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Routine induction in late-term pregnancies; long term follow-up of a new induction of labour paradigm. A population register-based study

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Title page:
Routine induction in late-term pregnancies; long term follow-up of a new induction of labour paradigm. A population register-based study.
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5 Keywords

Labour, induced [MeSH], Medicalization [MeSH], Adverse events [MeSH], Stillbirth
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Word count: 4058 words

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24	Abstract
21	ADSUALI

Objectives

For many years, routine elective induction of labour at gestational week 42+0 has been recommended in Denmark. A new protocol was introduced in 2011 with a more proactive regimen aimed at reducing stillbirth recommended routine induction of all women between gestational weeks 41+3 and 41+5. The present study analyses maternal and neonatal consequences of the new protocol by comparing the trend in stillbirths and perinatal deaths in the pre-intervention period (2000-2010) with the trend in the post-intervention period (2012-2016).

- Design
- A national retrospective register-based cohort study.
- Setting
- Denmark
- **Participants**
- All births in Denmark 41+3 to 45+0 gestational weeks between 2000 and 2016 (N =
- 152,887).

Outcome measures

Primary outcomes: stillbirths, perinatal death, and low Apgar scores. Additional outcomes:

birth interventions and maternal outcomes.

Results

For the primary outcomes, no differences in stillbirths, perinatal death, and low Apgar scores were found comparing the pre- and post-intervention period. Of additional outcomes, the trend changed significantly post-intervention concerning use of augmentation of labour, epidural analgesia, induction of labour, instrumental assisted birth, and uterine rupture (all p < 0.05). There was no significant change in the trend for caesarean section and instrumental delivery. Most notable for clinical practice was the increase in induction of labour from 41% to 65% (p<0.01) at 41+3 weeks during 2011 as well as the rare occurrence of uterine ruptures (from 2.6 to 4.2 per thousand, p < 0.02) Conclusions Evaluation of a more proactive regimen recommending induction of labour from gestational week 41+3 compared to 42+0 using national register data found no differences in neonatal

1 2		
3 4	52	outcomes including stillbirth. The number of women with induced labour increased
5 6	53	significantly.
7 8		
9 10	54	
11	55	Article summary
12 13	56	Strengths and limitations of this study
14 15	57	Retrospective national registry-based data (2000-2016)
16	58	 Diagnoses based only on ICD-10 classifications
17 18	59	 Includes all births at 41+3 gestational week and beyond in Denmark
19 20	60	• 13 years before and 5 years after a change in clinical practice on induction of labour
21 22	61	Access to relevant confounders
23	62	
24 25		
26 27	63	Introduction
28	64	In Denmark, a new proactive policy was introduced in 2011 aiming at preventing stillbirth
29 30	65	and other foetal and maternal complications in post-term pregnancies. The Danish Society
31 32	66	for Obstetrics and Gynaecology introduced the new protocol recommending routine
33	67	induction of labour in otherwise low-risk pregnant women between gestational week (GW)
34 35	68	41 plus 3 days (41+3 GW) and 41+5 GW to prevent the pregnancy from reaching the post-
36 37	69	term period of 42+0 GW. Women at risk (e.g. with diabetes or multiple gestations) are
38	70	according to national guidelines offered induction at earlier gestational ages[1]. The
39 40	71	argument for the new policy was a concern for the unborn child, as prolonged pregnancy
41 42	72	increases the risk of a malfunctioning placenta, shoulder dystocia, meconium aspiration
43	73	syndrome, foetal distress, and ultimately foetal death [1]. The new protocol was also aimed
44 45	74	at reducing post-term maternal complications such as dystocia, birth-related injuries,
46 47	75	caesarean section (CS), and post-partum haemorrhage [1]. This new protocol was a
48 49	76	deviation from the former guideline recommending induction at 42+0 GW. Induction of
50	77	labour may itself impose a risk of adverse consequences such as hyperstimulation, foetal
51 52	78	asphyxia, post-partum haemorrhage, uterine rupture, and in very rare cases, foetal and

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maternal death [2]. Induction has been shown to be related to additional interventions such

as epidural analgesia, continuous foetal monitoring, confinement to bed, instrumental

delivery, and emergency CS [3]. There is a lack of consensus on how to handle

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- - pregnancies beyond term, as both post-term pregnancy and induction of labour may independently be associated with adverse consequences [4].
 - Existing studies are limited to comparing benefits and harms of routine induction at 41 GW compared to previous standard of 42 GW. A systematic review by Wennerholm et al [5] found a non-significant reduction in stillbirths (RR 0.33, 95% CI 0.10, 1.09), and a significant reduction in meconium aspiration syndrome (RR 0.43, 95% CI 0.23, 0.79) using routine induction (41 to 42 GW) compared to expectant management (42 to 44 GW). Caughey et al [6] arrived at similar conclusions on studies inducing labour (39 to 41 GW) and found expectant management (41 to 45 GW) to increase the risk of CS (OR, 1.21 95%) CI 1.01 to 1.46). None of these reviews compared induction at 41 GW with the Danish standard at 42 GW, but based conclusions on a wider variation in gestational age. A recently published systematic review narrowed the scope to routine induction at 41+0/6 GW versus 42+0/6 GW [2]. The data lacked statistical power to draw conclusions on perinatal death, but found a significant reduction in oligohydramnios, and meconium-stained amniotic fluid in the induction group (41+0/6). However, the study also found an increased risk of low pH< 7.10, CS, chorioannionitis, precipitate labour, and uterine rupture [2].
- In a normal population, about 25% of the women will still be pregnant at 41+0 GW and 37 101 about 5% reach 42+0 GW without going into a spontaneous onset of labour [7,8]. Changing the protocol to offer routine induction between 41+3 and 41+5 GW thus changes 39 102 the number of ongoing pregnancies and could lead to an additional 13-15% of women being encouraged to have an induction, [4] with possible iatrogenic consequences [9]. One 44 105 year after the Danish shift in the protocol, the new induction paradigm was almost fully 46 106 implemented [10]. In the following year, two Danish studies evaluated the consequences and found a considerable reduction in stillbirths [11,12]. Hedegaard et al and Zizzo et al monitored one and three years of data, respectively, after implementation of the new protocol, but adjustment for ongoing trends was not performed [11,12]. The aim of this 51 109 ₅₃ 110 study was to evaluate perinatal outcomes, birth interventions and maternal outcomes after introducing the new 2011 protocol, during a 5-year follow-up period with adjustment for 56 112 ongoing trends.

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113 Material and Methods

This is a retrospective cohort study using data from the Danish Medical Birth Registry 114 (DMBR). Data were retrieved from the Medicalisation in Pregnancy and Childbirth dataset 8 115 9 10 116 (MIPAC), based on the DMBR, with additional patient level data from other Danish 11 administrative registries. MIPAC holds information on all births in Denmark since 1997 in 117 12 13 118 women with either a Danish civil registration number or a temporary registration number. 14 Undocumented migrants are probably also included, as it is legal to give birth 15 119 16 120 anonymously. Data were collected prospectively at all contacts with health care providers, 17 18 e.g. midwives and obstetricians [13]. For the purpose of this study, we restricted data to 121 19 20 122 include births in Denmark from 1 January 2000 to 31 December 2016 with a known 21 gestational age. Our analysis is limited to pregnancies that lasted at least 41+3 GW (290 ₂₂ 123 23 gestational days) Cases were excluded if both birth weight and length deviated 124 24 ²⁵ 125 substantially from the mean. A cut-off value of three SD was used to avoid including 26 foetuses wrongly coded as late or post term (Appendix 1). 27 126 28

30 128 The population of interest included all ongoing pregnancies from 41+3 GW and onwards. If 31 32 129 any important foetal or maternal morbidity was present such as multi-parity, Body Mass 33 Index (BMI)>30, maternal age>40, hypertension, diabetes mellitus or other medical 34 130 35 conditions, the usual clinical practice is to induce labour no later than 41+0 GW. Few 131 36 ³⁷ 132 women may object to advice of induction of labour and may be included in the present 38 study population. 39 133 40

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41 134 42 The exposure of interest was the new protocol from March 2011 and implemented during 135 43 ⁴⁴ 136 2011 at Danish hospitals offering routine induction at 41+3-41+5 GW [10]. 45 The outcomes of interest were stillbirth, perinatal death (stillborn or dead within the first 7 46 137 47 ₄₈ 138 days), and low Apgar score (<7 after 5 minutes). We also analysed trends in birth 49 interventions such as induction of labour (medical and/or mechanical), augmentation of 139 50 51 140 labour (synthetic oxytocin), epidural analgesia (pain relief during vaginal birth), and 52 maternal outcomes such as instrumental delivery (forceps or vacuum extraction), CS and 53 141 54 142 uterine rupture. 55 ⁵⁶ 143 Potential confounding variables of interest included advanced maternal age (\geq 40 years), 57 nulliparity, previous CS (among multiparous), light/moderate preeclampsia (blood pressure 58 144

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> 145 ≥140/90 & <160 /110 with proteinuria), pre-pregnancy obesity (BMI ≥ 30); smoking (any 146 smoking after 1 trimester), and high birth weight (> 4000 gram).

The variables in MIPAC are either based on the classification of Diseases (ICD10) or use conventionally accepted standards by e.g. WHO [14]. No information on meconium aspiration syndrome, manifest oligohydramnios, pH-value, precipitate labour, and hyperstimulation was available. Further, the post-partum haemorrhage code was changed in 2012 from including only severe bleeding to "any bleeding" and was thus too imprecise to apply.

We included a variable if at least 95% of cases were coded. The variables used in this study were generated from either of two different modes of registration practice. When health providers do the documentation, some information must be registered by ticking off a checkbox, if a given event occurs (e.g. epidural). In this case, missing values cannot be determined, because the extent to which the provider may have left out a code is unknown (particularly if it does not involve a billing code). Other types of information is mandatory to report (e.g. weight of the child). For mandatory variables, the number of observations with missing values was documented. We included a variable if at least 95% of cases were coded. We assumed a random misclassification with equal distribution of missing cases per year. None of the variables exceeded missing observations of more than 5%. The variable with the highest frequency of missing cases was maternal BMI> 30 with 3.7%. We did not include Patient Public Involvement in this study, that based solely on data registered by health personel. The STROBE cohort reporting guidelines were used [15]

57 Statistical analysis

Analyses were performed as Interrupted Time Series Analysis (ITSA) and, if not suitable, a
 Poisson regression analysis was conducted (explained below). The independent variable
 was years separated into quarters (n=68) or, in case of only a few observations, years
 (n=17). The time-period consisted of a pre-intervention period of 11 years (2000-2010),
 one year for implementation (2011), and 5 years for the post-intervention period (2012 2016). Single-group analysis was used. The model fitted an ordinary least square (OLS)
 line pre- and post-intervention. If interruptions occurred at other time points during the pre intervention period, the period was shortened to fit the best model. We tested robustness

by checking if results were sensitive to change of adjoining years. The regression model
used Newey-West standard errors and we conducted a Cumby-Huizinga test for autocorrelation [16]. The assumption in ITSA modelling is that any time-varying confounding
changes relatively slowly and will not cause concern as long as no other interruption
occurs coincidentally with the change in protocol in 2011 [16]. Visual inspection is
presented in Appendix 2.

16 182 The ITSA model is not optimal for rare outcomes, including less than four observations per time unit [16]; hence, Poisson regression was a more appropriate test for intrauterine and perinatal death with the year of birth as the explanatory variable. To increase precision of 21 185 the estimates, the time period between 2000 and 2016 was included in the analysis. We used the log (number of births) as an offset in the model to account for the varying number 23 186 of births. Two models were fitted to the data. The first model included a general time trend only; the second model included a general time trend and an effect of the change in the protocol from 2011. The adequacy of each model was assessed by Goodness-of-fit test 28 189 ₃₀ 190 and the impact of the change in the protocol was evaluated by comparing the slopes of the time trends before and after 2011.

