BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032815
Article Type:	Research
Date Submitted by the Author:	18-Jul-2019
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Keywords:	Labour, induced [MeSH], Medicalization [MeSH], Adverse events [MeSH], Stillbirth [MeSH], Perinatal death [MeSH]

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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Word count: 4058 words

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 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

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 delivery, 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 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, chorioamnionitis, precipitate labour, and uterine rupture [2].

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

Material and Methods

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

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

The exposure of interest was the new protocol from March 2011 and implemented during 2011 at Danish hospitals offering routine induction at 41+3-41+5 GW [10].
The outcomes of interest were stillbirth, perinatal death (stillborn or dead within the first 7 days), and low Apgar score (<7 after 5 minutes). We also analysed trends in birth interventions such as induction of labour (medical and/or mechanical), augmentation of labour (synthetic oxytocin), epidural analgesia (pain relief during vaginal birth), and maternal outcomes such as instrumental delivery (forceps or vacuum extraction), CS and uterine rupture.
Potential confounding variables of interest included advanced maternal age (≥ 40 years), nulliparity, previous CS (among multiparous), light/moderate preeclampsia (blood pressure

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

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 auto-correlation [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.

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 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 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 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. 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 "<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 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.

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

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 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 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 deaths (0.17%) (Appendix 1).

Trends in interventions and outcomes before and after the implementation of the new induction protocol are presented in Table 1 and further elaborated in Figures 1-3. Table 1 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 fit before and after 2011 is shown as an IRR and a significance test for difference in IRR.

Table 1 presents trend before and after intervention, together with interruption jump (2011)

Outcomes	Interruption jump 2011	Pre-intervention trend % per year (95% CI)	Post-intervention trend % per year (95% CI)	Difference in trends[a] 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:				
Caesarean section (%)	0.1	-0.16 (-0.36, -0.04)	-0.10 (-0.47, 0.27)	0.757
Uterine rupture (pr.1000)	1.6	0.21 (0.12, 0.30)	-0.24 (-0.60, 0.13)	0.001
Foetal outcome:				
Apgar score <7/5 min. (%)	-0.2	0.01 (-0.01, 0.02)	0.04 (0.01-0.07)	0.107
		Generel fit. IRR all years	**Generel fit. IRR all years**	**GOF [b]**
Stillbirths		0.90 (0.87, 0.93)	0.91 (0.87, 0.95)	0.562
Perinatal mortality		0.90 (0.88, 0.93)	0.90 (0.87, 0.94)	1.000

[a]IRR, Incidence Rate Ratio
[b]GOF, Goodness-of-fit test.

Primary outcome: Perinatal mortality and morbidity

Table 2 presents stillbirths and perinatal death in absolute numbers per 1000 births. A general decline of intrauterine deaths was observed during the study period, with an initial risk of stillbirth at 2.3 per 1000 births in the year 2000 dropping to a rate of <1 per 1000 from approximately 2009, after which it has generally remained between 1.0 and 0.5 per 1,000 births.

