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Interleukin-1 receptor antagonist and risk of caesarean delivery ~~occurring~~ after ~~the~~ onset of labour: a Mendelian randomisation analysis~~.~~

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~~**Clinical trial number:** UK Biobank study 62745.~~

Running Title: IL1-ra polymorphisms and labour outcomes.

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Editor's key points

Levels of interleukin-1 receptor antagonist (IL-1ra), anti-inflammatory cytokine, are associated with inflammation and epidural analgesia-related maternal fever.

The hypothesis that genetic variants determining IL-1ra levels are associated with caesarean delivery rates after the onset of labour was tested using Medelian randomisation analyses of UK Biobank data.

Genetic polymorphisms resulting in increased IL-1ra levels were associated with lower caesarean delivery rates, which was disrupted by use of neuraxial analgesia.

These findings establish the importance of genetically determined mechanisms regulating inflammation in affecting peripartum outcomes, opening the possibility of precision medicine tailored interventions in labour.

Abstract

Background: Lower circulating levels of the anti-inflammatory cytokine interleukin-1 receptor antagonist (IL-1ra) are associated with intra-partum inflammation and epidural analgesia-related maternal fever, both of which increase the rate of obstetric interventions. We hypothesised that genetic variants determining IL-1ra levels would be associated with higher caesarean delivery rates after the onset of labour.

Methods: We performed Mendelian randomisation analyses in parous women ≥16 years old who received either non-neuraxial or neuraxial analgaesia for their first two labours (UK Biobank). We used an established genetic score (calculated as 0-4, determined by presence/absence of rs6743376, rs1542176 alleles), in which the complete absence of both alleles causes the lowest IL-1ra levels. The primary outcome was caesarean delivery after the onset of labour (odds ratio (OR):, 95% confidence intervals).

Results: 7731 women (mean (SD) age at first birth:25y (5) yr) had complete genetic scores and delivery data. For women who received non-neuraxial analgesia, caesarean delivery rates were different across allele scores ($\chi2$=12.4; *P*=0.015):. 104/596 (17.4%) women with a zero allele score underwent caesarean delivery, compared to 654/5015 (13.0%) with allele score ≥1 (OR:1.41, 1.12-1.77). For women who had neuraxial analgaesia, caesarean deliveryies were was not different across allele scores, ranging from 18.1-20.8% ($\chi2$=0.29; *P*=0.99). Caesarean delivery ies wasere independent of type of analgesia for 818/7731 (10.6%) women with zero allele scores (OR:0.93, 0.63-1.39), but wasere higher in women receiving neuraxial analgesia with allele scores ≥1 (OR:1.55, 1.35-1.79; *P*<0.001).

Conclusion: Mendelian randomisation analysis suggests that genetically higher IL-1ra levels are associated with fewer reduced caesarean delivery rateies. Neuraxial analgesia appears to disrupt this link.

Clinical trial number: UK Biobank study 62745

~~Background~~

Intrapartum infection and fever are associated with more frequent obstetric interventions, including emergency ~~delivery during labour by~~ caesarean ~~section~~delivery.[1 2] Inflammation during active labour promotes fever, which promotes neonatal neurologic injury[3] and greater neonatal exposure to antibiotic treatment, which is associated with atopic disease in early childhood.[4]

Interleukin (IL)-1β, the main form of circulating IL-1, plays a pivotal role in the immune response activated by labour, by inducing the synthesis and expression of multiple secondary inflammatory mediators.[5] The natural interleukin-1 receptor antagonist (IL-1ra) directly inhibits the pro-~~-~~inflammatory effects of IL-1β through binding ~~-~~the interleukin-1 receptor[5] and prevents IL-1 induced preterm parturition.[6] Similarly, blockade of IL-1 signaling by recombinant IL-1ra inhibits f~~o~~etal lung and systemic inflammation following chorioamnionitis.[7] Neuraxial bupivacaine is also associated with ~~the~~ development of fever.[8] The change in the IL-1ra/IL-1beta ratio observed in women who receive epidural bupivacaine suggests that IL-1ra or IL-1beta may also play a role in epidural-related maternal fever~~ERMF~~.[8] Thus, bupivacaine as a component of epidural labour analgesia may contribute to increasing the risk of epidural-related maternal fever.[9 8] Fever increases the likelihood of caesarean deliveries occurring after the onset of labour.[10]

