symposium

Socioeconomic disparity in anaesthesia for caesarean birth – May 2023
Obstetric Anaesthetists' Association annual meeting **(1st prize oral presentation)**

Prizes

1. **First year research prize, 2021**
   "Comparison of ultra-low, low and high concentration local anaesthetic for labour epidural analgesia"
   University of Glasgow: School of Medicine, Dentistry and Nursing Postgraduate Research Day

2. **1st prize: Scottish Society of Anaesthetists Spring meeting – May 2022**
   "Socioeconomic deprivation and epidural analgesia"
   Scottish Society of Anaesthetists Annual Meeting

3. **Poster Prize: St Mungo symposium, May 2023**
   "Socioeconomic disadvantage and uptake of epidural labour analgesia"
   St Mungo symposium, University of Glasgow

4. **Poster category prize: Obstetric Anaesthetists' association, May 2023**
   "Socioeconomic disparity in anaesthesia for caesarean birth"
   Obstetric Anaesthetists' Association, Annual meeting

5. **Felicity Reynolds Oral Presentation Prize 2023**
   "*Socioeconomic disadvantage and uptake of epidural labour analgesia*"
   Obstetric Anaesthetists' Association, Annual meeting

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Author's Declaration

The work described in this thesis was carried out by me while employed as a Clinical Research Fellow in the department of Anaesthesia, Pain and Critical Care Medicine at the University of Glasgow, and as a Speciality Registrar in the West of Scotland School of Anaesthesia training scheme. This work was carried out between August 2020 and January 2024.

The eDRIS team of Public Health Scotland provided and linked the routinely collected healthcare data used in chapters 6 and 7 of this thesis. Analysis was carried out using their secure analytical platform within the National Safe Haven. Permissions for this use was obtained by Professor Scott Nelson.

Dr Martin Shaw and Dr Aizhan Kyzayeva carried out the imputation for the datasets in Chapters 6 and 7.

The remained of the work was carried out by myself. The writing of this thesis was entirely my own work.

Definitions/Abbreviations

aOR	Adjusted Odds Ratio
AR	Absolute Risk
ARM	Artificial Rupture of Membranes
AVB	Assisted Vaginal Birth
BARG	Bayesian Analysis Reporting Guidelines
BMI	Body Mass Index
Bulk-ESS	Bulk Effective Sample Size
CadjRR	Confounder Adjusted Relative Risk
CSA	Continuous Spinal Analgesia
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CI-PCEA	Computer Integrated Patient-Controlled Epidural Analgesia
COMET	Comparative Obstetric Mobile Epidural Trial
CONSORT	Consolidated Standards of Reporting Trials
CrI	Credible Interval
CRAN	Comprehensive R Archive Network
CSE	Combined Spinal Epidural
DAG	Directed Acyclic Graph
DHARMa	Residual Diagnostics for HierArchical Regression Models
DIC	Disseminated Intravascular Coagulation
DPE	Dural Puncture Epidural
eDRIS	Electronic Data Research and Innovation Service
FMU	Freestanding Midwifery Unit
GA	General anaesthesia
HC	High concentration

ICD-9	International Classification of Disease 9th edition
ICD-10	International Classification of Disease 10th edition
IMD	Index of Multiple Deprivation
LA	Local Anaesthetic
LC	Low concentration
MAP	*Maximum a Posteriori*
MAR	Missing At Random (data)
MBRRACE-UK	Mother and Babies: Reducing Risk through audits and confidential enquiries across the UK
MCAR	Missing Completely At Random (data)
µg	Microgram
MCMC	Markov Chain Monte Carlo
MD	Mean Difference
MeSH	Medical Subject Headings
mg	Milligram
MICE	Multiple Imputation with Chained Equations
ml	Millilitre
MLAC	Minimum Local Analgesic Concentration
MNAR	Missing Not At Random (data)
NAP-7	National Audit Project 7
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NMA	Network Meta-Analysis
OAA	Obstetric Anaesthetists' Association
OR	Odds Ratio

OU	Obstetric Unit
PCA	Patient-Controlled Analgesia
PCEA	Patient-Controlled Epidural Analgesia
PIEB	Programmed Intermittent Epidural Bolus
PMSS	Pregnancy Mortality Surveillance System
PPH	Post-Partum Haemorrhage
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PTSD	Post-Traumatic Stress Disorder
QQ	Quantile-Quantile
RCOA	Royal College of Anaesthetists
RCT	Randomised Controlled Trial
ROB-2	Risk Of Bias 2
RR	Relative Risk
SAS	Staff and Associate Specialist
SEP	Socio-economic Position
SIMD	Scottish Index of Multiple Deprivation
SMR01	Scottish Morbidity Record-01
SMR02	Scottish Morbidity Record-02
SSIDS	Scottish Stillbirth Infant Death Survey
ST3+	Speciality Trainee year 3 or above
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVB	Spontaneous Vaginal Birth
UK	United Kingdom
ULC	Ultra-low concentration
USA	United States of America

VAS	Visual Analogue Score
WHO	World Health Organisation
WMA	Weighted Mean Average
WMD	Weighted Mean Difference

Chapter 1 Introduction

1.1 Anaesthetists in obstetric care

In the UK 82% of women experience childbirth by the end of their childbearing years.[1] Anaesthetists are involved in around 60% of deliveries in the United Kingdom,[2] providing analgesia for labour and anaesthesia for birth. Epidural analgesia is now used by around 20% of labouring women in the United Kingdom[3] and over 70% in the United States of America.[4] Caesarean birth is the most commonly performed operation worldwide, and rates are increasing at a rate of 4% per year.

However, stark differences between countries are observed in the provision of obstetric care. Epidural rates vary between 10% and 90% depending on healthcare setting,[4,5] and worldwide, caesarean birth rates vary from 5% in sub-Saharan Africa to 42.8% in Latin America and the Caribbean.[6] In Scotland rates of spontaneous vaginal birth have been declining, with caesarean birth rates rising to 35% of all births in 2019/2020.[7] Despite its ubiquity, there are no international consensus guidelines for the management of epidural analgesia for labour or anaesthesia for birth. Within the UK, a country with a publicly funded National Health Service, no consensus guidelines exist.

Rates of high-risk pregnancies are increasing. As the age at which women give birth continues to rise, and as obesity and chronic diseases such as hypertension and diabetes are increasingly prevalent,[8] the challenges inherent in delivering safe and effective obstetric anaesthetic care continue to develop. Furthermore, advances in modern medicine and obstetric care mean that women with serious comorbidities who previously may have been unlikely to survive childbirth, such as those with severe congenital health disease, are able to become pregnant and give birth to a child. Maternal death is a rare event. In the most recent update from the Mothers and Babies Reducing Risk through Audit and Confidential Enquiries across the UK (MBRRACE-UK), the incidence of maternal mortality in the period 2020-2022 was 13.41 per 100,000 maternities (95% CI 11.86-15.10), a significant increase compared with the previous triennium (2017-2019) (8.79 per 100,000 maternities (95% CI 7.58-10.12)).[9,10] Severe maternal morbidity occurs at

a rate of around 100 times that of maternal mortality, is increasing in incidence, and can be considered a “near miss event”.[11]

Childbirth is a personal experience. All women have a birth plan, whether it is formalised with professional input, informed by personal experiences, or via unconscious biases. These plans may be shaped by societal norms as well as personal knowledge and experience. Birth trauma has been reported to affect over a third of UK women.[12] Both pain control and a woman’s sense of control during childbirth are key features in overall birth satisfaction.[13,14] Despite being the gold standard for pain relief and maternal satisfaction in labour, there is a taboo around utilisation of labour epidural analgesia, often fuelled by mistrust or unsupported misconceptions about safety.[15] As well as providing analgesia, in certain situations, labour epidural analgesia may even be recommended for maternal safety.[16-18] Unnecessary general anaesthesia for caesarean birth is associated with an increased risk of adverse maternal and neonatal outcomes.[19,20] However, women may elect to have a general anaesthetic for a caesarean birth, over neuraxial blockade. Anaesthetists have a role in counselling women as to the risks and benefits of these interventions.

1.2 Socio-economic position and obstetric anaesthetic care

The World Health Organization defines a disparity as a difference in care or outcome that is not only unnecessary and unavoidable but also unfair and unjust.[21] Healthcare (including maternity services) in the United Kingdom is provided by the National Health Service (NHS). It is publicly funded and aims to provide equitable treatment which is free at the point of care. The Mother and Babies: Reducing Risk through audits and confidential enquiries across the UK (MBRRACE-UK) reports maternal deaths in the UK and sets research priorities. These reports highlight that within our publicly funded healthcare system, serious maternal morbidity and mortality disproportionately affect women from a less advantaged socio-economic position.[9] This risk may be mediated through classical risk factors, such as obesity, smoking, illicit drug use and co-morbidities, known to be associated with low socio-economic position.[22] However there is evidence of discrepancies within their obstetric care, including reduced utilisation of prenatal care, and increased incidence of induction of labour.[7,23]

In the past few years, evidence of racial disparities in the provision of obstetric care has become apparent. Women of black ethnicity are four times more likely to die in childbirth compared to white women in the UK.[9] Research in the USA and the UK has demonstrated that women from racial minority groups have a lower utilisation of labour epidural analgesia,[24,25] and a higher utilisation of GA for caesarean birth, although the reasons behind this are unclear.[25]

In Scotland there are high levels of socio-economic inequality. Women living in areas of high socio-economic disadvantage experience 22 fewer years of good health compared to those who reside in the areas of least socio-economic disadvantage.[26] There is currently no research into the relationship between socio-economic inequality and the provision of obstetric anaesthesia in Scotland. Whilst the classical risk factors mentioned above undoubtedly play a role in the relationship between socio-economic disparity and severe maternal morbidity, they do not account for the whole picture. This has been highlighted as an important area for obstetric research both in the UK[9] and abroad.[27,28]

1.3 Data in healthcare research

The National Health Service (NHS) Scotland routinely collect healthcare and administrative data. The primary purpose for electronic health records is for medical billing, but this resource can also provide a resource for researchers to undertake secondary data analysis. Retrospective cohort studies can be hugely beneficial as they allow us to study entire populations, have real world applicability, and can answer questions that other study designs such as randomised controlled trials (RCT) are not able to. Randomised controlled trials are not useful when researching very rare outcomes, and in certain situation they may be unethical, such as randomly assigning whether a parturient receives an epidural in labour or not. Furthermore, very large samples sizes may offer the statistical power to study sub-populations, such as socio-economic position by strata. Retrospective cohort studies may indicate associations, but they do not prove causation.

Registry based analyses are retrospective and are limited to the available data. Prior to carrying out data analysis, there are a number of tasks to assess the quality of the data, and engineer it into a useable format. If data analysis is carried out without these steps, the analysis is unreliable and incorrect conclusions may be drawn. Coding errors, missing data and duplicate entries are possible sources of potential error. Whole population studies avoid the problem of selection bias, but the data must be assessed to avoid other biases that may affect output, and influence data-driven decision making. Measured and unmeasured confounding must be carefully considered to avoid introducing bias.

1.4 Aims of this thesis

The role of the anaesthetist in obstetric care is expanding. Alongside increasing rates of obesity and co-morbidities, women are choosing to give birth later, all of which contribute to an increased risk of serious maternal or neonatal adverse events. Women from less advantaged socio-economic positions are disproportionately affected. In this thesis, a mixture of surveys, meta-analysis and retrospective analysis of whole population routinely collected healthcare data will be used to: identify the most up to date research in labour epidural techniques; characterise current epidural practice in Scotland; investigate the use of ultra-low concentration local anaesthetic for labour epidural, with the aim of minimising side effects while preserving analgesic efficacy; and explore the associations of socio-economic position with both the utilisation of labour epidural analgesia, and the use of general anaesthesia for caesarean birth.

Chapter 2 Evidence to date: Epidural analgesia in labour

2.1 Introduction

Childbirth is one of the most painful events a woman will ever experience.[29] In the first stage of labour, uterine contractions and cervical dilatation stimulate nociceptive afferent fibres that travel to spinal nerves T10-L1 and produce a poorly localised visceral pain. In the second stage of labour, the fetal head descends. This results in stretching of the perineum and vagina, which stimulates pain fibres via the pudendal nerve that travel to the spinal roots S2-4.[30] These afferent pathways may be modified to achieve analgesia, by the administration of local anaesthetics, opioids, and other adjuvant agents into the epidural space via an epidural catheter. These agents act locally on the spinal nerves, but they may also be absorbed systemically and they may cross the placenta.[31]

The use of epidural analgesia in labour is common worldwide, but the prevalence varies greatly from country to country. In a recent study of 14 high income countries, prevalence was estimated between 10 – 64%.[4] Despite widespread use, there is not a worldwide consensus regarding the optimal epidural regime. The use of epidural analgesia is not without side effects. There are associations between the use of epidural analgesia and adverse events including reduced mobility, pruritis, hypotension, maternal fever and fetal heart rate abnormalities. Epidurals are also associated with, but probably do not cause, prolonged labour and increased rates of assisted vaginal birth.[32-34] Different combinations, concentrations and methods of administration of epidural medications are associated with varying effects. The requirement for adequate pain relief must be balanced with the avoidance of adverse effects. In addition, there are certain conditions in which the insertion of an epidural catheter may be relatively contraindicated; these include coagulopathy, severe thrombocytopenia and maternal sepsis.

There are many confounders to research into this area. Association is not the same as causation. Women with long painful labour are more likely to request an epidural. Epidural use is advised for medical reasons in high-risk patients, such

as those with pre-eclampsia, obesity and cardiac disease, as these conditions may otherwise be decompensated by the increased demands of childbirth.[35,36] For retrospective studies this creates an intrinsic selection bias. It is difficult to blind randomised controlled trials (RCT) and there are ethical issues surrounding consent and recruitment during labour. This chapter provides a narrative review of epidural literature, incorporating techniques of insertion, medications used, and associations with maternal and neonatal outcomes.

2.2 Epidural anatomy and insertion techniques

The epidural space is a potential space that lies between the ligamentum flavum and the dura mater, containing fat, blood vessels and spinal nerve roots (Figure 2.1).[37] In most adults the spinal cord ends around L1/L2 and becomes a loose bundle of intradural nerves – the cauda equina. Labour epidurals are sited below the level of the spinal cord to minimise risk of nerve injury.

There are three techniques described for initiating labour epidural analgesia; conventional lumbar epidural, combined spinal epidural (CSE) and dural puncture epidural (DPE).[38,39]

2.2.1 Conventional lumbar epidural

The conventional labour epidural is most commonly inserted using a hollow Tuohy needle and 'loss of resistance technique' (Figure 1a). The Tuohy needle is inserted into the interspinous ligaments. A low resistance syringe containing a column of saline or air is then attached to the Tuohy needle and pressure is applied to this syringe as the needle is slowly advanced. As the needle exits the ligamentum flavum, there is a sudden loss of resistance which identifies the epidural space. Once the epidural space is identified, a thin plastic catheter is threaded through the hollow Tuohy needle to lie 3-5cm within the epidural space, and the needle is removed. The tip of the epidural catheter lies near to the T10-L1 nerve roots, thus it provides excellent coverage for the first stage of labour. Pain from the second stage of labour is mediated via the sacral nerve roots, which lie further away from the epidural catheter. Second stage analgesia may therefore be less effective.[30] After insertion, safety checks should be performed such as negative aspiration with a syringe, and a 'falling meniscus' within the catheter. An initial "test dose" of local anaesthetic solution may be given. Following administration of a bolus of anaesthetic down the epidural catheter, observations should be performed every 5-minutes over a 30-minute period[40] to assess for catheter misplacement. The identification of the epidural space may be technically challenging, and even when catheters are inserted without difficulty, unilateral blocks and missed segments can result in inadequate analgesia, affecting up to one in eight women.[41]

2.2.1.1 Test dose

The use of a test dose of local anaesthetic or another agent in labour epidural has been controversial.[42,43] The purpose of a test dose is to assess for inadvertent intravascular placement (with signs of local anaesthetic toxicity) or intrathecal placement (with effects more in keeping with spinal anaesthesia), but it should not delay epidural analgesia or increase risk of complications. Rates of initial vascular cannulation have been reported as 6%[44], and rates of inadvertent intrathecal canulation 0.1-0.3%.[45-47] The use of a test dose does not eliminate the risk of intrathecal or intravenous catheter migration.[48,49]

There is no evidence that the use of test dose increases safety.[42] Safety checks such as catheter aspiration have a high sensitivity, and the risk of an intrathecal catheter following a negative aspiration has been reported between 1 in 1750 and 1 in 26,490.[50-52] The use of concentrated local anaesthetics may increase risk of motor blockade, and carry the risk of high spinal with associated risks to mother and fetus. The use of low concentration local anaesthetics may not achieve adequate effects to identify catheter misplacement, thus may produce false confidence and delay the onset of analgesia for the labouring parturient. For detection of motor blockade, a dose of 5.8mg levobupivacaine, 5.9mg bupivacaine, 8.3mg ropivacaine and 16mg lidocaine is adequate to detect 95% of intrathecal catheters.[53,54] Risk of a high spinal in negligible below 15mg bupivacaine and 45mg lidocaine.[45,55] The use of adrenaline to detect intravascular placement in obstetrics may not be appropriate due to alteration in haemodynamic parameters, altered autonomic nervous system response and decreased placental blood supply.[56] In the Seventh Nation Audit Project (NAP-7), the Royal College of Anaesthetists (UK) recommend the use of a test dose of local anaesthetic in labour epidural not exceeding the equivalent of 10 mg bupivacaine (e.g. 10 ml 0.1% bupivacaine and 2 $\mu g.ml^{-1}$ fentanyl or equivalent local anaesthetic).[57]

2.2.2 Combined spinal epidural

In the combined spinal epidural or CSE technique, the epidural space is identified as described above, then the dura mater is intentionally punctured with a spinal needle. This may be done using a specially designed CSE kit. This

allows visualisation of the cerebrospinal fluid (CSF) and the administration of intrathecal drugs prior to threading the epidural catheter into the epidural space (Figure 1).[39] The potential advantages of CSE are rapid onset analgesia, improved sacral analgesia and a reduced risk of failure.

There are a number of disadvantages to using the CSE technique. Performing a CSE is more challenging technically than a conventional lumbar epidural and is associated with a higher incidence of permanent neurological complications (9.6/100,000 vs 6.1/100,000 for conventional lumbar epidural).[58] It has been suggested that the administration of local anaesthetic into the CSF may mask a poorly functioning epidural catheter, thus increasing the risk of failure of conversion from labour analgesia to operative anaesthesia for caesarean birth.[44,59,60] This has, however, been contested by a study which found that CSE insertion actually allowed for the earlier detection of inadequate epidural analgesia.[61] There are also potential disadvantages to the fetus. The rapid onset of analgesia by the insertion of a CSE may cause a rapid decline in maternal adrenaline levels, which may lead to uterine tachysystole and compensatory increased maternal vascular resistance. These collectively reduce fetal oxygenation levels.[62] A 2016 systematic review and meta-analysis which compared CSE with conventional lumbar epidural demonstrated a significantly increased risk of non-reassuring fetal heart rate (FHR) tracings with CSE (RR1.31, 95% CI 1.02-1.67).[62] However a Cochrane review (27 trials, 3274 parturients) detected no difference between the two techniques in neonatal outcomes, caesarean birth rate, or maternal satisfaction.[63] CSE remains a popular technique in many centres worldwide, however there is insufficient evidence to suggest that it should replace conventional lumbar epidural for analgesia in labour.[63]

2.2.3 Dural puncture epidural

Dural puncture epidural (DPE) is a novel technique described in the literature. Similarly to CSE, the epidural space is identified, and the dura intentionally punctured with a spinal needle, however after visualisation of CSF, no intrathecal drugs are injected. The spinal needle is removed and a catheter threaded into the epidural space (Figure 1). The dural puncture creates a small channel for drugs to pass into the intrathecal space although this effect is not

noted if the spinal needle diameter is below 25G.[38] DPE may confer some of the advantages of CSE whilst avoiding the side-effect profile of injecting intrathecal drugs but there are concerns about deliberate dural puncture and the increased risk of post-dural puncture headache.[38]

A systematic review comparing DPE with conventional lumbar epidural found no significant difference for rates of catheter replacement/manipulation, unilateral block, or inadvertent intravascular catheter placement.[38] Three of five studies (239 women) found that DPE was associated with better sacral coverage and shorter median time to analgesia, although two of these studies were from the same institution. Within this systematic review there were not enough data on post-dural puncture headache and FHR abnormalities to draw any meaningful conclusions.[38] A more recent systematic review (10 trials, 1099 parturients) looked at DPE compared to conventional lumbar epidural reported a quicker onset of analgesia, and a reduced number of PCEA dose required, however they reported significant heterogeneity for this result.[64] No increase in incidence of post dural puncture headache was detected.[64] An RCT of 140 patients found a reduced onset time of operative anaesthesia following epidural top up with chloroprocaine for elective caesarean birth in DPE as compared to conventional lumbar epidural (422 vs 655 seconds).[65] They also reported DPE was associated with reduced incidence of poor quality blockade, which they defined as failure to develop adequate anaesthesia, onset of anaesthesia >15 minutes or a requirement for supplemental analgesia intraoperatively (15.7% vs 36.3% reporting poor quality blockade in DPE-initiated and conventional lumbar epidural group, respectively).[65] An RCT of 141 parturients with obesity comparing DPE with conventional labour epidural did not find any clinical or statistical differences to support the use of DPE.[66] Dural puncture epidural is a novel technique, however evidence for its use and specific clinical indications are limited.

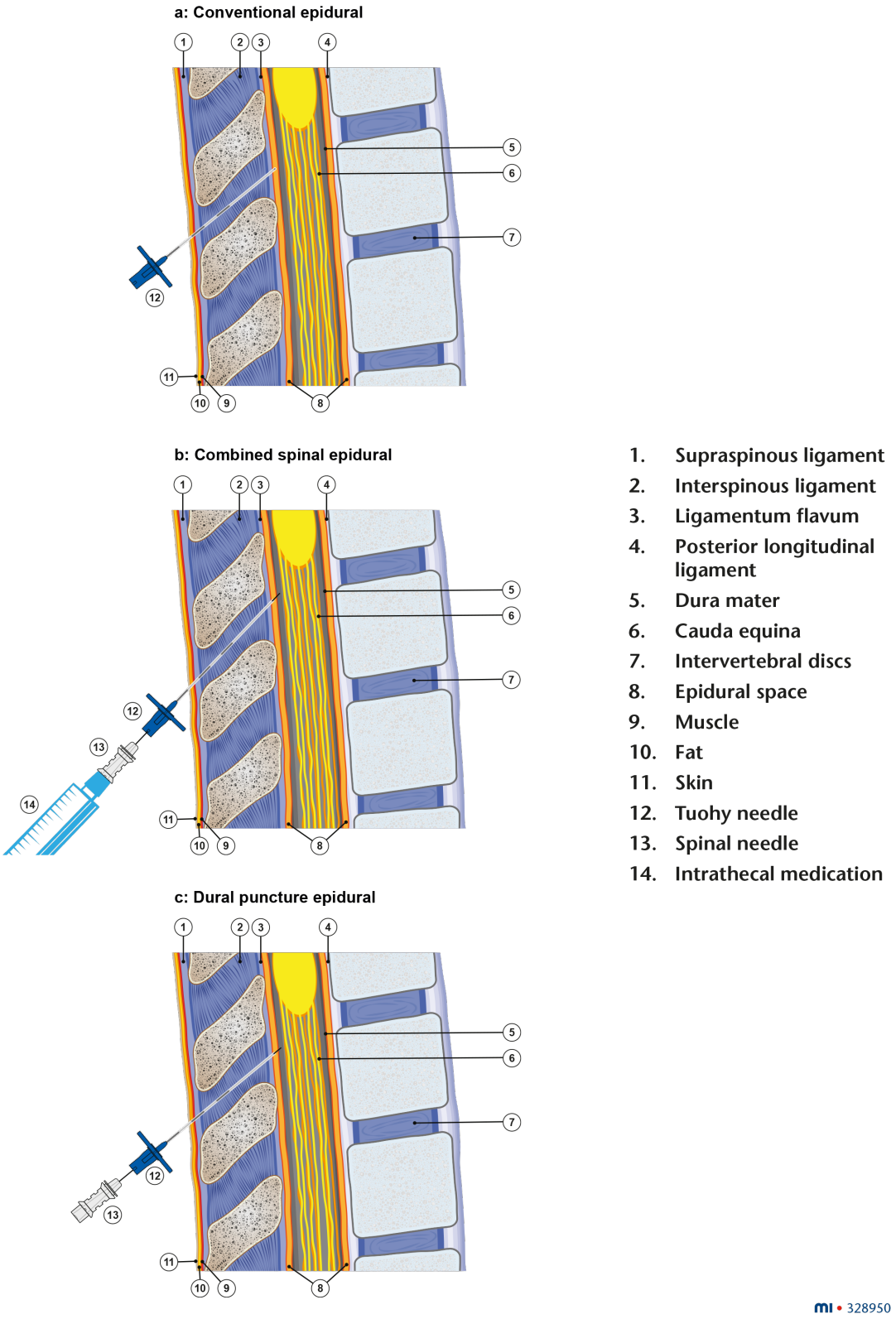


Figure 2-1 – Conventional epidural catheter insertion (a), Combined spinal epidural (b) and dural puncture epidural (c)

2.2.4 Ultrasound

The identification of a site for the insertion of a lumbar epidural is traditionally achieved by palpation of bony landmarks. The identification of a space can be challenging, in particular for those patients with obesity, scoliosis, or previous spinal surgery. One study of non-obstetric patients assessed the ability of anaesthetists to identify a lumbar interspace. They found that in just 29% of cases the correct interspace was identified, with 68% being one or more vertebral spaces higher than predicted, thus potentially increasing the risk of neurological injury.[67] The obstetric patient may have a limitation forward flexion due to large uterus, thus increasing the difficulty of lumbar interspace identification. Ultrasound can be used as a tool pre-procedure to identify specific intervertebral spaces and to measure the depth of epidural and intrathecal spaces. Three meta-analyses have investigated the use of pre-procedural ultrasound for epidural. The first meta-analysis of 14 RCTs (1786 patients) found a 49% reduction in procedural failure and a significantly reduced number of needle passes (mean difference 0.75) with pre-procedural ultrasound compared to palpation alone, but did not provide any results regarding the quality of analgesia produced.[68] Another meta-analysis (9 studies, 1014 patients, not limited to obstetric patients) considered both the ease of inserting epidural with ultrasound, and the efficacy of the analgesia produced, which included requirement for replacement of catheter for either labour analgesia or for operative birth. They demonstrated a reduced risk of both failed epidural (MD 0.23, [0.09, 0.60]) and of traumatic epidural insertion (MD 0.28 [0.09-0.92]).[69] A third meta-analysis compared pre-procedural ultrasound to palpation alone for obstetric patients undergoing any types of neuraxial analgesia and anaesthesia (spinal, epidural or CSE). They reported an increase in first pass success rate, with ultrasound compared to palpation alone (1253 parturients, 12 trials), but this was based on low quality evidence. They also reported no difference in time taken to perform the neuraxial block (709 patients, 8 trials), but evidence was assessed as very low.[70] Despite the low quality of evidence in its favour the use of pre-procedural ultrasound is endorsed in NICE guidelines [71].

2.2.5 Consent

As with any medical procedure, consent must be obtained prior to the insertion of a labour epidural. Parturients should be counselled as to the risks and benefit, to enable them to give informed consent. This is complicated by both the pain of labour, and by the administration of systemic analgesia medications. For this reason, it is important to discuss labour epidural in the antenatal period, as part of a wider discussion of a birth plan. The Obstetric Anaesthetists' Association provides information leaflets which can be downloaded from their website www.LabourPains.org. At the time of writing, these leaflets are available in 33 different languages. The anaesthetist performing the procedure should also be available to answer any further questions.

Risk	Frequency
Additional pain relief required on top of epidural	1 in 8
Epidural not functioning well enough for caesarean birth – require a spinal or general anaesthetic	1 in 20
Significant drop in blood pressure	1 in 50
Severe Headache	1 in 100
Temporary nerve damage (e.g. Patch of numbness on leg or weakness in leg)	1 in 1,000
Permanent nerve damage	1 in 13,000
Epidural abscess (infection)	1 in 50,000
Meningitis	1 in 100,000
Epidural hematoma (blood clot)	1 in 170,000
Severe Injury (including paralysis)	1 in 250,000

Table 2-1 Risks associated with use of labour epidural

2.3 Epidural agents

After insertion of an epidural catheter, local anaesthetics with or without adjuvant agents are used to provide analgesia. In the UK, levobupivacaine with fentanyl is the most commonly used injectate,[72] but there is no universally accepted standard. A number of different adjuvant agents have been investigated with the aim of prolonging duration of local anaesthetics and limiting overall dose, thus reducing the incidence of dose-dependent side effects. These are of particular interest for parturients wishing to avoid opioids.

2.3.1 Local anaesthetic agents

Bupivacaine is a local anaesthetic traditionally used for labour epidural in the UK.[72] Levobupivacaine, the pure levorotatory enantiomer of bupivacaine, is less cardiotoxic than racemic bupivacaine, and has replaced bupivacaine in many obstetric units.[72] Minimum local analgesic concentration (MLAC) studies suggest that levobupivacaine and bupivacaine are almost equipotent[73] and both produce a dose-dependent motor block. Ropivacaine is less cardiotoxic and neurotoxic and was thought to be more selective for sensory fibres than bupivacaine thus producing less motor block.[74] However, ropivacaine appears to be considerably less potent as an analgesic with a relative potency of 0.6 when compared to bupivacaine.[75] When ropivacaine and bupivacaine are used in equipotent doses, the incidence of adverse obstetric, neonatal and maternal outcomes including motor block are similar.[76] [77]

Traditionally, labour epidurals were maintained with 0.25% bupivacaine solution. In 2001 the COMET trial enrolled 1054 women and randomised them to receive a ‘traditional’ epidural or a low concentration epidural (0.1% bupivacaine combined with 2 μg.ml-1 fentanyl).[78] The lower concentration was associated with a reduction in the rate of assisted vaginal birth (AVB) of 25% with no compromise on analgesia. This difference was attributed to the preservation of motor tone, shorter second stage of labour, and reduced total dose of local anaesthetic.[78] A 2013 meta-analysis summarised data from 11 studies (including COMET) comparing low and high concentration epidurals and found a reduction in the incidence of AVB (odds ratio of 0.70) with no difference in the incidence of caesarean birth (OR 1.05). Pain scores and maternal outcomes were similar,

as were neonatal outcomes, with the exception of 1 minute APGAR scores which favoured the higher concentration with an odds ratio of 1.53, presumably due to the addition of fentanyl in the lower concentration group.[79] A 2021 meta-analysis (9 trials, 1334 parturients) compared moderately high concentrations without opiate (>0.1% but ≤0.125% bupivacaine or equivalent) to low concentrations with opiate (≤0.1% bupivacaine or equivalent). They reported a lower incidence of motor block in the low concentration group, but no significant differences in mode of birth or neonatal outcomes.[80] Since 2001 the use of lower concentration anaesthetics has increased, with 0.1% bupivacaine the standard concentration in the UK when surveyed by the OAA in 2014.[72]

Both the meta-analyses by Sultan et al[79] (2013), and Zhang et al[80] (2021) defined low concentration as less than or equal to 0.1% bupivacaine but a range of different concentrations were included within this category. There are a number of studies that compare low concentrations (~0.1%) with very low concentrations of bupivacaine and levobupivacaine (0.0568% - 0.0625%) which support the finding of a reduced incidence of AVB with lower concentrations.[81] [82] Baliuliene and colleagues compared 3 different concentrations of both bupivacaine and levobupivacaine (0.0625, 0.1 and 0.125%) with the hypothesis that 0.1% was the ideal concentration. This null hypothesis was rejected as lower cumulative doses of LA were required in 0.0625% group and although the analgesia was less effective, this had no effect on maternal satisfaction scores.[82]

Gogarten and colleagues studied 0.125% and 0.175% ropivacaine (approximate equivalent potency of bupivacaine is 0.075% and 0.1%), finding that the total ropivacaine dose was higher in the lower concentration group, and that pain scores were also higher, although this result was not explored in their discussion section.[83] A further randomised controlled trial by Boselli and colleagues compared 0.1% and 0.15% ropivacaine. The authors found that the lower concentration group had a significantly lower total consumption of local anaesthetic but they did not detect any reduction in incidence of motor block or assisted vaginal births or any difference in pain scores.[84] A network meta-analysis comparing ultra-low, low and high concentration local anaesthetics is included in chapter four of this thesis.

2.3.2 Opioids

Opioids can be used as adjuncts to epidural local anaesthetic or as sole agents. They work synergistically with local anaesthetics and can significantly reduce the cumulative dose of local anaesthetic required. Fentanyl is most commonly used in the UK.[72] Fentanyl has the desirable quality of being short acting, with effects lasting 1-2 hours. Fentanyl can reduce the MLAC of bupivacaine by 31-72% depending on the dose used.[85] Sufentanil is another opioid which also has a short duration of action but has a more rapid onset and is 4.5 times more potent than fentanyl. It can reduce the MLAC of bupivacaine by 91%.[86] Diamorphine and morphine are long-acting opiates and are less suitable for use in epidural maintenance solutions. The addition of opioids to epidural maintenance regimes is common.[72] In the UK, premixed solution bags are advised, either from the manufacturer or formulated by hospital pharmacy to avoid the risk of opioid overdose.[72] Epidural opioids can also be used in bolus doses for rescue analgesia.[87]

2.3.3 Adrenaline

The effects of adrenaline are thought to be due to both alpha receptor activation and local vasoconstriction limiting the systemic absorption of the local anaesthetic.[88] In a double blind RCT of 70 parturients randomised to epidural bupivacaine with or without adrenaline, the addition of adrenaline reduced the MLAC of bupivacaine by 29% though this did not result in any clinically significant maternal or fetal outcomes.[89] A 2018 meta-analysis of 8 RCTs looking at epidural or spinal adrenaline compared with no adrenaline found that adrenaline significantly increased the duration of local anaesthetic and reduced the cumulative dose. Apgar scores appeared to be lower in the adrenaline group but that result did not meet statistical significance.[90] Due to the proximity of the anterior spinal artery, epidural adrenaline caries the risk of vasoconstriction which can lead to serious long-term maternal neurological sequalae.[91]

2.3.4 Clonidine

Clonidine is an alpha-2 receptor agonist that has been shown to reduce local anaesthetic requirements by around 30% and increase the duration of anaesthesia both with and without opioids.[92] [93] There are concerns about side

effects of hypotension, bradycardia and maternal sedation which require further investigation. A randomised controlled trial of 98 parturients found no difference in analgesic efficacy between clonidine/bupivacaine and fentanyl/bupivacaine and no statistically significant difference in adverse outcomes.[94] A meta-analysis explored the use of clonidine compared to opiate as adjuvant in labour epidural (3 trials, 268 parturients). They reported no difference in pain scores, mode of birth or neonatal outcomes, but a reduced incidence of opiate related side effects in parturients in the clonidine group. However, they concluded that evidence was insufficient to draw firm conclusions.[95]

2.3.5 Neostigmine

Neostigmine prevents the breakdown of acetylcholine, which binds to receptors in the spinal cord and stimulates nitrous oxide production thus causing analgesia. It can cause nausea but is not associated with respiratory depression or pruritis, unlike opioids. A 2015 meta-analysis of 12 RTCs found that neostigmine reduced local anaesthetic consumption with no increased risk of adverse neonatal outcomes.[96] A more recent RCT looked at 152 parturients and compared fentanyl/bupivacaine with neostigmine/bupivacaine using patient-controlled epidural anaesthesia (PCEA). The authors were unable to find a significant clinical difference in local anaesthetic consumption, pain levels and neonatal outcomes. This supports a potential role for neostigmine in patients wishing to avoid opiates.[97]

2.4 Drug delivery systems

Drug delivery systems are another factor that can affect efficacy of labour epidural analgesia. Intermittent physician bolus, programmed intermittent epidural bolus (PIEB), continuous infusion, patient-controlled epidural analgesia (PCEA) and computer integrated patient-controlled analgesia have been described in the literature.[98-100] A meta-analysis comparing intermittent physician bolus with continuous infusion epidurals identified 22 RCTs containing data from 2573 parturients showing a significantly longer duration of labour in patients receiving a continuous epidural infusion compared to intermittent physician boluses (weighted mean different 21.46 minutes, 95% CI 25.07-17.85). This difference was irrespective of whether the parturient received supplementary PCEA. It also found that intermittent physician bolus was associated with a reduction in the dose of local anaesthetic administered per hour. There were no significant differences observed in the frequency of adverse events nor on mode of birth.[98] The differences in duration of labour and total local anaesthetic dose may be explained by better anaesthetic spread in the epidural space with a bolus technique.[101]

Patient-controlled epidural analgesia (PCEA) has been shown to improve maternal satisfaction, and reduce total local anaesthetic dose.[99] It can be used with or without a continuous background infusion or PIEB. The addition of a background continuous infusion has been shown to increase the risk of AVB and prolong the second stage of labour but reduces the number of anaesthetist-administered rescue doses required[102] when compared to PCEA alone. Computer integrated patient-controlled epidural analgesia (CI-PCEA) is a drug delivery system which uses a computer algorithm to automatically adjust a continuous background infusion based upon PCEA requirements. Only small trials have been conducted and more research into this delivery system will be required.[100 103]

A large network meta-analysis (73 trials, 10 comparisons) tried to identify the optimal mode of birth of labour epidural analgesia. They identified trials comparing PIEB, continuous infusion, PCEA and CI-PCEA, alone or in combination, as well as intravenous patient-controlled analgesia (PCA) with remifentanil and fentanyl. Overall they concluded that PIEB plus PCEA appeared to be the superior choice, but with a low quality of evidence.[104] Compared to

continuous infusion with PCEA, PIEB plus PCEA demonstrated improved pain scores at two- and four- hours, reduced consumption of local anaesthetic, reduced incidence of motor blockade and increased maternal satisfaction. Rate of spontaneous vaginal birth was also higher in the PIEB plus PCEA group compared to continuous infusion plus PCEA group, which the authors attributed to reduced motor blockade. Both remifentanil and fentanyl PCA were inferior to all modes of birth of epidural analgesia for pain scores (at 30 minutes, one hour, two hours and three hours), as well at rates of nausea and vomiting and sedation.[104]

2.5 Obstetric outcomes

2.5.1 Mode of birth and duration of labour

It is unclear whether labour neuraxial analgesia prolongs the duration of the first stage of labour.[105] Slow labour progression is associated with higher levels of plasma adrenaline and cortisol.[106] Both maternal cortisol and adrenaline levels decrease as pain reduces.[107,108] Relaxation of alpha receptors may improve uterine perfusion, leading to more effective contraction. In this way, labour neuraxial analgesia may shorten the first stage of labour. However, local anaesthetics may also block autonomic nerves, leading to less effective contraction.[33]

Epidural analgesia can impair motor function during the expulsive phase of labour. This has led to the concern that epidural analgesia is responsible for an increased risk of assisted vaginal birth or caesarean birth. A large meta-analysis looking at epidural versus non-epidural analgesia or no analgesia was published by Cochrane in 2018. It contained data from 40 RCTs and included over 11,000 women. There was a statistically significant increase in rates of AVB with an epidural compared to without epidural. A subgroup analysis excluding papers published after 2005 (when lower dose epidural regimes were common practice), found no increase in rates of AVB.[33] They assessed the quality of evidence as moderate to low quality using the GRADE criteria and found that most of the included studies were at high or unclear risk of bias.[33] A meta-analysis (10 RCTs, 1809 women) comparing epidurals with low concentrations of local anaesthetic with no epidural found that there was no statistically significant difference in the length of the first or second stage of labour.[109] A further meta-analysis (11 RCTs, 1997 women) comparing low (≤0.1% bupivacaine) and high concentration (>0.1% bupivacaine) epidurals, found that the lower concentration anaesthetics reduced the duration of the second stage of labour and the incidence of AVB (odds ratio 0.70), but did not alter caesarean birth rates.[79] Together these trials indicate that the concentration of local anaesthetic significantly affects duration of labour and incidence of AVB, but not of caesarean birth.

Trials comparing low concentrations (~0.1%) with very low concentrations of bupivacaine and levobupivacaine (0.0568% - 0.0625%) support the finding of a

reduced incidence of AVB with lower concentrations.[81,82] The hypothesis that 0.1% was the ideal concentration for labour analgesia was investigated in an RCT of 237 parturients randomised to three different concentrations of bupivacaine / levobupivacaine (0.0625, 0.1 and 0.125%). This null hypothesis was rejected as lower cumulative doses of LA were required in 0.0625% group and although the analgesia was less effective, this had no effect on maternal satisfaction scores.[82] More research is needed to determine whether reducing the concentration of LA further will improve outcomes.

Assisted vaginal birth is associated with increased risk of birth injuries including brachial plexus injury, scalp lacerations, facial nerve injury, need for mechanical ventilation and intracranial haemorrhage[110] as well as maternal complications such as urinary incontinence.[111] There is evidence that rates of AVB are falling independently of use or not of epidural,[112] and there is some concern that as obstetric practitioners become less experienced in AVB, patients who would previously have been managed by assisted vaginal birth may now be managed by caesarean birth.[112] Epidural labour analgesia has not been associated with an increased risk of caesarean birth.[33] There is a worldwide increase in caesarean birth rates of 4% per year.[113] These rates are of such concern that the WHO published recommendations on non-clinical interventions to reduce unnecessary caesarean births.[114] There are many confounders including increasing maternal age and BMI, however these alone are unlikely to account for this rise. Caesarean birth is associated with higher rates of neonatal (feeding difficulty, mechanical ventilation and convulsions[110]) and maternal complications, as well as risks in future pregnancies when compared to spontaneous vaginal birth or operative vaginal birth.

2.6 Maternal outcomes

2.6.1 Adverse effects of epidural medications

Adverse effects of epidural medications can be divided into those caused by blockade of nerves by local anaesthetic agents, and those caused by adjuvants, particularly opioids. Local anaesthetics block sensory nerves to produce analgesia, but they also block motor and autonomic nerves. Ambulation in labour has been shown to shorten labour time, and reduce the need for analgesia.[115] In addition, women may find the motor block and feeling of numbness uncomfortable.[116] Blockage of autonomic nerves may cause hypotension which can make parturient feel dizzy, nauseated and may be accompanied by fetal heart rate abnormalities.[117]

Epidural opioids can cause pruritis, nausea, vomiting and urinary retention. Pruritus affects 60-100% of parturients receiving epidural opioids and is often managed with antihistamines, although histamine is not thought to have a role in centrally induced pruritis, and benefit is likely due to the sedating properties of the drug. In severe cases, opioid receptor antagonists such as naloxone can be used.[118] Nausea / vomiting and urinary retention following the administration of epidural opioids have a prevalence of 30% and 21-53%, respectively. These side effects of epidural opiates are dose-dependent.[119]

2.6.2 Maternal satisfaction

Uncontrolled labour pain significantly affects maternal satisfaction.[120] Pain scores do not necessarily equate with maternal satisfaction as analgesia is only one component of maternal satisfaction. A randomised controlled trial comparing three different concentrations of local anaesthetic (0.125%, 0.1% and 0.0625%) found that the very low concentration was associated with higher pain scores, but that this did not affect maternal satisfaction.[82] This correlates with a prospective study of 294 women in Canada looking at using 0.0625% bupivacaine and fentanyl 2 $\mu g \cdot mL^{-1}$ which found that although almost a quarter of women required a clinician-administered top up, 92% were satisfied with their labour analgesia. It is worth noting that women who were overweight and those undergoing induced labour showed lower rates of maternal satisfaction.[121] This is

relevant to the UK anaesthetist as epidural rates in the UK are nearly half that in North America (31% vs 60%) [122, 123] and a greater proportion of UK patients receiving epidural may be living with obesity or undergo induced labour.[124] Other factors influencing maternal satisfaction include; the presence of a birthing partner and the involvement in decision making. In a prospective questionnaire-based study of 335 women, mode of birth did not appear to affect satisfaction.[120]

2.6.3 Maternal hyperthermia

Maternal hyperthermia may be caused by intrapartum infection or may be related to the presence of an epidural catheter. One in every five women who received epidural analgesia develop hyperthermia, but the aetiology is not fully understood.[125,126] There are two leading theories for the mechanism of epidural hyperthermia: sympathetic blockade and immunomodulation. Sympathetic nerve blockade may prevent vasodilatation and sweating, thus reducing heat loss through the skin.[127] The immunomodulation theory suggests that the administration of medications into the epidural space triggers the release of proinflammatory mediators which drive a centrally mediated increase in temperature.[128] These theories are not mutually exclusive and most likely both contribute to the development of hyperthermia related to epidural analgesia. The risk of developing hyperthermia whilst receiving labour epidural analgesia increases as the duration of epidural infusion increases.[129]

Intrapartum infection affects around 5% of parturients and is associated with worse neonatal outcomes. It is difficult to distinguish epidural hyperthermia from intrapartum infection and around a quarter of hyperthermic women with epidurals will have concurrent intrapartum infection. Epidural does not increase risk of intrapartum infection.[126] It is unknown whether epidural hyperthermia negatively impacts the neonate. A retrospective population study of 294,329 women looked at maternal intrapartum fever and epidural analgesia. They concluded that epidural hyperthermia did appear to correlate with lower Apgar scores at 5-minutes, but was not associated with the neonatal encephalopathy which is associated with maternal fever.[130]

Strategies to reduce rates of epidural related fever were considered in a recent meta-analysis. They suggested that reducing the dose of local anaesthetic delivered by epidural may be associated with a reduced rate of epidural related fever (13 trials, 4290 parturients, RR 0.74 [0.58–0.94]) but acknowledged a high risk of bias. When studies with a high risk of bias were removed, this result did not meet significance (7 trials, 857 parturients, RR 0.83 [0.41, 1.67]).[131] They also reported an 81% reduction in incidence of intrapartum fever when steroids were given alongside epidural analgesia, though this is not currently recommended in practice (3 trials, 270 parturients, RR 0.19 [0.05–0.71]).[131]

2.6.4 Post-natal depression

Labour is one of the most painful events that women will experience.[29] The effectiveness of analgesia may have psychological consequences for the mother and can impact on mother-baby bonding.[132] Post-natal depression is common, affecting 10-15% of new mothers.[133] Uncontrolled pain during childbirth has been shown to be a risk factor for the development of post-natal depression.[134,135] There is also evidence that a mis-match between intention to use, and actual use of labour epidural analgesia is associated with increased incidence of post-natal depression.[136] Maternal post-natal depression may be associated with impaired cognitive development for the child,[137] as well as a long term detrimental effect on mother-child relationship quality.[138] Post-traumatic stress disorder (PTSD) following childbirth is also common, with one study finding acute PTSD in 2.4% of study participants and significant symptoms of PTSD in 9.5% at one month postpartum.[139] There is also evidence that epidural analgesia decreases paternal anxiety and increases paternal satisfaction.[140] In this way epidural analgesia may have a protective impact on neurological development.

2.6.5 Severe maternal morbidity

There is evidence that neuraxial analgesia in labour is associated with a reduced risk of severe maternal morbidity.[141,142] A French cohort study (4,550 women) reported a 47% decrease in severe post-partum haemorrhage (PPH) (Hb drop >40 g/l) in women who received labour neuraxial analgesia compared to those who did not.[142] The mechanism for this reduction was proposed to be earlier recognition and treatment of haemorrhage due to indwelling epidural catheter,

preventing serious complications like disseminated intravascular coagulation (DIC) and acute kidney injury. Guglielminotti et al carried out a retrospective cohort study of 575,524 women who delivered vaginally in New York state (2010-2017 inclusive). After correction for confounders they found neuraxial labour analgesia for vaginal birth was associated with a reduced risk of severe maternal morbidity compared to women who did not receive neuraxial labour analgesia (aOR 0.86 [95% CI, 0.82-0.90]). Only 21% of this reduction was mediated by a reduction in PPH (21% [95% CI, 14-28]).[141] Other biological mechanisms that may contribute to this reduction may be due to relaxation in vascular smooth muscle, reducing cardiac afterload, preventing end organ damage due to severe hypertension and reducing the incidence of venous thrombo-embolism. Increased haemodynamic monitoring may also play a role.

2.7 Offspring outcomes

2.7.1 Neonatal outcomes

Epidural analgesia may have both positive and negative impacts on neonatal well-being. Although low doses of local anaesthetic are used in epidural analgesia, these infusions may last for many hours and cumulative doses may be high. Both local anaesthetics and opioids are able to cross the placenta and may be detected in the umbilical vein after birth.[143] Opioids have been detected in the urine of both mother and neonate more than 24 hours after birth.[144] These drugs may accumulate due to ion-trapping in the more acidic fetal circulation and impaired clearance due to immature liver enzymes.[145] This may lead to respiratory depression in the neonate.

The Apgar score is used to assess babies after birth at 1 and 5 minutes.[146] An Apgar score ≥ 7 is considered normal. Scores <7 at 5 minutes are associated with increased risk of birth asphyxia, seizures, neurodevelopmental disorders, and infant mortality.[147-150] Babies with low Apgar scores at 1 minute require neonatal resuscitative efforts. If these babies are successfully resuscitated by 5 minutes, they do not appear to have increase rate of morbidity.[151] Neonatal morbidity is associated with a pH ≤ 7.25.[152] A meta-analysis (11 RCTs, 1997 women) comparing high and low concentration epidural concentrations did not find any significant difference in fetal heart rate abnormalities, 5 minute Apgar score or need for neonatal resuscitation between the high and low concentrations. 1\one minute Apgar score <7 was more common in the low concentration group (OR 1.53; 95% CI 1.07 to 2.21) compared to high concentration group, and the author suggested this result may be due to increased dose of epidural opioid in the low concentration group.[79] This is contradicted by another meta-analysis (21 trials, 2859 participants) which looked at the neonates of mothers who received epidural or spinal opioid to those who did not. No significant differences in Apgar score <7 at 1 or 5 minutes were detected.[153]

Epidural analgesia is associated with a reduction in uterine artery blood flow during uterine contractions, even when using low concentrations of local anaesthetic. This is presumably because of vasodilatation due to sympathetic nerve blockade though it does not appear to correlate with any significant

difference in Apgar score or degree of neonatal acidosis.[154-156] It should be noted that these studies have small numbers of participants and were not powered to find these differences. No differences in rate of adverse neonatal outcome were detected in a Cochrane review comparing CSE and conventional lumbar epidural (27 trials, 3274 parturients).[63] The 2018 Cochrane review of epidural versus non-epidural labour analgesia found that epidural compared to parenteral opioids probably makes little or no difference to effects on baby at birth or rates of admission to neonatal intensive care.[33]

2.7.2 Breastfeeding

Breastfeeding is another important outcome measure, and has significant benefits for both neonates and mothers. Neonatal benefits include reduced risk of respiratory tract infections, asthma, diabetes, sudden infant death syndrome,[157] and improved neurodevelopmental outcomes.[158] Maternal benefits include decreased postpartum blood loss,[159] and lower risk of type two diabetes, hypertension and cardiovascular disease,[160] as well as reduced risk of breast and ovarian cancer.[158]

Epidural analgesia can modify the stress response of labour, which may increase oxytocin levels and thus, increase the chance of breastfeeding success. However as discussed above, potential prolongation of labour, effect on mode of birth and adverse neonatal outcomes may negatively impact on breastfeeding behaviours. A 2016 systematic review examining associations of epidural on breastfeeding was inconclusive. Half of included studies found no impact of epidural analgesia on breastfeeding success rates and half found evidence of negative impact. Only one study showed a positive association. The evidence quality was weak, mostly based upon observation studies or randomised controlled trials with small numbers. The two randomised controlled trials within this analysis showed no significant differences between breastfeeding rates in women who had and had not received epidural analgesia in labour.[161]

A study by Beilin published in 2006 looked at the effect of epidural fentanyl on breastfeeding behaviours, and found that women who received an intermediate dose of epidural fentanyl (1-150μg) were significantly less likely to be breastfeeding at 6-weeks, and those that received high dose fentanyl (>150μg)

were significant less likely to be breastfeeding at both 24 hours and at 6-weeks.[162] This may warrant consideration when administering high doses of epidural opioid for rescue analgesia. Another RCT looking at 305 motivated parous participants did not find any significant differences of breastfeeding rates at 6-weeks following an intermediate epidural opioid dose.[163]

2.7.3 Childhood outcomes

There are potential long term neurodevelopmental consequences for child associated with labour epidural analgesia, both positive and negative. This may be due to potential effects of the drugs administered on the developing brain, the effects of epidural hyperthermia and psychological consequences for the mother, such as post-natal depression.

Any long-term impact of anaesthesia on the developing brain is currently poorly understood. A cohort study from the USA looked at 4684 mother-baby pairs who birthed vaginally, 1495 of whom received epidural analgesia. They were unable to detect any significant difference in presence of learning difficulties before 19 years of age.[164] A controversial retrospective cohort study (147,895 vaginally born children) showed a 37% relative increase in the risk of developing autism in babies whose mothers had epidural analgesia compared to those without.[165] This study was widely criticised due to lack of adjustment for important confounders such as duration of labour, fetal distress, and method of birth. The Royal College of Anaesthetists released a statement concluding that *'This study should not alter the analgesia currently offered to women in labour'.*[166] Population-based studies from Denmark (479,178 children) and Canada (388,254 children) which both performed robust correction for confounding variables, found no association between labour epidural and autism.[167,168] A recent UK population-based cohort study of 435,281 mother-offspring pairs found that after adjustment for confounders including mode of birth, epidural analgesia was associated with small reduction in adverse childhood developmental outcomes.[169]

2.8 Conclusions

Labour epidural analgesia provides effective analgesia that is safe for mother and baby. It may even have protective benefits for the mother mediated by a reduction in severe maternal morbidity. Despite its widespread use, there is no universally agreed standard technique. Research into epidural is heterogeneous and there is inconsistency in outcome reporting. A summary of 9 key meta-analyses in included in Table 2.2. Areas for further research include the use of ultra-low concentration local anaesthetic (explored in chapter 4), defining current practice (explored in chapter 5) and the effect of epidural on severe maternal morbidity.

Name, authors and publication year	Trials and participants	Key findings
Epidural versus non-epidural or no analgesia for pain management in labour [33] Anim-Somuah et al, 2018	40 RCTs >11,000 parturients	Epidural compared to systemic opioids (34 trials): 1. Lower pain scores 2. Higher maternal satisfaction 3. Less additional pain relief 4. Longer first and second stages of labour 5. Increased risk of AVB – however a subgroup analysis excluding trials conducted before 2005 found no significant difference 6. More hypotension, motor block, fever and urinary retention 7. Less respiratory depression, less nausea and vomiting 8. Neonate less likely to receive naloxone 9. No difference for caesarean birth rates, long-term maternal backache or neonatal outcomes Epidural compared to no analgesia – 7 trials 1. Less pain reported 2. Few trials reported on maternal side effects
Effects of Epidural Labor Analgesia With Low Concentrations of Local Anesthetics on Obstetric Outcomes: A Systematic Review and Meta-analysis of Randomized Controlled Trials [109] Wang et al, 2017	10 RCTs 1809 parturients	No significant difference between groups in: 1. Duration of the first or second stage of labour 2. AVB rate 3. Caesarean birth rate 4. SVB rate
Comparison of ultra-low, low and high concentration local anaesthetic for labour epidural analgesia: a systematic review and network meta-analysis[170] Halliday et al, 2022	32 RCTs 3665 parturients	Compared to low concentration, ultra-low concentration local anaesthetics are associated with: 1. Reduced overall consumption of local anaesthetic 2. Reduced incidence of motor blockade No significant differences in pain scores or maternal satisfaction, or in rates of caesarean birth, AVB, adverse maternal or neonatal effects Compared to high concentration, ultra-low concentration local anaesthetics are associated with: 1. Increased incidence of SVB

		2. Reduced duration of second stage of labour 3. Reduced overall consumption of local anaesthetic 4. Reduced incidence of motor blockade No significant differences in pain scores or maternal satisfaction, or in rates of caesarean birth, AVB, adverse maternal or neonatal effects
The effect of low concentrations versus high concentrations of local anesthetics for labour analgesia on obstetric and anesthetic outcomes: a meta-analysis [79] **Sultan et al, 2013**	11 RCTs 1,997 parturients	Compared to high concentration, low concentration local anaesthetics are associated with: 1. Reduced incidence of AVB 2. Shorter second stage of labour 3. Less motor block 4. Less urinary retention 5. More pruritis 6. Greater incidence of 1 minute Apgar score <7 No significant differences for incidence of caesarean birth, pain scores, maternal nausea and vomiting, hypotension, fetal heart rate abnormalities, 5-minute Apgar scores or need for neonatal resuscitation.
Combined spinal-epidural versus epidural analgesia in labour [63] Simmons et al, 2012	27 RCTs 3,274 parturients	CSE versus traditional epidural: 1. CSE faster speed of onset of analgesia from time of injection 2. CSE less likely to need rescue analgesia 3. CSE less likely to go into urinary retention 4. CSE lower rate of AVB 5. Traditional epidural was more favourable in relation to umbilical venous pH CSE versus low-dose epidural: 1. Faster onset of effective analgesia from time of injection with CSE 2. More pruritus with CSE compared to low-dose epidural No significant difference in maternal satisfaction, need for rescue analgesia, mobilization in labour, incidence of post dural puncture headache, known dural tap, blood patch for post dural headache, urinary retention, nausea/vomiting, hypotension, headache, the need for labour augmentation, mode of birth, umbilical pH, Apgar score or admissions to the neonatal unit.
The Effect of Combined Spinal–Epidural Versus Epidural Analgesia in Laboring Women on Nonreassuring Fetal Heart Rate	17 RCTs	CSE showed an increased risk of non-reassuring FHR tracings overall and in 2 subgroup analyses:

Tracings: Systematic Review and Meta-analysis [62] Hattler et al, 2016	3947 parturients	1. Compared to conventional epidural (both high and low-dose epidural); RR: 1.31, p = 0.03 2. Subgroup analysis of 10 trials using low-dose epidural; RR: 1.12, p=0.12 3. Sensitivity analysis of low-dose epidural bupivacaine studies that ensured blinding of the outcome assessor; RR: 1.41, p = 0.06
Intermittent epidural bolus versus continuous epidural infusions for labor analgesia: A meta-analysis of randomized controlled trials [98] Liu et al, 2020	22 RCTs 2,573 parturients	No significant differences for the incidences of caesarean or AVB or risk of adverse events Intermittent bolus technique associated with: 1. Shorter duration of the total, first and second of stages of labour 2. Fewer anaesthetic interventions 3. Lower hourly consumption of local anaesthetic 4. Better maternal satisfaction
Patient-controlled epidural analgesia versus continuous infusion for labour analgesia: a meta-analysis [99] Van der Vyver et al, 2002	9 RCTs 640 parturients	Compared to continuous infusion group, the PCEA group had: 1. Less anaesthetic interventions 2. Lower totally dose of local anaesthetic 3. Less motor block
The effects of epidural/spinal opioids in labour analgesia on neonatal outcomes: a meta-analysis of randomized controlled trials [82] Wang et al, 2014	21 RCTs 2859 parturients	Neonates whose mother received neuraxial opiates in labour compared to those not receiving neuraxial opioids: 1. No difference in Apgar score <7 at 1 minute 2. No difference in Apgar score <7 at 5 minutes 3. No significant differences were found in umbilical cord arterial or venous pH

Table 2-2 Summary of 9 key meta-analyses on labour epidural analgesia

Chapter 3 Statistical methods

3.1 Introduction

Statistics is a branch of mathematics that is concerned with collecting, analysing, presenting and interpreting data. A statistical model is a set of assumptions about the probable distribution of sampled data. These models can be used to make real world predictions. The type of modelling undertaken depends on both the observed data being used to create the model, and what predictions we would like to generate from these. In this thesis a wide range of statistical techniques are used. A large proportion of this body of work is carried out using statistical computing software designed to analyse data and create graphics to aid the interpretation of results. The purpose of this chapter is to describe the core statistical concepts utilised in this thesis and provide background information to justify the use of the various statistical techniques employed in the succeeding chapters.

3.2 Software for analysis: R studio

R Studio software was used for statistical analysis in this thesis. R studio is a free open-source statistical software environment that uses the R programming language. It is a modular system, with 15 base 'packages' as standard. Further R packages can be downloaded from a central repository – the Comprehensive R Archive Network (CRAN).[171] Each package is an extension to the basic R programming language and contains code for new commands. Packages can be installed and loaded as required for use, making R studio a highly efficient system for data handling. As of the 17th of June 2023, 19711 packages are available for download via the CRAN repository.[171] It also provides sophisticated graphical tools for analysis and the production of publication quality graphics.

3.3 Regression modelling

3.3.1 Linear regression

Regression modelling is a method to examine the relationship between two or more variables. The basic form is linear regression, where an independent variable (x) is used to find the dependant variable (y). This is often represented graphically, with the independent variable (x) on the horizontal axis, and the dependant variable (y) on the vertical axis (Figure 3.1). In simple linear regression a straight line represents this relationship, and the linear regression model calculates the line of best fit that minimises the distance between the data points (the residuals). This is written as the formula: $y = mx + c$ where 'm' represents the gradient of the slope of the line, and 'c' is the value at which the line crossed the x axis. Linear regression is used to model continuous variables. When more than two independent variables are associated with the outcome, multiple linear regression is used.

3.3.2 Generalised linear regression

Not all relationships between variables can be modelled using linear regression. The difference between the actual value and the value predicted by the model for any given point is known as the residual. One of the key assumptions of a linear model is that the residuals have a normal distribution. However, there are some types of data for which plotting the residuals after applying a linear model would not form a normal distribution, for example binary data, or count data. To model these distributions, we need to transform the distribution into one that can be modelled. These models are referred to as generalised linear regression models.

3.3.2.1 Logistic regression

Logistic regression is used when the outcome variable is for binary. For example, (1) to receive epidural analgesia in labour, or (2) to not receive epidural analgesia in labour. It is also referred to as binomial regression. The goal of binomial regression modelling is to estimate the probability (p) of an event occurring (y=1). To do this, the dependant variable is transformed into a linear

form using a link function. For binominal regression the link function is the logit function, which is related to the log function:

$$\text{logit}(p) = \log\left(\frac{p}{1-p}\right)$$

This transforms the data into a sinusoidal shape which represents the relationship between the two variables. This transformed relationship can then be modelled. The output of a logistic regression is the ratio of the probability (odds) of an event occurring to the probability of the event not occurring – the odds ratio.[172] Due to the nature of the sinusoidal curve, the probability is always between 0 and 1. The curve is asymptotic, although it becomes infinite close to both y=0 and y=1, it never reaches these values.

A log-binomial model is similar to a binomial regression model in that it assumes the dependant variable is binary, but the log function (rather than the logit function) is used to transform the dependant variable. This transforms the relationship into an exponential curve which can be used to predict relative risk. In some cases, the exponential curve can be almost linear between p=0 and p=1. This means that sometimes the model can have difficulty in exploring the parameter space, especially at extreme values.[173] In these cases that model is described as having a problem with convergence and it is unable to provide a stable solution.

3.3.2.2 Poisson regression modelling

Poisson regression modelling is a generalised linear model used for categorical or count data. In Poisson regression modelling, the dependent variable is transformed using a different link function: the log function. For this reason, it is sometimes referred to as the log-linear model. The output of a Poisson regression model is incident rate ratio, or relative risk. Poisson regression modelling is based on a number of assumptions:

(1) The response variable follows a Poisson distribution

(2) Observations are independent of one another

(3) The mean of a variable is equal to its variance.

These assumptions can introduce bias into the model, for example in skewed data where the data will deviate from the Poisson distribution, or where the mean is not equal to variance, such as in overly dispersed data or data with outliers. To deal with these problems, a sandwich estimator can be introduced into the model, to create robust standard errors. The model is then referred to as a robust Poisson regression model. To do this, the sandwich estimator uses the estimated variance-covariance of x (the independent variables that are being used to predict y) and the estimated variance-covariance of the residuals and 'sandwiches' these together to create a more accurate calculation of the standard errors. Unlike a standard Poisson regression model, a robust Poisson regression model can be used to model binary data because of the relaxation of assumption that data follows a Poisson distribution.[173]

Robust Poisson regression is used in chapters 7 (Socio-economic disadvantage and uptake of labour epidural) and 8 (Socio-economic disparity in anaesthesia for caesarean birth), to examine the associations of variables with epidural compared to non-epidural in labour, and neuraxial compared to general anaesthesia for caesarean birth respectively. A robust Poisson regression model was selected over a binomial model because we wanted to calculate relative and absolute risks, as they are more intuitive than an odds ratio.[174] Log-binomial regression modelling was not used to avoid the problems with convergence described above, and to provide consistency across the analysis. Robust Poisson models are less sensitive to outliers compared to log-binomial models.[173]

3.3.3 Quantile regression

Quantile regression is an extension of linear regression modelling. It can be used in situations where linear modelling assumptions are not met. It does not make any assumptions about the distribution of the data and is not sensitive to outlying values. Rather than producing point estimates to describe the data, quantile regression is used to describe its distribution. It is computationally intensive and needs sufficient data to run.[175] In Chapters 6 and 7, quantile regression is used to estimate 95% confidence intervals for the associations between maternal age and maternal body max index with the Scottish Index of

Multiple Derivation (SIMD) deciles. This is because we had the point estimates from the dataset but wanted to describe the level of certainty attached to these estimates.

3.4 Approaches to statistical inference

3.4.1 Frequentist analysis

There are two main approaches to statistical inference - (1) frequentist analysis, and (2) Bayesian analysis. Frequentist analysis is based on the concept that probability is related to the long-term relative frequency of an event occurring under identical conditions. A frequentist analysis begins with the null hypothesis (that there is a significant difference or relationship between variables or groups within the population), and the observed data is used try to prove or disprove this hypothesis to a certain degree of significance which is referred to as the p value. Conventionally, a p value of <0.05 is deemed significant, although this is not always the case and some consider this value arbitrary.[176,177] The power of the study is its ability to correctly reject a null hypothesis. As the power increases, the chance of a low p value increases, as the study is more likely to detect a true difference. Frequentist analyses also produce a maximum likelihood estimate, a 'best-guess' of the true value, and an associated confidence interval (CI) (often set at 95%), which is the range in which the model is, for example 95% confident that it contains the true value.

Frequentist analysis is more commonly used, and less computationally demanding than Bayesian analysis.[178] Limitations of a frequentist analysis are that it assumes the sample size is large enough to detect a result if it exists, it is difficult to generalise the result as it does not provide direct probabilities, and that the choice of significance levels is arbitrary.[176] Frequentist analysis is used in the retrospective population studies described Chapters 6 (Socio-economic disadvantage and uptake of labour epidural), and 7 (Socio-economic disparity in anaesthesia for caesarean birth). Many of the disadvantages of frequentist analysis are not relevant to these studies. Both of these studies have very large numbers of parturients (593,230 and 179,562 respectively), which means there is adequate power to detect a difference if one exists. As these studies are population studies, as opposed to studies of a sample, power calculations are not relevant, and there is no need to generalise the results, since we have studied the entire population of interest. We can therefore present absolute risks. Frequentist analysis was preferable to Bayesian analysis due to the size of the data sets, which make using Bayesian analysis less practical due to the

available server space and time for analysis. Frequentist analysis is less opaque and easier to reproduce than a Bayesian analysis.

3.4.2 Bayesian inference

Bayesian analysis can be used to determine the probability of an event occurring given that another event has already occurred. Unlike frequentist analysis which accepts or rejects a null hypothesis, the Bayesian method calculates a probability that a hypothesis is true by updating prior information as new information becomes available. The output of a Bayesian analysis is referred to as the posterior distribution. Bayesian analysis was first described in the 18th century, but due to high computational demands, these methods were impractical to use widely until recently.[178] Bayesian statistical methods have been growing in popularity due to access to greater computational power, and secondly the invention of Markov Chain Monte Carlo methods (section 3.4.2.3).[179] Three benefits of Bayesian analysis are:

(1) Prior information can be incorporated into a Bayesian model

(2) A Bayesian analysis produces a probability, which can be directly applied to decision making

(3) New information can be added to the model as it becomes available.

Drawbacks of Bayesian analysis include the time taken to carry out the analysis which may be impractical for large datasets, and the lack of familiarity in the wider medical community, which can make interpretation and communication challenging.[180] For Chapter 4, a network meta-analysis of low and high concentration local anaesthetic for labour epidural analgesia, the advantages of a Bayesian analysis (particularly the ability to assign a probability to a hypothesis, and the intuitive nature of credible intervals) outweighed both the computational power required, and the challenges associated with communicating the results.

3.4.2.1 The prior distribution

Prior information or 'priors' may be informative (if specific information is known about the variable), or uninformative (if only vague or general information is available). Pre-existing knowledge can therefore be incorporated and the evidence in favour of one hypothesis over another may be quantified.[181] Since Bayesian inference works by updating the priors as new information becomes available, the smaller the sample size (the less new information), the more the model relies on priors. An example of informative prior is if you know a specific range between which the true value must lie. These can be referred to as hyperparameters: parameters that are defined before the machine-learning algorithm is applied to a dataset. The posterior distribution is thus influenced by this information. Uninformative priors are used when only vague information is known about a variable and the posterior distribution is not influenced by hyperparameters. Examples of uninformative prior distributions are the normal (Gaussian) distribution (Figure 3-1) and the Cauchy (Lorentz) distribution (Figure 3-2).