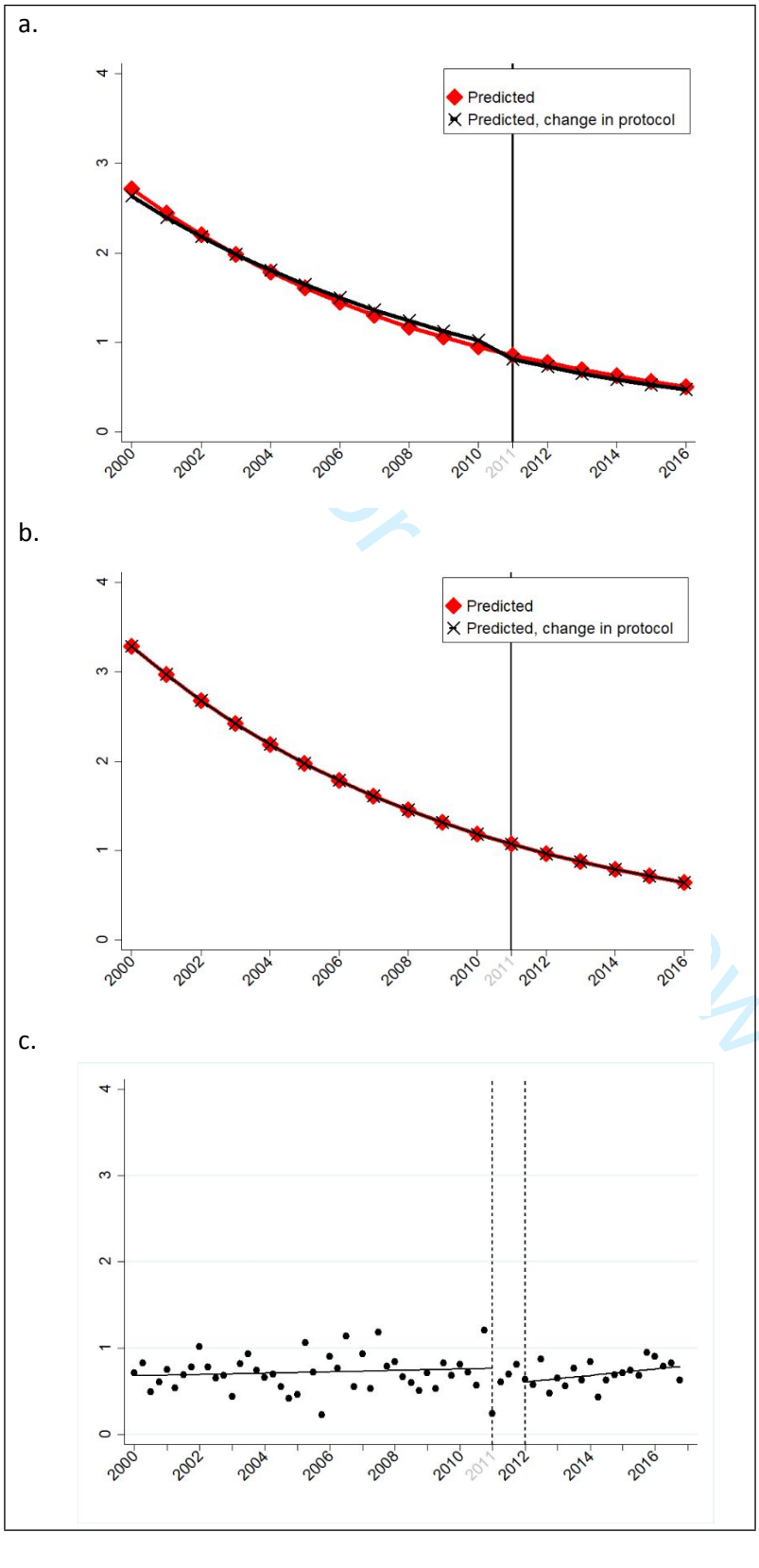
Table 2 presents stillbirths and perinatal death in years 2000-2016

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.

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- 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 (%).



