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ORIGINAL ARTICLE

Does the delivery mode affect post-birth neonatal serum C-reactive protein levels? A causal effect analysis

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Aim: To determine if the delivery mode has a causal effect on neonatal serum C-reactive protein (CRP) levels. If such a causal effect exists, we aim to quantify its magnitude.

Methods: We investigated the causal effect of the delivery mode on serum CRP levels 6–8 h after delivery, with appropriate statistical tools for retrospective studies, combining classical and machine-learning methods. The statistical inference is followed by sensitivity analysis to quantify the magnitude of unobserved bias required in order to alter the study's conclusion.

Results: This retrospective study reviewed laboratory records of neonates after birth who underwent blood tests due to suspected sepsis. A total of 440 newborns were included, 324 of which underwent a vaginal delivery, 59 an urgent caesarean delivery, and 57 an elective caesarean delivery. Our results revealed that serum CRP values following elective caesarean deliveries were 50% less than those following a vaginal delivery ($P = 0.030$; −0.907; 95% CI [−1.545, −0.268] in log-CRP units). No significant effect was found for urgent caesarean deliveries compared to vaginal deliveries ($P = 0.887$). Those results were strengthened by (1) a sensitivity magnitude of 1.6 to unobserved bias and (2) non-significant effects when analysis is repeated on blood collected 12–24 h after birth.

Conclusion: CRP concentrations in neonatal blood during the first 6–8 h of life are higher following vaginal deliveries compared to elective caesarean deliveries. Further studies with the intent of improving EONS detection should include information on the delivery mode.

Key words: causal effect; C-reactive protein; delivery mode; neonate.

What is already known on this topic

1 Early-onset neonatal sepsis is a life-threatening blood infection in newborns.
2 A common biomarker is the elevation of serum C-reactive protein (CRP).
3 Associations between delivery modes and CRP levels were investigated in heterogeneous studies and findings are ambiguous.

What this paper adds

1 The causal effect of delivery mode on CRP values had not yet been studied.
2 Our results revealed that the CRP values following elective caesarean deliveries were 50% less than those following a vaginal delivery.
3 No significant causal effect was found for urgent caesarean compared to vaginal deliveries.

Introduction

Early-onset neonatal sepsis (EONS) is a potentially life-threatening blood infection in newborns that manifests itself within 72 h of life. The incidence of EONS ranges between 0.5 and 1.2 cases per 1000 live births.[1] Despite the low incidence rate of sepsis in term and late preterm infants, rapid progression of an untreated infection may greatly increase morbidity.

The signs and symptoms of neonatal sepsis are subtle and non-specific, and clinically indistinguishable from various other non-infectious conditions. C-reactive protein (CRP) is one of the most studied biomarkers commonly used in laboratory tests for the diagnosis of neonatal sepsis.[2] It is a simple, rapid, and cost-effective marker for the diagnosis of neonatal infection.[3] The elevation of CRP concentration (usually considered as being higher than 10 mg/L) is suspicious for the development of sepsis. A single normal value determined at the initial sepsis work-up, however, is not sufficient to rule out neonatal infection.[4]

Although there are a number of observational studies on associations between delivery mode and CRP levels that did adjust to

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numerous covariates,[5–7] none of them quantified the causal effect of the delivery mode on neonatal CRP levels with appropriate statistical tools. In retrospective studies, unlike random control trials, there may be bias introduced from (non-randomised) treatment allocation.[8] Analysis of observational data should account for both observed and hidden biases in order to reliably identify the effects of treatments as well as their magnitudes on the measure in question. For example, such a bias can be caused by the allocation of neonates in the 90th quantile of weight to an elective caesarean delivery.

CRP plays an important role in the detection of sepsis, but, at the same time, a CRP level at 6–8 h after birth is known to be an unstable predictor of the onset of sepsis. Thus, we suggest testing whether the delivery mode affects the newborn's CRP levels and estimating the magnitude of the effect. Estimating such effects can pave the way to develop a more reliable screening tool for sepsis.