Two alleles (rs6743376, rs1542176) located upstream of *ILRN*, the gene that encodes IL-1ra, increase both *IL1RN* mRNA expression and soluble IL-1ra concentration in a log-linear, "dose–response" manner.[11] The construction of a genetic score for IL-1ra using these two alleles has enabled Mendelian randomisation studies to examine the causal relation between IL-1ra single nucleotide polymorphisms and outcomes in cardiovascular disease and rheumatoid arthritis. [11] Mendelian randomisation using allele scores provides evidence for a

causal relationship between an exposure variable and an outcome, given a set of well-characterised assumptions.[12] For example, the development of allele scores for *CRP* and *IL6R* genes have, in combination with laboratory data, demonstrated their causal role in coronary heart disease.[13, 14] Because Mendelian randomisation is less likely to be affected by confounding or reverse causation than conventional observational studies,[15] this approach offers mechanistic insight into the biological impact of IL-1ra on outcomes in active labour.[16]

~~Here, w~~We hypothesised that the absence of *IL1RN* gene variants increases the risk for caesarean delivery occurring after the onset of labour. Because circulating IL-1ra levels are associated with neuraxial analgaesia,[8] we performed two Mendelian randomisation analyses in UK Biobank participants who received either neuraxial or non-neuraxial analg~~a~~esia during labour.

Methods

Study design

We conducted two separate studies using the UK Biobank, which is a prospective cohort that recruited 502,492 men and women between 2006 and 2010, and collected anthropometric, health, and lifestyle data, as well as biological samples.[17] Hospital Episode Statistics (HES) Admitted Patient Care dataset on hospital inpatient admissions is provided to UK Biobank by the Data Access Request Service, managed by NHS Digital. UK Biobank received ethical approval from the NHS National Research Ethics Service North West (11/NW/0382). Our study was conducted following UK Biobank review and approval (study 62745). We adhered to STROBE Extension for Genetic Association Studies (STREGA) guidelines (see Supplementary data).

Study participants

We analysed data from women ≥16 years old, who had obstetric data recorded for their first two labours. We conducted two separate analyses in women who delivered after a labour and who had some form of non-neuraxial analgesia analgaesia, and women who had neuraxial analgaesia alone for delivery (codes 2 and 6; Supplementary Table 1). We excluded women who underwent elective caesarean delivery, and those for whom the mode of delivery and/or mode of analgaesia was classified as being unknown.

Genotyping, imputation and quality control

Our study was conducted on genome-wide genotyping data available for 57328 unrelated women. Details of sample processing specific to UK Biobank project are available at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583, including the use of the Affymetrix Axiom array. UK Biobank genotyping and the stringent quality control protocol applied-UKB

data before it was released can be found at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580.

Construction of genetic score

We used an established genetic score that selected two single nucleotide polymorphisms (rs6743376 and rs1542176) upstream of the *IL1RN* gene.[11] Both polymorphisms (or their strongly correlated proxies) are independently associated with circulating IL-1ra concentration from genome-wide association studies. [11, 18] rs6743376 and rs1542176 have similar, though independent, effects on IL-1ra concentration. The Interleukin 1 Genetics Consortium therefore combined information on both SNPs by constructing a genetic score.[11] Because rs6743376 and rs1542176 are not correlated with each other, the linear associations between the genetic score constructed by the Interleukin 1 Genetics Consortium and IL-1ra concentration mean that it is biologically highly unlikely that the score reflects a pathway other than IL1α/β signalling.[11] For the score to be confounded by a common alternative pathway, both non-correlated SNPs would have to be associated with the actual causal trait, either directly or through linkage disequilibrium with a third SNP (for which there is no evidence).

Data extraction

We extracted data collected from UK Biobank, which specifically captured labour outcomes including mode of analgaesia, delivery, neonatal outcomes using UK Biobank tools to decrypt (ukbunpack) and unpack (ukbconv) the dataset and/or Python code-generate .csv files.

~~Exposure of interest~~

The exposure of interest was the genetic score that correlates with circulating IL-1ra concentration (allele scores: 0, 1, 2, 3, 4).

Primary outcome~~.~~

The primary clinical outcome was caesarean delivery after ~~the~~ onset of active labour for the first two labours recorded in UK Biobank, compared between allele scores for IL-1ra for women receiving neuraxial or non-neuraxial analg~~a~~esia. The first two deliveries were analysed given that low ~~-r~~isk nulliparous women have substantially higher rates of complicated birth than ~~than~~ parous women who have never had a previous caesarean delivery, even if the latter have multiple risk factors.[19] We chose caesarean delivery after the onset of active labour because it is a clinically meaningful outcome to both patients and healthcare providers alike, was an unequivocal UK Biobank-defined outcome and has a direct relationship with infection [or suspected infection] and/or fever during active labour.[10] The definition used for the primary outcome, as defined by the Hospital Episode Statistics (HES) Admitted Patient Care dataset is: "Any caesarean section carried out immediately following the onset of labour."

Secondary outcomes

We analysed the UK Biobank for the following secondary outcomes using ~~UK Biobank~~ maternity-specific outcomes in combination with hospital-captured codes for pregnancy, childbirth and the puerperium (O00–O99), as defined by International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)~~:~~ ~~.~~

1. Instrumental delivery,~~:~~ classified by UK Biobank defined-categories (Supplementary table 2) for delivery requiring forceps or ventouse (vacuum extraction), excluding breech (including partial breech) extraction. Unknown outcomes were excluded.