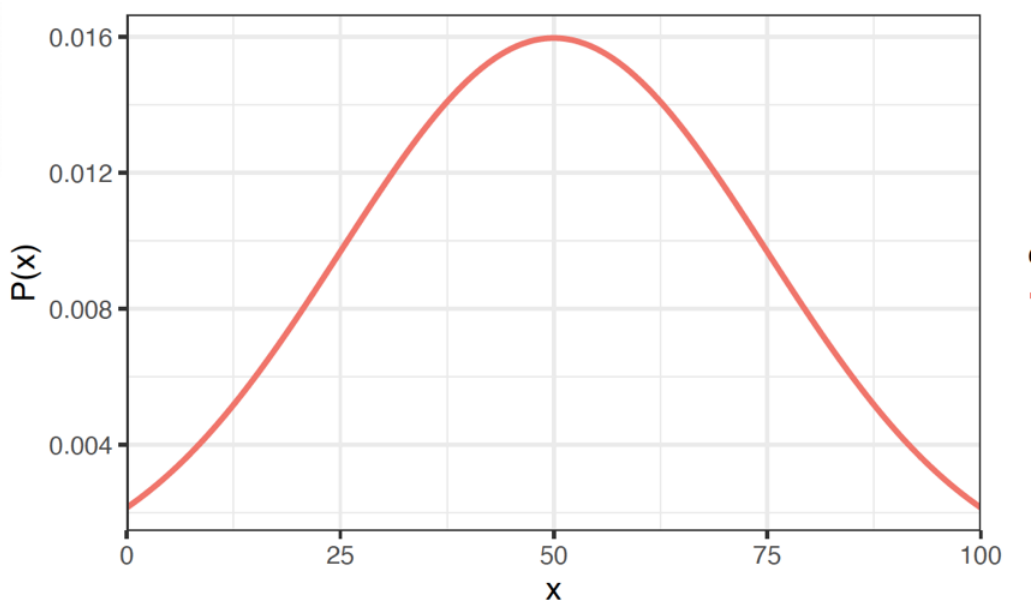


Figure 3-1 Normal distribution

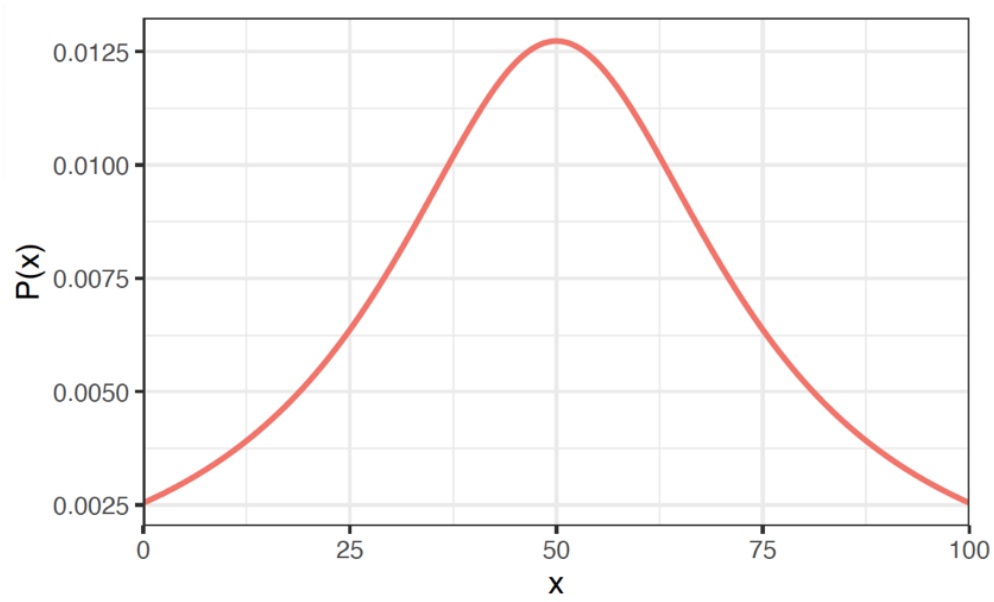


Figure 3-2 Cauchy distribution

A normal distribution is a continuous probability distribution that is symmetrical about the mean, which is equal to both the median and the mode. The spread of data is described by the standard deviation, with 68% of values lying within one standard deviation of the mean, 95% within two standard deviations and 99.7% within three standard deviations of the mean. Figure 3-1 is a normal distribution curve with a mean of 50 and a standard deviation of 25. The Cauchy distribution is a family of continuous probability distribution curves. The distribution does not have a mean or a standard deviation, the peak of the curve is referred to as the location (and is equal to the mode or median), and the scale is half the width of the curve at its half the maximum height. Compared to the normal distribution curve, the Cauchy distribution curve has a taller peak, and fat tails that has a slower decay (Figure 3-2). A half normal of a half Cauchy distribution are probability density functions that are truncated at the highest point of the curve, excluding the left half of the distribution. There are certain circumstances where prior knowledge might influence the choice of 'uninformative' prior distribution. For example, in chapter 4, the priors for two outcomes: maternal satisfaction and pain scores (both on a scale of 1-100), were Cauchy distributions with a location of 50 and a scale of 25 as the prior. Fifty was selected for the location, as it was a mid-point on the scale of 1 to 100, and the Cauchy distribution selected because of the fatter tails. Relatively more informative priors can improve the precision of the posterior distribution, especially if statistical power is low.

3.4.2.2 The posterior distribution

The output of a Bayesian analysis is known as the posterior distribution. It is a probability distribution from which point estimates and intervals can be derived. As these are probabilities, they can be directly applied to clinical decision making. The *Maximum a Posteriori* (MAP) is the value at the peak of the posterior distribution curve and is comparable to the maximum likelihood estimate in frequentist statistics. Credible intervals (CrI) describe the uncertainty related to the parameters being estimated and represent a range containing a specified percentage of probable values. For example, a 95% credible interval implies that there is a 95% probability that the true value of the parameter lies within the given interval. Different statistical significance levels for Bayesian analysis have been described in the literature.[181,182] A 95% significance level is commonly used as it is comparable to the use of 95% confidence levels in frequentist statistics. For this reason, we elected to present our results with 95% credible intervals, but for the primary outcome (mode of birth) we also presented the probabilities that certain concentrations of local anaesthetic increased the incidence of different modes of birth as compared to the other concentrations.

3.4.2.3 Markov Chain Monte Carlo methods

Markov Chain Monte Carlo methods (MCMC) are a class of algorithms that can be used to sample from a probability distribution.[181] Markov Chans refer to a set of transitions or steps with associated probabilities, where each step depends only on the preceding step, but not on any of the steps prior to this. Monte Carlo simulations are samplings from random walk over these sets of steps. For example in chapter 4, we use 8 Markov chains and each chain has 8,000 random samplings. From a practical viewpoint, MCMC methods are a tool to allow us to sample from a probability distribution more efficiently, thus reducing the number of calculations required and reducing the time taken to get a result. This reduction in need for computational power allows us to carryout Bayesian inference, where previously it was neither possible nor practical.

3.4.2.4 Testing of modelling assumptions in Bayesian analysis

There are several parameters to check the modelling assumptions in Bayesian analysis. The potential scale reduction factor (also referred to as Rhat or the Gelman-Rubin statistic) is the ratio of the average variance for each chain, compared to the pooled sample for all of the chains.[183] Thus it is indication of how well the Markov chains are converging, or mapping the same space. As this value moves towards one, there is less and less evidence that the Markov chains have not converged. A potential scale reduction factor of greater than 1.1 indicates that the model may not be sampling efficiently.[181] Bulk effective sample size (Bulk-ESS) is another diagnostic test which measures how efficiently the model is exploring the space. It is thus a measure of how much information each iteration of the chain is bringing to the overall model.[181] A bulk-ESS of greater than 1,000 is considered sufficient.[184]

Pairs plots are visual tools that can be used to check modelling assumptions. After the analysis, samples are obtained from the posterior distribution, these are plotted against the residual values (the differences between the observed and predicted value). These plots can then be assessed for linearity, homoscedacity (the spread of residuals should be consistent across the range of predicted values), and outliers.

3.4.2.5 Bayesian Analysis Reporting Guidelines

The Bayesian Analysis Reporting Guidelines (BARG) were published in 2021.[180] BARG was designed to standardise the way Bayesian analyses are reported, much like the STROBE Guidelines[185] for observational studies, the CONSORT guidelines[186] for randomised controlled trials, and the PRISMA statement for reporting systematic reviews.[187] The aim of the Guidelines are to: *improve the quality, transparency and reproducibility of Bayesian analyses'*.[180] BARG is a 32 point guideline defining the key points that should be reported, including a pre-amble to explain what Bayesian analysis is, and why it was selected over a frequentist analysis. It is used in Chapter 4 to describe the methods undertaken in the analysis.

3.5 Meta-analysis

Meta-analysis is the statistical combination of results from two or more separate studies.[188] The aims of a meta-analysis may be:

(1) To improve the statistical power to detect an effect

(2) To improve the precision of effect estimates

(3) To answer questions that may not have originally been asked by individual studies

For each included study an individual intervention effect is calculated, and these are weighted then combined together to produce an overall intervention effect. Prior to undertaking a meta-analysis, a systematic search of the literature must be undertaken to identify all relevant studies. Study quality and risk of bias should be assessed (section 3.5.3) and funnel plots can be used to assess for evidence of publication bias, all of which could bias the output of the meta-analysis. Alongside the main results, statistical heterogeneity should be reported. This is commonly done using the I^2 statistic, which estimates the degree to which variability in the results is due to statistical heterogeneity, as opposed to sampling error. The Cochrane group states that as a guide, an I^2 statistic <40% '*might not be important*'.[188] To aid the reproducibility and transparency of reporting, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement is a 27-point checklist to guide the reporting of a meta-analysis.[187]

3.5.1 Fixed and random effects modelling

A meta-analysis may be modelled using a fixed effects model or a random effects model, depending on the heterogeneity of the included studies. In a fixed effects model, an assumption is made that the studies sampled are from a population with a fixed effect size, so the effect sizes should be homogenous. They assume that any observed variation in the results from different studies is solely due to sampling error. A weighted mean is used to calculate an estimate of the effect size in a fixed effects model. In random effects models it is

assumed that the effect size varies from study to study. Each study is therefore estimating the true effects for its particular population, and the assumption of a random effects model is that these true effects will have a normal distribution. To calculate the overall effect, the variance from the mean in also considered in a random effects model, with effects further from the mean having less weight than those closer to the mean.[188] Random effects modelling is used in chapter 4 (Bayesian network meta-analysis of ultra-low, low and high concentration local anaesthetic for labour epidural analgesia) as there was some variation in the populations studied in the different trials (for example, some studies only looked at primiparous women, other at women of mixed parity).

3.5.2 Network meta-analysis

Network meta-analysis is a statistical technique that allows comparison of three (or more) treatments by assessing direct and indirect evidence to generate pairwise comparisons between each set of treatments. This is in contrast to pairwise meta-analysis in which only direct evidence is used to generate comparisons between two treatments. Using network meta-analysis is possible to estimate the superior treatment and a relative ranking based on statistical inference.[189] It can also be used to compare interventions that have not been compared in a single study. Pairwise comparisons may be carried out alongside a network meta-analysis, to aid the assessment of heterogeneity.[190]

3.5.3 Risk of bias

The risk of bias in each individual trial must be considered, prior to undertaking a meta-analysis. This is important to minimise bias in the combined result. The Cochrane risk-of-bias tool for randomized trials (ROB2)[191] is a popular tool that can be used to assess risk of bias in a meta-analysis. It separates the known causes of bias into 5 domains. These are:

1. Randomisation bias
2. Deviations from intended interventions
3. Missing outcome data
4. Outcome measurement bias

5. Selected result reporting

Each domain contains a series of ‘signalling questions’ designed to aid the researcher in identifying bias if any is present. This can be presented visually and should be available to the reader along with the published meta-analysis.

3.6 Measures of association

Odds ratios, relative risk and absolute risks are outcome measures used to present results for binary outcomes in medical and epidemiological research. Odds ratios and relative risk are both relative measures, whilst absolute risk is the likelihood of an event occurring in the population being studied. Relative measures of association are easier to interpret alongside absolute risk. In frequentist analysis the absolute risk refers to that of the sample population studied and may not be generalisable to the whole population of interest.

3.6.1 Odds ratio

The odds ratio is the most commonly presented outcome measure for binary variables. It can be defined as the odds of an event in the exposed group to the odds of the event in the non-exposed group (Figure 3-3).

	Event	Non-event
Exposed	A	B
Not exposed	C	D

$$\mathrm{OR} = \frac{\mathrm{A/B}}{\mathrm{C/D}} = \frac{\mathrm{AD}}{\mathrm{BC}}$$

$$\mathrm{RR} = \frac{A(A+B)}{C(C+D)}$$

Figure 3-3 Calculating Odds Ratio (OR) and Relative Risk (RR)

A benefit of the odds ratio is that they can be more straightforward to calculate as they are the natural output of a logistic regression model and avoid the problems of model misspecification described in 3.3.2. This means they are very commonly reported. One major drawback is that odds ratios can be mistaken for relative risk, but relative risk and odds ratio are not always similar when an event is common.[192] This is due to the properties of the sinusoidal curve produced from the logit transformation during modelling of an odds ratio. In its central portion the curve is almost linear, thus approximating the exponential relative risk curve. However, if the event is very common, approaching p=1, the curve becomes almost horizonal as it gets infinitely close to p=1, but never reaches it. This is unlike the exponential curve of relative risk which becomes

more vertical. At the extreme, the odds ratio can under- or overestimate relative risk by a sizable margin.

The odds ratio is the outcome measure reported in chapter 4. This is because the studies contained within the meta-analysis are reported as odds ratios, thus it is easier to compare the overall result with the output of the individual studies. As described in section 3.3.2.1, it also simplified the modelling, as the odds ratio is the natural output of logistic regression model.

3.6.2 Relative risk

The relative risk can be defined as the risk of an event occurring in an exposed group to the risk of an event in a non-exposed group (Figure 3.3). The benefit of relative risk is that it is considered more intuitive to interpret than an odds ratio, especially to those less familiar with statistical theory.[192] However, when using frequentist statistics, the relative risk is representative only of the sample population, and caution is required when generalising this result to the whole population of interest. Furthermore, as described above, modelling relative risk for binary outcomes involves misspecification of a model (binomial regression with a log link, or robust Poisson regression) which can cause the issues with modelling as described in sections 3.3.2.1 and 3.3.2.2 respectively.

Relative risk is reported in chapters 6 and 7. It was felt the relative risk (alongside absolute risk) was the clearest way to communicate our results most effectively, especially as the events being modelled were relatively common (using epidural for labour analgesia, and having a general anaesthetic for caesarean birth respectively). Furthermore, in these studies we have data for the whole population, thus we can report a relative risk for the whole population, rather than just a sample population. This avoids the issues of generalisability as discussed in section 3.4.1. We felt these benefits outweighed those of using a mis-specified model. As we know the size of the whole population, we were also able to calculate absolute risk and present these results alongside relative risk.

3.7 Summary chapter 3

- There are many different types of regression modelling that can be used to model data, depending on the type of data, and the desired output measure.

- Frequentist and Bayesian inference are based upon two different statistical theories.

- Frequentist methods determine the likelihood that a result occurred by chance.

- The output of Bayesian methods is a probability distribution.

- Meta-analysis is a tool to combine results for multiple randomised controlled trials, and network meta-analysis can compare three (or more) treatments by assessing direct and indirect evidence.

Chapter 4 Bayesian network meta-analysis of ultra-low, low and high concentration local anaesthetic for labour epidural analgesia

4.1 Introduction

The effect of epidural on the progress and outcome of labour and the minimisation of adverse effects has been identified by the James Lind Alliance as a research priority.[193] As described in Chapter 2, section 2.3.1, epidural has been associated with prolonged labour and increased rates of operative and assisted vaginal births, however it is unclear if these effects are causative or related to an increased analgesic requirement for more difficult labour.

Local anaesthetics block sodium channels to prevent nerve transmission. Smaller diameter and unmyelinated nerves are easier to block than large, myelinated nerve fibres. For this reason, sensory nerve fibres are blocked before motor fibres. The ideal agent for labour epidural analgesia would block the sensory nerves without any motor blockade, thus not inhibit the women's ability to push. Bupivacaine, levobupivacaine and ropivacaine are three local anaesthetic agents commonly used in labour epidural analgesia. Bupivacaine is a local anaesthetic traditionally used for labour epidural in the UK.[72] Levobupivacaine is the pure levorotatory enantiomer of bupivacaine, is less cardiotoxic than racemic bupivacaine, and has replaced bupivacaine in many obstetric units.[72] Ropivacaine is another long-acting local anaesthetic agent which it is less cardiotoxic and neurotoxic as compared to bupivacaine, and was initially thought to be more selective for sensory fibres thus producing less motor block.[74] However, ropivacaine appears to be considerably less potent as an analgesic[75] and when ropivacaine and bupivacaine are used in equipotent doses, the incidence of adverse obstetric, neonatal and maternal outcomes including motor block are similar.[76,77] In lower concentrations, local anaesthetics produce less motor blockade.[78]

In 2001 the Comparative Obstetric Mobile Epidural Trial (COMET) demonstrated a reduction in assisted vaginal birth (AVB) rates of around a third by reducing the concentration of local anaesthetic from 0.25% bupivacaine to 0.1% bupivacaine.[78] High concentrations have since fallen out of favour and 0.1%

bupivacaine or levobupivacaine are most commonly used in the UK.[87] A subsequent meta-analysis (2013) supported the association of low concentrations (≤0.1% bupivacaine or equivalent) with reduced rates of assisted vaginal birth (AVB) compared to higher local anaesthetic concentrations.[79] However, there is no universally agreed standard concentration of local anaesthetic used in labour analgesia worldwide. Much lower concentrations of local anaesthetic (<0.1% bupivacaine or equivalent) have been utilised in a number of randomised controlled trials, though any benefit of this remains unclear.[81,82,194] In this network meta-analysis we compare ultra-low (≤0.08% bupivacaine or equivalent), low (>0.08%, ≤0.1%), and high (>0.1%) concentrations of local anaesthetic to explore whether further reducing the concentration of local anaesthetic can maintain good analgesia and improve outcomes for both mother and baby.

Methods

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement and the Bayesian Analysis Reporting Guidelines (BARG).[180] The protocol was registered with the International Prospective Register of Systematic Reviews (CRD42020210878).

4.1.1 Search Strategy

A systematic literature search was conducted of relevant biomedical databases; Medline Ovid, Embase Ovid, CINAHL EBSCO, Cochrane Central Register of Controlled Trials (CENTRAL) and clinicatrials.gov. The search ran from the date of inception of the database to 5th October 2020, with repetition on 11th October 2021. There was no language restriction. Databases were searched using combinations of keywords; epidural, ropivacaine, bupivacaine, levobupivacaine, obstetric, labour, and synonyms and the search strategy was verified by an independent information specialist. The full search strategy for Medline Ovid is presented in Table 4-1. Medical Subject Headings (MeSH) terms and keywords were modified in accordance with the specific database being searched. Search results were imported into Covidence software for screening and study selection (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia).

Two reviewers (LH, MK) screened abstracts and identified papers for full text review. Full texts were retrieved, reviewed, and assessed by the two reviewers for eligibility. In the case of disagreement, the article was discussed between the two reviewers and a third reviewer (RK) was consulted where necessary. Risk of bias was assessed by two reviewers using the Cochrane risk of bias tool (ROB2) and presented graphically.

No.	Keyword
1	anesthesia/ or anesthesia, local/ or exp anesthesia, epidural/ or anesthesia, obstetrical/
2	analgesia/ or analgesia, epidural/ or analgesia, obstetrical/
3	((epidural or peridural or dural or lumbar or obstetric$ or intravenous or local$) adj5 (an?esthe$ or analges$ or block$)).tw.
4	1 or 2 or 3
5	exp bupivacaine/ or ropivacaine/
6	(bupivacaine or levobupivacaine or ropivacaine).tw.
7	5 or 6
8	4 and 7
9	delivery, obstetric/ or exp extraction, obstetrical/
10	labor pain/ or obstetric/ or exp labor onset/ or exp labor presentation/ or parturition/ or term birth/
11	obstetrical forceps/
12	(vaginal adj3 (birth or deliver$ or childbirth)).tw.
13	labo$r.tw.
14	((assist$ or vacuum or ventouse or breech or surg$ or operat$ or instrument$ or forceps or obstet$) adj5 (deliver$ or extract$ or evacuat$ or birth)).tw.
15	9 or 10 or 11 or 12 or 13 or 14
16	randomized controlled trial.pt.
17	controlled clinical trial.pt.
18	randomized.ab.
19	placebo.ab.
20	drug therapy.fs.
21	randomly.ab.
22	trial.ti.
23	groups.ab.
24	or/16-23
25	8 and 15 and 24

Table 4-1 Search strategy for Medline Ovid

4.1.2 Local anaesthetic considerations

Randomised controlled trials using bupivacaine, levobupivacaine and ropivacaine were included. Minimum local analgesic concentration studies suggest that levobupivacaine and bupivacaine are almost equipotent (relative potency of levobupivacaine is 0.98 compared to bupivacaine).[73] Ropivacaine appears to be considerably less potent as an analgesic with a relative potency of 0.6 when compared to bupivacaine.[75] No other local anaesthetic agents were included in this meta-analysis.

There are no universally accepted definitions of ultra-low (ULC), low (LC) or high (HC) concentration of local anaesthetic. 0.1% bupivacaine was chosen as the upper limit for LC as this was the value used to define LC in the COMET trial,[78] (the largest study in this meta-analysis), and the local anaesthetic concentration most commonly used in the UK. This is also in keeping with two previous meta-analyses by Sultan (2013)[79] and Zhang (2021)[80] which defined LC as ≤ 0.1% bupivacaine. Below or equal to 0.08% bupivacaine was chosen as a cut-off for the ULC category as this encompassed all studies examining the lowest concentrations of local anaesthetic. As levobupivacaine is almost equipotent with bupivacaine,[195] we used the same values for levobupivacaine. For ropivacaine, ULC was defined as ≤0.135%, LC as >0.135% and ≤0.175%, and HC as >0.175%. This is due to the analgesic potency of ropivacaine at 0.6 as compared to bupivacaine[75] (as described in section 4.2.2.1).

4.1.3 Inclusion and exclusion criteria

Randomised and pseudo-randomised controlled trials comparing 2 or more concentrations of local anaesthetic, in the following categories: ULC and/or LC and/or HC of bupivacaine, levobupivacaine or ropivacaine, and reported the primary outcome measure - mode of birth. Definitions of outcome measures are listed in section 4.2.4. Women of any parity were included. The use of any adjuvant agent was permitted, even if it differed in different arms of the trial. All methods of administration were included (continuous infusion, PIEB, patient-controlled epidural analgesia and computer integrated patient-controlled epidural analgesia or any combination thereof). Trials were excluded if they compare different local anaesthetics in different arms of the trial, or if the

initial local anaesthetic bolus differed from the local anaesthetic used for maintenance. There were no language or publication restrictions. A summary of inclusion and exclusion criteria can be found in Table 4-2.

	Inclusion criteria	Exclusion Criteria
Study design	Randomised Controlled Trials or Pseudo-randomised controlled trials	Observational studies
Participants	Primiparous and multiparous women receiving lumbar epidural for labour pain	Epidural initiated by CSE technique
Interventions	Two or more different concentrations of local anaesthetics for maintenance of labour epidural that fall into the following categories: Ultra-low (ULC): ≤ 0.08% bupivacaine (or equivalent levobupivacaine or ropivacaine) Low (LC): > 0.08, ≤ 0.1% bupivacaine High (HC): > 0.1% bupivacaine All adjuvant agents included All methods of administration included	Different local anaesthetics being compared in same trial Epidural initiated with different concentrations but same maintenance solution
Outcome measures	Obstetric – mode of birth, length of first and second stages of labour, incidence of second- and third-degree tears, and postpartum haemorrhage Maternal – total dose of local anaesthetic, number of rescue top-ups, 30-minute and 60-minute pain score (VAS), maternal satisfaction, rates of pruritis, nausea and vomiting, urinary retention, hypotension, Bromage score >0, ability to ambulate Neonatal – need for neonatal resuscitation, Apgar scores at one and five minutes, umbilical artery pH, admission to neonatal intensive care and breastfeeding rates at 24 hours and 6 weeks. Early Childhood – any childhood outcomes	None
Publication status	No language or publication restrictions	

Table 4-2 Inclusion and exclusion criteria for meta-analysis

4.1.4 Outcome definitions

Outcomes of interests fell into the following categories: obstetric, maternal, neonatal and early childhood outcomes. Obstetric outcomes were;

- Rate of assisted vaginal birth (AVB): count,
- Rate of spontaneous vaginal birth (SVB): count,
- Rate of caesarean birth: count,
- Duration of the first stage of labour: minutes,
- Duration of the second stage of labour: minutes,
- Incidence of second- and third-degree tears: count,
- Incidence of post-partum haemorrhage: count.

Maternal outcomes were;

- Total cumulative dose of local anaesthetic: milligrams (mg)
- number of epidural “rescue” top ups: count,
- 30-minute visual analogue score (VAS) pain score: scale 1 to 100 (1 = least pain, 100 = greatest pain),
- 60-minute VAS score: scale 1to 100 (1 = least pain, 100 = greatest pain),
- Maternal satisfaction score: scale 1 to 100 (1 = least satisfied, 100 = greatest satisfaction),
- Incidence of pruritis: count,
- Incidence of urinary retention: count,

- Incidence of nausea or vomiting: count,
- Incidence of hypotension: count,
- Incidence of motor blockade as defined as a Bromage score > 0[†]: count,
- Incidence of inability to ambulate: count.

Neonatal outcomes were;

- Incidence of neonatal resuscitation: count,
- Incidence of Apgar score <7 at 1-minute: count,
- Incidence of Apgar score <7 at 5-minutes: count,
- Umbilical cord pH,
- Incidence of admission to a neonatal intensive care unit (NICU): count,
- Breastfeeding within 24-hours of birth: count,
- Breastfeeding at 6-weeks: count,

Any reported childhood outcome measures were included.

[†] Bromage score>0 indicates full flexion of the knee and foot.

4.1.5 Statistical analysis

Variables were extracted as counts for binary data and as means and standard deviations for continuous variables. Where mean and standard deviations were not available, they were estimated from median, range, interquartile range and confidence intervals.[196,197] If there was no measure of central tendency, the data could not be analysed. Data presented in graphical form were extracted using the metaDigitise software on R studio (version 3.6.2, R Foundation for Statistical Computing) where possible. To assess heterogeneity for the primary outcome (mode of birth), direct evidence was assessed and presented as a forest plot.

4.1.5.1 Meta-analysis

A network meta-analysis with random effects modelling was carried out for this analysis. More information on meta-analysis can be found in chapter 3 (section 3.5).

4.1.5.2 Bayesian Inference

This Bayesian Network meta-analysis is reported according to the Bayesian Analysis Reporting Guidelines (BARG).[180] A Bayesian approach was selected over a frequentist approach, as we considered that probability is more intuitive to interpret compared the output of a frequentist model, the results are more generalisable and can be directly applied to clinical decision making. Bayesian inference is described in detail in Chapter 3 (section 3.4.2).

A Bayesian network meta-analysis (NMA) with non-informative priors was carried out using the multinma package on R studio.[198] A random effects model with Markov Chain Monte Carlo (MCMC) simulation was used to calculate the posterior distribution within the Bayesian network. Non-informative priors were used with a normal distribution (scale = 100), and prior heterogeneity was modelled using half Cauchy distribution (scale = 5). Eight thousand draws of 8 chains were carried out. For binary data, the median odds ratio (OR) and associated 95% credible intervals (CrI) were generated for each pair of comparisons by combining direct and indirect evidence in the network. For continuous data weighted mean average (WMA) was calculated with accompanying 95% CrI. A 95% cut-off for statistical significance was chosen to allow for easier comparison with

results from frequentist studies, and as a conservative estimate to aid reproducibility of results. For mode of birth, our primary outcome, further interpretation of the Bayesian analysis is directly presented as a probability to facilitate further understanding of our findings.

Trace plots were created to check MCMC chains are mixing. The trace plot for assisted vaginal birth is presented in Figure 4-1. The three trace plots represent the posterior draws for: d[2] the effect size of LC compared to ULC; d[3] the effect size of HC compared to ULC and; tau, the correlation between predicted and observed values. For all three variables, there is good chain mixing, implying that they are mapping the same distributional space.

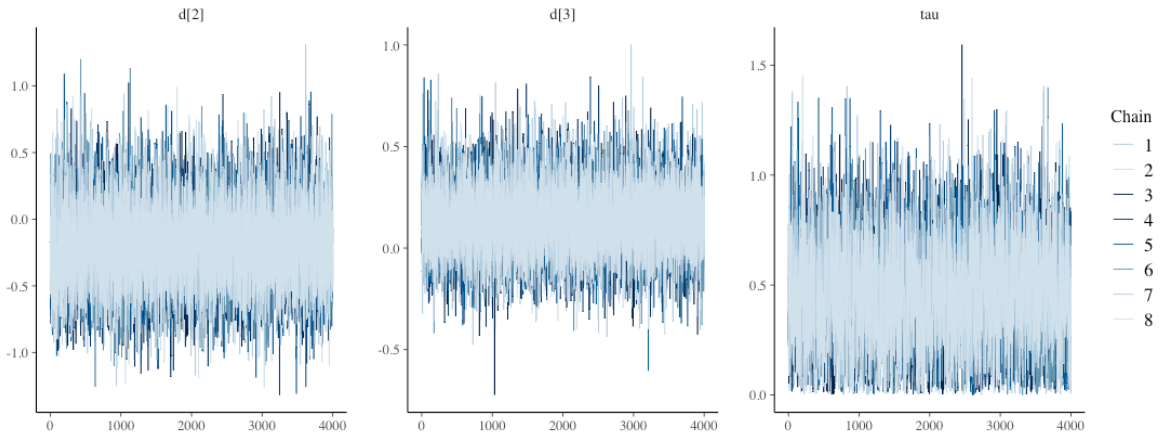


Figure 4-1 Trace plots for assisted vaginal birth

Model fit was visually assessed using residual plots The pairs plots for assisted vaginal birth are presented in Figure 4-2. These plots display the relationship between the predicted values and the observed values – these are known as the residual values for a regression model. The three histograms across the diagonal are:

- (a) : d[2] : Effect size, LC compared to ULC.
  This is roughly symmetrical and follows a normal distribution, which supports the use of a normal distribution as a prior.

- (e) : d[3] : Effect size, HC compared to ULC.
  This also appears to be roughly symmetrical and follow a normal distribution.

- (i) : tau: this displays the correlation between predicted and observed values for the mixed effects model. It is reasonably symmetrical but truncated at 0 – as specified by the half-Cauchy model. The spread of the residual values is roughly consistent across the entire range of predicted values indicating homoskaedacity.

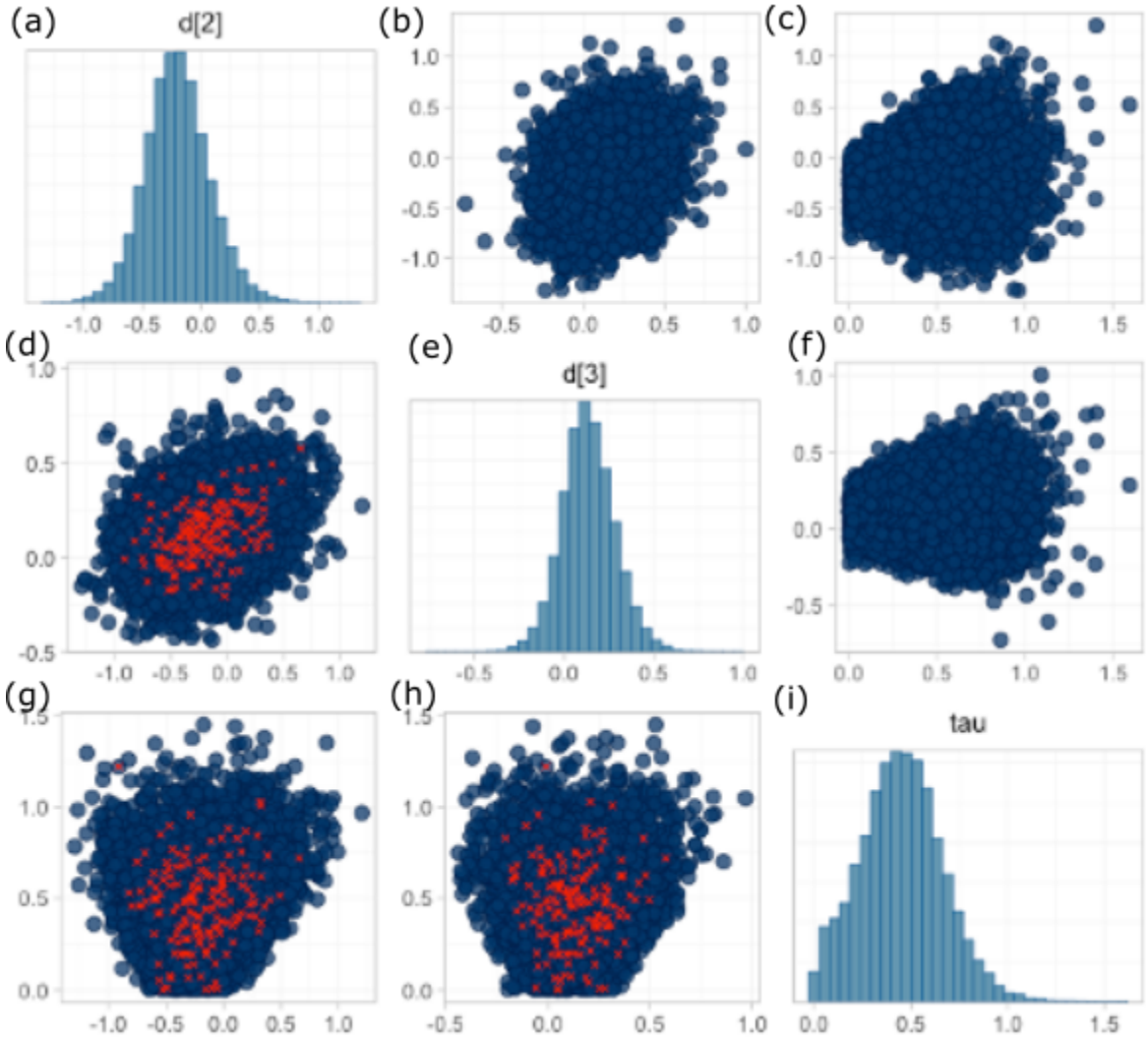


Figure 4-2 Pairs plots for assisted vaginal birth

The scatter plots are bivariate plots of the posterior draws form the model. These allow us to visualise the distributional space. The scatter plots to the right of the diagonal (b, c and f) represent the posterior draws from the first half of the split MCMC chains, and to the left of the diagonal (d, g and h) represent the posterior draws from the second half of the split MCMC chains. The scatter plots are smooth, implying that the model covered the distributional space well. In the plots on the left of the diagonal, the 'divergent transitions' are plotted in red. These are signals that the distributional space is difficult to map, and there might be a problem with how the MCMC chains are mapping the distributional space. In this case, they are small in number, and are distributed across the parameter space, rather than being concentrated in one specific area. Thus, they are unlikely to cause problems with the model when considered alongside other diagnostic checks.

Following sensitivity analysis, the priors for 30- and 60- minute visual analogue pain score and maternal satisfaction were changed to Cauchy distribution (location = 50, scale = 25). Potential scale reduction factor was 1 and bulk effective sample size was greater than 1000 for all variables indicating good MCMC chain convergence and resolution (see Chapter 3, Section 3.4.2.4).

4.1.5.3 Additional analyses

Additional frequentist pairwise analysis was performed using only direct evidence and presented as a forest plot for the outcome of assisted vaginal birth (AVB), as this has previously been identified as an area of clinical uncertainty.[33,78,79] Funnel plots were created to assess for evidence of publication bias. For mode of birth, point estimates of absolute risk for ULC compared to a HC and LC were also generated.

Subgroup analyses were performed for mode of birth restricting studies to only include those published within the past 10 years. This is to reflect the changing practice of epidural analgesia, the reduced use of assisted vaginal birth[112] and the increasing use of caesarean birth worldwide.[113]

4.2 Results

After performing the systematic literature search, 1723 references were retrieved, of which 472 were duplicates. Title and abstract screening were carried out for 1247 studies, and 53 of these were identified for full text evaluation. Thirty-two studies met the inclusion criteria with data from 3665 women. Details of included studies can be found in Table 4-3. All included studies were randomised, with the exception of one, which was quasi-randomised by month of birth.[199] Of the total 3665 parturients, 1578 received HC local anaesthetic, 746 received LC local anaesthetic, and 1341 patients received an ULC of local anaesthetic. Of the 32 studies, six compared ULC to LC, 27 compared ULC to HC, and five compared LC to HC (Figure 4-3). The PRISMA flow chart with reasons for exclusion is illustrated in Figure 4-4. A list of excluded studies with reasons for exclusion can be found in Appendix 1.

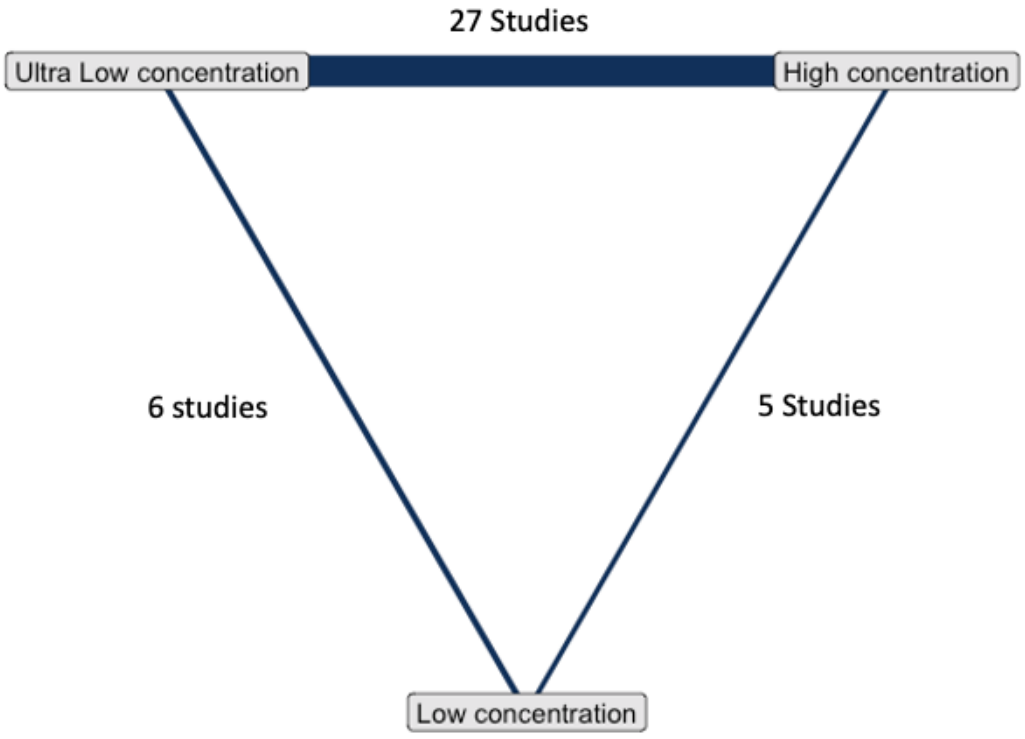


Figure 4-3 Network Comparisons for Assisted vaginal birth (AVB). Edges are weighted according to the number of studies included in each comparison.

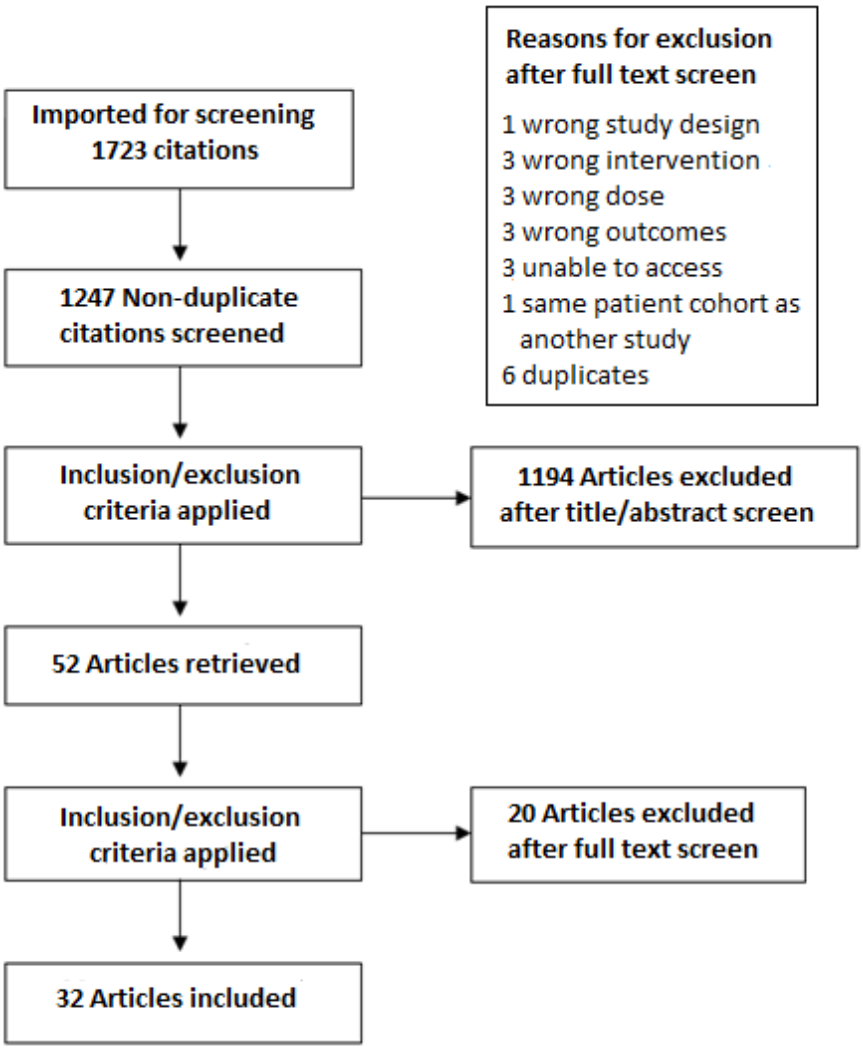


Figure 4-4 PRISMA flowchart for study selection

A summary of the study demographics is included in Table 4-3. Data for the primary outcome, mode of birth, was included in all included studies. Data for secondary outcomes was not provided by all the included papers. Twenty-four studies looked at bupivacaine, seven studies at ropivacaine and three studies at levobupivacaine. One study by Baliuliene[82] et al had two arms comparing bupivacaine and levobupivacaine which were counted as separate trials (BaliulieneB and BaliulieneL respectively). Fourteen studies included only primiparous women, 11 included women of mixed parity and seven did not specify. Opioid use varied between different concentration local anaesthetics. Twenty seven out of 30 trials included opioids in the epidural maintenance solution for ULC, all studies in the LC group (eight out of eight), and 16 out of 30 studies in the HC groups (Table 4-3)

Author, year	Ultra-Low Concentration (ULC) Number, test dose, initial dose, maintenance	Low Concentration (LC) Number, test dose, initial dose, maintenance	High Concentration (HC) Number, test dose, initial dose, maintenance	Comments
Atienzar[36] **2004**	N = 38 No test dose Initial dose: 9ml of 0.2% ropivacaine plus 50µg.ml-1 fentanyl Maintenance: Ropivacaine 0.1% with fentanyl 2µg.ml-1 @10ml/hr	NA	N = 39 No test dose Initial dose: 9ml of 0.2% ropivacaine plus 50µg.ml-1 fentanyl Maintenance: Ropivacaine 0.2% with fentanyl 2µg.ml-1 @8ml/hr	Primiparous, Continuous infusion
Bailey[37] **1994**	N = 25 Test dose: 3ml 0.5% bupivacaine Initial dose: 5ml 0.25% bupivacaine Maintenance: 0.0625% bupivacaine with diamorphine 50µg.ml-1 @10ml/hr	NA	N = 25 Test dose: 3ml 0.5% bupivacaine Initial dose: 5ml 0.25% bupivacaine Maintenance: 0.125% bupivacaine with diamorphine 50µg.ml-1 @10ml/hr	Mixed parity, Continuous infusion
Baliuliene[21] **2018**	N=35 Test dose: 3 mL 1.5% lidocaine with 5mg.ml-1 epinephrine Initial dose: 10ml of 0.0625% bupivacaine with 2µg.ml-1 fentanyl Maintenance: Bupivacaine 0.0625% with fentanyl 2µg.ml-1 @10ml/hr	N= 43 Test dose: 3 mL 1.5% lidocaine with 5mg.ml-1 epinephrine Initial dose: 10ml of 0.1% bupivacaine with 2µg.ml-1 fentanyl Maintenance: Bupivacaine 0.1% with fentanyl 2µg.ml-1 @10ml/hr	N=42 Test dose: 3 mL 1.5% lidocaine with 5mg.ml-1 epinephrine Initial dose: 10ml of 0.125% bupivacaine with 2µg.ml-1 fentanyl Maintenance: Bupivacaine 0.125% with fentanyl 2µg.ml-1 @10ml/hr	Primiparous, PCEA plus Continuous infusion
Baliuliene[21] **2018**	N=39 Test dose: 3 mL 1.5% lidocaine with 5mg.ml-1 epinephrine Initial dose: 10ml of 0.0625% levobupivacaine with 2µg.ml-1 fentanyl Maintenance: Levobupivacaine 0.0625% with fentanyl 2µg.ml-1 @10ml/hr	N=39 Test dose: 3 mL 1.5% lidocaine with 5mg.ml-1 epinephrine Initial dose: 10ml of 0.1% levobupivacaine with 2µg.ml-1 fentanyl Maintenance: Levobupivacaine 0.1% with fentanyl 2µg.ml-1 @10ml/hr	N=39 Test dose: 3 mL 1.5% lidocaine with 5mg.ml-1 epinephrine Initial dose: 10ml of 0.125% levobupivacaine with 2µg.ml-1 fentanyl Maintenance: Levobupivacaine 0.125% with fentanyl 2µg.ml-1 @10ml/hr	Primiparous, PCEA plus Continuous infusion
Benhamou[38] **2002**	N=35 No test dose Initial dose: 10-15ml of 0.0625% bupivacaine with sufentanil 0.25µg.ml-1 Maintenance: Bupivacaine 0.0625% with sufentanil 0.25µg.ml-1 @ 10-15ml/hr	NA	N=23 No test dose Initial dose: 10-15ml of 0.125% bupivacaine Maintenance: Bupivacaine 0.125% @ 10-15ml/hr	Mixed parity, Quasi randomised, Breech babies, Continuous infusion
Boselli[39] **2003**	N=63 Test dose: 3 ml of 2% lidocaine with 15µg adrenaline Initial dose: 2ml of 0.1% ropivacaine Maintenance: Ropivacaine 0.1% with 0.5 µg.ml-1 sufentanil @ 10ml/hr	N=67 Test dose: 3 ml of 2% lidocaine with 15µg adrenaline Initial dose: 12ml of 0.15% ropivacaine Maintenance: Ropivacaine 0.15% with 0.5 µg.ml-1 sufentanil @10ml/hr	NA	Mixed parity, PCEA plus Continuous infusion
Cakirca[22] **2013**	N=15 Test dose: 3 ml of 2% lidocaine Initial dose: 8-10 mL of 0.0625% bupivacaine with 0.5µg.ml-1 sufentanil Intermittent bolus 0.0625% bupivacaine with 0.5 µg.ml-1 sufentanil	N= 15 Test dose: 3 ml of 2% lidocaine Initial dose: 8-10 mL of 0.1% bupivacaine with 0.5µg.ml-1 sufentanil Intermittent bolus - 0.1% bupivacaine with 0.5 µg.ml-1 sufentanil	NA	Mixed parity, Intermittent bolus
Castro[40]	N=20	NA	N=20	Primiparous,

2000	No test dose Initial dose: 20 mg 0.25% bupivacaine with epinephrine 1: 200,000 Maintenance: bupivacaine 0.0625% with fentanyl 2µg.ml-1 @10ml/hr		No test dose Initial dose: 20 mg 0.25% bupivacaine with epinephrine 1: 200,000 Maintenance: bupivacaine 0.125% with fentanyl 2µg.ml-1 @10ml/hr	Continuous infusion
Chestnut[41] **1988**	N=41 Test dose: 3ml 0.5% bupivacaine with 1 in 200,000 adrenaline Initial dose: 6ml 0.125% bupivacaine and 8µg.ml-1 fentanyl Maintenance: bupivacaine 0.0625% @12.5ml/hr fentanyl 2µg.ml-1 for first 4 hours only	NA	N=39 Test dose: 3ml 0.5% bupivacaine with 1 in 200,000 adrenaline Initial dose: 6ml 0.25% bupivacaine Maintenance: bupivacaine 0.125% @12.5ml/hr	Primiparous, Continuous infusion
COMET[9, 42-45] **2001 (5 papers)**	NA	N=350 No test dose Initial dose: 15ml of 0.1% bupivacaine with fentanyl 2µg.ml-1 Maintenance: 0.1% bupivacaine with fentanyl 2µg.ml-1 @ 10ml/hr	N=353 Test dose: 3ml lidocaine 2% Initial dose: 10ml 0.25% bupivacaine Maintenance: Intermittent boluses of 10ml 0.25% bupivacaine	Primiparous, Continuous infusion (low), Intermittent bolus (high)
Dahl[46] **1999**	N=95 Test dose: 5ml bupivacaine 0.0625% with sufentanil 0.1µg.ml-1 +/- epinephrine 1µg.ml-1 Initial dose: 5ml bupivacaine 0.0625% with sufentanil 0.1µg.ml-1 Maintenance: bupivacaine 0.0625% with sufentanil 0.1µg.ml-1 +/- epinephrine 1µg.ml-1 @5ml/hr	NA	N=45 Test dose: 5ml 0.25% bupivacaine Initial dose: 5ml 0.25% bupivacaine Maintenance: bupivacaine 0.25% @ 5ml/hr	Mixed parity, Continuous infusion
El-Shaarawy[23] **2018**	N=18 No test dose Initial dose: 15 ml of levobupivacaine 0.0625% plus fentanyl 2µg.ml-1 Maintenance: 0.0625% levobupivacaine with fentanyl 2µg.ml-1 continuous infusion	NA	N=36 No test dose Initial dose: 15 ml of levobupivacaine 0.125% or 0.25% plus fentanyl 2µg.ml-1 Maintenance: levobupivacaine 0.125% or 0.25% with fentanyl 2µg.ml-1	? Mixed parity, Continuous infusion
Kocoglu[24] **2016**	N=30 No test dose Initial dose: 20ml of 0.0625% bupivacaine+25 µg fentanyl Maintenance: 0.0625% bupivacaine with fentanyl 2µg.ml-1 PCEA	NA	N=30 No test dose Initial dose: 20ml of 0.125% bupivacaine+25 µg fentanyl Maintenance: 0.125% bupivacaine with fentanyl 2µg.ml-1 PCEA	? Mixed parity, PCEA
Ewen[47] **1986**	N=25 Test dose: 3ml 0.5% bupivacaine Initial dose: 8ml 0.5% bupivacaine Maintenance: 0.08% bupivacaine continuous infusion	NA	N=28 Test dose: 3ml 0.5% bupivacaine Initial dose: 8ml 0.5% bupivacaine Maintenance: 0.25% bupivacaine continuous infusion	? Mixed parity, Continuous infusion
Ferrer Gomez[48] **2000**	N=42 No test dose Initial dose: 10ml of 0.2% ropivacaine and 50µg fentanyl Maintenance: 0.1% ropivacaine with fentanyl 2µg.ml-1 continuous infusion	NA	N=42 No test dose Initial dose: 10ml ropivacaine 0.2% Maintenance: Ropivacaine 0.2% continuous infusion	? Mixed parity, Continuous infusion
Ginosar[49] **2010**	N=43 No test dose Initial dose: 20ml 0.0625% bupivacaine plus 1µg/kg fentanyl Maintenance: 0.0625% bupivacaine continuous @ 20ml/hr plus PCEA	NA	N=24 No test dose Initial dose: 20ml 0.25% bupivacaine plus 1µg/kg fentanyl Maintenance: 0.25% bupivacaine continuous at 5ml/hr plus PCEA	Primiparous, PCEA plus Continuous infusion
Gogarten[50] **2004**	N=103 No test dose	N=100 No test dose	N=106 No test dose	Mixed parity, PCEA,

	Initial dose: 10ml ropivacaine 0.125% with sufentanil 0.75µg.ml-1 Maintenance: 0.125% ropivacaine and sufentanil 0.75µg.ml-1 PCEA	Initial dose: 10ml ropivacaine 0.175% with sufentanil 0.75µg.ml-1 Maintenance: 0.125% ropivacaine and sufentanil 0.75µg.ml-1 PCEA	Initial dose: 10ml ropivacaine 0.2% Maintenance: 0.2% ropivacaine PCEA	Study also had bupivacaine group (excluded from this analysis)
James[51] 1998	NA	N=35 No test dose Initial dose: 15 ml of 0.1% bupivacaine with fentanyl 50µg.ml-1 Maintenance: 0.1% bupivacaine and fentanyl 2µg.ml-1	N=38 No test dose Initial dose: 15 ml of 0.25% bupivacaine Maintenance: 0.1% bupivacaine and fentanyl 2µg.ml-1	? Mixed parity, Intermittent bolus
Khan[52] 2004	N=25 Test dose: 3ml 2% lidocaine with adrenaline Initial dose: 10ml 0.0625% bupivacaine and 1µg.ml-1 fentanyl Maintenance: 0.0625% bupivacaine plus fentanyl 1µg.ml-1 @ 8ml/hr	NA	N=25 Test dose: 3ml 2% lidocaine with adrenaline Initial dose: 10ml 0.125% bupivacaine Maintenance: 0.0625% bupivacaine@ 8ml/hr	Mixed parity, Continuous infusion
Lee[53] 2002	N=39 No test dose Initial dose: 10 mL of 0.2% ropivacaine plus further 5ml after 10mins if required Maintenance: 0.1% ropivacaine +/- 2µg.ml-1 fentanyl @10ml/hr	NA	N=19 No test dose Initial dose: 10 mL of 0.2% ropivacaine plus further 5ml after 10mins if required Maintenance: 0.2% ropivacaine @ 10ml/hr	Primiparous, Continuous infusion
Lowson[54] 1995	N=40 Test dose: 3ml 0.5% bupivacaine Initial dose: 5ml 0.5% bupivacaine Maintenance 0.062% or 0.031% bupivacaine and 25µg.ml-1 diamorphine @ 10ml/hr	NA	N=23 Test dose: 3ml 0.5% bupivacaine Initial dose: 5ml 0.5% bupivacaine Maintenance: 0.125% bupivacaine with 25µg.ml-1 diamorphine @8ml/hr	Primiparous, Continuous infusion
Narayanan[55] 2009	N=50 No test dose Initial dose: 10 ml 0.0625%,bupivacaine and 20µg.ml-1 sufentanil Maintenance: 0.0625%,bupivacaine and 20µg.ml-1 sufentanil	NA	N=50 No test dose Initial dose: 10 ml 0.125%,bupivacaine and 20µg.ml-1 sufentanil Maintenance: 0.125%,bupivacaine and 20µg.ml-1 sufentanil	Mixed parity, Intermittent bolus
Nobel[56] 1991	N=35 Test dose: 3ml 0.5% bupivacaine Initial dose: 5ml 0.5% bupivacaine plus further increments of 3ml as required Maintenance 0.062% or 0.031% bupivacaine and 2µg.ml-1 fentanyl	NA	N=21 Test dose: 3ml 0.5% bupivacaine Initial dose: 5ml 0.5% bupivacaine plus increments of 3ml as required Maintenance 0.125% bupivacaine and 2µg.ml-1 fentanyl	Primiparous, Continuous infusion
Nunes[25] 2016	N=33 No test dose Initial dose: 10 mL with 0.15% ropivacaine plus 10 µg sufentanil Maintenance: 0.1% ropivacaine and 0.2µg.ml-1 sufentanil PCEA	N=97 No test dose Initial dose: 10 mL 0.15% ropivacaine with 10µg sufentanil Maintenance: 0.15% ropivacaine and 0.2µg.ml-1 sufentanil	NA	Mixed parity, PCEA or Continuous infusion
Paech[57] 1993	N=20 No test dose Initial dose: 10ml bolus of 0.25% bupivacaine plus additional 4ml of 0.5% bupivacaine if required Maintenance: 0.0625% bupivacaine with fentanyl 3µg.ml-1 and adrenaline 1 in 250,000	NA	N=23 No test dose Initial dose: 10ml bolus of 0.25% bupivacaine plus additional 4ml of 0.5% bupivacaine if required Maintenance: 0.125% bupivacaine +/- fentanyl 3µg.ml-1 PCEA	? Mixed parity, PCEA

Rodriguez[58] 1990	N=16 Test dose: 2 ml 0.5% bupivacaine Initial dose: 7.5ml of 0.125% bupivacaine and 1mg butorphanol Maintenance: 0.125% bupivacaine and 0.002% butorphanol	NA	N=16 Test dose: 2 ml 0.5% bupivacaine Initial dose: 8ml of 0.25% bupivacaine Maintenance: 0.125% bupivacaine	? Mixed parity, Continuous infusion
Russell[59] 1996	N=199 Test dose: 2 ml 0.5% bupivacaine Initial dose: 10 ml 0.25% plain bupivacaine with supplementary doses of 5ml 0.25% plain bupivacaine until pain free Maintenance: 0.0625% bupivacaine plus 2.5µg.ml-1 fentanyl or 0.25µg.ml-1 sufentanil	NA	N=200 Test dose: 2 ml 0.5% bupivacaine Initial dose: 10 ml 0.25% plain bupivacaine with supplementary doses of 5ml 0.25% plain bupivacaine until pain free Maintenance: 0.125% bupivacaine	Mixed parity, Continuous infusion
Sanchez-Pereles[60] 1999	N=38 Test dose: 4ml of 0.25% bupivacaine with 1in 200,000 adrenaline Initial dose: 4ml of 0.25% bupivacaine Maintenance: 0.0625% bupivacaine with 1 in 1,600,000 adrenaline and fentanyl 1µg.ml-1 continuous @ 10ml/hr	NA	N=38 Test dose: 4ml of 0.25% bupivacaine with 1in 200,000 adrenaline Initial dose: 4ml of 0.25% bupivacaine Maintenance: 0.125% bupivacaine with 1 in 1,600,000 adrenaline and fentanyl 1µg.ml-1 continuous @ 10ml/hr	Primiparous, Continuous infusion
Sanchez-Pereles[61] 1993	N=20 Test dose: 4ml of 0.25% bupivacaine with 1in 200,000 adrenaline Initial dose: 4ml of 0.25% bupivacaine with 1in 200,000 adrenaline Maintenance: 0.0625% bupivacaine with 1 in 1,600,000 adrenaline and fentanyl 1µg.ml-1	NA	N=20 Test dose: 4ml of 0.25% bupivacaine with 1in 200,000 adrenaline Initial dose: 4ml of 0.25% bupivacaine with 1in 200,000 adrenaline Maintenance: 0.125% bupivacaine with 1 in 1,600,000 adrenaline and fentanyl 1µg.ml-1	Primiparous, Continuous infusion
Sia[62] 1999	N=25 Test dose: 3.5ml of 1.5% lidocaine Initial dose: 8ml 0.2% ropivacaine Maintenance: 0.125% ropivacaine	NA	N=25 Test dose: 3.5ml of 1.5% lidocaine Initial dose: 8ml 0.2% ropivacaine Maintenance 0.2% ropivacaine PCEA	Primiparous, PCEA
Stoddart[63] 1994	N=38 Test dose: 3ml 0.5% bupivacaine Initial dose: 5 or 6ml 0.5% bupivacaine (8 if below 165cm, 9 is above 165cm) plus 5-8ml 0.25% bupivacaine if required Maintenance: bupivacaine 0.0625% plus fentanyl 1µg.ml-1 @10ml/hr	NA	N=40 Test dose: 3ml 0.5% bupivacaine Initial dose: 5 or 6ml 0.5% bupivacaine (8 if below 165cm, 9 is above 165cm) plus 5-8ml 0.25% bupivacaine if required Maintenance: bupivacaine 0.125% plus fentanyl 1µg.ml-1 @10ml/hr	Primiparous, Continuous infusion
Tixier[64] 2010	N=65 Test dose: 5ml of 0.0568% levobupivacaine with 0.45µg.ml-1 sufentanil Initial dose: 15ml of 0.0568% levobupivacaine with 0.45µg.ml-1 sufentanil Maintenance: 0.0568% levobupivacaine with 0.45µg.ml-1 sufentanil	NA	N=60 Test dose: 5ml of 0.1136% levobupivacaine with 0.45µg.ml-1 sufentanil Initial dose: 15ml of 0.1136% levobupivacaine with 0.45µg.ml-1 sufentanil Maintenance: 0.1136% levobupivacaine with 0.45µg.ml-1 sufentanil	Primiparous, PCEA plus Continuous infusion
Vilaplana[65] 1995	N=31 No test dose Initial dose: 10ml bupivacaine 0.125% with 1:400,000 adrenaline and 50µg fentanyl Maintenance: bupivacaine 0.0625% with fentanyl 1µg.ml-1 plus adrenaline 1 in 800,000	NA	N=66 No test dose Initial dose: 8ml bupivacaine 0.25% with 1:200,000 adrenaline and 50µg fentanyl Maintenance: bupivacaine 0.125% or bupivacaine 0.25%, with adrenaline 1 in 200,000 or 1 in 400,000	Mixed parity, PCEA

Table 4-3 Characteristics of included studies

4.2.1 Risk of bias

Risk of bias assessment is illustrated in Figure 4-5. Thirteen studies were assessed as being at a low risk of bias, nine at moderate risk and 10 at a high or unclear risk of bias.

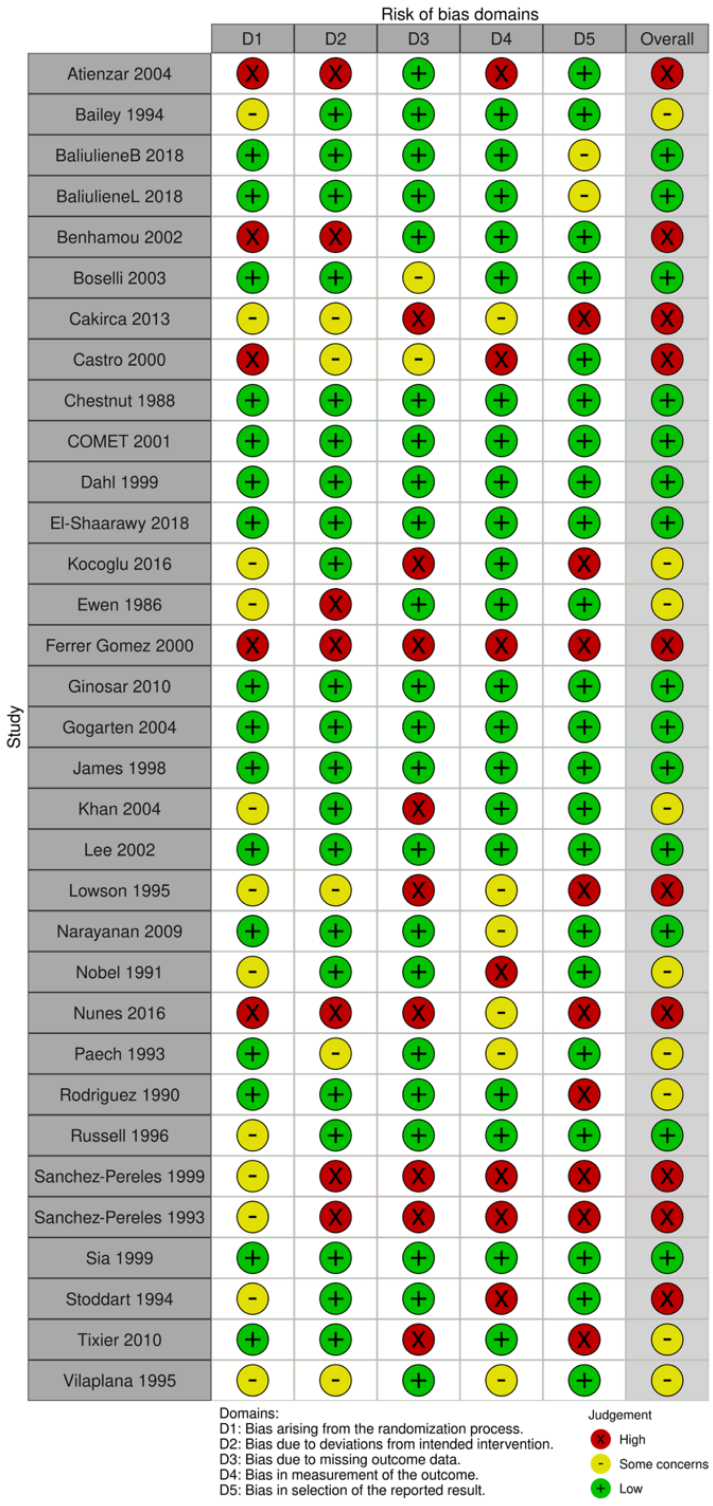
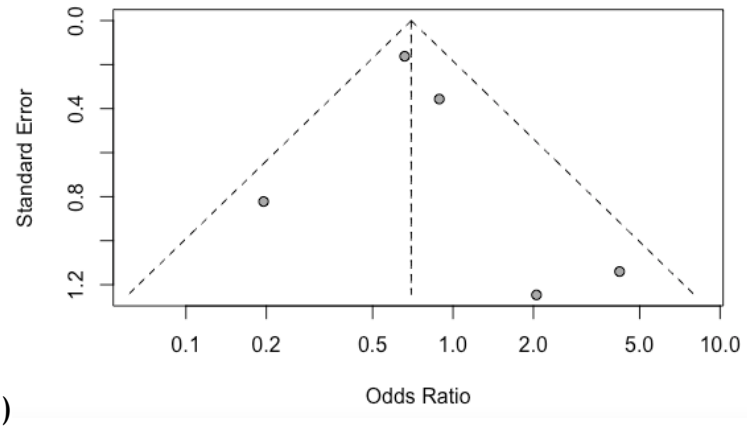
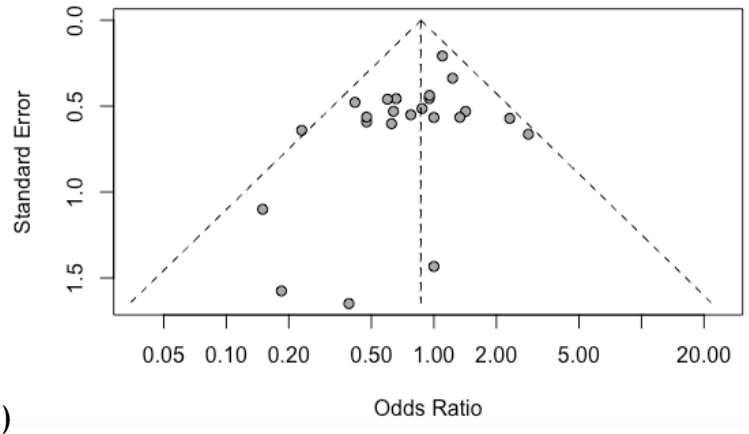


Figure 4-5 Risk of Bias Assessment (ROB2)

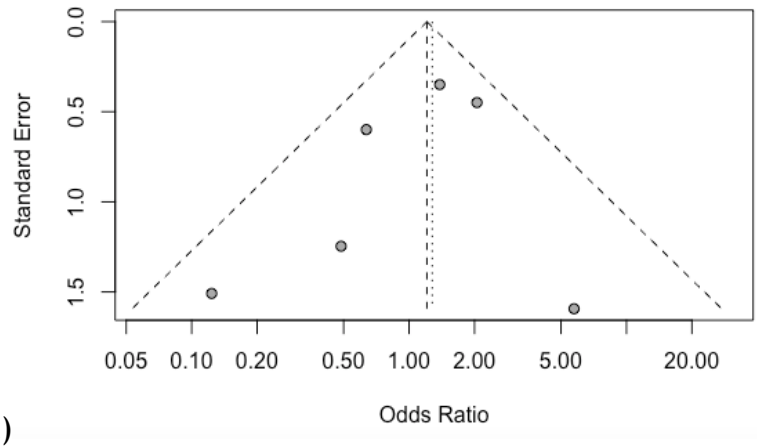
Funnel plots were used to assess for evidence of publication bias. For assisted vaginal birth, three plots were created, for each of the three pair-wise comparisons of local anaesthetic concentration (Figure 4-6). Funnel plots appeared reasonably balanced, suggesting minimal publication bias.



(a)



(b)



(c)

Figure 4-6 Funnel plots to assess for publication bias in results for Assisted vaginal birth. (a) High : Low concentration, (b)High : Ultra-Low concentration, (c) Low : Ultra-low concentration

4.2.2 Spontaneous vaginal birth

All thirty-two studies (n = 3665) reported rates of SVB as an outcome measure. Of these, six compared ULC with LC, 27 compared ULC with HC concentration and five compared LC with HC (Figure 4-3). For ULC compared with HC, the rate of spontaneous vaginal birth was increased (median OR 1.46, 95% credible interval [1.18 to 1.86]). Whilst the comparisons of ULC vs. LC (1.07, [0.75, 1.56]) and LC vs. HC (1.36 [0.97, 1.94] did not reach statistical significance (Table 4-4, Figure 4-7), we are able to use the results of the Bayesian analysis to infer that the estimated probability of LC increasing the incidence of spontaneous vaginal birth compared with HC is 96%. Furthermore, there is a 65.5% probability that ULC increases the chance of a spontaneous vaginal birth compared with LC.

