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# The long-term effects of birth by caesarean section: The case for a randomised controlled trial

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ABSTRACT

Birth by caesarean section is rising rapidly around the world and is associated with a range of adverse short and long-term outcomes in offspring. The latter include features of the metabolic syndrome, type-1 diabetes, and asthma. Though there are several plausible candidate biological mechanisms, evidence of a causal relationship between mode of delivery and long-term outcomes remains lacking. Here we review the evidence to date, and examine ways in which future studies might advance understanding. We conclude that a randomised controlled trial of mode of delivery for the healthy term, cephalic pregnancy, is neither unethical nor unfeasible and should be seriously considered as the optimum means of addressing a question of great relevance to public health.



## 1. Introduction

In 2011 the UK National Institute for Health and Clinical Excellence (NICE) guidelines [1] were modified to support offering caesarean section (CS) to women who, after discussion with a mental health expert, feel unwilling to accept a vaginal delivery (VD). This guideline is likely to fuel further increase in an already high and rapidly rising CS delivery rate worldwide.

The reasons for the exponential rise in CS deliveries are complex. Whilst maternal choice is often considered the major factor, many studies suggest otherwise [2]. Both pre-labour CS (PLCS) and in-labour CS (ILCS) [3] are on the rise, suggesting clinicians may play a significant role. Indeed, pregnant women may accept higher risks to give birth by VD, than obstetricians [4]. A meta-analysis of women's preference for CS delivery (38 studies; n = 19403) gave a pooled preference for CS of 15.6% [95% confidence-intervals (95% CI) 12.5–18.9] [5]; but this was lower in women who had not previously given birth by CS (10.1 [95% CI 7.5–13.1]), compared to women who had (29.4 [95% CI 24.4–34.8]). A randomised controlled trial (RCT) of standard care, compared to decisional aids, to inform women who had had a previous CS delivery about birth choices for subsequent pregnancies, showed that use of decisional aids increased VD [6]. These data suggest that standard care may not adequately empower mothers to make an informed decision about birthing choices, possibly increasing the CS rate. The authors concluded that use of appropriate decisional aids in antenatal clinics could substantially reduce the rate of CS in the UK. We believe that understanding the long-term impact of CS on the offspring is vital to reassessment of the increasing role of CS in the obstetric population. We will review current evidence of long-term outcomes following CS, and consider possible research strategies to test causality and advance understanding of underlying biological mechanisms.

## 2. Long term health outcomes of CS delivery

Many studies have suggested that CS affects long-term health. These can be loosely grouped into conditions associated with the metabolic syndrome, the immune system, dentition, malignancies, and the nervous system. We will review each of these in turn.

### 2.1. Features of the metabolic syndrome

The term "metabolic syndrome" is used to describe a constellation of features, namely abdominal adiposity, hypertension, dyslipidaemia and insulin resistance, that are associated with type-2 diabetes and cardiovascular disease.

#### 2.1.1. Increased BMI and obesity

Several studies report on the relationship between CS and greater body mass index (BMI) or obesity in offspring; these are contradictory. In the USA, a prospective cohort study of 1255 mother–child pairs, showed no association between CS and risk of overweight at age 3 after adjustment for maternal age, education, ethnicity, pre-pregnancy BMI, and offspring birth weight, age at measurement and sex (OR 1.24 [95% CI 0.86, 1.77]) [7], although an increased risk of obesity following CS (OR 2.10 [95% CI 1.36, 3.23]) and a 0.20 unit increase in BMI

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z-score [95% CI 0.07–0.33] were noted. These data may indicate a non-normal data distribution. In sub-group analyses there was no difference between types of CS (planned-CS OR 2.32 [95% CI 1.18–4.55] and unplanned-CS OR 2.42 [95% CI 1.52–3.83]), comparing each against VD, although after adjustment, only unplanned-CS was significantly associated with increased obesity (OR 2.19 [95% CI 1.34–3.55]). A cohort study of nearly 200,000 adolescents (15–19 years) applying for driving licences in Utah, USA, showed those born by CS were 1.4 times more likely to be overweight than those born by VD [8].