All analyses are presented in graphs or fitted curves depending on the method of analysis. 36 193 Descriptive statistics on stillbirth and perinatal death are presented as absolute numbers and percentages by year. If the absolute number was less than 5, results are presented as 38 194 "<5" and rates as "<0,5 per 1000" and absolute numbers are omitted from the Poisson fitted curves to avoid identification [17]. Outcomes are further presented in a table including the interruption jump and slopes of the curves before and after the intervention 43 197 45 198 with 95% confidence intervals (CI). P-values present the statistical difference between the pre- and post-intervention slopes. For the Poisson regression, Incidence Rate Ratio (IRR) 48 200 for both fitted curves, p-values and Goodness-of-fit are presented.

Data were analysed in STATA/SE 15.1 software package (StataCorp. 2017. Stata
 Statistical Software) adding the STATA ITSA-package 17-4. All reported p-values are two sided, and statistical significance was 5%.

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Results

The dataset included 1.057,453 births from 1 January 2000 to 31 December 2016. Of those, we excluded 2,712 records with missing information on GW (0.3%). Of the ₁₁ 207 remaining cases, 153,120 pregnancies (14.5%) lasted until 41+3 GW or beyond. We excluded an additional 233 cases (0.15%), all live births, where both the weight and the 14 209 length were more than 3 SD from the mean for a final working total of 152,887 pregnancies. In the final population, there were 213 stillbirths (0.14%) and 262 perinatal 16 210 deaths (0.17%) (Appendix 1).

Trends in interventions and outcomes before and after the implementation of the new 21 213 induction protocol are presented in Table 1 and further elaborated in Figures 1-3. Table 1 23 214 presents the results of the interrupted time-series analysis, a pre- and post-intervention slope for each variable, the interruption jump in 2011 and a test for significance between the pre- and post-intervention slopes is presented. For the Poisson regression, a general 28 217 ₃₀ 218 fit before and after 2011 is shown as an IRR and a significance test for difference in IRR.

Outcomes	Interruption	Pre-intervention trend	Post-intervention trend	Difference
	jump	(050) OIN		trends ^a
	2011	% per year (95% CI)	% per year (95% CI)	p-value
Maternal interventions:				
Augmentation of labour (%)	-3.1	-0.87 (-1.14, -0.61)	0.11 (-0.16, 0.40)	0
Epidural analgesia (%)	4.1	2.80 (2.48, -3.12)	0.13 (-0.44, 0.70)	0
Induction of labour (%)	22.4	1.70 (1.53, 1.87)	-2.36 (-3.03, -1.72)	0
Instrumental birth (%)	-0.5	-0.10 (-0.22, -0.05)	-0.12 (-0.33, 0.08)	0
Maternal outcome:				
Caesarean section (%)	0.1	-0.16 (-0.36, -0.04)	-0.10 (-0.47, 0.27)	0
Uterine rupture (pr.1000)	1.6	0.21 (0.12, 0.30)	-0.24 (-0.60, 0.13)	0
Foetal outcome:				
Apgar score <7/5 min. (%)	-0.2	0.01 (-0.01, 0.02)	0.04 (0.01-0.07)	0
		Generel fit. IRR all	Generel fit. IRR all	GOF ^b
		years	years	
Stillbirths		0.90 (0.87, 0.93)	0.91 (0.87, 0.95)	0
Perinatal mortality		0.90 (0.88, 0.93)	0.90 (0.87, 0.94)	1

Table 1 presents trend before and after intervention, together with interruption jump (2011)
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^aIRR. Incidence Rate Ratio

^bGOF, Goodness-of-fit test.

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Primary outcome: Perinatal mortality and morbidity 222

6 Table 2 presents stillbirths and perinatal death in absolute numbers per 1000 births. A 223 7 8 general decline of intrauterine deaths was observed during the study period, with an initial 224 9 10 225 risk of stillbirth at 2.3 per 1000 births in the year 2000 dropping to a rate of <1 per 1000 11 from approximately 2009, after which it has generally remained between 1.0 and 0.5 per 226 12 13 227 1,000 births. 14

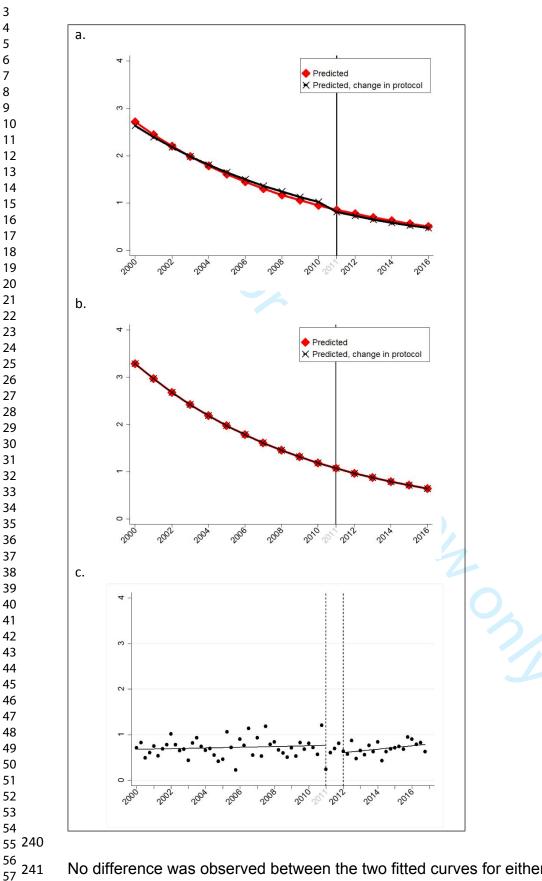
15 228	Table 2 p	resents stillb	oirths and p	perinatal death	in years 2000-2	016
16 17 18	Year	Births n=152,887	Stillborn n=213	Stillborn per 1000 births	Perinatal death n=262	Perinatal death per 1000 births
18	2000	10670	25	2,3	35	3,3
20	2001	10765	31	2,9	36	3,3
21	2002	9887	19	1,9	23	2,3
22 23	2003	9702	18	1,9	20	2,1
25 24	2004	9025	15	1,7	18	2,0
25	2005	9181	18	2,0	20	2,2
26	2006	9041	19	2,1	24	2,7
27 28	2007	8681	12	1,4	15	1,7
28	2008	9173	12	1,3	16	1,7
30	2009	8943	8	0,9	8	0,9
31	2010	9326	7	0,8	8	0,9
32	2011	8462	<5	<0,5	5	0,6
33 34	2012	7801	<5	<0,5	<5	<0,5
35	2013	7700	8	1,0	10	1,3
36	2014	7716	<5	<0,5	<5	<0,5
37	2015	8072	6	0,7	9	1,1
38 39	2016	8742	7	0,8	8	0,9

228	Table 2 presents	stillbirths and	perinatal death in	years 2000-2016
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According to EU's General Data Protection Regulation no data <5 observations may be provided. The rate pr.1000 births is corrected accordingly.

230 Figures 1a and 1b present the two fitted curves for stillbirths and perinatal death, respectively. The red curve/diamond shows predicted values for the years 2012-2016 231 based on the 2000-2010 trend without a change in protocol and the black curve/cross 47 232 represents a fitted curve after the change in protocol. Figure 1c presents the ITSA model 49 233 234 for low Apgar scores with 2011 as an interim year for implementation. The OLS lines pre-52 235 and post-intervention are presented.

55 ₅₆ 237 Fig. 1a-c. Presents perinatal outcomes, year 2000-2016 with change in protocol, 2011 (a) Stillbirths per 1000 births (b) Perinatal death per 1000 births (c) Apgar score <7 after 5 minutes, percent (%). 57 238 58 239



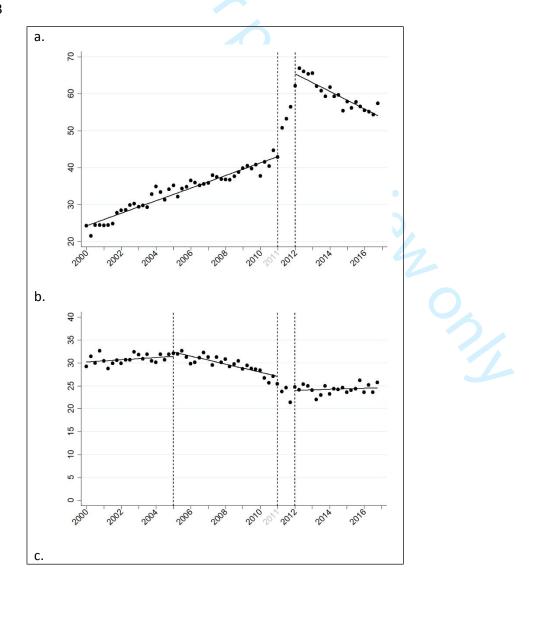
No difference was observed between the two fitted curves for either stillbirth (p=0.56) or perinatal death (p=1.00). The goodness-of-fit test was p=0.40 for stillbirth and p=0.24 for

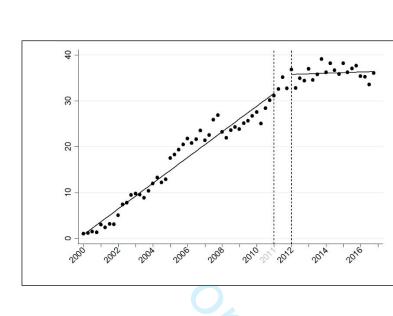
perinatal mortality. Figure 1c presents low Apgar score before and after the intervention showing no difference in the slope before and after the new protocol (p=0.11). See Table 1 for details.

12 247 Birth interventions and maternal outcome

Interventions in birth are presented in Figure 2a-2c, and maternal outcomes are presented in Figure 3. (See Appendix 3 for details)

Fig. 2a-c. Presents interventions in childbirth(%), year 2000-2016 with change in protocol, 2011. (a) Labor induction (b) Augmentation (c) Epidural analgesia.

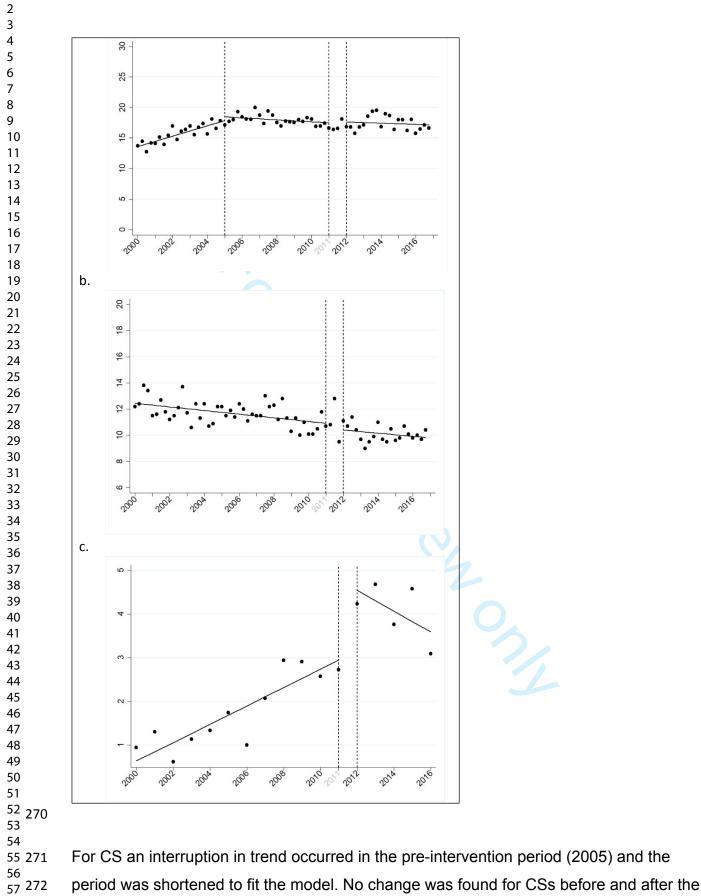




⁴³ 267

Induction of labour increased during the pre-intervention period with an annual average ²⁴ 256 increase of 1.7% and rates rising from 25% to 41%. By 2011, a significant jump from 41% to 65% annual inductions was seen (p < 0.00). After the substantial jump in the rate in 2011, 26 257 the annual decline of 2.4% in the induction of labour brought the rate down to 55% (p<0.01). A significant change in trend was observed for augmentation of labour after 31 260 implementation of the new protocol. As interruption in trend occurred in the preintervention period (2005) the period was shortened to fit the model. From 2005 until 2011 33 261 there was a slight annual decrease (-0.9%) in augmentation changing to a marginal annual increase of 0.1% (p<0.01) from 2012-2016. Use of epidural analgesia for pain relief during labour increased during the entire pre-intervention period at approximately 4.1% annually. 38 264 The observed increase of epidural analgesia flattened in 2011 after the intervention, resulting in a marginal increase of 0.1% (p<0.01).