Materials and Methods

Patients and data collection

In this retrospective case–control study, data were extracted from the real-time computerised database of our tertiary, university-affiliated medical centre between January 2017 and December 2018. The study population included all neonates born at our hospital that were transferred to the well-baby nursery after birth, and had at least one blood test taken for CRP analysis. Eligibility for study entry was limited to neonates of at least 35 weeks of gestation and < 12 h of age at admission who were suspected of developing EONS based upon prenatal risk factors. They underwent blood CRP tests at 6–8 h and 12–24 h after birth as part of the sepsis evaluation.

We reviewed and collected the neonates' laboratory data and information retrieved from the medical charts including sex, birth weight, presence of respiratory distress, mode of delivery, and maternal disease before, during, and after birth. The delivery mode was our treatment allocation variable and it was vaginal, elective caesarean, or urgent caesarean. The CRP level was our target variable. This study was approved by the Institutional Review Board of Tel Aviv Medical Center (approval number: 0216-18-TLV). Informed consent was waived because all data were de-identified. There was no interaction with patients or their families, and their anonymity was maintained.

Statistical analysis

The Conditional Average Treatment Effect (CATE)[9] should allow us to better understand the causal mechanism of a treatment allocation on the measure in question ('the treatment effect'). CATE is defined as the expected difference of the measure in question between an allocation to a treatment group versus an allocation to the control group.[10] Here, the treatment effect is the effect of either an elective or urgent caesarean delivery compared to the effect of a vaginal delivery (the control group's effect). The measure in question is the log-CRP levels. The analysis is done with log-transformed CRP values due to the CRP measure's natural skewness. *P*-values smaller than 0.05 were considered significant.

Three methods were used to estimate CATE: T-learner,[11] S-learner,[11] and propensity score matching[8] followed by permutational *t*-test.[12]

Each method was used for estimation of the causal effect, once for a vaginal delivery *versus* an elective caesarean delivery, and once for a vaginal delivery *versus* an urgent caesarean delivery. The S and T learners' analyses were repeated with 400 bootstrap samples in order to generate a confidence interval for the expected causal effect by using quantiles $q_{0.025}$ and $q_{0.975}$. For a brief description of each of the methods used see Appendix S1 (Supporting Information).

Causal graph

The first step in this observational study was to map the variables into groups according to their relationship with the treatment (delivery mode) and target variables (log-CRP value). The causal graph is used to help us decide which measures should be involved in the causal effect estimation models as covariates, and/or to produce matching pairs of subjects. Moreover, the causal graph is a tool that visually validates a strong assumption required in observational studies in which d-separate variables are used[13,14], that is, a nonexistent hidden bias caused by hidden variables. Since we make this strong assumption, and in order to provide evidence that it is reasonable as well, we conducted a sensitivity analysis after estimating each treatment effect's sizes on our target variable.

Sensitivity analysis

The sensitivity analysis is designed to provide us with an objective quantitative statement about whether unmeasured biases are present (due to hidden variables) and the bias magnitude would be required to change our conclusions. We used Rosenbaum's method[15] for this purpose. A study is considered sensitive if even a small departure from random assignment of treatment leads to inferences that are different from those obtained while assuming the study was free of hidden bias. As the departure level required increases, the chance of there being no hidden biases decreases, and the 'ignorability' assumption[16] weakens. We used the *sensitivitymw* R package for this purpose.[17]

Results

Four-hundred and forty neonates were included in this study of whom 258 (56.82%) were males, 324 were born via a vaginal delivery, 57 via an elective caesarean delivery, and 59 via an urgent caesarean delivery. Out of the 440 neonates, 285 had another CRP measurement taken 12–24 h after birth. Of those, only two (0.45% of the entire sample) had positive blood cultures correlates to EONS. A detailed demographic and clinical background of our sample is presented in Table 1. One can notice that the delivery mode groups are heterogeneous. For example, maternal diabetes is a common reason to elect a caesarean delivery, and it was more prevalent among the elective caesarean deliveries than the vaginal deliveries. That finding was also associated with neonates above the 90th weight percentile. Additionally, as expected, there was a longer time to rupture of membranes in the vaginal delivery group than among the other