A case–control study in China of 162 pre-school children, produced an adjusted OR of 5.23 [95% CI 1.24–22.04] for obesity following CS compared to VD [9]. In Brazil, a study measuring BMI at 4, 11, 15 and 23 years of age, reported increased obesity prevalence in CS compared to VD offspring up to 15 years, but not at 23 years [10]. When adjusted for covariates, obesity prevalence was reduced and there were no differences between the birth groups at any age excepting the 4 year old males (OR 2.03 [95% CI 1.20, 3.42] following CS). However, another Brazilian cohort ($n=2057$) of 23–25 year olds demonstrated increased obesity prevalence following CS compared to VD (prevalence ratio: 1.46 [95% CI 1.15, 1.85]); the prevalence ratio remained significant after adjusting for covariates (1.58 [95% CI 1.23, 2.02]) [11].

Most differences in obesity following CS delivery are reported in children. Importantly, a recent estimate suggests that >10,000 individuals would be required to achieve 80% power to detect differences in obesity between offspring born by CS or VD [12]. The study of 28,354 Danish children aged 7, by Ajslev et al. [13], reported an unadjusted association between CS and childhood overweight (OR 1.15 [95% CI 1.02–1.29]) [13], but after adjustment for maternal and infant factors (e.g. maternal BMI, birth weight and breastfeeding) the association was attenuated (OR 1.01 [95% CI 0.82–1.24]).

#### 2.1.2. Adiposity

A study in which skinfold measurements in 1255 American 3 year olds were measured reported a 0.94 mm [95% CI 0.36. 1.51] increase in the sum of skinfolds in CS compared to VD children [7]. However, there was no association between mode of delivery and subscapular: triceps skinfold ratio, a measure of central adiposity ($\beta$ −0.18 [95% CI −2.30, 1.94]).

#### 2.1.3. Possible mechanisms driving increased BMI in CS delivered infants

There are several postulated mechanisms that might link CS and increased offspring BMI [14]. In animals, alterations in metabolism, in particular preferential storage of fat and lower gluconeogenic flux, following PLCS birth may drive increased BMI and adiposity [15]. Alternatively, in our meta-analysis, including over half a million subjects, of breast feeding following CS [16], we showed that the OR for breast feeding initiation following CS compared to VD was 0.57 [95% CI 0.50–0.64]. Significantly, this association only held when comparing PLCS with VD (OR 0.83 [95% CI 0.80–0.86]) and not when comparing ILCS with VD (OR 1.00 [95% CI 0.97–1.04]). Differences in breast feeding consequent upon mode of delivery may contribute to later-life obesity [17]. Differences in circulating concentrations of orexigenic peptides in early life may also programme appetite regulation [18]. The infant microbiome, which is known to differ according to mode of delivery, may also drive obesity, with certain microbial species being associated with altered energy harvesting and consequently with a risk of obesity [13].

#### 2.1.4. Interaction between maternal BMI and mode of delivery

Several confounding factors may account for the association between CS and offspring BMI, especially maternal BMI which is closely associated with increased risk of CS delivery. We reported that infant intrahepatocellular lipid (IHCL) is associated with maternal pre-pregnancy BMI, but the association is dependent on the mode of delivery (mode of delivery $p=0.025$, maternal BMI $p=0.030$, interaction between mode of delivery and maternal BMI $p=0.022$). Maternal BMI is associated with a significant increase in IHCL in PLCS infants (32% increase [95% CI 10%, 59%] per kg/m$^2$ increase in maternal BMI); but has no effect in ILCS infants (6% [95% CI −17%, 35%] per kg/m$^2$ increase in maternal BMI) or infants born by VD (0.4% [95% CI −6%, 7%] per kg/m$^2$ increase in maternal BMI) [19]. In 3 year old American children, the association between CS and obesity was reduced in offspring of obese mothers (BMI≥25 kg/m$^2$; OR 2.97 [95% CI 1.58, 5.60]) compared to normal weight mothers (<25 kg/m$^2$; OR 1.61 [95% CI 0.88, 2.96]) [7].

#### 2.1.5. Blood pressure

There are reports of lower neonatal blood pressure following CS, [20–24], including the suggestion that these differences persist up to three months of age [21]. In children aged 7–9 years, born preterm ($n=756$), systolic blood pressure was lower if born by CS compared to VD (CS: 99.3 ± 10.0 (mean ± SD), VD: 104.4 ± 9.4 mm Hg; $p=0.003$) [25], whilst in the term born control cohort ($n=166$) there was no difference in blood pressure between children born by CS or VD, even after adjustment for sex, gestational age, age at measurement and height [25]. These data suggest that blood pressure may be affected by a complex interaction between gestational age and mode of delivery, although mechanisms driving this are unknown. In the short-term reduced plasma concentrations of renin [26] and angiotensin II [27] in CS neonates, possibly driven by higher cord blood pH [28], could conceivably drive altered blood pressure between CS and VD infants [26].