Fig. 3a-c. Present maternal outcome, year 2000-2016 with change in protocol, 2011.(a) Cesarean 45 268 46 269 section (%). (b) Instrumental delivery (%). (c) Uterine ruptures per 1000 births. a.



change in the protocol (p=0.76) with a non-significant declining trend from 2005 and

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onwards. The number of instrumental birth declined during the entire study period with an 274 annual decrease of 0.1%, and no change was observed after 2011 (p=0.88). Uterine 275 rupture is a rare event and is presented as a rate per 1000 births. During the pre-276 intervention period, a steady increase of 0.2 % yearly was observed. It was followed, 277 similarly to the case of induction, by a substantial increase between 2010 and 2012 from 278 2.6‰ to 4.2‰ (p<0.02). In the post-intervention period, a decline of uterine rupture of 13 279 15 280 0.3% yearly was noted (p<0.01).

Other relevant changes in population 281

19 282 Changes over time for possible confounders and interruptions occurring simultaneously as 21 283 the intervention of interest (2011) may have biased the results. We explored the changes 284 in maternal age > 40 years, nulliparity, preeclampsia, previous CS, BMI>30 and smoking 285 status. No changes in trend were noted after 2011. See Appendix 2.

Discussion ²⁹ 287

Principal findings 288

33 This study included all births in Denmark (N=152,887) from 41+3 GW between 2000 and 289 34 2016. We evaluated maternal and neonatal outcomes after a change in the induction of 35 290 36 labour protocol in 2011. Once the trend from 2000-2010 was taken into account, no 291 37 38 differences were found in stillbirth, perinatal death, or low Apgar score. There was 292 39 40 293 however a 59% increase in the use of labour induction within the first year after the new 41 protocol as well as a significant increase in uterine ruptures. The use of epidural analgesia 42 294 43 295 and augmentation both levelled off after the change in protocol and there was no change 44 45 in number of CSs in the pre- and post-intervention period. 296 46

47 Strengths and weaknesses of the study 48 297

49 No randomised trials were conducted before or concurrent with the implementation of the 298 50 51 299 new protocol, and the ITSA design provides a robust guasi-experimental alternative [18]. 52 53 300 The present design may provide a high degree of internal validity [16] as a single-group 54 ITSA offers an advanced approach to evaluation of before and after an intervention 55 301 56 302 including analysis of the ongoing trends [16]. The data used for this present study was 57 ⁵⁸ 303 collected prospectively for other purposes. Thus interpretations of causality is not possible. 59

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In the case of rare outcomes, we used a Poisson regression model. Estimating the trend before 2011 was used to predict the expected outcomes after the implementation. Two Danish retrospective cohort studies monitored the impact of the intervention and found about a 50% reduction of stillbirths after 2011 [10,12]. One study monitored pregnancies from 41+0 GW and found an adjusted odds ratio of 0.5, (95% CI 0.29-0.89) [12], whereas the other study monitored pregnancies from 41+2 and did not arrive at significant results (OR 0.34, 95% CI 0.09-1.24) [10]. Both studies compared the years before and after but did not consider the ongoing trend which revealed a 63% decrease in the stillbirth rate in the five years prior to the intervention and a marginal *increase* in the five years after the intervention to the point where the rate was the same in 2016 as it was in 2010 (0.8 per 1,000)(Table 2). This highlights the importance of including trends and longer time frames in the analysis of trends to ensure the most valid conclusions.

A strength of this register-based study is that it includes all Danish births at or beyond 41 + 27 3 GW. Denmark has universal health care coverage and selection bias is unlikely, as all 28 317 29 ₃₀ 318 women on all income levels and demographic characteristics are covered. The most 31 recent study from 2003 validated the registration data and found that common surgical 32 33 interventions and procedures matched the medical records [19]. ICD-10 main categories 34 were validated and found acceptable [19]. Interventions are reimbursed if registered, which 35 321 36 further increases accuracy [13]. 37

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Not all known adverse effects are available in the register. Oligohydramnios and 40 ⁴¹ 324 meconium aspiration syndrome usually increase with gestational age [2,6], but since these 42 43 325 data were not available, low Apgar, stillbirth and perinatal death were used as the best 44 45 326 possible proxy outcome for these conditions. Post-partum haemorrhage (PPH) is an 46 adverse effect of both ongoing pregnancies in late gestation and induction of labour [20]. 47 48 328 Due to a change in the definition of PPH, we considered PPH data to be unreliable in its 49 present form. Information on labour dystocia is not available in the registry and instead 50 329 51 labour augmentation was used as a proxy measure. Information on hyperstimulation of the 52 53 uterus and precipitate labour was not available, but uterine rupture may be a severe 54 55 332 consequence of an over-stimulated uterus.

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333 Why the intervention seems to fail its purpose

The main finding of this study is a lack of immediate benefits for the foetus. A possible 334 explanation may be that, in a country like Denmark with a generally high standard in public 335 10 336 health and a low mortality rate, there would be fewer opportunities to prevent perinatal deaths [21]. European countries, including Denmark, have experienced a steady decrease 337 338 in stillbirths and perinatal mortality during this millennium. A cross-European study found this decrease in all gestational ages which, points to multifactorial explanations [21]. 15 339 17 340 Changed screening policies, early termination of pregnancies with lethal abnormalities, 341 better postnatal management, preconception counselling, detection of foetal growth 342 restriction, and a higher quality of prenatal care were mentioned as explanations [21,22]. In addition, a decline in smoking in pregnancy was emphasized as one of the main 22 343 344 contributors to the decline in stillbirths [21]. In Denmark the rate of prenatal smoking decreased from 19% in 2000 to 5% in 2016 (Appendix 2). 345

28 346 It is estimated that suboptimal care accounts for 20 to 50% of stillbirths [21,23]. 347 Nonetheless, a number of stillbirths and perinatal deaths are not preventable, especially in case of undetected severe congenital malformations [24]. Several studies have found a 31 348 33 349 marked increase in stillbirths with increasing gestational age [25-27], which is a relevant 350 argument for routine induction at late term. However, these studies rely on data collected ³⁶ 351 from 1985-96 and may not represent contemporary risks. The same challenges may exist 38 352 in the evidence base behind the Danish change in guideline [25,28,29], where data collection draws on stillbirth studies back to the year 1969, long before the general health 353 improvements noted above. This may explain the lack of benefit found in this study 354 43 355 associated with offering routine inductions a few days earlier than usual practice.

¹⁵ 356 Intervening in the normal processes of childbirth

47 The few days change in the recommended time for induction of labour caused no 357 48 49 358 improvement in perinatal outcomes, but it affected the physiological birth. The rate of 50 labour inductions increased from 41% to 65% in the first year after implementation. 51 359 52 360 Induction interferes with the physiological birth, as induction may prolong time in labour 53 54 and in hospital, confine the woman to the bed attached to monitoring devices and an 361 55 56 362 intravenous drip [30]. This more proactive induction of labour regimens was also 57 ₅₈ 363 implemented in Great Britain in 2008 [31]. Scandinavian countries, in general, are more 59

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likely to practice expectant management with regard to induction, [32] weighing the 364 benefits against the potentially harmful consequences of induction of labour [33]. 365

Since induction has been found to be a risk factor for hyperstimulation and heavy pressure 366 on the uterine cavity, uterine rupture is a well-known adverse effect [2,7,34]. A systematic 367 review comparing inducing labour in women at 41 GW versus 42 GW showed a doubling 368 of the risk of uterine rupture (RR 1.97, 95% CI 1.54-2.52) [2]. This study found a 369 significant increase in uterine rupture (p<0,02) with a change from 2,6 to 4,2‰ after the 370 intervention. A long term trend toward increasing use of epidural analgesia for pain relief 371 leveled off after the new protocol (Figure 2c). In the present study, the need for 372 augmentation of labour increased slightly after a long period of a decreased use (Figure 373 2b). Knowledge of risks associated with augmentation at 41 GW versus 42 GW is limited. 374 One cohort study of 51,473 women found an increase in labour dystocia when induction of 375 labour was performed at 41 GW (RR=1.29, 95% 1.22-1.37) [35] while a randomised trial of 376 508 women found no difference (RR 0.55, 95% CI 0.20-1.45) [36]. Conflicting results have 377 been published regarding induction of labour and risk of CS [2,37,38]. In this study, no 378 379 change in the CS trend was found, despite the substantial increase in induction of labour. Studies that have monitored the normal course of pregnancy between 41 GW and 42 GW 380 have found 70-75% of the women went into spontaneous labour before 42 GW. The rest 381 were induced due to medical reasons or induced at 42 GW [36,37,39,40]. 382

Possible implications for clinicians and policymakers 383

The World Health Organization recommends induction of labour for medical reasons if the 41 384 385 expected benefits outweigh the potential harms [1]. The current study highlights the importance of evidence based practice and careful monitoring of trends after 386 implementation of new interventions in pregnancy and childbirth. 46 387

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48 Unanswered questions and future research 388 49

50 The intention behind implementation of a new induction of labour protocol was an 51 389 52 ₅₃ 390 expected reduction in stillbirth and perinatal mortality. Based on the results from this 54 391 present study, the expected reduction in mortality after introducing earlier induction of 55 56 392 labour was not achieved. As low stillbirth rates already exist in Scandinavian countries, 57 medicalisation of a large group of low risk women may be ineffective or even provide more 58 393 59

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harms than benefits. As most register studies only provide the absolute numbers of 394 adverse outcomes, a more detailed study of case fatality is needed not only taking into 395 account congenital abnormalities, but also underlying social mechanisms and suboptimal 396 care, to provide knowledge on how to reduce adverse outcomes in counties with a low 397 398 stillbirth rate [41].

399 Universal and free access to healthcare with focus on health literacy during pregnancy and 400 childbirth and with a continuing and ongoing focus on socioeconomic disadvantages may reduce adverse outcomes for mothers and infants [42,43]. 17 401

Conclusion 20 402

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21 The aim of this study was to evaluate changes in maternal and neonatal outcomes after 403 22 23 404 implementing earlier routine induction of labour after 41+3 GW in the entire Danish 24 population of pregnant women. No change in trend was found in low Apgar scores, 25 405 26 27 406 stillbirths or perinatal deaths after implementation of earlier routine inductions of labour. 28 407 The most substantial impact was the number of inductions of otherwise low risk 29 30 408 pregnancies and an increased number of uterine ruptures. The use of epidural analgesia, 31 augmentation of labour, instrumental births, and CSs remained stable. The study 32 409 33 ₃₄ 410 highlights a need for a more balanced discussion among health providers on routine 35 411 induction at late term. 36

37 Author contribution 38 412

₄₀ 413 ER and RM planned the study. ER & RM analysed data from MIPAC dataset. ER wrote 414 the manuscript in close correspondence with RM, MJ, and GD. ER, RM; MJ, and GD 43 415 revised the manuscript and accepted the final version. ER is the guarantor.