2. Neonatal outcomes,~~:~~ classified by UK Biobank defined-categories (Supplementary table 3) for the use of positive pressure ventilation by mask or ~~endo~~tracheal tube, need for drug therapy but excluding stillborn babies where no method of resuscitation was attempted.

~~**3.**~~ Fever and/or infection,~~:~~ using ICD-10 defined episodes captured in UK Biobank, we combined maternal fever during labour (O75.2), genito-urinary infections (O23), maternal sepsis (O75.3) and premature rupture of membranes (O42).

3.

Statistical Analysis

Mean (SD) or median values (interquartile range) are presented, unless stated otherwise. For continuous data, normality of distribution was assessed (Kolmogorov–Smirnov test). For ~~the~~ primary and secondary outcomes, we first performed a chi-squared test to establish whether there was independence between allele scores. We then used Fisher's exact test (two-tailed) for *post hoc* analysis of each chi-squared test undertaken, since simulation studies recommend the proposed exact p-value for use in practice as a valuable *post hoc* analysis technique for chi -squared analysis.[20] Odds ratio (95% confidence intervals (95%CI)) are presented for *post hoc* testing. Where indicated, data were analysed by one-way ANOVA. We did not replace missing data by data imputation. All reported *p* values are two-sided. Significance was accepted at p ~~values~~ ≤0.05. Statistical analyses were performed using NCSS 2020 (Kaysville, UT, USA).

Sensitivity and post hoc analyses

We re-analysed the primary outcome for women with long labour (ICD-10 code: O63-O66), and f~~o~~etal distress (ICD-10 code: O68), comparing between neuraxial and non-neuraxial analg~~a~~esia. The comparison between allele scores across analg~~a~~esia types was requested during the peer review process.

Sample size estimation

Although the sample size is determined chiefly by the number of women in UK Biobank with complete genetic data plus clinical data on genetics, delivery and mode of analgesia, we estimated *post hoc* whether the sample size<u>s</u> for both forms of analgesia during labour were sufficient. Over the period of UK Biobank data collection, ~~approximately~~ <u>~</u> 15% women underwent delivery by caesarean delivery following ~~the~~ onset of labour in the UK.[18] We hypothesised that a pro-inflammatory state promoted by relative IL-1ra deficiency (zero allele score) would increase the risk for a clinically relevant higher rate of caesarean delivery in ~18% women, compared to ~12% ~~rate than~~<u>of</u> women with allele scores ≥1. Using a specific sample size estimation for Mendelian randomisation studies,[21] and assuming ~15% women would have a zero allele score, the true odds ratio for the association between zero allele score and caesarean delivery was 1.5 and the proportion of the variance explained by the association between zero allele score and caesarean delivery was 50%, we therefore estimated that at least 1296 women with UK Biobank data reporting modes of delivery would be required for each type of analgesia group (α=0.05, 1-β=99%).

Results

Participants

From 249,470 female participants with IL-1ra SNP data in the UK Biobank cohort, 99.5% were of white British or Irish origin. Of these,11% had a zero allele score, with 2.7% having all four alleles that increase IL-1Ra protein expression ~~maximally~~ (Table 1). At least one live birth was recorded for 202,512 women, with the majority of women (70.9%) giving birth to two children and a similar number of births across allele scores. For the majority of pregnancy and labour-related comorbidities, similar proportions were observed across allele scores for both neuraxial and non-neuraxial modes of analg~~a~~esia (Supplementary Table 4).

Primary outcome: caesarean delivery occurring after ~~the~~ onset of labour.

Allele scores were constructed for 7731 women with complete genetic data and outcomes recorded for the first two deliveries (Figure 1), of whom 10.6% had a zero allele score (Figure 2). For labouring women who did not receive neuraxial analg~~a~~esia (Figure 2), caesarean delivery rates were different across allele scores ($\chi 2$=12.4; *P*=0.015). *Post -hoc* analysis showed that 104/596 (17.4%) women with a zero allele score underwent caesarean delivery, compared to 654/5015 (13.0%) with allele scores ≥1 (OR:1.41, 1.12-1.77); *P*=0.005; Fisher's exact test). For labouring women who had neuraxial analg~~a~~esia (Figure 2), caesarean delivery rates were not different across allele scores (range:18.1-20.8%; $\chi 2$=0.29; *P*=0.99).

Between allele scores, caesarean delivery rates were independent of type of analgesia for 818/7731 (10.6%) women with zero allele scores (OR:0.93, 0.63-1.39), but caesarean delivery rates were higher in women receiving neuraxial analgesia with allele scores ≥1 (OR:1.55, 1.35-1.79; *P*<0.001).