### 2.2. Dentition

A study of 102 Spanish children (51% low-birth weight (LBW)) assessed at age 4–5, showed that CS delivered infants had increased risk of enamel hypoplasia compared to VD infants ($p=0.024$) [29]. The number of LBW infants in the cohort may be a confounder; LBW infants have ≈4 four times more hypoplasia than normal-birth weight children, and LBW is an independent risk factor for CS. However, a study of the width of the neonatal line in primary tooth enamel, suggested it was altered by birth experience (11.9 ± 4.8 μm (mean ± SD) in children born by normal VD; 18.6 ± 5.7 μm in children born by "difficult operative delivery"; 7.6 ± 1.5 μm in children born by CS) [30]. Perinatal stress, can determine the size of the neonatal line [31]. Another study showed no significant difference between the neonatal line in children born by CS compared to VD [32].

### 2.3. Immune related conditions

#### 2.3.1. Type-1 diabetes

Infants born by CS have greater incidence of type-1 diabetes mellitus (T1DM). A meta-analysis (20 independent data-sets; 2,133,236 subjects; 205,941 delivered by CS and 9938 cases of T1DM), showed higher incidence of T1DM in children born by CS compared to VD (OR 1.23 [95% CI 1.15, 1.32] $p\leq0.001$; random effects model; heterogeneity: $I^2=0\%$, $p=0.54$) [33].

In a German cohort study of 1650 children born to a parent with T1DM, the association between CS delivery and increased risk of T1DM in childhood was confirmed (Hazard ratio 2.5 [95% CI 1.4, 4.3]) [34]. However, CS was not associated with increased islet autoantibodies ($p=0.6$), but there was an association with a faster progression to symptoms of T1DM after the first identification of islet autoantibodies in CS compared to VD children ($p=0.015$). Additionally there were interactions between mode of delivery and genetic susceptibility; T1DM and expression of the interferon-induced helicase-1 gene were only associated in CS delivered children. In another study, CS appeared to protect against the association between T1DM and expression of the gene *PTPN22* [35]. Altered gut microflora, the hygiene hypothesis and perinatal stress have been postulated as plausible mechanisms linking CS and T1DM [36].

#### 2.3.2. Asthma

A meta-analysis of 23 studies showed that the OR for asthma in offspring born by CS compared to VD was 1.22 [95% CI 1.14, 1.29], however there was significant heterogeneity [37]. Restricting analysis to childhood asthma, reduced the heterogeneity, with an OR for asthma after CS birth of 1.20 [95% CI 1.14, 1.26]. The pooled OR for the three studies reporting asthma in adults born by CS was 1.87 [95% CI 1.03, 3.41].

Other large studies have since supported these findings. A prospective cohort of 2 million Norwegians showed an increased hazard ratio for asthma in children born by CS compared to VD (1.52 [95% CI 1.42, 1.62]) [38], but the risk of asthma appeared to be slightly higher following ILCS (1.42 [95% CI 1.25, 1.61]) than PLCS (1.59 [95% CI 1.44, 1.75]), when compared to VD children. Analysis of hospital admissions for asthma in children in the Oxford Record Linkage study (n = 248,612) showed increased incidence of asthma following CS vs. VD birth (OR 1.2 [95% CI 1.0–1.3]) [39]. These data suggest an association between CS and later-life asthma, but conflicting data is available in the literature [40]. Given later-life asthma is associated strongly with respiratory morbidity at birth [41] and that CS delivery is also associated with short-term changes in lung function at birth [42]; there may be confounding in this association.