Pairwise meta-analysis was carried out for incidence of SVB (Figure 4-8). These results are similar to those from Bayesian analysis. Incidence of SVB is increased in ULC vs. HC, but the comparisons of ULC vs. LC and LC vs. HC did not reach statistical significance.

Outcome	Totals	High : Low (OR, [95% CrI])	High : Ultra-low (OR, [95% CrI])	Low : Ultra-low (OR, [95% CrI])
Spontaneous vaginal birth	32 studies (n=3665)	1.36 [0.97, 1.94]	1.46 [1.18, 1.86]	1.07 [0.75, 1.56]
Assisted vaginal birth	32 studies (n= 3665)	0.71 [0.43, 1.25]	0.87 [0.64, 1.16]	1.23 [0.68, 2.04]
Caesarean birth	32 studies (n=3665)	1.03 [0.65, 1.57]	0.78 [0.58, 1.05]	0.76 [0.49, 1.22]
Top up dose required	16 studies (n=1494)	1.15 [0.31, 4.35]	1.27 [0.75, 2.16]	1.10 [0.30, 4.04]
Pruritis	20 studies (n=2048)	4.13 [0.94, 20.4]	5.55 [2.18, 16.3]	1.35 [0.31, 5.74]
Nausea and vomiting	19 studies (n=1912)	1.09 [0.51, 2.18]	1.30 [0.85, 2.08]	1.20 [0.63, 2.47]
Hypotension	20 studies (n=1584)	0.85 [0.02, 29.89]	1.08 [0.36, 2.95]	1.28 [0.04, 40.13]
Urinary retention	10 studies (n=1078)	1.06 [0.24, 4.59]	0.83 [0.29, 2.10]	0.78 [0.18, 3.04]
Bromage score >0	27 studies (n=2529)	0.72 [0.26, 2.05]	0.32 [0.18, 0.54]	0.44 [0.16, 1.17]
Apgar score <7 at 1 minute	18 studies (n=2315)	2.00 [1.16, 3.81]	0.85 [0.55, 1.27]	0.43 [0.21, 0.79]
Apgar score <7 at 5 minutes	19 studies (n=2428)	3.05 [0.17, 243.69]	0.35 [0.02, 4.49]	0.11 [0, 2.26]

Table 4-4 Odds ratios and 95% credible Intervals for all binary outcomes

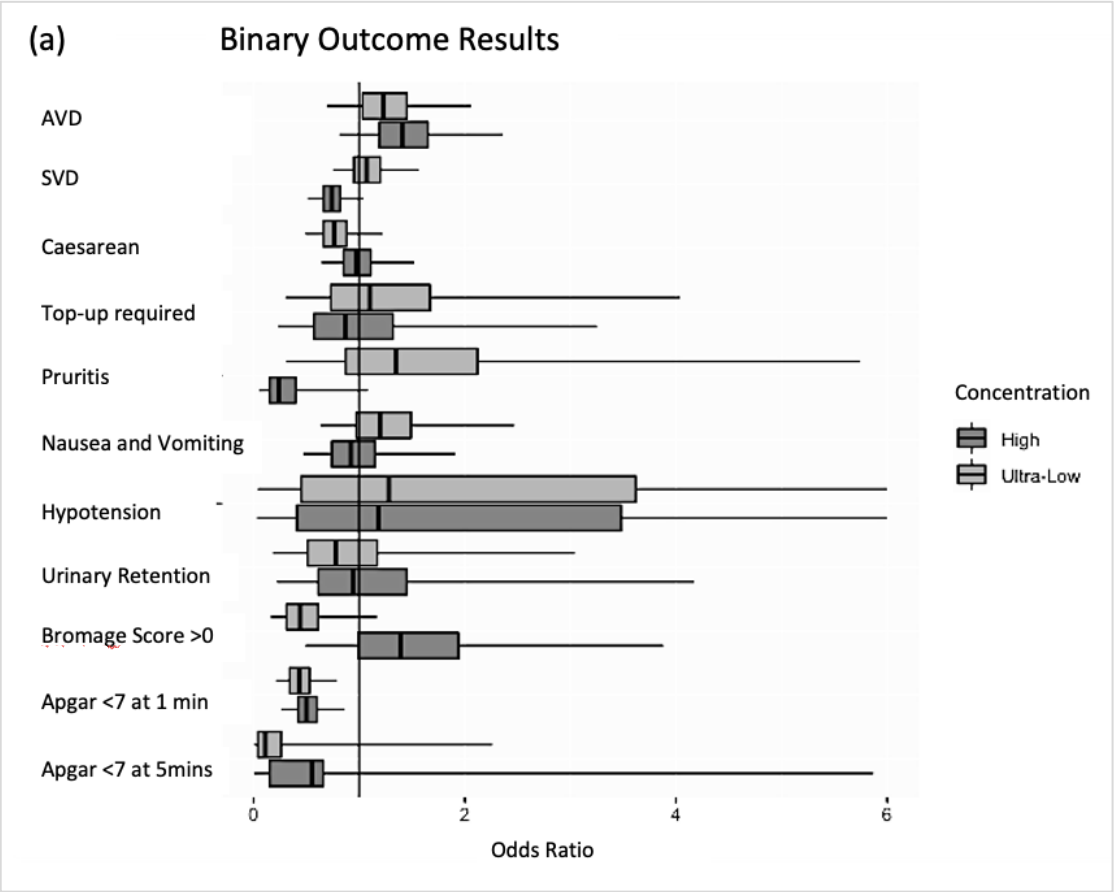
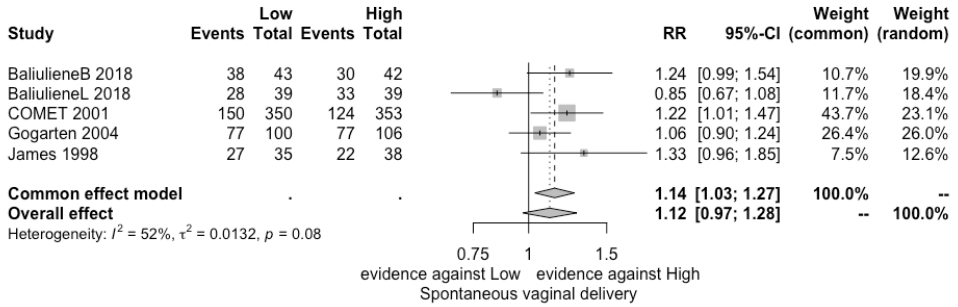
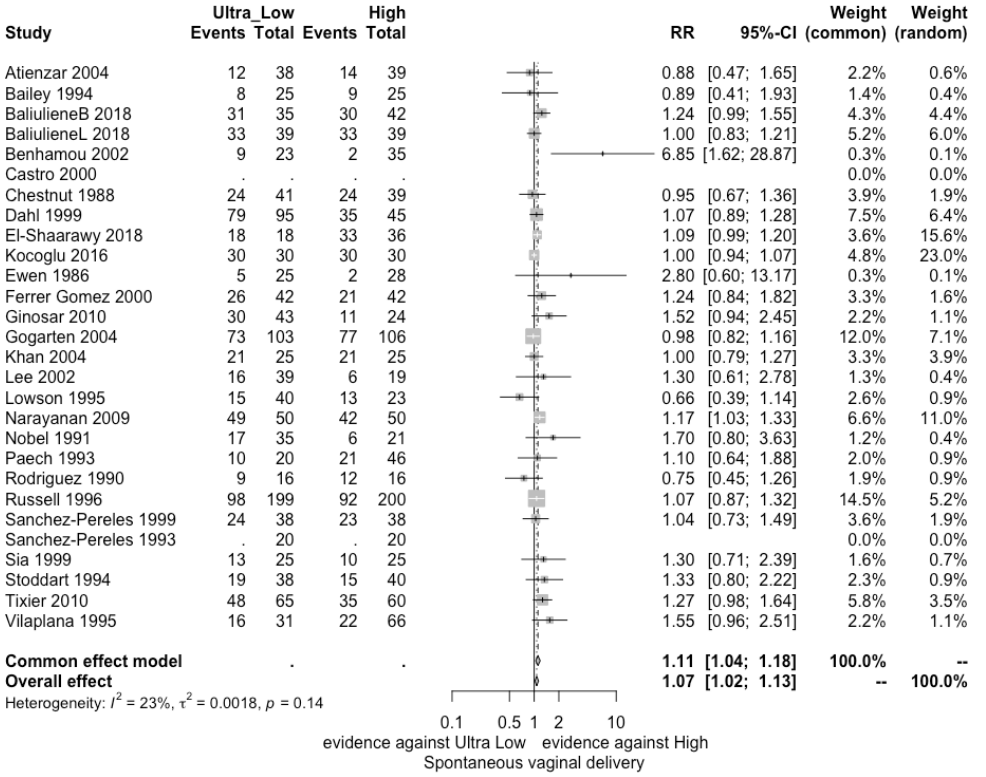


Figure 4-7 Box and whisker plot for binary and outcomes. Low concentration is the reference concentration to which high and ultra-low concentrations are compared. The box represents the interquartile range and the whiskers represent the 95% Credible intervals. The credible intervals for hypotension have been truncated to fit onto graph (see Table 4-4 for upper limits of credible intervals)

(a)



(b)



(c)

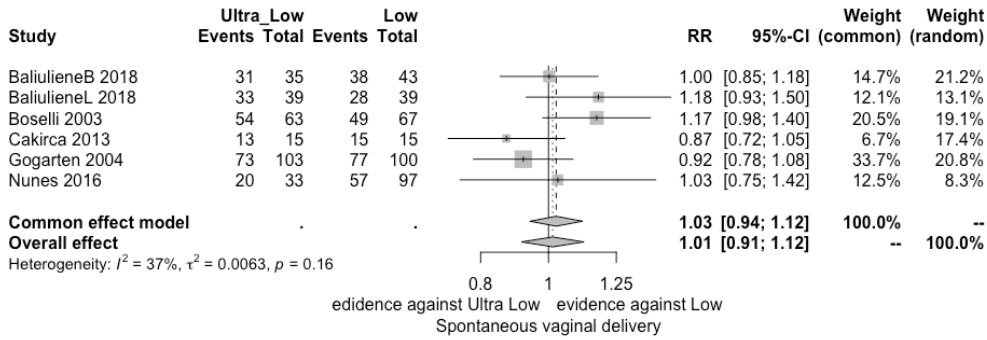


Figure 4-8 Forest plots for rate of spontaneous vaginal birth (a) High : Low concentration, (b) High : Ultra-Low concentration and (c) Low : Ultra-Low concentration.

4.2.3 Caesarean birth

Caesarean birth rates were reported in all 32 studies. None of the three comparisons reach statistical significance for caesarean birth (Table 4-5, Figure 4-7). From Bayesian analysis, we can estimate the probability that the incidence of caesarean birth is decreased in LC as compared with HC at 45%, and for ULC to HC at 96%. The estimated probability that the incidence of caesarean birth is decreased in ULC compared with LC is 88.5%.

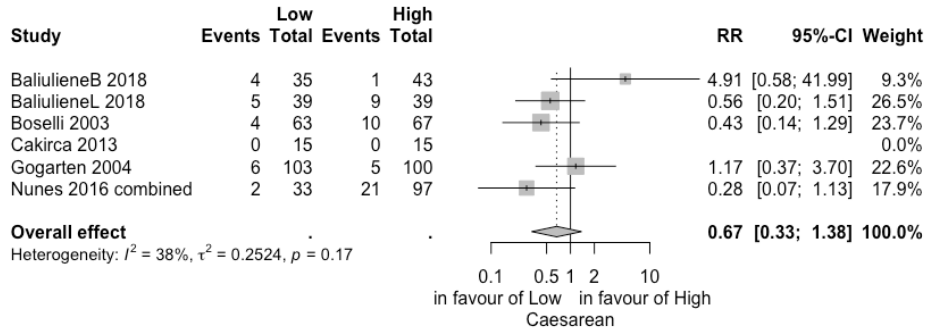
The results of the pairwise meta-analysis for incidence of caesarean birth (Figure 4-9) are similar to those from Bayesian analysis.

4.2.4 Assisted vaginal birth

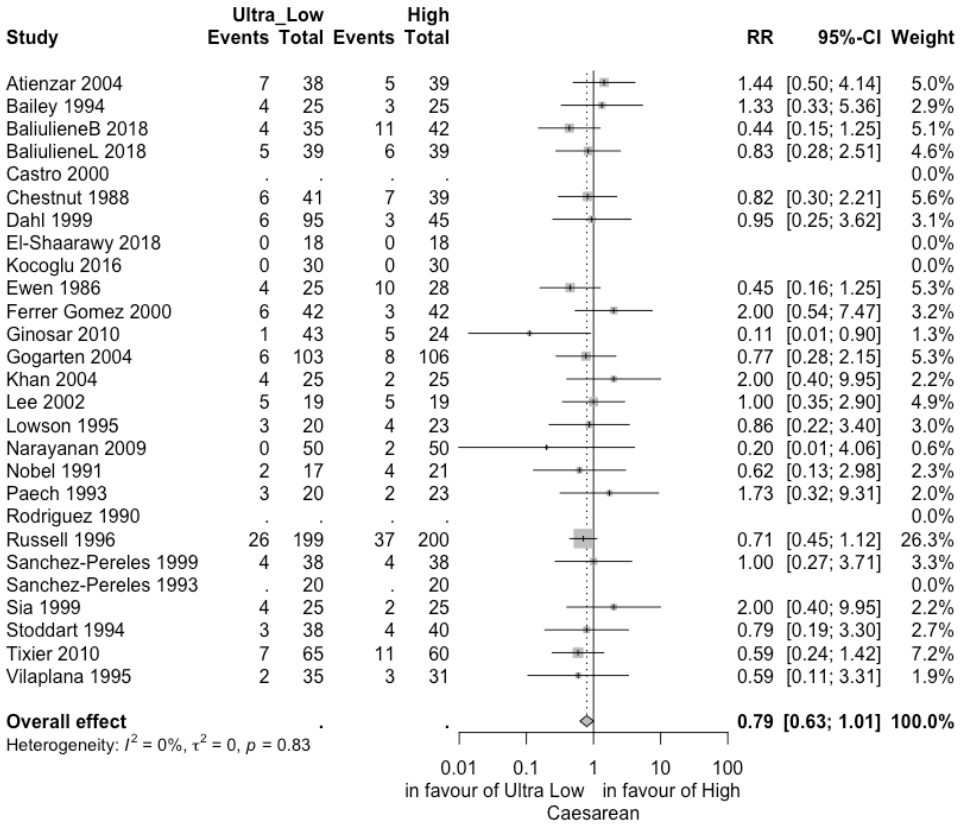
Thirty-two studies reported AVB as an outcome measure. The risk of AVB was lowest in the LC group, followed by the ULC group and highest in the HC group, though none of these comparisons reached statistically significant (LC vs HC median odds ratio (OR) 0.62 (95% CrI 0.38, 1.09); ULC vs HC OR 0.84 (95% Cr1 [0.62, 1.12]); ULC vs LC OR 1.35 (95% CrI [0.75, 2.26]) (Table 4-4, Figure 4-7).

The results of the pairwise meta-analysis for incidence of AVB (Figure 4-10) corroborate with those from the Bayesian analysis.

(a)



(b)



(c)

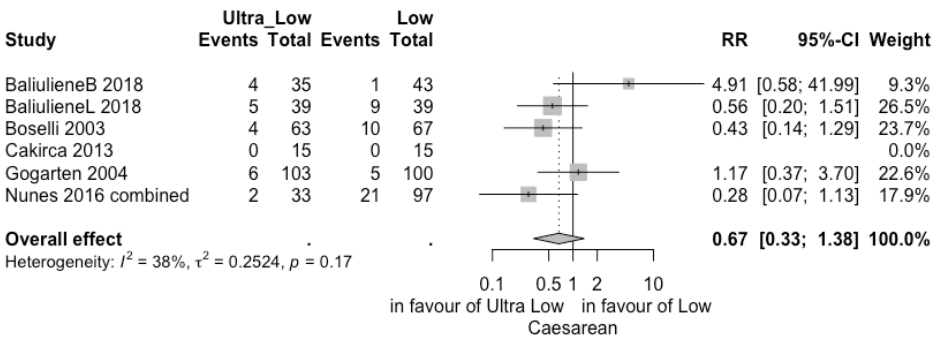
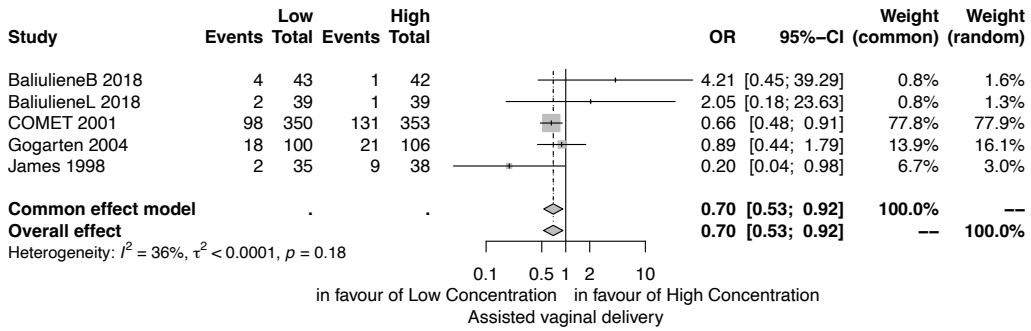
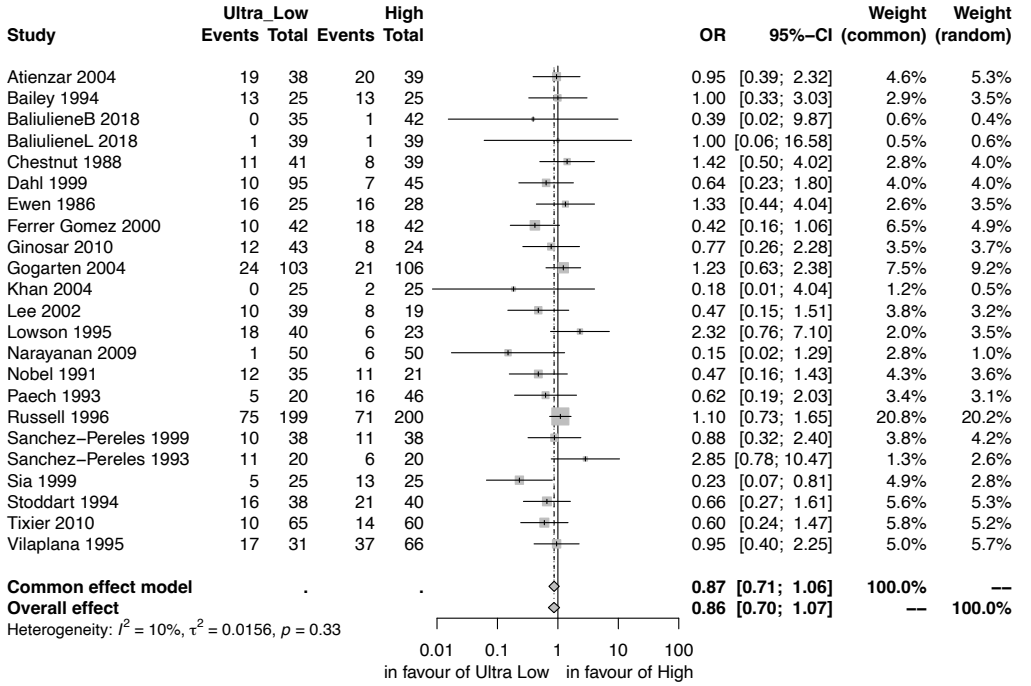


Figure 4-9 Forest plots for Rate of Caesarean birth (a) High : Low concentration, (b) High : Ultra-Low concentration and (c) Low : Ultra-Low concentration.

(a)



(b)



(c)

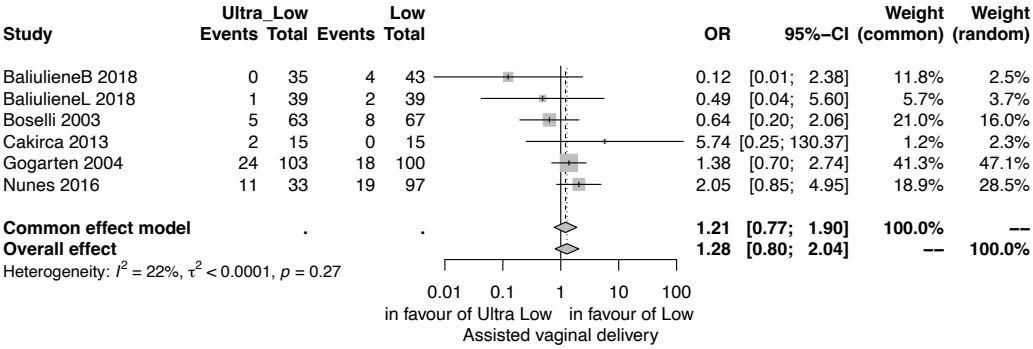


Figure 4-10 Forest plots for Rate of Assisted vaginal birth (a) High : Low concentration, (b) High : Ultra-Low concentration and (c) Low : Ultra-Low concentration.

4.2.5 Mode of birth limited to papers published in the last 10 years

Five of the 32 studies were published between 2011 and 2021. This included 511 parturients: 170 received ULC; 194 received LC and 147 women received HC. The results are presented in Table 4-5. None of the results reach significant significance. For spontaneous vaginal birth and caesarean birth, the results appear to be similar to those found in the main analysis, but the credible intervals are wider. No conclusions can be drawn from the results for assisted vaginal birth due to the wide credible intervals.

Outcome	Totals	High : Low (OR, [95% CrI])	High : Ultra-Low (OR, [95% CrI])	Low : Ultra-low (OR, [95% CrI])
Spontaneous vaginal birth	5 studies (n = 511)	1.74 [0.24, 30.85]	1.94 [0.25, 23.09]	1.10 [0.11, 6.18]
Assisted vaginal birth	5 studies (n = 511)	1.58 [0, 249.03]	1.54 [0, 258.18]	0.99 [0.01, 74.94]
Caesarean birth	5 studies (n = 511)	0.24 [0.10, 4.04]	0.40 [0.15, 9.23]	0.61 [0.02, 16.29]

Table 4-5 Subgroup analysis for mode of birth of papers published in 2011-2021: Odds ratios (OR) and 95% credible Intervals [95% CrI]

4.2.6 Total local anaesthetic dose

Twenty-three studies reported the total dose of local anaesthetic received as an outcome measure (2825 women). As the concentration decreased, there was a step-wise reduction in total amount of local anaesthetic received. Parturients receiving ULC received the lowest total dose, followed by parturients receiving LC, and women receiving HC received the greatest cumulative dose of local anaesthetic. UL total dose was significantly lower than LC (weighted mean difference -14.96mg, 95% credible interval [-28.38, -1.00]). The total dose of local anaesthetic was significantly lower for both LC and ULC compared with HC (Table 4-6, Figure 4-11). Sixteen studies (1494 women) reported number of

rescue top-ups required. There were no significant differences in the between ultra-ULC, LC or HC groups (Table 4-4, Figure 4-7).

Outcome	Totals	High : Low (WMD, [95% CrI])	High : Ultra-Low (WMD, [95% CrI])	Low : Ultra-low (WMD, [95% CrI])
Duration 1st stage of labour	14 studies (n=2319)	39.96 [10.84, 70.58]	3.50 [-15.33, 27.88]	-36.15 [-63.23, -8.52]
Duration 2nd stage of labour	17 studies (n=2559)	-11.14 [-23.45, 0.97]	-13.02 [-21.54, -4.77]	-1.92 [-14.35, 10.20]
Total dose local anaesthetic	23 studies (n=2825)	-14.99 [-28.79, -2.04]	-30.10 [-38.21, -22.20]	-14.96 [-28.38, -1.00]
Visual Analogue Score at 30 mins (scale 1:100)	8 studies (n=687)	8.68 [-2.34, 20.03]	3.09 [-0.10, 7.69]	-5.44 [-16.75, 5.93]
Visual Analogue Score at 60 mins (scale 1:100)	9 studies (n=940)	4.49 [-2.43, 12.07]	3.16 [-1.10, 7.21]	-1.36 [-9.00, 5.54]
Maternal satisfaction (scale 1:100)	6 studies (n=527)	4.45 [-4.87, 13.54]	-0.65 [-7.14, 6.31]	-5.04 [-13.11, 3.93]
Umbilical Artery pH	4 studies (n=590)		0.01 [-0.03,0.06]	

Table 4-6 Weighted mean difference and 95% Credible Intervals for all outcomes

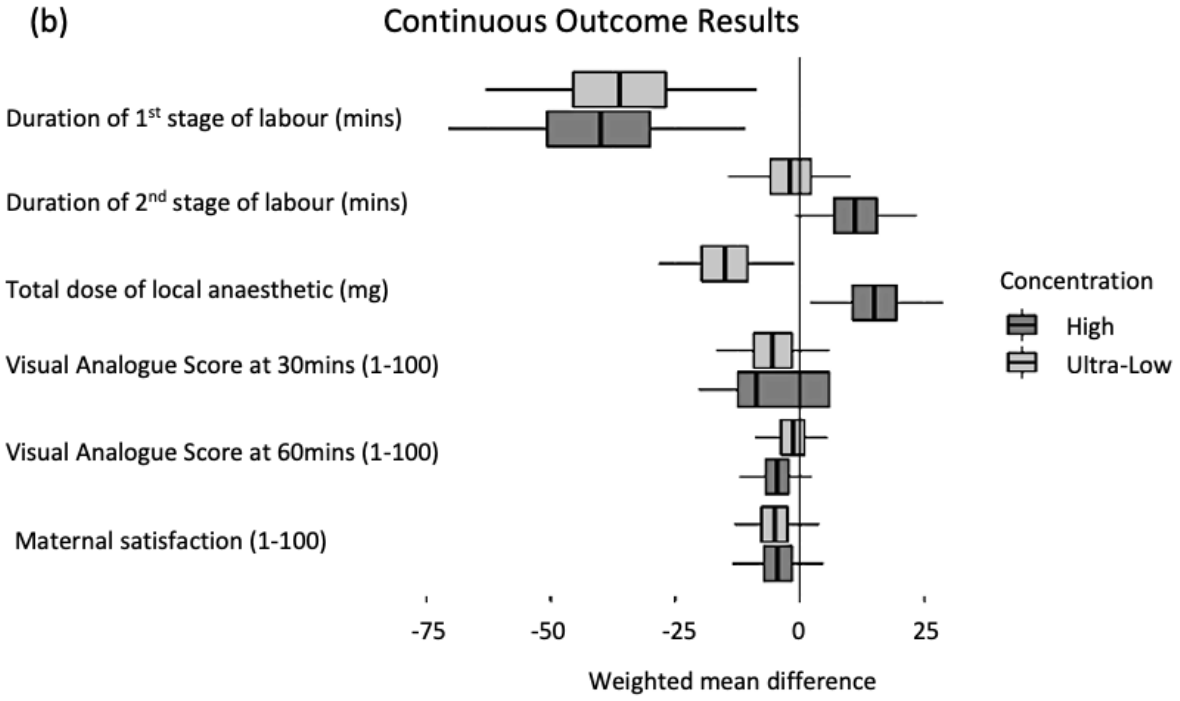


Figure 4-11 Box and whisker plot for continuous outcomes. Low concentration is the reference concentration to which high and ultra-low concentrations are compared. The box represents the interquartile range and the whiskers represent the 95% Credible intervals.

4.2.7 Maternal outcomes

4.2.7.1 Duration of Labour

Fourteen studies reported results for the duration of the first stage of labour. Duration of the first stage of labour was significantly increased in the LC group compared to HC groups (weighted median difference (WMD) 39.96 minutes, 95% CrI [10.84, 70.58]). The duration of the first stage of labour was significantly reduced in the ULC compared to the LC group (WMD -36.15 minutes, 95% CrI [-63.23, -8.52]). Duration of the first stage of labour for the ULC group was not different to that of the HC group (Table 4-6, Figure 4-11).

Duration of the 2nd stage labour was decreased in both LC and ULC groups compared to the HC group. This difference was significant for UL vs HC (WMD -13.02 minutes, 95% CrI [-21.54, -4.47]) but did not reach significance for the LC vs HC (WMD -11.14 minutes, 95% CrI [-23.45, 0.97]). There were no significant differences between LC and ULC groups for duration of the second stage of labour (Table 4-6, Figure 4-11).

4.2.7.2 Pain scores and maternal satisfaction

Eight studies (687 women) reported 30-minute visual analogue (VAS) pain scores, 9 studies (940 women) reported 60-minute VAS scores, and 6 studies (527 women) reported maternal satisfactions scores. The 30- or 60- min VAS pain scores and maternal satisfaction scores were similar between the three groups (Table 4-6, Figure 4-11).

4.2.7.3 Maternal adverse effects

There were no significant differences in rates of pruritus, nausea and vomiting, urinary retention, or hypotension (Table 4-4, Figure 4-7). Parturients receiving ULC were significantly less likely to have a Bromage score > 0 compared with HC (OR 0.32, 95% credible interval [0.18, 0.54]) but there was no difference between LC and ULC (Table 4-4, Figure 4-7). Only two studies reported inability to ambulate as an outcome measure. James *et al* (1998) found that 2.9% of women in the LC group were unable to ambulate compared to 84.2% in the HC group. Narayanan *et al* (2009) found that 8% in the ULC group and 38% in the HC group were unable to ambulate. No studies reported second or third-degree tears or post-partum haemorrhage.

4.2.8 Neonatal outcomes

4.2.8.1 Apgar Scores

Eighteen trials (2315 women) reported Apgar score < 7 at 1 minute (Table 4-4, Figure 4-7). The neonates in the LC group had a significantly higher risk of having an Apgar score < 7 at 1 minute compared to those in the HC group (OR 2.00, 95% credible interval [1.16 to 3.81]). The difference between ULC and HC concentration was not significant (Table 4-4, Figure 4-7). Compared with the LC group, neonates in the ULC group were significantly less likely to have an Apgar score < 7 at 1 minute (OR 0.43 [0.21 to 0.79]). A subgroup analysis was carried out after removing results from the COMET study.[78] This was the largest study which was included in the analysis (703 women), and therefore its finding of a less favourable Apgar at 1 minute in the LC group compared to the HC group was highly influential in the overall meta-analysis of this outcome. Nevertheless,

when the COMET study was excluded from the analysis this finding persisted (OR 0.34 [0.10 to 0.98]).

The incidence of 5 minute Apgar Score <7 was reported in 19 trials. There were no significant differences between the three concentrations for incidence of low 5-minute Apgar score (with HC as reference, LC OR 3.05 (95% CrI [0.20-165.32]), ULC OR 0.36 (95%CrI [0.03, 4.51]) and with LC as a reference, ULC OR 0.12 (95% CrI [0.00, 2.10]). The credible intervals are wide due to this being an infrequent occurrence (Table 4.4, Figure 4.7).

4.2.8.2 Neonatal resuscitation

Four studies (823 women) reported need for 'high level' neonatal resuscitation (which was defined as one or more of bag/mask ventilation, intubation or administration of naloxone) as an outcome measure. None of the neonates in three of these studies had any requirement for resuscitation. Only one study (COMET)[78] reported any high-level resuscitative events. The LC group was associated with an increased rate of 'high-level' resuscitation than the HC group (5% vs 1% p = 0.02). The COMET studies also reported "any requirement" for neonatal resuscitation (which they did not specifically define). Rates of "any requirement" neonatal resuscitative events did not differ between the LC and HC groups. COMET was the only trial to report on rates of admission to neonatal intensive care, these did not differ significantly between the LC and HC groups (28% vs 25%, p = 0.4).

4.2.8.3 Umbilical artery pH

Umbilical artery pH was recorded in four studies (590 women). There were no significant differences between ULC and HC groups (HC as reference, WMD 0.01 (95% CrI [-0.03, 0.06])). None of the LC studies reported umbilical artery pH. The study by Baliuliene et al. was excluded from this analysis as it did not specify whether umbilical cord pH was arterial or venous.

4.2.8.4 Breastfeeding

Breastfeeding at six weeks was only recorded in the COMET trial (703 women), where they did not find a significant difference between the LC and HC groups. No studies reported rates of breastfeeding within 24 hours.

4.2.9 Early Childhood outcomes

None of the 32 studies reported any early childhood outcomes.

4.3 Discussion

This network meta-analysis found that when compared with LC, ULC local anaesthetic is associated with reduced total local anaesthetic dose, shorter first stage of labour, and reduced incidence of Apgar <7 at 1 minute. Despite the lower concentration, there was no compromise in maternal analgesia or maternal satisfaction, and no difference in the incidence of adverse maternal effects or adverse neonatal outcomes. Both ULC and LC appear to increase the chance of an SVB compared to HC. From the results of the Bayesian analysis, there is evidence that ULC may increase the likelihood of SVB and reduce the incidence of caesarean birth compared to LC. Rates of AVB were not affected. HC local anaesthetics do not offer any advantages compared with ULC local anaesthetic.

Mode of birth is the primary outcome measure for this meta-analysis. Parturients must deliver by either SVB, AVB or caesarean birth, so the fact that only the result for SVB reaches this level of statistical significance would suggest that either our sample size was not adequately powered for the other two outcomes, or that the result for SVB happened by chance. An advantage of using Bayesian methods is that we can calculate the probability of a treatment effect, given the observed data. Using Bayesian analysis, we were able to demonstrate a 99.9% probability that rates of spontaneous vaginal birth were increased with ULC compared to HC, and a 96% probability that LC increased rates of SVB compared to HC. This corroborates previous research, and is reassuring as using HC local anaesthetics has fallen out of favour. We are also able to estimate the probability that ULC increases the incidence of SVB when compared to LC at 65.5%. The estimated probability that ULC compared to LC decreases the incidence of AVB is 22% and the probability that it decreases incidence of caesarean birth 88.5%. Although these results do not meet the predetermined cut off level of 95% specified in our methods section, they may represent a potential benefit for further reducing local anaesthetic concentrations from LC to ULC to increase the rate of SVB and reduce rates of caesarean birth. The benefit of a Bayesian analysis is that we can directly present these probabilities. This allows individual clinicians to interpret them into the wider clinical context and deciding for themselves whether they consider 65.5% or 88.5% probabilities represent a potential benefit for their clinical practice.

As mentioned in the introduction, both epidural and obstetric practices are evolving. Rates of AVB are falling,[112] and caesarean birth rates are increasing at a rate of 4% per year worldwide.[113] Accumulating evidence supports the use of PIEB plus PCEA rather than continuous epidural regimes to reduce the total dose of local anaesthetic given.[98,99] As many of the studies included in this analysis were more than 10 years old, and to evaluate more contemporary clinical practice, we performed a subgroup analysis limiting studies to included only those published in the past 10 years. Only 5 studies (511 women) were published between 2011 and 2021, which limited this analysis. The results for SVB and caesarean birth were similar to those in the main analysis, but did not reach statistical significance. For AVB no conclusions could be drawn (Table 4.5). Reducing the concentration of local anaesthetic is a straightforward intervention that would be easy to implement. It appears to provide at least as good maternal and neonatal outcomes, and does not compromise on analgesia. A large multicentre randomised controlled trial that compared LC with ULC local anaesthetics could potentially further clarify whether there are any benefits of lowering the concentration of local anaesthetic in labour epidurals.

Two previous meta-analyses have examined epidural versus non-epidural analgesia.[33,109] A Cochrane analysis with over 40,000 parturients found an increased risk of AVB with epidural, but this effect disappeared when studies prior to 2005 were excluded – when higher concentrations of local would have been more common.[33] A more recent meta-analysis (10 studies and 1809 parturients) examined low-dose LA epidural versus non-epidural analgesia and did not detect any significant difference in the rates of AVB, SVB or caesarean birth.[109] Our study was considerably larger, hence has more power to detect differences. On comparison of the dose of anaesthetics a 2013 meta-analysis (11 studies, 1997 women) comparing HC (>0.1% bupivacaine or equivalent ropivacaine) and LC (≤0.1% bupivacaine), found an increased risk of AVB but not of caesarean birth when high concentrations were compared to low.[79] A recent meta-analysis looked at LC local anaesthetics with opioid (≤0.1% bupivacaine or equivalent) and moderately HC local anaesthetic (>0.1% but ≤0.125% bupivacaine or equivalent) without opioid for labour epidural. They did not detect any significant differences in mode of birth or neonatal outcomes.[80] Eight of the 9 included studies in this meta-analysis are included in our study. One study was

excluded from our analysis as it compared different local anaesthetics, bupivacaine and ropivacaine, in the different arms of the trial.[200] Together, these studies have influenced obstetric anaesthetic practice and the underlying trials have led to the widespread adoption of LC of local anaesthetics in epidurals. Our own study reaffirms the benefits of LC versus HC local anaesthetics, by reducing cumulative local anaesthetic consumption, reducing risk of assisted vaginal birth, improving chance of a SVB, as well as generally improved maternal and neonatal outcomes. This analysis was designed to provide further evidence regarding comparison of HC and LC, but more importantly to specifically compare the effects of ULC to LC. We are not aware of any other meta-analysis that has compared these.

The use of ULC local anaesthetic was associated with a significantly lower cumulative dose of local anaesthetic than LC. This may be associated with potential benefits for the parturient in a lesser degree of motor block (as demonstrated by the reduced incidence of Bromage score <0 in ultra-low concentration as compared to high concentration), which may be more comfortable for the patient, and a reduced risk of local anaesthetic toxicity. In addition, high doses of local anaesthetic are more likely to block the activity of autonomic nerves involved in uterine contraction. Reducing the total dose of local anaesthetic in labour epidural may also reduce rates of epidural related fever.[131] (see section 2.4.3)

The effect of local anaesthetic concentration on the duration of the first stage of labour is unclear. It appears that LC local anaesthetics significantly increase the duration of the first stage of labour when compared to both HC and ULC, but that no difference is observed between HC and ULC. It has been suggested that epidural analgesia can both reduce and increase duration of the first stage of labour.[105,201] Slow labour progression is associated with higher levels of plasma adrenaline and cortisol.[106] Both maternal cortisol and adrenaline levels decrease as pain reduces.[107,108] Relaxation of alpha receptors may improve uterine perfusion, leading to more effective contraction. In this way, labour neuraxial analgesia may shorten the first stage of labour. However, local anaesthetics may also block autonomic nerve, leading to less effective contraction.[33] These results may also reflect the lack of a clearly defined starting point for the first stage of

labour. The first stage of labour can be divided into a latent 1st stage of labour, where there are irregular contractions and cervix is long and less than 4cm dilated, and the active first stage of labour, when the cervix is more than 4cm dilated and contractions regular. None of the papers clarify a definition for the starting point of labour, so this result may reflect heterogeneity of outcome reporting. Heterogeneity of duration of the first stage of labour has been reported in other meta-analyses.[105] Data on duration of epidural analgesia were not available.

It is reassuring that there do not appear to be any significant differences in neonatal outcomes, with the exception of 1 minute Apgar score <7. A 5 minute Apgar score <7 is more predictive of poor neonatal outcomes than 1 minute scores.[202,203] We found no significant differences in rate of 5 minute Apgar score <7 nor umbilical cord pH between the three different local anaesthetic concentrations. However, patients in the LC group were around twice as likely to have a 1-minute Apgar score <7 compared to HC and ULC groups. This difference persisted when we performed a sensitivity analysis excluded the COMET study from the analysis. The authors of the COMET study suggested that the increased incidence of low Apgar score in the LC group may reflect an increased use of epidural opioids in the LC group. However, this suggestion is disputed by a meta-analysis looking at the effects of epidural or spinal opioids for labour analgesia (21 RCTs, 2859 participants). They found no difference in Apgar scores at 1 or 5 minutes compared with those not receiving neuraxial opioids.[153] Furthermore, we would expect that patients receiving ULC would be as likely to receive epidural opioids as those in the LC group. When the COMET study was excluded from our analysis, ULC was still significantly less likely to be associated with 1 minute Apgar score <7 than LC. It is perhaps reassuring that unlike 5 minute Apgar score, a 1 minute Apgar score <7 is not associated with poorer long-term developmental outcomes.[151] Adverse neonatal outcomes are rare, and whilst the results of this meta-analysis are reassuring, only nine of the included studies are powered appropriately to answer the question of the association of LA concentrations with neonatal outcomes. None of the included studies reported any childhood developmental outcome data. A recent population-based cohort study of 435,281 mother-offspring pairs found that after adjustment for

confounders including mode of birth, epidural analgesia was associated with small reduction in adverse childhood developmental outcomes.[169]

Our study has several strengths, including a systematic search strategy, a large robust Bayesian network meta-analysis design incorporating 32 studies and 3665 women, and the use of Bayesian inference to calculate the probabilities of attaining an SVB or requiring operative birth for each local anaesthetic group. We also acknowledge that our study has several weaknesses, particularly the heterogeneity of the underlying studies. Local anaesthetic concentrations were not the only intervention in these studies, as adjuvant agents such as adrenaline or opioids were frequently used. In current clinical practice, most places providing labour epidural analgesia use opioids routinely as part of epidural maintenance solutions. In some of the included studies the addition of opioids varied between different local anaesthetic concentrations with ultra-low (27 of 30 studies) and low concentration (8 of 8 studies) local anaesthetic solutions more likely to be combined with an opioid than high concentration solutions (16 of 30 studies). Despite this we were unable to find any significant differences between these, with the exception of the Apgar score at 1-minute which we explored in detail above and increased local anaesthetic concentration being associated with higher Bromage score, which is much more likely explained by the increased local anaesthetic concentration. Although we have not explored it in this study, reducing the concentration of local anaesthetic may increase requirements for epidural opioids. We do not know the 'threshold' local anaesthetic concentrations that requires co-administration with epidural opioids. This may be an area to explore in the future. We included all methods of administration of the epidural maintenance solution (continuous, PCEA, PIEB, intermittent physician bolus, or any combination of the above). This may influence our results as there is evidence that women require lower total doses of local anaesthetic when using patient-controlled epidural analgesia, or PIEB rather than continuous infusions[98,99] (this is explored in more depth in the introduction to this thesis). As only two out of 32 studies used different methods of administration of epidural maintenance for different arms of the trial, this is unlikely to significantly affect our results. Local anaesthetic requirement of labouring women may be different for primiparous and parous patients. In 14 of the 32 studies, only primiparous participants were included, 11 studies included

patients of mixed parity, and 7 did not specify parity. Since there was no difference in the inclusion criteria between groups of differing concentration, and given that participants were randomised, again this is unlikely to have significantly affected the results. Finally, the decisions on whether or not to intervene by the obstetrician were not standardised. Different geographical settings and local clinical practices may result in the variable background rates of operative birth. The individual studies within this meta-analysis show considerable variability in rates of both AVB and caesarean birth. It may be that the reduced rate of AVB and increased rate of caesarean birth reflects a global trend of changing obstetric practice rather than factors related to epidural technique per se. Again, this is unlikely to significantly affect our results as this would be common to all arms of study. Differences in the co-administration of opioids, method of local anaesthetic administration, and obstetric practice between studies remain a limitation of this meta-analysis.

4.4 Conclusions

This network meta-analysis finds that ULC local anaesthetic for labour epidural achieves similar or better maternal and neonatal outcomes to LC and HC local anaesthetics, but with reduced local anaesthetic consumption. This information can be used to aid clinician decision making towards further optimising epidural local anaesthetic regimes in labour. A randomised controlled trial comparing LC and ULC local anaesthetics for labour epidural analgesia would be useful.

There are many unanswered questions about the effects of varying concentrations of local anaesthetic for labour epidural. There is no universally agreed standard technique for epidural analgesia and there is considerable variability between the different studies. Outcome measures are inconsistently reported which makes comparison difficult. We do not know what epidural regimes are routinely used, and it would be useful to characterise this. We will explore this in chapter 5. Maternal outcomes such as perineal tears, postpartum haemorrhage, severe maternal morbidity, and long-term childhood outcomes were not addressed by any of the included studies, and further research is warranted to assess these.

Chapter 5 Current epidural practice in Scotland: a survey of practice

5.1 Rationale

Despite widespread use, there is no standardised regime for establishing and maintaining labour epidural analgesia. In the preceding chapter we have demonstrated the impact of the concentration of the local anaesthetic solution on obstetric and maternal outcomes. As discussed in chapter 2, other variables, such as the use of opioids or different drug delivery systems, can reduce total local anaesthetic dose, improve maternal satisfaction and affect the duration of labour. Little is known about the impact of test doses or solutions for initiating blocks.

In Scotland women may give birth in an obstetric unit, a midwife-led unit or at home. There are 18 obstetric units (OU), 6 alongside midwife-led units, and 19 free-standing midwife-led units (FMU).[204] Obstetric units have direct access to obstetric, neonatal and anaesthetics services, including labour epidural analgesia. Within an obstetric unit, midwives provide care to all women and take responsibility for low risk parturients. High risk women – those with comorbidities or complications relating to pregnancy are advised to give birth in an OU. Obstetric doctors are responsible for these high-risk women, as well as those who develop complications whilst in an OU. Within the umbrella term of obstetric unit, the size and scope of a unit can vary. In areas of lower population density, for example on the Scottish Islands, the unit may be small, with fewer cases per year. Tertiary referral centres exist to care for women with very high-risk pregnancies, such as women with placenta accreta spectrum,[205] or cardiac disease. “Alongside” midwife led units are co-located with an obstetric unit, so the patient does not have to be transferred to access these services. Free standing midwifery units are geographically distant from an obstetric unit, and women would have to be transferred by ambulance if an intervention is required. The majority of women give birth within a hospital setting. In 2015, only 2.6% of births took place in a freestanding community midwifery unit or at home.[204]

The aim of this survey is to establish current epidural regimes used in Scottish maternity units to identify possible areas for improvement. We also aim to provide more context to aid interpretation of the retrospective population studies of obstetric anaesthetic practice in Scotland that are described in the later chapters of this thesis.

5.2 Methods

Ethical approval was not required for this study as participation was voluntary and the results are anonymised. The initial draft of the survey was prepared by the author (Lucy Halliday) using the free online survey tool 'SurveyMonkey' (https://www.surveymonkey.co.uk). Feedback for this initial draft was provided by Dr Rachel Kearns MD, an anaesthetic consultant specialising in obstetric anaesthesia. Following revision, a pilot survey was then distributed via SurveyMonkey among the ten consultant obstetric anaesthetists at the Princess Royal Maternity Hospital in Glasgow, U.K., who provided comment on readability, range of answer options available, and suggestions for alternative questions. Following further revision and review, the survey was re-created using another free web platform: 'Google Forms' (https://www.google.co.uk/forms/). Google Forms was selected as it provided a larger range of question options plus space for free text answers.

An invitation to participate in the survey was emailed to all anaesthetic secretaries in Scotland (n=40) for distribution amongst anaesthetic doctors working in obstetric units (estimated n = 380, see section 5.4 for further details). An accompanying letter explaining the purpose of the study was provided with the survey. The survey contained fourteen multiple choice questions, and space for free text answers. It was estimated to take around 5 minutes to fill out. A print version of the survey and accompanying letter can be found Appendix 2. Data were collected between July and November 2021, and analysed in December 2021. Descriptive statistics were performed using Microsoft Excel (version 16.73). Pie charts were created in Excel to demonstrate relative proportions for (1) grade of anaesthetist, (2) number of deliveries per year, (3) annual epidural rate, and (4) drug delivery system.

5.3 Results

5.3.1 Demographics of survey responders

Sixty-eight responses to the survey were received (68/380, 17.9%). Over half of those who responded were consultant anaesthetists, with the other 48.5% being made up of anaesthetists in training and Staff and Associate Specialist (SAS) doctors (Figure 5-1).

- 35 (51.5%) consultants
- 23 (33.8%) ST3 or above
- 7 (10.3%) CT1/2
- 3 (4.4%) Staff and Associate Specialist (SAS) doctors.

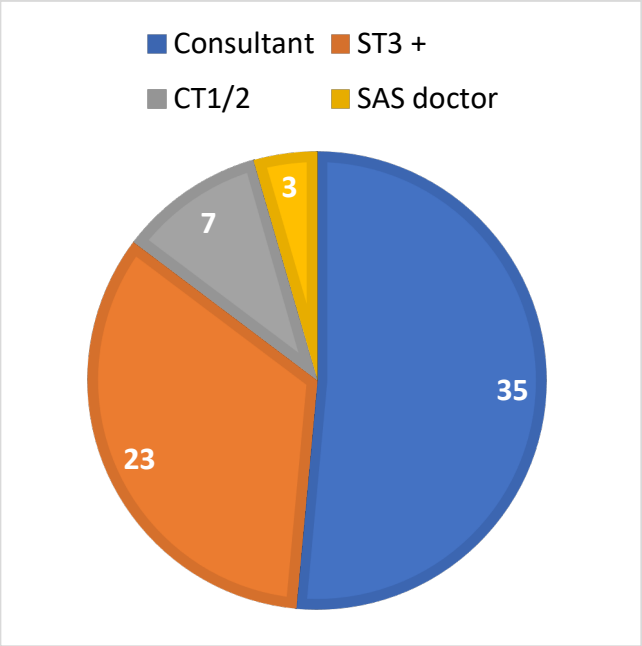


Figure 5-1 Grade of anaesthetist

The number of births in each unit varied from < 2000 in 5 units (7.4%) to >5000 deliveries in 10 units (14.7%). The majority of the respondents (38, 55.9%) worked at obstetric units which oversaw 2000-5000 births per year (Figure 5-2).

- 5 (7.4%) <2000 births/year
- 21 (30.9%) 2000-3500
- 17 (25.0%) 3500-5000
- 10 (14.7%) >5000
- 15 (22.1%) Unsure

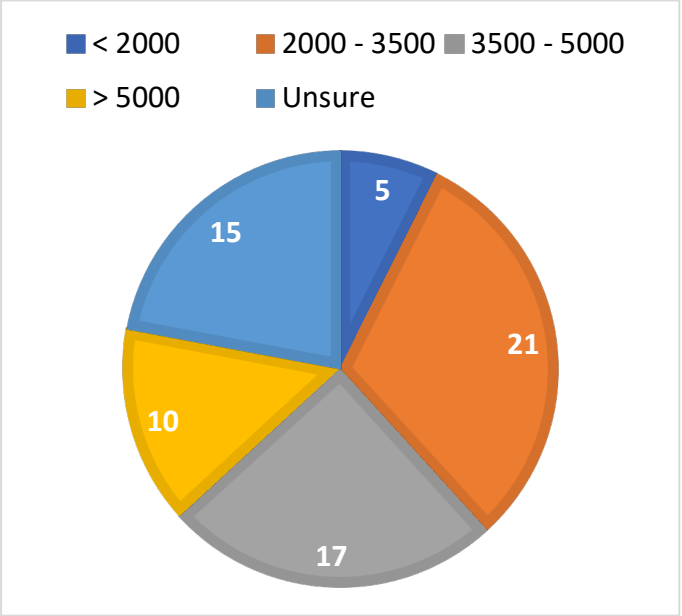
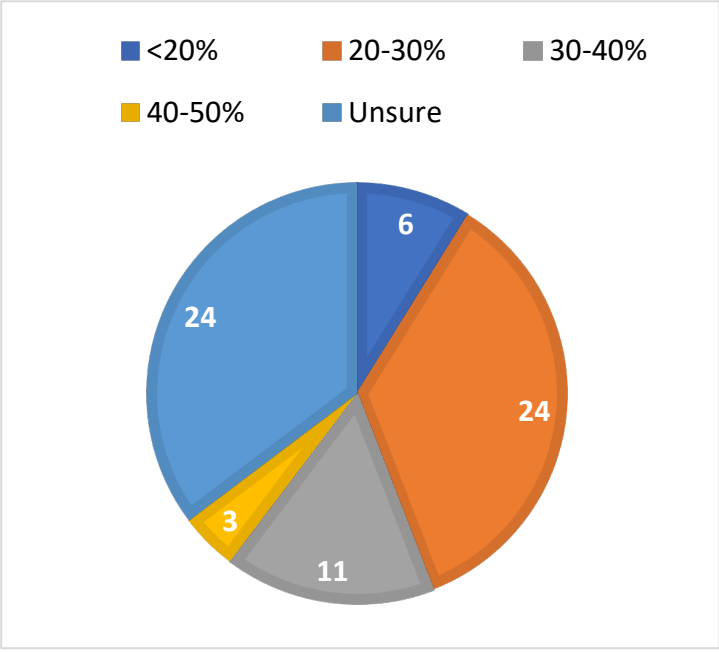


Figure 5-2 Births per year

The response rate for questions examining each unit's annual epidural rate was low, with over a third of survey respondents unable to report this. Of the responses received, the annual epidural rate varied between 20-50%, with 20-30% being the most common response. No respondent reported an epidural rate >50% (Figure 5-3).



- 6 (8.8%) <20%
- 24 (35.3%) 20-30%
- 11 (16.2%) 30-40%
- 3 (4.4%) 40-50%
- 0 (0%) >50%
- 24 (35.3%) Unsure

Figure 5-3 Annual epidural rate of delivery unit

5.3.2 Anaesthetic agents used for epidural test doses

A test dose was routinely used by 63/68 (92.6%). Of the 63 responses, 16 different tests doses were described. The most commonly used test dose was 3ml 0.25% levobupivacaine (20, 31.7%) followed by 4ml 2% lidocaine (9, 14.3%) and 5ml 0.1% levobupivacaine (7, 11.1%) (Table 5-1).

Local anaesthetic	Concentration	Volume	Count (n, %)
Levobupivacaine	0.1%	5ml	7 (11.1%)
Levobupivacaine	0.1%	10ml	2 (3.2%)
Levobupivacaine	0.1%	15ml	1 (1.6%)
Levobupivacaine	0.125%	5ml	4 (6.3%)
Levobupivacaine	0.125%	10ml	3 (4.8%)
Levobupivacaine	0.25%	2ml	1 (1.6%)
Levobupivacaine	0.25%	3ml	20 (31.7%)
Levobupivacaine	0.25%	4ml	2 (3.2%)
Levobupivacaine	0.25%	5ml	3 (4.8%)
Levobupivacaine	0.5%	2ml	1 (1.6%)
Levobupivacaine	0.5%	3ml	5 (7.9%)
Bupivacaine	0.125%	5ml	1 (1.6%)
Bupivacaine	0.25%	3ml	1 (1.6%)
Lidocaine	1%	5ml	1 (1.6%)
Lidocaine	2%	3ml	2 (3.2%)
Lidocaine	2%	4ml	9 (14.3%)

Table 5-1 Anaesthetic agent used in test dose

Bupivacaine was uncommonly used (2/63, 3.2%), and ropivacaine was not used as an agent for a test dose by any of the survey respondents.

5.3.3 Anaesthetic agents for initiation and maintenance of epidural analgesia

Levobupivacaine with fentanyl was the most common agent to both establish and maintain analgesia (Table 5-2). No respondents reported using ropivacaine for the establishment or maintenance of labour analgesia.

Question	Response	Response, n(%)
Initial bolus solution	Levobupivacaine + fentanyl	48 (70.6%)
	Levobupivacaine	13 (19.1%)
	Bupivacaine + fentanyl	4 (5.9%)
	Bupivacaine	2 (2.9%)
	Other	1 (1.5%)
Maintenance solution	0.1% levobupivacaine + fentanyl	42 (61.8%)
	0.125% levobupivacaine + fentanyl	20 (29.4%)
	0.0625% bupivacaine + fentanyl	3 (4.4%)
	0.1% bupivacaine + fentanyl	2 (2.9%)
	0.125% bupivacaine + fentanyl	1 (1.5%)
Administration	Patient-controlled epidural analgesia (PCEA)	42 (61.8%)
	PCEA + infusion	19 (27.9%)
	PCEA + PIEB	2 (2.9%)
	Continuous infusion	5 (7.4%)

Table 5-2 Characteristics of labour epidural analgesia administration

5.3.4 Epidural adjuvants

All respondents co-administered fentanyl in the epidural maintenance infusion, though the concentration varied (5-20µg.ml-1 , Table 5-2). Nine (13.2%) used clonidine as an epidural adjunct when needed and 59 (86.8%) did not use any adjuvants other than opioids.

5.3.5 Anaesthetic drug delivery systems

Patient-controlled epidural analgesia (PCEA) was the most commonly used epidural maintenance infusion delivery mechanism, followed by continuous infusion + PCEA (Table 5-2, Figure 5-4).

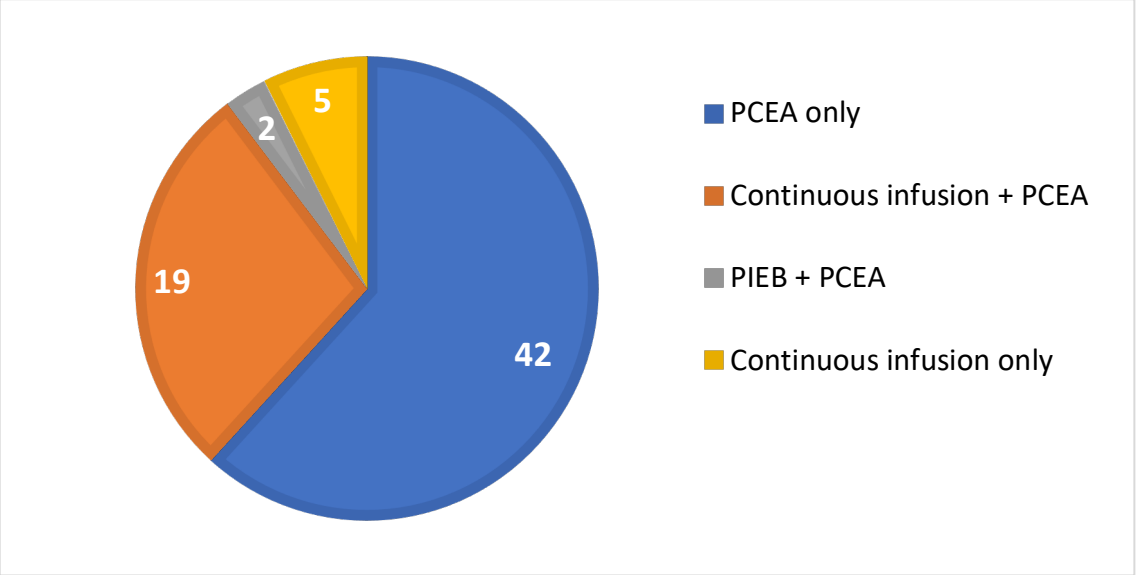


Figure 5-4 Anaesthetic drug delivery system

5.3.6 First line management for low block

The final question in the survey was free text and presented the following clinical situation:

'Which 'rescue drug' would you use for a fit and healthy primiparous 28-year-old at 6cm cervical dilation in uncomplicated spontaneous labour complaining of a low block with breakthrough pain?'

Eleven different management strategies were proposed, which are grouped as follows:

- 26 (38.3%) used up to 10ml 0.1-0.125% levobupivacaine,
- 24 (35.3%) used up to 10ml 0.25% levobupivacaine
- 3 (4.4%) respondents used up to 50µg fentanyl
- 2 (3%) used a combination of 0.25% levobupivacaine and clonidine
- 1 (1.5%) used up to 75µg clonidine.

The remaining 12 (17.6%) used combinations of levobupivacaine and fentanyl.

5.4 Discussion

Labour epidural analgesia is widely used but there is no nationally agreed technique and practice varies considerably throughout Scotland. This survey represents anaesthetists of all levels of experience, who work at obstetric units of varying size and epidural utilisation rates, despite the low uptake. The use of 16 different test doses was reported, including 3 different anaesthetic agents of various concentrations, and of volumes between 2 and 15ml. Five different solutions were used for the maintenance of epidural analgesia, with high (HC), low (LC) and ultra-low concentrations (ULC) local anaesthetic use reported. Clonidine was used as an adjuvant by 9 respondents (13.2%). Eleven different management strategies were proposed for the management of a low block in an otherwise uncomplicated primiparous women. There appears to be many different epidural techniques used within Scotland. Further work is required to define the epidural regime which optimises patient satisfaction and safety.

The first question in this survey was designed to estimate the spread of doctors represented in this sample. Official figures are not published for the number of anaesthetic doctors in Scotland and we were unable to obtain exact numbers from each anaesthetic department. The Royal College of Anaesthetists (RCOA) Medical Workforce Census Report 2020 reported that there are 776 consultant anaesthetists in Scotland. Overall in the UK 10.5% of consultant anaesthetists work in obstetric anaesthesia.[206] I can thus estimate there are 81 consultant obstetric anaesthetics in Scotland, and 35/81 represents a response rate of roughly 43%. Uptake among anaesthetic trainees and SAS doctors was lower. It was not possible to obtain accurate trainee numbers in Scotland. The number of anaesthetics trainees is estimated from the most recently available job numbers published by Scottish Medical Training (2012/2013, 2013/2014).[207,208] An average from the 2 latest reports available was taken and multiplied by 6 to cover CT2-ST7, giving an overall estimate of 279 trainees. No more recent estimates were available, and these number are plausible as the West of Scotland deanery has an average intake of 24 doctors per year[209] and provides care for just under 50% of Scotland's population according to the latest census estimates (2,672,260/5,479,900).[210] This is likely an overestimate of the number of trainees in obstetric anaesthesia, as not all doctors at CT2 level will have undertaken this speciality rotation at the time of survey. The RCOA Medical

Workforce Census Report (2020) reported 99 SAS anaesthetists in Scotland of which 20% had regular sessions in obstetric anaesthesia.[206] I can therefore estimate that the response rate for doctors in training was 10.8% (30/279), and SAS doctors 15% (3/20). This low response rates for trainees may in part reflect the distribution channels used. A national database of obstetric anaesthetists including a list of appropriately trainees would be a useful development to not only facilitate future research but also to disseminate guidelines and ensure alignment of clinical practice.

The second and third questions in this survey were designed to assess the variety of units represented in this sample. The reported number of deliveries per year ranged from less than 2000 births, to over 5000 per births per year and there was great variation in reported epidural use from <20% to >40%. However, one third of survey responders were unable to report the epidural rate at their unit. Whole population studies have estimated epidural rates in Scotland at 22%.[169,170] Variation in epidural uptake is to be anticipated. Units that provide care for women with uncomplicated deliveries would be expected to have a lower rate of epidural compared to those which provide obstetric care for higher risk parturients. Together the variation in reported deliveries and variation in epidural use suggests that those who responded to the survey represented a good mix or large medium and smaller obstetric units.

A test dose was used by over 90% of those surveyed. A historic survey carried out by the OAA reported that 90% used a test dose for labour analgesia in 1999-2000.[211] To our knowledge, no studies have been carried out examining the use of a test dose for labour epidural analgesia. At the time of reporting this survey, there was some controversy regarding the use of a test dose for labour epidural analgesia,[42,43] and there were no clinical recommendations regarding their use, however, the Royal College of Anaesthetists have subsequently endorsed their use.[57] The 7th National Audit Project (NAP-7) report recommends the use of a test dose of local anaesthetic of no more than the equivalent of 10mg bupivacaine.[57] Doses higher than 45mg intrathecal lidocaine increase the risk of high spinal.[45] Over a third of respondents used test doses above these thresholds (22/63 34.9%). As discussed in section 2.2.1.1 the ED95 of levobupivacaine to produce a motor block is 5.8mg.[53] Eight reported using test doses of

levobupivacaine below this amount, 8/63 (12.7%) which may represent an inadequate test dose to reliably detect accidental spinal catheter placement.

For the maintenance of epidural analgesia, levobupivacaine and fentanyl was used by 62/68 (91.2%) with the remainder using bupivacaine and fentanyl. It is reassuring that no respondents reported using 0.25% bupivacaine or levobupivacaine for the maintenance solution, as it is well established that these can increase rates of AVB compared to lower LA concentrations.[78] As discussed in Chapter 3, the definition of high (HC), low (LC) and ultra-low concentration (ULC) local anaesthetic is not clearly defined. In our Bayesian network meta-analysis, 0.1% bupivacaine / levobupivacaine or ropivacaine equivalent was the cut off for LC. Of the HC studies, 21 out of 29 studies with a HC arm used 0.125% bupivacaine/levobupivacaine or ropivacaine equivalent. It appears the HC local anaesthetics of maintenance of epidural analgesia are still used in Scotland (21/68, 30.9%), and ULC is uncommonly used (3/68, 4.4%). In Chapter 4 we demonstrated that the use of HC local anaesthetics offer no advantage compared with ULC local anaesthetics, and that compared to LC, ULC may increase the likelihood of SVB and reduce the incidence of caesarean birth without compromising maternal analgesia or satisfaction.

Patient controlled epidural analgesia has been shown to improve maternal satisfaction, and reduce total local anaesthetic dose.[99] In this survey, 92.6% reported use of PCEA with or without background infusion/PIEB. This is an increase compared to the 2014 UK report, which reported PCEA use in only 50% of hospitals.[3,87] As described in Chapter 2, for maintenance of analgesia, PIEB is associated with a significantly shorter duration of labour when compared to continuous infusion, irrespective of the use of supplementary patient-controlled epidural analgesia (PCEA).[98] After the results of this survey were reported, a 2023 systematic review and network meta-analysis (73 trials 10 comparisons) was published, which reported superior pain scores at two hours and four hours, reduced consumption of local anaesthetic, reduced incidence of motor blockade, increased rate of spontaneous vaginal birth and increased maternal satisfaction for PIEB + PCEA compared to continuous infusion with PCEA.[104] Only 2/63 (2.9%) of respondents reported using PIEB + PCEA.

The final question was designed to ask about the management of a healthy primiparous women with a low block. We acknowledge that this question is artificial, as in practice management of an epidural would be based on clinical findings including examination. Nevertheless, 11 different management strategies from 68 respondents implies that there is wide variability in clinical practice. Over two thirds would use a solution of levobupivacaine alone, but 1/3 would elect to use fentanyl or clonidine as first line management of a low block. Rescue doses for poorly functioning epidural is an understudied area, and the use of one-off bolus doses of either high concentration local anaesthetic solutions or other adjuvants is unknown.

5.5 Limitations

We acknowledge that there are limitations to the use of this survey to derive conclusions about current labour epidural practice. The uptake rate of this survey was low, with only 68 responses. Although the exact number of practicing obstetric anaesthetic doctors in Scotland is not known, this likely represents around 40% of consultants, 11% of trainees and 15% of SAS doctors practicing in obstetric anaesthesia. Some hospitals may not have a dedicated obstetric anaesthetic consultant rota, and these estimates do not include consultants that may cover the labour ward on an ad hoc basis. Many of the respondents were not well informed about their obstetric unit, with nearly one third being unaware of the epidural utilisation rate. These were mostly trainees, who may provide the first point of contact for epidural insertion and troubleshooting. As participation in this survey was voluntary, there is a selection bias among those who choose to respond, and those who do not. Notwithstanding these limitations, this survey indicates that there are a significant number of different labour epidural analgesic techniques which are employed across the country. This suggests that there may be a benefit to developing centralised guidelines in the future.

5.6 Conclusions

Despite the low response rate of this survey, we are able to conclude that there appears to be significant variability in labour epidural technique within Scotland. We already know that both epidural uptake and practice vary widely between countries, and this survey provides evidence of technique practice within a single country. In the next two chapters we will move to explore factors that are associated with variations in epidural utilisation using population databases as a tool to accumulate large amounts of unselected patient data for interpretation.

Chapter 6 Socio-economic disadvantage and utilisation of labour epidural analgesia

6.1 Introduction

6.1.1 Socio-economic status and health disparity

The World Health Organisation defines health inequalities as: 'systematic differences in the health status of different population groups'.[214] The higher the degree of health inequality, the worse the relative health of the most disadvantaged people. Lower socio-economic position has been consistently associated with poorer health outcomes.[26,215] The Scottish Burden of Disease Study (2016) Deprivation Report showed that those residing in poorer areas have double the rate of illness or early death than those who reside in more affluent areas.[216] Women living in areas of high socio-economic disadvantage experience 22 fewer years of good health compared to those who reside in the areas of least socio-economic disadvantage.[26] Tackling this inequality is a major public health challenge due to the complex interactions between health and environment, including housing, income, education and employment. Relative measures of deprivation have been derived as a tool to aid governments in the allocation of resources and to focus spending in less advantaged areas.

6.1.2 Maternal health disparity

Reducing adverse maternal health outcomes is a public health priority.[204] Maternal morbidity and mortality continue to climb in the context of an evolving maternal demographic of increasing age, obesity, and chronic disease.[217] Maternal socio-economic disadvantage is associated with an increased incidence of adverse maternal and perinatal outcomes[218] and poorer long-term outcomes for offspring. The Mothers and Babies: Reducing Risk through Audits and Confidential Enquires across the UK (MBRRACE-UK) published a 2021 report highlighting the importance of social determinants of health such as ethnic disparities, social disadvantage, and multi-morbidity as significant risk factors for poor maternal, obstetric and neonatal outcomes.[219] Similarly, a 2022 report by the US Pregnancy Mortality Surveillance System (PMSS) has emphasised the

increased risk of adverse maternal and perinatal outcomes in patients with socio-economic and multiple disadvantage.[220]

Ethnic disparities in obstetric anaesthetic care have been reported in studies from the United States of America (USA) and the United Kingdom (UK). In the USA, it has been reported that general anaesthesia is more commonly performed in black women undergoing caesarean birth,[221] and lower epidural use is observed in ethnic minority and socio-economically disadvantaged groups.[222,223] In the UK, Bamber et al found that women of African or Caribbean ethnicity were significantly more likely to received general anaesthesia for caesarean birth, and that women of Bangladeshi, Pakistani and Caribbean ethnicity were significantly less likely to use labour neuraxial analgesia.[25] Women from ethnic minorities are up to three times more likely to experience severe maternal morbidity, and in the UK, maternal mortality rates remain more than four times higher for black compared with white women.[219] Pregnant women living in the most deprived areas of the UK are twice as likely to die as those living in the most affluent areas[219] The impact of socio-economic disadvantage on obstetric anaesthetic care remains poorly understood.