Table 1 Descriptive means (SD) of all available covariates

	Vaginal ($n = 324$)	Urgent caesarean ($n = 59$)	*P* value urgent versus vaginal	Elective caesarean ($n = 57$)	*P* value elective versus vaginal
Sex (%)	0.44 (0.5)	0.41 (0.5)	0.694	0.39 (0.49)	0.499
Gestational age	39.38 (1.39)	38.94 (1.96)	0.107	37.79 (1.16)	<0.001
Pre-term (%)	0.05 (0.22)	0.17 (0.38)	0.002	0.16 (0.37)	0.006
Post-term (%)	0.01 (0.11)	0.03 (0.18)	0.232	0 (0)	NA
Gestational weight (>90%)	0.09 (0.29)	0.08 (0.28)	1.000	0.18 (0.38)	0.099
Meconium aspiration syndrome (%)	0.27 (0.45)	0.39 (0.49)	0.092	0.04 (0.19)	<0.001
Maternal diabetes (%)	0.07 (0.26)	0.1 (0.3)	0.643	0.21 (0.41)	0.003
SSRI treatment (%)	0.08 (0.28)	0.12 (0.33)	0.530	0.09 (0.29)	0.801
GBS positive (%)	0.25 (0.44)	0.12 (0.33)	0.037	0.16 (0.37)	0.166
Rupture of membranes (h)	8.41 (11.86)	11.47 (14.08)	0.121	1.07 (4.46)	<0.001
Maternal body temperature	37.1 (0.62)	37.25 (0.71)	0.121	36.68 (0.2)	<0.001
Temperature instability (%)	0.34 (0.47)	0.36 (0.48)	0.887	0.12 (0.33)	0.002
Grunting (%)	0.4 (0.49)	0.34 (0.48)	0.504	0.74 (0.44)	<0.001
Tachypnea/dyspnea (%)	0.3 (0.46)	0.2 (0.41)	0.164	0.47 (0.5)	0.017
Desaturation (%)	0.15 (0.36)	0.17 (0.38)	0.823	0.16 (0.37)	1.000
Chest X-ray irregularity (%)	0.45 (0.5)	0.34 (0.48)	0.160	0.75 (0.43)	<0.001
Log CRP	0.26 (1.77)	−0.2 (1.88)	0.081	−1.02 (1.29)	<0.001

GBS, group B streptococcus; SSRI, selective serotonin reuptake inhibitors. Binary variables are described with percentage of positive occurrences. *P*-values are obtained from a two-sample (elective caesarean delivery vs. vaginal delivery or urgent caesarean delivery vs. vaginal delivery) *t*-test for continuous measures, a χ^2 test for binary measures and an exact Fisher test if at least one cell in a contingency table has fewer than five observations.

two treatment groups. The log-CRP variable means comparison suggests that neonates from elective and urgent caesarean deliveries have lower CRP concentrations than neonates of vaginal deliveries (Fig. 1).

Next, we explored the causal relationships between the available variables with the treatment variable (delivery mode) and with the log-CRP, our target variable (Fig. 2). One can think of a more detailed representation of the problem that considers some hidden variables (H) that may affect the log-CRP values, and we do not observe them. In order to continue with our observational study, we assume that we observe the d-separate variables,[13,14] that is, we observed mediators variables instead of those hidden ones. A representative case of hidden variables and their d-separation sets is illustrated in Figure 3.

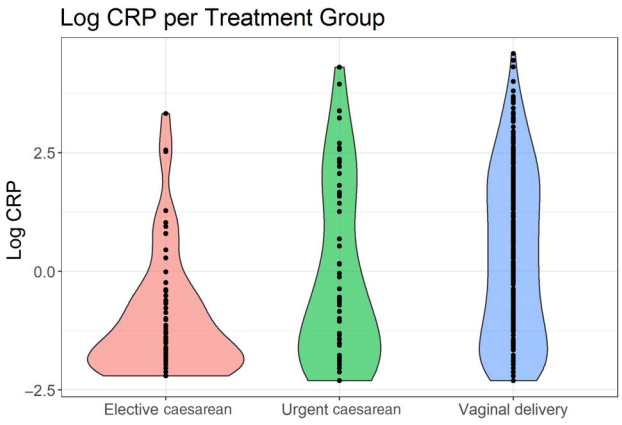

Fig. 1 Log-CRP values per Treatment Group.