#### 2.3.3. Atopy

An association between CS and atopy, the diagnosis of which varies widely, is more difficult to ascertain. In 2008, a meta-analysis of the risk of atopy and allergy in offspring born by CS compared to VD showed an increased risk for food allergy (OR 1.45 [95% CI 1.12, 1.86]) and allergic rhinitis (OR 1.24 [95% CI 1.08, 1.43]), but not for inhalant atopy (OR 1.07 [95% CI 0.82, 1.38]) or eczema/atopic dermatitis (OR 1.03 [95% CI 0.98, 1.09]) [43]. A systematic review of food allergy suggested that development of IgE-associated food allergen sensitisation was associated with CS compared to VD infants [44]. Since then, a prospective cohort study failed to show increased food allergy associated with CS [45]; whilst a further prospective cohort showed increased IgE mediated cow's milk allergy in children born by CS (OR 2.14 [95% CI 1.02, 4.49]) [46].

#### 2.3.4. Gastrointestinal diseases

A case–control study demonstrated a significant association between CS and coeliac disease (OR 1.80 [95% CI 1.13–2.88]), but not with Crohn's disease or ulcerative colitis [47]. A Norwegian study of 171 inflammatory bowel disease (IBD) patients, compared to a national birth cohort (n = 698452), showed that IBD patients were less likely to be delivered by CS compared to controls (OR 0.27 [95% CI 0.10, 0.73]) [48]. A large matched case–control study with medical record linkage in Sweden (case n = 11,749; control n = 53887), found no difference in OR for coeliac disease between CS vs. VD delivered subjects (1.04 [95% CI 0.98–1.10]) [49], however, when CS deliveries were divided into PLCS and ILCS, the association held only for PLCS delivered subjects (OR 1.11 [95% CI 1.01–1.22]; after adjustment for gender, maternal age at delivery, parity and birth date: OR 1.12 [95% CI 1.04–1.26]).

#### 2.3.5. Mechanisms

Several mechanisms may link CS and later-life immunological conditions. Principally, differences in microbiome between CS and VD delivered infants [50]; speciation and rates of colonisation of the neonatal gastrointestinal tract [51], mouth [52] and skin are dependent on the mode of delivery, although skin commensals of VD infants can be markedly different from the maternal vaginal flora [53]. The microbiome regulates the neonatal immune system, provoking production of regulatory T cells, determining the Th1/Th2 balance [54]. The metabolome of gut microflora probably induces host epigenetic imprinting, including the immune system [55]. Although the impact is poorly understood, infants with atopy have a gut microbiome distinct from those without atopy [56]. Despite identification of *Clostridium difficile* as a species associated with the link between CS birth and asthma [57], the causal pathway is unknown.

We have shown reduced breast feeding following CS compared to VD [16]. Breastfeeding alters infant gut microflora, particularly colonisation with *C. difficile* [58], possibly mediated by milk oligosaccharides [59]. Several studies show an association between breast feeding and reduced incidence of asthma [60] and T1DM [61].

Differences have however been reported in immune function between CS and VD neonates before microbiome establishment. Cord concentrations of immune cell types [62] and activity of immune cells, differ post-partum in PLCS compared to VD neonates [63,64]. Furthermore, in piglets, gene expression related to the innate immune system, at 7 days post birth, differs between PLCS and VD born animals [15]. The association between CS and asthma is probably multi-factorial [65] and future studies must consider multiple potential interacting determinants.

### 2.4. Malignancies

A few reports link CS and increased malignancy. An association between CS birth and childhood myeloid leukaemia (OR 2.5 [95% CI 1.3, 4.8]), which was not explained by Down syndrome, asphyxia, maternal smoking, or multiple birth, has been reported [66], and an association between CS and nonseminomatous testicular cancer (adjusted OR 2.44 [95% CI 1.25, 4.78]) [67]. These studies are small, and require confirmation in larger cohorts. Nevertheless, the association may indicate epigenetic changes driven by mode of delivery. Perinatal stress has epigenetic programming effects, mediated by glucocorticoids [68]. Functionally, short-term epigenetic imprinting of leukocytes is modulated by mode of delivery, with increased DNA methylation in CS compared to VD infants [69]. Furthermore, there are well reported links between early life DNA methylation and several later-life health outcomes, particularly adiposity [70].

### 2.5. Neurodevelopment

At 1, 2 and 5 days post-partum PLCS delivered infants are hypotonic and less excitable than VD infants, potentially attributable to the catecholamine surge during VD [71]. However in a further study comparing PLCS with ILCS (to determine the effect of labour) two day old infants, the latter were more hypotonic and had lower patellar reflex than PLCS counterparts [72]. At 8 weeks post-partum, salivary cortisol concentrations and crying response to inoculation were lower in PLCS compared to VD infants [73]. At 6 months, there were no differences in neurological outcome between CS and VD infants [74].