6.1.3 Labour epidural analgesia and socio-economic position

Epidural is the gold standard for labour analgesia and is recommended by the World Health Organisation (WHO).[224] It is associated with improved maternal satisfaction and pain scores,[33] reduced rates of post-traumatic stress disorder[139] and post-natal depression.[135] There is accumulating evidence that having an epidural in labour may be associated with reduced severe maternal morbidity.[141] In certain health conditions labour epidural analgesia is recommended for maternal safety, and it can be used to provide anaesthesia for emergency operative birth. Uptake of epidural analgesia varies and is influenced by obstetric status (e.g. parity, prolonged labour) and healthcare setting, as well as patient choice, culture, and beliefs around childbirth. In fee-paying healthcare systems, lack of health insurance and financial costs represent further barriers to receiving epidural analgesia.[222] In a study of 13 high income countries, rates of labour epidural varied between 10 and 64%.[4] Previous studies that have assessed indicators of socio-economic position (SEP) with labour epidural analgesia have yielded inconsistent results.[5,225] Similarly, lower levels of

education have been associated with both increased[226] and decreased labour epidural utilisation.[227] Lower SEP is associated with a higher prevalence of risk factors associated with adverse pregnancy outcome,[9] and therefore a greater underlying obstetric risk and potential need for obstetric anaesthetic interventions. The associations of socio-economic status on epidural uptake in the UK population are unknown. Ensuring that all patients have equitable access to epidural analgesia is paramount if these potential benefits to maternal health outcomes are to be realised.

Healthcare in Scotland is publicly funded and provided by the National Health Service (NHS) aiming to deliver equitable treatment that is free at the point of care. We sought to determine associations of socio-economic disadvantage with uptake of epidural analgesia in labour in a population cohort of Scottish mothers. The aims of this study were to:

(i) Investigate the association of SEP with utilisation of labour epidural analgesia,

(ii) Determine whether any inequality differed between women with a defined medical indication and no relative contraindication for labour epidural analgesia, and

(iii) Determine how the interaction with ethnicity is associated with SEP and labour epidural analgesia utilisation.

6.2 Methods

6.2.1 Electronic Data Research and Innovation service

The electronic Data Research and Innovation Service (eDRIS) is a division of Public Health Scotland. It is a service that was set up to allow researchers to access and link routinely collected healthcare and administrative data for research purposes. They provide support in applying to the Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) of NHS Scotland for ethical approval for the data linkage. They also manage the National Safe Haven, which is a secure online environment to which data are uploaded, accessed and analysed.

6.2.2 Databases

Five Scottish population databases were linked and de-identified by eDRIS. These were: Scottish Morbidity Record-1 (SMR01); Scottish Morbidity Record-2 (SMR02); Scottish Birth Record; National Records of Scotland and the Scottish Stillbirth Infant Death Survey (SSIDS).

SMR01 records all in-patient and day case admissions and records diagnoses according to the International Classification of Diseases 9th or 10th revision (ICD-9/ICD-10).[228,229] SMR02 records all maternity admissions and births in the 19 Scottish maternity units. Each entry into the SMR datasets undergoes data validation checks and Public Health Scotland reported 99% completeness for SMR02 in 2020/21.[7] The Scottish Birth Record contains more information on each birth, as well as all neonatal care. The National Records of Scotland records all births, including stillbirths and infant deaths in Scotland. Up to 2012, at each hospital, an SSIDS co-ordinator (an obstetrician, paediatrician, or midwife) collected further information on late fetal and infant deaths, congenital abnormalities, and both therapeutic and spontaneous terminations. This information is found in the SSIDS. Data governance procedures were approved by the NHS Scotland Public Benefit and Privacy Panel for Health (ref 1920-0097), and Social Care and NHS Greater Glasgow and Clyde Research and Development (ref GN20PH059). Participant-level consent was not required. The NHS Scotland

electronic Data Research and Innovation Service (eDRIS) linked and de-identified data prior to analysis.

6.2.3 Study population

The data available for analysis included all birth events in Scotland from 1st January 1981 – 23rd October 2020, over 2.4 million mother-infant pairs in total. From preliminary exploration and visualisation of the dataset, it was found that data after 2007 appeared to be more consistently recorded, with fewer missing data. It was decided that our cohort for analysis would include all birth events in Scotland from 1st January 2007 up to and including 23rd October 2020 – the latest date available at the time of analysis. There were 735,650 deliveries in Scotland between these dates. All mother-infant pairs between 24+0 and 43+6 weeks gestation, who delivered vaginally or via unplanned caesarean birth, including stillbirths and known congenital abnormalities were included. Patients were excluded if no mode of birth was recorded. As data were available for the entire population, no power calculation was required and there was no risk of selection bias. This analysis is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[185]

6.2.4 Definitions

6.2.4.1 Anaesthetic interventions

Epidural was defined as conventional lumbar epidural and excluded combined spinal epidural (CSE). Use of CSE was not an *a priori* exclusion criteria, rather we were unable to identify use of CSE in labour in our data, which is classified as "spinal anaesthesia" in SMR02. In our experience CSE is uncommon is Scotland, a UK survey of practice which has been presented as a conference abstract,[230] suggested that CSE accounted for only 1% of labour epidurals. This small proportion of women will be included in the non-epidural group. The recording of anaesthetic intervention is hierarchical, which means it is not possible to identify whether a parturient used labour epidural analgesia if they went on to have either a spinal or general anaesthetic for operative birth afterwards. This group of women will be recorded as 'No epidural', which mirrors the unpredictable course of labour and birth following epidural analgesia utilisation. The reported rate of conversion from epidural analgesia to spinal or general

anaesthesia is around 5%.[231] Parturients for which mode of anaesthesia was missing were excluded in this study.

6.2.4.2 Scottish Index of Multiple Deprivation

The Scottish Index of Multiple Deprivation (SIMD) was used to proxy individual-level socio-economic position. SIMD is a tool derived by the Scottish government to assess relative deprivation by postcode of residence. Multiple deprivation is a concept developed in the 1970s by Professor Peter Townsend.[232] It involves the calculation of a composite 'score' that accounts for numerous different types of socio-economic deprivation, to give an overall relative indicator of deprivation. Area deprivation is widely used as a measure of socio-economic position in social science and health research. It covers a comprehensive set of measures, rather than using a single, or small number of individual measures. For this study, the use of an area-based measure is highly appropriate, as we aim to assess the use of a health care provision in which the area of residence of a parturient influences which health care provider they can access, for example, which maternity unit she is referred to for birth.

Scotland is divided into 6,976 data zones of roughly equal population and each area is assessed across seven domains. These domains are employment, income, health, education/skills/training, geographical access to services, crime and housing. Each domain is given a weighted score and the total score divides the data zones into quintiles or deciles. The seven domains are further divided into 32 sub-domains, which are listed in Table 6.1. The tool is designed to effectively target policies or funding to take account of areas with a high concentration of multiple measures of deprivation.

The SIMD tool was first published in 2004 and there have been 5 updates: 2006, 2009, 2012, 2016, 2020. The purpose of these updates are to account for the natural fluctuation in the relative level of deprivation or affluence of an area with time. For SIMD 2004/2006, 5 represents the most deprived quintile, 10 represents the most deprived decile and 1 represents the least deprived quintile/decile. The order was reversed for SIMD 2009 onwards, so 1 represents the most deprived and 5/10 represents the least deprived (Table 6.2). For the purpose of this research, we re-coded the SIMD column, to reflect the version in

current use. Therefore, SIMD1 represents the most socio-economically disadvantaged area and SIMD10 represents the least disadvantaged area.[233] During the study period of this analysis, (1st January 2007 – 31st October 2020) four updates took place (2009, 2012, 2016, 2020).

SIMD	Most deprived quintile	Least deprived quintile	Most deprived decile	Least deprived decile
2004	5	1	10	1
2006	5	1	10	1
2009v2	1	5	1	10
2012	1	5	1	10
2016	1	5	1	10
2020v2	1	5	1	10

Table 6-1 Least and most deprived SIMD quintiles/deciles according to SIMD update

Domain	Description
Income	Percentage of people who are income deprived
	Number of people who are income deprived
Employment	Percentage of people who are employment deprived
	Number of people who are employment deprived
Health	Comparative Illness Factor: standardised ratio
	Hospital stays related to alcohol use: standardised ratio
	Hospital stays related to drug use: standardised ratio
	Standardised mortality ratio
	Proportion of population being prescribed drugs for anxiety, depression or psychosis
	Proportion of live singleton births of low birth weight
	Emergency stays in hospital: standardised ratio
Education, Skills and Training	School pupil attendance
	Attainment of school leavers
	Working age people with no qualifications: standardised ratio
	Proportion of people aged 16-19 not participating in education, employment or training
	Proportion of 17–21-year-olds entering university
Geographic Access to Services	Average drive time to a petrol station in minutes
	Average drive time to a GP surgery in minutes
	Average drive time to a post office in minutes
	Average drive time to a primary school in minutes
	Average drive time to a retail centre in minutes
	Average drive time to a secondary school in minutes
	Public transport travel time to a GP surgery in minutes
	Public transport travel time to a post office in minutes
	Public transport travel time to a retail centre in minutes
	Percentage of premises without access to superfast broadband (at least 30Mb/s download speed)
Crime	Number of recorded crimes of violence, sexual offences, domestic housebreaking, vandalism, drugs offences, and common assault
	Recorded crimes of violence, sexual offences, domestic housebreaking, vandalism, drugs offences, and common assault per 10,000 people
Housing	Number of people in households that are overcrowded
	Number of people in households without central heating
	Percentage of people in households that are overcrowded
	Percentage of people in households without central heating

Table 6-2 Scottish Index of Multiple Deprivation Domains and Indicator Descriptions

In England the 'Index of Multiple Deprivation' (IMD) is used as the equivalent of SIMD. It uses the same 7 domains with 39 subdomains, which are allocated a slightly difference weighting to their Scottish counterparts. The IMD is the tool used by the MBRRACE-UK to report that women who live in more deprived areas are more likely to experience disparities in maternal mortality rates compared to those who live in more affluent areas.[9] There are limitations to the use of SIMD as a measure of a socio-economic position that have particular relevance to these studies. SIMD is based upon area of residence, rather than to an individual's circumstances. This has particular implications in the rural setting where areas may be socio-economically diverse, potentially affecting the SIMD level allocated to parturients, which may introduce an ecological bias. A further criticism is that SIMD and health are not fully independent variables as the health domain accounts for 14% of the final SIMD score. In theory, this may introduce an endogeneity bias, or a correlation between the predictor variable and the outcome variable that cannot be interpreted as causal. In practice this risk is likely to be minimal as the health domain has been shown to be highly correlated with the overall index.[234]

SIMD is not the only area-based deprivation tool used to assess relative socio-economic position in Scotland. The Carstairs and Morris Index is an example of another relative deprivation scale. Similar to SIMD, the Carstairs and Morris Index is based upon small population pockets by postcode and produces a score based upon 4 variable domains: male unemployment, household overcrowding, car/van ownership and low social class (class IV and V). It is not updated as regularly as the SIMD tool, and is less comprehensive. For these reasons, and because SIMD is the official tool of the Scottish government, SIMD is used as the proxy measure of individual socio-economic position for this analysis.

6.2.4.3 Comorbidities

Comorbidities were identified using the ICD-9 and ICD-10 codes from the SMR01 data set.[228,229] Comorbidities were defined as no comorbidities (0), single comorbidity (1), or multiple comorbidities (2+). Comorbidities were defined using the Elixhauser Comorbidity Index.[235] This was selected as we were interested in the baseline demographics of the women, and how these were associated with socio-economic position.

The Elixhauser Comorbidity Index is a method for categorising comorbidity data using the International Classification of Diseases 9th and 10th edition codes (ICD-9, ICD-10) from administrative data. It is a list of 30 dichotomous diagnoses present or absent) and their corresponding ICD codes. For closely related comorbidities (e.g. diabetes without chronic complications and diabetes with chronic complications) only the more severe comorbidity is counted.

The comorbidities included in the Elixhauser Comorbidity Score are: AIDS/HIV; Alcohol Abuse; Anaemia Deficiency; Rheumatoid Arthritis; Blood Loss Anaemia; Cardiac Arrhythmia; Congestive Heart Failure; Chronic Pulmonary Disease; Coagulopathy; Depression; Diabetes without Chronic Complications; Diabetes with Chronic Complications; Drug Abuse; Hypertension; Hypothyroidism; Liver Disease; Lymphoma; Fluid and Electrolyte Disorders; Metastatic Cancer; Other Neurological Disorders; Obesity; Paralysis; Peripheral Vascular Disease; Psychoses; Pulmonary Circulation Disorder; Renal Failure; Solid Tumour without Metastasis; Peptic Ulcer Disease; Valvular Disease and Weight Loss.

6.2.4.4 Other patient factors

Ethnic groups were defined according to the 2011 Scottish census categories.[236] Pre-eclampsia was defined according to ICD9 (644, 645, 646, 647) and ICD10 (O11, O14, O15) codes from SRM01. Both pre-existing diabetes and gestational diabetes were recorded as diabetes and were identified using the SMR02 dataset. Gestational age at birth was defined as completed weeks of gestation based on ultrasound assessment in the first half of pregnancy. Induction of labour was defined as artificial rupture of membranes (ARM), oxytocics or prostaglandins (including cervical priming) or any combination of the three.

6.2.4.5 Indications and relative contraindications to epidural

There are certain medical conditions in which epidural analgesia is highly advisable for maternal safety, and others in which epidural analgesia may be relatively contraindicated. To explore the relationship between SIMD, epidural uptake and clinical indication without relative contraindication to labour epidural, a new variable was created. We defined the medical indications for epidural analgesia using a UK obstetric anaesthesia guideline;[237] (i) serious

cardiovascular or respiratory disease as identified from the Bateman Comorbidity Index;[238] (ii) pre-eclampsia; (iii) previous caesarean birth; (iv) breech birth; (v) multiple pregnancy; and (vi) patients with severe obesity, as defined by a body max index (BMI) ≥40, and in a sensitivity analysis with a BMI threshold of ≥ 50, as listed within the SMR02 record. Collectively these indications are also recognised within obstetric guidelines.[16-18] Relative contraindications to labour epidural analgesia were coagulation factor deficits, Von Willebrand disease, thrombocytopenia, fever or infection during labour and chorioamnionitis.[141] These relative contraindications were selected as they have previously been defined in the literature.[141] They do not necessarily represent absolute contraindications to neuraxial analgesia or anaesthesia. The ICD 9 and ICD 10 codes for indications and relative contraindications are listed in Table 6.3.

	ICD-9 code	ICD-10 code
Indications		
Pre-eclampsia	644, 645, 646, 647	O11, O14, O15
Asthma	493	J44, J45
Cardiac valve disease	394, 395, 396, 397, 424	I05-I09, I34-39
Congestive cardiac failure	428.2, 428.3, 428.4	I50
Congenital heart disease	648.5, 745-747	Q20-Q26
Ischemic heart disease	412-414	I20, I25
Pulmonary hypertension	416.0, 416.8, 416.9	I27.0, I27.2, I27.8, I27.9
Relative contraindications		
Coagulation factor deficit, Von Willebrand disease, and thrombocytopenia	286, 287	D65-D69
Fever or infection during labor	659.2, 659.3	O75.2, O75.3
Chorioamnionitis	658.4	O41.1

Table 6-3 ICD-9 and ICD-20 codes used to define indications and relative contraindications to labour epidural analgesia

Another sensitivity analysis was carried out, with asthma excluded as a 'medical indication'. Asthma is a spectrum of disease from mild to severe. Mild cases of asthma would not constitute a serious medical condition for which labour

epidural analgesia would be recommended, however severe asthma would. Due to the nature of the SMR01 dataset, we were unable to distinguish the severity of asthma, and therefore we presented results both including and excluding asthma as an 'indication' for labour epidural analgesia.

6.2.4.6 Hospital characteristics

Location of birth was divided into obstetric unit (OU) or freestanding midwifery unit (FMU) or home births. An OU was defined as a hospital with on-site obstetric and obstetric anaesthetic services, (including the provision of epidural analgesia), or an alongside midwifery-led unit, which was co-located with an obstetric-led unit, and which had direct access to obstetric and anaesthetic services. FMU were defined as midwifery-led units without direct access to obstetric or anaesthetic services.[239] All parturients who received labour epidural analgesia, or underwent caesarean birth must have access to an anaesthetist, thus any patient that was recorded as having an epidural, spinal or GA was coded as having delivered within an OU. A map of Scotland by SIMD decile with the location of obstetric units is shown in Figure 6-1.

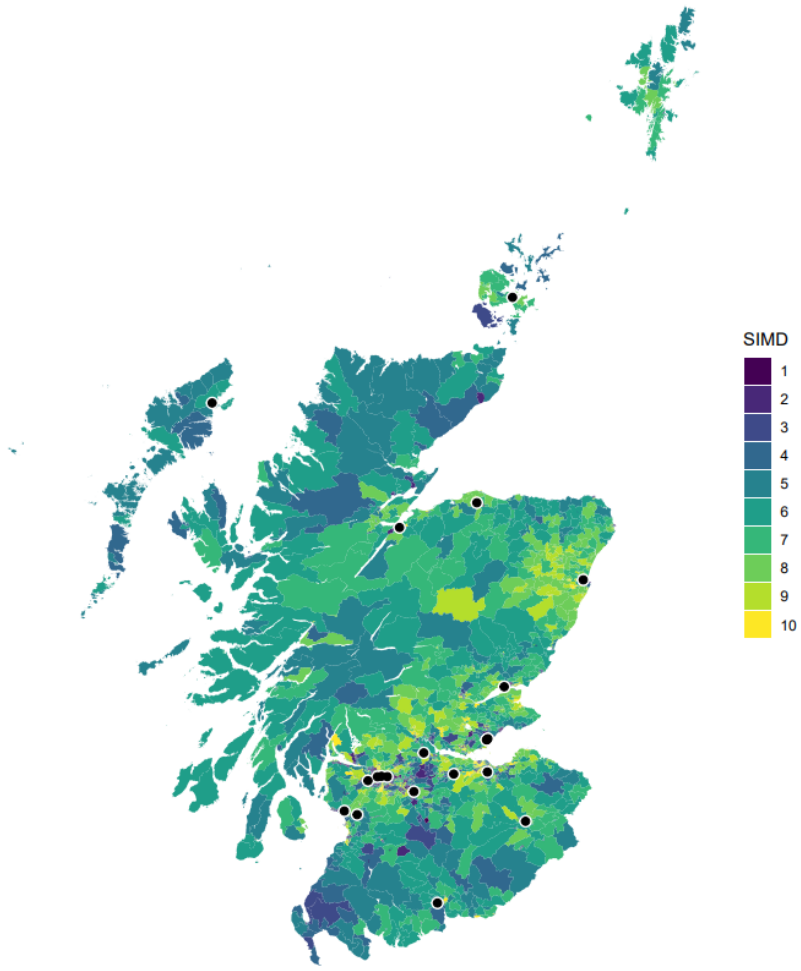


Figure 6-1 Map of Scottish Index of Multiple Deprivation areas and Scottish obstetric units. The black dots indicate the location of Scottish obstetric units.

6.2.4.7 Inner-city hospitals in one major Scottish city with 24 access to an obstetrician and an anaesthetist

A subgroup of parturients who delivered within one major Scottish city, in hospitals with 24-hour access to obstetricians and anaesthetists was identified. The aim of creating this subgroup was to investigate whether having a rural location or lack of access to obstetric and anaesthetic care was biasing our results. The Scottish city and relevant hospitals are not specifically identified in this study, as our aim was not to single out specific institutions as evidence of good or poor practice, but rather look for trends at a population level.

6.2.4.8 Date of delivery

Date of delivery was identified as a potential confounder. The SIMD status of areas, and of those who live within them may fluctuate with time, and as does obstetric anaesthetic practice. Furthermore, the SIMD tool was updated on four

occasions during of period of our study *(2009, 2012, 2016, 2020)*. For this reason two sensitivity analyses were carried out; the first which adjusted for date of delivery as a continuous variable, and a second which adjusted for date of delivery as a categorical variable. These categories were devised in accordance with the SIMD tool updates. These five categories were: 2007-2008, 2009-2011, 2012-2015, 2016-2019, 2020.

6.2.5 Data visualisation and cleaning

Data visualisation is a useful tool that allows us to look at the data and decided whether it fits into a distribution that can be modelled, or if it requires transformation (log, inverse, square, square root, etc) prior to modelling. It is also useful to perform a sense check of the data, and decided whether the results fit in with expert knowledge and falls roughly within the bounds of the expected result. It can be used to look for outliers and errors due to coding, which can aid the cleaning of data, as described above. In this analysis data were visualised using the 'ggstatsplot' package in R.[240]

6.2.5.1 Visualisation of categorical data

For categorical data, such as SIMD decile, bar charts were generated (Figure 6-2). The results in the top lefthand corner of Figure 6-2 are from a frequentist analysis. The first equation in the Pearson chi squared test, which is a test for categorical data that calculates the likelihood that the observed differences occurred by chance. The formula below is used to calculate the Chi-squared value. By itself this value is not useful, but when considered alongside the degrees of freedom (number of rows -1, multiplied by the number of columns -1, in this case 9), the p value can be calculated. As discussed in chapter 5, a p value of <0.05 is generally considered to be significant (less than 1 in 20 probability that the difference occurred by chance). In this case the p value is $p= 6.62 \times 10^{-118}$ therefore well below this cut-off for significance.

$$X^2 = \sum_{i=1}^{n} \frac{(O - E)^2}{E}$$

The next statistic in the top left corner (Figure 6-2) is the Cramér V statistic (also referred to as the Cramér phi or ϕc). This is the measure of the strength of association between the two variables (SIMD and utilisation of epidural). The statistic is always between 0 (no association) and 1 (perfect association). In this case the Cramér V is 0.03 indicating that there is a weak association between these variables. This is accompanied by a 95% CI for the Cramér V [0.03, 0.03], and the total number of observations.

In the bottom righthand corner of Figure 6-2 is a Bayesian analysis. The first equation is based upon the Bayes Factor hypothesis test: H0 = no relationship exists between the two variables, H=1 indicates that there is relationship between these two variables. BF01 indicates the Bayes factor that is in favour of H0 over H1. In this case the natural log of the Bayes Factor is -235.35, which is negative, so in favour of the H=1, that there is a difference between these variables. This is followed by the posterior means of the Cramér V test and associated confidence intervals. This is the Bayesian equivalent of Cramér V (measure of strength of association between the two variables, i.e. SIMD and utilisation of epidural) and the value is 0.03 [0.03, 0.03], identical to the frequentist analysis. The final equation is the prior type and value. Gunel-Dickey is a sampling model for contingency tables that provides corresponding Bayes factors for the independence assumption.[241]

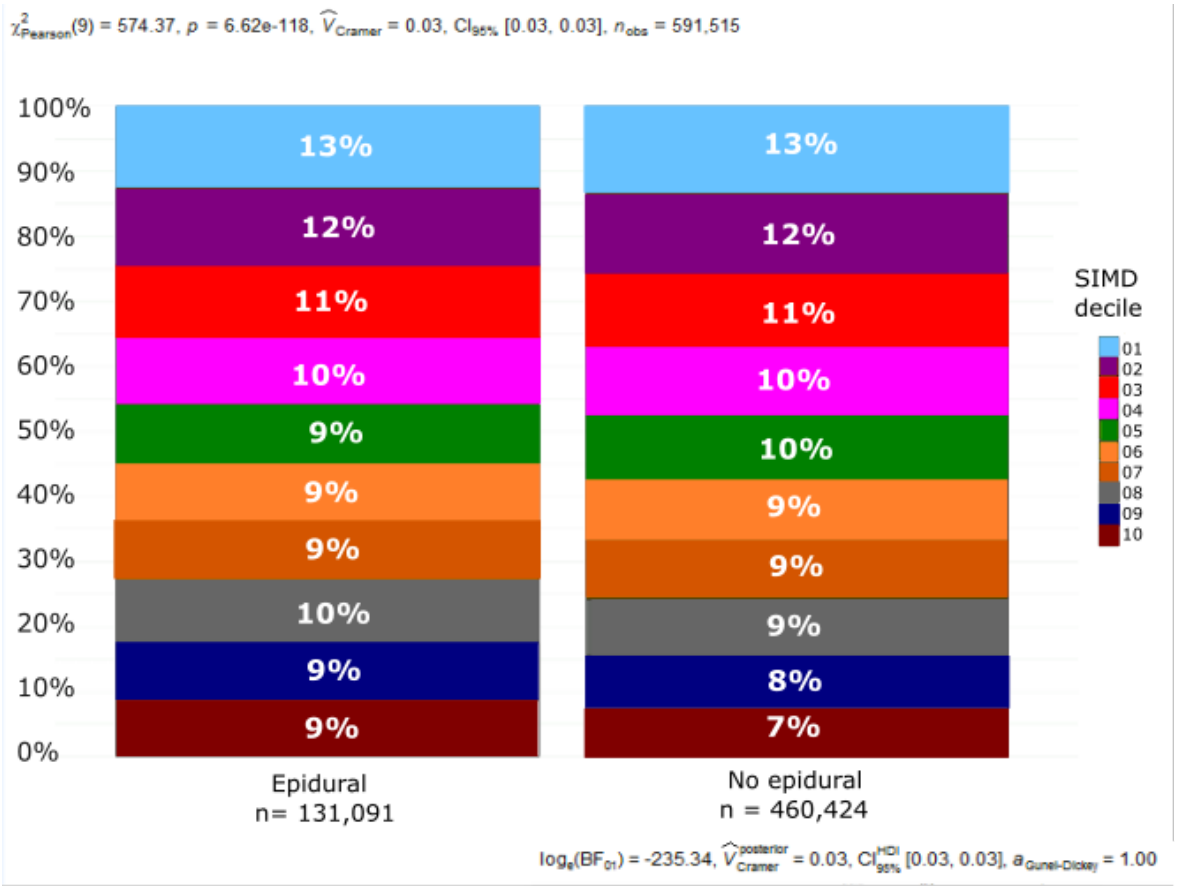


Figure 6-2 Visualisation of variable 'SIMD decile' by whether they received labour epidural analgesia or not

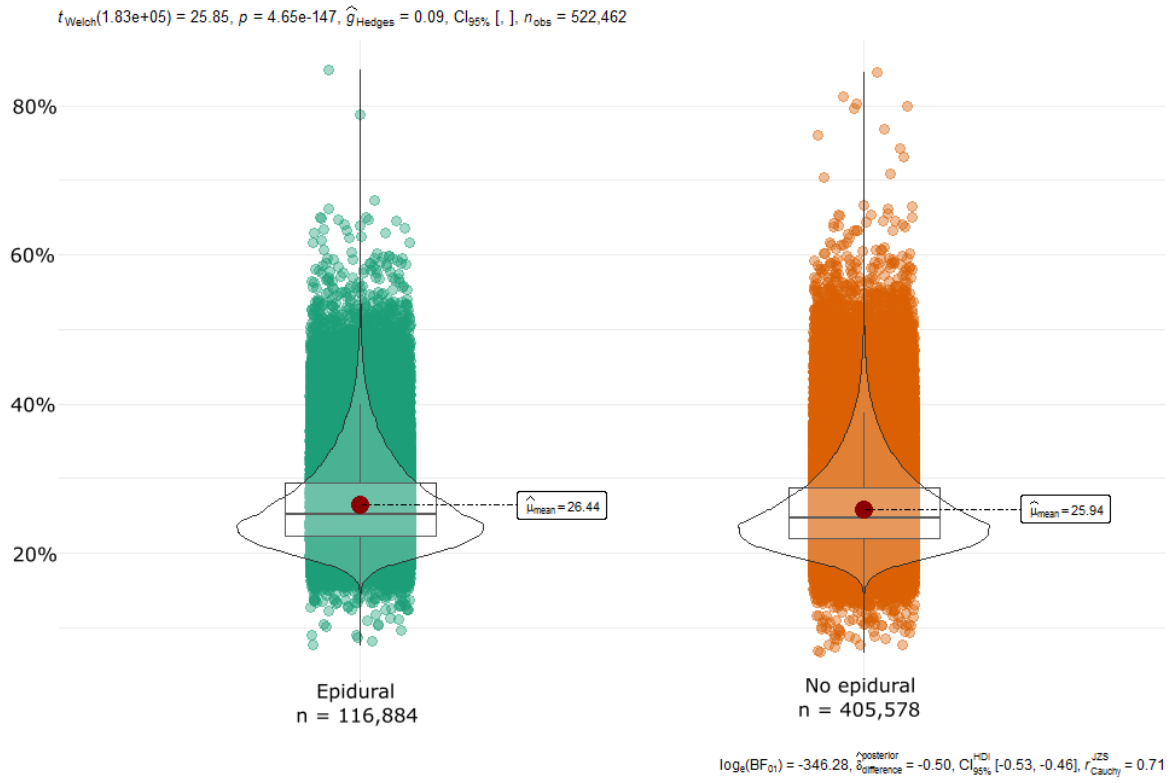


Figure 6-3 Visualisation of variable 'BMI' by whether they received labour epidural analgesia or not

6.2.5.2 Visualisation of continuous data

For continuous variables, such as maternal body max index (BMI) a combination box/violin plots with jitter points allow comparison between the two groups (epidural compared to no epidural). An example plot is included in Figure 6-3. The plot allows us to visually assess the similarity of the two groups, as well as identify outliers. The mean, median and interquartile ranges of each group can also be identified. We can see that the mean BMI of women who received epidural analgesia is slightly increased as compared to those who did not (mean BMI 26.44 vs 25.94). Otherwise visually these groups appear reasonably similar.

As in the bar charts created for the categorical data, in the in the top lefthand corner of Figure 6-3, a frequentist analysis is presented. The first equation is a Welch T test (favoured for hypothesis testing when the two samples have unequal groups sizes, but a normal distribution is assumed). The t-statistic estimate is 25.85, with 1.83×10^{5} degrees of freedom and an associated p value: 4.65×10^{-147}. Again, this is well below this cut-off for significance. The next statistic is the Hedges g test, a measure of effect size. As a rule of thumb, anything over 0.08, such as in this case (0.09), is considered to be a large effect size. Bayesian statistics are presented in the bottom righthand corner. As described above BF01 indicates the Bayes factor that is in favour of H0 over H1. In this case the natural log of the Bayes Factor is -346.28, which is negative, so in favour of the H=1, that there is a difference between these variables. The effect size estimate is -0.50 [-0.53, -0.46]. The final equation is the prior type and value used to calculate these estimates, in this case it is the Jeffreys-Zellener-Siow (JZS) prior: a default prior commonly used for ANOVA testing.[242]

6.2.5.3 Feature engineering

Following data visualisation, extreme outliers were excluded. Feature engineering is presented in Table 6-4.

Variable	Feature engineering
Age of mother	In years, truncated at age < 10 years
Anaesthetic type	“Epidural”, “Spinal”, “GA” or “None”
Comorbidities	“0”, “1” or “2+”
Diabetes	“Yes” or “No”
Estimated gestation	Completed weeks
Ethnic group	Five categories: “Asian”, “black”, “mixed”, “white” and “other”
Height of mother	To nearest cm, truncated at <100cm and >200cm
Induction of labour	“Induction” or “No induction”
Injected illicit drugs	“Yes” or “No”
Location of birth	“OU”, “FMU” or “Home”
Maternal BMI	Weight of mother (kg) / (Height of mother(m))^2
Multiple births	“Yes” or “No”
Parity	Count
Pre-eclampsia	“Yes” = ICD-10 code (O11, O14, O15) or ICD-9 code (644,645,646,647)
Previous caesarean birth	“Yes” or “No”
Previous spontaneous abortion	“Yes” or “No”
Previous therapeutic abortion	“Yes” or “No”
Scottish Index of Multiple Deprivation (SIMD) decile	“01” to “10”
Smoker during pregnancy	“Current”, “Former” or “Never”
Term	categorised as “≥37+0 - 43+6”
Weight of mother	To nearest kg, truncated at < 15kg and > 544kg

Table 6-4 Variables that underwent feature engineering.

6.2.6 Missing data

6.2.6.1 Types of missing data

Missing data is data that is not captured for a variable for the observation in question. Missing data can reduce the statistic power of an analysis and may distort the results. The first step in dealing with missing data is deciding why the data is missing. The reasons behind data missingness underly the potential solutions. Missing data may be classified[243] as:

(1) Data missing completely at random (MCAR)

MCAR data is missing for a reason that is external and unrelated to the value of the variable. It can be removed as it remains unbiased, however the statistical power of the study will be affected.

(2) Data missing at random (MAR)

MAR data is caused by a process related to a covariate or the variable of interest, for example it may be missing only for a subset of the data.

(3) Data missing not at random (MNAR)

MNAR data is missing for a reason that is related to the value of the variable, so removing the observation may create a bias. MNAR data is difficult to deal with and requires statistical modelling and sensitivity analyses to try to create unbiased estimates.

In practice it is difficult to distinguish between these three categories, and a mixture often occurs.

6.2.6.2 Analysis and visualisation of missing data

Within our dataset, missingness of data ranged from 0% to 50.9% (Table 6-9). Three variables in our analysis had over 30% of data points missing - ethnic group, marital status and history of illicit drug use (38.3%, 50.9% and 31.4% respectively). Marital status was removed from the analysis due to having over 50% missing data. Data on ethnic group and history of injected illicit drugs had a

high percentage of missingness (38.3% and 31.4% respectively), however these variables were included in the analysis as they are important contributors to an individual's deprivation status and may cause considerable confounding if excluded. Missing data were only imputed for dependant variables, not for the outcome variable (epidural analgesia or no epidural analgesia). Cases for which data on epidural use was not available were excluded from the analysis (38,646/631,876 = 6.1%).

The R package 'nanair'[244] was used to visualise the structure of the missing data. Due to the very large number of data points, a sample of 10,000 women was taken. Missing data were visualised for each variable (Figure 6-4). Percentage missing was then visualised by epidural, or non-epidural use (Figure 6-5). After visual inspection data were deemed to be missing at random (MAR).

Variable	Missing % (n), (total = 593,230)
Analgesia during labour/birth	NA
Age of mother	0
Height of mother	9.4% (55,563)
Weight of mother	10.3% (61,125)
BMI of mother	11.9% (70,768)
Ethnic Group	38.3% (227,415)
SIMD decile	0.3% (1,715)
Marital Status	50.9% (301,848)
Smoking history at booking	4.4% (25,845)
History of injected illicit drug use	31.4% (186,255)
Diabetes	3.6 % (21,267)
Pre-eclampsia	0
Comorbidities	0
Previous spontaneous abortion	0.4% (2,453)
Previous therapeutic abortion	0.4% (2,440)
Previous caesarean birth	0.3% (1,673)
Parity	0.5% (3,179)
Estimated gestation	0
Induction of labour	1.3% (7,578)
Multiple birth	0

Table 6-5 Percentage of missingness for the dependant variables

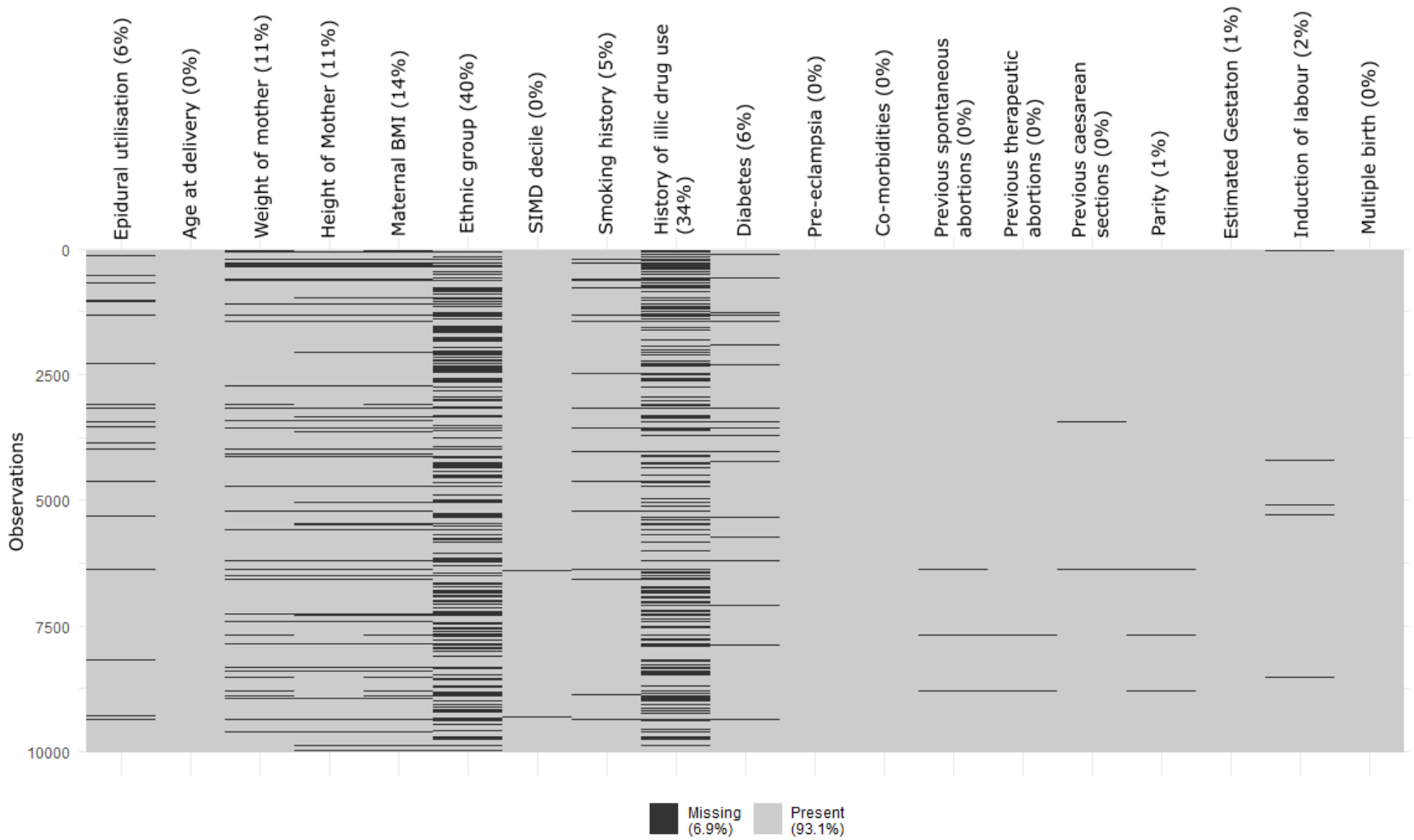


Figure 6-4 Figure 6 4 Pictogram illustrating the structure of missing data. The light grey depicts available data, and the black lines represent missing data for each variable

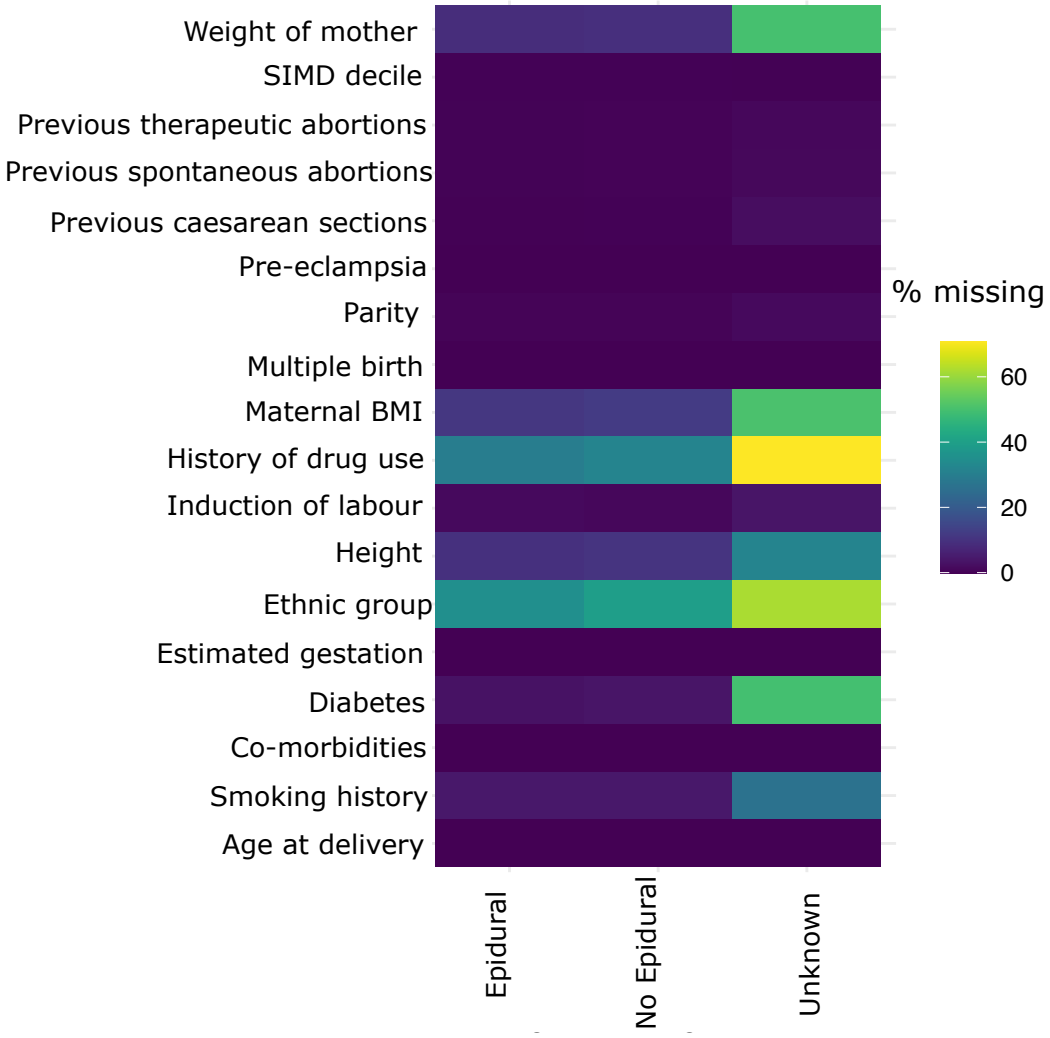


Figure 6-5 Pictogram depicting percentages of missing data for each variable

6.2.6.3 Techniques for dealing with missing data

There are a number of different techniques for dealing with missing data. The simplest method is complete case analysis or listwise deletion. This is where all cases that have any missing data are excluded from the analysis. There are two main drawbacks to this approach (1) If the cases with missing data are not representative of the overall sample it can create a biased result (so only suitable for MCAR data), and (2) a large amount of data may be discarded it can reduce sample size, especially if there are a large number of variables. Other approaches include, in order of increasing complexity: mean substitution (replacing all missing values with the mean of the observed values of that

variable), hot desk substitution (missing values replaced with an observed value from a similar case), regression imputation (creating a regression model with information from other variables to predict the variable) and multiple imputation.[245] in this analysis I use multiple imputation which is generally considered the best technique for dealing with data that is missing at random.[246]

6.2.6.4 Multiple imputation

Multiple imputation is a simulation-based technique for dealing with missing data. Multiple copies of the data set are created, and the missing data values are imputed (predicted) using the observed, non-missing data, with an appropriate variability built into the model. This is repeated for each copy of the data set, thus producing multiple complete data sets.[243] The inbuilt variability means that multiple imputation can reflect the uncertainty around the missing data.

Multiple imputation by chained equations (MICE) was used to undertake multiple imputation. It involves the creating of a series of regression models, whereby the missing data is modelled using the other observed variables within the dataset. The value of each missing data point is borrowed from another matched case via a set of predictive models (chained equations) in a process known as predictive mean matching. Each set of predictive models is known as an iteration, these iterations run until the values converge. This process is then carried out multiple times as described above.

The imputation created for this analysis used all the available data in the dataset, including that of the outcome, and other informative variables not used for the analysis. This is to increase the performance of the imputed dataset.[247] For the purpose of this analysis, estimates were stable after 10 iterations, and 10 imputed datasets were created to ensure that pooled effect estimates and standard errors were accurate. The results from the unimputed dataset are presented alongside those of the imputed dataset for the primary outcome. This dataset was imputed as described above by Dr Martin Shaw and Dr Aizhan Kyzayeva.

6.2.7 Statistical analysis

6.2.7.1 Variables for adjustment

The primary analysis was unadjusted as SEP was considered an upstream exposure that would not be affected by, for example women's behaviours, such as smoking, diet, or body mass index (BMI). The definition of a confounder is anything that is either known to cause, or may influence both the exposure and the outcome,[248] in this case socio-economic position and epidural utilisation respectively. A Directed Acyclic Graph (DAG) is presented in Figure 6-6. This presents some (but not all) of the key factors that may influence labour epidural analgesia utilisation. This graph illustrates that whilst women's characteristics, such as age, body mass index (BMI), or smoking status could plausibly influence the use of labour epidural analgesia, however they are downstream effects, rather than causes of a women's socio-economic position at the start of pregnancy. Since these factors do not influence socio-economic position, they are not confounders. The variables which are on the causal path between socio-economic position and epidural analgesia utilisation are potential mediators. If the analysis was adjusted for these mediators, it would not be possible to determine the total effect of socio-economic position on epidural utilisation. The results would be biased as some of the effect which we are aiming to measure would be removed.

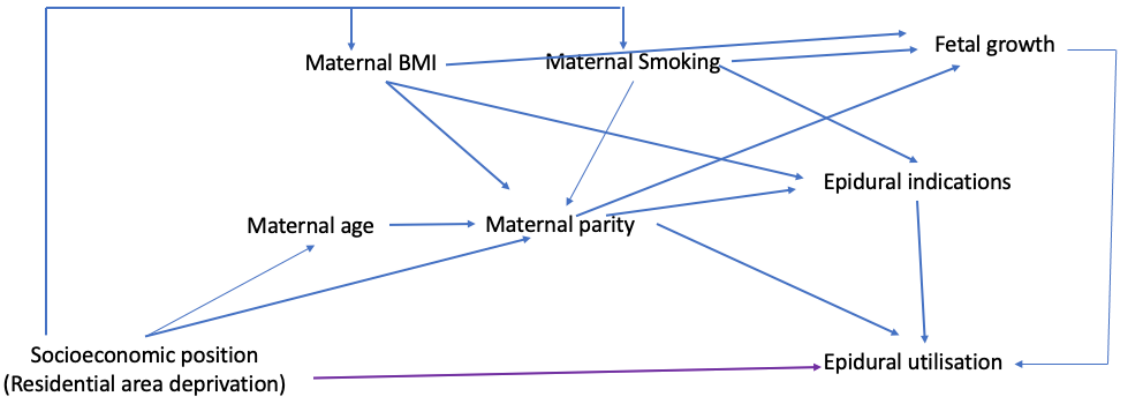


Figure 6-6 Directed Acyclic Graph (DAG) demonstrating some of the key factors which may influence epidural utilisation.

Multivariable regression approaches to mediation analysis can be used to distinguish the effect of mediators between exposure and outcome however these are based on six strong assumptions,[249] which this analysis does not meet.

These assumptions are:

(1) The mediator and outcome must be continuous variables.

(2) There are no unmeasured confounders of the exposure on the outcome, or vice-versa.

(3) The exposure must not be causally related to a confounder between the mediator and the outcome.

(4) The correct function for the model must be specified (ie. non-linear relationships must not be modelled with a linear model and vice-versa).

(5) There are no interactions between exposure and mediator on the outcome.

(6) There is no measurement error.

Date of delivery is a potential confounder variable in this analysis. SIMD is an area-based measure, and we are using this to proxy individual socio-economic position. Deprivation of an area can fluctuate with time, as does peripartum practice. For this reason we present a sensitivity analysis adjusting for date of delivery as a continuous variable. The SIMD tool is updated every few years to reflect the waxing and waning of area deprivation. During our study period, it was updated four times (2009, 2012, 2016 and 2020), for this reason we also include a sensitivity analysis that adjusts for date of delivery as a categorical variable with 5 categories based upon the years of the SIMD updates.

6.2.7.2 Modelling

Robust Poisson regression modelling with sandwiched errors was used to calculate relative risk (RR) and absolute risk (AR) of receiving epidural analgesia per incremental change in SIMD decile. Associated 99% confidence intervals (95%

CI) were also calculated. To calculate the RR of receiving epidural analgesia, SIMD 10, the least deprived decile was used as a reference category. A sandwich estimator was used to correct the inflated variance from a standard Poisson model. Robust Poisson regression modelling was used instead of log-binomial modelling to allow the calculation of relative risk, rather than odds ratio. Robust Poisson regression modelling also avoided problems with convergence that may be seen in log-binomial modelling, and allowed us to be consistent across the analysis. Regression modelling is covered in more detail in Chapter 3, section 3.3. P values < 0.05 indicated statistical significance, these were calculated using 2-sided Wilcoxon rank sum and x^2 tests. The results from the unimputed analysis are presented alongside those of the primary analysis.

The association between SIMD and: maternal age, maternal BMI, smoking history, illicit drug use history, ethnicity and comorbidities is presented graphically with confidence intervals calculated using quantile regression using the R package 'qgam'.[250]

6.2.7.3 Sensitivity analyses

Four stratified analyses to explore the relationship between SIMD, epidural uptake and interaction variables were carried out. The first explores the interaction with 'clinical indication without relative contraindication to labour epidural', a new variable as described in section 6.2.4.5. The second stratified analysis looks at the interaction with the same variable, but extreme obesity is set with a higher threshold of BMI 50 rather than 40. In the third stratified analysis, the definition of 'clinical indication without relative contraindication to labour epidural' is altered to exclude asthma as a medical indication. The final stratified analysis explores the influence of white as compared to non-white ethnicity on the relationship between SIMD and epidural utilisation. Whilst we would have preferred to stratify each ethnicity separately, Scotland has a largely white population, and we did not have the sufficient data to carry out the analysis of each ethnicity separately and produce meaningful results. The purpose of this stratified analysis was to identify if there was an interaction between socio-economic status and ethnicity rather than to draw strong conclusions.

Two subgroup analyses were carried out looking at only women who delivered in one major Scottish city with 24-hour access to obstetric and anaesthetic care as described in section 6.2.4.7. The second subgroup analysis restricted the analysis to only include primiparous women, as they may have differing analgesic requirements to those of multiparous women. Finally two adjusted analyses were carried out for date of delivery as a continuous and categorical variable respectively (as described in section 6.2.4.8).

6.2.8 Model validation

The final stage of modelling is checking that our model accurately reflects the data, this is known as model validation. As discussed in Chapter 3, section 3.3, regression models are based upon assumptions. If our data does not meet these assumptions, the model may not accurately reflect the data and the model predictions may not be accurate. In the model validation stage, we verify that the data is a good fit to the model, and that our modelling assumptions hold true.

Residuals are the difference between the observed data and the data predicted by the model. In a residual plot a 'line of best fit' is plotted to represent the data predicted by the model, and the true data points are plotted. For linear models, this allows us to visually inspect the plots for evidence of model misspecification. The ideal plot would be homogenous, with the data points evenly distributed along the line of best fit. This technique is not so straightforward for generalised linear models, such as the Poisson model which is used in this analysis. This is due to the data being transformed as part of the model (in this analysis it is transformed with the log link), making the plots more difficult to visually interpret.

The 'DHARMa' (Diagnostics for HierArchical Regression Models) package in R [251] was used post-hoc to check modelling assumptions. The DHARMa package scales the residuals of a generalised linear model to a 'standard value' on this scale of 0 to 1. It can then be plotted and interpreted like a linear model. Two plots were created using this package – a residual vs model prediction plot (Figure 6-7), and a Quantile-Quantile (QQ) plot (Figure 6-8).

Figure 6-7 is a plot of DHARMa residuals versus model predictions. The DHARMa residual is created by plotting the empirical cumulative density function of data simulated from the model, for each value of the observed data.[251] Thus a DHARMa residual of 0 means that all the values from the model are greater than the observed data, and a DHARMa residual of 1 mean that all of the values from the model are smaller than the observed data. Ideally, we would want 50% of modelled values to be greater than the observed data, thus an empirical cumulative density function, or DHARMa residual of 0.5. In Figure 6-7 the red dashed line plotted forms a roughly horizonal band at a value of 0.5. No data points stand out as being abnormal. This implies good model fit.

Figure 6-8 is a QQ plot was created using the DHARMa package. The purpose of a QQ plot is to detect deviations from the expected distribution by plotting quantiles of the observed values against the quantiles of the model (the thick black line). We can see in Figure 6-8 that the distribution of the modelled data is similar to that of the observed data, as it approximates the line y = x.

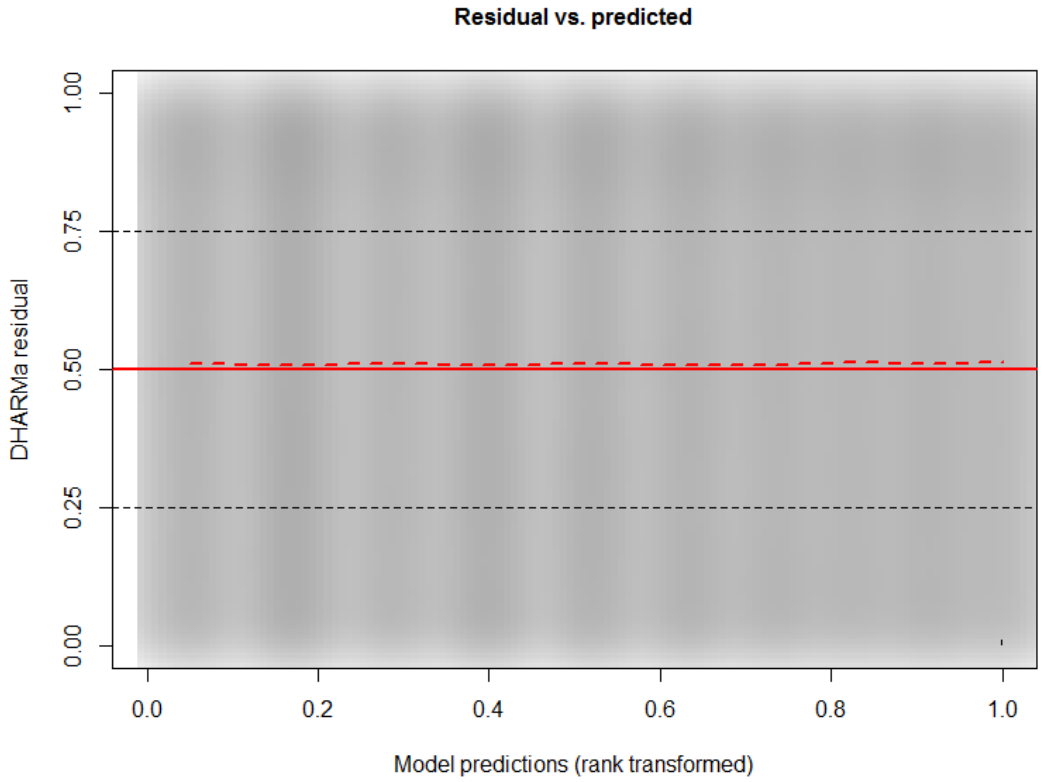


Figure 6-7 DHARMa scaled residuals plotted against model predictions (relative risk of epidural by SIMD decile)

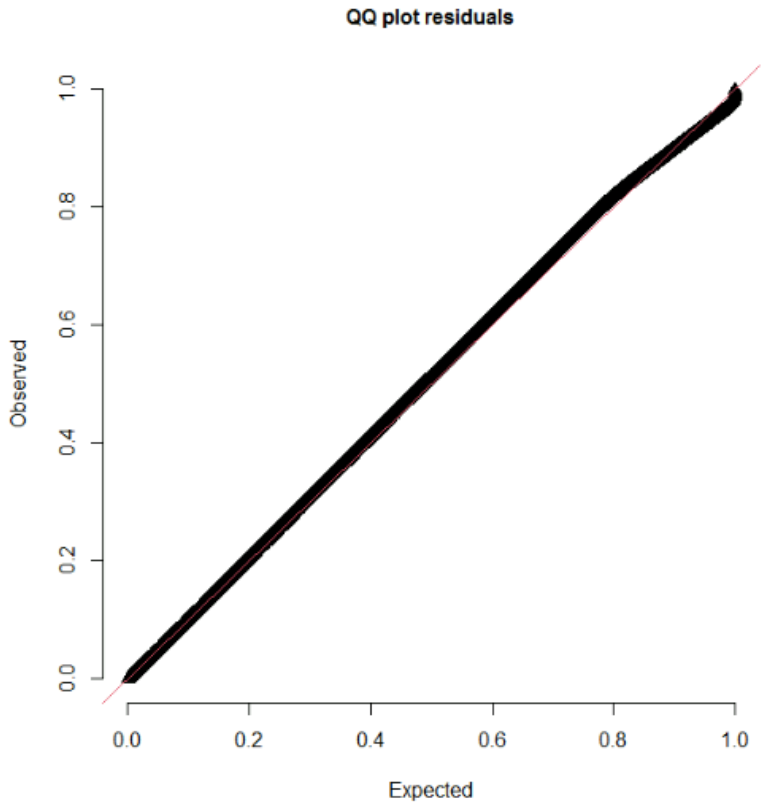


Figure 6-8 QQ plot for observed vs modelled data relative risk of epidural by SIMD decile

6.3 Results

6.3.1 Study population

Between the 1st of January 2007 and the 23rd of October 2020, 735,650 deliveries were recorded in Scotland. Of these 3,334 were excluded for being extreme pre-or post-term, 97,996 for being delivered by elective caesarean birth and 2,444 for having no mode of birth recorded. Of the remaining 631,876 deliveries, a further 38,646 (6.1%) were excluded for having data missing on epidural use. The remaining 593,230 women made up our study cohort. Of these 131,521 (22.2%) received epidural analgesia during labour and 461,709 women (77.8%) received no epidural analgesia in labour (Figure 6-9).

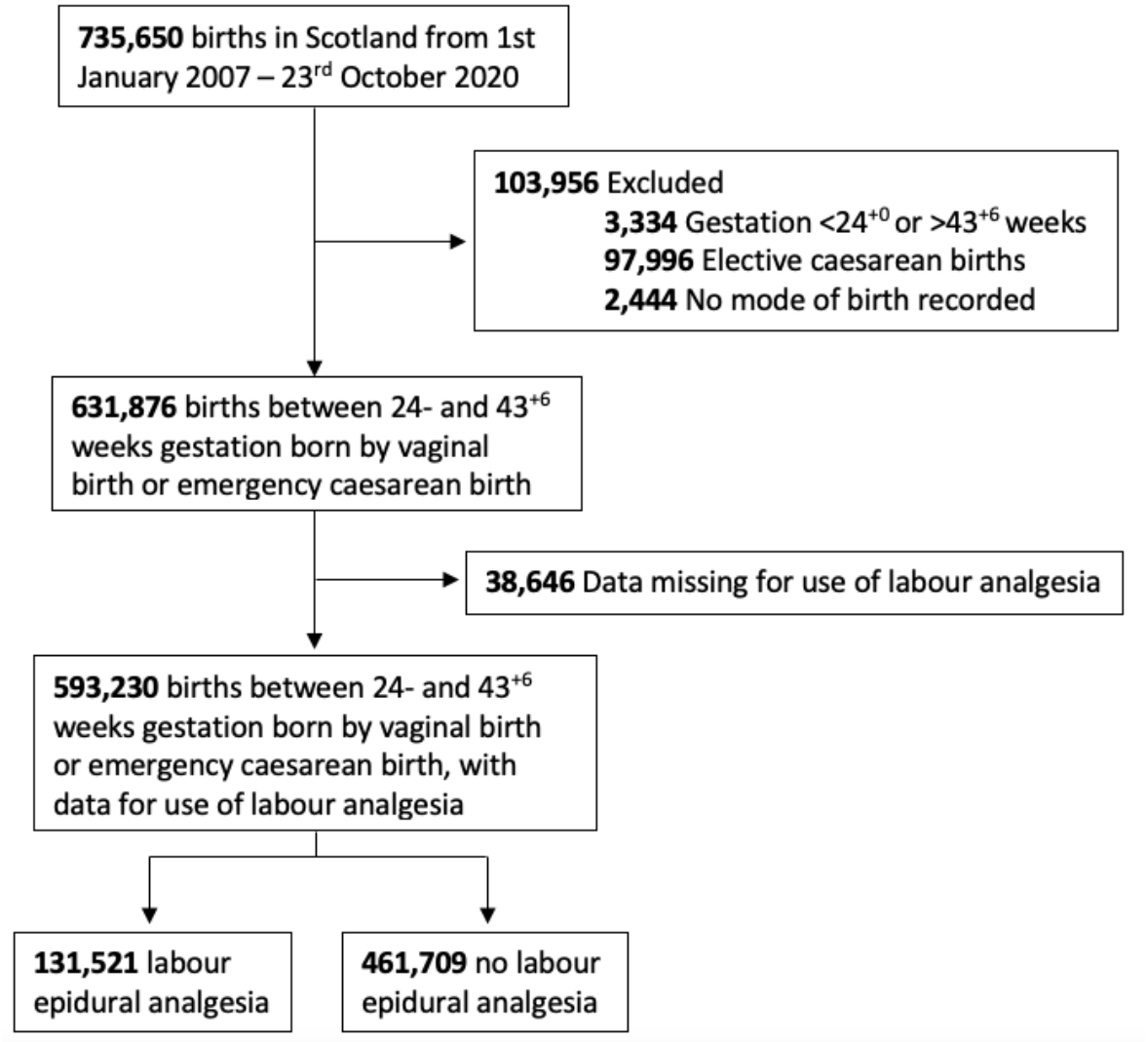


Figure 6-9 Definition of study population cohort for analysis

6.3.2 Cohort demographics by utilisation of epidural analgesia

A table of cohort demographics by utilisation of labour epidural analgesia is presented in Table 6-6. The cohort demographics are unimputed. Median maternal age at delivery was 29 for both women who received epidural analgesia in labour, and those who did not. As compared to women who did not receive epidural analgesia during labour, women who received epidural analgesia were more likely to have a higher BMI, be of non-white ethnicity, be diabetic or pre-eclamptic, have comorbidities, and be primiparous. They were more likely to have had a previous caesarean birth, be undergoing induced labour and have a multiple birth. The interquartile rage of estimated gestational age at birth (completed weeks) was increased in the epidural analgesia group and compared to the non-epidural group (median completed weeks 40 [39, 41] vs 40 [38,40]), (Table 6-6).

Characteristic	Epidural, N = 131,521	No epidural, N = 461,709
Age of Mother, Median (IQR), years	29 (24, 33)	29 (25, 33)
Maternal BMI, Median (IQR)	25.1 (22.3, 29.4)	24.7 (22.0, 28.7)
Missing	14,637 (11.1%)	56,131 (12.2%)
Ethnic Group		
White	79,274 (60.3%)	259,485 (56.2%)
Asian	3878 (2.9%)	12,236 (2.7%)
Black	1184 (0.9%)	4322 (0.9%)
Mixed	482 (0.4%)	1301 (0.3%)
Other	892 (0.7%)	2761 (0.6%)
Missing	45,811 (34.8%)	181,604 (39.3%)
SIMD[2] decile, No. (%)		
10 (least deprived)	11,320 (8.6%)	33,608 (7.3%)
09	11,623 (8.9%)	37,392 (8.1%)
08	12,659 (9.7%)	40,281 (8.7%)
07	11,887 (9.1%)	42,024 (9.1%)
06	11,593 (8.8%)	42,871 (9.3%)
05	12,041 (9.2%)	45,780 (9.9%)
04	13,592 (10%)	48,169 (10%)
03	14,480 (11%)	51,645 (11%)
02	15,464 (12%)	56,758 (12%)
01 (most deprived)	16,532 (13%)	61,896 (13%)
Missing	430 (0.3%)	1285 (0.3%)
Smoking History, No. (%)		
Current smoker	20,763 (17%)	85,576 (19%)
Former smoker	19,750 (16%)	53,420 (12%)
Never smoked	85,107 (68%)	302,769 (69%)
Missing	5901 (4.5%)	19,944 (4.3%)
Injected illicit Drugs, No. (%)	638 (0.7%)	2604 (0.8%)
Missing	38,840 (29.5%)	147,415 (31.9%)
Number of Comorbidities *, (%)		
0	113,914 (87%)	401,184 (87%)
1	13,938 (11%)	47,921 (10%)
2 or more	3669 (2.8%)	12,604 (2.7%)
Pre-eclampsia	2645 (2.0%)	5468 (1.2%)

[2] SIMD = Scottish Index of Multiple Deprivation

* Comorbidities classified according to the Elixhauser co-morbidity index

Characteristic	Epidural, N = 131,521	No epidural, N = 461,709
Diabetes	3915 (3.1%)	10,750 (2.4%)
Missing	4160 (3.2%)	17,107 (3.7%)
Previous spontaneous abortions		
Missing	503 (0.4%)	1950 (0.4%)
Previous therapeutic abortions	11,801 (9.0%)	37,638 (8.2%)
Missing	501 (0.4%)	1939 (0.4%)
Previous caesarean births	7878 (6.0%)	24,884 (5.4%)
Missing	272 (0.2%)	1401 (0.3%)
Parity	0 (0, 1)	1 (0, 1)
Missing	654 (0.5%)	2525 (0.5%)
Estimated gestation (weeks)	40 (39, 41)	40 (38, 40)
Location of Birth		
Midwife led unit	0	25,830 (5.6%)
Obstetric unit	131,521 (100%)	435,454 (94.3%)
Home	0	415 (0.1%)
Missing	0	10 (<0.1%)
Induction of labour	60,839 (47%)	123,972 (27%)
Missing	2056 (1.6%)	5522 (1.2%)
Multiple birth	2344 (1.8%)	4216 (0.9%)

Table 6-6 Baseline demographics of study population by utilisation of epidural analgesia in labour.

6.3.3 Cohort demographics by SIMD decile

The baseline demographics of women changed significantly with degree of relative deprivation. The average age of women in the most deprived decile (SIMD 1) had a median age of 26 years [22, 31], compared to 32 years [29, 36] for women in the least deprived decile (SIMD 10). Women in the most deprived decile (SIMD 1) were significantly more likely to be diabetic (RR 1.49 [1.37-1.61]) and more than three times more likely to have multiple co-morbidities (RR 3.34 [3.05-3.66]), despite being on average 6 years younger than women in the least deprived decile (SIMD 10). Figure 6-10 presents plots of SIMD decile to maternal health characteristics, with 95% confidence intervals calculated by quantile regression (see section 3.3.3). For each incremental increase in SIMD level, women were on average; 0.6 years younger (Figure 6-10), had a BMI 0.14 unit higher (Figure 6-11), were 0.8 times as likely to smoke (Figure 6-12), and were 1.8 times more likely to take illicit drugs (Figure 6-13). Women in SIMD 10 (least deprived) were the least likely to be of white ethnicity, followed by SIMD 1 (most deprived) (Figure 6-14). Prevalence of both single or multiple co-morbidity increased as SIMD decile decreased (Figure 6-15). The prevalence of pre-eclampsia did not vary according to the SIMD decile (Table 6-7). Women in SIMD 10 were most likely to give birth within an obstetric unit, followed by women in SIMD 1 (Table 6-7).