46 47 417 **Competing interests**

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- 56 422 57 423 Funding
- 58 59

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1 2 3		
4 5 424	ER re	eceived a grant from Danish Association of Midwifery and Herlev Hospital supported
6 425 7	the s	cholarship.
, 8 426 9	Data	a sharing statement
10 427 11	All da	ata relevant to the study are included in the article or uploaded as supplementary
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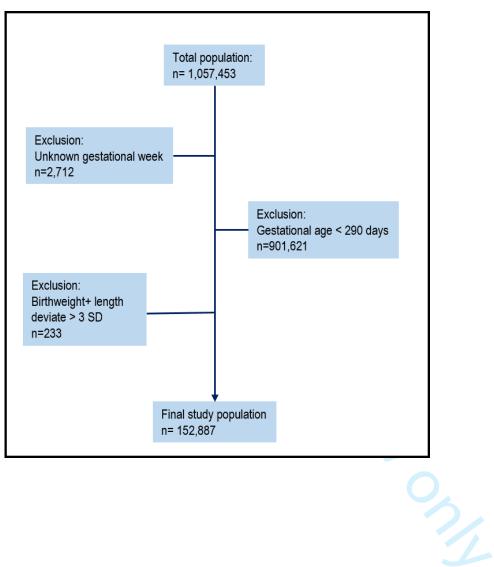
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45 Appendix
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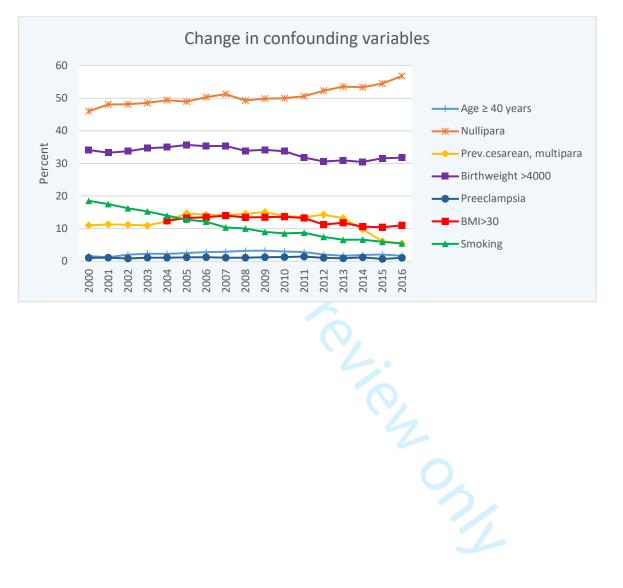
Appendix 1

Flowchart



Appendix 2





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Appendix 3.

Number of births, interventions and maternal outcome

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Numbe	r of births	, intervent	ions and m	aternal ou	ıtcome				ng for u	on 16 Dece		
Year	Quarter	No. births	Instrumental	Induction	epidural	Augment	Cesarean	Epis	Tears 3&4	Rungtures	No. births Apgar	Apgar<7/5
2000	2000q1	2598	318	631	27	760	357	376	98 elate	er 20	2567	18
	2000q2	2686	334	577	33	845	388	357	88 č	nen:	2666	22
	2000q3	2716	375	663	41	815	346	365	104 É		2676	13
	2000q4	2670	357	653	36	871	379	345	108 and	nload	2632	16
2001	2001q1	2699	310	658	82	822	381	349	113 da	⊢ed 14 A	2659	20
	2001q2	2802	324	685	68	806	424	303	140 m in	rom	2766	15
	2001q3	2780	354	691	88	831	387	341	108 j	http:	2741	19
	2001q4	2484	292	691	78	759	383	299	109 L tra	//bm	2450	19
2002	2002q1	2378	266	675	121	712	403	242	86 ining	6 8	2344	24
	2002q2	2472	285	705	183	758	364	300	103 an	1.bm	2433	19
	2002q3	2659	323	794	208	816	429	285	112 a	j.cor	2632	17
	2002q4	2378	325	719	225	770	390	279	Tears 3&4 S related to 98 88 104 108 data 108 113 140 108 data mining, AI training, and similar technologies. 109 86 103 112 100 93 101 97 97 97 97 97 97 97 97 97 97 98 101 97	n/ on	2350	16
2003	2003q1	2285	267	671	224	726	387	277	93 tech	11 5	2255	10
	2003q2	2369	251	706	227	731	368	253	101 nolo	e 9,	2331	19
	2003q3	2728	337	799	243	869	457	339	97 gies	2025	2684	25
	2003q4	2320	261	761	242	706	403	267	65	ы С	2292	17
2004	2004q1	2299	286	802	276	692	360	247	93	12 n	2269	15
	2004q2	2168	232	723	288	692	392	223	82	ë Bil	2143	15
	2004q3	2377	260	744	290	729	394	228	84	t Agence Bibliogr	2351	13

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2005	2005q1	2191	267	771	384	704	376	197	U		10
	2005q2	2305	265	741	422	736	408	247	75 luding for	2 273	24
	2005q3	2526	300	868	488	825	455	231	⁸⁸ u E	2 490	18
	2005q4	2159	247	752	442	675	417	208	106 Inse	2132	5
2006	2006q1	2043	253	745	445	610	377	186	84 elate	2 009	18
	2006q2	2366	283	851	492	713	428	197	113 d nen t	2330	18
	2006q3	2403	267	845	520	747	433	194	102 te Sup	2361	27
	2006q4	2229	258	793	524	719	446	168	86 and o	2191	12
2007	2007q1	2067	237	741	443	646	387	188	93 data	2036	19
	2007q2	2092	241	794	472	617	363	159	85 mini	2066	11
	2007q3	2335	303	874	604	730	453	198	109 .	2297	27
	2007q4	2187	266	806	587	659	409	147	75 Iuding 97 88 106 ses related to text and data mining, Al training, Al training, and similar 93 85 109 82 87 27 92 111 103 103	2159	17
2008	2008q1	2176	268	800	505	670	382	160	87 j 27	2148	18
	2008q2	2267	254	832	497	663	384	149	92 an	2237	15
	2008q3	2536	325	955	598	754	451	165	111 sin	2509	15
	2008q4	2194	248	852	533	668	387	157	103 nilar	e 2173	11
2009	2009q1	2155	222	859	514	618	378	118	84 26	•	15
	2009q2	2273	257	920	571	669	409	114	95	9 2245	12
	2009q3	2431	244	965	623	700	430	127		2400	20
	2009q4	2084	230	850	557	597	382	112		2054 2054	14
2010	2010q1	2262	229	854	623	642	410	108	104 24	2231	18
	2010q2	2388	240	991	599	638	404	128	89 104 24 112 94 - 	2364	17
	2010q3	2485	260	1005	705	637	422	134	94	2459	14

	2010q4	2191	258	979	660	594	382	117	108	njopen-2019-0328 bv copyright. inc	2153	26
2011	2011q1	2115	227	907	658	538	351	104	118		2094	5
	2011q2	2150	232	1090	700	511	352	87	103	23 on 16	2121	13
	2011q3	2313	296	1230	813	569	383	110	96	6 Dec	2285	16
	2011q4	1884	179	1064	617	403	341	71	84	December Enseig or uses rei	1862	15
2012	2012q1	1879	208	1168	692	465	317	88	96	er 20 elate	1861	12
	2012q2	1932	206	1292	633	467	324	88	95	ment d to	1913	11
	2012q3	2090	239	1380	730	530	330	89	94	t Sup	2064	18
	2012q4	1900	197	1242	654	474	319	89	78	nload berieu and	1882	9
2013	2013q1	1865	180	1222	689	449	319	69	75	led fr	1839	12
	2013q2	1979	179	1227	684	435	367	79	81	rom BES	1952	11
	2013q3	2095	199	1274	749	482	405	84	77	na. /	2070	16
	2013q4	1761	174	1044	688	440	344	85	60	2019. Downloaded from http://bmjdpen.l mement Superieur (ABES) .	1737	11
2014	2014q1	1810	200	1117	655	420	305	103	60		1776	15
	2014q2	1878	182	1114	717	457	356	80	62	.bmj	1852	8
	2014q3	2108	200	1258	773	510	394	87	78	bmj.com/ or and similar	2079	13
	2014q4	1920	201	1064	688	472	315	92			1891	13
2015	2015q1	1847	177	1069	705	436	332	107		technologia	1820	13
	2015q2	1937	190	1087	702	466	348	103	52	,e ,e	1896	14
	2015q3	2247	240	1299	832	548	364	107	71		2220	15
	2015q4	2041	206	1154	769	534	368	126	60	at Ag	2005	19
2016	2016q1	2032	200	1127	719	479	320	108	76	27 nce	2001	18
	2016q2	2185	219	1205	770	551	359	116	72	e Bik	2144	17
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Page 29 of 33						BMJ O	pen			njopen-2 1 by cop			
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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

		Reporting Item	Page Number
Title and abstract			
Title	<u>#1a</u>	A population register-based study.	1
Abstract	<u>#1b</u>	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			<u>ت</u> 2 2
Background / rationale	<u>#2</u>	Explain the scientific background and rationale for the investigation being reported	3
Objectives	<u>#3</u>	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	<u>#4</u>	Present key elements of study design early in the paper	5
Setting	<u>#5</u>	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	<u>#6a</u>	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5-6
Eligibility criteria	<u>#6b</u>	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	<u>#7</u>	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	<u>#8</u> For p	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5-6

Page	31 of 33		BMJ Open			
1 2			more than one group. Give information separately for for exposed and unexposed groups if applicable.			
3 4 5	Bias	<u>#9</u>	Describe any efforts to address potential sources of bias	5-6		
6 7	Study size	<u>#10</u>	Explain how the study size was arrived at	5		
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33	Quantitative variables	<u>#11</u>	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6 Protecte		
	Statistical methods	<u>#12a</u>	Describe all statistical methods, including those used to control for confounding	6-7 by copyri		
	Statistical methods	<u>#12b</u>	Describe any methods used to examine subgroups and interactions	6-7 6-7 n/a according to ITSA design 6		
	Statistical methods					
	Statistical methods	<u>#12d</u>	If applicable, explain how loss to follow-up was addressed	n/a ted to tex		
	Statistical methods	<u>#12e</u>	Describe any sensitivity analyses	6-7 data		
34 35 26	Results			nining		
36 37 38 39 40 41 42 43	Participants	<u>#13a</u>	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	Table 1 and additional Appendix 1+3 n/a Appendix 1 Appendix 1 Appendix 2		
44 45 46	Participants	<u>#13b</u>	Give reasons for non-participation at each stage	n/a rtechn		
47 48	Participants	<u>#13c</u>	Consider use of a flow diagram	Appendix 1		
48 49 50 51 52 53 54 55 56 57	Descriptive data	<u>#14a</u>	 #14a Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable. 			
58 59 60	Descriptive data	<u>#14b</u> For pe	Indicate number of participants with missing data for each eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6		

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			BMJ Open	Page 32 of 33
1			variable of interest	do rws
2 3	Descriptive data	<u>#14c</u>	Summarise follow-up time (eg, average and total amount)	n/a fi
4 5 6 7 8 9	Outcome data	<u>#15</u>	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	Table 1 and Published as
10 11 12 13 14 15	Main results	<u>#16a</u>	Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a Table 1 and Appendix 1 n/a according to the ITSA model n/a Table 1 r/a r/a according to the ITSA model n/a
16 17 18 19	Main results	<u>#16b</u>	Report category boundaries when continuous variables were categorized	n/a n/a
20 21 22 23	Main results	<u>#16c</u>	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 1 In the formula to the formul
24 25 26 27	Other analyses	<u>#17</u>	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	December 2019. Enseignemer or uses related t
28 29	Discussion			9. Dow to tex
30 31 32	Key results	<u>#18</u>	Summarise key results with reference to study objectives	o text and data m 14-15
33 34 35 36 37	Limitations	<u>#19</u>	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	ad from http://r r (ABES) lata mining, Al
38 39 40 41 42	Interpretation	<u>#20</u>	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	n http://bmjopen.bmj.com/ on June 9, 2025 ining, Al training, and similar technologies 17-18
43 44 45 46	Generalisability	<u>#21</u>	Discuss the generalisability (external validity) of the study results	17-18 imilar techn
47 48	Other			9, 20: ologie
49 50	Information			95.
51 52 53 54 55 56 57 58	Funding	<u>#22</u>	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n http://bmjopen.bmj.com/ on June 9, 2025 at Agence Bibliographique de l S) . 16-17 17-18 18
59 60		For pe	eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	ue de l

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Routine induction in late-term pregnancies; follow-up of a Danish induction of labour paradigm.