In China, where the CS rate exceeds 50%, CS is associated with a 3.9 unit [95% CI 0.6, 7.2] increase in full-scale IQ and a 4.8 unit [95% CI 1.2, 8.4] increase in verbal IQ in children aged 4–6 years, but this was attenuated after adjustment for maternal IQ, education and occupation, and infant gender and birth weight (full-scale IQ: 1.6 [95% CI −1.3, 4.5]; verbal IQ 2.3 [95% CI −0.8, 5.5]) [75]. These data require confirmation in other populations.

One of the few RCTs of mode of delivery examined neurodevelopmental outcome at 2 years, and reported no difference between the two groups in the risk for a composite outcome of death and neurodevelopmental delay (relative risk: 1.09 [95% CI 0.52, 2.30]) [76]. Significantly, 12 (of 457 births) reported neurodevelopmental delay in the PLCS group, compared to 7 (of 463 births) in the VD group; but there was only one death before 28 days in the PLCS group, but 5 in the VD group. These data possibly indicate an increased risk of neurodevelopmental delay in the PLCS group, although given that an inclusion criterion for the RCT was a term breech delivery, generalisation of these data to the normal population is complex.

*2.5.1. Mechanistic data from animal studies*

In the absence of strong evidence of poorer neurodevelopmental outcomes in PLCS delivered infants, it is difficult to postulate possible causal mechanisms. However, PLCS increases dopamine D1-like receptor binding and D1 receptor activation in pre-pubertal rats [77], and at 2 months post-partum (post-pubertal) PLCS rats have 53% higher dopamine concentrations in the prefrontal cortex and 40% higher in the nucleus accumbens and striatum, compared to VD pups [78]. In adult rats PLCS delivery increased glial fibrillary acidic protein in the hippocampus and cortex of the frontal lobe, compared to VD [79]; potentially triggering neuronal apoptosis. Importantly, these changes were independent of the type of anaesthesia used during the PLCS. Similar responses are seen in guinea pigs [80]. Additionally amygdal and thalamus noradrenaline concentrations in adult rats differ between PLCS and VD animals, but were gender dependant (CS males: decreased noradrenaline; CS females: increased) [81]. Functionally, dopamine-mediated behaviours in animals born by PLCS differed from those born by VD [80]. The implications of these data are unknown and animal data are of limited value alone, but they indicate that PLCS alters the offspring's fundamental biology.

## 3. The case for further study

The evidence that CS impacts on short- and long-term offspring health is strong. Whether this is a causal relationship remains unclear. Given the rise in both medically indicated, and personal preference CS, this has become an issue relevant to both personal and public health, and requires further elucidation.

On the basis of an OR 1.23 [82] for obesity in offspring born by CS compared to VD, and a prevalence of obesity and CS at 26% and 24% respectively [83,84], we estimate that the proportion of the population burden of obesity that might be attributable to CS is around 3.7%. Reducing the CS rate in the UK from the current 24% to the WHO recommendation of 15%, would result in a 1.4% reduction in obesity, and would cut the obesity budget of the NHS, currently estimated at £5 billion per annum, by £70 million per annum. Similar relative reductions would be seen in childhood asthma (assuming OR 1.22 [37] and overall prevalence of 15%) and Type-1 diabetes (assuming OR 1.19 [33] and overall prevalence of 1 in 850 [85]). These figures do not account for the fact that reducing CS deliveries would arise from CS without clinical indication, and not the entire CS population, consequently they are at best rough estimates of the potential financial savings.

*3.1. Problems with cohort observation studies*

To date, most data on long-term outcomes of CS birth are from observational studies and prospective epidemiological studies. However, inferring a causal relationship even in the most rigorously designed and well executed observational studies is problematic. Several risk factors for CS (including maternal obesity, diabetes [86], social-economic status [87]), are also associated with altered risks for long-term outcomes of interest, particularly the metabolic syndrome [88].