Secondary outcomes

The proportion of women undergoing an instrumental delivery (Table 2) was not different between allele scores for either women who received neuraxial ($\chi 2$=8.5; *P*=0.08) or non-neuraxial analgaesia ($\chi 2$=6.3; *P*=0.18). Neither infectious/inflammatory complications nor a requirement for neonatal cardiorespiratory support differed across allele scores for neuraxial and non-neuraxial modes of analgaesia (Table 2).

Sensitivity analyses

Neuraxial analgaesia was associated with higher rates of long labour (odds ratio:5.25 (95%CI:4.57-6.03)) and foetal distress (odds ratio:3.71 (95%CI:3.32-4.15)). In the absence of foetal distress, IL-1ra allele score remained associated with higher caesarean delivery rates in women receiving non-neuraxial analgesia ($\chi 2$=15.0; *P*=0.005; zero allele score:74/484 ~~*versus*~~ *vs* allele scores ≥1:431/4052). There was no difference between allele scores for 342 women who received non-neuraxial analgesia but experienced long labours (odds ratio, 1.35; 95% CI, 0.63 to 2.87; P=0.44; Supplementary data).

Discussion

This Mendelian randomisation study of women in active labour suggest that women who have genetic variants that encode for lower IL-1ra production are more likely to require emergency ~~delivery by~~ caesarean delivery. This finding was related to the mode of analg~~a~~esia employed, since women who received non-neuraxial analgesia with allele scores ≥1 (corresponding to higher circulating IL-1ra levels) had lower rates of caesarean delivery than women with neuraxial analgesia. Taken together, these data support the hypothesis proposed by laboratory and translational studies indicating a mechanistic anti-inflammatory role for IL-1ra influencing outcomes in labour and delivery.[7, 8, 22]

The key assumption in our study is that the Mendelian randomisation approach we have undertaken is not merely an association study. The allele score we used has been constructed for IL1-ra on the basis of its[2] exclusive association with *IL1RN* mRNA levels in two tissues, a log-linear dose–response with soluble IL-1Ra concentration and an anti-inflammatory effect on biomarkers concordant with anakinra (recombinant human interleukin 1 receptor antagonist protein).[11] Thus, there is a fundamental difference between a SNP association study and the allele score approach we have taken, which is anchored by a consistent and reproducible relationship between genetic score, gene transcription and protein levels.

In humans, a ratio of IL-1ra/IL-1β >100 correlates with functional inhibition of the biological effects of IL-1β.[23, 24] The NLRP3 inflammasome is a ubiquitous and essential mediator of host inflammatory responses to danger and pathogen-associated molecular patterns through the activation of caspase-1 and interleukin-1 beta (IL-1β)/IL-18.[25] Mature IL-1β is a potent proinflammatory mediator, including the recruitment of innate immune cells to sites of infection and modulation of the adaptive immune response.[26] The failure to

temper the downstream activation of other proinflammatory cytokines as a results of impaired production and/or release of IL-1ra promotes pathological sequelae, ranging from exuberant tissue damage to ~~-~~fever. Adequate levels of IL1-ra contribute to the uncomplicated progression of labour through a number of anti-inflammatory and anti-infective mechanisms.[27] IL-1 is produced by human decidua in response to bacterial products and directly induces preterm labour when administered to pregnant animals, an effect that is blocked by IL-1ra. Recombinant IL-1ra decreases f~~o~~etal systemic inflammation generated by the release of IL-1β through chorioamnionitis in sheep. [7] Similarly, in rats, placental inflammation stimulated by microbial challenge is alleviated by the co-administration of IL-1ra. [28] The redundancy of the proinflammatory cytokine network involving additional cytokines and chemokines, rather than the anti-inflammatory actions of IL-1ra, suggests that a focus on pro-inflammatory mediators in determining complicated labours may be misplaced.

We have previously identified a potential role for impaired release of IL-1ra from immune cells being involved in intrapartum fever associated with neuraxial analg~~a~~esia using bupivacaine.[8] Secretion of IL-1ra from cells requires an extracellular ATP-dependent mechanism involving the purinergic P2X7 receptor in both macrophages and the endothelium.[29] The analgesic and inflammatory actions of lidocaine[30] and bupivacaine[31] are modulated by P2X7 receptors, suggesting a plausible mechanism through which the release of IL1-ra may be impaired. By undertaking two separate Mendelian randomisation studies in women receiving different modes of analg~~a~~esia during labour, our data ~~has~~ reveal~~ed~~ a potential differential role for IL-1ra in determining outcomes between women receiving neuraxial *versus* non-neuraxial analg~~a~~esia. The finding that higher levels of IL-1ra reduced the need for caesarean delivery in active labour suggest~~s~~ a mechanism whereby only a subset of patients develop epidural-related maternal fever~~ERMF~~, which is consistent with our

previous laboratory work examining mechanisms of epidural-related maternal fever.[8] From the current study, neuraxial analgaesia may abolish the apparently protective benefits of being a higher genetic producer of IL-1ra during active labour observed in the absence of neuraxial analgaesia (summarised in Figure 3). Because IL-1-ra is a leaderless protein residing in the cytoplasm awaiting extracellular release, local anaesthetic agents may disproportionately affect cells with larger amounts of residual IL-1-ra.