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Secondary Subject Heading:	Epidemiology, Evidence based practice, Public health, Health economics, Medical management
Keywords:	Labour, induced [MeSH], Medicalization [MeSH], Adverse events [MeSH], Stillbirth [MeSH], Perinatal death [MeSH]



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Title page:

Routine induction in late-term pregnancies; follow-up of a Danish induction of labour paradigm.

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15 Keywords

- Labour, induced [MeSH], Medicalization [MeSH], Adverse events [MeSH], Stillbirth
 [MeSH], Perinatal death [MeSH]
- 19 Word count: 4058 words

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Abstract

Objectives

For many years, routine elective induction of labour at gestational week 42+0 has been recommended in Denmark. A new protocol was introduced in 2011 with a more proactive regimen aimed at reducing stillbirth recommended routine induction of all women between gestational weeks 41+3 and 41+5. The present study evaluates a national change in induction of labour regime. The trend of maternal and neonatal consequences are monitored in the pre-intervention period (2000-2010) compared with the the post-intervention period (2012-2016).

- Design
- A national retrospective register-based cohort study.
- Setting
- Denmark
- **Participants**
- All births in Denmark 41+3 to 45+0 gestational weeks between 2000 and 2016 (N =
- 152,887).

Outcome measures

Primary outcomes: stillbirths, perinatal death, and low Apgar scores. Additional outcomes:

birth interventions and maternal outcomes.

Results

For the primary outcomes, no differences in stillbirths, perinatal death, and low Apgar scores were found comparing the pre- and post-intervention period. Of additional outcomes, the trend changed significantly post-intervention concerning use of augmentation of labour, epidural analgesia, induction of labour, instrumental assisted birth, and uterine rupture (all p < 0.05). There was no significant change in the trend for caesarean section and instrumental birth. Most notable for clinical practice was the increase in induction of labour from 41% to 65% (p<0.01) at 41+3 weeks during 2011 as well as the rare occurrence of uterine ruptures (from 2.6 to 4.2 per thousand, p < 0.02) Conclusions Evaluation of a more proactive regimen recommending induction of labour from gestational week 41+3 compared to 42+0 using national register data found no differences in neonatal

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outcomes including stillbirth. The number of women with induced labour increased
significantly.
Article summary
Strengths and limitations of this study
Retrospective national registry-based data (2000-2016)
 Diagnoses based only on ICD-10 classifications
 Includes all births at 41+3 gestational week and beyond in Denmark
• 13 years before and 5 years after a change in clinical practice on induction of labour
Access to relevant confounders
Introduction
In Denmark, a new proactive policy was introduced in 2011 aiming at preventing stillbirth
and other foetal and maternal complications in post-term pregnancies. The Danish Society
for Obstetrics and Gynaecology introduced the new protocol recommending routine
induction of labour in otherwise low-risk pregnant women between gestational week (GW)
41 plus 3 days (41+3 GW) and 41+5 GW to prevent the pregnancy from reaching the post-
term period of 42+0 GW. Women at risk (e.g. with diabetes or multiple gestations) are
according to national guidelines offered induction at earlier gestational ages[1]. The
argument for the new policy was a concern for the unborn child, as prolonged pregnancy
increases the risk of a malfunctioning placenta, shoulder dystocia, meconium aspiration
syndrome, foetal distress, and ultimately foetal death [1]. The new protocol was also aimed
at reducing post-term maternal complications such as dystocia, birth-related injuries,
caesarean section (CS), and post-partum haemorrhage [1]. This new protocol was a
deviation from the former guideline recommending induction at 42+0 GW. Induction of
labour may itself impose a risk of adverse consequences such as hyperstimulation, foetal
asphyxia, post-partum haemorrhage, uterine rupture, and in very rare cases, foetal and
maternal death [2]. Induction has been shown to be related to additional interventions such
as epidural analgesia, continuous foetal monitoring, confinement to bed, instrumental birth,
and emergency CS [3]. There is a lack of consensus on how to handle pregnancies

beyond term, as both post-term pregnancy and induction of labour may independently be

Existing studies are limited to comparing benefits and harms of routine induction at 41 GW

significant reduction in meconium aspiration syndrome (RR 0.43, 95% CI 0.23, 0.79) using

Caughey et al [6] arrived at similar conclusions on studies inducing labour (39 to 41 GW)

CI 1.01 to 1.46). None of these reviews compared induction at 41 GW with the Danish

recently published systematic review narrowed the scope to routine induction at 41+0/6

standard at 42 GW, but based conclusions on a wider variation in gestational age. A

GW versus 42+0/6 GW [2]. The data lacked statistical power to draw conclusions on

perinatal death, but found a significant reduction in oligohydramnios, and meconium-

increased risk of low pH< 7.10, CS, chorioannionitis, precipitate labour, and uterine

In a normal population, about 25% of the women will still be pregnant at 41+0 GW and

the number of ongoing pregnancies and could lead to an additional 13-15% of women

year after the Danish shift in the protocol, the new induction paradigm was almost fully

implemented [10]. In the following year, two Danish studies evaluated the consequences

and found a considerable reduction in stillbirths [11,12]. Hedegaard et al and Zizzo et al

monitored one and three years of data, respectively, after implementation of the new

protocol, but adjustment for ongoing trends was not performed [11,12]. The aim of this

introducing the new 2011 protocol, during a 5-year follow-up period with adjustment for

study was to evaluate perinatal outcomes, birth interventions and maternal outcomes after

Changing the protocol to offer routine induction between 41+3 and 41+5 GW thus changes

being encouraged to have an induction, [4] with possible iatrogenic consequences [9]. One

about 5% reach 42+0 GW without going into a spontaneous onset of labour [7,8].

stained amniotic fluid in the induction group (41+0/6). However, the study also found an

and found expectant management (41 to 45 GW) to increase the risk of CS (OR, 1.21 95%)

compared to previous standard of 42 GW. A systematic review by Wennerholm et al [5]

found a non-significant reduction in stillbirths (RR 0.33, 95% CI 0.10, 1.09), and a

routine induction (41 to 42 GW) compared to expectant management (42 to 44 GW).

associated with adverse consequences [4].

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rupture [2].

ongoing trends.

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113 Material and Methods

This is a retrospective cohort study using data from the Danish Medical Birth Registry 114 (DMBR).with additional patient level data from other Danish administrative registries. The 8 115 9 10 116 dataset holds information on all births in Denmark since 1997 in women with either a 11 Danish civil registration number or a temporary registration number. Undocumented 117 12 13 migrants are probably also included, as it is legal to give birth anonymously. Data were 118 14 collected prospectively at all contacts with health care providers, e.g. midwives and 15 119 16 120 obstetricians [13]. For the purpose of this study, we restricted data to include births in 17 18 Denmark from 1 January 2000 to 31 December 2016 with a known gestational age. Our 121 19 analysis is limited to pregnancies that lasted at least 41+3 GW (290 gestational days). 20 122 21 Cases were excluded if both birth weight and length deviated substantially from the mean. ₂₂ 123 23 A cut-off value of three SD was used to avoid including foetuses wrongly coded as late or 124 24 25 125 post term (Appendix 1). 26

28 The population of interest included all ongoing pregnancies from 41+3 GW and onwards. If 127 29 30 any important foetal or maternal morbidity was present such as multi-parity, Body Mass 128 31 32 129 Index (BMI)>30, maternal age>40, hypertension, diabetes mellitus or other medical 33 conditions, the usual clinical practice is to induce labour no later than 41+0 GW. Few 34 130 35 women may object to advice of induction of labour and may be included in the present 131 36 ³⁷ 132 study population. 38

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40 41 134 The exposure of interest was the new protocol from March 2011 and implemented during 42 2011 at Danish hospitals offering routine induction at 41+3-41+5 GW [10]. 135 43 44 136 The outcomes of interest were stillbirth, perinatal death (stillborn or dead within the first 7 45 days), and low Apgar score (<7 after 5 minutes). We also analysed trends in birth 46 137 47 ₄₈ 138 interventions such as induction of labour (medical and/or mechanical), augmentation of 49 labour (synthetic oxytocin), epidural analgesia (pain relief during vaginal birth), and 139 50 51 140 maternal outcomes such as instrumental birth (forceps or vacuum extraction), CS and 52 53 141 uterine rupture.

- ⁵⁴₅₅ 142 Potential confounding variables of interest included advanced maternal age (\geq 40 years), ⁵⁶₅₇ 143 nulliparity, previous CS (among multiparous), light/moderate preeclampsia (blood pressure
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- 59 60

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 \geq 140/90 & <160 /110 with proteinuria), pre-pregnancy obesity (BMI \geq 30); smoking (any

The variables in the dataset are either based on the classification of Diseases (ICD10) or

hyperstimulation was available. Further, the post-partum haemorrhage code was changed

in 2012 from including only severe bleeding to "any bleeding" and was thus too imprecise

use conventionally accepted standards by e.g. WHO [14]. No information on meconium

aspiration syndrome, manifest oligohydramnios, pH-value, precipitate labour, and

smoking after 1 trimester), and high birth weight (> 4000 gram).

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to apply. We included a variable if at least 95% of cases were coded. The variables used in this 152 study were generated from either of two different modes of registration practice. When 153 health providers do the documentation, some information must be registered by ticking off 154 23 a checkbox, if a given event occurs (e.g. epidural). In this case, missing values cannot be 155 24 25 156 determined, because the extent to which the provider may have left out a code is unknown 26 (particularly if it does not involve a billing code). Other types of information is mandatory to 27 157 28 158 report (e.g. weight of the child). For mandatory variables, the number of observations with 29 30 159 missing values was documented. We included a variable if at least 95% of cases were 31 coded. We assumed a random misclassification with equal distribution of missing cases 32 160 33 per year. None of the variables exceeded missing observations of more than 5%. The 34 161 35 variable with the highest frequency of missing cases was maternal BMI> 30 with 3.7%. 162 36 37 163 The STROBE cohort reporting guidelines were used [15] 38

39 Patient and Public Involvement 40 164

41 Patients were not directly involved in the study, as it was based on register data. However, 165 42 43 in the inial phase of the study, the consumer organisation for Parenthood and Childbirth 166 44 was contacted to discuss relevance of the aim of this present study. The results from the 45 167 46 ₄₇ 168 study will be published in the consumer organisation's journal as well as in other relevant 48 169 sites of public interest. 49

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Statistical analysis 172

Analyses were performed as Interrupted Time Series Analysis (ITSA) and, if not suitable, a 173 Poisson regression analysis was conducted (explained below). The independent variable 174 10 175 was years separated into guarters (n=68) or, in case of only a few observations, years (n=17). The time-period consisted of a pre-intervention period of 11 years (2000-2010), 176 177 one year for implementation (2011), and 5 years for the post-intervention period (2012-2016). Single-group analysis was used. The model fitted an ordinary least square (OLS) 15 178 16 ₁₇ 179 line pre- and post-intervention. If interruptions occurred at other time points during the pre-18 intervention period, the period was shortened to fit the best model. We tested robustness 180 19 20 181 by checking if results were sensitive to change of adjoining years. The regression model 21 used Newey-West standard errors and we conducted a Cumby-Huizinga test for auto-22 182 23 183 correlation [16]. The assumption in ITSA modelling is that any time-varying confounding 24 25 changes relatively slowly and will not cause concern as long as no other interruption 184 26 27 185 occurs coincidentally with the change in protocol in 2011 [16]. Visual inspection is 28 29 186 presented in Appendix 2.