*3.2. RCTs to date*

To date there have been fourteen RCTs comparing mode of delivery, comprising 118 randomised preterm deliveries (CS 60; VD 58) and 3144 randomised term deliveries (including 62 twin deliveries; CS 1529; VD 1615); publication of data from the Twin Birth Study (ISRCTN74420086; 2804 deliveries) will significantly increase this population (See Table 1). A systematic review reports a further four RCTs of mode of delivery to study vertical hepatitis B virus, but none of the included studies was randomised in any normal manner [89], consequently these reported RCTs are not included in this review. One RCT recruited very-low birth-weight infants [90]. Five RCTs have been conducted in preterm babies [91–95], of which three were for breech delivery [92,93,95].

Of the term birth RCTs, six achieved target recruitment. The exception was the Australian "Birth after Caesarean" study, which utilised a restricted prospective cohort study design, with the cohort recruited on the basis of patient preference into a PLCS or VD arm, with a smaller nested RCT coupled with planned intention to treat analysis [96]. Of 2345 women enrolled, only 22 consented to be randomised in the nested RCT (randomised as: CS 10; VD 12), consequently the RCT was too small to draw any conclusions.

In the preterm RCTs, none reached their recruitment target, and all (with the exception of one which states no endpoint [93]) terminated early due to unexpectedly low recruitment. Penn et al. demonstrated a 50% uptake in an acceptability study, but only randomised 13 women, despite "substantial numbers" of eligible births [92]. They attributed this lack of success to the fact that with breech deliveries in preterm labour, the optimal mode of delivery for the baby may be at discord with that for the mother; recruitment when a mother is in labour is difficult and preterm breech presentation is statistically rare. Significantly, many women who consented to the study in antenatal

**Table 1**
Published randomised controlled trials of mode of delivery in term pregnancies.

| Name of study/lead author | Reason for study | Centres; countries | Enrolment dates | Primary outcomes | Randomised to: | Recruitment: actual/[target]: |
|---|---|---|---|---|---|---|
| Collea [110] | Breech delivery | 1; USA | 1975–1979 | Perinatal mortality and morbidity | 1: PLCS<br>2: VD | 208 (PLCS 137; ILCS 11; VD 60)/[208] |
| Gimovsky [111] | Breech delivery | 1; USA | 1981–1982 | Perinatal mortality and morbidity | 1: PLCS<br>2: Trial of labour | 105 (PLCS 31, ILCS 39, VD 35)/[105] |
| Term Breech Study [98] | Breech delivery | 121; 26 (hosted Canada) | 1997–2000 | Perinatal mortality or morbidity | 1: PLCS<br>2: VD | 2083 (PLCS 545, ILCS 847, VD 691)/[2800] |
| Law [112] | VBAC | 1; Hong Kong | 2003–2007 | Maternal psychiatric morbidity | 1: PLCS<br>2: VD | 258 (PLCS 133, ILCS 52, VD 73)/[262] |
| Birth after Caesarean [96,97] | VBAC | 14; Australia | 2002–2007 | Neonatal lung disease; neonatal morbidity and mortality | 1: PLCS<br>2: VD | 22 (PLCS 9, ILCS 4, VD 9)/[2314] |
| Rabinovici [113] | Twin birth | 1; Israel | 1983–1985 | Apgar score, birth trauma, neonatal mortality and morbidity | 1: PLCS<br>2: VD | 60 (PLCS 29, ILCS 0, VD 31)/[60] |
| The Twin Birth Study | Twin birth | 175; 25 (hosted Canada) | 2003–2011 | Perinatal mortality | 1: PLCS<br>VD | Data not available [2800] |
| The EMDC [114] | HIV-1 transmission | 43; 6 (hosted Italy) | 1993–1998 | HIV infection of infant | 1: PLCS<br>2: VD | 408 (PLCS 185, ILCS 40, VD 183)/[450] |

Abbreviations: VBAC, vaginal birth after caesarean; PLCS, pre-labour caesarean section; ILCS, in-labour caesarean section; and VD, vaginal delivery.

clinic appointments were not approached when they presented in labour, because the clinical staff dealing with them felt it was inappropriate. This emphasises that maternal acceptability and clinical acceptability are not the same; any successful study of mode of delivery requires acceptability in both parties. These issues may explain the problems recruiting into pre-term, compared to term, RCTs.

### 3.3. Follow-up of these cohorts

Regrettably few studies incorporate long-term follow-up. Only one of the RCTs has included follow-up; this was to assess neurodevelopment at two years of age [76]. In a further RCT two-year follow-up is planned (ISRCTN74420086). The offspring of the RCTs to date currently have an age range of 1–37 years, and over 2000 infants born in two large RCTs [97,98] are currently aged 5–15 years. Consideration should be given to enrolling these offspring in follow-up studies to assess the long term impact of mode of delivery on children's health.