We found that the frequency of the two common variants located upstream of *IL1RN*, were as reported previously.[11] The use of an established allele score is a major strength, as this reduces the likelihood of ''canalization'', where adaptation to a genetically determined phenotype might alter the expected genotype-disease association.[32] A further strength of our study was the detailed data on analgaesia and a clear cut, clinically relevant outcome (unscheduled caesarean delivery) following active labour where women and clinicians were masked to genotype, using a prespecified analysis plan. Since the genetic score we used has been exclusively associated with *IL1RN* mRNA concentrations in adipose tissue and lymphoblastoid cell lines, employing this score is unlikely to be driven by neighbouring genes or variants (that is, there is no evidence for linkage disequilibrium).[11] The apparent lack of gene-dose dependent relationship in active labour requires further investigation, although this may reflect the lack of more granular, specific biological readouts including fever and other inflammatory markers.

The relationship between IL-1ra polymorphisms and antibiotic therapy in response to epidural-related maternal fever and/or the time to develop fever requires prospective data collection to determine whether knowledge of IL-1ra variants could influence clinical practice. To that end, we have recently commenced a prospective Mendelian randomisation study exploring the role of the IL1-ra genetic score in epidural-related maternal fever and antibiotic use (ISRCTN99641204). A further major limitation of this study is the dominance

of just two ethnic backgrounds as defined by the UK Biobank, with more than 93% of women with British or Irish white ethnicity. Severe maternal morbidity is more frequent among non-white women than among white women in the UK, particularly in black African and Caribbean ethnic groups.[33] The characteristics of this population are therefore consistent with fewer comorbidities of pregnancy, and appear to minimise genetic confounding by population stratification.[34]

The limitation of missing data not captured either by the UK Biobank for delivery and ~~anaesthetic~~ analgesia modes, as well as hospital episodes, is partly mitigated by the "randomised controlled" design of this study. The lack of more granular, time-stamped detail on the precise clinical reasons for caesarean delivery and the well-recognised uncertainty about the accuracy of ICD-10 coding[35] are further limitations. Because short- or long-term blockade of IL-1 signaling by IL-~~1Ra~~ 1ra prolongs and potentiates morphine analgesia in mice, we cannot rule out an influence of quality of analgesia and delivery outcomes.[36] A minimum local analg~~a~~esic concentration study in IL-1-ra genotyped humans may provide further insight into any interaction between pain and inflammation.[37] The sensitivity analyses for long labour and f~~o~~etal distress were hampered by low event rates for these complications, although the relationship between zero genetic variants in IL-1ra and higher rates for caesarean delivery appeared to be robust in the absence of f~~o~~etal distress.

In summary, our Mendelian randomisation analyses suggest that genetically-determined higher ~~IL-1ra~~interleukin-1 receptor antagonist levels are associated with a lower rate of intrapartum caesarean delivery. Neuraxial analgesia appears to disrupt this link. Our data reinforce the importance of inflammatory biology in determining outcomes for women and their newborn in active labour. Given the impact of labour management on longer-term child development, including fever and the use of intrapartum antibiotics, our data reinforce the need to understand how outcomes ~~may be~~are influenced through the interaction between

clinical interventions and endogenous mechanisms regulating the inflammatory response during active labour. ~~Genomically~~ Ttailored analgesic and obstetric interventions may shape inflammatory biology favourably to improve outcomes from active labour using a precision medicine approach in the future.

Author~~:~~s' contributions

~~:~~ GLA: concept, design, analysis, first draft

~~;~~ SVD: data extraction

~~;~~ TEFA: data processing

~~;~~ AGDA: data interpretation and writing first draft

~~;~~ MJW, ALD: critical revision of draft

~~; Anna L. David: critical revision of draft;~~ EPIFEVER-2 investigators: revision and approval of first draft.

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~~Conflicts~~ Declarations of interest

~~:~~ GL A is an e~~A: E~~ditor of the~~,~~ *British Journal of Anaesthesia*,~~;~~ and does consultancy work for GlaxoSmithKline~~,~~ unrelated to ~~-~~this work. TEFA is~~:~~ ~~Associate Editorial Board,~~social media editor of the *British Journal of Anaesthesia*, and does~~;~~ consultancy work for MSD, unrelated to ~~-~~this work.