31 ₃₂ 187 The ITSA model is not optimal for rare outcomes, including less than four observations per 33 time unit [16]; hence, Poisson regression was a more appropriate test for intrauterine and 188 34 35 189 perinatal death with the year of birth as the explanatory variable. To increase precision of 36 the estimates, the time period between 2000 and 2016 was included in the analysis. We 37 190 38 191 used the log (number of births) as an offset in the model to account for the varying number 39 40 192 of births. Two models were fitted to the data. The first model included a general time trend 41 42 193 only; the second model included a general time trend and an effect of the change in the 43 44 194 protocol from 2011. The adequacy of each model was assessed by Goodness-of-fit test 45 195 and the impact of the change in the protocol was evaluated by comparing the slopes of the 46 47 196 time trends before and after 2011. 48

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50 197 All analyses are presented in graphs or fitted curves depending on the method of analysis. 51 52 198 Descriptive statistics on stillbirth and perinatal death are presented as absolute numbers 53 199 and percentages by year. If the absolute number was less than 5, results are presented as 54 55 200 "<5" and rates as "<0,5 per 1000" and absolute numbers are omitted from the Poisson 56 57 201 fitted curves to avoid identification [17]. Outcomes are further presented in a table 58 ₅₉ 202 including the interruption jump and slopes of the curves before and after the intervention

with 95% confidence intervals (CI). P-values present the statistical difference between the pre- and post-intervention slopes. For the Poisson regression, Incidence Rate Ratio (IRR) for both fitted curves, p-values and Goodness-of-fit are presented.

11 206 Data were analysed in STATA/SE 15.1 software package (StataCorp. 2017. Stata Statistical Software) adding the STATA ITSA-package 17-4. All reported p-values are two-sided, and statistical significance was 5%.

Results

32 217

The dataset included 1,057,453 births from 1 January 2000 to 31 December 2016. Of 20 210 those, we excluded 2,712 records with missing information on GW (0.3%). Of the ²³ 212 remaining cases, 153,120 pregnancies (14.5%) lasted until 41+3 GW or beyond. We excluded an additional 233 cases (0.15%), all live births, where both the weight and the 25 213 27 214 length were more than three SD from the mean for a final working total of 152,887 pregnancies. In the final population, there were 213 stillbirths (0.14%) and 262 perinatal 30 216 deaths (0.17%) (Appendix 1).

Trends in interventions and outcomes before and after the implementation of the new induction of labour protocol are presented in Table 1 and further elaborated in Figures 1-3. 37 220 Table 1 presents the results of the interrupted time-series analysis, a pre- and postintervention slope for each variable, the interruption jump in 2011 and a test for 39 221 significance between the pre- and post-intervention slopes is presented. For the Poisson ⁴² 223 regression, a general fit before and after 2011 is shown as an IRR and a significance test for difference in IRR. 44 224

Outcomes	Interruption jump	Pre-intervention trend	Post-intervention trend	Difference in trends ^a
	2011	% per year (95% CI)	% per year (95% CI)	p-value
Maternal interventions:				
Augmentation of labour (%)	-3.1	-0.87 (-1.14, -0.61)	0.11 (-0.16, 0.40)	0.000
Epidural analgesia (%)	4.1	2.80 (2.48, -3.12)	0.13 (-0.44, 0.70)	0.000
Induction of labour (%)	22.4	1.70 (1.53, 1.87)	-2.36 (-3.03, -1.72)	0.000
Instrumental birth (%)	-0.5	-0.10 (-0.22, -0.05)	-0.12 (-0.33, 0.08)	0.881
Maternal outcome:				

2							
3 4	Caesarea	n section (%)	0.1	-0.	16 (-0.36, -0.04)	-0.10 (-0	
5 6		pture (pr.1000)			21 (0.12, 0.30)	-0.24 (-0	
6 7	Foetal ou	,					
8		ore <7/5 min. (%	b) -0.2	0.	01 (-0.01, 0.02)	0.04 (0.	
9		Υ.	,		neral fit. IRR all	general	
10				U	ars	J	
11 12	Stillbirths				90 (0.87, 0.93)	0.91 (0.	
12	Perinatal	mortality		0.	90 (0.88, 0.93)	0.90 (0.	
14		nce Rate Ratio	I		. , ,		
15	^b GOF, Good	dness-of-fit test.					
¹⁶ 227							
17 18							
18 19 228	Primar	y outcom	e: Perir	natal mort	ality and mo	rbidity	
20 21 229	Table 2	presents sti	llbirths an	d perinatal	death in absolui	te numbe	
²² 230 23	general	decline of ir	ntrauterine	e deaths wa	s observed duri	ng the st	
24 231	risk of st	illbirth at 2.3	3 per 100	0 births in th	ne year 2000 dro	opping to	
25 26 232	from app	proximately	2009, afte	er which it h	as generally rer	nained be	
²⁷ 28 233	1,000 births.						
²⁹ 234	Table 2 p	oresents stillb	oirths and p	perinatal dea	th in years 2000-	2016	
30 31	Year	Births	Stillborn	Stillborn per	Perinatal death	Perinata	
32		n=152,887	n=213	1000 births	n=262	per 1000	
33	2000	10670	25	2,3	35	3,3	
34	2001	10765	31	2,9	36	3,3	
35	2002	9887	19	1,9	23	2,3	
36 37	2003	9702	18	1,9	20	2,1	
38	2004	9025	15	1,7	18	2,0	
39	2005	9181	18	2,0	20	2,2	
40	2006	9041	19	2,1	24	2,7	
41 42	2007	8681	12	1,4	15	1,7	
42	0000	0.170	40	1.0	10		

Perinatal mortality		0.90 (0.88, 0.93)	0.90 (0.87, 0.94)	1.000
Stillbirths		0.90 (0.87, 0.93)	0.91 (0.87, 0.95)	0.562
		years		
		general fit. IRR all	general fit. IRR all years	GOF ^b
Apgar score <7/5 min. (%)	-0.2	0.01 (-0.01, 0.02)	0.04 (0.01-0.07)	0.107
Foetal outcome:				
Uterine rupture (pr.1000)	1.6	0.21 (0.12, 0.30)	-0.24 (-0.60, 0.13)	0.001
Caesarean section (%)	0.1	-0.16 (-0.36, -0.04)	-0.10 (-0.47, 0.27)	0.757

ble 2 presents stillbirths and perinatal death in absolute numbers per 1000 births. A

neral decline of intrauterine deaths was observed during the study period, with an initial k of stillbirth at 2.3 per 1000 births in the year 2000 dropping to a rate of <1 per 1000 m approximately 2009, after which it has generally remained between 1.0 and 0.5 per

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00 births.

ble 2 presents stillbirths and perinatal death in years 2000-2016

Year	Births n=152,887	Stillborn n=213	Stillborn per 1000 births	Perinatal death n=262	Perinatal death per 1000 births
2000	10670	25	2,3	35	3,3
2001	10765	31	2,9	36	3,3
2002	9887	19	1,9	23	2,3
2003	9702	18	1,9	20	2,1
2004	9025	15	1,7	18	2,0
2005	9181	18	2,0	20	2,2
2006	9041	19	2,1	24	2,7
2007	8681	12	1,4	15	1,7
2008	9173	12	1,3	16	1,7
2009	8943	8	0,9	8	0,9
2010	9326	7	0,8	8	0,9
2011	8462	<5	<0,5	5	0,6
2012	7801	<5	<0,5	<5	<0,5
2013	7700	8	1,0	10	1,3
2014	7716	<5	<0,5	<5	<0,5
2015	8072	6	0,7	9	1,1
2016	8742	7	0,8	8	0,9

According to EU's General Data Protection Regulation no data <5 observations may be provided. The rate pr.1000 births is corrected accordingly.

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Figures 1a and 1b present the two fitted curves for stillbirths and perinatal death, respectively. The red curve/diamond shows predicted values for the years 2012-2016 based on the 2000-2010 trend without a change in protocol and the black curve/cross represents a fitted curve after the change in protocol. Figure 1c presents the ITSA model for low Apgar scores with 2011 as an interim year for implementation. The OLS lines pre-13 241 and post-intervention are presented.

Fig. 1a-c. Presents perinatal outcomes, year 2000-2016 with change in protocol, 2011 (a) Stillbirths per 1000 births (b) Perinatal death per 1000 births (c) Apgar score <7 after 5 minutes, percent (%).

(Fig 1a-c perinatal outcomes) а b С

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> No difference was observed between the two fitted curves for either stillbirth (p=0.56) or perinatal death (p=1.00). The goodness-of-fit test was p=0.40 for stillbirth and p=0.24 for perinatal mortality. Figure 1c presents low Apgar score before and after the intervention showing no difference in the slope before and after the new protocol (p=0.11). See Table 1 for details.

⁴⁰ 254 Birth interventions and maternal outcome

Interventions in birth are presented in Figure 2a-2c, and maternal outcomes are presented 42 255 in Figure 3. (See Appendix 3 for details)

Fig. 2a-c. Presents interventions in childbirth (%), year 2000-2016 with change in protocol, 2011. (a) Labour induction (b) Augmentation (c) Epidural analgesia.

а	(Fig 2a-c interventions in childbirth)
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	<u>.</u>

Induction of labour increased during the pre-intervention period with an annual average increase of 1.7% and rates rising from 25% to 41%. By 2011, a significant jump from 41% to 65% annual inductions was seen (p<0.00). After the substantial jump in the rate in 2011, the annual decline of 2.4% in the induction of labour brought the rate down to 55% (p<0.01). A significant change in trend was observed for augmentation of labour after implementation of the new protocol. As interruption in trend occurred in the preintervention period (2005) the period was shortened to fit the model. From 2005 until 2011 there was a slight annual decrease (-0.9%) in augmentation changing to a marginal annual increase of 0.1% (p<0.01) from 2012-2016. Use of epidural analgesia for pain relief during labour increased during the entire pre-intervention period at approximately 4.1% annually. The observed increase of epidural analgesia flattened in 2011 after the intervention, resulting in a marginal increase of 0.1% (p<0.01).

Fig. 3a-c. Present maternal outcome, year 2000-2016 with change in protocol, 2011. (a) Cesarean section (%). (b) Instrumental birth (%). (c) Uterine ruptures per 1000 births.

а	(Fig 3a-c maternal outcomes)
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С	

For CS an interruption in trend occurred in the pre-intervention period (2005) and the period was shortened to fit the model. No change was found for CSs before and after the change in the protocol (p=0.76) with a non-significant declining trend from 2005 and onwards. The number of instrumental birth declined during the entire study period with an annual decrease of 0.1%, and no change was observed after 2011 (p=0.88). Uterine rupture is a rare event and is presented as a rate per 1000 births. During the preintervention period, a steady increase of 0.2 % yearly was observed. In 73% of cases, uterine rupture occurred in women with previous caesarean section. Uterine rupture was followed, similarly to the case of induction, by a substantial increase between 2010 and 2012 from 2.6% to 4.2% (p<0.02). In the post-intervention period, a decline of uterine rupture of 0.3‰ yearly was noted (p<0.01).

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290 Other relevant changes in population

Changes over time for possible confounders and interruptions occurring simultaneously as
the intervention of interest (2011) may have biased the results. We explored the changes
in maternal age > 40 years, nulliparity, preeclampsia, previous CS, BMI>30 and smoking
status. No changes in trend were noted after 2011. See Appendix 2.