Characteristic	SIMD 10, N = 44,928[1]	SIMD 09, N = 49,015[1]	SIMD 08, N = 52,940[1]	SIMD 07, N = 53,911[1]	SIMD 06, N = 54,464[1]	SIMD 05, N = 57,821[1]	SIMD 04, N = 61,761[1]	SIMD 03, N = 66,125[1]	SIMD 02, N = 72,122[1]	SIMD 01, N = 78,428[1]
Epidural	11,320 (25%)	11,623 (24%)	12,659 (24%)	11,887 (22%)	11,593 (21%)	12,041 (21%)	13,592 (22%)	14,480 (22%)	15,364 (21%)	16,532 (21%)
Maternal age	32 (29, 36)	32 (28, 35)	31 (27, 34)	30 (26, 34)	30 (26, 34)	29 (25, 33)	28 (24, 33)	28 (23, 32)	27 (23, 31)	26 (22, 31)
Maternal BMI	23.9 (21.6, 27.0)	24.3 (21.9, 27.8)	24.5 (22.0, 28.2)	24.7 (22.1, 28.4)	24.8 (22.1, 28.7)	25.0 (22.2, 29.1)	25.2 (22.2, 29.4)	25.2 (22.1, 29.7)	25.3 (22.1, 29.8)	25.3 (22.0, 29.9)
White ethnicity	27,654 (91%)	28,321 (92%)	30,956 (93%)	30,868 (94%)	30,584 (93%)	32,178 (93%)	34,503 (93%)	37,651 (93%)	41,139 (93%)	44,188 (91%)
Asian ethnicity	1,803 (5.9%)	1,578 (5.1%)	1,500 (4.5%)	1,269 (3.9%)	1,330 (4.1%)	1,418 (4.1%)	1,739 (4.7%)	1,668 (4.1%)	1,688 (3.8%)	2,069 (4.3%)
Black ethnicity	448 (1.5%)	401 (1.3%)	405 (1.2%)	356 (1.1%)	376 (1.1%)	456 (1.3%)	451 (1.2%)	554 (1.4%)	788 (1.8%)	1,236 (2.6%)
Mixed ethnicity	248 (0.8%)	170 (0.6%)	151 (0.5%)	122 (0.4%)	145 (0.4%)	174 (0.5%)	165 (0.4%)	153 (0.4%)	170 (0.4%)	281 (0.6%)
Other ethnicity	394 (1.3%)	340 (1.1%)	291 (0.9%)	278 (0.8%)	301 (0.9%)	310 (0.9%)	347 (0.9%)	374 (0.9%)	471 (1.1%)	538 (1.1%)
Current smoker	1,813 (4.2%)	3,035 (6.5%)	4,674 (9.2%)	5,985 (12%)	7,302 (14%)	9,640 (17%)	12,341 (21%)	15,730 (25%)	20,569 (30%)	25,019 (34%)
Former smoker	5,020 (12%)	5,318 (11%)	6,013 (12%)	6,685 (13%)	7,234 (14%)	7,678 (14%)	8,439 (14%)	8,846 (14%)	9,216 (13%)	8,487 (11%)
Non-smoker	36,239 (84%)	38,695 (82%)	40,166 (79%)	39,078 (76%)	37,565 (72%)	37,963 (69%)	38,326 (65%)	38,718 (61%)	39,390 (57%)	40,698 (55%)
Injected drug use	48 (0.1%)	69 (0.2%)	95 (0.2%)	155 (0.4%)	183 (0.5%)	255 (0.6%)	386 (0.9%)	574 (1.3%)	660 (1.4%)	808 (1.8%)
Diabetes	848 (1.9%)	1,019 (2.1%)	1,194 (2.3%)	1,317 (2.5%)	1,272 (2.4%)	1,490 (2.7%)	1,628 (2.7%)	1,727 (2.7%)	2,003 (2.9%)	2,141 (2.9%)
Pre-eclampsia	621 (1.4%)	632 (1.3%)	715 (1.4%)	809 (1.5%)	804 (1.5%)	784 (1.4%)	853 (1.4%)	913 (1.4%)	1,050 (1.5%)	916 (1.2%)
No comorbidities	41,225 (92%)	44,277 (90%)	47,147 (89%)	47,741 (89%)	47,866 (88%)	50,085 (87%)	53,159 (86%)	56,125 (85%)	60,657 (84%)	65,245 (83%)
1 comorbidity	3,170 (7.1%)	4,001 (8.2%)	4,825 (9.1%)	4,964 (9.2%)	5,301 (9.7%)	6,102 (11%)	6,744 (11%)	7,707 (12%)	8,857 (12%)	10,070 (13%)
2 or more comorbidities	533 (1.2%)	737 (1.5%)	968 (1.8%)	1,206 (2.2%)	1,297 (2.4%)	1,634 (2.8%)	1,858 (3.0%)	2,293 (3.5%)	2,608 (3.6%)	3,113 (4.0%)
Obstetric unit birth	43,722 (97%)	46,622 (95%)	49,965 (94%)	50,124 (93%)	50,957 (94%)	54,685 (95%)	58,569 (95%)	62,548 (95%)	69,492 (96%)	76,475 (98%)
Free-standing Midwifery unit birth	1,179 (2.6%)	2,348 (4.8%)	2,935 (5.5%)	3,731 (6.9%)	3,443 (6.3%)	3,072 (5.3%)	3,152 (5.1%)	3,543 (5.4%)	2,603 (3.6%)	1,926 (2.5%)
Home birth	27 (<0.1%)	45 (<0.1%)	40 (<0.1%)	56 (0.1%)	62 (0.1%)	58 (0.1%)	38 (<0.1%)	34 (<0.1%)	27 (<0.1%)	27 (<0.1%)

Table 6-7 Cohort characteristics by SIMD decile 1-10

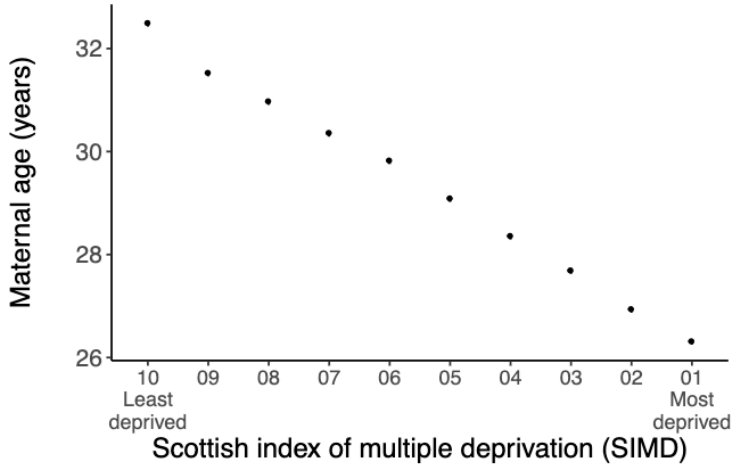


Figure 6-10 Age by SIMD decile

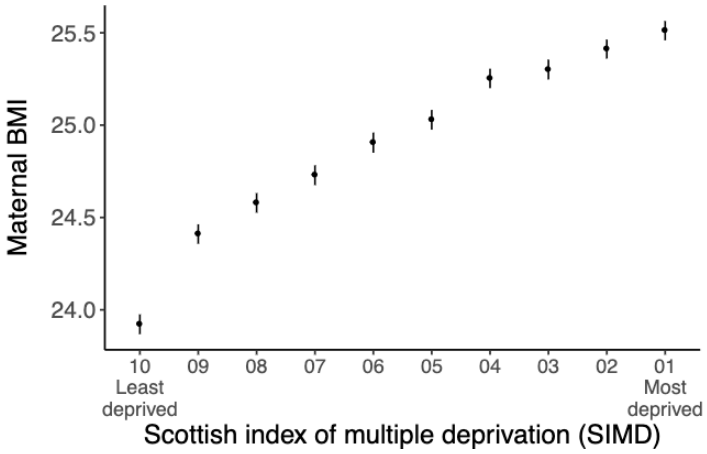


Figure 6-11 Maternal BMI by SIMD decile

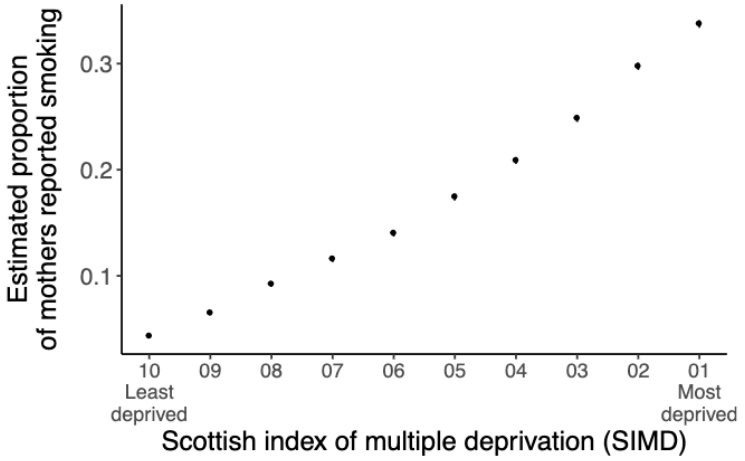


Figure 6-12 Proportion of mothers who smoke by SIMD decile

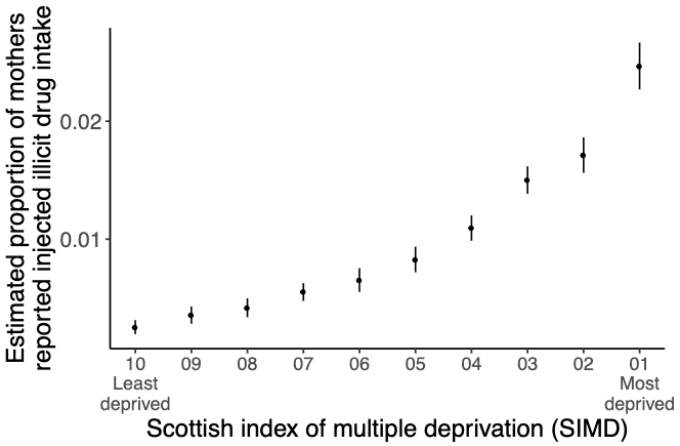


Figure 6-13 Proportion of mother who have ever injected illicit drugs by SIMD decile

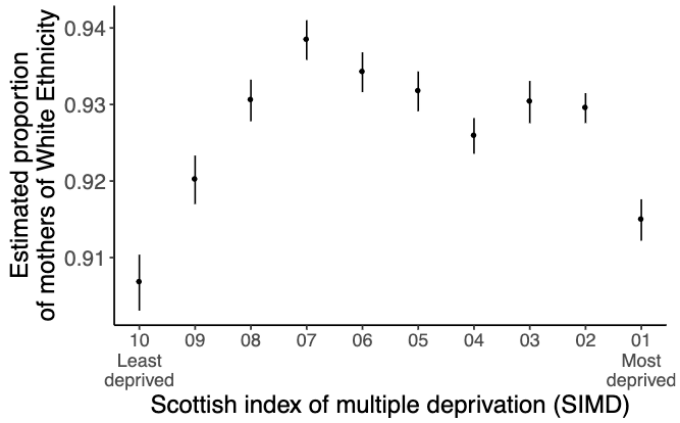


Figure 6-14 proportion of mothers of white ethnicity by SIMD decile

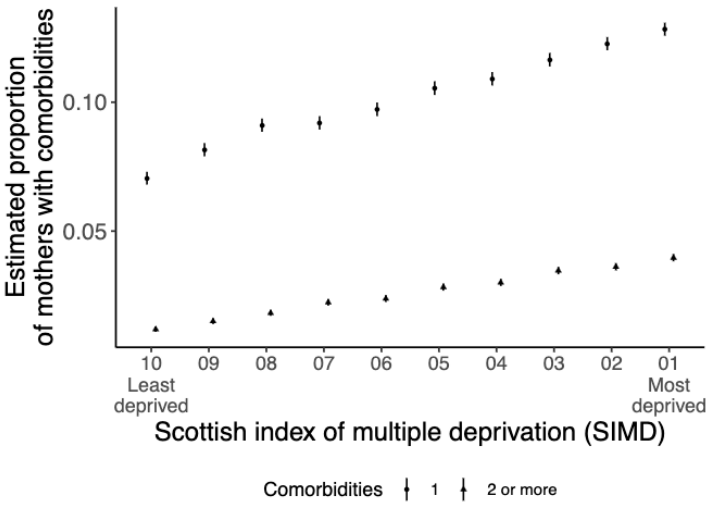


Figure 6-15 Proportion of mothers with single or multiple comorbidities by SIMD decile

6.3.4 Primary analysis

Increased maternal age, higher BMI, Asian or mixed ethnicity, higher SIMD, comorbidities, and being primiparous were independently associated with utilisation of labour epidural analgesia. Lower utilisation of labour analgesia was associated with younger age, smoking and a history of injected illicit drug use (Table 6.8). Epidural analgesia was used by 21.1% of women who lived in the most socio-economically deprived areas (SIMD 1) compared to 25.2% of women in the least socio-economically deprived areas (SIMD 10) (Table 6-9). The absolute risk difference is 4.1% (SIMD 1; AR 0.211 [0.208, 0.214], SIMD 10; AR 0.252[0.248, 0.256]) (Table 6-9). This represents a relative difference of 16% (SIMD 1 compared to SIMD10; RR 0.84 [0.82, 0.85]) (Table 6-8, Figure 6-16). The probability of using epidural analgesia in labour decreased as the SIMD decile decreased, and the level of socio-economic disadvantage increased, with the exception of SIMD deciles 5 and 6. This exception may be due to these middle deciles often representing more rural locations which may be very remote from an obstetric unit with 24-hour access to anaesthetic and obstetric services. The mean change is utilisation of labour epidural analgesia is estimated as -2.0% [-1.7%, -2.2%] per unit deprivation decrease.

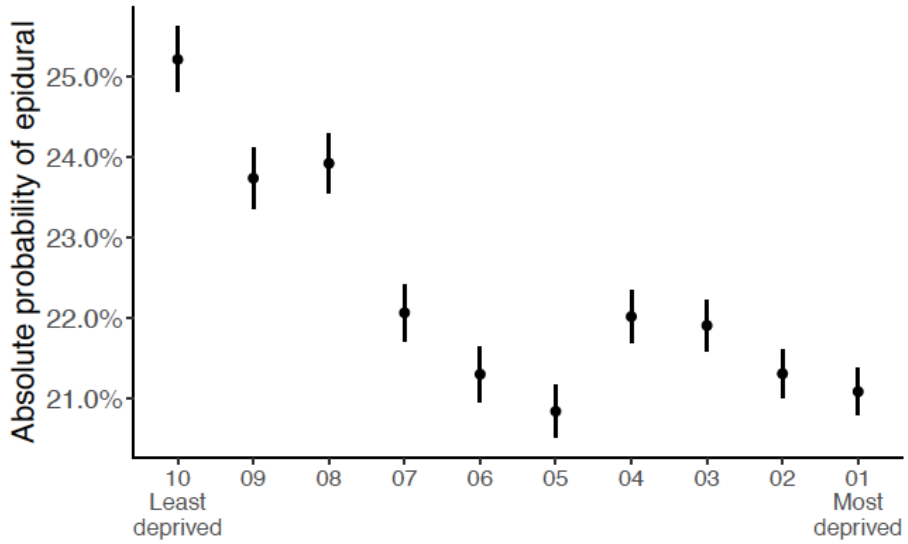


Figure 6-16 Scottish Index of Multiple Deprivation decile and absolute probability of utilisation of labour epidural analgesia

Characteristics	RR	95% CI	p-value
Age at delivery	0.99	0.99, 0.99	<0.001
Maternal BMI	1.01	1.01, 1.01	<0.001
Ethnic group			
White	—	—	
Asian	1.04	1.01, 1.07	0.010
Black	0.96	0.92, 1.01	0.12
Mixed	1.10	1.02, 1.19	0.018
Other	1.04	0.98, 1.10	0.2
Not white (combined)	1.02	0.99, 1.04	0.15
SIMD[3] decile			
10 (least deprived)	—	—	
09	0.94	0.92, 0.96	<0.001
08	0.95	0.93, 0.97	<0.001
07	0.88	0.86, 0.90	<0.001
06	0.84	0.83, 0.86	<0.001
05	0.83	0.81, 0.85	<0.001
04	0.87	0.85, 0.89	<0.001
03	0.87	0.85, 0.89	<0.001
02	0.85	0.83, 0.86	<0.001
01 (most deprived)	0.84	0.82, 0.85	<0.001
Booking smoking history			
Non-smoker	—	—	
Current smoker	0.89	0.88, 0.90	<0.001
Former smoker	1.22	1.20, 1.24	<0.001
Injected illicit drugs			
No	—	—	
Yes	0.86	0.80, 0.93	<0.001
Comorbidities			
0	—	—	
1	1.02	1.00, 1.03	0.018
2 or more	1.02	0.99, 1.05	0.2
Pre-eclampsia			
No pre-eclampsia	—	—	
Pre-eclampsia	1.48	1.43, 1.53	<0.001
Diabetes			

[3] SIMD = Scottish Index of Multiple Deprivation

Characteristics	RR	95% CI	p-value
No	—	—	
Yes	1.20	1.17, 1.24	<0.001
Previous spontaneous abortions			
No	—	—	
Yes	0.93	0.92, 0.94	<0.001
Previous therapeutic abortions			
No	—	—	
Yes	1.08	1.07, 1.10	<0.001
Previous caesarean births			
No	—	—	
Yes	1.09	1.07, 1.11	<0.001
Parity	0.64	0.63, 0.64	<0.001
Estimated gestation	1.09	1.09, 1.10	<0.001
Location of birth			
Obstetric Unit	—	—	
Freestanding midwifery unit	0.00	0.00, 0.00	<0.001
Home	0.00	0.00, 0.00	<0.001
Multiple birth			
No	—	—	
Yes	1.62	1.57, 1.68	<0.001

Table 6-8 Relative risk of epidural analgesia in labour

SIMD decile	Absolute probability	Standard Error	Lower 95% CI	Upper 95% CI
10	0.252	0.002	0.248	0.256
09	0.237	0.002	0.234	0.241
08	0.239	0.002	0.236	0.243
07	0.221	0.002	0.217	0.224
06	0.213	0.002	0.210	0.216
05	0.208	0.002	0.205	0.212
04	0.220	0.002	0.217	0.223
03	0.219	0.002	0.216	0.222
02	0.213	0.002	0.210	0.216
01	0.211	0.001	0.208	0.214

Table 6-9 SIMD decile and absolute probability of labour epidural analgesia utilisation

6.3.5 Unimputed analysis results

The results of the unimputed analysis are presented and are consistent of those with the primary analysis (Table 6-10).

Characteristic	N	RR[1]	95% CI[1]	p-value
Age at delivery	593,230	0.99	0.99, 0.99	<0.001
Maternal BMI	522,462	1.01	1.01, 1.01	<0.001
Ethnic group	365,815			
White		—	—	
Asian		1.03	1.00, 1.06	0.089
Black		0.92	0.87, 0.97	0.004
Mixed		1.16	1.05, 1.26	0.002
Other		1.04	0.98, 1.11	0.21
SIMD decile	591,515			
10		—	—	
09		0.94	0.92, 0.97	<0.001
08		0.95	0.93, 0.97	<0.001
07		0.88	0.85, 0.90	<0.001
06		0.84	0.82, 0.87	<0.001
05		0.83	0.81, 0.85	<0.001
04		0.87	0.85, 0.90	<0.001
03		0.87	0.85, 0.89	<0.001
02		0.85	0.83, 0.87	<0.001
01		0.84	0.82, 0.86	<0.001
Booking smoking	567,385			
Non-smoker		—	—	
Current smoker		0.89	0.88, 0.90	<0.001
Former smoker		1.23	1.21, 1.25	<0.001
Injected illicit drugs	406,975			
No		—	—	
Yes		0.86	0.80, 0.93	<0.001
Diabetes	571,963			
No		—	—	
Yes		1.21	1.17, 1.24	<0.001
Pre-eclampsia	593,230			
No pre-eclampsia		—	—	
Pre-eclampsia		1.48	1.42, 1.54	<0.001
Comorbidities	593,230			
0		—	—	
1		1.02	1.00, 1.04	0.037
2 or more		1.02	0.99, 1.05	0.25
Previous spontaneous abortions	590,777			

Characteristic	N	RR[1]	95% CI[1]	p-value
No		—	—	
Yes		0.93	0.92. 0.94	<0.001
Previous therapeutic abortions	590,790			
No		—	—	
Yes		1.08	1.06. 1.10	<0.001
Previous caesarean births	591,557			
No		—	—	
Yes		1.09	1.06, 1.11	<0.001
Parity	590,051	0.63	0.63, 0.64	<0.001
Estimated gestation	593,230	1.09	1.09, 1.10	<0.001
Induction of labour	585.652			
No		—	—	
Yes		1.92	1.90. 1.94	<0.001
Multiple birth	593.230			
No		—	—	
Yes		1.62	1.56, 1.69	<0.001

[1]RR = Rate Ratio, CI = Confidence Interval

Table 6-10 Relative risk of labour epidural analgesia (unimputed analysis)

6.3.6 Date of delivery adjustment as a continuous variable

The results of analysis of relative risk of labour epidural analgesia by SIMD decile, adjusted for date of delivery as a continuous variable, are identical to those of the primary analysis (Table 6-11, Figure 6-17).

Characteristic	RR[1]	95% CI[2]	p-value
Date of delivery	1.00	1.00, 1.00	<0.001
SIMD decile			
10	—	—	
09	0.94	0.92, 0.96	<0.001
08	0.95	0.93, 0.97	<0.001
07	0.88	0.86, 0.90	<0.001
06	0.84	0.83, 0.86	<0.001
05	0.83	0.81, 0.85	<0.001
04	0.87	0.85, 0.89	<0.001
03	0.87	0.85, 0.89	<0.001
02	0.84	0.83, 0.86	<0.001
01	0.84	0.82, 0.85	<0.001

[1]RR = Relative Risk, [2]CI = Confidence Interval

Table 6-11 Scottish Index of Multiple Deprivation decile and relative risk of epidural analgesia (imputed), adjusted for date of delivery as a continuous variable.

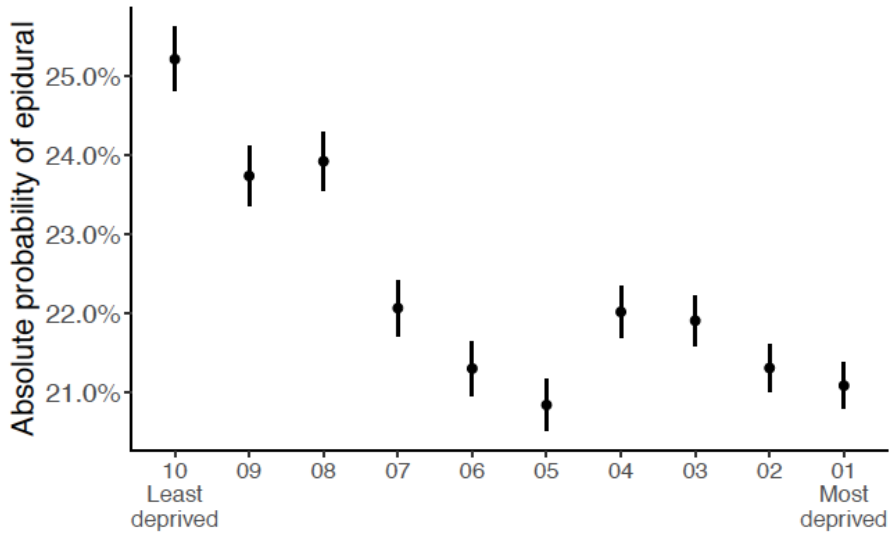


Figure 6-17 Scottish Index of Multiple Deprivation and absolute risk of labour epidural analgesia, analysis adjusted by date of delivery as a continuous variable

6.3.7 Date of delivery adjustment as a categorical variable

The results of analysis of relative risk of labour epidural analgesia by SIMD decile, adjusted for date of delivery as a categorical variable, according to the years of the SIMD updates, are identical to those of the primary analysis (Table 6-12). When compared to epidural use in 2007-2008 (reference category). Years 2009-2011, and 2020 were associated with a slight increase in epidural analgesia use. Whilst years 2012-2015 were associated with similar use. The increase seen in the in 2020 cohort may be linked to the COVID-19 pandemic where use of general anaesthesia was restricted and epidural use was encouraged.[252]

Characteristic	RR[1]	95% CI[2]	p-value
SIMD update			
2007 - 2008	—	—	
2009 - 2011	1.12	1.10, 1.13	<0.001
2012 – 2015	0.97	0.96, 0.99	0.002
2016 – 2019	0.99	0.97, 1.00	0.10
2020	1.15	1.12, 1.18	<0.001
SIMD decile			
10	—	—	
09	0.94	0.92, 0.96	<0.001
08	0.95	0.93, 0.97	<0.001
07	0.88	0.86, 0.90	<0.001
06	0.84	0.83, 0.86	<0.001
05	0.83	0.81, 0.85	<0.001
04	0.87	0.85, 0.89	<0.001
03	0.87	0.85, 0.89	<0.001
02	0.84	0.83, 0.86	<0.001
01	0.84	0.82, 0.85	<0.001

[1]RR = Relative Risk, [2]CI = Confidence Interval

Table 6-12 Scottish Index of Multiple Deprivation decile and relative risk of epidural analgesia (imputed), adjusted for date of delivery as a categorical variable according to the years of the SIMD update.

6.3.8 Subgroup delivering within one major Scottish city with 24-hour access to obstetric and anaesthetic services

During the study period, 143,007 women gave birth within one major Scottish city, in one of the obstetric units where there was 24-hour access to anaesthetic and obstetric services. Similar to the primary analysis, increased maternal age, higher BMI and primiparity were associated with an increased use of labour epidural analgesia, while younger maternal age, smoking, history of injected illicit drug use and residing in the least socio-economically advantaged areas (SIMD 1-3) were associated with lower use of epidural analgesia in labour. Compared with SIMD 10, women living in SIMD 1-3 were significantly less likely to use labour epidural analgesia (SIMD1 vs SIMD 10, RR 0.86 [0.83, 0.90]; SIMD2 vs SIMD 10, RR 0.90 [0.87, 0.94]; SIMD3 vs SIMD10 RR 0.95 [0.91, 1.00]) (Table 6-13). The absolute risk difference between SIMD 1 and SIMD 10 was 3.6% (SIMD1 AR 0.226 [0.222, 0.232], SIMD 10 AR 0.262 [0.253, 0.271]) (Figure 6-18). No difference was seen between women from SIMD 4-9 and SIMD 10. In contrast to the primary analysis, Asian and black ethnicities were associated with significantly lower epidural use than their white counterparts (RR 0.85 [0.81, 0.89], and 0.79 [0.73, 0.86], respectively) (Table 6-13).

Characteristic	RR[1]	95% CI[1]	p-value
Age at delivery	0.99	0.99, 0.99	<0.001
Maternal BMI	1.01	1.01, 1.01	<0.001
Ethnic group			
White	—	—	
Asian	0.85	0.81, 0.89	<0.001
Black	0.79	0.73, 0.86	<0.001
Mixed	0.91	0.78, 1.05	0.2
Other	0.85	0.75, 0.96	0.009
SIMD decile			
10	—	—	
09	0.98	0.93, 1.03	0.4
08	1.03	0.98, 1.08	0.2
07	0.97	0.92, 1.02	0.3
06	0.97	0.92, 1.02	0.2
05	0.98	0.93, 1.02	0.3
04	0.97	0.92, 1.01	0.2
03	0.95	0.91, 1.00	0.035
02	0.90	0.87, 0.94	<0.001
01	0.86	0.83, 0.90	<0.001
Booking smoking history			
Non-smoker	—	—	
Current smoker	0.95	0.93, 0.98	<0.001
Former smoker	1.14	1.11, 1.18	<0.001
Injected illicit drugs			
No	—	—	
Yes	0.86	0.75, 0.99	0.040
Diabetes			
No	—	—	
Yes	1.04	0.98, 1.10	0.2
Pre-eclampsia			
No pre-eclampsia	—	—	
Pre-eclampsia	1.13	1.02, 1.25	0.018
Comorbidities			
0	—	—	
1	1.02	0.99, 1.05	0.2
2 or more	0.96	0.90, 1.02	0.15
Previous spontaneous abortions			
No	—	—	
Yes	0.92	0.90, 0.94	<0.001
Previous therapeutic			
No	—	—	
Yes	1.03	0.99, 1.07	0.15

Characteristic	RR[1]	95% CI[1]	p-value
Previous caesarean births			
No	—	—	
Yes	1.08	1.03, 1.13	<0.001
Parity	0.59	0.58, 0.60	<0.001
Estimated gestation	1.11	1.10, 1.11	<0.001
Multiple birth			
No	—	—	
Yes	1.52	1.42, 1.62	<0.001

Table 6-13 Subgroup analysis, population limited to only include women who delivered in one major Scottish city with 24-hour access to anaesthetic and obstetric services

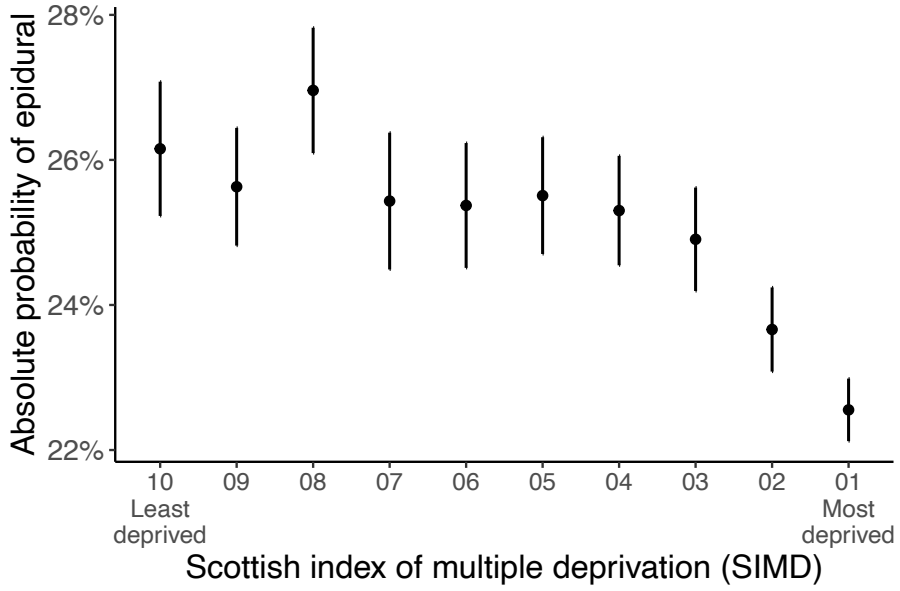


Figure 6-18 Scottish Index of Multiple Deprivation decile and absolute probability of utilisation of labour epidural analgesia, analysis restricted to only include women who delivered within one major Scottish city with 24-hour access to obstetric and anaesthetic services

6.3.9 Primiparous subgroup

The primiparous subgroup was made up of 282,340 women (47.6% of total cohort). Of these, 88,339 women used epidural analgesia in labour (31.3%). Women living in SIMD 1 (most deprived) were significantly less likely to use epidural analgesia in labour compared to women residing in SIMD 10 (RR 0.91 [0.89, 0.93]) (Table 6-14). Women who reside in SIMD 5 and 6 are the least likely to receive epidural analgesia in labour in this subgroup (RR 0.84 [0.82, 0.06], and 0.86 [0.84, 0.88], for SIMD 5 and SIMD 6 as compared to SIMD 10 respectively. This is demonstrated in Figure 6-19. Absolute risk of epidural analgesia in labour by SIMD decile are presented in Table 6-15.

Characteristic	RR[1]	95% CI[1]	p-value
Age at delivery	1.01	1.01, 1.01	<0.001
Maternal BMI	1.02	1.02. 1.02	<0.001
Ethnic group			
White	—	—	
Asian	1.01	0.95. 1.08	0.7
Black	1.06	0.97. 1.16	0.2
Mixed	1.04	0.97. 1.11	0.2
Other	1.09	1.05. 1.13	<0.001
SIMD decile			
10	—	—	
09	0.94	0.91. 0.96	<0.001
08	0.95	0.92. 0.97	<0.001
07	0.88	0.86. 0.91	<0.001
06	0.86	0.84. 0.88	<0.001
05	0.84	0.82. 0.86	<0.001
04	0.89	0.87. 0.91	<0.001
03	0.90	0.88. 0.93	<0.001
02	0.91	0.88. 0.93	<0.001
01	0.91	0.89. 0.93	<0.001
Booking smoking history			
Non-smoker	—	—	
Current smoker	0.97	0.96. 0.99	<0.001
Former smoker	1.15	1.13. 1.17	<0.001
Injected illicit drugs			
No	—	—	
Yes	1.01	0.91. 1.11	0.9
Diabetes			
No	—	—	
Yes	1.21	1.17. 1.25	<0.001
Pre-eclampsia			

Characteristic	RR[1]	95% CI[1]	p-value
No pre-eclampsia	—	—	
Pre-eclampsia	1.21	1.17, 1.25	<0.001
Comorbidities			
0	—	—	
1	1.05	1.03, 1.07	<0.001
2 or more	1.09	1.05, 1.13	<0.001
Previous spontaneous abortions			
No	—	—	
Yes	1.08	1.06, 1.09	<0.001
Previous therapeutic abortions			
No	—	—	
Yes	1.10	1.08, 1.12	<0.001
Previous caesarean births			
No	—	—	
Yes	0.82	0.59, 1.14	0.2
Estimated gestation	1.10	1.10, 1.10	<0.001
Multiple birth			
No	—	—	
Yes	1.27	1.22, 1.33	<0.001

Table 6-14 Subgroup analysis, population limited to only include primiparous women

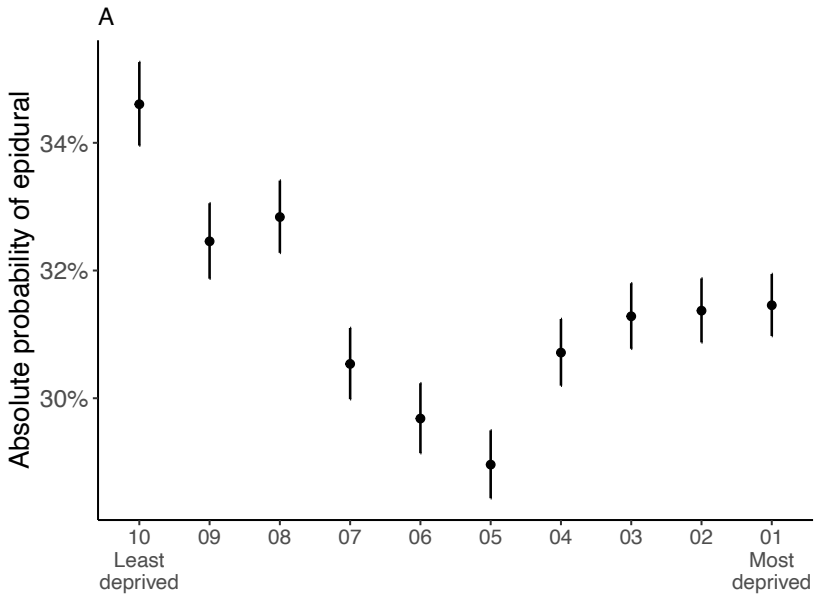


Figure 6-19 Scottish Index of Multiple Deprivation decile and absolute probability of utilisation of labour epidural analgesia, analysis restricted to only include primiparous women

SIMD decile	Absolute probability	Standard error	Lower 95% CI	Upper 95% CI
10	0.346	0.003	0.340	0.353
09	0.325	0.003	0.319	0.331
08	0.328	0.003	0.323	0.334
07	0.305	0.003	0.300	0.311
06	0.297	0.003	0.291	0.302
05	0.290	0.003	0.284	0.295
04	0.307	0.003	0.302	0.312
03	0.313	0.003	0.308	0.318
02	0.314	0.003	0.309	0.319
01	0.315	0.002	0.310	0.319

Table 6-15 SIMD decile and absolute probability of labour epidural analgesia utilisation in primiparous women

6.3.10 Medical indication and no relative contraindication to epidural

Of the 593,230 women made up our study cohort, 90,924 (15.3%) had a documented medical indication for epidural, and 26,078 (4.4%) had a documented relative contraindication. In total, 85,530 women (14.4%) had both a documented medical indication and no relative contraindication for labour epidural analgesia (Table 6-16). Of these,83,826 (98%) gave birth in an obstetric unit and 21,219 women received epidural analgesia in labour (24.8%).

Epidural analgesia	Documented indication	Documented relative contraindication	Count (%)
No	No	No	383,020 (64.6%)
No	No	Yes	11,147 (1.9%)
No	Yes	No	64,311 (10.8%)
No	Yes	Yes	3,231 (0.5%)
Yes	No	No	98,602 (16.6%)
Yes	No	Yes	9,537 (1.6%)
Yes	Yes	No	21,219 (3.6%)
Yes	Yes	Yes	2,163 (0.4%)
Total with documented indication and no relative contraindication			85,530 (14.4%)

Table 6-16 Incidence of epidural analgesia and documented indication or relative contraindication to labour epidural analgesia

The breakdown of the incidence of each indication and relative contraindication is listed in Table 6-17. The most frequently occurring medical indication were asthma (34,949 women), followed previous caesarean birth (32,762), and BMI greater than or equal to 40 (13,289). The most frequently occurring relative contraindication was fever or infection during labour (21,238 women).

	Counts[1]
Indications	
Breech presentation	1743
Multiple pregnancy	6560
Pre-eclampsia	8113
Previous caesarean birth	32762
BMI >= 40	13289
BMI >=50	957
Asthma	34949
Congestive cardiac failure	106
Congenital heart disease	860
Ischaemic heart disease	124
Pulmonary hypertension	32
Cardiac valve disease	443
Contraindications	
Coagulation factor defect, Von Willebrand disease, and thrombocytopaenia	3689
Fever or infection during labour	21238
Chorioamnionitis	1563

[1] Women may be included in more than one category

Table 6-17 Incidence of indications and relative contraindications to labour epidural analgesia

Overall, women with a medical indication and no relative contraindication to labour epidural analgesia were more likely to use it. However, the socio-economic gradient observed in the primary analysis persisted. Women who lived in the most deprived area (SIMD 1) were significantly less likely to use epidural analgesia in labour as compared to women who lived in the least deprived areas (SIMD 10), (SIMD 1 vs SIMD10; RR 0.79 [0.75, 0.84]) (Table 6-18). The inter-decile mean change in utilisation of epidural analgesia is estimated at -2.5% [-3.1%, -2.0%] with each increasing unit of deprivation (Table 6-18, Figure 6-20).

	RR	95% CI[1]	p-value
SIMD decile			
10	—	—	
09	0.97	0.92, 1.03	0.3
08	1.00	0.95, 1.06	>0.9
07	0.91	0.86, 0.96	0.001
06	0.86	0.81, 0.91	<0.001
05	0.83	0.78, 0.87	<0.001
04	0.87	0.82, 0.91	<0.001
03	0.84	0.80, 0.88	<0.001
02	0.80	0.76, 0.84	<0.001
01	0.79	0.75, 0.84	<0.001

[1]CI = Confidence Interval

Table 6-18 Relative risk of receiving an epidural for subgroup of women with a medical indication / no relative contraindication for epidural (n= 85,530). SIMD 10 is the reference category.

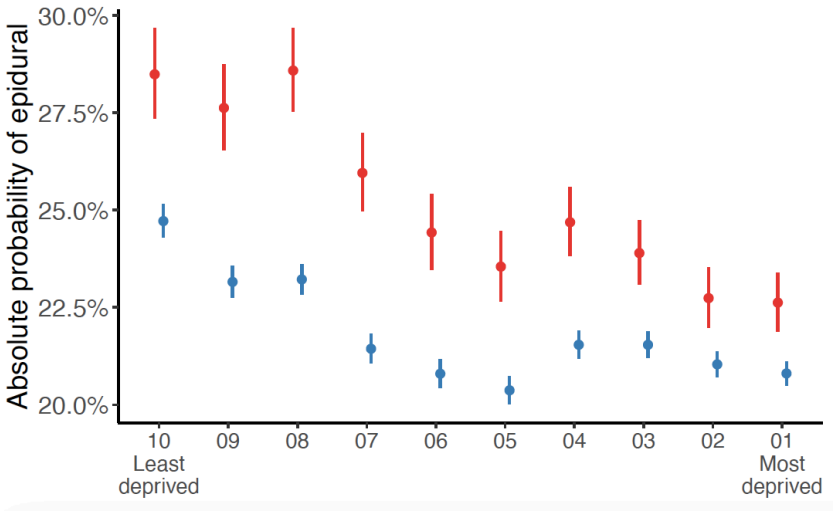


Figure 6-20 Scottish Index of Multiple Deprivation decile and absolute risk of epidural analgesia. The red line represents the women who had a medical indication and no relative contraindication to labour epidural analgesia, and the blue represents the women who did not have a medical or indication, or had a relative contraindication.

Table 6-19 presents the absolute probability of labour epidural per unit SIMD decile, stratified by documented medical indication and no relative contraindication to epidural analgesia or not. Women from the most deprived areas (SIMD 1) who had a documented indication and no relative contraindication were still less likely to use labour epidural analgesia than women from the least

deprived areas (SIMD 10), that had no medical indication or a relative contraindication to labour epidural analgesia (AR 0.23 [0.22, 0.24]) compared to AR 0.25 [0.24, 0.25]) (Table 6-19, Figure 6-20).

	YES				NO			
SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.285	0.007	0.272	0.299	0.247	0.003	0.242	0.252
09	0.276	0.007	0.264	0.290	0.232	0.002	0.227	0.236
08	0.286	0.006	0.274	0.299	0.232	0.002	0.228	0.237
07	0.260	0.006	0.248	0.271	0.214	0.002	0.210	0.219
06	0.244	0.006	0.233	0.256	0.208	0.002	0.204	0.212
05	0.235	0.005	0.225	0.246	0.204	0.002	0.200	0.208
04	0.247	0.005	0.237	0.257	0.215	0.002	0.211	0.219
03	0.239	0.005	0.230	0.249	0.215	0.002	0.212	0.219
02	0.227	0.004	0.219	0.236	0.210	0.002	0.207	0.214
01	0.226	0.004	0.218	0.235	0.208	0.002	0.205	0.212

Table 6-19 Scottish Index of Multiple Deprivation decile and absolute probability of epidural analgesia. Risk stratified by documented indication and no relative contraindication to epidural.

6.3.11 Medical indication and no relative contraindication to epidural with higher threshold for BMI as an indication

A second stratified analysis was carried out looking at medical indication and no relative contraindication for labour epidural analgesia, but with a higher threshold of BMI as an indication (BMI 50 rather than BMII 40). Of these,74,724 (97.9%) gave birth in an obstetric unit and 18,778 women received epidural analgesia in labour (24.6 %). Similar to the preceding analysis, the socio-economic gradient in persisted in women with a medical indication and no relative contraindication, even when the threshold for obesity indicting recommendation of labour epidural was increased to BMI ≥50. In this subgroup of women (n = 76,294) those living in SIMD 1 were significantly less likely to receive epidural analgesia in labour that those without an indication in SIMD 10 (AR 0.22 [0.22, 0.23] compared to 0.28 [0.27, 0.30]) (Table 6-20), Figure 6-21). Despite a

medical indication, women with a medical indication and no relative contraindication for epidural analgesia in SIMD1 were still less likely to receive it that those without an indication in SIMD 10 (SIMD 1 medical indication AR 0.22 [0.22, 0.23] compared to SIMD 10 no medical indication 0.25 [0.24, 0.25]) (Table 6-20, Figure 6-21). The inter-decile mean change was -2.2% [-2.5%, -1.9%].

	YES				NO			
SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.283	0.007	0.269	0.297	0.248	0.003	0.243	0.253
09	0.273	0.007	0.260	0.286	0.233	0.002	0.228	0.237
08	0.280	0.007	0.268	0.294	0.234	0.002	0.229	0.238
07	0.256	0.006	0.244	0.268	0.216	0.002	0.211	0.220
06	0.246	0.006	0.234	0.258	0.208	0.002	0.204	0.213
05	0.234	0.006	0.223	0.245	0.205	0.002	0.201	0.209
04	0.244	0.005	0.233	0.255	0.217	0.002	0.213	0.221
03	0.237	0.005	0.227	0.248	0.216	0.002	0.212	0.220
02	0.224	0.005	0.215	0.234	0.211	0.002	0.208	0.215
01	0.224	0.005	0.215	0.233	0.209	0.002	0.205	0.212

Table 6-20 Scottish Index of Multiple Deprivation decile and absolute probability of epidural analgesia. Risk stratified by documented indication and no relative contraindication to epidural, BMI 40-49.9 excluded as an indication.

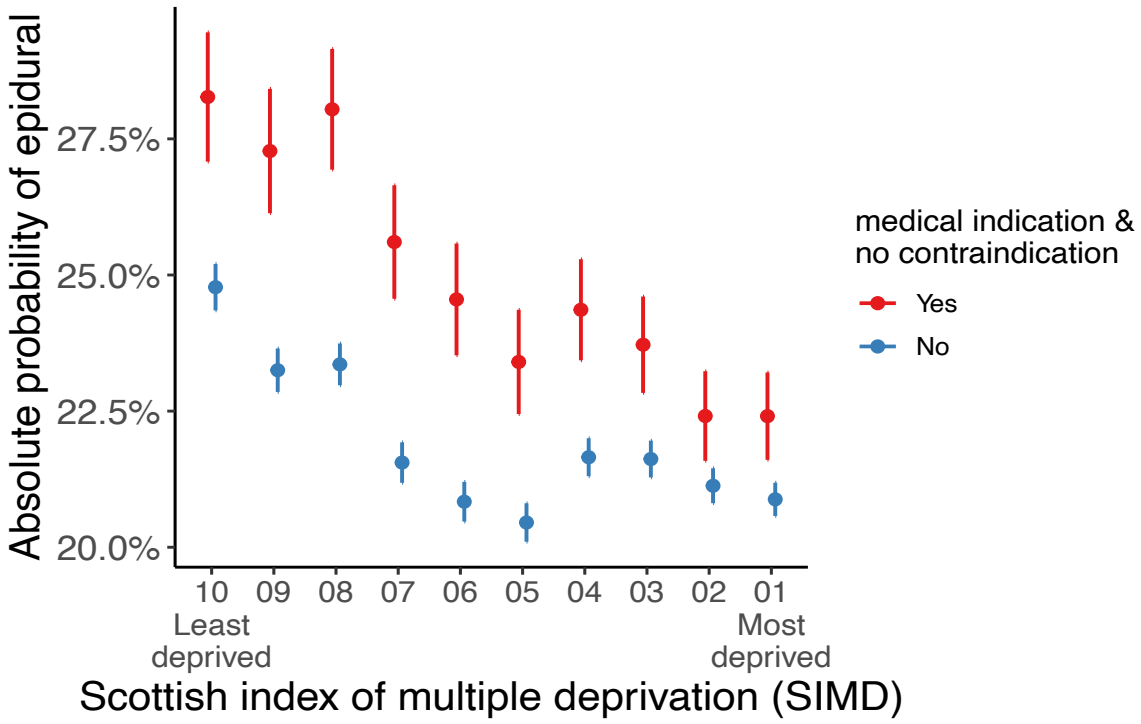


Figure 6-21 Scottish Index of Multiple Deprivation decile and absolute risk of epidural analgesia. Risk stratified by documented indication and no relative contraindication to epidural, threshold for extreme obesity increased to BMI ≥50

6.3.12 Medical indication and no relative contraindication to epidural with asthma excluded as an indication

A third stratified analysis was carried out looking at medical indication and no relative contraindication for labour epidural analgesia, with asthma excluded as a medical indication (n = 56,964). Of these, 55,915 (98.2%) gave birth in an obstetric unit and 14,905 women received epidural analgesia in labour (26.2 %). This subset of women were more likely to received epidural analgesia in labour than the original subset of medically indicated women (where the definition included asthma), however, the socio-economic gradient persisted (SIMD1 AR 0.24 [0.23, 0,25]; SIMD 10 AR 0.30 [0.29, 0.32]), inter-decile mean change (-2.3% [-2.6%, -1.9%]). Women residing in SIMD1 women with a medical indication were again less likely to receive epidural analgesia that those who did not have an indication in SIMD10 (AR 0.24 [0.23, 0.25]) compared to 0.25 [0.24, 0.25]).

	YES				NO			
SIMD	Absolute probability	SE	Lower 95% CI	Upper 95% CI	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.304	0.008	0.288	0.321	0.247	0.002	0.242	0.252
09	0.292	0.008	0.276	0.308	0.232	0.002	0.227	0.236
08	0.304	0.008	0.289	0.320	0.233	0.002	0.229	0.237
07	0.272	0.007	0.258	0.287	0.215	0.002	0.211	0.219
06	0.253	0.007	0.239	0.267	0.209	0.002	0.205	0.213
05	0.249	0.007	0.237	0.263	0.204	0.002	0.200	0.208
04	0.257	0.007	0.245	0.270	0.216	0.002	0.212	0.220
03	0.249	0.006	0.237	0.261	0.216	0.002	0.212	0.219
02	0.241	0.006	0.230	0.252	0.210	0.002	0.206	0.214
01	0.237	0.006	0.227	0.248	0.208	0.002	0.205	0.211

Table 6-21 Scottish Index of Multiple Deprivation decile and absolute probability of epidural analgesia. Risk stratified by documented indication and no relative contraindication to epidural, asthma excluded as an indication for epidural analgesia.

6.3.13 Interaction between epidural utilisation, SIMD and white/non-white ethnicity

The final stratified analysis compared women of white and non-white ethnicity. As mentioned in the introduction, the data available to us did not permit that stratification of each ethnicity separately. When this analysis was stratified by white as compared to non-white ethnicity, a steeper socio-economic gradient was observed in women of non-white ethnicity as compared to those of white ethnicity (Table 6-22, Figure 6-17), with an inter-decile mean change of -3.5% [-4.0%, -3.0%]. Women in the least deprived decile were more likely to utilise labour epidural analgesia in the non-white strata as compared to the white strata (AR 0·29, [0·27, 0·31] vs 0.26, [0.26, 0.27], respectively) (Table 6-22, Figure 6-22). However for women residing in the most disadvantaged areas, this relationship was reversed and women in the non-white strata were less likely to utilise labour epidural analgesia than those in the white strata (AR 0·19 [0·17, 0·20]) vs (0.22 [0.22, 0.22], respectively) (Table 6-22, Figure 6-22).

	White				Not white			
SIMD	Absolute probability	SE	Lower 95% CI	Upper 95% CI	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.264	0.003	0.259	0.271	0.293	0.010	0.274	0.314
09	0.247	0.003	0.242	0.253	0.273	0.010	0.253	0.294
08	0.251	0.003	0.245	0.256	0.271	0.011	0.251	0.293
07	0.235	0.003	0.229	0.240	0.242	0.011	0.222	0.265
06	0.228	0.003	0.223	0.234	0.258	0.011	0.237	0.280
05	0.219	0.003	0.214	0.224	0.252	0.010	0.232	0.273
04	0.236	0.003	0.231	0.241	0.224	0.009	0.207	0.243
03	0.232	0.002	0.227	0.236	0.229	0.009	0.212	0.248
02	0.224	0.002	0.220	0.229	0.194	0.008	0.179	0.210
01	0.220	0.002	0.215	0.224	0.187	0.007	0.174	0.201

Table 6-22 Scottish Index of Multiple Deprivation decile and absolute probability of epidural analgesia. Risk stratified by white or non-white ethnicity.

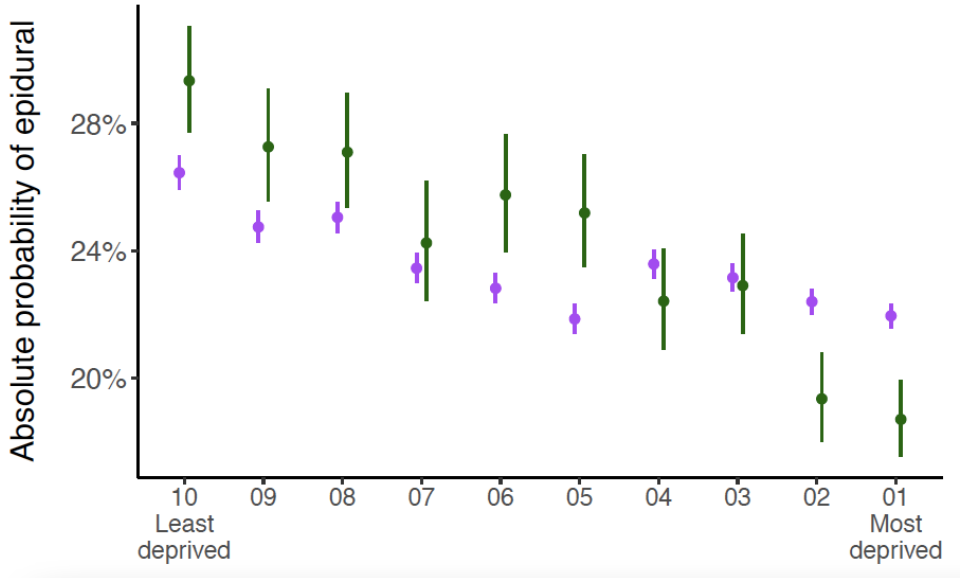


Figure 6-22 Scottish Index of Multiple Deprivation decile and absolute risk of epidural analgesia, the purple represents women of white origin and the green represents women of a non-white origin.

6.4 Discussion

In this population-based study of 593,230 deliveries, we demonstrate that living in areas of socio-economic disadvantage was associated with reduced utilisation of epidural analgesia in labour. Women residing in the lowest socio-economic decile were 17% less likely to receive epidural analgesia in labour when compared with women residing in the least socio-economically disadvantaged areas. These results were consistent when the analysis was restricted to only include primiparous women, or to only include women who delivered in an inner-city environment with 24-hour uniform access to anaesthetic and obstetric services. Correction for date of delivery as either a continuous or categorical variable did not alter these results. In addition, residing in area of increasing socio-economic status was associated with stepwise increases in a range of adverse maternal characteristics such as increased maternal BMI, comorbidities, and lifestyle choices such as smoking and drug use. These characteristics are all causally linked to adverse perinatal outcomes. This socio-economic gradient persisted even in women who had a medical condition that would make epidural analgesia in labour advisable. This relationship was accentuated in women of non-white ethnicity, with socio-economically deprived women of non-white ethnicity being the least likely to utilise labour epidural analgesia. These results are in the setting of publicly funded National Health Service (NHS) which aims to deliver equitable treatment that is free at the point of care. Addressing unequal pathways of care, is an institutional prerequisite to reduce the health inequalities that result from socio-economic deprivation.

The relationship between socio-economic position and utilisation of epidural analgesia has been explored in six previous published studies in the last 15 years.[5,222,225,226,253,254] These have largely used one or two individual measures of socio-economic position, for example occupation, income, education level or insurance status, and in general, consistent with our own analysis, they have found that markers of lower socio-economic position are associated with reduced utilisation of labour epidural analgesia. The largest of these was an observation analysis of 2,625,950 women who delivered in the USA in 2015. The authors found that women that had fewer years of education and/or without private health insurance were less likely to use labour epidural analgesia, along with women of older age, non-white ethnicity and having late or no prenatal

care.[222] However, it is difficult to compare with our data as maternity healthcare in the USA is not free at the point of care. Four observational studies were from countries with a publicly funded healthcare system. In Finland (521,179 women) a small reduction in utilisation of labour epidural analgesia was found in multiparous (but not primiparous) women of lower socio-economic status as measured by occupation type, however, data on occupation was missing for 17.4% and authors included an 'other' category where occupation ranged from entrepreneur to unemployed.[225] A Canadian study of 220,814 women found lower use of labour epidural analgesia in women of lower socio-economic position as measure by income and education level, they also found substantial differences between epidural utilisation in community (32%) as compared to teaching hospital settings (74%).[253] A French study of 10,419 women found a reduced use of labour neuraxial analgesia in those who had not completed high-school education (aOR 0.80 [0.72, 0.89, p = 0.0001). When they categorised women as 'socio-economically deprived' or not, they did not find a significant difference in epidural utilisation (aOR 0.97 [0.87, 1.07], p = 0.54). In France, rates of labour neuraxial analgesia are considerably higher compared to Scotland, (over 90% in their cohort) and all women undertake a mandatory pre-anaesthetic evaluation at 33-37 weeks.[5] The results of one study conflicted with those of this analysis. A population study of primiparous women delivering vaginally in Sweden between 2002 and 2005 (106,775 women), found that socio-economic disadvantage, as measured by education level, increased likelihood of epidural utilisation (women who had completed only primary education aOR 1.29 [1.22,1.36], women who had completed university education 0.85 [0.82, 0.87], both compared to women who had completed secondary education.[226] However, this period coincides with the publication of the COMET study in 2001[78] and the subsequent transitioning to widespread use of low dose epidural analgesia, which is not associated with many of the adverse effects of traditional epidural analgesia dosing regimens.[33]

This is the first study to investigate the interaction between socio-economic status, epidural utilisation in labour and the presence of a medical conditions that may make epidural analgesia in labour advisable for maternal safety. This is a group in which we would expect there to be no (or at least a reduced) socio-economic gradient. Surprisingly, that this socio-economic gradient still exists, even to the extent that women who had a medical indication and no relative

contraindication to labour epidural analgesia in the most deprived areas were less likely to use it than women who did not have a medical indication or a relative contraindication to labour epidural analgesia in the least disadvantaged population. In addition, whilst geographic location and type of birthing unit have been shown to influence epidural analgesia utilisation,[253] we were able to carry out a sensitivity analysis that restricted our study cohort to those delivering in inner-city teaching hospitals with 24-hour access to obstetric and anaesthetic services, in which we demonstrated that this gradient persists even in a uniform environment. This is not the only example of disparities in care associated with socio-economic disadvantage and labour interventions. A UK-wide observational study (2020) found that socio-economically disadvantaged women were more likely to be induced for labour.[23] Women from the most deprived areas of Scotland are also less likely to have an antenatal appointment within 12 weeks than women from the least deprived areas (88.5% vs 94% in 2020/21).[7] Maternal outcomes mirror these disparities, with the MBRRACE–UK reports highlighting that women from the most socio-economically deprived areas have twice the mortality risk compared with the least socio-economically deprived areas.[9]

The socio-economic gradient in utilisation of labour epidural analgesia in Scotland was compounded by being of non-white ethnicity. Women of non-white ethnicity in the most disadvantaged decile were more than a third less likely to receive labour epidural analgesia than women on non-white ethnicity in the least disadvantaged decile. Worldwide, significant disparity in neonatal outcomes have been observed in non-white compared to white populations. Neonatal death rates are doubled in black populations, and tripled in Hispanic populations as compared to the white population.[255] Labour epidural has been linked to improved neonatal outcomes.[169] Two large recent population studies have looked at the association of ethnicity with epidural utilisation. In the USA, Butwick et al found that (2,625,950 million women) women of Hispanic, black and 'other' ethnicity were significantly less likely to use epidural analgesia in labour compared to women of white ethnicity (aOR 0.75 [0.75, 0.76], 0.86 [0.85, 0.87] and 0.81[0.81, 0.83], respectively), but did not find a significant difference for women of Asian ethnicity (aOR 0.99 [0.98, 1.01]).[222] In England, Bamber et al investigated ethnicity and neuraxial anaesthesia utilisation for women undergoing spontaneous vaginal birth, and found that women of Bangladeshi,

Pakistani and Caribbean ethnicity had significantly lower utilisation than their white British counterparts (adjusted incidence rate (IR) 0.76 [0.74–0.78]), (0.85 [0.84–0.87]) and (0.92 [0.89–0.94] respectively).[3] Among other variables, the results in this analysis were adjusted for IMD quintiles (index of multiple deprivation) however, no results are presented for the relationship between IMD and neuraxial anaesthesia utilisation. As far as we are aware this is the first analysis which looks at the interaction between ethnicity and socio-economic position with regard to epidural analgesia utilisation. Although we are limited with our data, and only look at white compared to non-white ethnicity, the socio-economic gradient we have found suggests that this relationship is more nuanced that has previously been described. There is evidence that women in Scotland of a non-white ethnicity have healthier maternal behaviours.[256]

The association between lower epidural utilisation in women who reside in areas of lower socio-economic position is likely multifactorial. Age, smoking status, use of illicit drugs and comorbidities are likely to be mediators of this relationship, thus adjusting for these variables would bias the analysis. In the most deprived areas, issues with housing or income may make making and maintaining contact with prenatal services difficult.[257] Women from the most deprived part of Scotland are more likely to receive late, or no pre-natal care.[7] Poor health literacy may render the patient less aware of available labour analgesic options, or about indications for epidural analgesia. However, this does not explain the stepwise increase as the SIMD decile increases. Furthermore, it does not explain why SIMD decile 5 would be associated with the lowest uptake of labour epidural analgesia. It is possible that mistrust of medical staff, feelings of disempowerment in labour, misinformation regarding epidural safety, or simply differing expectations of pain associated with childbirth are societal pressures which may make women less likely to use epidural analgesia. Differences in midwifery, obstetric and anaesthetic attitudes may also influence epidural utilisation, with institutional and structural biases a potential modifiable determinant. Understanding the social, cultural, and community context within which our patients live, and the institutional context in which we work, is vital if we are to address implicit bias. Furthermore, ensuring cross-disciplinary education and appropriate patient information and education for all cultures and levels of health literacy is paramount if we are to be effective in realising true

shared decision making. The use of group antenatal care has shown promise in achieving these goals.[258] The huge scope of the problem in wider society will requires strategies that address both the systems and policies that may unintentionally perpetuate classism, racism and the widening economic divide. We know that modern epidural analgesic regimes are safe for both mother and baby,[33] are associated with improved maternal outcomes,[135,139,141] and may even be associated with improved neonatal outcomes.[169]

The burden of morbidity and mortality is inequitable, with vulnerable and marginalised populations at greatest risk.[259] The mechanism by which socio-economic disparities contribute to maternal health inequalities and poor health outcomes,[22] is likely to be mediated through classical risk factors, including obesity, smoking and illicit drug use which we demonstrate are monotonically linked with lower socio-economic status. The fact that these risk factors do not directly contribute to any of the domains or indicators used to generate the SIMD decile, further supports our findings and the need to address these risk factors before pregnancy. That multimorbidity also increases progressively with lower socio-economic status highlights the contribution of pre-existing non-obstetric morbidity during pregnancy in determining perinatal outcomes.

This study has many strengths. It is a large, high quality unselected whole patient cohort representing all women who went into labour in Scotland between 1st January 2007 and 31st October 2020. This time frame is reflective of contemporary clinical practice, following the publication of evidence supporting low concentrations of local anaesthetics[78] and the use of patient-controlled epidural analgesia (PCEA),[99] with a large Cochrane review finding no evidence for an increased incidence of assisted vaginal birth or caesarean birth with epidural analgesia after 2005.[33] The use of SIMD as a measure of deprivation is another strength as it included 7 domains that relate to deprivation status, rather than just level of employment, income or highest education level as used in the other studies mentioned here. In this study, SIMD status was determined for almost 100% of patients. Whilst there are limitations in the use of SIMD, an area-based measure, to proxy individual level socio-economic position (discussed below), it has advantages in this study as we are assessing the use of healthcare provision which is also area based (i.e. which maternity unit a woman is referred to for birth). The presentation of results by SIMD decile, and the stratification of

results dependant on whether epidural analgesia is medically advisable are unique to this study, and allow further exploration of this nuanced topic.

We acknowledge several limitations to this study, including the observational design and the use of an area-based SEP measure. Socio-economic inequalities, including those observed here are unlikely to be confounded, as SEP is an 'upstream' risk factor unlikely to be determined by factors such as smoking, diet or BMI. The aim of this paper was to explore the association between socio-economic status and epidural utilisation, and this study did not match the assumptions required to render mediation analysis unbiased, as described in section 6.2.7.1. For this reason, we did not adjust for any mediator variables in our primary analysis. The socio-economic gradient of labour epidural analgesia utilisation was slightly diminished in this primiparous cohort, this may be due to parity explaining some of the observed inequality, but may also be due to bias due to the exposure and mediator not being continuous variables, to confounding between socio-economic position and parity, and between parity and epidural use, to measurement error or to other violations of multivariable mediation analyses.[248,260] Due to hierarchical recording in this routinely collected data set, we could not identify women who had combined spinal epidural (CSE) as they were coded as having undergone spinal anaesthesia. Similarly, those receiving spinal or general anaesthesia following a conventional lumbar epidural could not be identified. Conversion of epidural to spinal or GA is thought to be around 5%.[231] We could only find one conference abstract pertaining to frequency of CSE utilisation in the UK (1%).[230] This corroborates with our collective experience in Scotland, that CSE is very uncommon, however more data are required here. Whilst there are benefits to the use of area-based measure to measure assess area-based healthcare provision, the use of SIMD to proxy individual socio-economic position may introduce an ecological bias, thus it may be possible that there is little if any association between individual socio-economic position and labour epidural analgesia use. Rural areas are likely to include areas of mixed deprivation, which may affect the SIMD level allocated to these women, when the differences we observed may be due to proximity to an obstetric unit and availability of anaesthetist delivered labour analgesic services. The sensitivity analysis limited to include women delivering in an inner-city hospital within one major Scottish city with uniform access to obstetric and

anaesthetic service may partially but not completely mitigate this. Furthermore, as discussed above, our results are in accord with previous studies that look at individual measure of socio-economic position, such as income or level of education,[9,17-19,50,51] and the MBRRACE-UK reports highlight that women who reside in more deprived areas are at increased risk of adverse maternal and perinatal outcomes.[9] Some practitioners may disagree with our lists of conditions for which epidural analgesia may be advisable or inadvisable for maternal safety (medical indications and relative contraindications). The aim of this stratification was to identify if our socio-economic gradient would reduce or disappear in these women, perhaps as they may be more likely to been seen prenatally by an anaesthetist. However, the socio-economic gradient in these women was steeper than those of the overall analysis, even in the two sensitivity analyses, which removed two of the more contestable medical indications. We acknowledge even when an epidural may be recommended, maternal choice is still paramount, and women always have a right to refuse. It is of interest that of the women who were identified as having a medical indication and no relative contraindication for labour epidural analgesia, only 24.8% utilised it, regardless of socio-economic position. This persistent socio-economic gradient suggests that either patients have deeply entrenched beliefs or social pressures regarding epidural analgesia in labour, or that they are experiencing different interactions with medical or midwifery staff and perhaps institutional bias. Finally, we acknowledge that our stratification of ethnicity into white and non-white is rudimentary. Scotland has a predominantly white population, representing more than 90% of our cohort, thus our results may not generalise to more ethnically diverse populations. Furthermore, it does not consider immigration status, or differences between first, second and third generation immigrants. The purpose of this stratification was to identify trends and potential explanations or possible areas for further research. We were unable to carry out a more refined analysis than ‘white’ or ‘non-white’ and acknowledge that the true picture will be more complex than this binary definition. Furthermore, 38.3% of data were missing for this variable. This analysis serves to highlight that the interaction between socio-economic position, epidural utilisation and ethnicity would be valuable.

6.5 Conclusion

Socio-economic disadvantage is associated with lower utilisation of labour epidural analgesia in a universal healthcare system that is free at the point of care. This socio-economic gradient persists even in women who have a medical condition for which labour epidural analgesia may be advised for maternal safety. We have demonstrated a stepwise increase in adverse health characteristics that are known to be associated with adverse maternal and neonatal outcomes with increasing level of socio-economic deprivation. Ethnicity appears to interact with this relationship between socio-economic position and labour epidural analgesia utilisation.

It is of paramount importance that we address institutional and societal barriers to equitable access for an established and internationally recommended intervention that alleviates pain and may mitigate adverse maternal and neonatal outcomes. Future work is required to dissect the complex reason why women elect to utilise labour epidural analgesia or not, especially in women who are more socio-economically disadvantaged. The interaction between ethnicity, SEP and epidural utilisation is another area for future work. It would be valuable to investigate how socio-economic position is associated with other aspects of obstetric anaesthetic care, such as anaesthesia for caesarean birth (Chapter 7), as well as outcomes such as severe maternal morbidity.

Chapter 7 Socio-economic disparity in anaesthesia for caesarean birth

7.1 Introduction

7.1.1 Caesarean birth

Caesarean birth or C-section (USA) is a surgical procedure used to deliver a baby through the abdomen and uterus. It is indicated when vaginal birth is unsafe or not possible and may be a lifesaving intervention for mother and babies, particularly in cases of maternal or fetal compromise, including antepartum haemorrhage, hypertensive disease, fetal malpositioning and fetal distress. Caesarean birth may also be performed on maternal request.

Caesarean birth is one of the most common operations worldwide, with around 27.9 million performed each year,[261] increasing at a rate of approximately 4% per year.[113] Prevalence varies between different countries, from 0.6% in South Sudan, to 58.1% in the Dominican Republic.[262] The World Health Organisation recommends a caesarean rate no higher than 10-15%,[263] based on two studies which demonstrate a reduction in both maternal and neonatal mortality at 10%, but no further improvement when the caesarean rate increases above this level.

7.1.2 Urgency of caesarean birth

Caesarean birth may be performed as an elective or emergency procedure. An elective caesarean birth may take place at a time to suit the patient and maternity team usually after the 39th week of pregnancy.[264] Indications for an elective caesarean birth are wide ranging but may include previous caesarean birth, breech presentation, multiple pregnancy or placental abnormalities such as placenta praevia or placenta accreta spectrum.[265] An emergency or unplanned caesarean birth may take place if there are concerns for the health of the mother or baby during pregnancy or after the onset of labour. Emergency caesarean birth is associated with higher rates of fetal complications, which may be due to the underlying pathology as one of the most common indication for emergency caesarean birth is fetal distress.[266] Emergency caesarean birth is also association with high rates of adverse maternal outcomes, including psychological distress.[267]

In the UK there is a four grade classification system for the urgency of caesarean birth; (1) immediate threat to life of woman or fetus; (2) maternal or fetal compromise which is not immediately life-threatening; (3) needing early birth but no maternal or fetal compromise; (4) at a time to suit the patient and maternity team.[264] Categories 1-3 represent non-elective caesarean birth and category 4 represents elective caesarean birth.

7.1.3 Anaesthesia for caesarean birth

Anaesthesia for caesarean birth may be performed by general or neuraxial techniques. Neuraxial techniques may be: (1) spinal (intrathecal) block, (2) de novo epidural, (3) epidural top-up or (4) combined spinal epidural (CSE) block. In a spinal block, a non-cutting needle (usually 24-27g) is used to puncture the dura mater and deliver local anaesthetic (plus or minus adjuvants) into the intrathecal space. To reduce the risk of nerve injury, it is performed below L1/2, where the spinal cord commonly terminates and becomes the loose nerves of the cauda equina. Epidural and CSE are described in sections 2.2.1 and 2.2.2 respectively (Figure 2-1). Epidural may be inserted de novo, or an existing labour epidural may be topped up with local anaesthetic and converted to operative anaesthesia. Since the epidural catheter remains in situ, anaesthesia can be topped up during the surgical procedure, if required. This may be beneficial in cases where operative times are predicted to be prolonged, such as in women with very high BMI, or those who have undergone previous obstetric surgeries. Continuous spinal anaesthesia (CSA) involves the use of a thin plastic catheter threaded directly into the intrathecal space. The insertion may be unintentional, such as following accidental dural puncture during epidural insertion, or intentional. The intentional use of CSA may be considered in high risk parturients where none of the above methods are considered desirable. It is not used in routine obstetric practice.[268] Spinal anaesthesia has advantages over epidural analgesia as it is faster to perform, and has a more rapid onset of anaesthesia.[269,270] General anaesthesia (GA) is considered to be faster than regional anaesthesia, and avoids the risk of failed regional blockade.[20,271]

International guidelines recommend neuraxial anaesthesia over general anaesthetic techniques for most women.[16,265] This is due to improved maternal outcomes including lower rates of maternal death, failed intubation, aspiration

of gastric contents, post-partum haemorrhage, wound infections and postoperative pain, and improved fetal outcomes, such as lower rates of resuscitation, Apgar scores<7 at 5 minutes and admission to neonatal intensive care.[19,20,272-275] Neuraxial anaesthesia for elective caesarean births may be associated with improved early educational outcomes compared to GA.[270] In certain situations GA may be indicated, for example severe maternal or fetal compromise, where time is critical, and in cases where regional techniques may be contraindicated, such as disorders of coagulation or sepsis. Mothers may also elect for a GA in the absence of another indication. Obstetric anaesthetists may offer advice but the decision rests with a mother who has capacity.[3] The Royal College of Anaesthetists recommend that more than 95% of elective caesarean births should be carried out under regional anaesthesia, and over 50% for category 1 emergency caesarean births[276] (Table 7-1). For women who already have labour epidural analgesia *in situ,* they suggest utilisation of GA should not be more than 3%.[276] These recommendations are controvertial as using these as a metric of quality has its potential risks of harm, for example the delaying of surgery due to multiple attempts at regional anaesthesia, or not converting to GA if pain is reported under regional anaesthesia.