Table 1. Characteristics of entire UK Biobank cohort of women who gave birth.

Mean (SD) age are shown. Numbers are unadjusted for complete single nucleotide polymorphism data.

	IL1-ra allele score				
	0	**1**	**2**	**3**	**4**
Women (n)	18673 (11.0%)	56335 (33.2%)	61766 (36.4%)	28296 (16.7%)	4602 (2.7%)
1-2 births (n, %)	15792 (71.0%)	47639 (70.9%)	52373 (71.0%)	23845 (70.6%)	3949 (71.8%)
Maternal age, yr (first birth)	25.4 (4.7)	25.4 (4.6)	25.5 (4.7)	25.4 (4.7)	25.6 (4.9)
Maternal age, yr (final birth)	30.1 (5.1)	30.1 (5.1)	30.1 (5.1)	30.1 (5.2)	30.2 (5.2)

Table 2. Secondary outcomes.

1. Instrumental delivery: classified by UK Biobank defined-categories for delivery requiring forceps or ventouse (vacuum extraction), excluding breech (including partial breech) extraction. Unknown outcomes were excluded.

2. Neonatal resuscitation modes, as classified by UK Biobank defined -categories for the use of positive pressure ventilation by mask or ~~endo~~tracheal tube, need for drug therapy but excluding stillborn babies where no ~~method of~~ resuscitation was attempted;

3. Fever and/or infection: using ICD-10 defined episodes captured in UK Biobank, combining maternal fever during labour (O75.2), genito-urinary infections (O23), maternal sepsis (O75.3) and premature rupture of membranes (O42).

	Non-neuraxial (allele score)						**Neuraxial** (allele score)					
	0	**1**	**2**	**3**	**4**	**$\chi 2$ (p)**	**0**	**1**	**2**	**3**	**4**	**$\chi 2$ (p)**
Instrumental[1]	59 (9.9%)	197 (10.6%)	241 (11.6%)	121 (12.9%)	10 (7.9%)	6.3 (0.18)	36 (16.2%)	170 (23.2%)	173 (22.3%)	90 (26.3%)	9 (18.8%)	8.5 (0.08)
Resuscitation[2]	66 (14.6%)	230 (15.9%)	272 (16.9%)	119 (16.3%)	15 (15.6%)	1.8 (0.77)	32 (16.2%)	91 (14.5%)	104 (15.2%)	56 (18.6%)	5 (12.2%)	3.3 (0.50)
Infection/inflammation[3]	27 (4.5%)	65 (3.5%)	78 (3.7%)	35 (3.7%)	9 (7.1%)	5.3 (0.26)	42 (18.9%)	151 (20.6%)	174 (22.5%)	80 (23.4%)	17 (35.4%)	7.6 (0.11)

Figure Legends

Figure 1. Flowchart showing analysis workstream for women with data on both delivery and mode of analgaesia in UK Biobank database.

Both the rs6743376 and rs1542176 single nucleotide polymorphism (SNP) are independently associated with circulating IL-1ra concentration from genome-wide association studies [11, 18] with similar, though independent, effects on IL-1ra concentration.[11]

Figure 2. Primary outcome: caesarean deliveries occurring after the onset of labour.

Proportion of women in each allele score undergoing caesarean deliveries occurring after the onset of labour, for neuraxial and non-neuraxial modes of analgaesia. Absolute numbers are shown within bar for each allele score. Percentage figures refer to proportion of women with outcome within each allele score. Allele scores were compared by Chi square test, with *post-hoc* testing by Fishers exact test. For labouring women who had neuraxial analgaesia (left panel), caesarean delivery rates were not different across allele scores ($\chi 2$=0.29; P=0.99). For labouring women who received non-neuraxial analgesia (right panel), caesarean delivery rates were different across allele scores ($\chi 2$=12.4; P=0.015). *Post-hoc* Fisher's exact tests found that 104/596 (17.4%) women with a zero allele score underwent caesarean delivery, compared to 654/5015 (13.0%) with allele scores ≥1 (P=0.005).

Figure 3. Proposed mechanism underpinning impact of IL-1ra polymorphisms on different outcomes between neuraxial and non-neuraxial modes of delivery.

Red dots represent IL-1α/β and/or other pro-inflammatory mediators. MyD88, myeloid differentiation primary response 88; NF-ĸB, nuclear factor kappa B. Blue stars represent IL1-ra.

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Table 3. Secondary outcomes.

1. Instrumental delivery: classified by UK Biobank defined-categories for delivery requiring forceps or ventouse (vacuum extraction), excluding breech (including partial breech) extraction. Unknown outcomes were excluded.