Discussion

7 Principal findings

This study included all births in Denmark (N=152,887) from 41+3 GW between 2000 and 2016. We evaluated maternal and neonatal outcomes after a change in the induction of labour protocol in 2011. Once the trend from 2000-2010 was taken into account, no differences were found in stillbirth, perinatal death, or low Apgar score. There was however a 59% relative increase in the use of labour induction within the first year after the new protocol as well as a significant increase in uterine ruptures. The use of epidural analgesia and augmentation both levelled off after the change in protocol and there was no change in number of CSs in the pre- and post-intervention period.

5 306 Strengths and weaknesses of the study

No randomised trials were conducted before or concurrent with the implementation of the new protocol, and the ITSA design provides a robust quasi-experimental alternative [18]. The present design may provide a high degree of internal validity [16] as a single-group ITSA offers an advanced approach to evaluation of before and after an intervention including analysis of the ongoing trends [16]. The data used for this present study was collected prospectively for other purposes. Thus interpretations of causality is not possible.

In the case of rare outcomes, we used a Poisson regression model. Estimating the trend
 before 2011 was used to predict the expected outcomes after the implementation. Two
 Danish retrospective cohort studies monitored the impact of the intervention and found
 about a 50% reduction of stillbirths after 2011 [10,12]. One study monitored pregnancies
 from 41+0 GW and found an adjusted odds ratio of 0.5, (95% CI 0.29-0.89) [12], whereas
 the other study monitored pregnancies from 41+2 and did not arrive at significant results
 (OR 0.34, 95% CI 0.09-1.24) [10]. Both studies compared the years before and after but

did not consider the ongoing trend which revealed a 63% decrease in the stillbirth rate in the five years prior to the intervention and a marginal *increase* in the five years after the intervention to the point where the rate was the same in 2016 as it was in 2010 (0.8 per 1,000)(Table 2). This highlights the importance of including trends and longer time frames in the analysis of trends to ensure the most valid conclusions.

A strength of this register-based study is that it includes all Danish births at or beyond 41 + 3 GW. Denmark has universal health care coverage and selection bias is unlikely, as all women on all income levels and demographic characteristics are covered. The most recent study from 2003 validated the registration data and found that common surgical interventions and procedures matched the medical records [19]. ICD-10 main categories were validated and found acceptable [19]. Interventions are reimbursed if registered, which further increases accuracy [13].

Not all known adverse effects are available in the register. Oligohydramnios and 332 29 333 meconium aspiration syndrome usually increase with gestational age [2,6], but since these data were not available, low Apgar, stillbirth and perinatal death were used as the best 31 334 335 possible proxy outcome for these conditions. Post-partum haemorrhage (PPH) is an adverse effect of both ongoing pregnancies in late gestation and induction of labour [20]. 336 36 337 Due to a change in the definition of PPH, we considered the PPH data in the study period 38 338 to be unreliable. Information on labour dystocia is not available in the registry, instead 339 labour augmentation was used as a proxy measure. Information on hyperstimulation of the ⁴¹ 340 uterus and precipitate labour was not available, but uterine rupture may be a severe consequence of an over-stimulated uterus. 43 341

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46 342 Why the intervention seems to fail its purpose

The main finding of this study is a lack of immediate benefits for the foetus. A possible 48 343 explanation may be that, in a country like Denmark with a generally high standard in public 344 345 health and a low mortality rate, there would be fewer opportunities to prevent perinatal deaths [21]. European countries, including Denmark, have experienced a steady decrease 53 346 ₅₅ 347 in stillbirths and perinatal mortality during this millennium. A cross-European study found 348 this decrease in all gestational ages which, points to multifactorial explanations [21]. 57 58 349 Changed screening policies, early termination of pregnancies with lethal abnormalities, 59

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better postnatal management, preconception counselling, detection of foetal growth restriction, and a higher quality of prenatal care were mentioned as explanations [21,22]. In addition, a decline in smoking in pregnancy was emphasized as one of the main contributors to the decline in stillbirths [21]. In Denmark the rate of prenatal smoking decreased from 19% in 2000 to 5% in 2016 (Appendix 2).

It is estimated that suboptimal care accounts for 20 to 50% of stillbirths [21,23]. Nonetheless, a number of stillbirths and perinatal deaths are not preventable, especially in case of undetected severe congenital malformations [24]. Several studies have found a 17 357 19 358 marked increase in stillbirths with increasing gestational age [25-27], which is a relevant argument for routine induction at late term. However, these studies rely on data collected from 1985-96 and may not represent contemporary risks. The same challenges may exist in the evidence base behind the Danish change in guideline [25,28,29], where data 24 361 collection draws on stillbirth studies back to the year 1969, long before the general health improvements noted above. This may explain the lack of benefit found in this study 29 364 associated with offering routine induction of labour a few days earlier than usual practice.

Intervening in the normal processes of childbirth

The few days change in the recommended time for induction of labour caused no improvement in perinatal outcomes, but it affected the physiological birth. The rate of labour inductions increased from 41% to 65% in the first year after implementation. 37 368 Induction of labour interferes with the physiological birth, as it may prolong time in labour and in hospital, confine the woman to the bed attached to monitoring devices and an 42 371 intravenous drip [30]. This more proactive induction of labour regimens was also implemented in Great Britain in 2008 [31]. Scandinavian countries, in general, are more ₄₄ 372 likely to practice expectant management with regard to induction of labour, [32] weighing the benefits against the potentially harmful consequences of induction of labour [33].

Since induction of labour has been found to be a risk factor for hyperstimulation and 51 376 pressure on the uterine cavity, uterine rupture is a well-known adverse effect [2,7,34]. A systematic review comparing inducing labour in women at 41 GW versus 42 GW showed a 53 377 doubling of the risk of uterine rupture (RR 1.97, 95% CI 1.54-2.52) [2]. This study found an increase in uterine rupture (p<0,02) with a change from 2,6 to 4,2%. A long term trend towards an increased use of epidural analgesia for pain relief levelled out after 58 380

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implementation of the new protocol (Figure 2c). In the present study, the use of 381 augmentation of labour increased slightly after a long period of a decreased use (Figure 382 2b). Knowledge of risks associated with augmentation at 41 GW versus 42 GW is limited. 383 One cohort study of 51,473 women found an increase in labour dystocia after induction of 384 labour was performed at 41 GW (RR=1.29, 95% 1.22-1.37) [35] while a randomised trial of 385 508 women found no difference (RR 0.55, 95% CI 0.20-1.45) [36]. Conflicting results have 13 386 been published regarding induction of labour and risk of CS [2,37,38]. In this study, no 15 387 388 change in the CS trend was found, despite the substantial increase in induction of labour. Studies monitoring the normal course of pregnancy between 41 GW and 42 GW have 389 found 70-75% of the women went into spontaneous labour before 42 GW. The rest were 20 390 21 induced due to medical reasons or induced at 42 GW [36,37,39,40]. 391 22

24 Possible implications for clinicians and policymakers 392 25

26 The World Health Organization recommends induction of labour for medical reasons if the 393 27 28 394 expected benefits outweigh the potential harms [1]. The current study highlights the 29 importance of evidence based practice and careful monitoring of trends after 30 395 31 32 396 implementation of new interventions in pregnancy and childbirth.

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34 Unanswered questions and future research 397 35

36 The intention behind implementation of a new induction of labour protocol was an 398 37 38 expected reduction in stillbirth and perinatal mortality. Based on the results from this 399 39 40 400 present study, the expected reduction in mortality after introducing earlier induction of 41 42 401 labour was not achieved. As low stillbirth rates already exist in Scandinavian countries, 43 402 medicalisation of a large group of low risk women may be ineffective or even provide more 44 ⁴⁵ 403 harms than benefits. As most register studies only provide the numbers of adverse 46 47 404 outcomes, a more detailed study of case fatality is needed not only taking into account 48 congenital abnormalities, but also underlying social mechanisms and suboptimal care, to 405 49 50 406 provide knowledge on how to reduce adverse outcomes in counties with a low stillbirth rate 51 52 407 [41]. 53

54 Universal and free access to healthcare with focus on health literacy during pregnancy and 408 55 56 409 childbirth and with a continuing and ongoing focus on socioeconomic disadvantages may 57 reduce adverse outcomes for mothers and infants [42,43]. 58 410

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Conclusion 411

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6 The aim of this study was to evaluate changes in maternal and neonatal outcomes after 412 7 413 implementing earlier routine induction of labour after 41+3 GW in the entire Danish 8 9 10 414 population of pregnant women. No change in trend was found in low Apgar scores, 11 415 stillbirths or perinatal deaths after implementation of earlier routine inductions of labour. 12 13 416 The most substantial impact was the number of inductions of labour in women with 14 otherwise low risk pregnancies and an increased number of uterine ruptures. The use of 15 417 16 17 418 epidural analgesia, augmentation of labour, instrumental births, and CSs remained stable. 18 The study highlights a need for a more balanced discussion among health providers on 419 19 20 420 routine induction at late term. 21

22 Author contribution 421 23

24 ER and RM planned the study. ER & RM analysed data. ER wrote the manuscript in close 422 25 26 423 correspondence with RM, MJ, and ED. ER, RM; MJ, and ED revised the manuscript and 27 28 424 accepted the final version. ER is the guarantor.

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42 43 432 Competing interests

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52 437 Funding 53 438 54

⁵⁵ 439 ER received a grant from Danish Association of Midwifery and Herlev Hospital supported 56 the scholarship. 57 440

58 Data sharing statement 59 441

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3 4 5 442	All data relevant to the study are included in the article or uploaded as supplementary						
6 443 7	information (Appendix 2 and 3)						
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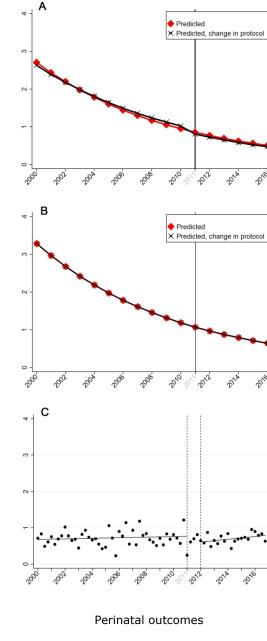
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⁴⁹ 558		6736(15)01020-X [doi].
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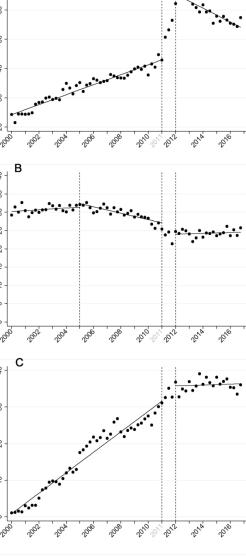
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98x208mm (300 x 300 DPI)



Interventions in childbirth 98x207mm (300 x 300 DPI)

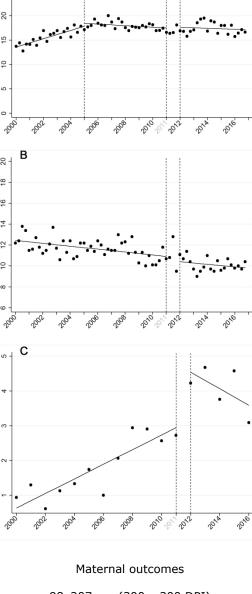


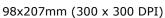
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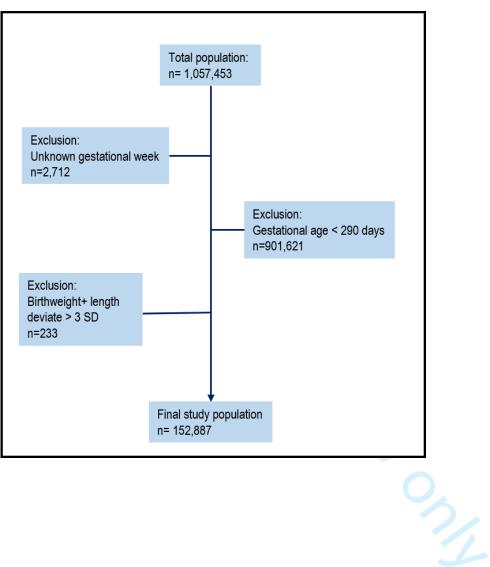
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Appendix 1

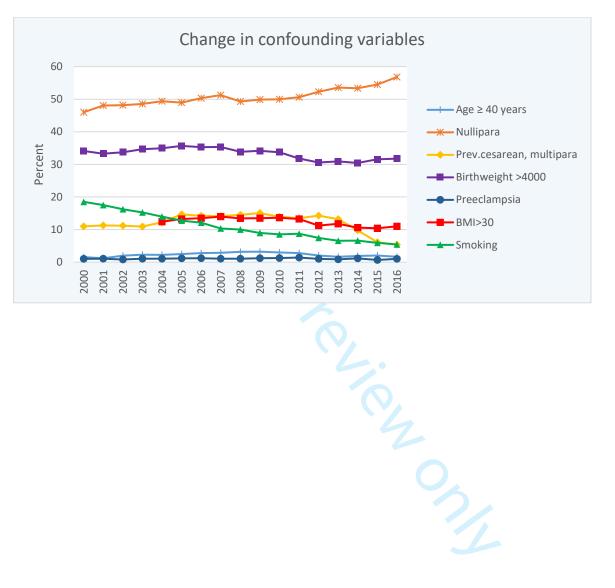
Flowchart



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Appendix 2





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Appendix 3.