Caesarean birth	Category 1	Category 2-3	Category 4 (elective)
Percentage undergoing regional anaesthesia	>50	>85	>95
Percentage conversion from regional to general anaesthesia	<15	<5	<1

Table 7-1 Royal College of Anaesthetists

7.1.4 Socio-economic position and caesarean birth

Socio-economic disparity has already been described in relation to caesarean birth.[261] Differences in within-country caesarean birth rates have been described. An analysis of 82 low and middle income countries found large

discrepancies in the provision of caesarean birth for women in the poorest and wealthiest quintiles (median 4.1%, IQR [1.9-12.0] vs 19.1% [10.6-33.8]).[261] In China and Brazil, caesarean birth rates were around 60% higher in private rather than public healthcare facilities.[261] Within high income countries, ethnicity has been associated with higher rates of GA utilisation for caesarean birth.[24,25] In the preceding chapter we have demonstrated that socio-economic disadvantage is associated with reduced use of labour epidural analgesia in Scotland. A key benefit of labour epidural analgesia is that they may be extended to anaesthesia for emergency caesarean birth when required, potentially reducing the need for GA.

In this chapter, we explore associations of socio-economic disadvantage with utilisation of GA for caesarean birth in Scotland. We aim to:

(i) Characterise the interaction between socio-economic position and use of GA for caesarean birth.

(ii) Determine whether urgency of caesarean birth alters this relationship.

(iii) Explore the effect of ethnicity on this relationship.

7.2 Methods

7.2.1 Data sources

This was a whole population study using Scottish National Health Service administrative data. No power calculation was required. Five Scottish population databases of routinely collected data were linked and deidentified by the electronic Data Research and Innovation service (eDRIS) of NHS Scotland. These were: Scottish Morbidity Record-1 (SMR01); Scottish Morbidity Record-2 (SMR02); Scottish Birth Record; National Records of Scotland and the Scottish Stillbirth Infant Death Survey (SSIDS). These databases are described in detail in Chapter 6, section 6.2.2. The NHS Scotland Public Benefit and Privacy Panel for Health and Social Care (ref 1920-0097), and Social Care and NHS Greater Glasgow and Clyde Research and Development (ref GN20PH059) approved all study data governance procedures. All data were linked and de-identified prior by eDRIS, so no participation level consent was required.

7.2.2 Patient population

All live births in Scotland between 1st January 2009 and 23rd October 2020 were included. All mother-infant pairs between 24+0 and 43+6 weeks gestation, who had a caesarean birth, including known congenital abnormalities were included. All vaginal births (spontaneous or operative vaginal birth) were excluded. Patients were excluded if data were missing for: mode of birth, SIMD decile, or mode of anaesthesia.

7.2.3 Definitions

7.2.3.1 Anaesthesia for caesarean birth

Anaesthesia was classified as either neuraxial (epidural or spinal) anaesthesia or GA. Due to the nature of the recorded data, only one type of anaesthetic intervention is recorded per birth. It was not possible to identify whether patients receiving a GA had received neuraxial analgesia or anaesthesia prior to GA. Equally it was not possible to identify patients who received epidural analgesia prior to spinal anaesthesia. Around 5% of epidurals are converted to spinal or GA[231] and around 1.7% of spinals require conversion to GA.[277]

Parturients for which mode of anaesthesia was missing were excluded in this study.

7.2.3.2 Scottish Index of Multiple Deprivation

The Scottish Index of Multiple Deprivation (SIMD) deciles were used to proxy individual socio-economic position. This area-based tool is based on a comprehensive set of socio-economic indicators and is comparable to the English Index of Multiple Deprivation (IMD) which is used in the MBRRACE-UK reports.[9,233] We did not have information on individual socio-economic position. SIMD is described in more detail in chapter 6, section 6.2.4.2. SIMD 1 represents the most socio-economically disadvantaged population, and SIMD 10 represents the least socio-economically disadvantaged population. The SIMD tool is updated every few years to account for the fluctuations in relative affluence of an area. During our study period, SIMD was updated on four occasions: 2009, 2012, 2016, and 2020.

7.2.3.3 Bateman comorbidity index

The Bateman index is a validated maternal comorbidity index used to predict severe maternal morbidity, defined as the occurrence of acute maternal end-organ injury, or mortality.[238] It includes maternal age and 20 maternal conditions. In contrast to other commonly used comorbidity indices, such as Elixhauser or Charleston, it includes pregnancy related risk factors, such as multiple gestation, eclampsia and previous caesarean birth. This contrasts with the Elixhauser comorbidity index, which was developed for non-obstetric patients to estimate hospital length of stay and in-hospital mortality, and the Charleston index which was developed to predict mortality at 1 year.

The comorbidities included in the Bateman co-morbidity index are: acute heart failure; acute renal failure; acute liver disease; acute myocardial infarction; acute respiratory distress syndrome/respiratory failure; disseminated intravascular coagulation/coagulopathy; coma; delirium; puerperal cerebrovascular disorders; pulmonary oedema; pulmonary embolism; sepsis; shock; status asthmaticus and status epilepticus.

In this study comorbidities were defined according to the Bateman comorbidity index.[238]

7.2.3.4 Other patient factors

Ethnic group was defined according to the 2011 Scottish census categories.[236] Pre-eclampsia was defined according to ICD9 (644, 645, 646, 647) and ICD10 (O11, O14, O15) codes from SRM01. Both pre-existing diabetes and gestational diabetes were recorded as diabetes, and were identified using the SMR02 dataset. Gestational age at birth was defined as completed weeks of gestation based on ultrasound assessment in the first half of pregnancy. Induction of labour was defined as: artificial rupture of membranes (ARM), oxytocics or prostaglandins (including cervical priming) or any combination of the three.

7.2.3.5 Urgency of caesarean birth

Urgency of caesarean birth was classified as either elective (taking place at a time to suit the patient and maternity team),[264] or emergency. This was identified from the SMR02 dataset. Deliveries via elective and emergency caesarean birth were considered separately, as the indications for birth may be different. From the Scottish Birth Record, a subgroup of parturients where category of caesarean birth was recorded were identified, with category 1 defined as 'immediate threat to life of the women or fetus' as per the Lucas classification.[264,265] Examples of pathologies that would stipulate a category 1 caesarean birth are provided by the National Institute for Clinical Excellence (NICE): suspected uterine rupture, major placental abruption, cord prolapse, fetal hypoxia or persistent fetal bradycardia.[265] NICE recommends the category 1 caesarean birth is carried out as soon as possible but in most cases a decision to birth interval of no more than 30 minutes.[265]

7.2.3.6 Irreversible causes of fetal bradycardia

A subset of irreversible causes of fetal bradycardia was created. This was in an effort to distinguish the most urgent causes of fetal distress, for which there is evidence that a shorter decision to birth interval (which may necessitate a GA) improves outcome.[278] Furthermore, urgency of caesarean birth was only available for a small subset of the whole cohort. The subset of 'irreversible'

causes of fetal bradycardia were defined as: placental abruption; uterine rupture; umbilical cord prolapse; and fetal haemorrhage.[279] These were identified using ICD-9 and ICD-10 codes [228,229] from the SMR02 dataset (Table 7.2).

	ICD-9 code	ICD-10 code
Placental abruption	641.2	O45
Uterine cord prolapse	663.0, 762.4	O69.0, O69.1
Uterine rupture	665.0, 665.1	O71.0, O71.1
Fetal haemorrhage	656.0, 772.0	O43.0, P50

Table 7-2 ICD 9 and ICD 10 codes used to define causes of irreversible fetal bradycardia

7.2.3.7 Relative contraindications to neuraxial analgesia

There are certain medical conditions for which neuraxial analgesia may be relatively contraindicated. A stratified analysis was undertaken to explore the relationship between SIMD decile, utilisation of GA for caesarean birth and relative contraindications to neuraxial analgesia. Relative contraindications to labour epidural analgesia were coagulation factor deficits, Von Willebrand disease, thrombocytopenia, fever or infection during labour and chorioamnionitis.[141] These relative contraindications were selected as they have previously been defined in the literature.[141] They do not necessarily represent absolute contraindications to neuraxial analgesia or anaesthesia. ICD-9 and 10 codes are listed in Table 7-3.

	ICD-9 code	ICD-10 code
Coagulation factor deficit, Von Willebrand disease, and thrombocytopenia	286, 287	D65-D69
Fever or infection during labor	659.2, 659.3	O75.2, O75.3
Chorioamnionitis	658.4	O41.1

Table 7-3 ICD-9 and ICD-20 codes used to define relative contraindications to neuraxial anaesthesia

Unlike in the previous chapter, we were not able to find any specific guidelines of indication for GA. Medical conditions, such as severe cardiac disease or placenta accreta spectrum, which had historically been indications for GA may now by undertaken safely using neuraxial analgesia.[205,280,281] In the Practice Guidelines for Obstetric Anesthesia (2016), the American Society of Anaesthesiologists state that:

'*The decision to use a particular anesthetic technique for cesarean delivery should be individualized, based on anesthetic, obstetric, or fetal risk factors (e.g., elective vs. emergency), the preferences of the patient, and the judgment of the anesthesiologist;*'.[16]

For this reason we have not undertaken a stratification including potential medical indications for GA.

7.2.3.8 Date of delivery

Date of delivery could be a potential confounder due to the fluctuation of affluence of an area, and changes in obstetric anaesthetic practice. As in the previous analysis, two sensitivity analyses were carried out, one which adjusted for date of delivery as a continuous variable, and a second which adjusted for date of delivery as a categorical variable according to the dates of SIMD tool updates. During our study period, the SIMD tool was updated four times to account for the fluctuation in relative deprivation of an area with time (2009, 2012, 2016, 2020). Therefore, the four categories were: 2009-2011, 2012-2015, 2016-2019, 2020.

7.2.4 Data visualisation

Prior to analysis, data visualisation and exploratory analysis were carried out as described in chapter 6. For the first exploratory analysis, a date range of 1st January 2007 – 23rd October 2020 (the latest date we had available) was selected, in keeping with the previous chapter on epidural utilisation. During this, a discrepancy was noted in the recording of anaesthesia for elective caesarean birth. The absolute risk of GA for elective caesarean birth for women in SIMD 10 (most affluent group) did not appear congruent with the result for the women in SIMD 9 (Figure 7-1).

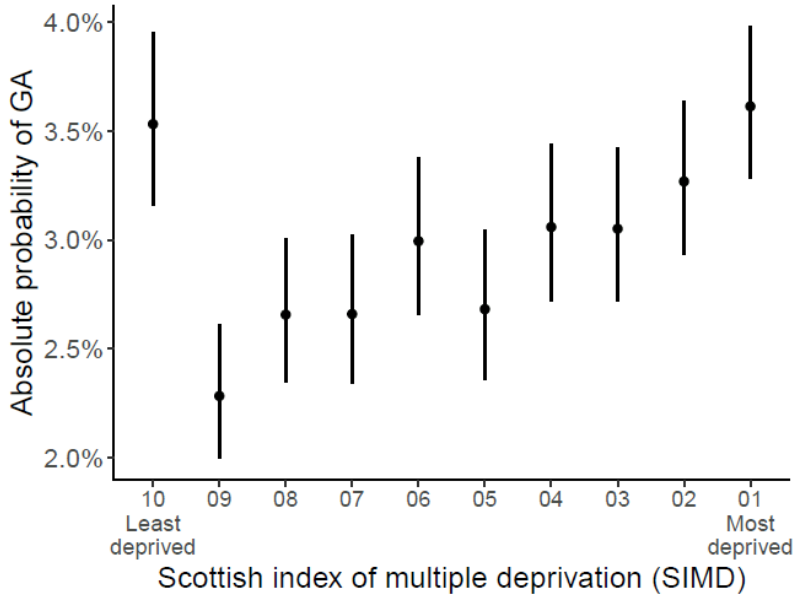


Figure 7-1 Exploratory analysis: absolute probability of GA for caesarean birth by SIMD decile for years 2007-2020

A stratified analysis was undertaken, exploring the influence of hospital of birth on absolute risk of GA for elective caesarean birth (Figure 7-2) (hospitals deidentified). One hospital appears to be an outlier ('Hospital P', blue) with an absolute risk of GA for elective caesarean birth rate of 9.2%, which is significantly higher than the overall absolute risk of GA for elective CS (3.0%).

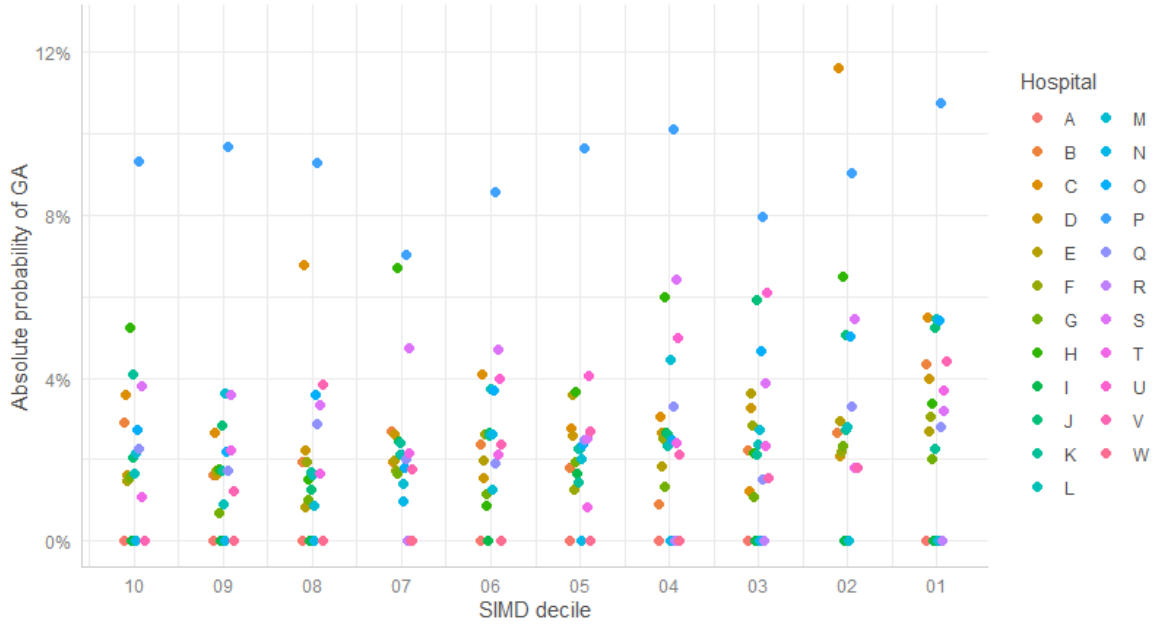


Figure 7-2 Exploratory analysis: absolute probability of GA for elective caesarean birth by SIMD decile for years 2007-2020 by hospital of birth. The different colours represent different hospitals, which are not identified.

A further exploratory analysis was then undertaken looking at GA rates for 'Hospital P' in more detail, for both elective and emergency caesarean birth. In 2007/2008 GA rates for elective caesarean birth were recorded as 50% and 47% (Figure 7-3). From 2009, recorded rates of GA for elective caesarean birth fell to below 5%, in keeping with the results from all other institutions combined (Figure 7-4). A similar exploratory analysis was carried out looking at emergency caesarean birth. In the same institution ('Hospital P'), GA for emergency caesarean birth rates in 2007/2008 were incongruent with their GA rates after 2009 (Figure 7-5) and were more than double the average GA rates for all of the other birth units combined during this time period (Figure 7-6). We felt that this was most likely to reflect a coding error. To avoid bias due to potential recording error, the date of delivery for population cohort for analysis was decided as 1st January 2009 to 23rd October 2020.

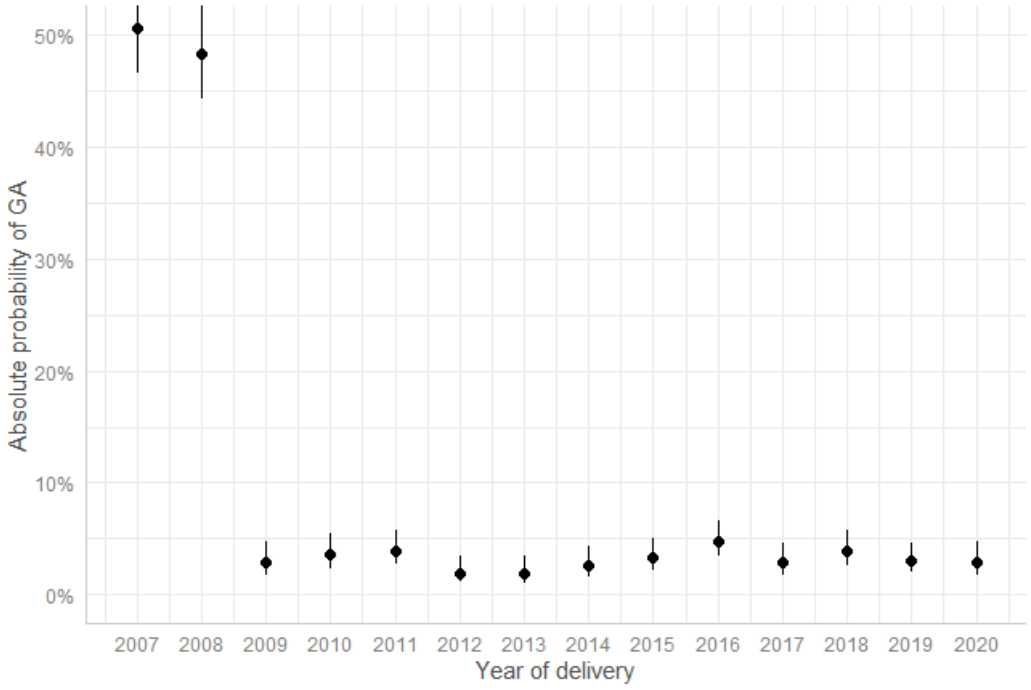


Figure 7-3 Absolute probability of GA for elective caesarean birth by year of birth for one obstetric unit ('Hospital P')

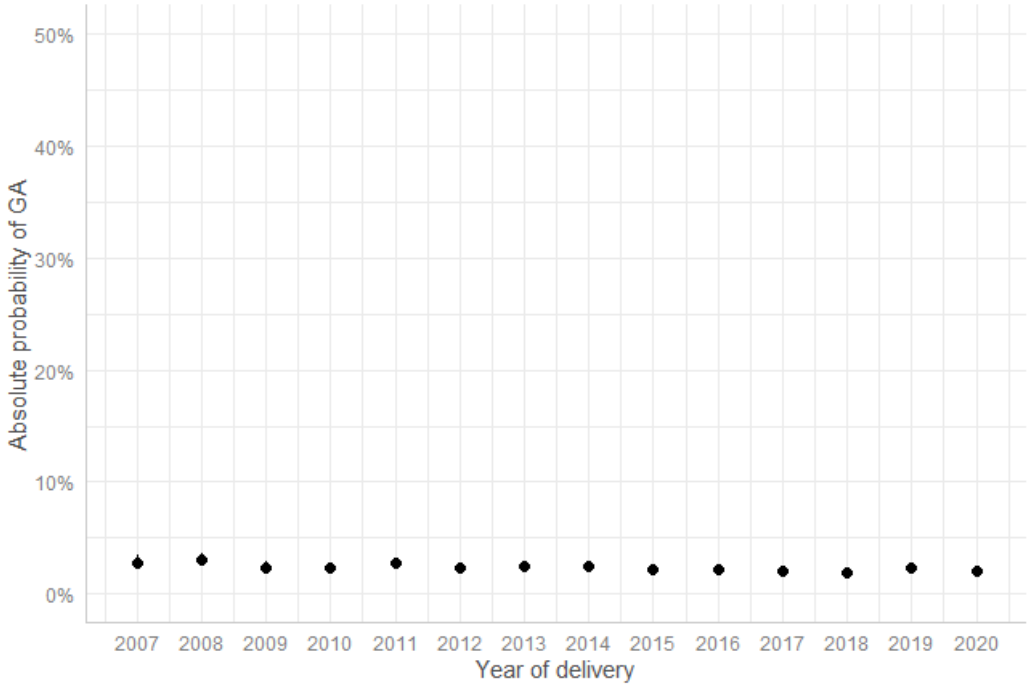


Figure 7-4 Absolute probability of GA for elective caesarean birth in Scotland by year of birth, excluding one obstetric unit ('Hospital P')

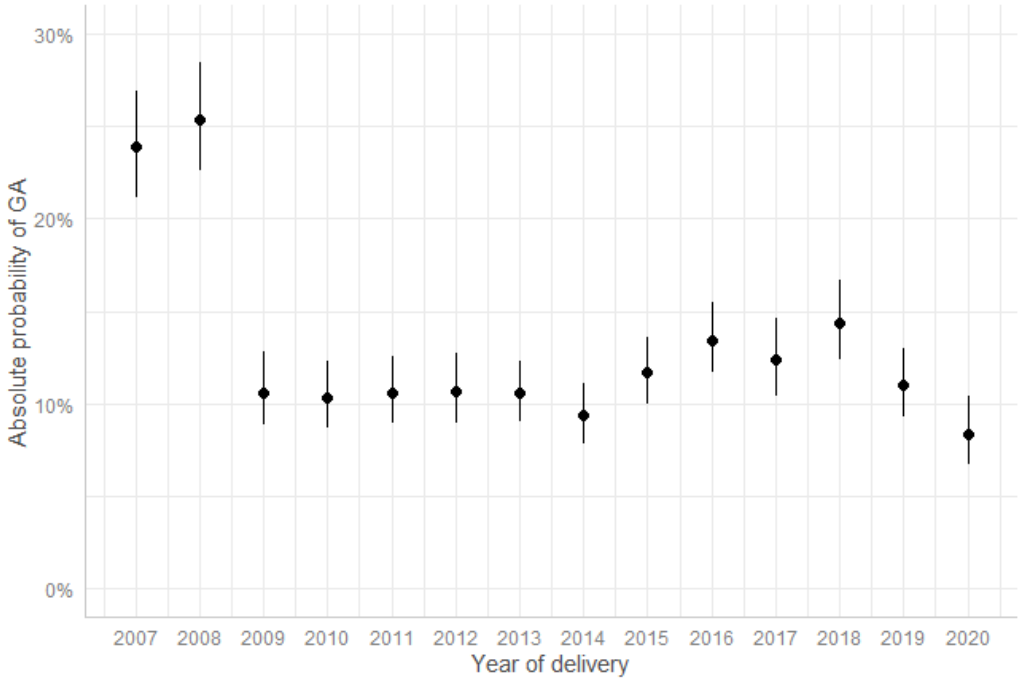


Figure 7-5 Absolute probability of GA for emergency caesarean birth by year of birth for one obstetric unit ('Hospital P')

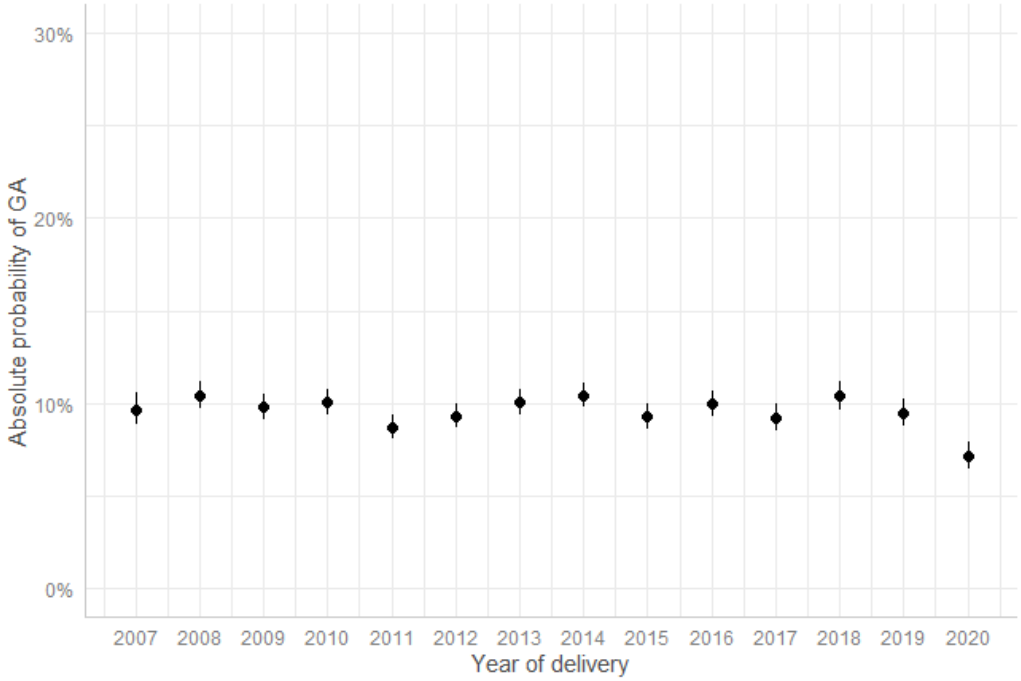


Figure 7-6 Absolute probability of GA for emergency caesarean birth in Scotland by year of birth, excluding one obstetric unit ('Hospital P' excluded)

7.2.5 Feature engineering

Feature engineering was carried out following data visualisation and cleaning.

Variable	Feature engineering
Age of mother (years)	In years, truncated at age < 10 years
Anaesthetic type	“Epidural”, “Spinal”, “GA”
Category of caesarean birth	“category 1” or “not category 1”
Comorbidities	“0”, “1” or “2+”
Diabetes	“Yes” or “No”
Estimated gestation	Completed weeks
Ethnic group	Five categories: “Asian”, “black”, “mixed”, “white” and “other”
Height of mother	To nearest cm, truncated at <100cm and >200cm
Induction of labour	“Induction” or “No induction”
Injected illicit drugs	“Yes” or “No”
Maternal BMI	Weight of mother (kg) / (Height of mother(m))^2
Multiple births	“Yes” or “No”
Parity	Count
Pre-eclampsia	“Yes” = ICD-10 code (O11, O14, O15) or ICD-9 code (644,645,646,647)
Previous caesarean birth	“Yes” or “No”
Previous spontaneous abortion	“Yes” or “No”
Previous therapeutic abortion	“Yes” or “No”
Scottish Index of Multiple Deprivation (SIMD) decile	“1” to “10”
Smoker during pregnancy	“Current”, “Former” or “Never”
Term	categorised as “≥37+0 - 41+6”
Weight of mother	To nearest kg, truncated at < 15kg and > 544kg

Table 7-4 Variables that underwent feature engineering

7.2.6 Missing data

In this data set the missingness of data ranged from 0% to 29.3% (Table 7-5). As in the previous study, ethnicity and history of injected illicit drug use had the highest degree of missing (25.7%/29.3% and 25.7%/25.0% respectively). As in the previous study, these variables are important contributors to socio-economic status and exclusion of these variables could cause considerable confounding. Cases were excluded from the analysis if data on anaesthesia use was not available (9,383/188,945 = 5.0%).

Characteristic	**Elective caesarean** N = 82,687[1] **Missing % (n)**	**Emergency caesarean** N = 96,875[1] **Missing % (n)**
Analgesia during birth	NA	NA
Maternal age	0	0
Maternal height	6.7% (5,568)	8.5% (8,191)
Weight of mother	6.6% (5,484)	7.4% (7,197)
Maternal BMI	8.7% (7,159)	9.8% (9,519)
Ethnic group	25.6% (21,197)	29.3% (28,399)
SIMD decile	0.3% (219)	0.3% (267)
Smoking history	4.2% (3,523)	4.6% (4,410)
History of injected illicit drug use	25.7% (21,277)	25.0% (24,221)
Diabetes	3.1% (2,571)	3.2% (3,066)
Pre-eclampsia	0	0
Comorbidities	0	0
Multiple birth	0	0
Previous spontaneous abortions	0.4% (370)	0.5% (451)
Previous therapeutic abortions	0.5% (375)	0.5% (446)
Previous caesarean births	0.3% (209)	0.3% (277)
Parity	0.6% (469)	0.6% (545)
Estimated gestation	0	0
Induction of labour	0.3% (241)	2.0% (1,971)

[1]n (%); Median (IQR)

Table 7-5 Percentage of missingness for the dependant variables for elective and emergency caesarean births

The R package 'nanair'[244] was used to visualise the structure of the missing data. A sample of 10,000 women was taken to visualise missing data for each variable (Figure 7-7). Percentage missing was then visualised by utilisation of GA, spinal or epidural anaesthesia (Figure 7-8). After visual inspection data were deemed to be missing at random.

Missing data were only imputed for dependant variables, not for the outcome variable (GA or neuraxial anaesthesia for caesarean birth). Imputation was carried out by using multiple imputation by chained equations (MICE) using a classification and regression trees methodology. Ten imputations of 10 iterations provided stability of data output and accuracy of the pooled variable effect. The distribution of characteristics was similar in the imputed and non-imputed datasets, which are both are presented. Techniques to deal with missing data are covered in more detail in section 6.2.4.

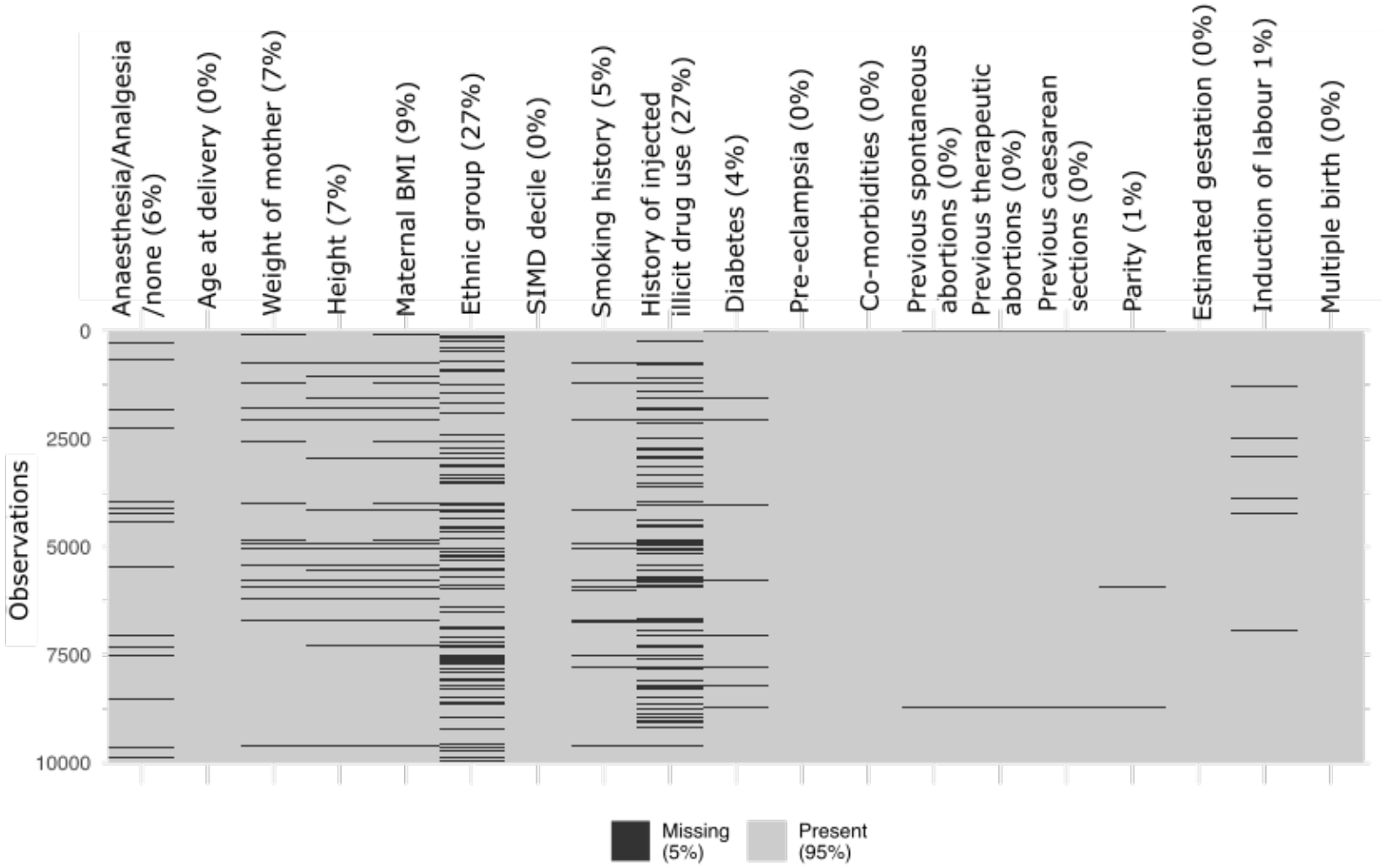


Figure 7-7 Pictogram illustrating the structure of missing data. The light grey depicts available data, and the blacks lines represent missing data for each varibale

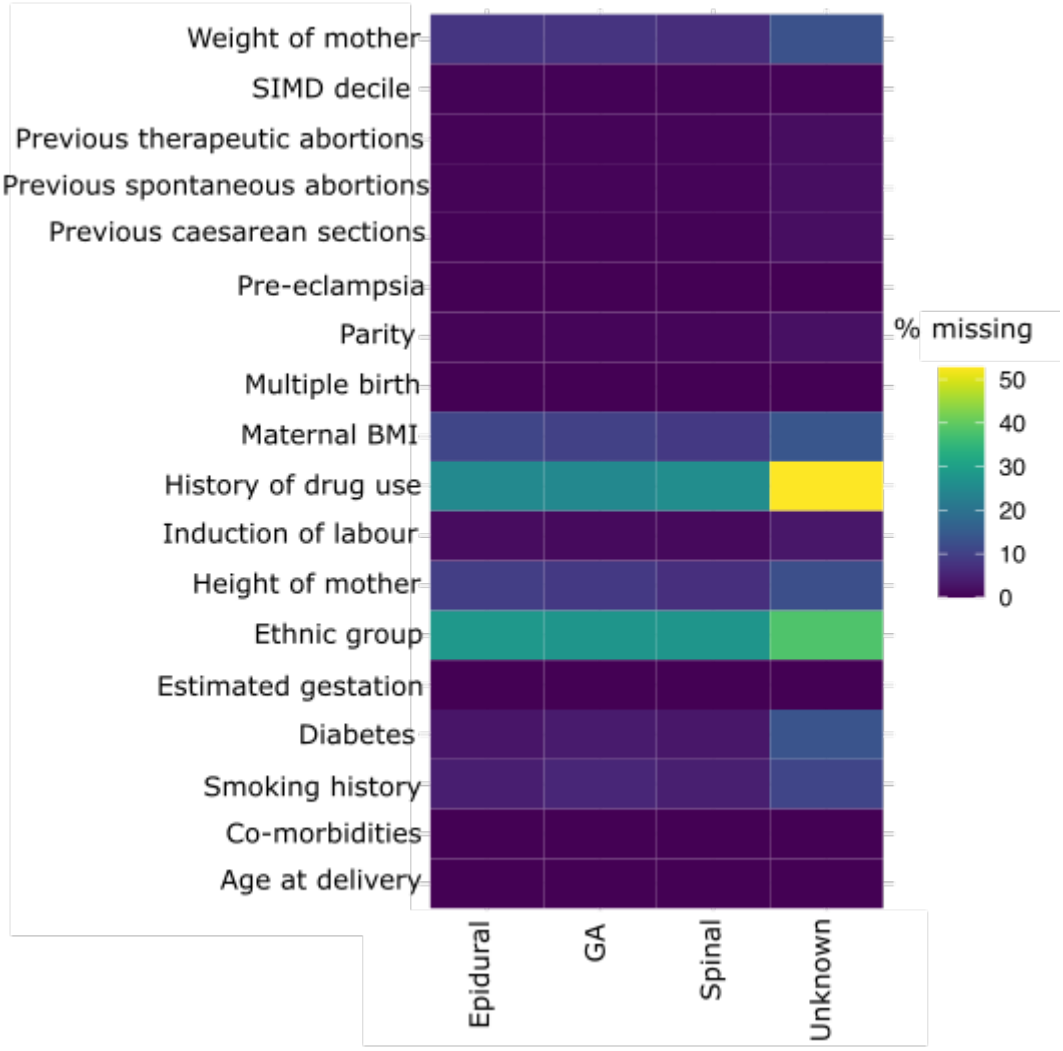


Figure 7-8 I Pictogram depicting percentages of missing data for each variable by anaesthesia utilisation

7.2.7 Statistical analysis

7.2.7.1 Variables for adjustment

The primary analyses were unadjusted as our aim was to determine the total effect of SEP on epidural utilisation. There were two primary analyses, as deliveries via elective and emergency caesarean birth were analysed separately. A Directed Acyclic Graph (DAG) is presented in Figure 7-9, this presents some but not all of the factors that may influence utilisation of GA for caesarean birth. Whilst we considered that women characteristics, such as BMI, age or history of previous caesarean birth may influence utilisation of GA for caesarean

birth, we considered them downstream effects of a women socio-economic position at the start of pregnancy. Thus, they may be mediators of this relationship, but do not meet the definition of confounder. Adjustment for these factors may therefore bias our analysis as described in section 6.2.7.

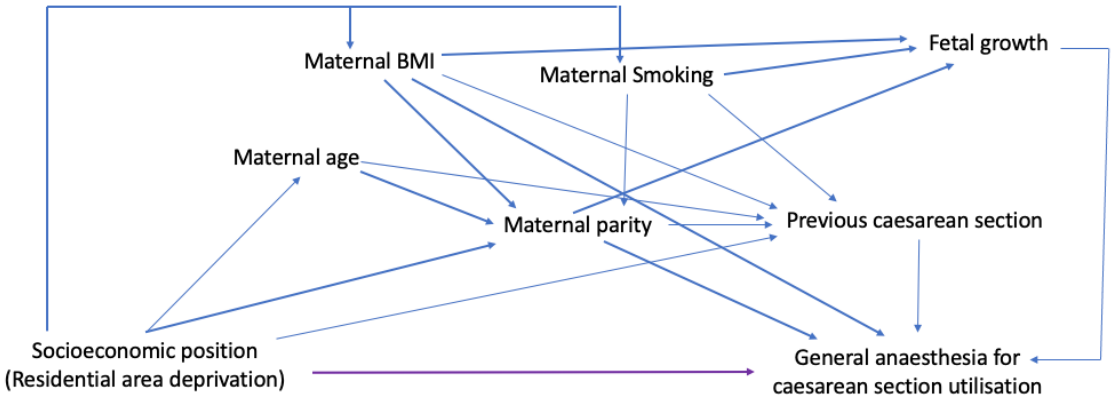


Figure 7-9 Directed Acyclic Graph (DAG) demonstrating some of the key factors which may influence GA utilisation for caesarean birth

Date of delivery as a potential confounder variable is adjusted for in the sensitivity analyses, as both a continuous variable, and separately as a categorical variable based upon the years if SIMD updates (2009, 2012, 2015 and 2020).

7.2.7.2 Modelling

Robust Poisson modelling with sandwiched errors was used to calculate absolute and relative risks of GA for elective caesarean birth, and for emergency caesarean birth, for each SIMD decile. 95% confidence intervals were calculated alongside each estimate. For relative risk, SIMD 10, the least deprived category, was used as a reference to which all other deciles were compared. Robust Poisson regression modelling was chosen over log-binomial modelling to allow the calculation of relative risk (as opposed to odds ratio) and to avoid problems with model convergence. The sandwich estimator is used to correct the inflated variance found from the standard Poisson model. The distribution of characteristics was similar in the imputed and non-imputed datasets, which are both presented. P values < 0.05 indicated statistical significance, these were

calculated using 2-sided Wilcoxon rank sum and x^2 tests. Regression modelling is described in section 3.3.

The association between SIMD and: maternal age, maternal BMI, smoking history, illicit drug use history, ethnicity and comorbidities is presented graphically with confidence intervals calculated using quantile regression using the R package 'qgam'.[250]

7.2.7.3 Sensitivity analyses

Six sensitivity analyses were carried out for both the elective and emergency cohorts, and two further subgroup analyses were carried out just on the emergency cohort. The first restricted the analysis to only include women that had not had a previous caesarean birth. The second restricted the analysis to only include births at term or post-term (37+0 to 41+6 weeks gestation). The third and fourth adjusted for date of delivery as both a continuous and a categorical variable. In the fifth, women with a documented relative contraindication to neuraxial analgesia were excluded. The sixth sensitivity analysis was a stratified analysis to explore influence of white or non-white ethnicity on the relationship between SEP and use of GA for caesarean birth. In the emergency cohort the two further subgroup analyses were; (1) women who were documented as having a category 1 caesarean birth, and (2) women who had an 'irreversible' causes of fetal distress listed as an indication for delivery. Following the results of the descriptive analysis, all of the results of the elective cohort, including sensitivity analyses, are presented in sections 7.3.5 - 7.3.11, followed by all of the results for the emergency cohort in sections 7.3.12 – 7.3.20.

7.2.7.4 Model validation

Modelling assumptions were checked and validated post-hoc using the 'DHARMa' package in R.[251] This package is used to transform the residuals of a generalised linear model to a 'standard value' on a scale of 0 to 1. These transformed residuals can then be plotted and interpreted like a linear model (see chapter 6, section 6.2.8). Four plots were created using this package – two residual vs model prediction plot for the elective and emergency subsets (Figures 7-10 and

7-12 respectively) and two Quantile-Quantile (QQ) plots (Figures 7-11 and 7-13 for elective and emergency models respectively). In the scaled residual plots in both Figures 7-10 and 7-12, no abnormal data points can be visualised, and the red dashed line plotted forms a roughly horizonal band at a value of 0.5. In the two QQ plots, the observed data very closely approximates the line y = x (Figure 7-11 and 7-13). Together these indicate good model fit for both the elective and emergency models.

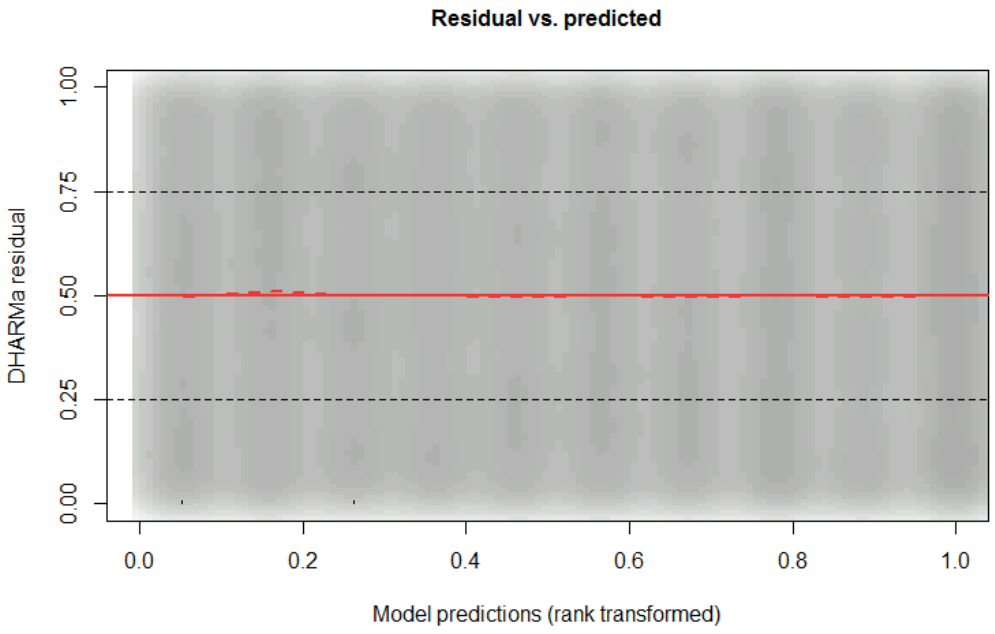


Figure 7-10 DHARMa scaled residuals plotted against model predictions (relative risk of GA for elective caesarean birth by SIMD decile)

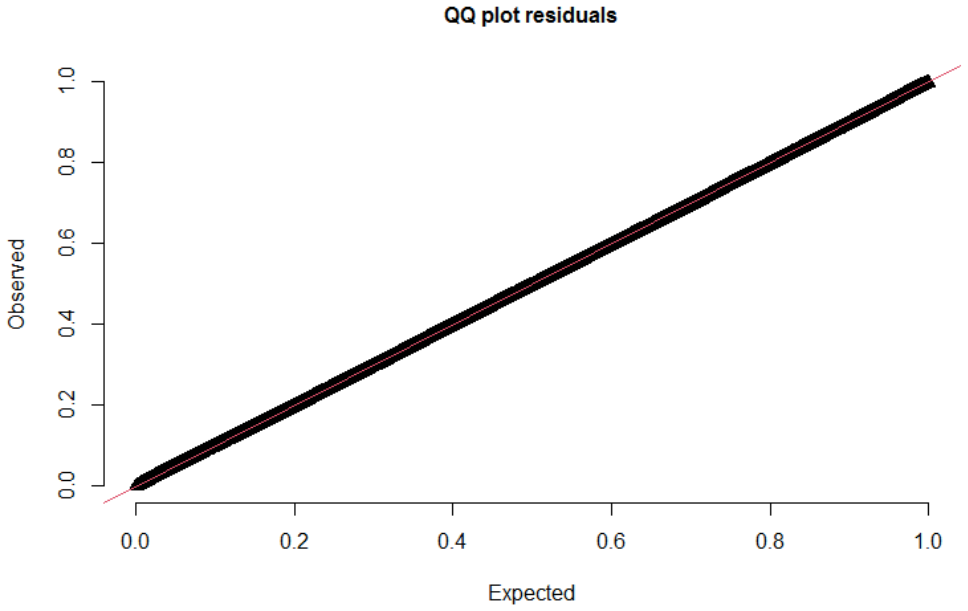


Figure 7-11 QQ plot for observed vs modelled data relative risk of GA for elective caesarean birth by SIMD decile

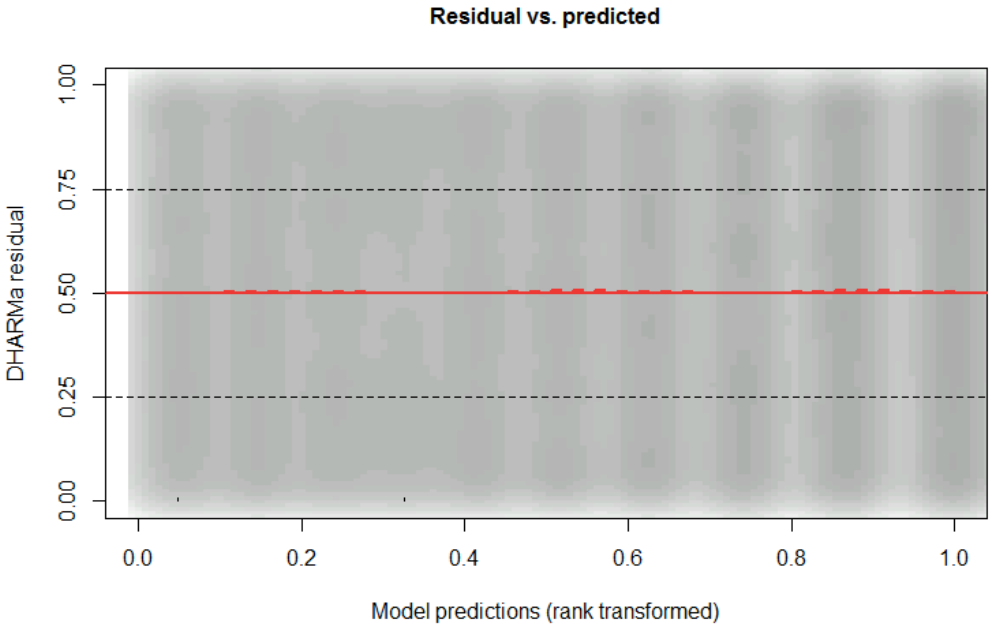


Figure 7-12 DHARMa scaled residuals plotted against model predictions (relative risk of GA for emergency caesarean birth by SIMD decile)

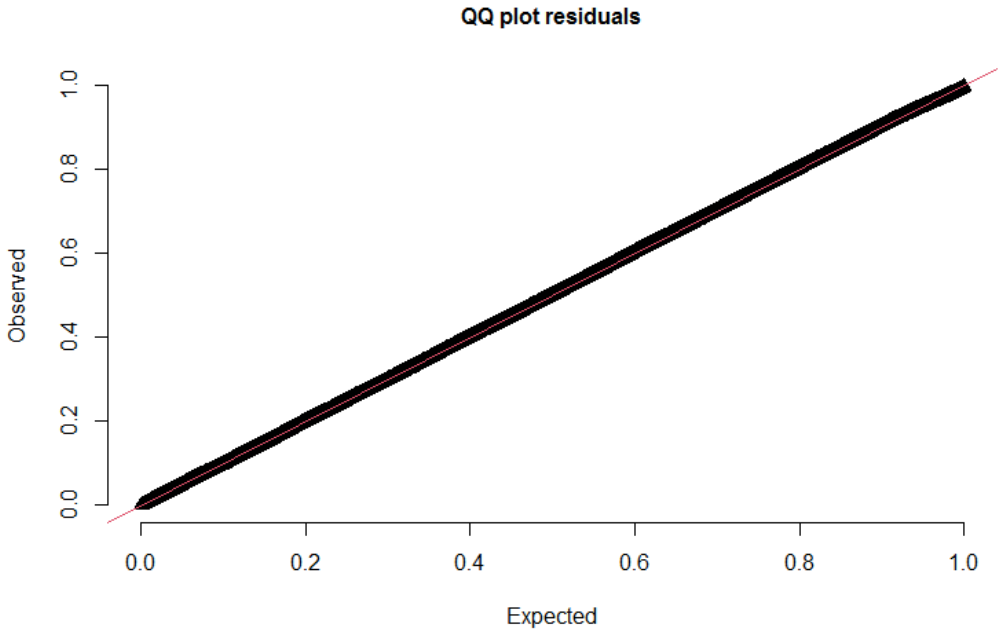


Figure 7-13 QQ plot for observed vs modelled data relative risk of GA for emergency caesarean birth by SIMD decile

7.3 Results

7.3.1 Study population

624,507 birth events occurred in Scotland between January 1st 2009 and 23rd October 2020. Parturients were excluded if gestational age was less than 24 weeks, or greater than 44 weeks, or if no data were available for either mode of birth or SIMD decile. Of the remaining 619,620 parturients, 188,945 (30.5%) delivered by caesarean birth. For the primary analyses a further 9,383 entries were removed due to having missing data for mode of birth. Our study cohort comprised 179,562 parturients (Figure 7-14).

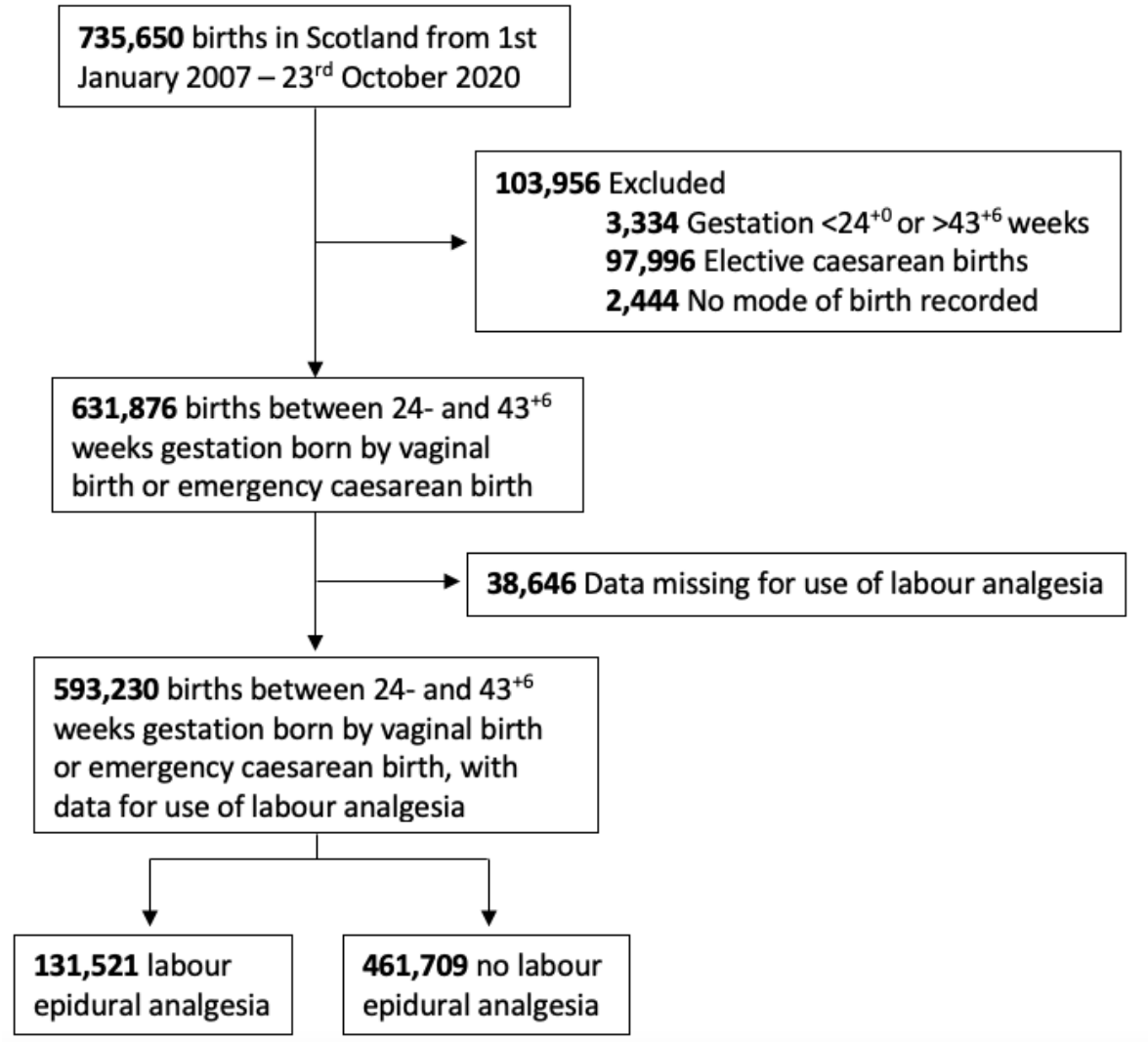


Figure 7-14 Cohort flow for analysis

7.3.2 Descriptive analysis of the overall cohort

A descriptive analysis was carried out of the overall cohort, for which we had 619,620 birth events of neonates with a gestational age 24- 44 weeks, for which we had data for mode of birth and SIMD decile. Of these 86,384 women (14%) delivered by elective caesarean birth and 102,561 women (17%) delivered by emergency caesarean birth. 79,134 (13%) of women had undergone a caesarean birth for a prior birth, and 173,289 (28%) were undergoing induced labour. The presentation of the baby (or of the first baby in the case of multiple births) at birth was recorded as breech in 21,887 (4.0 %) which is in keeping with the estimated prevalence of breech presentation of 3-4%[282]. Of these 12,223 (55.8%) delivered by elective caesarean birth, 8,221 (37.6%) delivered by emergency caesarean birth, and 1,453 (6.6%) delivered vaginally. Multiple birth occurred in 9,355 women (1.5%) (Table 7-6).

In the overall cohort, women in the most deprived decile (SIMD 1) were more likely to be undergoing induced labour (30% vs 24%) and were less likely to: undergo an elective caesarean birth (13% vs 16%), have had a previous caesarean (13% vs 14%), have a baby in breech presentation (3.7% vs 4.3%) or a multiple birth (1.3% vs 1.8%), as compared to women in the most advantaged decile (SIMD 1). Prevalence of emergency caesarean birth was similar (Table 7-6, Figures 7-15 to 7-20).

Characteristic	**Overall**, N = 619,620[1]	**10**, N = 47,751[1]	**09**, N = 52,715[1]	**08**, N = 56,161[1]	**07**, N = 56,303[1]	**06**, N = 56,898[1]	**05**, N = 59,669[1]	**04**, N = 63,495[1]	**03**, N = 68,083[1]	**02**, N = 74,369[1]	**01**, N = 84,176[1]	**p-value**[2]
Elective caesarean birth	86,384 (14%)	7,735 (16%)	8,530 (16%)	8,657 (15%)	8,125 (14%)	8,125 (14%)	7,950 (13%)	8,373 (13%)	8,714 (13%)	9,372 (13%)	10,803 (13%)	<0.001
Emergency caesarean birth	102,561 (17%)	7,622 (16%)	8,672 (16%)	9,359 (17%)	9,211 (16%)	9,283 (16%)	9,962 (17%)	10,678 (17%)	11,418 (17%)	12,516 (17%)	13,840 (16%)	<0.001
Previous caesarean birth	79,134 (13%)	6,668 (14%)	7,037 (13%)	7,209 (13%)	7,260 (13%)	7,215 (13%)	7,457 (13%)	7,823 (12%)	8,454 (12%)	9,306 (13%)	10,705 (13%)	<0.001
Induction of labour	173,389 (28%)	11,297 (24%)	13,845 (27%)	15,159 (27%)	15,518 (28%)	15,502 (28%)	17,111 (29%)	18,286 (29%)	19,826 (29%)	21,813 (30%)	25,032 (30%)	<0.001
Breech	21,887 (4.0%)	1,901 (4.3%)	1,991 (4.2%)	2,162 (4.3%)	2,127 (4.3%)	2,079 (4.1%)	1,975 (3.8%)	2,258 (4.0%)	2,310 (3.9%)	2,450 (3.8%)	2,634 (3.7%)	<0.001
Multiple birth	9,355 (1.5%)	880 (1.8%)	916 (1.7%)	928 (1.7%)	870 (1.5%)	869 (1.5%)	883 (1.5%)	943 (1.5%)	1,003 (1.5%)	981 (1.3%)	1,082 (1.3%)	<0.001

[1]n (%)

[2]Pearson's Chi-squared test

Table 7-6 Cohort characteristic of overall cohort by SIMD decile

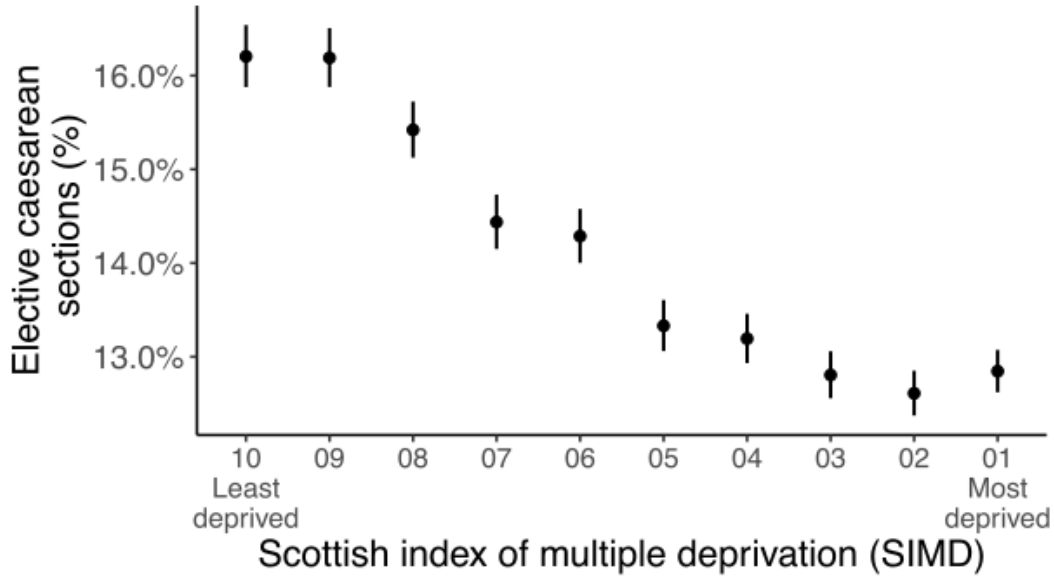


Figure 7-15 Percentage of births by elective caesarean birth by SIMD decile

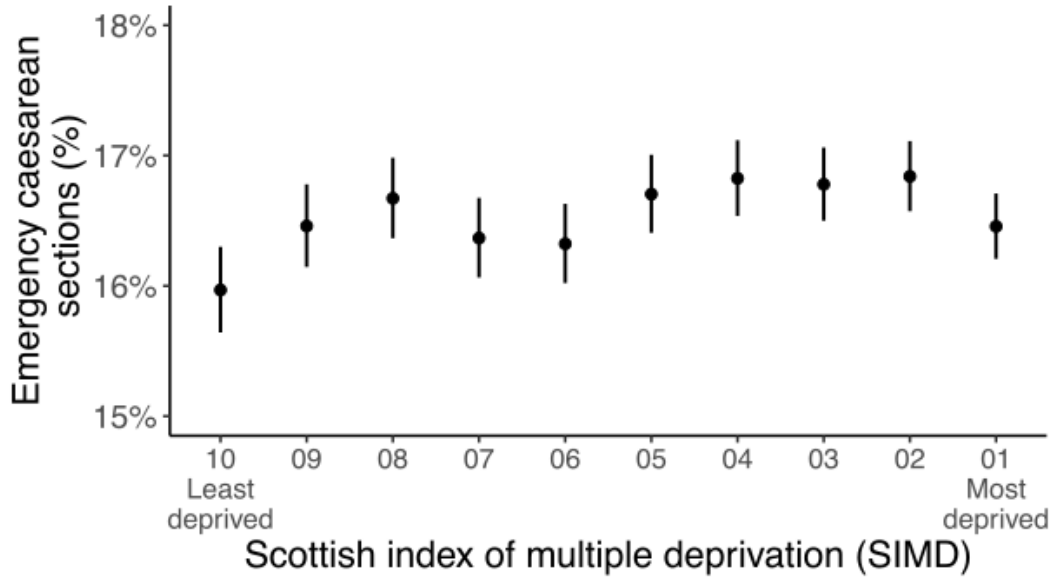


Figure 7-16 Percentage of births by emergency caesarean birth by SIMD decile

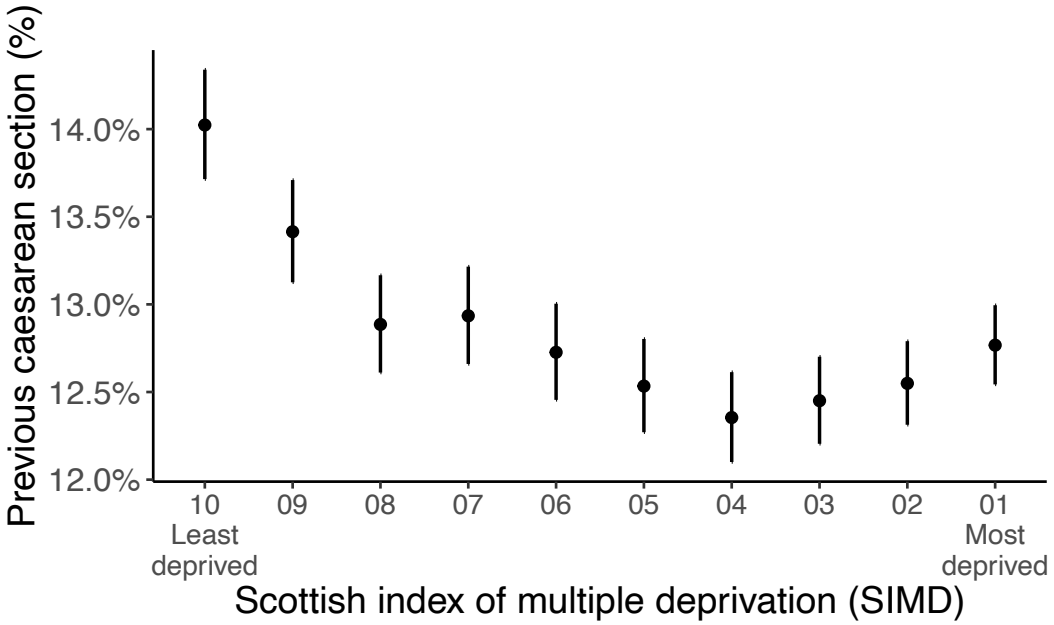


Figure 7-17 Percentage of births by women who had undergone previous caesarean birth by SIMD decile

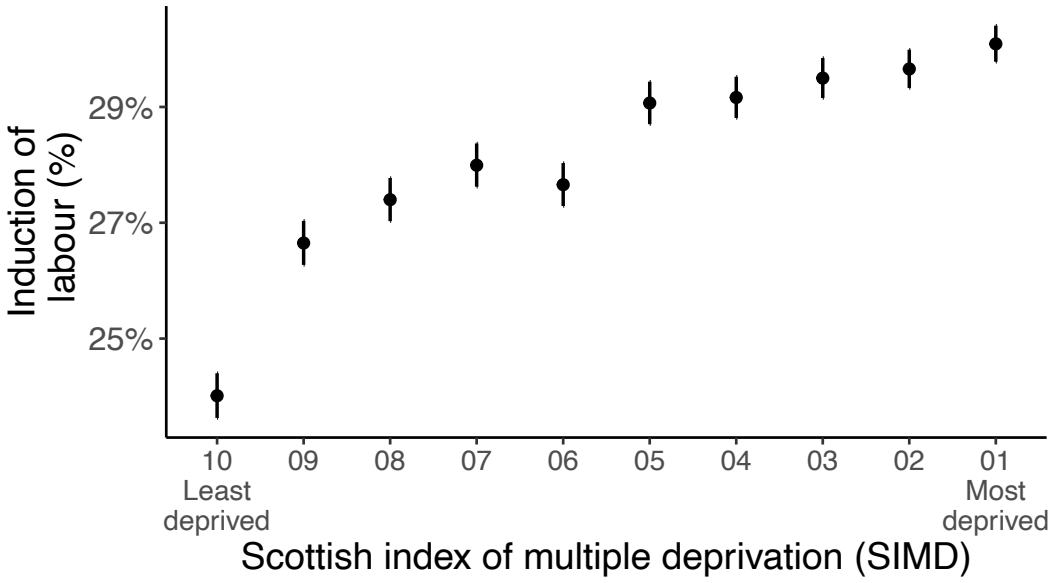


Figure 7-18 Percentage of births where labour was induced by SIMD decile

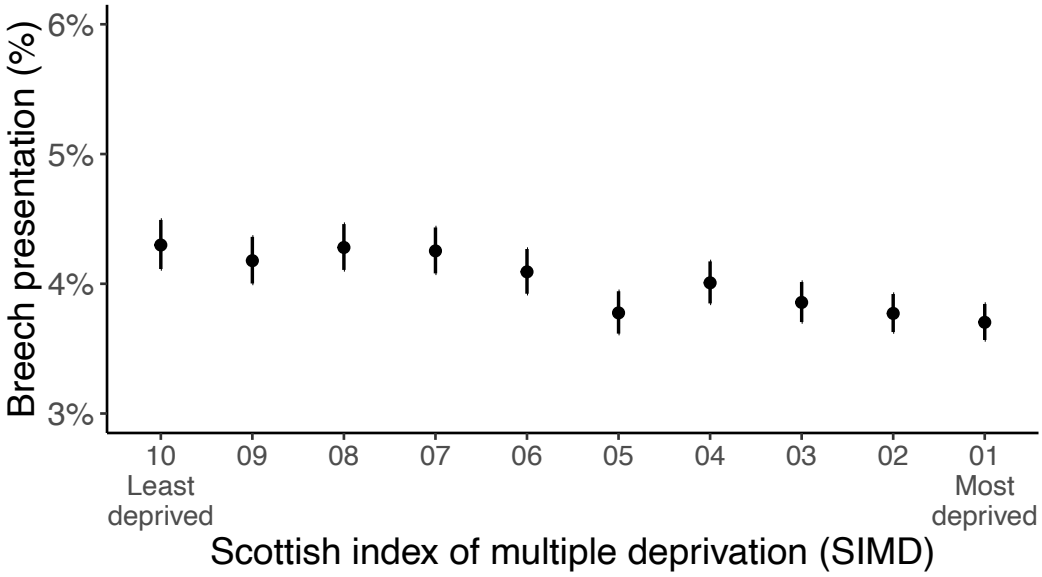


Figure 7-19 Percentage of births with baby in breech presentation by SIMD decile

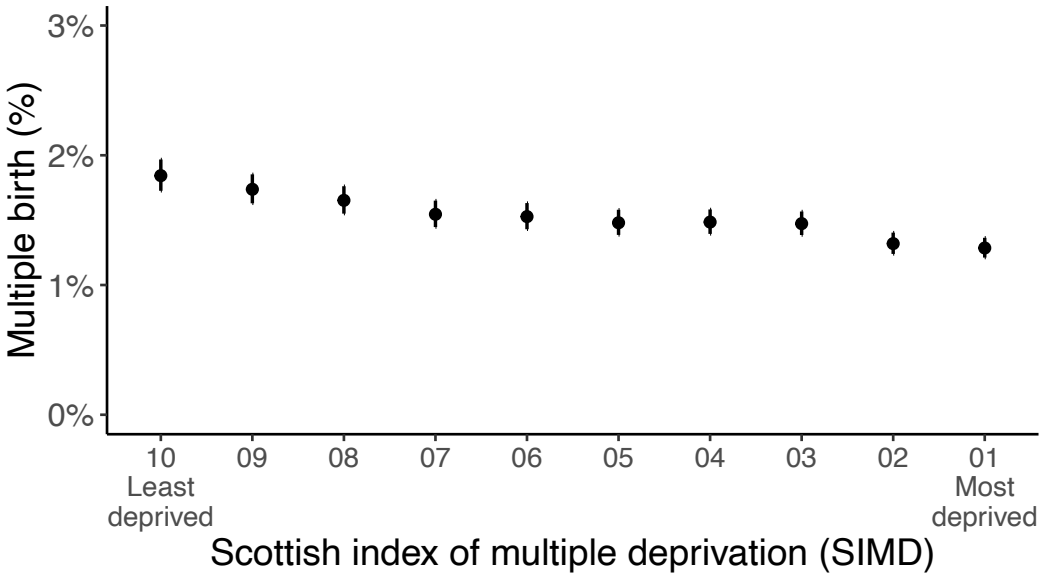


Figure 7-20 Percentage of multiple births by SIMD decile

7.3.3 Descriptive analysis of the study cohort by SIMD decile

In the study cohort (179,564 parturients), there was significant variation of the baseline characteristics according to degree of relative deprivations. Similarly to those observed in the labouring cohort described in chapter 6, stepwise increases in adverse maternal health characteristics are observed with increasing deprivation. Women who lived in the most deprived decile (SIMD 1) were on average 5 years younger (median age 29 [24,33] vs 34 [31,37]) (Figure 7-21), had a BMI 2.5 units higher (median BMI 27.3 [23.4, 32.8] vs 24.8 [22.3, 28.4]) (Figure 7-22), 8 times more likely to smoke (28% vs 3.3%) (Figure 7-23), 16 times more likely to have ever used injected illicit drugs (1.6% vs 0.1%) (Figure 7-24), more likely to have a single comorbidity (18% vs 14%), and twice as likely to have multiple comorbidities (3.5% vs 1.7%) (figure 7-25) than women who lived in the most socio-economically advantaged areas (SIMD10). Women in SIMD 1 (most deprived) were the least likely to be of white ethnicity, followed by SIMD 10 (least deprived) (Figure 7-26). They were more likely to be undergoing induced labour prior to caesarean birth (22% vs 18%), less likely to be having a multiple birth (2.9% vs 4.2%) and were more likely to deliver by emergency caesarean birth (56%) rather than elective caesarean birth (44%). The proportion of emergency caesarean births increased linearly as level of socio-economic disadvantage increased (SIMD 1 56% vs 49% SIMD 10). Prevalence of pre-eclampsia and previous caesarean birth were similar (Table 7-7).