2. Neonatal resuscitation modes, as classified by UK Biobank defined-categories for the use of positive pressure ventilation by mask or endotracheal tube, need for drug therapy but excluding stillborn babies where no method of resuscitation was attempted;

3. Fever and/or infection: using ICD-10 defined episodes captured in UK Biobank, combining maternal fever during labour (O75.2), genito-urinary infections (O23), maternal sepsis (O75.3) and premature rupture of membranes (O42).

	Non-neuraxial (allele score)						**Neuraxial** (allele score)					
	0	**1**	**2**	**3**	**4**	**χ2 (p)**	**0**	**1**	**2**	**3**	**4**	**χ2 (p)**
Instrumental[1]	59 (9.9%)	197 (10.6%)	241 (11.6%)	121 (12.9%)	10 (7.9%)	6.3 (0.18)	36 (16.2%)	170 (23.2%)	173 (22.3%)	90 (26.3%)	9 (18.8%)	8.5 (0.08)
Resuscitation[2]	66 (14.6%)	230 (15.9%)	272 (16.9%)	119 (16.3%)	15 (15.6%)	1.8 (0.77)	32 (16.2%)	91 (14.5%)	104 (15.2%)	56 (18.6%)	5 (12.2%)	3.3 (0.50)
Infection/inflammation[3]	27 (4.5%)	65 (3.5%)	78 (3.7%)	35 (3.7%)	9 (7.1%)	5.3 (0.26)	42 (18.9%)	151 (20.6%)	174 (22.5%)	80 (23.4%)	17 (35.4%)	7.6 (0.11)