### 3.4. Perceptions of RCTs of mode of delivery

Initial reaction to the possibility of conducting an RCT of mode of delivery can be very negative. That randomisation is feasible, is shown by the number of women who have been randomised to date. It is unclear however, how acceptable randomisation is as data are not available on the number of women that declined to participate. Published acceptability studies conducted before commencement of the RCTs indicated that recruitment was feasible: in the term breech trial 18% of women consented [99,100] and in the twin birth study, 48% [101]. Both of these studies focussed on specific conditions and consequently it may not be realistic to extrapolate to healthy, cephalic, term pregnancies. An RCT addressing subtle, long-term health outcomes in low risk, uncomplicated pregnancies may also be less acceptable to mothers, fathers, and clinicians.

A national survey of consultant obstetricians and heads of midwifery in the UK found that whilst nearly half thought an RCT of PLCS vs. VD was desirable, only 37% said they would recruit into such a study, with even fewer believing it was feasible [102], although this has to be interpreted in the light of 15% of obstetricians within London opting for a PLCS, given a pregnancy with the criteria for entering the proposed RCT [103]. A similar study in UK mothers found only 3 out of 64 women would have agreed to take part [104]; however, this information was collected retrospectively, 12 months after the birth of their first baby (only 9 of 64 were pregnant at time of interview) and they were given no details of the proposed RCT, nor its outcome measures. By contrast, when women were provided with this information, such as in acceptability studies prior to the commencement of the term breech trial [99,100], the number of women indicating a willingness to participate was much higher (18% said yes; 60% said yes, or not sure). An Australian study of mothers and clinicians at antenatal clinics, showed only 14% of pregnant women, and 31% of clinicians would participate in an RCT; the most commonly cited reasons for not taking part were, removal of the right to choose how they gave birth (73%), feeling that the question of the relative complications of PLCS compared to VD were too complex for assessment using an RCT design, and an RCT was unethical [105]. Timing of recruitment for an RCT of mode of delivery is important, particularly given that a woman's birth preference might change as pregnancy progresses [106].

### 3.5. Room for a new study of mode of delivery?

Despite experience to date, we believe there are good reasons to conduct a RCT of mode of delivery. No RCT has compared planned PLCS with planned VD for the healthy, term, cephalic, singleton pregnancy. Concerns about the safety of either mode of delivery for mother or for baby, ethical, or practical issues, have possibly held back such a study. However, the 2011 UK NICE guidelines [1] reviewed the extensive literature and concluded that there was no substantial difference in the risk of complications between PLCS and VD to the mother. No RCT to date has been designed, or powered, to examine long-term offspring health outcomes [12]. Follow-up of babies born in RCTs of mode of delivery has been inadequate. Finally, few studies have separated pre-labour and in-labour CS, to address whether it is labour, or the physical process of VD, that drives differences in outcomes. Where data exist comparing PLCS, ILCS and VD, it is evident that ILCS offspring often group with the VD rather than the PLCS offspring, suggesting that absence of the hormonal milieu of labour is a potential mechanism responsible for the long-term outcomes.

If it can be established that labour is essential for programming long-term health, a pharmacological intervention to mimic labour may be feasible, or ILCS could be encouraged as the preferred route for planned CS. There has been some work in this area. PLCS babies are at increased risk of short-term hypoglycaemia post-partum [107] but administration of terbutaline, a β-agonist to mothers prior to delivery normalised the blood glucose concentrations of the offspring to those found in the VD control group [108]. Rat pups born by PLCS show reduced suckling behaviour compared to VD counterparts; suckling in PLCS rats could be induced by drawing the rat pups through a rubber ring, mimicking VD [109].

## 4. Conclusions

CS is associated with detrimental long-term offspring outcomes. Many of these associations have plausible biological mechanisms, but causality remains unproven. We suggest that a RCT of mode of delivery in the healthy, term, cephalic pregnancy, is feasible and when coupled with evaluation of biomarkers of outcome and long-term follow-up, the only reliable means of resolving an issue of international importance.

## Conflict of interest

The authors declare no conflicts of interest.

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