Number of births, interventions and maternal outcome

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Year	Quarter	No. births	Instrumental	Induction	epidural	Augment	Cesarean	Epis	Tears 3&4	Runder	No. births Apgar	Apgar<7/5
2000	2000q1	2598	318	631	27	760	357	376	98 elate	er 20	2567	18
	2000q2	2686	334	577	33	845	388	357	88 to	19. [ment	2666	22
	2000q3	2716	375	663	41	815	346	365	104 É		2676	13
	2000q4	2670	357	653	36	871	379	345	108 and	nload	2632	16
2001	2001q1	2699	310	658	82	822	381	349	113 data	<u>∓ e</u> 44 A <u>÷</u>	2659	20
	2001q2	2802	324	685	68	806	424	303	140 B	rom	2766	15
	2001q3	2780	354	691	88	831	387	341	108 ing	http://	2741	19
	2001q4	2484	292	691	78	759	383	299	Tears 3&4 ** 98 related to text 98 88 104 108 113 140 108 Al training, Al training, and similar technologies. 103 112 100 93 101 97	//bmj	2450	19
2002	2002q1	2378	266	675	121	712	403	242	86 in	6 8	2344	24
	2002q2	2472	285	705	183	758	364	300	103 an	n.bm	2433	19
	2002q3	2659	323	794	208	816	429	285	112 a	j.cor	2632	17
	2002q4	2378	325	719	225	770	390	279	100 nilar	n/ on	2350	16
2003	2003q1	2285	267	671	224	726	387	277	93 tech	11 4	2255	10
	2003q2	2369	251	706	227	731	368	253	101 Noi	e 9,	2331	19
	2003q3	2728	337	799	243	869	457	339	97 gies	2025	2684	25
	2003q4	2320	261	761	242	706	403	267	65	at A	2292	17
2004	2004q1	2299	286	802	276	692	360	247	93	12 9	2269	15
	2004q2	2168	232	723	288	692	392	223	82	ë Bi	2143	15
	2004q3	2377	260	744	290	729	394	228	84	bliog	2351	13
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			For pe	eer review o	nly - http://l	bmjopen.bn	nj.com/site/a	about/guic	lelines.xhtml	ue de l		

	2004q4	2181	265	745	282	696	389	254	100	njopen-2019-03281 d by copyright, inc	2164	9
2005	2005q1	2191	267	771	384	704	376	197	75	0 _	2171	10
	2005q2	2305	265	741	422	736	408	247		9 1 C	2273	24
	2005q3	2526	300	868	488	825	455	231	88	6 Dec	2490	18
	2005q4	2159	247	752	442	675	417	208	106	December Enseig	2132	5
2006	2006q1	2043	253	745	445	610	377	186	84	er 20 elate	2009	18
	2006q2	2366	283	851	492	713	428	197	113)19. [ment id to	2330	18
	2006q3	2403	267	845	520	747	433	194	102	text text	2361	27
	2006q4	2229	258	793	524	719	446	168	86	ar 2019. Downloaded gnement Superieur∜ slated to text and da	2191	12
2007	2007q1	2067	237	741	443	646	387	188	93	led fi data	2036	19
	2007q2	2092	241	794	472	617	363	159	85	om BES	2066	11
	2007q3	2335	303	874	604	730	453	198	109	ng, /	2297	27
	2007q4	2187	266	806	587	659	409	147	82	led from http://bmjdpen.l ur (ABES) . data mining, Al training,	2159	17
2008	2008q1	2176	268	800	505	670	382	160	87		2148	18
	2008q2	2267	254	832	497	663	384	149	92	ppen.bmj.com/ (2 ² ning, and simila	2237	15
	2008q3	2536	325	955	598	754	451	165	111	i.com	2509	15
	2008q4	2194	248	852	533	668	387	157		¥ 9	2173	11
2009	2009q1	2155	222	859	514	618	378	118	84	1 June 26ne	2127	15
	2009q2	2273	257	920	571	669	409	114	95	9, 9	2245	12
	2009q3	2431	244	965	623	700	430	127	102		2400	20
	2009q4	2084	230	850	557	597	382	112	89	at Ag	2054	14
2010	2010q1	2262	229	854	623	642	410	108	104	24nce	2231	18
	2010q2	2388	240	991	599	638	404	128	112	e Bik	2364	17
	2010q3	2485	260	1005	705	637	422	134	94	Bibliographique de l	2459	14

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	2010q4	2191	258	979	660	594	382	117	by copyright, in	njopen 2019-0328 2153	26
2011	2011q1	2115	227	907	658	538	351	104		23 07 2094	5
	2011q2	2150	232	1090	700	511	352	87	103 ing	1 2121	13
	2011q3	2313	296	1230	813	569	383	110	96 g	2285	16
	2011q4	1884	179	1064	617	403	341	71	84 Ses T	235 2094 235 2094 2121 6 De 2285 Enseine 1862	15
2012	2012q1	1879	208	1168	692	465	317	88	96 e	ign ³ 20 1861	12
	2012q2	1932	206	1292	633	467	324	88	95 č	1913 1913	11
	2012q3	2090	239	1380	730	530	330	89	94 text	Sup 2064	18
	2012q4	1900	197	1242	654	474	319	89	78 and	2019. 1861 Superieur Superieur 4 1882 1882 1882	9
2013	2013q1	1865	180	1222	689	449	319	69	75 data		12
	2013q2	1979	179	1227	684	435	367	79	81 mining 77 g	BES 1952	11
	2013q3	2095	199	1274	749	482	405	84	77 ng ,	2070	16
	2013q4	1761	174	1044	688	440	344	85	60 Al training,	Image: Second state 1839 ABES) 1952 . 2070 . 1737	11
2014	2014q1	1810	200	1117	655	420	305	103	60 1	· 29 1776	15
	2014q2	1878	182	1114	717	457	356	80			8
	2014q3	2108	200	1258	773	510	394	87	62 and similar	292 1776 1852 2079 2079	13
	2014q4	1920	201	1064	688	472	315	92		Q 1091	13
2015	2015q1	1847	177	1069	705	436	332	107	59 52 52 71 52 55 55 55 55 55 55 55 55 55 55 55 55	. 37 56 1820	13
	2015q2	1937	190	1087	702	466	348	103	52	. 9 1896	14
	2015q3	2247	240	1299	832	548	364	107	71 gie s.	. 2025 2220	15
	2015q4	2041	206	1154	769	534	368	126	60	at 2005	19
2016	2016q1	2032	200	1127	719	479	320	108	76	2005 27 77 2001	18
	2016q2	2185	219	1205	770	551	359	116	72	D 2144	17
	2016q3	2445	237	1329	820	578	419	107	71	Bibliog 2144 2405 aphique de l	20

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

		Reporting Item	Page Num
Title and abstract			
Title	<u>#1a</u>	A population register-based study.	1
Abstract	<u>#1b</u>	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	<u>#2</u>	Explain the scientific background and rationale for the investigation being reported	3
Objectives	<u>#3</u>	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	<u>#4</u>	Present key elements of study design early in the paper	5
Setting	<u>#5</u>	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	<u>#6a</u>	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5-6
Eligibility criteria	<u>#6b</u>	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	<u>#7</u>	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	<u>#8</u> For p	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5-6

			BMJ Open	Page 32 of 34
1 2			more than one group. Give information separately for for exposed and unexposed groups if applicable.	BMJ Open: first published as 5-6 5 6
3 4 5 6 7 8 9 10 11 12	Bias	<u>#9</u>	Describe any efforts to address potential sources of bias	5-6 first pu
	Study size	<u>#10</u>	Explain how the study size was arrived at	5 Julishe
	Quantitative variables	<u>#11</u>	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	2
13 14 15 16	Statistical methods	<u>#12a</u>	Describe all statistical methods, including those used to control for confounding	10.1136/bmjopen-2019-032815 6-7 by copyright, inclu n/a according to ITSA
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33	Statistical methods	<u>#12b</u>	Describe any methods used to examine subgroups and interactions	0.1136/bmjopen-2019-032815 on 16 Decem Ens n/a according for uses to ITSA design 6
	Statistical methods	<u>#12c</u>	Explain how missing data were addressed	6 December Enseig for uses rel
	Statistical methods	<u>#12d</u>	If applicable, explain how loss to follow-up was addressed	6 Enseignement Superieur (n/a 6-7
	Statistical methods	<u>#12e</u>	Describe any sensitivity analyses	/nloaded fro perieur (AB) t and data m
34 35	Results			om htt BES) . mining
36 37 38 39 40 41 42 43	Participants	<u>#13a</u>	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	Table 1 and additional Appendix 1+3 ^g , and simila
44 45 46	Participants	<u>#13b</u>	Give reasons for non-participation at each stage	n/a rechn
47 48	Participants	<u>#13c</u>	Consider use of a flow diagram	Appendix 1
49 50 51 52 53 54 55 56 57	Descriptive data	<u>#14a</u>	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Item intp://bmjopen.bmj.com/ on June 9, 2025 at Agence Bibliographique de ITable 1 and additional Appendix 1+3n/aAppendix 1Appendix 1Appendix 26
58 59 60	Descriptive data	<u>#14b</u> For pe	Indicate number of participants with missing data for each eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6 6

Page	33	of	34	

1			variable of interest	
2 3	Descriptive data	<u>#14c</u>	Summarise follow-up time (eg, average and total amount)	n/a
4 5 6 7 8 9 10 11 12 13 14 15	Outcome data	<u>#15</u>	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	Table 1 and Appendix 1
	Main results	<u>#16a</u>	Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a according to the ITSA model
16 17 18 19	Main results	<u>#16b</u>	Report category boundaries when continuous variables were categorized	n/a
20 21 22 23	Main results	<u>#16c</u>	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 1
24 25 26 27	Other analyses	<u>#17</u>	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
28 29	Discussion			
30 31 32 33 34 35 36 37	Key results	<u>#18</u>	Summarise key results with reference to study objectives	14
	Limitations	<u>#19</u>	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14-15
38 39 40 41 42	Interpretation	<u>#20</u>	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	16-17
43 44 45 46	Generalisability	<u>#21</u>	Discuss the generalisability (external validity) of the study results	17-18
47 48 49 50	Other Information			
51 52 53 54 55 56 57 58	Funding	<u>#22</u>	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
59 60		For pe	eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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