Causal inference

The analysis started with propensity score matching, and it quickly emerged that there was a lack of any overlap between elective caesarean and vaginal deliveries when the propensity score was 0.75 or higher (Fig. 4). We therefore decided to carry out our analysis twice – once on all of the data while ignoring this lack of overlap, and once using only those samples that had propensity scores lower than 0.75 (this filtering is done to create a more balanced dataset). Since the propensity score measures a neonate's probability of being allocated to one of the caesarean section deliveries, having another neonate with a similar probability in the vaginal delivery group may reduce bias. Sub-setting the data in such a way resulted in dropping approximately 1/3 of the elective caesarean delivery subjects (22 from 57) and a single sample from the vaginal delivery group. Similarly, we applied the same dropping mechanism for the urgent caesarean delivery versus the vaginal delivery group but used a 0.55 threshold.

Table 2 displays the results in terms of estimated causal effects resulted from applying the three methods described in the Methods section – once on all observations and once with the extreme propensity score filter – for both birth types comparisons. These CATE estimations represent the expected difference in log-CRP values between allocating a subject to one of the caesarean section deliveries versus a vaginal delivery. The average CATE estimators for elective caesarean deliveries ranged between −0.554 and − 0.119 when estimated on the full dataset and

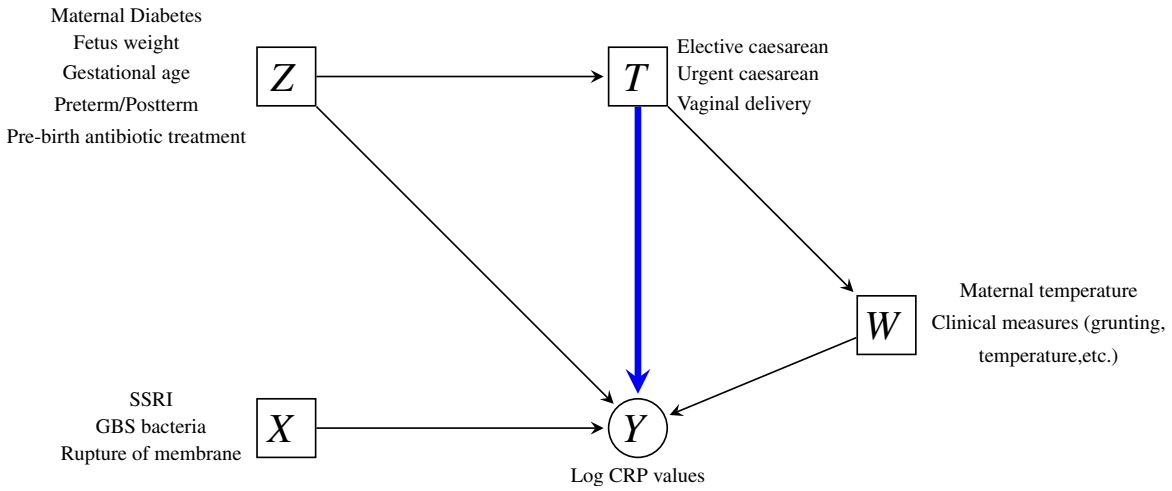

Fig. 2 Causal graph of observed covariates. Causal graph of available variables and their relationship with the treatment (*T*) and the outcome measure (*Y*). Group *Z* contains variables that may influence both treatment and outcome, group *X* includes variables that may affect only the outcome, and group *W* includes measures that may be affected by the treatment allocation and affect the outcome. Variables in groups *W*, *X*, and *Z* are used for matching and/or as covariates in each analysis method that was used.

between −0.829 to −0.907 when estimated on the filtered dataset. Interestingly, effect sizes were consistent across the three methods when estimated with the filtered dataset, in contrast to when they were estimated with the full data. Furthermore, the difference in log-CRP levels was significant for an elective caesarean section delivery compared to a vaginal delivery.

Translating the effect observed in log-CRP units back to the original CRP values means that for two neonates who are similar in terms of their characteristics, where one is randomly allocated to an elective caesarean delivery and the other to a vaginal delivery (under the assumption this kind of random allocation is feasible), we would expect that the CRP levels of the neonate who was born *via* an elective caesarean delivery will be roughly half of those observed for an infant who was born via a vaginal delivery.