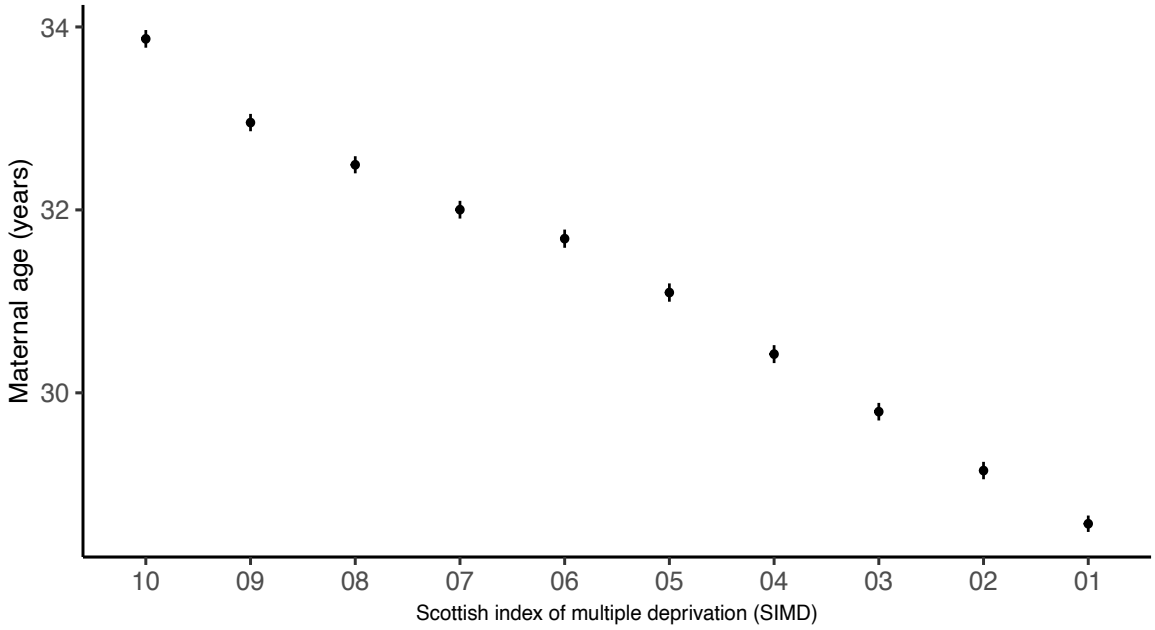


Figure 7-21 Average maternal age by SIMD decile

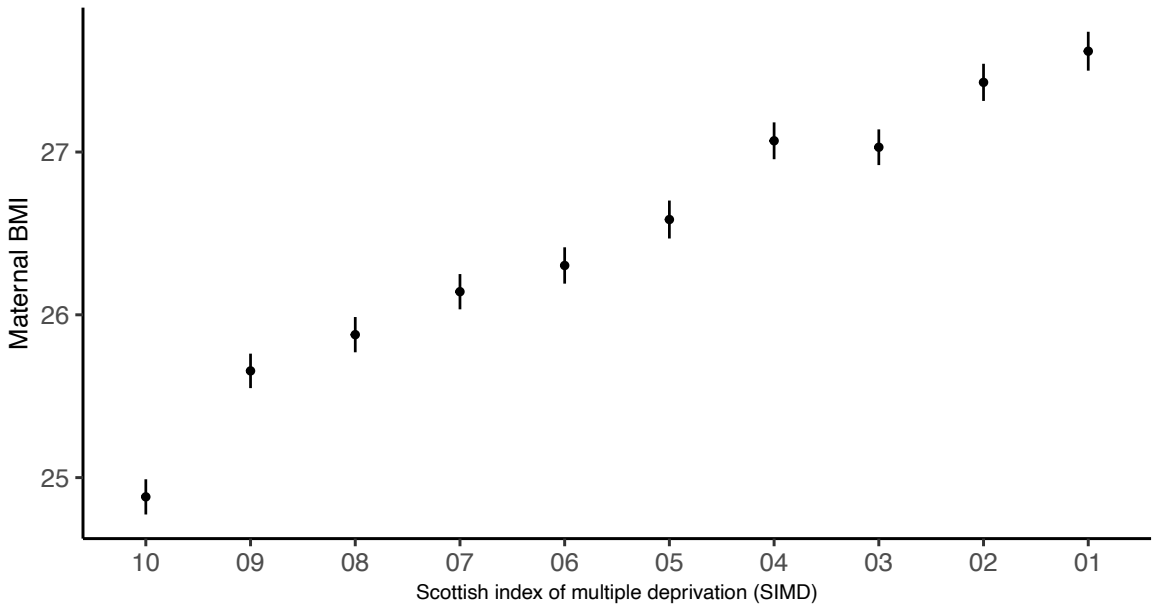


Figure 7-22 Average maternal BMI by SIMD decile

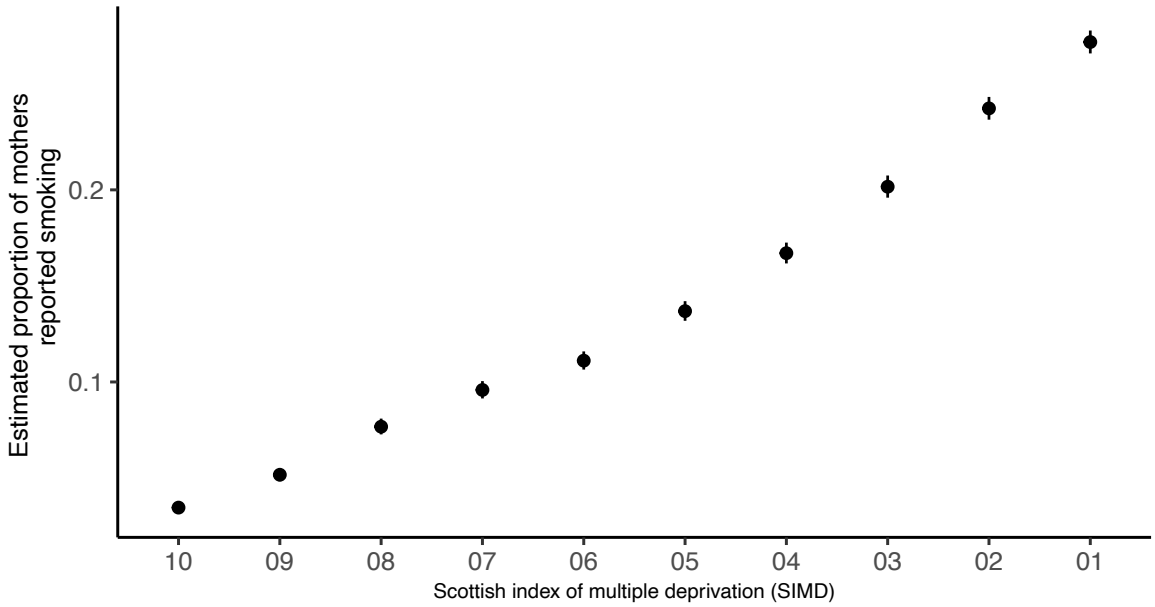


Figure 7-23 Proportion of mothers who reported being a current smoker by SIMD decile

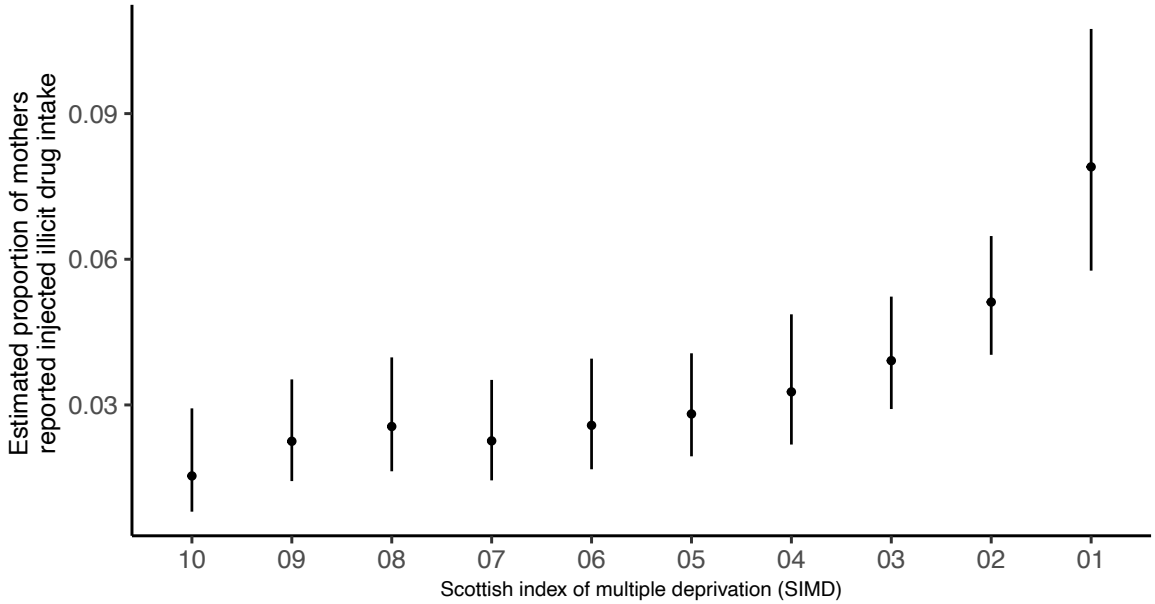


Figure 7-24 Proportion of mothers who had a history of injecting illicit drugs by SIMD decile

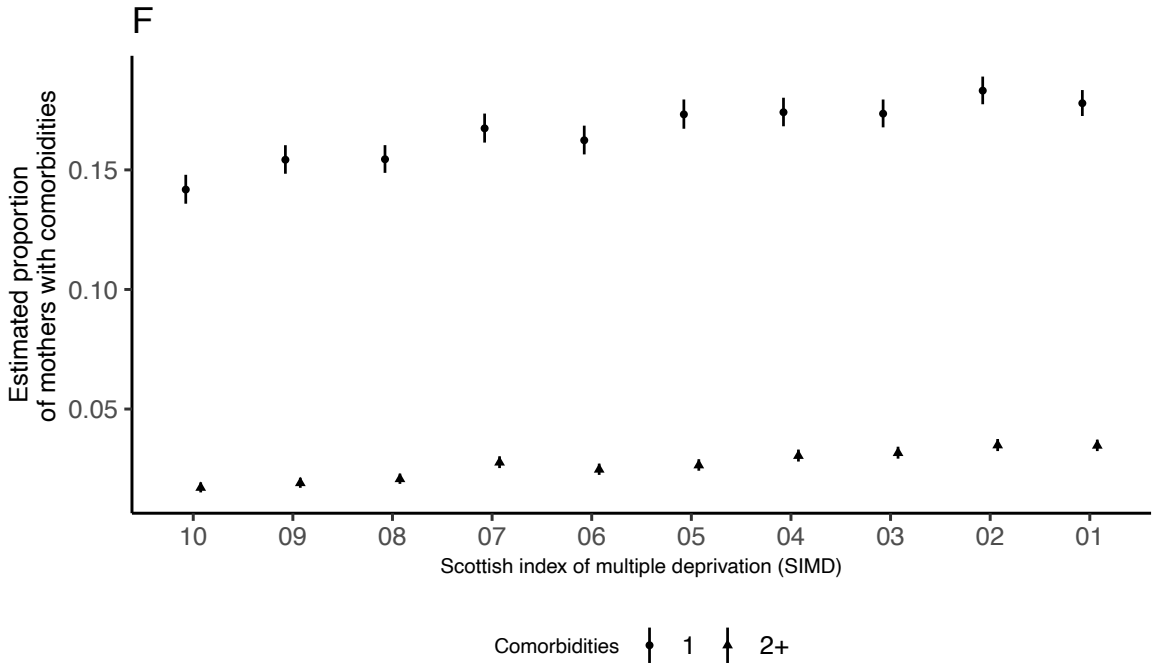


Figure 7-25 Proportion of mothers with comorbidities by SIMD decile (• = single comorbidity, Δ = multiple comorbidities)

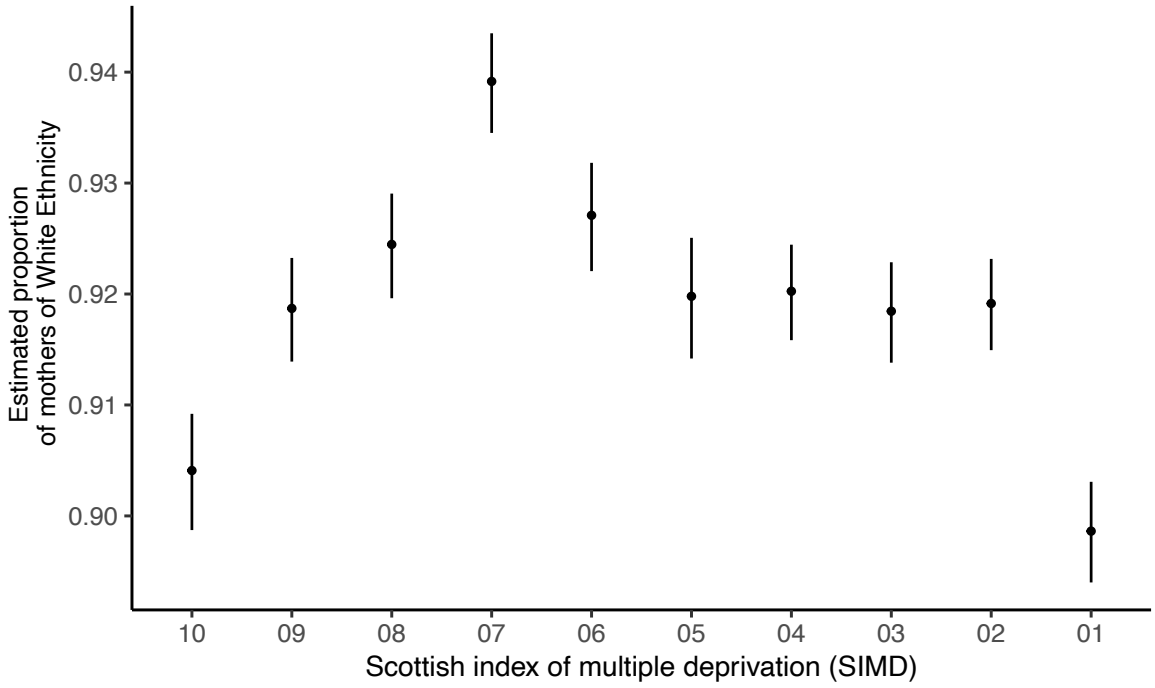


Figure 7-26 Proportion of mothers of white ethnicity

Characteristic	**10**, N = 14,726[1]	**09**, N = 16,305[1]	**08**, N = 17,154[1]	**07**, N = 16,547[1]	**06**, N = 16,593[1]	**05**, N = 17,058[1]	**04**, N = 18,193[1]	**03**, N = 19,134[1]	**02**, N = 20,637[1]	**01**, N = 22,729[1]
Epidural	3,509 (24%)	3,738 (23%)	4,083 (24%)	3,738 (23%)	3,502 (21%)	3,582 (21%)	3,888 (21%)	4,139 (22%)	4,308 (21%)	4,574 (20%)
GA	725 (4.9%)	819 (5.0%)	864 (5.0%)	891 (5.4%)	1,016 (6.1%)	1,061 (6.2%)	1,194 (6.6%)	1,419 (7.4%)	1,615 (7.8%)	1,806 (7.9%)
Spinal	10,492 (71%)	11,748 (72%)	12,207 (71%)	11,918 (72%)	12,075 (73%)	12,415 (73%)	13,111 (72%)	13,576 (71%)	14,714 (71%)	16,349 (72%)
Elective CS	7,483 (51%)	8,133 (50%)	8,281 (48%)	7,782 (47%)	7,791 (47%)	7,615 (45%)	8,058 (44%)	8,336 (44%)	8,890 (43%)	10,099 (44%)
Emergency CS	7,243 (49%)	8,172 (50%)	8,873 (52%)	8,765 (53%)	8,802 (53%)	9,443 (55%)	10,135 (56%)	10,798 (56%)	11,747 (57%)	12,630 (56%)
Age of Mother	34.0 (31.0, 37.0)	33.0 (30.0, 36.0)	32.0 (29.0, 36.0)	32.0 (28.0, 36.0)	32.0 (28.0, 35.0)	31.0 (27.0, 35.0)	30.0 (26.0, 34.0)	30.0 (26.0, 34.0)	29.0 (25.0, 33.0)	29.0 (24.0, 33.0)
Maternal BMI	24.8 (22.3, 28.4)	25.5 (22.7, 29.7)	25.7 (22.8, 30.0)	26.0 (22.9, 30.4)	26.2 (23.0, 30.8)	26.5 (23.1, 31.2)	27.0 (23.3, 32.0)	26.9 (23.3, 31.7)	27.3 (23.4, 32.4)	27.3 (23.4, 32.8)
White ethnicity	10,415 (90%)	11,009 (92%)	11,582 (92%)	11,152 (94%)	10,882 (93%)	11,014 (92%)	11,962 (92%)	12,642 (92%)	13,861 (92%)	14,607 (90%)
Asian ethnicity	663 (5.7%)	590 (4.9%)	554 (4.4%)	434 (3.7%)	500 (4.3%)	535 (4.5%)	618 (4.8%)	637 (4.6%)	621 (4.1%)	715 (4.4%)
Black ethnicity	195 (1.7%)	186 (1.6%)	206 (1.6%)	154 (1.3%)	189 (1.6%)	224 (1.9%)	225 (1.7%)	297 (2.2%)	335 (2.2%)	633 (3.9%)
Mixed ethnicity	97 (0.8%)	78 (0.7%)	72 (0.6%)	42 (0.4%)	62 (0.5%)	68 (0.6%)	65 (0.5%)	52 (0.4%)	72 (0.5%)	113 (0.7%)
Other ethnicity	162 (1.4%)	127 (1.1%)	122 (1.0%)	84 (0.7%)	105 (0.9%)	123 (1.0%)	121 (0.9%)	114 (0.8%)	180 (1.2%)	198 (1.2%)

Characteristic	**10**, N = 14,726[1]	**09**, N = 16,305[1]	**08**, N = 17,154[1]	**07**, N = 16,547[1]	**06**, N = 16,593[1]	**05**, N = 17,058[1]	**04**, N = 18,193[1]	**03**, N = 19,134[1]	**02**, N = 20,637[1]	**01**, N = 22,729[1]
Never smoked	11,969 (84%)	12,994 (83%)	13,157 (80%)	12,210 (77%)	11,879 (75%)	11,623 (71%)	11,922 (69%)	11,920 (65%)	12,087 (61%)	12,795 (60%)
Current smoker	470 (3.3%)	774 (5.0%)	1,237 (7.5%)	1,505 (9.5%)	1,762 (11%)	2,238 (14%)	2,909 (17%)	3,690 (20%)	4,844 (25%)	6,026 (28%)
Former smoker	1,742 (12%)	1,861 (12%)	2,032 (12%)	2,140 (13%)	2,231 (14%)	2,468 (15%)	2,547 (15%)	2,762 (15%)	2,812 (14%)	2,584 (12%)
Injected illicit Drugs	15 (0.1%)	24 (0.2%)	40 (0.3%)	43 (0.3%)	53 (0.4%)	71 (0.5%)	106 (0.8%)	140 (1.0%)	212 (1.4%)	222 (1.6%)
Diabetes	588 (4.1%)	750 (4.7%)	854 (5.1%)	885 (5.5%)	920 (5.7%)	983 (5.9%)	1,111 (6.3%)	1,102 (5.9%)	1,312 (6.6%)	1,387 (6.4%)
Pre-eclampsia	285 (1.9%)	306 (1.9%)	315 (1.8%)	396 (2.4%)	388 (2.3%)	377 (2.2%)	404 (2.2%)	435 (2.3%)	502 (2.4%)	436 (1.9%)
No comorbidities	12,394 (84%)	13,495 (83%)	14,181 (83%)	13,385 (81%)	13,511 (81%)	13,671 (80%)	14,492 (80%)	15,212 (80%)	16,156 (78%)	17,912 (79%)
1 comorbidity	2,080 (14%)	2,508 (15%)	2,619 (15%)	2,720 (16%)	2,683 (16%)	2,945 (17%)	3,171 (17%)	3,341 (17%)	3,757 (18%)	4,032 (18%)
2+ comorbidities	252 (1.7%)	302 (1.9%)	354 (2.1%)	442 (2.7%)	399 (2.4%)	442 (2.6%)	530 (2.9%)	581 (3.0%)	724 (3.5%)	785 (3.5%)
Previous C-section	5,308 (36%)	5,575 (34%)	5,730 (34%)	5,638 (34%)	5,665 (34%)	5,881 (35%)	6,121 (34%)	6,603 (35%)	7,259 (35%)	8,321 (37%)
Parity	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 2.00)
Induction of labour	2,631 (18%)	3,249 (20%)	3,517 (21%)	3,563 (22%)	3,481 (21%)	3,832 (23%)	4,127 (23%)	4,376 (23%)	4,818 (24%)	4,978 (22%)
Multiple birth	616 (4.2%)	634 (3.9%)	621 (3.6%)	598 (3.6%)	562 (3.4%)	579 (3.4%)	646 (3.6%)	638 (3.3%)	636 (3.1%)	669 (2.9%)

[1]n (%); Median (IQR)

Table 7-7 Cohort characteristics by SIMD decile

7.3.4 Descriptive analysis of the study cohort by anaesthesia for caesarean birth

Data for mode of anaesthesia was available for 179,564. Of these, elective caesarean birth was performed in 82,687 (46.0%) and 96,875 (54.0%) were performed as an emergency. General anaesthesia was used in 1,979 (2.4%) and 9,459 (9.8%) respectively (Table 7-8). Compared with women who received neuraxial anaesthesia, women who received a GA were more likely to smoke, have injected illicit drugs, have comorbidities, and reside in a lower socio-economic area (Table 7-8). Compared to women who had a GA for emergency caesarean birth, those who had it for elective caesarean birth were on average 3 years older (32 [28, 26] vs 29 [25,34]), had a BMI 1.2 units higher (27.0 [23.0, 33.0] vs 25.8 [22.8 30.8]), more likely to live in the least deprived area (SIMD 7.3% vs 6.1%), more likely to live with diabetes (7.8% vs 4.2%), more likely to have a multiple birth, and more likely to have had a previous caesarean birth (55% vs 14%). Women who had a GA were less likely to be white, less likely to live in a deprived area less likely to smoke, less likely to have pre-eclampsia, and less likely to have comorbidities.

	Emergency			Elective		
Characteristic	**Epidural**, N = 33,555[1]	**GA**, N = 9,459[1]	**Spinal**, N = 53,861[1]	**Epidural**, N = 5,611[1]	**GA**, N = 1,979[1]	**Spinal**, N = 75,097[1]
Age of Mother	30.0(26.0, 34.0)	29.0(25.0, 34.0)	30.0(26.0, 35.0)	32.0(28.0, 36.0)	32.0(28.0, 36.0)	32.0(28.0, 36.0)
Maternal BMI	26.1 (23.0, 30.8)	25.8 (22.6, 30.8)	26.1 (22.9, 30.8)	26.0 (23.0, 31.0)	27.0 (23.0, 33.0)	27.0 (23.0, 31.0)
Unknown	3,602	952	4,965	672	204	6,283
White ethnicity	21,972 (91%)	6,252 (92%)	34,349 (91%)	3,780 (93%)	1,344 (89%)	51,664 (92%)
Asian ethnicity	1,248 (5.2%)	294 (4.3%)	1,810 (4.8%)	166 (4.1%)	92 (6.1%)	2,274 (4.1%)
Black ethnicity	507 (2.1%)	135 (2.0%)	839 (2.2%)	80 (2.0%)	39 (2.6%)	1,059 (1.9%)
Mixed ethnicity	131 (0.5%)	36 (0.5%)	198 (0.5%)	19 (0.5%)	12 (0.8%)	327 (0.6%)
Other ethnicity	242 (1.0%)	56 (0.8%)	407 (1.1%)	25 (0.6%)	26 (1.7%)	583 (1.0%)
Non-white (combined)	2,128 (8.8%)	521 (7.6%)	3,254 (8.6%)	290 (7.2%)	169 (11%)	4,243 (7.6%)
Unknown	9,455	2,686	16,258	1,541	466	19,190
SIMD 10	2,881 (8.6%)	580 (6.1%)	3,782 (7.0%)	628 (11%)	145 (7.3%)	6,710 (9.0%)
SIMD 09	3,089 (9.2%)	693 (7.3%)	4,390 (8.2%)	649 (12%)	126 (6.4%)	7,358 (9.8%)
SIMD 08	3,364 (10%)	694 (7.4%)	4,815 (9.0%)	719 (13%)	170 (8.6%)	7,392 (9.9%)
SIMD 07	3,197 (9.6%)	722 (7.7%)	4,846 (9.0%)	541 (9.6%)	169 (8.6%)	7,072 (9.4%)
SIMD 06	2,986 (8.9%)	821 (8.7%)	4,995 (9.3%)	516 (9.2%)	195 (9.9%)	7,080 (9.5%)
SIMD 05	3,122 (9.3%)	895 (9.5%)	5,426 (10%)	460 (8.2%)	166 (8.4%)	6,989 (9.3%)
SIMD 04	3,404 (10%)	991 (11%)	5,740 (11%)	484 (8.6%)	203 (10%)	7,371 (9.8%)
SIMD 03	3,648 (11%)	1,196 (13%)	5,954 (11%)	491 (8.8%)	223 (11%)	7,622 (10%)
SIMD 02	3,799 (11%)	1,355 (14%)	6,593 (12%)	509 (9.1%)	260 (13%)	8,121 (11%)
SIMD 01	3,964 (12%)	1,489 (16%)	7,177 (13%)	610 (11%)	317 (16%)	9,172 (12%)
Unknown	101	23	143	<5	<5	210
Never smoked	22,815 (71%)	5,420 (61%)	36,032 (70%)	4,193 (77%)	1,246 (67%)	53,165 (74%)
Current smoker	4,161 (13%)	2,231 (25%)	8,299 (16%)	748 (14%)	352 (19%)	9,706 (13%)
Former smoker	5,112 (16%)	1,304 (15%)	7,091 (14%)	472 (8.7%)	252 (14%)	9,030 (13%)
Unknown	1,467	504	2,439	198	129	3,196
Injected illicit Drugs	111 (0.4%)	108 (1.5%)	317 (0.8%)	26 (0.6%)	28 (1.9%)	338 (0.6%)
Unknown	8,260	2,300	13,661	1,442	511	19,324

	Emergency			Elective		
Characteristic	**Epidural**, N = 33,555[1]	**GA**, N = 9,459[1]	**Spinal**, N = 53,861[1]	**Epidural**, N = 5,611[1]	**GA**, N = 1,979[1]	**Spinal**, N = 75,097[1]
Diabetes	1,330 (4.1%)	379 (4.2%)	3,029 (5.8%)	244 (4.5%)	150 (7.8%)	4,776 (6.6%)
Unknown	975	371	1,720	128	64	2,379
Pre-eclampsia	823 (2.5%)	433 (4.6%)	2,020 (3.8%)	31 (0.6%)	25 (1.3%)	519 (0.7%)
No comorbidities	27,675 (82%)	7,150 (76%)	42,581 (79%)	4,784 (85%)	1,464 (74%)	61,170 (81%)
1 comorbidity	5,319 (16%)	1,880 (20%)	9,608 (18%)	723 (13%)	419 (21%)	11,968 (16%)
2+ comorbidities	561 (1.7%)	429 (4.5%)	1,672 (3.1%)	104 (1.9%)	96 (4.9%)	1,959 (2.6%)
Previous spontaneous abortions	7,125 (21%)	2,325 (25%)	12,661 (24%)	1,592 (28%)	569 (29%)	20,873 (28%)
Unknown	136	44	271	7	13	350
Previous therapeutic abortions	2,746 (8.2%)	904 (9.6%)	4,259 (7.9%)	485 (8.7%)	163 (8.3%)	5,855 (7.8%)
Unknown	135	43	268	7	13	355
Previous caesarean births	3,243 (9.7%)	1,331 (14%)	9,844 (18%)	3,099 (55%)	1,084 (55%)	43,656 (58%)
Unknown	76	27	174	<5	8	198
Parity	0.00(0.00, 0.00)	0.00(0.00, 1.00)	0.00(0.00, 1.00)	1.00(1.0, 2.0)	1.00(0.00, 2.00)	1.00(1.00, 2.00)
Unknown	165	54	326	10	17	442
Estimated gestation	40.0 (39.0, 41.0)	39.0 (36.0, 40.0)	39.0 (37.0, 40.0)	39.0 (38.0, 39.0)	39.0 (37.0, 39.0)	39.0 (38.0, 39.0)
Induction of labour	16,989 (52%)	2,921 (31%)	18,024 (34%)	77 (1.4%)	17 (0.9%)	647 (0.9%)
Unknown	616	140	1,215	11	10	220
Multiple birth	546 (1.6%)	300 (3.2%)	1,925 (3.6%)	256 (4.6%)	59 (3.0%)	3,138 (4.2%)

[1]Median (IQR); n (%)

Table 7-8 Cohort demographics by mode of anaesthesia for elective and emergency caesarean birth

7.3.5 Primary analysis: GA for elective caesarean birth and SIMD

An elective caesarean birth was performed in 82,687 women. In the most socio-economically deprived areas (SIMD1) 3.2% of women underwent GA for elective caesarean birth as compared to 2.0% in the least socio-economically deprived areas (SIMD 10). The absolute risk difference is 1.2% (SIMD 1; AR 0.032 [0.029, 0.035], SIMD 10; AR 0.020 [0.017, 0.023] (Table 7-9). This is a relative increase of 62% (SIMD 1 as compared to SIMD 10, RR 1.62 [1.34, 1.96]) (Table 7-10). As the level of disadvantage increased, the probability of GA for elective caesarean birth increased with a mean change in relative risk of +5.5% per unit deprivation decrease 95% CI[3.3%, 7.8%])(Figure 7-27). Younger age, higher BMI, the presence of single or multiple comorbidities, smoking, the use of injected illicit drugs and parity were associated with an increased probability of GA in the elective cohort. Women of Asian or 'other' ethnicity were significantly more likely to receive a GA for an elective caesarean birth than their white counterparts. Having undergone a previous caesarean birth and multiple birth reduced the likelihood of GA (Table 7-10).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.020	0.002	0.017	0.023
09	0.016	0.002	0.014	0.019
08	0.020	0.002	0.017	0.023
07	0.022	0.002	0.019	0.026
06	0.024	0.002	0.021	0.028
05	0.021	0.002	0.018	0.025
04	0.026	0.002	0.023	0.030
03	0.028	0.002	0.025	0.032
02	0.030	0.002	0.026	0.034
01	0.032	0.002	0.029	0.035

Table 7-9 Absolute risk of GA for elective caesarean birth by SIMD decile

	RR	95% CI[1]	p-value
Age at delivery	0.98	0.97, 0.99	<0.001
Maternal BMI	1.02	1.01, 1.03	<0.001
Ethnic group			
White	-	-	-
Asian	1.44	1.19, 1.74	<0.001
Black	1.26	0.91, 1.74	0.2
Mixed	1.35	0.75, 2.43	0.3
Other	1.51	1.03, 2.21	0.035
SIMD decile			
10	-	-	-
09	0.83	0.66, 1.05	0.11
08	1.01	0.81, 1.26	>0.9
07	1.13	0.91, 1.40	0.3
06	1.23	0.99, 1.52	0.057
05	1.10	0.88, 1.36	0.4
04	1.35	1.10, 1.66	0.004
03	1.43	1.17, 1.75	<0.001
02	1.52	1.25, 1.86	<0.001
01	1.62	1.34, 1.96	<0.001
Booking smoking history			
Never smoked, non-smoker	-	-	-
Current smoker	1.53	1.37, 1.72	<0.001
Former smoker	1.19	1.05, 1.36	0.008
Injected illicit drugs			
No	-	-	-
Yes	1.72	1.26, 2.35	0.001
Bateman comorbidities			
0	-	-	-
1	1.48	1.34, 1.64	<0.001
2+	2.03	1.67, 2.47	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	-	-	-
Yes	1.06	0.97, 1.17	0.2
Previous therapeutic abortions			
No	-	-	-
Yes	1.04	0.89, 1.22	0.6
Previous caesarean births			
No	-	-	-
Yes	0.88	0.81, 0.96	0.005
Parity	1.05	1.01, 1.10	0.018
Induction of labour			
No	-	-	-
Yes	0.90	0.56, 1.45	0.7
Multiple birth			
No	-	-	-
Yes	0.68	0.53, 0.89	0.004

[1]CI = Confidence Interval

Table 7-10 Relative risk of GA for elective caesarean birth (imputed analysis)

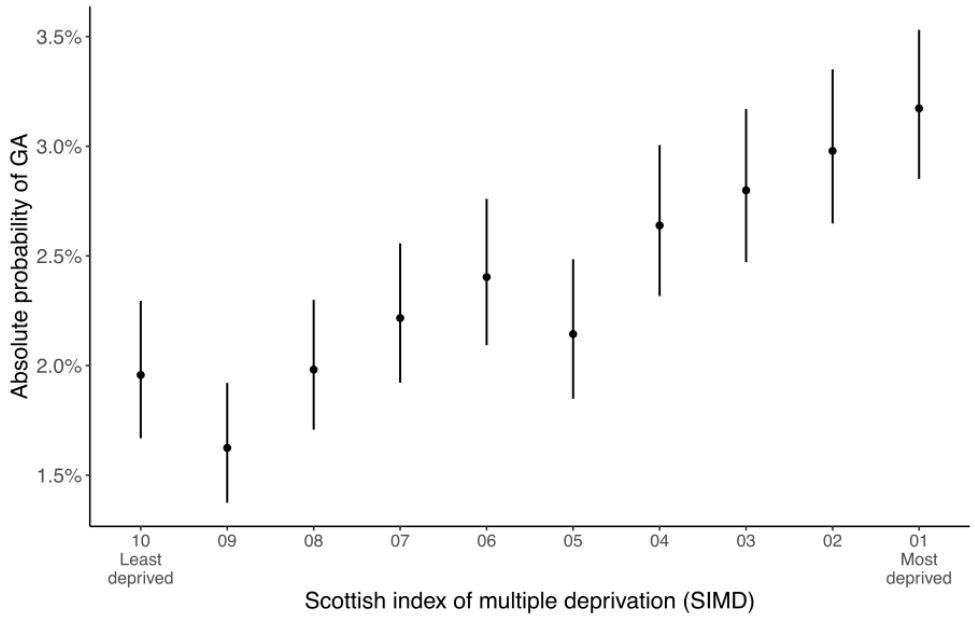


Figure 7-27 Absolute probability of GA for elective caesarean birth by SIMD decile

7.3.6 General anaesthesia for elective caesarean birth and SIMD: unimputed analysis

The results for the unimputed cohort are almost identical to those of the imputed cohort (Table 7-11). In the imputed cohort, previous caesarean birth and multiple birth both reduced probability of GA for elective caesarean birth, but these results did not meet significance in the unimputed cohort. In the unimputed cohort women of black ethnicity were more likely to have a GA for elective caesarean birth, but this result did not meet significance in the imputed cohort.

	RR	95% CI[1]	p-value
Age at delivery	0.98	0.97, 0.99	<0.001
Maternal BMI	1.02	1.01, 1.03	<0.001
Ethnic group			
White	—	—	
Asian	1.54	1.23, 1.88	<0.001
Black	1.40	1.00, 1.89	0.039
Mixed	1.42	0.76, 2.38	0.23
Other	1.73	1.15, 2.50	0.005
SIMD decile			
10	—	—	
09	0.80	0.63, 1.01	0.066
08	1.06	0.85, 1.32	0.61
07	1.12	0.90, 1.40	0.31
06	1.29	1.04, 1.60	0.020
05	1.12	0.90, 1.41	0.30
04	1.30	1.05, 1.61	0.016
03	1.38	1.12, 1.70	0.003
02	1.51	1.23, 1.85	<0.001
01	1.62	1.33, 1.98	<0.001
Booking smoking history			
Never smoked, non-smoker	—	—	
Current smoker	1.53	1.36, 1.72	<0.001

	RR	95% CI[1]	p-value
Former smoker	1.22	1.06, 1.39	0.005
Injected illicit drugs			
No	—	—	
Yes	3.03	2.03, 4.31	<0.001
Bateman comorbidities			
0	—	—	
1	1.47	1.32, 1.64	<0.001
2+	2.05	1.65, 2.50	<0.001
Previous spontaneous abortions			
No	—	—	
Yes	1.05	0.95, 1.15	0.34
Previous therapeutic abortions			
No	—	—	
Yes	1.05	0.89, 1.23	0.52
Previous caesarean births			
No	—	—	
Yes	0.88	0.81, 0.97	0.007
Parity	1.06	1.01, 1.10	0.009
Induction of labour			
Yes	—	—	
No	1.04	0.67, 1.75	0.87
Multiple birth			
No	—	—	
Yes	0.71	0.54, 0.90	0.008

Table 7-11 Relative risk of GA for elective caesarean birth (unimputed analysis)

7.3.7 General anaesthesia for elective caesarean birth restricted to those who have not had a previous caesarean birth

Elective caesarean birth was performed in 33,752 women who had not previously had a caesarean birth. In the most socio-economically deprived areas (SIMD 1) there was small increase in utilisation of GA as compared to the primary analysis (AR 0.020 [0.016, 0.025]). In the least socio-economically deprived areas (SIMD 10) similar rates of GA utilisation were observed compared to the primary analysis (AR 0.034 [0.029, 0.041]) (Table 7-12). This is a relative increase of 67% (SIMD 1 as compared to SIMD 10, RR 1.67 [1.32, 2.35]) (Table 7-13). The socio-economic gradient was increased as compared to the primary analysis with an inter-decile mean change of +6.5% [3.1%, 10.0%] (Figure 7-28). Younger age, higher BMI, smoking and single or multiple comorbidities were associated with increased utilisation of GA in this cohort.

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.020	0.002	0.016	0.025
09	0.016	0.002	0.012	0.020
08	0.021	0.002	0.017	0.026
07	0.024	0.003	0.019	0.030
06	0.024	0.003	0.020	0.030
05	0.022	0.003	0.018	0.028
04	0.028	0.003	0.023	0.034
03	0.033	0.003	0.028	0.040
02	0.036	0.003	0.030	0.043
01	0.035	0.003	0.029	0.041

Table 7-12 Absolute probability of GA for elective caesarean birth by SIMD decile, analysis restricted to only include women who had not had a previous caesarean birth

	RR	95% CI[1]	p-value
Age at delivery	0.97	0.96, 0.98	<0.001
Maternal BMI	1.03	1.02, 1.04	<0.001
Ethnic group			
White	-	-	-
Asian	0.99	0.69, 1.42	>0.9
Black	0.81	0.38, 1.74	0.6
Mixed	1.97	1.06, 3.66	0.033
Other	1.44	0.79, 2.65	0.2
SIMD decile			
10	-	-	-
09	0.78	0.56, 1.11	0.2
08	1.07	0.78, 1.47	0.7
07	1.21	0.88, 1.65	0.2
06	1.22	0.89, 1.67	0.2
05	1.13	0.82, 1.56	0.5
04	1.42	1.05, 1.92	0.023
03	1.68	1.25, 2.25	<0.001
02	1.83	1.37, 2.44	<0.001
01	1.76	1.32, 2.35	<0.001
Booking smoking history			
Never smoked, non-smoker	-	-	-
Current smoker	1.45	1.21, 1.74	<0.001
Former smoker	1.39	1.16, 1.67	<0.001
Injected illicit drugs			
No	-	-	-
Yes	1.46	0.99, 2.14	0.053
Bateman comorbidities			
0	-	-	-
1	1.54	1.31, 1.80	<0.001
2+	2.08	1.50, 2.88	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	-	-	-
Yes	1.21	1.05, 1.39	0.008
Previous therapeutic abortions			
No	-	-	-
Yes	0.96	0.76, 1.23	0.8
Parity	0.95	0.88, 1.03	0.2
Induction of labour			
No	-	-	-
Yes	1.11	0.69, 1.78	0.7
Multiple birth			
No	-	-	-
Yes	0.68	0.51, 0.90	0.007

[1]CI = Confidence Interval

Table 7-13 Relative risk of GA for elective caesarean birth, analysis restricted to only include women who had not had a previous caesarean birth

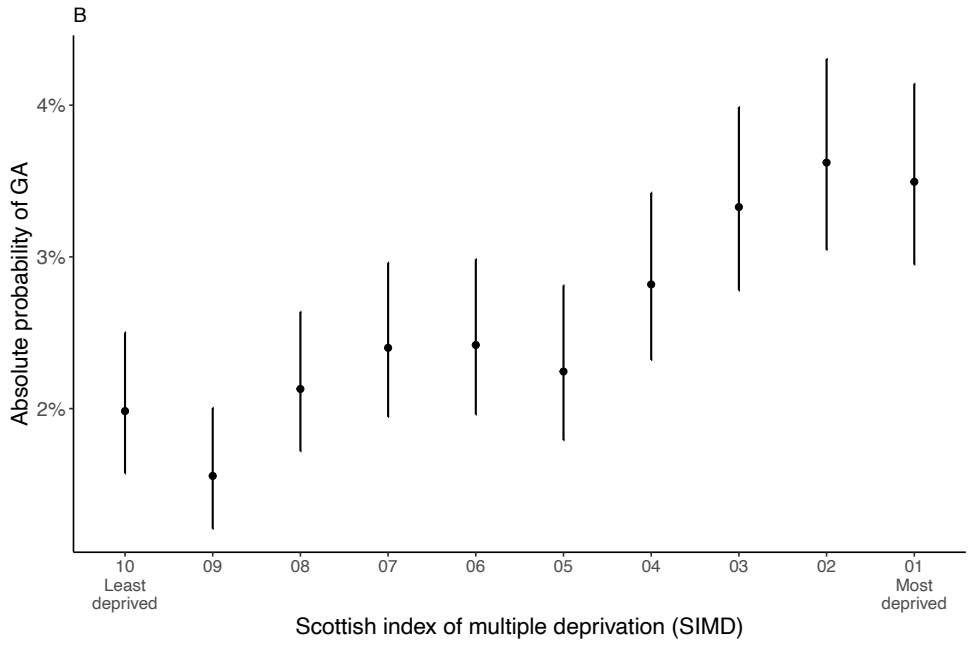


Figure 7-28 Absolute probability of GA for elective caesarean birth by SIMD decile, analysis restricted to only include women who had not undergone a previous caesarean birth

7.3.8 General anaesthesia for elective caesarean birth restricted to women who gave birth to an infant at term

Elective caesarean birth was performed in 74,991 women who gave birth to an infant at term (37+0 to 41+6 weeks gestation). Results were similar to those of the primary analysis, with a slight decrease in utilisation of GA across all deciles. In the most deprived areas (SIMD 1), 2.8% of women had a GA for an elective caesarean section of a baby born at term, as compared to 1.8% of those in the least deprived areas (SIMD 10) (SIMD 1 AR 0.028 [0.024, 0.031] vs SIMD 10 0.017 [0.015, 0.021] (Table 7-14). This is a relative difference of 57% (Table 7-15). Utilisation of GA increased with increasing deprivation with an inter-decile mean change of + 5.1% [2.7%, 7.8%] (Figure 7-29).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.018	0.002	0.015	0.021
09	0.015	0.001	0.012	0.018
08	0.018	0.002	0.016	0.022
07	0.021	0.002	0.018	0.024
06	0.022	0.002	0.019	0.025
05	0.020	0.002	0.017	0.024
04	0.025	0.002	0.022	0.029
03	0.025	0.002	0.022	0.028
02	0.029	0.002	0.025	0.032
01	0.028	0.002	0.024	0.031

Table 7-14 Absolute probability of GA for elective caesarean birth by SIMD decile in women who gave birth to an infant at term

	RR	95% CI[1]	p-value
Age at delivery	0.97	0.97, 0.98	<0.001
Maternal BMI	1.02	1.01, 1.03	<0.001
Ethnic group			
White	-	-	-
Asian	1.42	1.15, 1.75	<0.001
Black	1.19	0.83, 1.71	0.3
Mixed	1.21	0.62, 2.35	0.6
Other	1.47	0.98, 2.21	0.061
SIMD decile			
10	-	-	-
09	0.84	0.65, 1.08	0.2
08	1.05	0.83, 1.33	0.7
07	1.17	0.92, 1.47	0.2
06	1.23	0.98, 1.55	0.075
05	1.16	0.92, 1.47	0.2
04	1.44	1.15, 1.80	0.001
03	1.41	1.13, 1.75	0.003
02	1.63	1.31, 2.01	<0.001
01	1.57	1.27, 1.93	<0.001
Booking smoking history			
Never smoked, non-smoker	-	-	-
Current smoker	1.58	1.40, 1.79	<0.001
Former smoker	1.22	1.06, 1.41	0.006
Injected illicit drugs			
No	-	-	-
Yes	1.60	1.13, 2.26	0.010
Bateman comorbidities			
0	-	-	-
1	1.41	1.26, 1.59	<0.001
2+	1.76	1.37, 2.25	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	-	-	-
Yes	1.07	0.97, 1.19	0.2
Previous therapeutic abortions			
No	-	-	-
Yes	1.08	0.91, 1.27	0.4
Previous caesarean births			
No	-	-	-
Yes	0.89	0.81, 0.98	0.014
Parity	1.03	0.98, 1.08	0.3
Induction of labour			
No	-	-	-
Yes	1.00	0.60, 1.64	>0.9
Multiple birth			
No	-	-	-
Yes	0.57	0.38, 0.87	0.008

[1]CI = Confidence Interval

Table 7-15 Relative risk of GA for elective caesarean birth, analysis restricted to only include women who gave birth to a baby at term

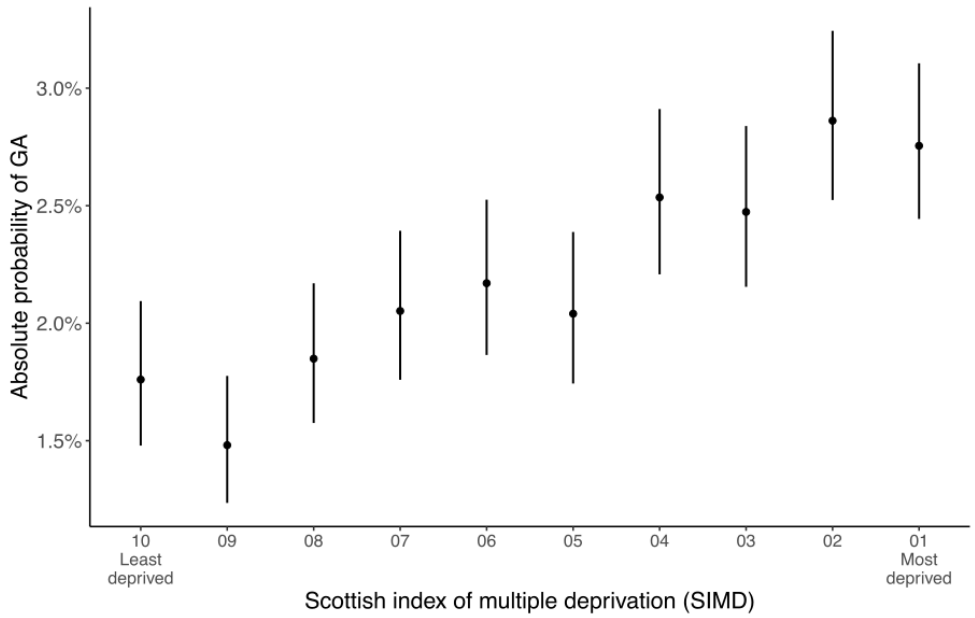


Figure 7-29 Absolute probability of GA for elective caesarean birth by SIMD decile in women who gave birth to an infant at term

7.3.9 General anaesthesia for elective caesarean birth and SIMD, adjusted for date of delivery

The results of analysis of relative risk of GA for elective caesarean birth by SIMD decile, adjusted for date of delivery as a categorical variable, according to the years of the SIMD updates, are almost identical to those of the primary analysis (Table 7-16). The only difference is for women residing in SIMD 5 (RR 1.10 [0.88, 1.36] in the primary analysis, and RR 1.09 [0.88, 1.35] in the categorical date adjusted analysis. The differences in GA utilisation in the SIMD categories do not reach significance (Table 7-16). The results of the primary analysis are identical to those of the continuous date adjusted analysis (Table 7-17).

Characteristic	RR	95% CI[1]	p-value
SIMD update			
2009-2011	-	-	-
2012-2015	0.94	0.84, 1.05	0.3
2016 -2019	0.91	0.81, 1.01	0.089
2020	0.83	0.68, 1.01	0.062
SIMD decile			
10	-	-	-
09	0.83	0.66, 1.05	0.12
08	1.01	0.82, 1.26	0.9
07	1.13	0.92, 1.40	0.3
06	1.23	0.99, 1.52	0.057
05	1.09	0.88, 1.36	0.4
04	1.35	1.10, 1.66	0.005
03	1.43	1.17, 1.75	<0.001
02	1.52	1.25, 1.86	<0.001
01	1.62	1.34, 1.96	<0.001

[1]CI = Confidence Interval

Table 7-16 SIMD decile and relative risk of GA for elective caesarean birth, adjusted for date of delivery as a categorical variable.

Characteristic	RR	95% CI[1]	p-value
Date of delivery	1.00	1.00, 1.00	0.078
SIMD decile			
10	-	-	-
09	0.83	0.66, 1.05	0.12
08	1.01	0.82, 1.26	>0.9
07	1.13	0.92, 1.40	0.3
06	1.23	0.99, 1.52	0.057
05	1.09	0.88, 1.36	0.4
04	1.35	1.10, 1.66	0.004
03	1.43	1.17, 1.75	<0.001
02	1.52	1.25, 1.85	<0.001
01	1.62	1.34, 1.96	<0.001

[1]CI = Confidence Interval

Table 7-17 SIMD decile and relative risk of GA for elective caesarean birth, adjusted for date of delivery as a continuous variable.

7.3.10 General anaesthesia for elective caesarean birth and SIMD, women with relative contraindications to neuraxial analgesia excluded

Elective caesarean birth was performed in 2,232 women who had a relative contraindication to neuraxial anaesthesia. When these women were excluded from the analysis, the absolute probability of GA was reduced in most SIMD deciles (Table 7-18). However, the socio-economic gradient persisted with women in the most deprived SIMD decile (SIMD 1) 65% more likely to have a GA for an elective caesarean birth as compared to women in the most advantage decile (SIMD 10 (RR 1.67 [1.34, 2.02]) (Table 7-19). The mean change per unit decile was + 5.7% [3.3%, 8.1%] (Figure 7-30).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.018	0.002	0.015	0.021
09	0.015	0.001	0.013	0.018
08	0.020	0.002	0.017	0.023
07	0.021	0.002	0.018	0.025
06	0.024	0.002	0.021	0.028
05	0.021	0.002	0.018	0.025
04	0.024	0.002	0.021	0.028
03	0.026	0.002	0.023	0.030
02	0.029	0.002	0.025	0.032
01	0.030	0.002	0.027	0.033

Table 7-18 Absolute probability of GA for elective caesarean birth by SIMD decile in women with no relative contraindication to neuraxial anaesthesia

	RR	95% CI[1]	p-value
Age at delivery	0.98	0.97, 0.99	<0.001
Maternal BMI	1.02	1.01, 1.03	<0.001
Ethnic group			
White	—	—	
Asian	1.38	1.12, 1.71	0.003
Black	1.29	0.94, 1.78	0.12
Mixed	1.29	0.72, 2.32	0.4
Other	1.67	1.11, 2.51	0.014
SIMD decile			
10	—	—	
09	0.84	0.66, 1.08	0.2
08	1.11	0.88, 1.40	0.4
07	1.18	0.94, 1.48	0.2
06	1.35	1.08, 1.68	0.009
05	1.17	0.93, 1.48	0.2
04	1.34	1.07, 1.67	0.009
03	1.44	1.16, 1.79	<0.001
02	1.58	1.28, 1.95	<0.001
01	1.65	1.34, 2.02	<0.001
Booking smoking history			
Never smoked, non-smoker	—	—	
Current smoker	1.51	1.34, 1.70	<0.001
Former smoker	1.22	1.06, 1.40	0.005
Injected illicit drugs			
No	—	—	
Yes	1.61	1.29, 2.01	<0.001
Bateman comorbidities			
0	—	—	
1	1.49	1.33, 1.66	<0.001
2+	2.02	1.63, 2.49	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	—	—	
Yes	1.03	0.93, 1.14	0.5
Previous therapeutic abortions			
No	—	—	
Yes	1.06	0.90, 1.24	0.5
Previous caesarean births			
No	—	—	
Yes	0.91	0.83, 1.00	0.040
Parity	1.06	1.01, 1.11	0.018
Estimated gestation	0.83	0.82, 0.85	<0.001
Induction of labour			
No	—	—	
Yes	1.00	0.62, 1.60	>0.9
Multiple birth			
No	—	—	
Yes	0.65	0.50, 0.86	0.002

[1]CI = Confidence Interval

Table 7-19 Relative risk of GA for elective caesarean birth in women who have no relative contraindication to neuraxial anaesthesia

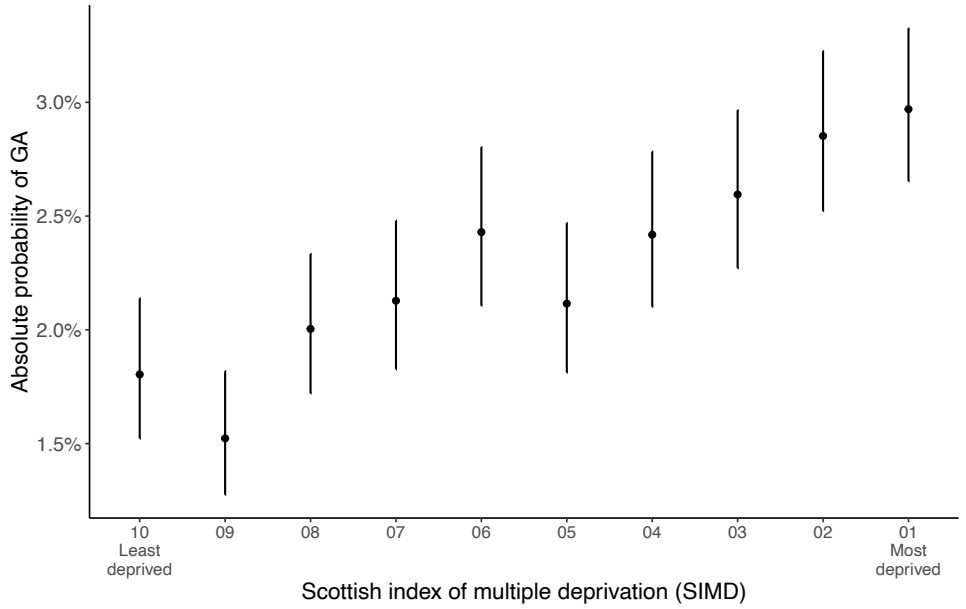


Figure 7-30 Absolute probability of GA for elective caesarean birth by SIMD decile in women with no relative contraindication to neuraxial anaesthesia

7.3.11 Interaction between general anaesthesia for elective caesarean birth, SIMD and white/non-white ethnicity

In the elective caesarean birth group, women of non-white ethnicity had a higher rate of GA for caesarean birth in almost all SIMD deciles except SIMD 3, although confidence intervals overlapped for 7 of the 10 deciles (Table 7-20, Figure 7-31). Non-white women living in the least disadvantaged areas (SIMD 10) were more than twice as likely to undergo a GA for elective caesarean birth compared to their white counterparts (AR 0.037 [0.24, 0.056] vs 0.018 [0.015, 0.021] for white and non-white women in SIMD 10 respectively). This is higher than white or non-white women in the least advantaged decile (SIMD 1), where non-white women were as likely as white women to undergo a GA for elective caesarean birth (AR 0.032 [0.006, 0.022] vs 0.032 [0.028, 0.036] for white and Non-white women in SIMD 1 respectively) (Table 7-20). A socio-economic gradient was detected in the white but not the non-white strata (inter-decile mean change 6.5% [4.1%, 9.0%] and -1.6% [-7.3%, +4.5%] for white and non-white respectively) (Figure 7-31).

	White				Not white			
SIMD	Absolute probability	SE	Lower 95% CI	Upper 95% CI	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.018	0.002	0.015	0.021	0.037	0.008	0.024	0.056
09	0.016	0.001	0.014	0.019	0.018	0.006	0.009	0.035
08	0.019	0.002	0.016	0.022	0.029	0.008	0.017	0.049
07	0.022	0.002	0.019	0.025	0.033	0.009	0.020	0.056
06	0.022	0.002	0.019	0.026	0.046	0.010	0.031	0.069
05	0.021	0.002	0.018	0.024	0.029	0.008	0.017	0.048
04	0.025	0.002	0.022	0.029	0.047	0.009	0.032	0.069
03	0.028	0.002	0.025	0.032	0.023	0.007	0.013	0.042
02	0.029	0.002	0.026	0.033	0.036	0.008	0.023	0.056
01	0.032	0.002	0.028	0.036	0.032	0.006	0.022	0.046

Table 7-20 Absolute probability of GA for elective caesarean birth by SIMD decile, risk stratified by white or non-white ethnicity

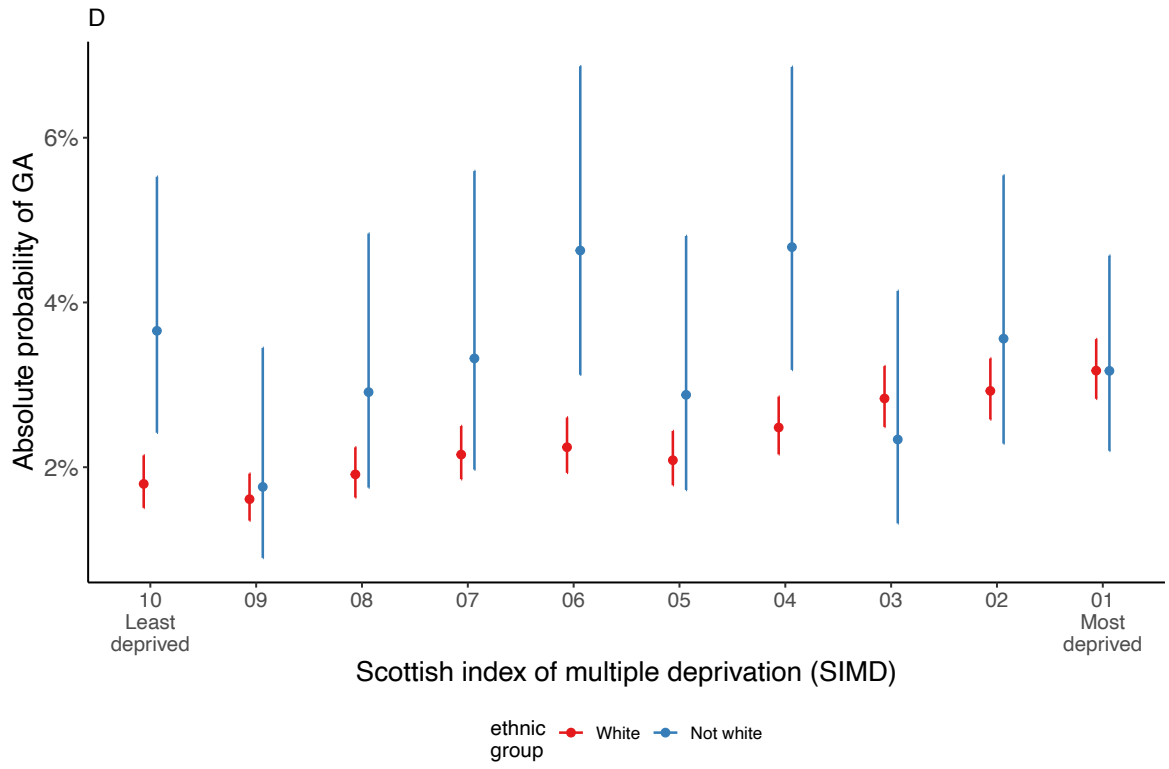


Figure 7-31 Absolute probability of GA for elective caesarean birth by SIMD decile, risk stratified by white or non-white ethnicity (red represents the women of white ethnicity and blue represents the women of non-white ethnicity)

7.3.12 Primary analysis: General anaesthesia for emergency caesarean birth and SIMD

Emergency caesarean birth was performed in 96,875 women. Women who lived in the most deprived areas (SIMD1) were significantly more likely to receive a GA for emergency caesarean birth compared to those who lived in the highest SIMD decile (RR 1.50, 95% CI [1.37 1.64]). The likelihood of GA increased with degree of socio-economic disadvantage with an inter-decile mean change per unit SIMD of + 4.6% [3.5%, 5.6%] (Figure 7-32). Absolute probability of caesareans section was 11.9% in SIMD 1 compared to 8.0% in SIMD 10 (AR 0.119 [0.113, 0.125] and 0.080 [0.074, 0.086] for SIMD 1 and SIMD 10 respectively) (Table 7-21, Figure 7-32). Younger age, the presence of single or multiple comorbidities, smoking, the use of injected illicit drugs, previous spontaneous or therapeutic abortions and parity all increased likelihood of GA in emergency caesarean birth were associated with an increased probability of GA. Previous caesarean birth and induction of labour reduced likelihood of GA (Table 7-22).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.080	0.003	0.074	0.086
09	0.085	0.003	0.079	0.091
08	0.078	0.003	0.073	0.084
07	0.083	0.003	0.078	0.089
06	0.094	0.003	0.088	0.100
05	0.096	0.003	0.090	0.102
04	0.097	0.003	0.092	0.103
03	0.109	0.003	0.103	0.115
02	0.116	0.003	0.110	0.121
01	0.119	0.003	0.113	0.125

Table 7-21 Absolute probability of GA for emergency caesarean birth by SIMD decile

	RR	95% CI[1]	p-value
Age at delivery	0.98	0.98, 0.98	<0.001
Maternal BMI	1.0	0.99, 1.00	0.002
Ethnic group			
White	-	-	-
Asian	0.94	0.85, 1.04	0.2
Black	0.94	0.80, 1.10	0.4
Mixed	1.00	0.71, 1.39	>0.9
Other	0.86	0.68, 1.09	0.2
SIMD decile			
10	-	-	-
09	1.06	0.96, 1.18	0.2
08	0.99	0.89, 1.09	0.8
07	1.05	0.94, 1.16	0.4
06	1.18	1.07, 1.31	0.001
05	1.21	1.09, 1.33	<0.001
04	1.22	1.11, 1.35	<0.001
03	1.37	1.24, 1.50	<0.001
02	1.45	1.32, 1.59	<0.001
01	1.50	1.37, 1.64	<0.001
Booking smoking history			
Never smoked, non-smoker	-	-	-
Current smoker	1.78	1.70, 1.86	<0.001
Former smoker	1.15	1.09, 1.22	<0.001
Injected illicit drugs			
No	-	-	-
Yes	1.48	1.22, 1.79	<0.001
Bateman comorbidities			
0	-	-	-
1	1.21	1.15, 1.27	<0.001
2+	1.74	1.60, 1.90	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	-	-	-
Yes	1.11	1.06, 1.16	<0.001
Previous therapeutic abortions	-	-	-
No			
Yes	1.19	1.12, 1.27	<0.001
Previous caesarean births			
No	-	-	-
Yes	0.94	0.89, 1.0	0.032
Parity	1.21	1.20, 1.23	<0.001
Induction of labour			
No	-	-	-
Yes	0.68	0.66, 0.71	<0.001
Multiple birth			
No	-	-	-
Yes	1.10	0.99, 1.23	0.076

[1]CI = Confidence Interval

Table 7-22 Relative risk of GA for emergency caesarean birth

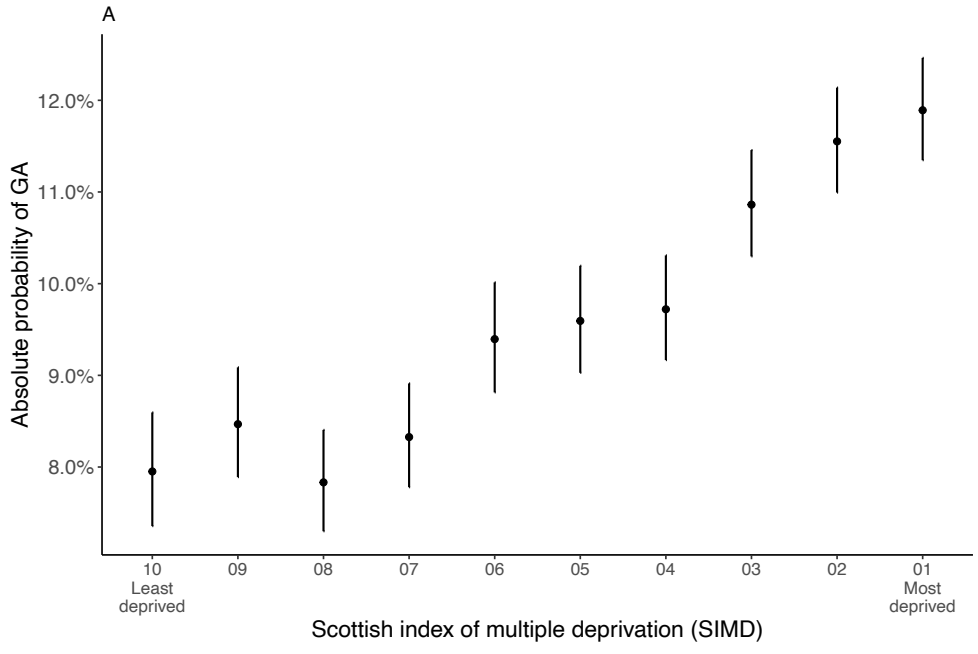


Figure 7-32 Absolute probability of GA for emergency caesarean birth by SIMD decile

7.3.13 General anaesthesia for emergency caesarean birth and SIMD: unimputed analysis

The results for the unimputed emergency cohort are almost identical to those of the imputed cohort. Lower SIMD, younger age, the presence of single or multiple comorbidities, smoking, the use of injected illicit drugs, previous spontaneous or therapeutic abortions and parity were associated with increased probability of GA for emergency caesarean birth. Previous caesarean birth and induction of labour were both associated with decreased probability of GA. In the unimputed cohort Asian ethnicity was also associated with a decrease in GA utilisation in emergency caesarean birth. This did not reach significance in the imputed cohort, and is in contrast to the elective cohort, where Asian ethnicity was associated with an increase in GA utilisation (RR 0.88 [0.78, 0.98]) (Table 7-23).