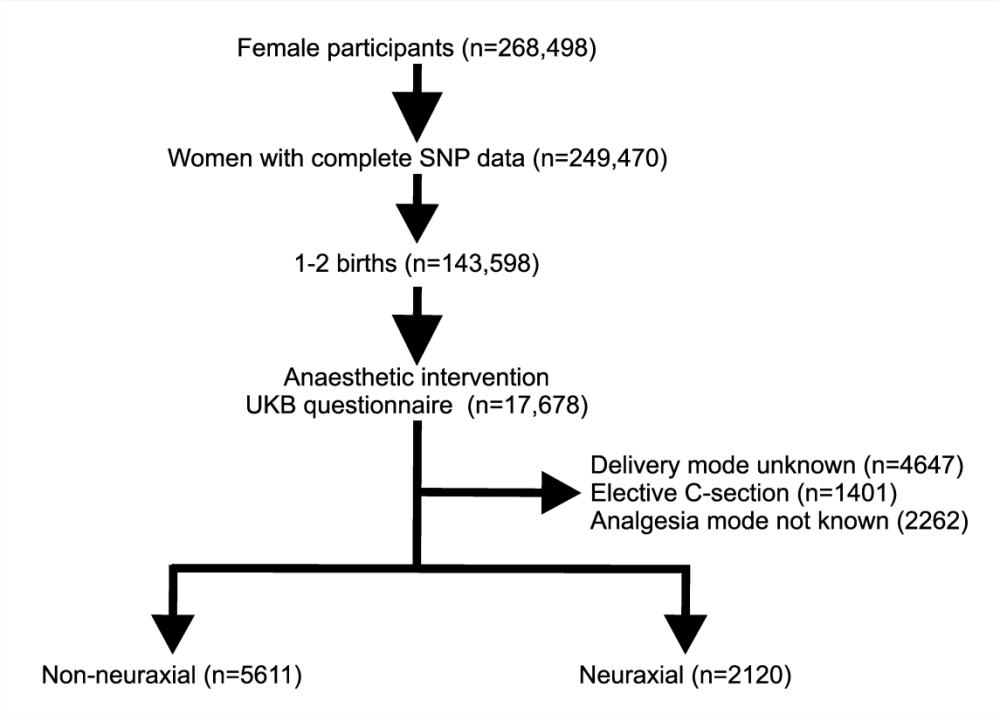

Figure 1. Flowchart showing analysis workstream for women with data on both delivery and mode of analgaesia in UK Biobank database.
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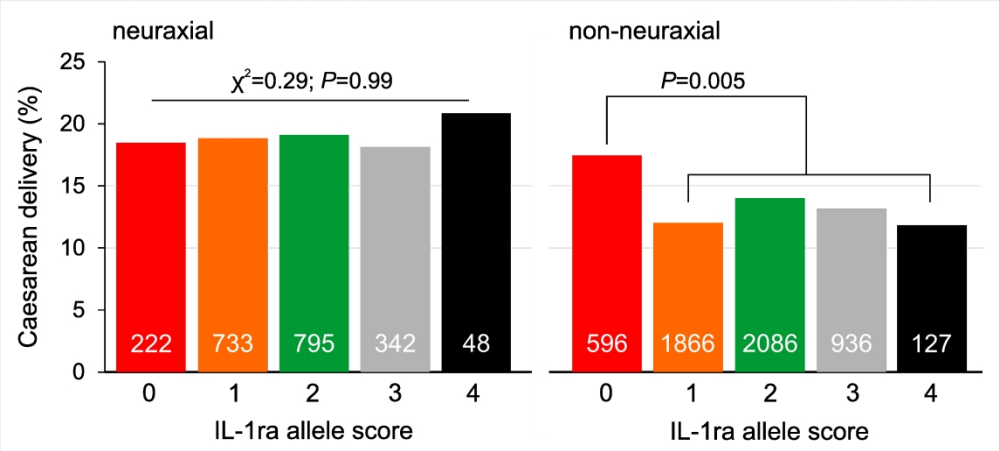
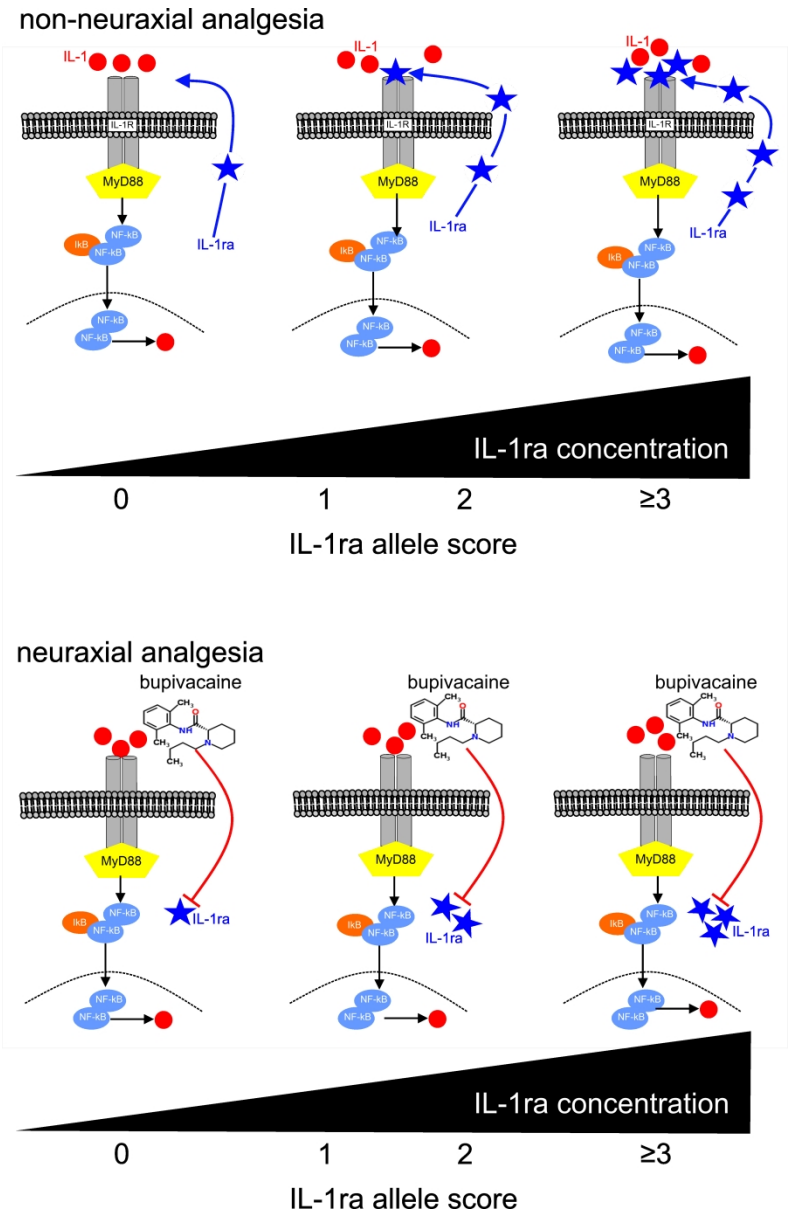


Figure 2. Primary outcome: Caesarean deliveries occurring after the onset of labour. Proportion of women in each allele score undergoing Caesarean deliveries occurring after the onset of labour, for neuraxial and non-neuraxial modes of analgaesia. Absolute numbers are shown within bar for each allele score. Percentage figures refer to proportion of women with outcome within each allele score. Allele scores were compared by Chi square test, with post-hoc testing by Fishers exact test. For labouring women who had neuraxial analgaesia (left panel), Caesarean delivery rates were not different across allele scores ($\chi 2=0.29$; P=0.99). For labouring women who received non-neuraxial analgesia (right panel), Caesarean delivery rates were different across allele scores ($\chi 2=12.4$; P=0.015). Post-hoc Fisher's exact tests found that 104/596 (17.4%) women with a zero allele score underwent Caesarean delivery, compared to 654/5015 (13.0%) with allele scores ≥1 (P=0.005).



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