The average CATE estimators for urgent caesarean deliveries ranged between −0.048 and −0.151 for both datasets and were not significantly different from those of a vaginal delivery. In order to validate our results, we repeated the CATE estimation process with a target variable of a second CRP measure taken 12–24 h after birth. The second CRP measure was available for 285 neonates out of the 440 (64.8%). All of the comparisons between the CRP levels were non-significant (Table 3).

Sensitivity analysis

As mentioned earlier, we are assuming the inexistence of hidden variables that might enter some bias to our CATE estimators. We therefore conducted a sensitivity analysis aimed to quantify the

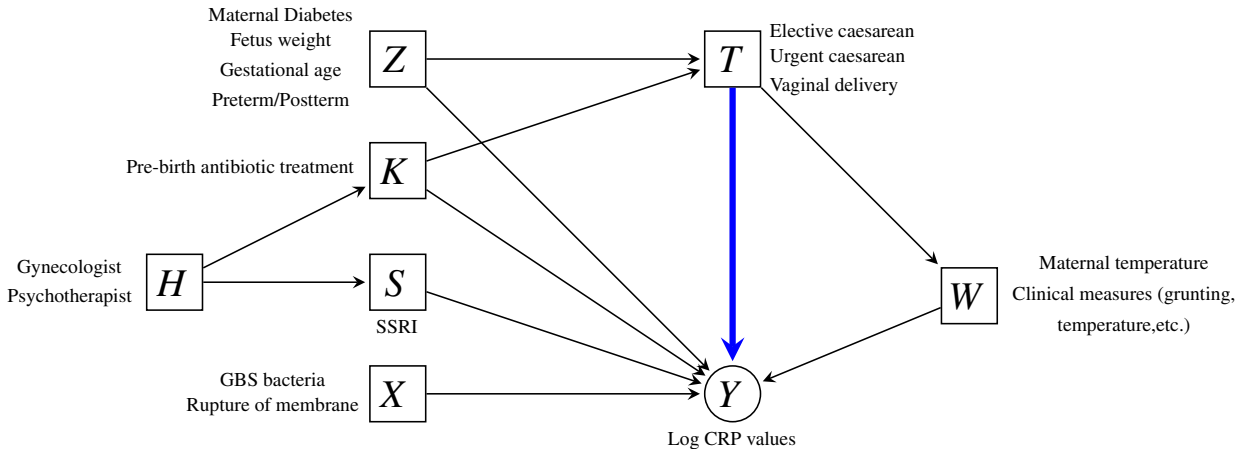

Fig. 3 Causal graph when assuming hidden variables. Causal graph of available variables and their relationship with the treatment (*T*) and the outcome measure (*Y*), with an illustration of hidden variables (*H*). Groups *K* and *S* are the mediators variables that are assumed to capture the effect of the unobserved hidden variables. Group *Z* contains variables that may influence both treatment and outcome, while group *X* includes variables that may affect only the outcome.

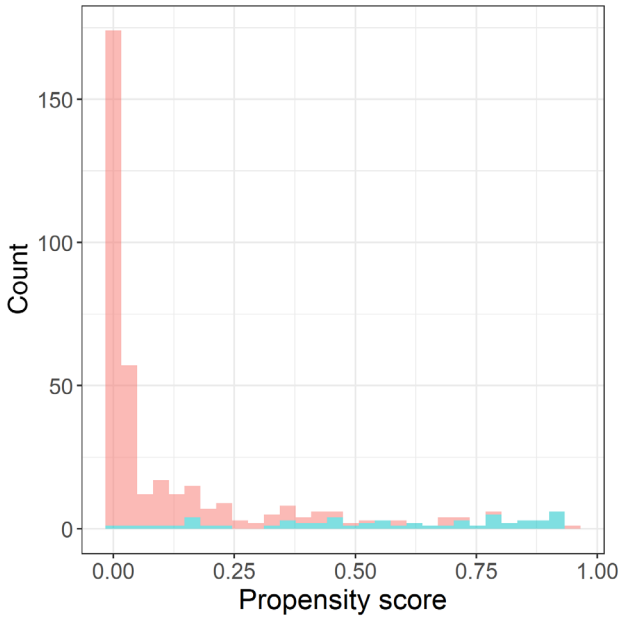

Fig. 4 Propensity score histograms colour coded by treatment allocation group. Treatment group: (■), Vaginal delivery; (■), elective caesarean