	RR	95% CI[1]	p-value
Age at delivery	0.98	0.98, 0.98	<0.001
Maternal BMI	1.00	0.99, 1.00	0.015
Ethnic group			
White	—	—	
Asian	0.88	0.78, 0.98	0.029
Black	0.91	0.77, 1.08	0.29
Mixed	0.99	0.70, 1.35	0.94
Other	0.79	0.60, 1.02	0.087
SIMD decile			
10	—	—	
09	1.06	0.95, 1.18	0.31
08	0.98	0.87, 1.09	0.68
07	1.03	0.92, 1.15	0.61
06	1.16	1.05, 1.30	0.005
05	1.18	1.07, 1.31	0.002
04	1.22	1.10, 1.35	<0.001
03	1.38	1.25, 1.53	<0.001
02	1.44	1.31, 1.59	<0.001
01	1.47	1.34, 1.62	<0.001

	RR	95% CI[1]	p-value
Booking smoking history			
Never smoked, non-smoker	—	—	
Current smoker	1.80	1.71, 1.89	<0.001
Former smoker	1.14	1.08, 1.22	<0.001
Injected illicit drugs			
No	—	—	
Yes	2.06	1.69, 2.48	<0.001
Bateman comorbidities	2.06	1.69, 2.48	<0.001
0	—	—	
1	1.21	1.15, 1.27	<0.001
2+	1.74	1.58, 1.92	<0.001
Previous spontaneous abortions			
No	—	—	
Yes	1.10	1.05, 1.15	<0.001
Previous therapeutic abortions			
No	—	—	
Yes	1.19	1.11, 1.27	<0.001
Previous caesarean births			
No	—	—	
Yes	0.94	0.88, 0.99	0.027
Parity	1.21	1.19, 1.23	<0.001
Induction of labour			
Yes	—	—	
No	1.46	1.40, 1.52	<0.001
Multiple birth			
No	—	—	
Yes	1.11	0.99, 1.56	0.070

Table 7-23 Relative risk of GA for emergency caesarean birth, analysis (unimputed)

7.3.14 General anaesthesia for emergency caesarean birth and SIMD: restricted to those who have not had a previous caesarean birth

Emergency caesarean birth was performed in 74,079 women who had not previously had a caesarean birth. The results of this subgroup analysis are almost identical to those of the primary analysis for emergency caesarean birth. Absolute probability of GA was 11.9% in SIMD 1 compared to 8.0% in SIMD 10 (AR 0.119 [0.114, 0.126] and 0.080 [0.074, 0.087] for SIMD 1 and SIMD 10 respectively) (Table 7-24) with an inter-decile mean change of + 4.5% [3.4%, 5.7%] (Figure 7-33). As in the overall cohort, younger age, lower BMI, the presence of single or multiple comorbidities, smoking, the use of injected illicit drugs, previous spontaneous or therapeutic abortions and parity all increased likelihood of GA (Table 7-25).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.080	0.004	0.074	0.087
09	0.085	0.003	0.079	0.092
08	0.079	0.003	0.073	0.085
07	0.085	0.003	0.079	0.092
06	0.094	0.003	0.088	0.101
05	0.095	0.003	0.089	0.102
04	0.099	0.003	0.093	0.105
03	0.110	0.003	0.103	0.116
02	0.118	0.003	0.111	0.124
01	0.119	0.003	0.114	0.126

Table 7-24 Absolute probability of GA for emergency caesarean birth by SIMD decile, analysis restricted to only include women who had not undergone a previous caesarean birth

	RR	95% CI[1]	p-value
Age at delivery	0.98	0.98, 0.98	<0.001
Maternal BMI	0.99	0.99, 1.00	0.002
Ethnic group			
White	-	-	-
Asian	0.94	0.84, 1.06	0.3
Black	0.94	0.78, 1.14	0.5
Mixed	0.96	0.67, 1.37	0.8
Other	0.86	0.66, 1.14	0.3
SIMD decile			
10	-	-	-
09	1.06	0.95, 1.19	0.3
08	0.99	0.88, 1.11	0.8
07	1.06	0.95, 1.19	0.3
06	1.17	1.05, 1.31	0.005
05	1.19	1.07, 1.32	0.002
04	1.23	1.11, 1.37	<0.001
03	1.37	1.23, 1.52	<0.001
02	1.47	1.33, 1.62	<0.001
01	1.49	1.35, 1.65	<0.001
Booking smoking history			
Never smoked, non-smoker	-	-	-
Current smoker	1.77	1.69, 1.86	<0.001
Former smoker	1.15	1.08, 1.22	<0.001
Injected illicit drugs			
No	-	-	-
Yes	1.44	1.18, 1.75	0.001
Bateman comorbidities			
0	-	-	-
1	1.20	1.14, 1.27	<0.001
2+	1.79	1.62, 1.98	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	-	-	-
Yes	1.11	1.06, 1.16	<0.001
Previous therapeutic abortions			
No	-	-	-
Yes	1.17	1.09, 1.26	<0.001
Parity	1.26	1.25, 1.28	<0.001
Induction of labour			
No	-	-	-
Yes	0.66	0.63, 0,69	<0.001
Multiple birth			
No	-	-	-
Yes	1.11	0.99, 1.24	0.083

[1]CI = Confidence Interval

Table 7-25 Relative risk of GA for emergency caesarean birth, analysis restricted to only include women who had not undergone a previous caesarean birth

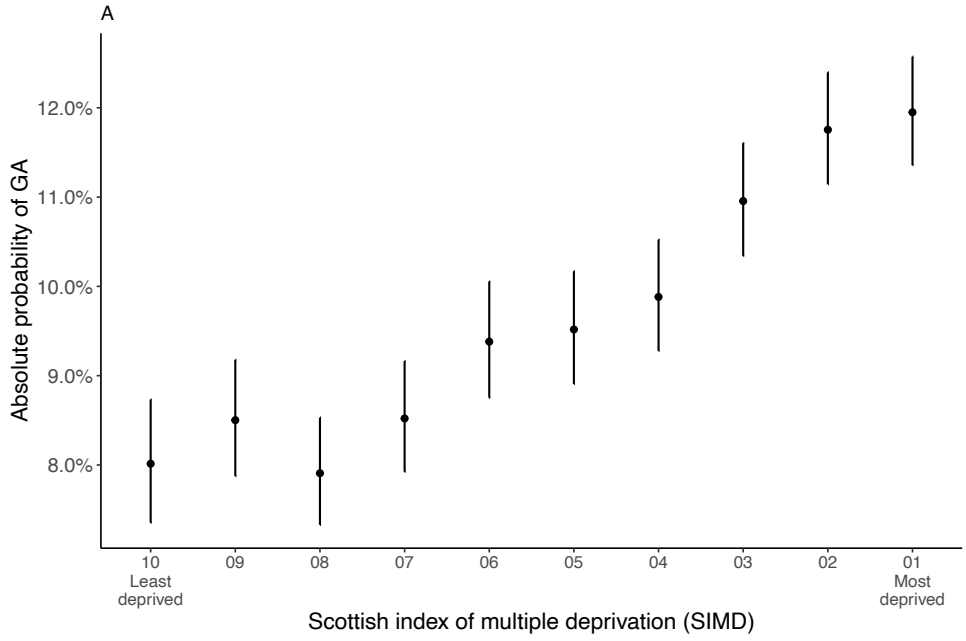


Figure 7-33 Absolute probability of GA for emergency caesarean birth by SIMD decile, analysis restricted to only include women who had not undergone a previous caesarean birth

7.3.15 General anaesthesia for emergency caesarean birth and SIMD, restricted to women who delivered an infant at term

Emergency caesarean birth was performed in 71,219 women who gave birth to an infant at term (37+0 to 41+6 weeks gestation). Absolute probability of GA was reduced in this group compared to the primary emergency caesarean birth analysis, although the relative increase per deprivation decile was slightly increased. For women living in the most deprived areas (SIMD 1), absolute probability of GA was 10.5% compared to 6.9% of those residing in the least deprived areas (SIMD 10) (AR 0.105 [0.099, 0.111] and 0.069 [0.063, 0.076] for SIMD 1 and SIMD 10 respectively) (Table 7-26). This is a relative increase of 53% (SIMD 1 as compared to SIMD 10, RR 1.53 [1.37, 1.71]) (Table 7-27) with an inter-decile mean change of +4.8% [3.6%, 6.1%] (Figure 7-34).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.069	0.003	0.063	0.076
09	0.076	0.003	0.070	0.082
08	0.068	0.003	0.063	0.074
07	0.073	0.003	0.067	0.079
06	0.082	0.003	0.076	0.088
05	0.084	0.003	0.078	0.091
04	0.084	0.003	0.078	0.090
03	0.094	0.003	0.088	0.100
02	0.101	0.003	0.095	0.107
01	0.105	0.003	0.099	0.111

Table 7-26 Absolute probability of GA for emergency caesarean birth by SIMD decile, analysis restricted to women who delivered an infant at term

	RR	95% CI[1]	p-value
Age at delivery	0.98	0.97, 0.98	<0.001
Maternal BMI	1.00	0.99, 1.00	0.021
Ethnic group			
White	-	-	-
Asian	0.91	0.79, 1.05	0.2
Black	0.90	0.74, 1.09	0.3
Mixed	0.97	0.65, 1.45	0.9
Other	0.85	0.63, 1.14	0.3
SIMD decile			
10	-	-	-
09	1.10	0.97, 1.25	0.12
08	0.99	0.87, 1.12	0.9
07	1.06	0.94, 1.20	0.4
06	1.19	1.05, 1.34	0.006
05	1.23	1.09, 1.38	<0.001
04	1.23	1.09, 1.38	<0.001
03	1.36	1.22, 1.53	<0.001
02	1.47	1.32, 1.64	<0.001
01	1.53	1.37, 1.71	<0.001
Booking smoking history			
Never smoked, non-smoker	-	-	-
Current smoker	1.75	1.66, 1.85	<0.001
Former smoker	1.20	1.12, 1.28	<0.001
Injected illicit drugs			
No	-	-	-
Yes	1.42	1.11, 1.81	0.009
Bateman comorbidities			
0	-	-	-
1	1.15	1.09, 1.22	<0.001
2+	1.69	1.49, 1.92	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	-	-	-
Yes	1.07	1.01, 1.13	0.015
Previous therapeutic abortions			
No	-	-	-
Yes	1.17	1.08, 1.27	<0.001
Previous caesarean births			
No	-	-	-
Yes	0.85	0.79, 0.91	<0.001
Parity	1.20	1.18, 1.22	<0.001
Induction of labour			
No	-	-	-
Yes	0.83	0.78, 0.87	<0.001
Multiple birth			
No	-	-	-
Yes	0.72	0.54, 0.97	0.029

[1]CI = Confidence Interval

Table 7-27 Relative risk of GA for emergency caesarean birth, analysis restricted to only include women who delivered an infant at term

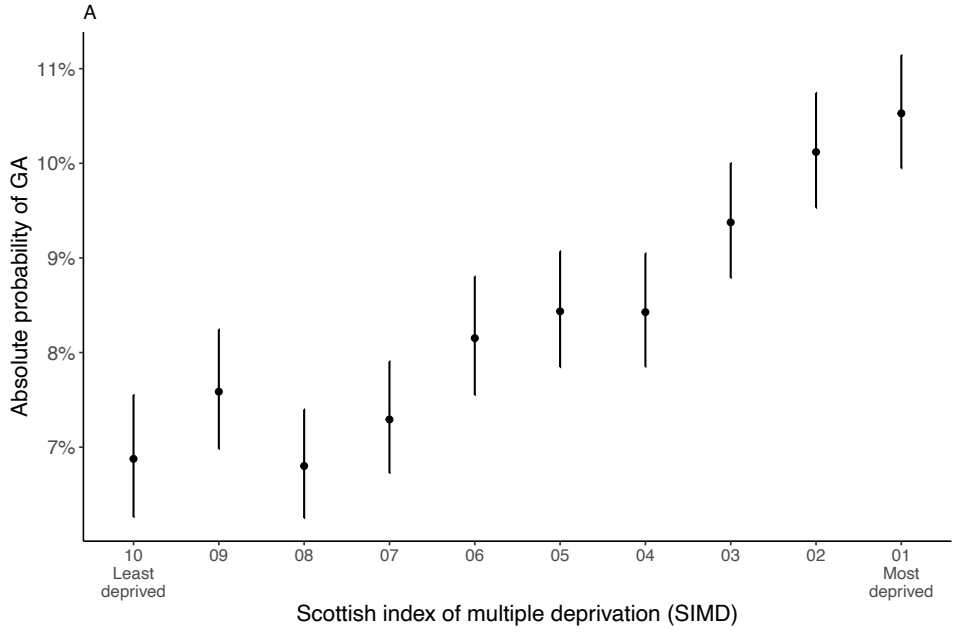


Figure 7-34 Absolute probability of GA for emergency caesarean birth by SIMD decile, analysis restricted to only include women who delivered an infant at term

7.3.16 General anaesthesia for emergency caesarean birth and SIMD, adjusted for date of delivery

The results of analysis of relative risk of GA for emergency caesarean birth by SIMD decile, adjusted for date of delivery as a categorical variable, according to the years of the SIMD updates, are almost identical to those of the primary analysis (Table 7-28). General anaesthesia utilisation increased between the dates 2016-2019 (RR 1.07, [1.02,1.12]) as compared to 2009-2012, however in 2020 the GA rates dropped (RR 0.77 [0.70, 0.85])(Table 7-28). This may be related to the COVID-19 pandemic which began in March 2020, where utilisation of GA was discouraged.[252] The results of the primary analysis are identical to those of the continuous date adjusted analysis (Table 7-29).

Characteristic	RR	95% CI[1]	p-value
SIMD update			
2009-2011	-	-	-
2012-2015	1.04	0.99, 1.09	0.2
2016 -2019	1.07	1.02, 1.12	0.011
2020	0.77	0.70, 0.85	<0.001
SIMD decile			
10	-	-	-
09	1.06	0.96, 1.18	0.3
08	0.98	0.89, 1.09	0.8
07	1.05	0.94, 1.16	0.4
06	1.18	1.07, 1.31	0.001
05	1.20	1.09, 1.33	<0.001
04	1.22	1.11, 1.35	<0.001
03	1.36	1.24, 1.50	<0.001
02	1.45	1.32, 1.59	<0.001
01	1.49	1.36, 1.64	<0.001

[1]CI = Confidence Interval

Table 7-28 SIMD decile and relative risk of GA for emergency caesarean birth, adjusted for date of delivery as a categorical variable

Characteristic	RR	95% CI[1]	p-value
Date of delivery	1.00	1.00, 1.00	0.2
SIMD decile			
10	-	-	-
09	1.07	0.96, 1.18	0.2
08	0.99	0.89, 1.09	0.8
07	1.05	0.94, 1.16	0.4
06	1.18	1.07, 1.31	0.001
05	1.21	1.09, 1.33	<0.001
04	1.22	1.11, 1.35	<0.001
03	1.37	1.24, 1.50	<0.001
02	1.45	1.32, 1.59	<0.001
01	1.49	1.36, 1.64	<0.001

[1]CI = Confidence Interval

Table 7-29 SIMD decile and relative risk of GA for emergency caesarean birth, adjusted for date of delivery as a continuous variable

7.3.17 General anaesthesia for emergency caesarean birth and SIMD, women with relative contraindications to neuraxial analgesia excluded

Emergency caesarean birth was performed in 6,928 women who had a relative contraindication to neuraxial analgesia. When these women were excluded from the analysis, the absolute probability of GA is reduced in all deciles as compared to the primary analysis (Table 7-30). However, the socio-economic gradient persisted with women in the most deprived SIMD decile (SIMD 1) 47 % more likely to have a GA for an elective caesarean birth as compared to women in the most advantage decile (SIMD 10) (RR1.47 [1.33, 1.62]), (Table 7-31). The mean change per unit decile was + 4.4% [3.2%, 5.5%] (Figure 7-35).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.078	0.003	0.072	0.085
09	0.083	0.003	0.077	0.089
08	0.076	0.003	0.070	0.082
07	0.080	0.003	0.075	0.086
06	0.091	0.003	0.085	0.098
05	0.093	0.003	0.087	0.099
04	0.096	0.003	0.090	0.102
03	0.109	0.003	0.103	0.115
02	0.114	0.003	0.108	0.120
01	0.115	0.003	0.110	0.121

Table 7-30 Absolute probability of GA for emergency caesarean birth by SIMD decile in women with no relative contraindication to neuraxial anaesthesia

	RR	95% CI[1]	p-value
Age at delivery	0.98	0.98, 0.98	<0.001
Maternal BMI	1.0	0.99, 1.00	0.004
Ethnic group			
White	—	—	
Asian	0.88	0.78, 0.99	0.031
Black	0.84	0.71, 1.00	0.056
Mixed	1.02	0.76, 1.36	>0.9
Other	0.83	0.64, 1.07	0.14
SIMD decile			
10	—	—	
09	1.05	0.94, 1.18	0.4
08	0.97	0.87, 1.08	0.6
07	1.02	0.92, 1.14	0.7
06	1.16	1.04, 1.29	0.006
05	1.19	1.07, 1.32	0.002
04	1.22	1.10, 1.36	<0.001
03	1.39	1.26, 1.53	<0.001
02	1.45	1.31, 1.60	<0.001
01	1.47	1.33, 1.62	<0.001
Booking smoking history			
Never smoked, non-smoker	—	—	
Current smoker	1.81	1.73, 1.90	<0.001
Former smoker	1.15	1.08, 1.22	<0.001
Injected illicit drugs			
No	—	—	
Yes	1.44	1.28, 1.62	<0.001
Bateman comorbidities			
0	—	—	
1	1.22	1.16, 1.28	<0.001
2+	1.71	1.56, 1.88	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	—	—	
Yes	1.11	1.06, 1.16	<0.001
Previous therapeutic abortions			
No	—	—	
Yes	1.19	1.11, 1.27	<0.001
Previous caesarean births			
No	—	—	
Yes	0.92	0.87, 0.97	0.004
Parity	1.21	1.20, 1.23	<0.001
Estimated gestation	0.90	0.90, 0.91	<0.001
Induction of labour			
No	—	—	
Yes	0.70	0.67, 0.74	<0.001
Multiple birth			
No	—	—	
Yes	1.06	0.95, 1.19	0.3

[1]CI = Confidence Interval

Table 7-31 Relative risk of GA for emergency caesarean birth in women who have no relative contraindication to neuraxial anaesthesia

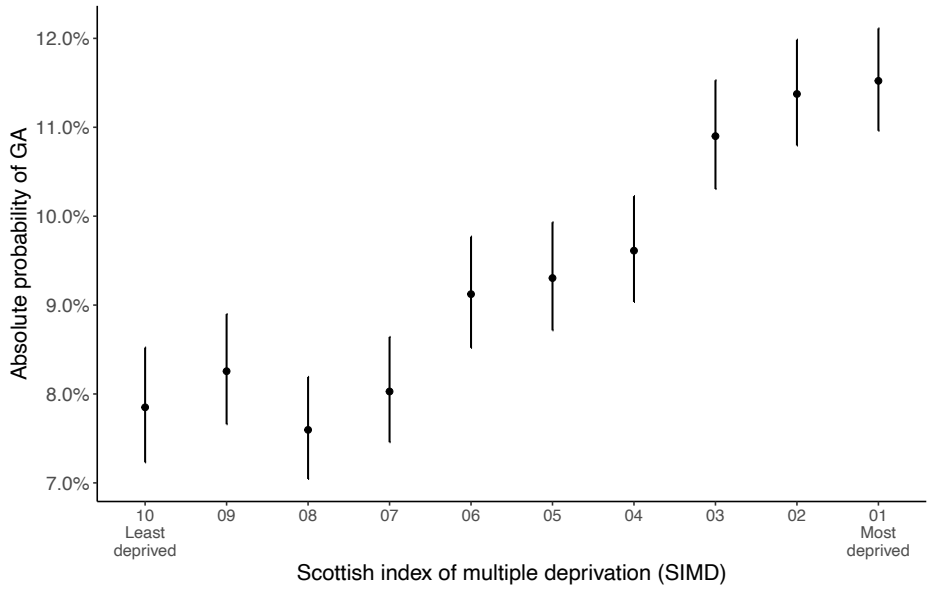


Figure 7-35 Absolute probability of GA for emergency caesarean birth by SIMD decile in women with no relative contraindication to neuraxial anaesthesia

7.3.18 Interaction between general anaesthesia for emergency caesarean birth, SIMD and white/non-white ethnicity

Non-white women living in the least disadvantaged areas (SIMD 10) were more likely to undergo a GA for emergency caesarean birth compared to their white counterparts (AR 0.079 [0.072, 0.086] vs 0.086 [0.067, 0.110] for white and non-white women in SIMD 10 respectively). However, the opposite was true for non-white women in the most disadvantaged areas (SIMD 1) who were less likely to undergo a GA for emergency caesarean birth than their white counterparts (AR 0.121 [0.115, 0.128] vs 0.099 [0.010, 0.082] for white and non-white women in SIMD 1 respectively) (Table 7-32). A socio-economic gradient was detected in the white but not the non-white strata (inter-decile mean change + 4.9% [3.8%, 6.0%] and +1.6% [-1.7%, +5.1%] for white and non-white respectively) (Figure 7-36).

	White				Not white			
SIMD	Absolute probability	SE	Lower 95% CI	Upper 95% CI	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.079	0.003	0.072	0.086	0.086	0.011	0.067	0.110
09	0.084	0.003	0.077	0.090	0.095	0.012	0.074	0.123
08	0.079	0.003	0.073	0.085	0.071	0.010	0.053	0.094
07	0.084	0.003	0.078	0.091	0.071	0.012	0.051	0.099
06	0.093	0.003	0.087	0.100	0.105	0.014	0.080	0.137
05	0.097	0.003	0.090	0.103	0.089	0.012	0.069	0.116
04	0.097	0.003	0.091	0.104	0.095	0.011	0.076	0.119
03	0.110	0.003	0.103	0.117	0.096	0.011	0.077	0.120
02	0.117	0.003	0.111	0.124	0.097	0.011	0.077	0.120
01	0.121	0.003	0.115	0.128	0.099	0.010	0.082	0.120

Table 7-32 Absolute probability of GA for emergency caesarean birth by SIMD decile, risk stratified by white or non-white ethnicity

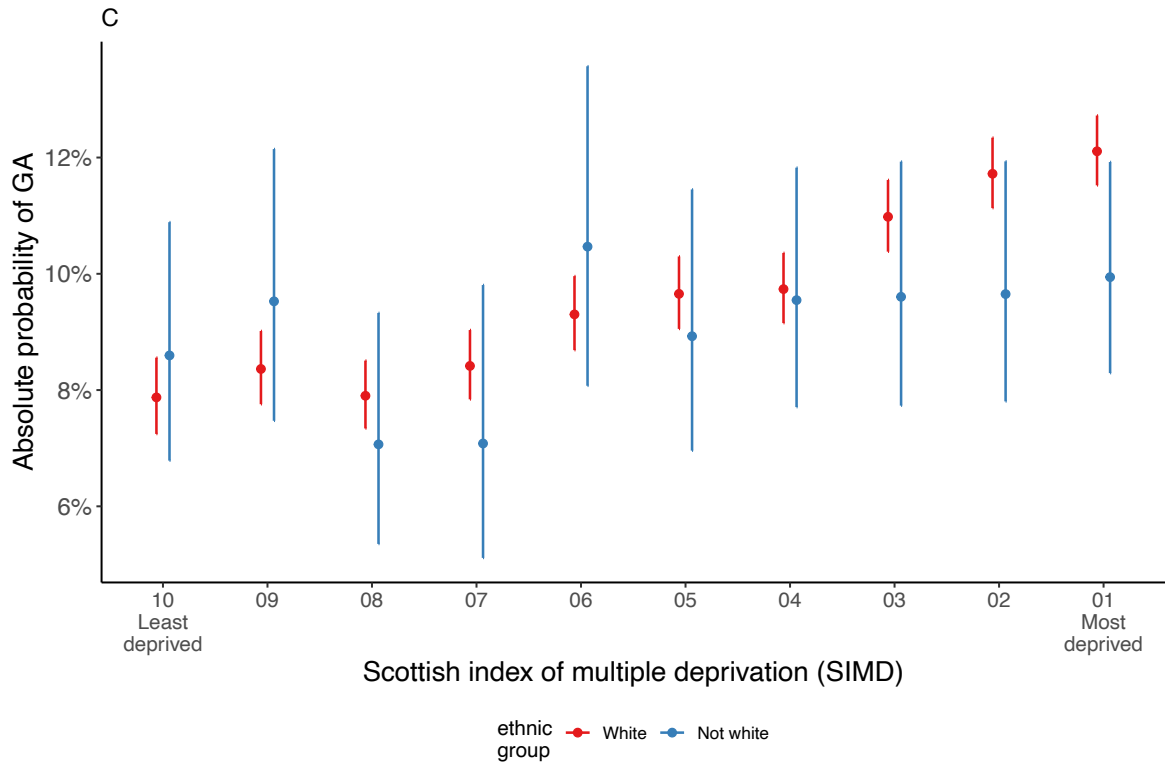


Figure 7-36 Absolute probability of GA for emergency caesarean birth by SIMD decile, risk stratified by white or non-white ethnicity. The red represents women of white ethnicity, and blue represents women of non-white ethnicity

7.3.19 General anaesthesia for category 1 caesarean birth and SIMD

For 23,201 parturients, the Lucas category of caesarean birth was recorded, and of these,15,029 women underwent category 1 caesarean birth. Women from the lowest SIMD category were 66% more likely to receive a GA for caesarean birth compared to women in the highest (RR 1.66, 95% CI [1.26, 2.17]) (Table 7-34), this represents an absolute difference of 3.6% (SIMD1 AR 0.107 [0.097, 0.117] vs SIMD 10 AR 0.071 [0.056, 0.089]) (Table 7-33). The socio-economic gradient was more pronounced than in the primary analysis, with an inter-decile mean change of + 5.8% [2.6%, 9.0%] per unit increase in SIMD decile (Figure 7-37).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.071	0.008	0.056	0.089
09	0.077	0.007	0.065	0.092
08	0.066	0.006	0.055	0.078
07	0.082	0.006	0.072	0.094
06	0.079	0.006	0.069	0.091
05	0.083	0.006	0.073	0.095
04	0.081	0.006	0.071	0.093
03	0.086	0.006	0.075	0.099
02	0.097	0.006	0.085	0.109
01	0.107	0.005	0.097	0.117

Table 7-33 Absolute probability of GA for emergency caesarean birth by SIMD decile for women undergoing a category 1 caesarean birth

	RR	95% CI[1]	p-value
Age at delivery	0.99	0.98, 0.99	<0.001
Maternal BMI	1.00	1.00, 1.01	0.3
Ethnic group			
White	-	-	-
Asian	1.14	0.91, 1.42	0.3
Black	0.87	0.55, 1.36	0.5
Mixed	0.81	0.34, 1.92	0.6
Other	0.86	0.49, 1.52	0.6
SIMD decile			
10	-	-	-
09	1.19	0.87, 1.63	0.3
08	0.94	0.69, 1.29	0.7
07	1.27	0.95, 1.70	0.10
06	1.23	0.92, 1.65	0.2
05	1.22	0.91, 1.63	0.2
04	1.21	0.90, 1.61	0.2
03	1.21	0.90, 1.62	0.2
02	1.38	1.03, 1.83	0.030
01	1.66	1.26, 2.17	<0.001
Booking smoking history			
Never smoked, non-smoker	-	-	-
Current smoker	1.54	1.37, 1.72	<0.001
Former smoker	1.00	0.86, 1.16	>0.9
Injected illicit drugs			
No	-	-	-
Yes	1.58	1.23, 2.04	<0.001
Bateman comorbidities			
0	-	-	-
1	1.01	0.89, 1.15	0.8
2+	1.57	1.24, 1.97	<0.001
Previous spontaneous abortions			

	RR	95% CI[1]	p-value
No	-	-	-
Yes	1.06	0.95, 1.19	0.3
Previous therapeutic abortions			
No	-	-	-
Yes	0.87	0.72, 1.06	0.2
Previous caesarean births			
No	-	-	-
Yes	1.05	0.91, 1.21	0.5
Parity	1.24	1.20, 1.28	<0.001
Induction of labour			
No	-	-	-
Yes	0.70	0.64, 0.78	<0.001
Multiple birth			
No	-	-	-
Yes	0.95	0.71, 1.28	0.7

[1]CI = Confidence Interval

Table 7-34 Relative risk of GA for category 1 caesarean birth

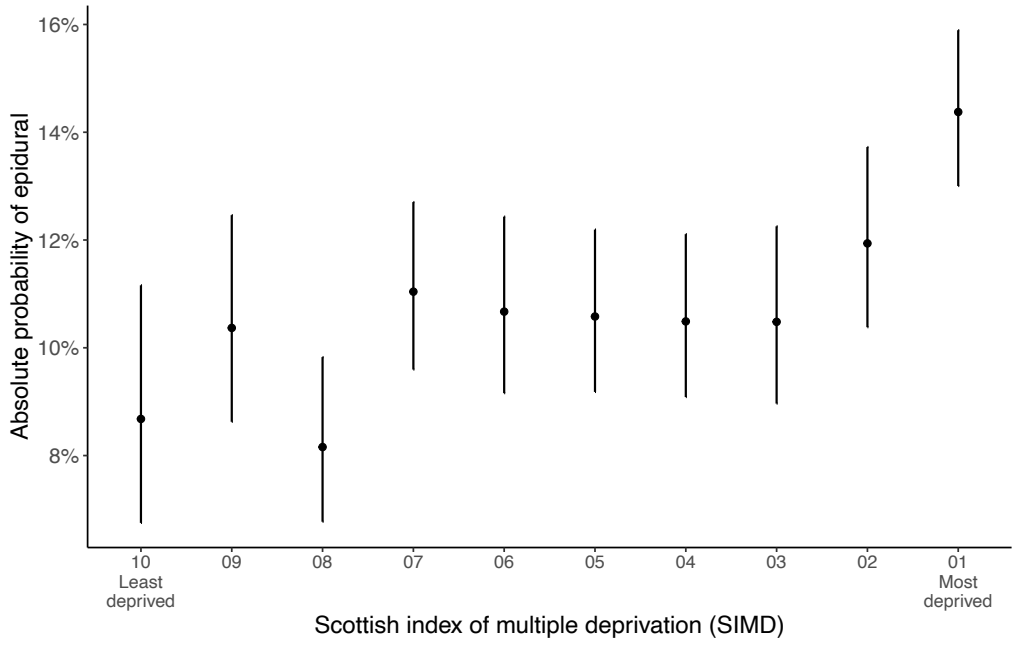


Figure 7-37 Absolute probability of GA for emergency caesarean birth by SIMD decile for women undergoing a category 1 caesarean birth

7.3.20 General anaesthesia for emergency caesarean birth and SIMD in women who had an irreversible cause of fetal distress

Emergency caesarean birth was performed in 2,389 women who had an 'irreversible' cause of fetal distress listed as an indication for delivery (placental abruption; uterine rupture; umbilical cord prolapse; fetal haemorrhage). Absolute risk of GA varied between 45.0% [95% CI, 39.3%, 51.5%] and 55.4% [50.6%, 60.8%] (Table 7-35). Relative risk of GA for caesarean birth as compared to SIMD 10 was lowest in SIMD 4 (RR 0.97 [0.78, 1.20]) and highest in SIMD 1 (RR 1.19 [0.98, 1.45]) (Table 7-36). For all SIMD deciles, 95% confidence intervals overlapped with an inter-decile mean change with increasing deprivation of 2.0% [-0.2, 4.2%] (Figure 7-38).

SIMD decile	Absolute probability	SE	Lower 95% CI	Upper 95% CI
10	0.465	0.041	0.392	0.552
09	0.528	0.039	0.456	0.611
08	0.495	0.035	0.431	0.568
07	0.466	0.035	0.401	0.540
06	0.521	0.034	0.459	0.592
05	0.481	0.032	0.422	0.549
04	0.450	0.031	0.393	0.515
03	0.476	0.027	0.425	0.533
02	0.550	0.027	0.499	0.605
01	0.554	0.026	0.506	0.608

Table 7-35 Absolute probability of GA for emergency caesarean birth by SIMD decile for women undergoing an emergency caesarean birth with an irreversible cause of fetal distress

	RR	95% CI[1]	p-value
SIMD decile			
10	-	-	-
09	1.13	0.91, 1.42	0.3
08	1.06	0.85, 1.33	0.6
07	1.00	0.80, 1.26	>0.9
06	1.12	0.91, 1.39	0.3
05	1.03	0.83, 1.28	0.8
04	0.97	0.78, 1.20	0.8
03	1.02	0.83, 1.26	0.8
02	1.18	0.97, 1.44	0.10
01	1.19	0.98, 1.45	0.077

[1]CI = Confidence Interval

Table 7-36 Relative risk of GA for emergency caesarean birth by SIMD decile for women undergoing an emergency caesarean birth with an irreversible cause of fetal distress. SIMD 10 (least deprived) is the reference category

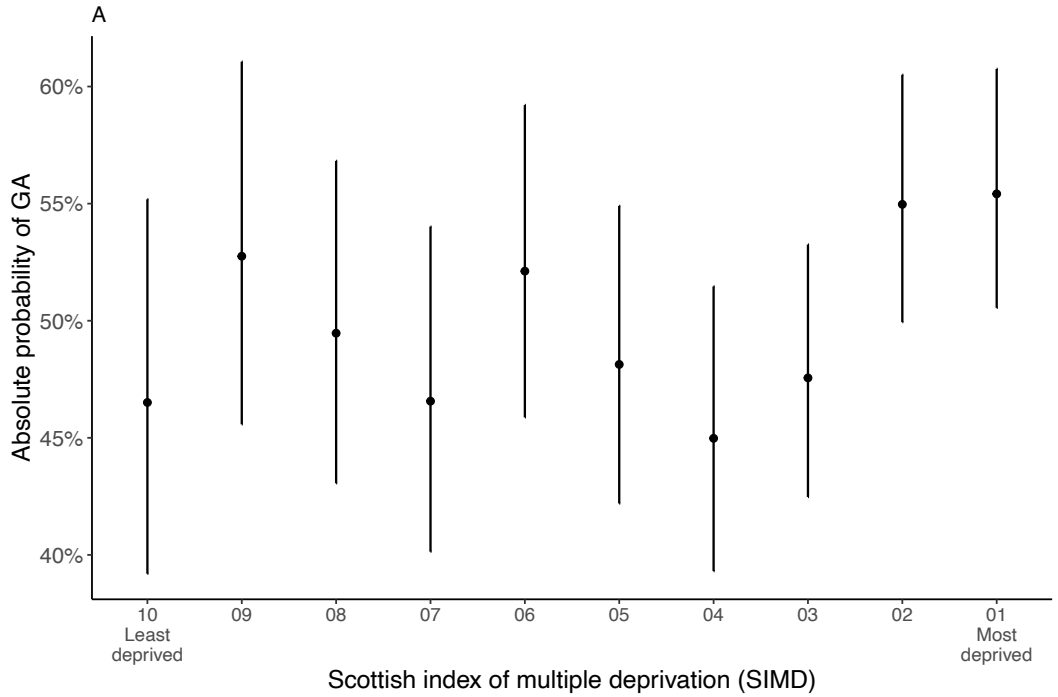


Figure 7-38 Absolute probability of GA for emergency caesarean birth by SIMD decile for women undergoing an emergency caesarean birth with an irreversible cause of fetal distress

7.4 Discussion

In this Scottish population level study of 179,562 women delivering by caesarean birth, we have demonstrated that the use of GA for both elective and emergency caesarean birth increases with increasing socio-economic disadvantage. As compared to women who live in area of the least socio-economic disadvantage (SIMD 10), women who live in areas of the greatest social disadvantage (SIMD 1) were 62% and 50% more likely to have a GA for elective and emergency caesarean birth respectively. These socio-economic gradients persisted when the analysis was restricted to exclude women who had undergone a previous caesarean birth, in women delivering term infants, when women with relative contraindications to neuraxial analgesia were excluded, or when the analyses were adjusted for by date of delivery. For women undergoing a category 1 (immediate threat to maternal or fetal life) caesarean birth, this result persisted, however, we did not identify this trend in women undergoing caesarean birth for 'irreversible' causes of fetal distress, although the low incidence means that no firm conclusions can be drawn. Women of non-white ethnicity were more likely than white women to receive GA for elective (though not emergency) caesarean and this did not vary by socio-economic decile. Regardless of socio-economic position or being of white or non-white ethnicity, rates of GA for caesarean birth fall under the recommended guidelines from the RCOA of <5% and <15% respectively.[276] However, these increased rates of GA in both elective and emergency caesarean birth, which is known to be associated poorer maternal and offspring outcomes, is concerning in a population which is already at a higher risk as baseline.

Previous research into socio-economic position and mode of anaesthesia for caesarean birth is limited. In a historical analysis from 1992, Obst et al found that mothers in New York State undergoing caesarean birth under Medicaid were approximately twice as likely to receive GA as those with private coverage.[283] Two papers exploring the impact of ethnicity on anaesthesia for caesarean birth mention socio-economic position. Tangel et al[284] carried out an exploratory analysis of 1,825,099 women undergoing caesarean birth in New York State 2007-2014. They reported an increased incidence of GA in women of black ethnicity as compared to white (aOR 1.44 [1.39, 1.49]). Although they did not report the

effect of sociodemographic on mode of anaesthesia specifically, they comment that a larger proportion of black women than white women lived in the lowest quartile of median income. An observational study of 1,486,323 women over a 10 year period in England found that black Caribbean and African women were more likely, and Bangladeshi and Pakistani (Asian or British Asian) women were less likely to have GA for caesarean birth, in both elective and emergency cases.[25] Pakistani and Bangladeshi ethnic groups had the highest proportion of women living in deprived areas, however they commented that:

"*Deprivation and region of residence had only small confounding effects on the relationship between ethnicity and general anaesthesia for elective caesarean births and did not materially affect these results"*[25]

No further information on socio-economic status was presented. In this study an overall GA rate of 2.7% was reported, compared to 6.8% in our study, and 8.75% in a recent UK wide survey of obstetric anaesthetic practice published by the same group.[3] In contrast, in Scotland women of Asian ethnicity are more likely to reside in the most affluent areas (SIMD 10) as compared to women of white ethnicity. In our analysis, being of Asian ethnicity was associated with an increased incidence of GA as compared to women of white ethnicity for elective but not emergency caesarean birth (RR 1.44 [1.19, 1.84] vs 0.94 [0.85, 1.04] for elective and emergency caesarean birth respectively). We were not able to detect any socio-economic gradient in the strata of women of non-white ethnicity. We acknowledge that the division into 'white' and 'non-white' ethnicity is crude and this was dictated by the data we had available. However, the aim of this stratification was to acknowledge that women of different ethnicities have differing degrees of socio-economic advantage, and that, for example a second or third generation immigrant born in Scotland and working as a professional will have different healthcare interactions to a newly arrived refugee.

The indications for a pre-term caesarean birth may be different to those at term, and there is evidence that the relative risk to the neonate of GA compared to neuraxial blockade increases with increasing gestational age.[270] We caried out a subgroup analysis of women delivering term infants (≥37+0 - 41+6) and were

able to demonstrate a persisting socio-economic gradient for GA utilisation in both elective and emergency caesarean births.

To our knowledge, this is the first paper examining the association between socio-economic status, anaesthesia and urgency of caesarean birth. Both race and sociodemographic status have been shown to influence physicians' perceptions of their patients which may be further exacerbated by stress.[285] However, we found stronger associations between GA utilisation and lower socio-economic position in elective rather than emergency caesarean birth. Information on category of emergency caesarean birth was only available for 23.9% of birth events. In the most urgent, category 1 caesarean births, one might expect that any socio-economic gradient would disappear as the high degree of urgency would result in a higher incidence of GA as the quickest method of anaesthesia. However this socio-economic gradient persisted even in these cases, and paradoxically GA utilisation was reduced compared to the overall GA utilisation for emergency caesarean birth, though not when the analysis was restricted to women delivering infants at term. There are potential criticisms of the use of the documented category of caesarean birth. Firstly, it may be recorded retrospectively, thus it is possible that if a women required a GA or the pathology identified was more serious, the category could be recorded as more urgent after the event. Furthermore, it has been suggested that category 1 caesarean birth is 'over-called', and some women recorded as requiring a category 1 caesarean birth may not have required such urgent delivery.[279,286] An analysis from New York State (466,014 women) looking at the recorded indications for GA in caesarean birth and concluded that 44% of GAs were potentially avoidable, and that these cases were associated with an increase in adverse maternal outcomes.[287] The overall GA rate was similar to this analysis (7.0% vs 6.8%). To mitigate these potential criticisms, a further sensitivity analysis was carried out using a subgroup of women with a recorded diagnosis of an 'irreversible' cause of fetal compromise. These were selected as pathologies which may require a shorter decision to birth interval than is suggested for a category 1 caesarean birth.[279] Whilst we acknowledge that there may be other 'irreversible' causes of fetal distress, the aim of this subgroup was to identify trends for some of the most urgent cases of caesarean birth. It is reassuring that no socio-economic gradient was found in this subgroup, however

these pathologies are rare and the subgroup identified may not be adequately powered to detect a difference.

We have identified numerous socio-economic discrepancies in obstetric care. This includes increased utilisation of elective caesarean birth in women of higher socio-economic position, which is not fully explained by small increases in multiple births, breech presentation or previous caesarean birth and this may represent patient choice. When women of higher socio-economic position undergo elective caesarean birth, these women are less likely to receive a GA than women from a lower socio-economic position. The difference in GA utilisation may also represent patient choice, however these arguments are contradictory. Furthermore, given the benefits of neuraxial over GA to both mother and child, this could potentially be modified with improved antenatal education. Being of lower socio-economic status was also associated with increased utilisation of induction of labour (which corroborates with previous literature on this subject).[23] In emergency caesarean birth, labour neuraxial analgesia can be converted to surgical anaesthesia, and in the preceding chapter I have demonstrated reduced utilisation of labour epidural analgesia, especially in women with medical conditions in which epidural analgesia is highly advisable for maternal safety as described in the preceding chapter.[170] Given that there is growing evidence that labour neuraxial analgesia is associated with a reduction in severe maternal morbidity,[141] we must ensure equitable access to both regional anaesthetic and analgesic techniques. Most concerningly, women from lower socio-economic groups are at an increased risk of severe maternal morbidity[22] and are more likely to die during childbirth.[219] It is of vital importance that we address structural and institutional barriers to the best possible obstetric care. Both patient and caregiver focus groups may be a way to tackle these inequalities and help us foster true shared decision making.

This study has many strengths. To our knowledge this is the first paper looking at mode of anaesthesia for caesarean birth and socio-economic inequality in a fully funded public healthcare situation. We include a large, unselected cohort of almost 180,000 parturients representing all women delivering by caesarean birth over an 11-year time frame. The SIMD index is a robust multidimensional measure of socio-economic status, and the use of an area-based deprivation

measure when assessing an area-based health care provision is advantageous, and corroborates the MBRRACE reports.[9] Elective and emergency caesarean births were analysed separately as GA may have different indications in each of these clinical scenarios. We acknowledge that this analysis has some weaknesses. It is an observational study and thus can only demonstrate association, not causality. As discussed in the preceding chapter, SIMD was utilised as a proxy measure, but may not always accurately reflect individual socio-economic position. Although efforts are made to identify and correct for confounders, we cannot account for all potential biases. In particular, we did not have data regarding indication for GA and the influence of maternal choice. Only a small proportion of cases had data available of category of caesarean birth. There were missing data, especially for ethnicity and for this reason we have presented both an imputed and unimputed analysis.

7.5 Conclusion

Our data from a large, ethnically similar population with freely available healthcare show that women from the most compared with the least deprived socio-economic groups are more likely to receive GA for both elective and emergency caesarean birth. Reasons for this discrepancy remain undetermined and should be explored to address cultural and institutional beliefs and mitigate against adverse maternal and neonatal outcomes.

Chapter 8 Conclusions

8.1 Summary of findings

The first half of this thesis explores the current literature related to labour epidural analgesia utilisation, describes what current practice in Scotland looks like, and explores reducing the concentration of local anaesthetic as a potential avenue to reduce adverse effects of epidural, whilst retaining its analgesic benefits. The second half of this thesis explores associations of socio-economic position on labour epidural analgesia utilisation, and on anaesthesia for caesarean birth at a population level. In this final chapter I will summarise the findings from each section before contextualising my research, exploring the strengths and weaknesses, and suggesting directions for future work.

8.1.1 Narrative review: Epidural analgesia in labour

Chapter two is a narrative review exploring all recent research into labour epidural analgesia. Labour epidural analgesia provides superior pain relief to all other forms of analgesia in labour, and is safe for mother and baby. However, there is no universally agreed standard technique, and often trials do not compare like with like, which means it can be difficult to pinpoint which variable (change in technique) is influencing outcomes. Furthermore, childbirth is associated with a vast number of uncontrollable variables. The adoption of low (LC) as opposed to high concentration (HC) local anaesthetics (LA) has been associated with a reduction in incidence of assisted vaginal birth (AVB). A small number of studies have investigated ultra-low concentration (ULC) LA for labour epidural to reduce incidence of motor blockade and therefore incidence of AVB, whilst maintaining adequate analgesia. These studies are heterogenous and no firm conclusions can be drawn from the research to date. Reassuringly, there is no evidence of an association between incidence of caesarean birth and labour epidural analgesia utilisation. However, it is noted that AVB rates are reducing worldwide, independently of epidural utilisation, whilst caesarean birth rates are increasing. Reduction of motor blockade that may impact on the second stage of labour, whilst maintaining adequate analgesia, remains a research priority.

Other key areas of labour epidural research are the different drug delivery systems. Programmed intermittent bolus (PIEB) plus patient-controlled epidural analgesia (PCEA) appears to be the optimal drug delivery system with respect to incidence of spontaneous vaginal birth (SVB), motor tone and overall utilisation of LA. Labour epidural analgesia does not appear to be associated with adverse maternal or neonatal outcomes. There is some evidence that labour epidural analgesia may reduce severe maternal morbidity, without detriment to either short- or longer-term neonatal outcomes. There is mounting evidence to refute an association between labour epidural analgesia and incidence of autism in offspring.[288] The impact of epidural related hyperthermia on neonatal outcomes remains uncertain.

8.1.2 Bayesian network meta-analysis of ultra-low, low and high concentration local anaesthetic for labour epidural analgesia

In the preceding chapter, the utilisation of ULC local anaesthetic for labour epidural was identified as an area of research that was incompletely answered. The definition of ULC local anaesthetic was defined as equal to or below 0.08% bupivacaine or equivalent, LC above 0.08%, up to and including 0.1%, and HC above 0.1%. A network meta-analysis (32 studies and 3665 parturients) was carried out using Bayesian statistics to make a three-way comparison between ULC, LC and HC local anaesthetics for labour epidural analgesia. We found an increase in SVB in ULC compared to HC local anaesthetic (odds ratio (OR) 1.46 95% Credible interval (95% CrI) [1.18, 1.86], >99.9% probability), but results did not reach significance for the comparison of ULC to LC (1.07 [0.75, 1.56], 65% probability) or LC to HC (1.36, [0.97, 1.94], probability 96%). Results for caesarean birth and AVB did not reach significance. There was a step wise reduction in total local anaesthetic does as concentration decreased, and a reduction in both duration of 2nd stage labour (weighted mean difference (WMD) -13.02 mins, 95% CrI [-21.54, -4.47]), incidence or motor block (OR 0.32 [0.18, 0.54]) in ULC as compared to HC. No significant differences were found in maternal satisfaction, pain scores, maternal side effects or neonatal outcomes. Data for perineal tears and postpartum haemorrhage was not available. There was some heterogeneity between studies including the method of epidural analgesic delivery and addition of opiates. Overall, we concluded that ULC local

anaesthetics were superior to HC, and that there was probably a benefit in reducing local anaesthetic concentrations from LC to ULC, but more information is needed. I believe this meta-analysis produces evidence that would justify a randomised controlled trial comparing LC and ULC local anaesthetics (see section 8.4).

8.1.3 Current epidural practice in Scotland: a survey of practice

Chapter 5 focused on a 14-question survey about obstetric anaesthetic practice that was distributed amongst anaesthetists in Scotland who work in obstetric anaesthesia. Overall, uptake was low with 68 of an estimated 380 (17.9%) responding, but uptake among consultants was higher with 35 of an estimated 81 obstetric anaesthetic consultants responding (43%). Those who responded represented a variety of size of obstetric unit. Test doses were used by the majority of respondents, (63/68) but 3 different local anaesthetic agents of up to 4 concentrations were utilised, and size of test dose varied from 2 to 15ml. Five different solutions were utilised for maintenance of labour epidural analgesia, with 0.1% levobupivacaine + fentanyl being most common (43/68 (61.8%)) and 0.125% levobupivacaine + fentanyl being the second most common response (20/68 (29.4%)). Only 3 respondents (4.4%) used ultra-low concentrations (0.0625% bupivacaine). Patient controlled epidural analgesia without infusion or PIEB was the most common method of administration (42/68 (61.8%)). In the final question of the survey we describe a case of low sensory block in an otherwise healthy primiparous women, and asked for the most likely first line management strategy. Eleven different responses were received, with the most common answers being up to 10ml of 0.1-0.125% levobupivacaine (26/68 (38%)) or up to 10ml 0.25% levobupivacaine (24/68 (35.3%)).

Due to the low response rate to this survey it is difficult to draw any firm conclusions. However there appears to be substantial variability in practice across Scotland. High concentration local anaesthetics are still used in labour epidural analgesia in Scotland by over a quarter of responders, and ultra-low concentration local anaesthetic utilisation appears uncommon. We were not able to identify any recent literature on labour epidural analgesia utilisation in other countries for comparison.

8.1.4 Socio-economic disadvantage and utilisation of labour epidural analgesia

In the second half of this thesis I progressed to identifying a potential at risk population (those who reside in areas of low socio-economic position), and examined how socio-economic status is associated with obstetric analgesia utilisation at a population level. Firstly, labour epidural analgesia is considered. All births by vaginal birth or emergency caesarean birth in Scotland over a 13-year period for which data were available was analysed (593,230 deliveries). Women residing in areas of the most socio-economic disadvantage were 16% less like to use labour epidural analgesia than women residing in the least deprived areas. This discrepancy remained when the analysis was restricted to include only primiparous women, or only women who delivered within one major Scottish city with 24-hour access to obstetric anaesthetic care, and concerningly in those with a medical condition in which epidural analgesia may be advised for maternal safety. Being of non-white ethnicity appears to compound this relationship, with non-white women residing in the areas of the least disadvantage more likely to utilise labour analgesia than their white counterparts, and non-white women in areas of the most disadvantage being significantly less likely to utilise labour epidural analgesia than their white neighbours. We also demonstrated that increasing levels of socio-economic deprivation was associated with a stepwise increase in adverse maternal health characteristics, including adiposity, smoking, comorbidity and illicit drug use.

8.1.5 Socio-economic deprivation and anaesthesia for caesarean birth

The final chapter of this thesis looked at the associations between socio-economic status and anaesthesia for caesarean birth. All caesarean deliveries in Scotland over an 11-year period for which data on anaesthesia utilisation was analysed (179,562 parturients). A significant socio-economic gradient for utilisation of general anaesthesia (GA) over neuraxial analgesia for both elective and emergency caesarean birth was detected. Women who lived in areas of the greatest social disadvantage (SIMD 1) were 62% and 50% more likely to have a GA for elective and emergency caesarean birth respectively, as compared to the least deprived women. These results were consistent when exclusions were

made for: women having undergone a previous caesarean birth, women delivering infants pre- or post- term, or women with relative contraindications to neuraxial anaesthesia. General anaesthesia rates in category 1 caesarean birth were the same as the primary analysis, and the same socio-economic gradient was detected. This gradient was not detected in a subset of women with irreversible causes of fetal bradycardia, although this group was small and likely underpowered to detect such differences. This socio-economic gradient was not detected in women of non-white ethnicity.

8.2 How does this thesis fit into current research

Epidural analgesia is the most effective form of labour analgesia. Despite its widespread use, no international consensus guidelines exist on best practice. In Chapter 2 we try to address this gap with a narrative review of the current evidence to date for the utilisation of labour epidural analgesia, which was published in the *International Journal of Gynaecology & Obstetrics* (2022). One research gap identified in the narrative review was the utilisation of ultra-low concentrations (ULC) of local anaesthetic for labour epidural. In the meta-analysis in Chapter 4, we have further explored this, demonstrating that ULC local anaesthetics are associated with the same or better outcomes than low concentrations (LC), whilst maintaining good analgesia and maternal satisfaction. This research was published as an original research paper in *Anaesthesia* (2022). It has also been presented orally at the West of Scotland Obstetric Anaesthesia Study Day (2022), the Gynaecological Visiting Society annual meeting (2022), and the University of Glasgow College of Medical, Veterinary and Life Sciences forum (2021) for which it won the first-year research prize. There is minimal research into current epidural practice in the UK, and this was addressed in the survey of obstetric practice in Scotland. Although survey uptake was low, a significant variability in epidural technique within Scotland was observed. These results were presented as a poster at the Obstetric Anaesthetists' Association (2023).

Women who reside in areas of high deprivation have higher rates of adverse maternal health characteristics, which are known to be associated with higher rates of maternal and neonatal adverse outcomes. These women are at higher risk from baseline, and we know from the MBRRACE reports that this population carries a disproportionately high burden of morbidity and mortality. Labour epidural analgesia has an excellent safety profile and is associated with superior psychological outcomes, and there is growing evidence for an association with a reduction in severe maternal morbidity. By international consensus neuraxial anaesthesia is recommended over general anaesthesia for caesarean birth in the majority of women, due to the associations with superior maternal and neonatal outcomes with neuraxial blockade. In this body of work, we have demonstrated that there is socio-economic inequality within the provision of obstetric

anaesthesia, for both labour analgesia and anaesthesia for caesarean birth. Regardless of the reasons behind this, whether it is patient choice or institutional and structural biases, these are potentially modifiable risk factors. Socio-economic disadvantage and utilisation of labour epidural analgesia in Scotland – a population-based study is published in Anaesthesia (2024), with accompanying editorials in Anaesthesia[289] and in the British Medical Journal (BMJ),[290] articles in the Telegraph and Daily Mail Newspapers, and an online interview on PainRelief.com. This work has been presented locally, regionally and nationally, including winning 1st prize at Scottish Society of Anaesthetists Spring meeting 2022 and the Felicity Reynolds Prize at the Obstetric Anaesthetists' Association annual meeting 2023 for best oral presentation. It also won the poster prize at the St Mungo research symposium in Glasgow 2023. Socio-economic disparity in anaesthesia for caesarean birth was presented as a Poster at the Obstetric Anaesthetists' Association annual meeting 2023, for which it won a Poster category prize. Alongside the racial inequalities that have been observed in provision of obstetric anaesthesia we must work to understand and address socio-economic inequity. The identification of these discrepancies allows us to address them and meet the principals of the NHS in delivering equitable treatment that is free at the point of care.

8.3 Strengths and weaknesses of this thesis

This thesis has a number of strengths. It uses a mixture of surveys, meta-analysis, and retrospective analysis of whole population healthcare data. It employs a large variety of robust statistical techniques to analyse and model data from thousands to hundreds of thousands of parturients. Systematic search strategies for both the narrative review and network meta-analysis were employed. In chapter 4, a large robust meta-analysis with data from 32 studies with 3665 parturients is presented. The main weakness of this meta-analysis was heterogeneity between studies, especially utilisation of opioids or not, and the epidural drug delivery technique. We attempted to address this with a survey of practice in chapter 5, which had low uptake, but demonstrated that this heterogeneity was present in real life practice, as well as in research studies.

Chapters 6 and 7 utilise large, unselected whole population cohorts of routinely collected healthcare data over a 13- and 11- year time frame respectively, which is reflective of contemporary clinical practice. A major limitation, as with all retrospective research, is that we are only able to determine associations between variables, and not causality. There was missing data, especially for ethnicity, and both the imputed and unimputed analyses were presented to account for this. There was no data available to indicate the decisions behind neuraxial blockade or GA utilisation. Decision making around labour and caesarean birth is truly multidisciplinary, particularly in emergencies, with input from midwives, obstetricians, paediatricians, anaesthetists and, importantly, patients. We cannot definitively know to what extent patient choice plays a role. A major strength of these studies is the stratification of results to partially address this. In chapter 6, women with a medical condition for which epidural analgesia may be recommended for maternal safety (medical indication) without relative contraindication, are considered separately from those without an indication or with a relative contraindication. The aim of this was to identify a subset of women who would be more likely to be advised to use labour analgesia, rather than purely maternal choice. This stratification is unique to this study. Similarly, in chapter 7 elective and emergency caesarean birth were considered this patient group separately, and a further sensitivity analysis considered only women undergoing category 1 caesarean birth. In more urgent situations, GA may be preferential due to speed on onset, however, we were

able to demonstrate that the socio-economic gradients persisted irrespective of urgency, except for a small subset of women who had an irreversible cause of fetal distress, though the sample size may have been too small to demonstrate differences. The analyses stratifying white and non-white women are rudimentary, and we did not have data to present individual ethnicities separately. The inclusion of these sensitivity analyses was to show that these discrepancies in care could not be explained by ethnicity alone, and to acknowledge the vast differences in socio-economic position which are equally present amongst women of non-white ethnicity in Scotland.

The Scottish Index of Multiple Deprivation (SIMD) was used as a proxy measure for individual socio-economic position. This is a both a strength and a weakness of these analyses. It is a multifaceted measure of 7 domains which allows a more holistic view of overall relative deprivation, rather than using a single indicator, such as income, employment of level of education, as employed in similar studies. A major criticism of SIMD and other area-based measure is that they may not reflect individual socio-economic position, particularly in rural areas as where each area may cover a wide geographical area. However, Scottish healthcare provision is also area-based, thus the utilisation of an area-based measure of deprivation in these studies has advantages. It also corresponds with the IMD utilised in the MBRRACE reports, which highlight that women living in areas of high socio-economic disadvantage shoulder a disproportionate burden of maternal morbidity and mortality.[9] The ability to detect socio-economic gradients by presenting results by SIMD decile is unique to these studies, and adds nuance to these analyses. A further strength of these analyses was the conscious decision to present univariate analyses for the primary outcomes to allow the full association of SIMD and epidural utilisation, and of GA for caesarean birth to be presented. We did not adjust for mediator variables, as these analyses did not meet the required assumptions for unbiased mediation analysis.

8.4 Considerations for future work and clinical practice

Women from more socio-economically disadvantaged backgrounds have higher rates of adverse health characteristic that pre-dispose them to higher rates of obstetric complications. In this body of work, it has been demonstrated these women are also less likely to utilise labour epidural analgesia and more likely to undergo a GA for caesarean birth. It is well established that GA is associated with worse maternal and neonatal outcomes than GA, and there is a growing evidence body that epidural analgesia in labour may reduce severe maternal morbidity. Deprivation is associated with poorer mental and physical health,[291] and adverse obstetric outcomes. Obstetric anaesthetic interventions may be even more beneficial in socially disadvantaged women than the general population. Group antenatal classes for women from marginalised backgrounds may be a useful tool to communicate the risks and benefits of these analgesic and anaesthetic choices, and help create an environment of patient centred, informed shared decision making. For many women this will be the first interaction with healthcare services, and a positive experience may have health benefits for mother and baby that extend beyond childbirth.

Future work should include qualitative studies in different ethnic and socio-economic groups as well as in obstetric staff to examine the reasons behind the choice of labour analgesia or caesarean anaesthesia. This could allow specific questions to be addressed, and if required help direct future research into answering the questions that are important to future healthcare users. Focus groups, particularly for marginalised women are required to address specific queries and improve future conversations about labour and childbirth options. It also would be beneficial to consider the interaction between socio-economic position, ethnicity and obstetric anaesthetic interventions using datasets from more ethnically diverse populations, to identify healthcare barriers and further individualise care.

I believe the network meta-analysis presented in Chapter 3 provides sufficient evidence to justify a randomised controlled trial comparing ULC and LC local anaesthetic, with a primary outcome of incidence of spontaneous vaginal birth (SVB), and secondary outcomes including maternal satisfaction post-birth and pain score at 1 hour after initiation of labour epidural analgesia. A non-

inferiority trial with a significance level of 5% and a power of 90%, and a non-inferiority limit of 10%, based on an estimated incidence of SVB of 60% would require 412 patients per group, or 824 parturients in total. This is a feasible number of patients to recruit in a UK based multi-centre trial, and is in keeping with recruitment numbers from recent National Institute for Health and Care Research (NIHR) funded studies.[292,293,294]

Finally, substantial variability in clinical practice was reported in the survey of labour epidural analgesia. To move forward it would be useful to create a larger survey, and utilise the survey system of the Obstetric Anaesthetists' Association (OAA) to carry this out. If we can demonstrate substantial variability in practice, for example the utilisation of high concentration (HC) local anaesthetics for labour epidural, this information can be used to identify areas for improvement in clinical practice, and areas for further study. Looking further into the future, it would be useful to be able to access anaesthetic electronic health records in Scotland. At least 11 of Scotland's 14 health boards now use the Badgernet maternity system, which includes a section for the recording of anaesthetic procedures. In my clinical experience, this section is currently poorly completed. If certain sections were made compulsory (such as concentration of local anaesthetic in labour epidural) and researchers were able to access this data, the potential of this data is almost limitless. It would allow us to join up the results of RCTs and other forms of research with patient interventions and outcomes, providing integration of research with clinical practice, whilst identifying barriers to implementing change.

8.5 Conclusion

Optimising epidural analgesia in labour is important if adverse effects are to be minimised and advantages optimised. Reducing concentrations of local anaesthetic and thus reducing side effects may be a measure to widen access to labour epidural analgesia and the associated improved outcomes for mother. Women who live in areas of relative deprivation have higher rates of adverse maternal health characteristics which are independently associated with poorer maternal and neonatal outcomes. It is well established that neuraxial rather than general anaesthesia for caesarean birth is associated with improved maternal and neonatal outcomes. Despite this, we observe socio-economic

inequality in the provision of labour analgesia and anaesthesia for both elective and emergency caesarean birth. These are potentially modifiable risk factors in a climate of static maternal mortality and increasing maternal morbidity. Measures to address these inequities are urgently required.

Appendix 1

List of excluded studies from meta-analysis (Chapter 4), with reasons for exclusion.

Wrong outcomes 3 (4)

1. Wang - Comparison of bupivacaine, ropivacaine and levobupivacaine with sufentanil for patient-controlled epidural analgesia during labor: a randomized clinical trial.
2. Wilson - Long-term effects of epidural analgesia in labor: a randomized controlled trial comparing high dose with two mobile techniques.
3. Beilin - Epidural ropivacaine for the initiation of labor epidural analgesia: a dose finding study.

Wrong dose 3 (6)

1. Cheng - Dexmedetomidine versus sufentanil with high- or low-concentration ropivacaine for labor epidural analgesia: A randomized trial
2. Marcoux - Bupivacaine concentration and obstetric delivery
3. Milon - Analgésie péridurale au cours du travail : comparaison de trois associations fentanyl-bupivacaïne et de la bupivacaïne seule

Wrong study design 2 (8)

1. Brow - Comparison of the length of stage II labor and incidence of forceps and cesarean delivery after epidural infusion of 0.125% bupivacaine with 2 mu/mL fentanyl as compared with 0.0625% bupivacaine with 2 mu/mL fentanyl
2. Wang - A Randomized Controlled Comparison of Epidural Analgesia Onset Time and Adverse Reactions During Labor With Different Dose Combinations of Bupivacaine and Sufentanil

Wrong intervention 3 (11)

1. Harms - Initiating extradural analgesia during labour: Comparison of three different bupivacaine concentrations used as the loading dose
2. Hemanth Kumar - Ultra low concentrations of epidural bupivacaine with fentanyl along with intrathecal fentanyl for labor analgesia
3. Lee - Epidural Labor Analgesia-Fentanyl Dose and Breastfeeding Success: A Randomized Clinical Trial.

Duplicate 5 (16)

1. Dahl - Bupivacaine 2.5 mg.ml-1 versus bupivacaine 0.625 mg/ml-1 and sufentanil l microg/ml with or without epinephrine 1 microg/ml for epidural analgesia in labour.
2. Atienzar - Ropivacaine 0.1% with fentanyl 2 mug mL-1 by epidural infusion for labour analgesia
3. Boseli - Ropivacaine 0.15% plus sufentanil 0.5 microg/mL and ropivacaine 0.10% plus sufentanil 0.5 microg/mL are equivalent for patient-controlled epidural analgesia during labor
4. Benhamou - Continuous epidural analgesia with bupivacaine 0.125% or bupivacaine 0.0625% plus sufentanil 0.25 microg.mL(-1): a study in singleton breech presentation
5. Ferrer Gomez - 0.2% ropivacaine vs. 0.1% ropivacaine plus fentanyl in obstetric epidural analgesia

Same patient cohort as another study 1 (17)

1. Russell - Motor block during epidural infusions for nulliparous women in labour. A randomized double-blind study of plain bupivacaine and low dose bupivacaine with fentanyl

Unable to access 3 (20)

1. Gamela - Conventional versus ambulatory epidural: Effects during labor on pregnant women
2. Shrestha - Comparative study of epidural administration of 10 ml of 0.1% bupivacaine with 2 mg butorphanol and 10 ml of 0.25% plain bupivacaine for analgesia during labor
3. ArechigaOrnelas - Peridural butorphanol in labor

Appendix 2

Copy of the survey on neuraxial analgesia in labour and accompanying letter (Chapter 5)

I've invited you to fill out a form:

Neuraxial analgesia in Labour

Thank you for taking the time to complete this short survey on epidural practice in Scotland.
It contains 14 multiple choice questions, plus space for free text answers.
It should take around 5 minute to complete.

What grade anaesthetist are you?

- CT1/2
- ST3+
- SAS
- Consultant

Approximately how many deliveries per year in your unit?

- <2000
- 2000-3500
- 3500-5000
- >5000
- unsure

What is the annual epidural rate in your unit?

- <20%
- 20-30%
- 30-40%
- 40-50%
- >50%

unsure

Do you use a test dose? If so what local anaesthetic solution and concentration?

	Lidocaine	Bupivacaine	Levobupivacaine	Ropivacaine	none	other
0.0625%						
0.1%						
0.125%						
0.15%						
0.2%						
0.25%						
0.5%						
1%						
2%						
none						
other						

What volume do you use for test dose?

1ml

2ml

3ml

4ml

5ml

none

Other:

What solution do you use for your initial dose?

Bupivacaine

Bupivacaine with opiate

Levobupivacaine

Levobupivacaine with opiate

Ropivacaine

Ropivacaine with opiate

Other:

What volume and concentration is your initial dose? Excluding test dose if used

	5ml	8ml	10ml	12ml	15ml	20ml	other
0.0625%							
0.1%							
0.125%							
0.15%							
0.2%							
0.25%							
0.375%							
0.5%							
Other							

Which local anaesthetic and at what percent concentration do you use for maintenance of labour analgesia?

	0.0625%	0.1%	0.125%	0.15%	0.2%	0.25%	other
Levobupivacaine							
Bupivacaine							
Ropivacaine							
other							

Please state which local anaesthetics was used if other was selected, otherwise leave blank

Which opioid and concentration do you use in your epidural maintenance solution?

	0.4mcg/ml	0.5mcg/ml	0.75mcg/ml	1.0mcg/ml	2.0mcg/ml	other	none
Fentanyl							
Sufentanil							
other							

Please state which opioid if other has been selected, otherwise leave blank

What method of maintenance do you use for epidural analgesia?

- Patient controlled epidural analgesia (PCEA)
- PCEA and background infusion
- Computer integrated PCEA
- Continuous infusion
- Physician or midwife intermittent top ups

Do you add any other adjuvants for maintenance of labour epidurals? please tick all that apply (excluding top up for theatre)

- Clonidine
- Neostigmine
- Adrenaline
- Magnesium
- Dexmetatomadine
- Tramadol
- Sodium bicarbonate
- None
- Other:

Which 'rescue drug' would you use for a fit and healthy primiparous 28 year old at 6cm dilation in uncomplicated spontaneous labour complaining of a low block with breakthrough pain?

- up to 10ml bolus of epidural maintenance solution
- up to 10ml 0.125% levobupivacaine
- up to 10ml 0.25% levobupivacaine
- up to 50mcg fentanyl
- Other:

What solutions do you use to top up epidural for operative delivery? please tick all that apply

- Lidocaine 2% plus adrenaline
- Bupivacaine 0.5%
- Levobupivacaine 0.5%
- Ropivacaine 0.75%
- 1:1 mixture of levobupivacaine 0.5% and lidocaine 2% plus adrenaline
- Other:

Do you use any other neuraxial adjuvant agents for top up for caesarean delivery?

- Diamorphine prior to delivery

Fentanyl prior to delivery

Fentanyl after delivery

Diamorphine after delivery

Other:

Thank you so much! Please add any other comments if you have them

Submit

Never submit passwords through Google Forms.

20th July 2021

Survey of practice: Neuraxial analgesia in labour

Dear Colleague,

Epidural analgesia is a key component of obstetric anaesthesia. Epidural rates are increasing, and in 2019 around 31% of labouring women in the UK received an epidural.[1] In 2001, the COMET trial showed a significant reduction in the number of instrumental deliveries when using lower concentrations of local anaesthetic solution.[2] Since then, a range of epidural regimes with lower concentrations of local anaesthesia, different adjuvants, and new technologies having been trialled with the aim of improving outcomes for mother and baby.

Current practice in Scotland is not clearly defined and we would like to assess this. The results will form part of a larger project looking at epidural practice in Scotland and factors associated with improved obstetric, maternal, neonatal and early childhood outcomes. The overall result of the survey will be circulated around Scotland and may be presented or published but individual data will not. We hope that the results of this survey may be useful to both obstetricians and anaesthetists as a part of ongoing service development and improvement for obstetric units across the country.

The survey contains 14 multiple choice questions, and space for free text answers. It should take around 5 minutes to complete.

Your participation in this short survey is greatly appreciated.

Dr Lucy Halliday
Clinical Research Fellow, University of Glasgow/NHS Greater Glasgow & Clyde

Dr Rachel Kearns
Consultant Anaesthetist, Glasgow Royal Infirmary & Princess Royal Maternity Hospital
Honorary Associate Clinical Professor, University of Glasgow

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