hidden bias magnitude needed to alter the study's conclusions. This magnitude is denoted as Γ. Γ represents the required ratio between the probabilities to be allocated to the treatment group *versus* the control group to change our conclusions. Tables 4 and 5 list the sensitivity results of the matching analysis applied to compare elective caesarean deliveries with vaginal deliveries on the full dataset and the extreme propensity score filtered dataset, respectively. No sensitivity analysis for urgent caesarean deliveries is presented since we did not find any significant differences in the effects of urgent caesarean deliveries in comparison to vaginal deliveries. Our sensitivity analysis on the full dataset of the elective caesarean delivery analysis revealed a modest magnitude of sensitivity to hidden bias ($\Gamma > 1.3$). For $\Gamma = 1.6$, the *P*-value is 0.056. In other words, our analysis on the extreme propensity score filtered dataset was sensitive to unmeasured biases of a magnitude $\Gamma \approx 1.6$ (Table 4).

Discussion

In the present study, we found that CRP concentrations in neonatal blood during the first 6–8 h of life are higher among neonates who are born *via* vaginal deliveries and urgent caesarean deliveries compared to elective caesarean deliveries. This is likely due to perinatal stress experienced during the former two modes of delivery. Few published studies investigated associations between CRP levels and the mode delivery.[5–7] Perrone *et al.*[7] aimed to find CRP reference values during the perinatal period in healthy term newborns during the first 48 h. The conclusions of those authors were that gestational age and mode of delivery significantly influence CRP values. That association was found to be significant for CRP measures taken 48 h after birth and not for 6–

Table 2 Causal effect of caesarean section deliveries versus vaginal delivery on log-CRP values obtained 6–8 h after birth

	Elective caesarean versus vaginal		Urgent caesarean versus vagina	
	Full dataset	Propensity score filtered dataset	Full dataset	Propensity score filtered dataset
S-learner	−0.119; [−0.470, 0.058]	−0.832; [−1.528, −0.196]	−0.132; [−0.705, 0.411]	−0.151; [−0.789, 0.454]
T-learner	−0.384; [−0.954, 0.107]	−0.829; [−1.529, −0.143]	−0.127; [−0.711, 0.427]	−0.137; [−0.734, 0.464]
Propensity score matching	−0.554; [−0.996, −0.112], $p = 0.015$	−0.907; [−1.545, −0.268], $p = 0.030$	−0.048; [−0.734, 0.638], $p = 0.887$	−0.048; [−0.734, 0.638], $p = 0.8887$

Estimations provided by applying three analysis methods: (i) propensity score matching followed by a permutational *t*-test – mean; [95% CI] and *P*-value, (ii) T-learner – median; $[q_{0.025}, q_{0.975}]$ and (iii) S-learner – median; $[q_{0.025}, q_{0.975}]$.

Table 3 Causal effect of caesarean section deliveries versus vaginal deliveries on log-CRP values obtained 12–24 h after birth

	Elective caesarean versus vaginal		Urgent caesarean versus vaginal	
	Full dataset	Propensity score filtered dataset	Full dataset	Propensity score filtered dataset
S-learner	−0.165; [−0.558, 0.032]	−0.517; [−1.414, 0.325]	−0.682; [−1.253, −0.036]	−0.686; [−1.285, 0.009]
T-learner	−0.550; [−1.233, 0.135]	−0.509; [−1.400, 0.380]	−0.653; [−1.343, −0.109]	−0.678; [−1.311, 0.034]
Propensity score matching	−0.620; [−1.284, 0.044], *P*-value = 0.067	−0.693; [−1.607, 0.219], *P*-value = 0.130	−0.756; [−1.658, 0.146], *P*-value = 0.098	−0.756; [−1.658, 0.146], *P*-value = 0.098

Estimations provided by applying three analysis methods: (i) propensity score matching followed by a permutational *t*-test – mean; [95% CI] and *P*-value, (ii) T-learner – median; $[q_{0.025}, q_{0.975}]$ and (3) S-learner – median; $[q_{0.025}, q_{0.975}]$.

Table 4 Sensitivity analysis output of the causal inference, on the full dataset, of elective caesarean deliveries versus vaginal deliveries

	$\Gamma = 1$	$\Gamma = 1.1$	$\Gamma = 1.2$	$\Gamma = 1.3$
Upper bound *P*-value	0.008	0.016	0.029	0.047
One-sided CI	[0.186, Inf]	[0.121, Inf]	[0.061, Inf]	[0.006, Inf]

The columns indicate different magnitudes of hidden bias. The first row details the respective upper bound *P*-value on the one-sided permutational *t*-test, and second line presents a one-sided CI of the causal effect.

8 h as was observed in our study. Contrarily, Rouatbi *et al.*[6] did not find any significant associations between CRP levels and delivery modes, even when adjusting for numerous covariates. Moreover, Logan *et al.*,[5] who aimed to find associations between delivery mode and labour duration with CRP while adjusting to numerous confounders, found such associations to be significant for mode of delivery, labour duration, and most confounders. All the above studies were reporting on trends and significant associations, but none of them had focused on the causal effect and the magnitude one delivery mode has upon CRP levels compared to another.

By conducting an observational study in order to better understand the mechanisms of different delivery modes on post-delivery CRP levels measured in neonates, we managed to find a significant reducing effect of elective caesarean deliveries on CRP levels measures. Moreover, the causal effect magnitude of elective caesarean was around one-half of what is expected from allocating the same neonate to the vaginal delivery group. Although the sensitivity analysis revealed modest sensitivity towards bias magnitudes of at least 1.3 and 1.6 for the analysis conducted on the full dataset and the extreme propensity score filtered dataset, respectively, we believe that we managed to capture most, if not all, of the bias factors in the observed covariates.

The limitations of this study are that the current study population excluded newborns transferred to the neonatal intensive care unit immediately after delivery. It is possible that this population of more severely symptomatic neonates may have yielded different results. Moreover, the analysis was further restricted to neonates that underwent an EONS evaluation, indicative of their having either been symptomatic or they had perinatal risk factors for infection, both of which were included as confounders. Another limitation is the fact that we used only 1–1 (treatments-control) matching (and not, for example, 1–3 matching) in the matching process. We decided to focus only upon 1–1 matching since we lacked overlapping medium-high propensity scores for the vaginal delivery group.

Table 5 Sensitivity analysis output of the causal inference, on the propensity score filtered dataset of elective caesarean deliveries versus vaginal deliveries

	$\Gamma = 1$	$\Gamma = 1.2$	$\Gamma = 1.5$	$\Gamma = 1.6$
Upper bound *P*-value	0.004	0.013	0.042	0.056
One-sided CI	[0.376, Inf]	[0.224, Inf]	[0.033, Inf]	[−0.024, Inf]

The columns indicate different magnitudes of hidden bias. The first row details the respective upper bound *P*-value on the one-sided permutational *t*-test, and the second line presents the one-sided CI of the causal effect.

EONS can be a highly fatal condition that requires immediate treatment. Blood culture is the gold standard for sepsis diagnosis, but it is time-consuming and has a low positivity rate. Thus, CRP is often used as a biomarker to support the clinical diagnosis of EONS. CRP measure is also considered for deciding the duration, adjustment, and discontinuation of antibiotic therapy. On the opposite, there is a broad agreement that a biomarker such as CRP is insufficient to decide if to start antibiotic therapy due to a poor positive predictive value.[4,18,19] Nevertheless, and although controversy is issued in this matter, CRP remains a marker for deciding whether to start or continue antibiotic therapy.[20] In our sample, out of the 440 neonates suspicious of EONS, all received antibiotic treatment, although only two had blood cultures positive to EONS after 24 h of life. Thus, developing a reliable set of early-indicator for EONS may help reduce the stress and trouble caused to the parents and neonate from the repeated blood measures and the medical staff from the long supervision required currently to verify the diagnosis of sepsis.

In conclusion, the mode of delivery can affect the level of CRP in the first 6–8 h of life. Therefore, when deciding whether to start antibiotic treatment or not, the practitioner needs to consider the mode of delivery. Moreover, further studies with the intent of improving EONS detection by finding early markers for EONS, or thresholds establishment for EONS high suspicion, based on the first 6–8 h of life, need to take into account the delivery mode.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Description on each of the three methods used for CATE estimation.

Banana by Alex Kim (aged 13) from "A Pop of Colour" art competition, Youth Arts, Children's Hospital at Westmead