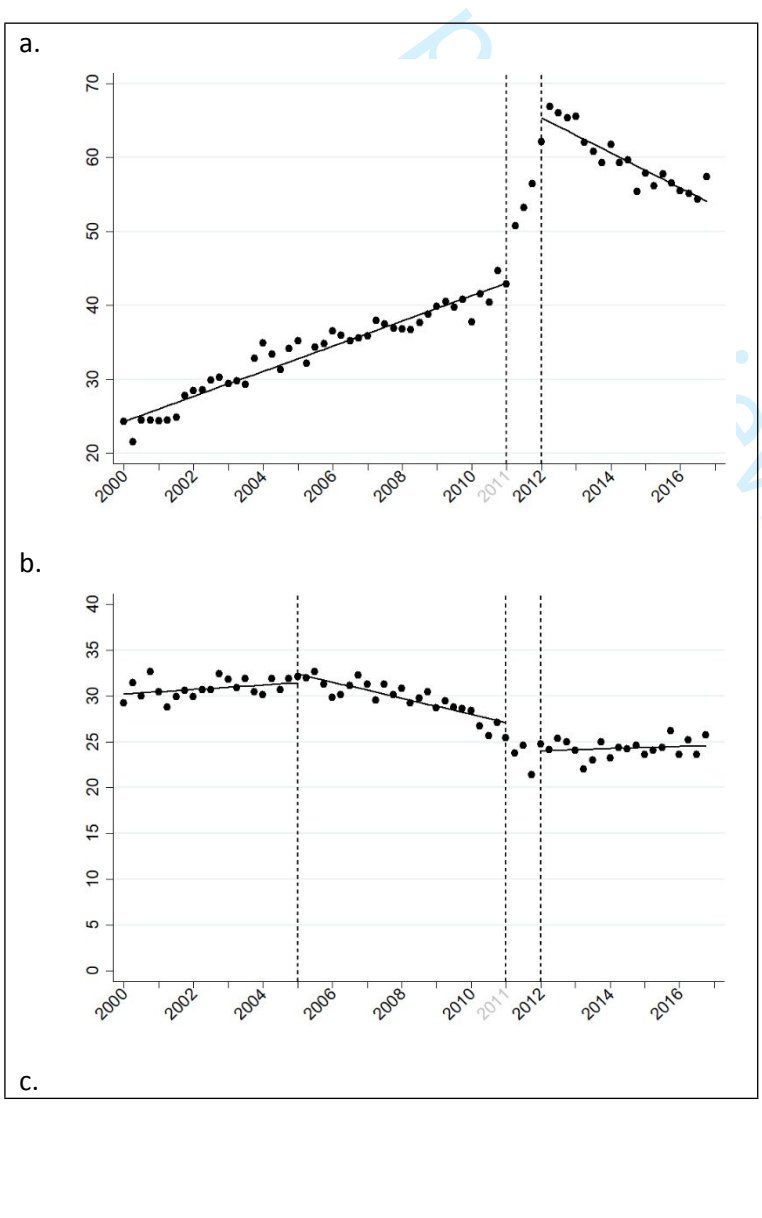
No difference was observed between the two fitted curves for either stillbirth (p=0.56) or perinatal death (p=1.00). The goodness-of-fit test was p=0.40 for stillbirth and p=0.24 for

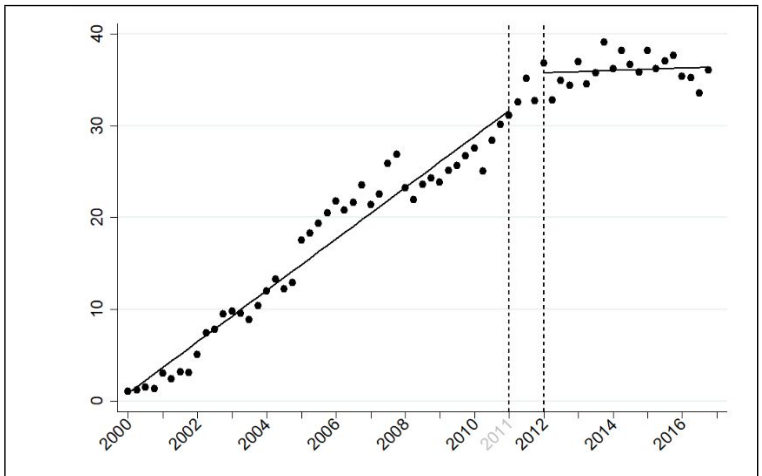
perinatal mortality. Figure 1c presents low Apgar score before and after the intervention showing no difference in the slope before and after the new protocol (p=0.11). See Table 1 for details.

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.

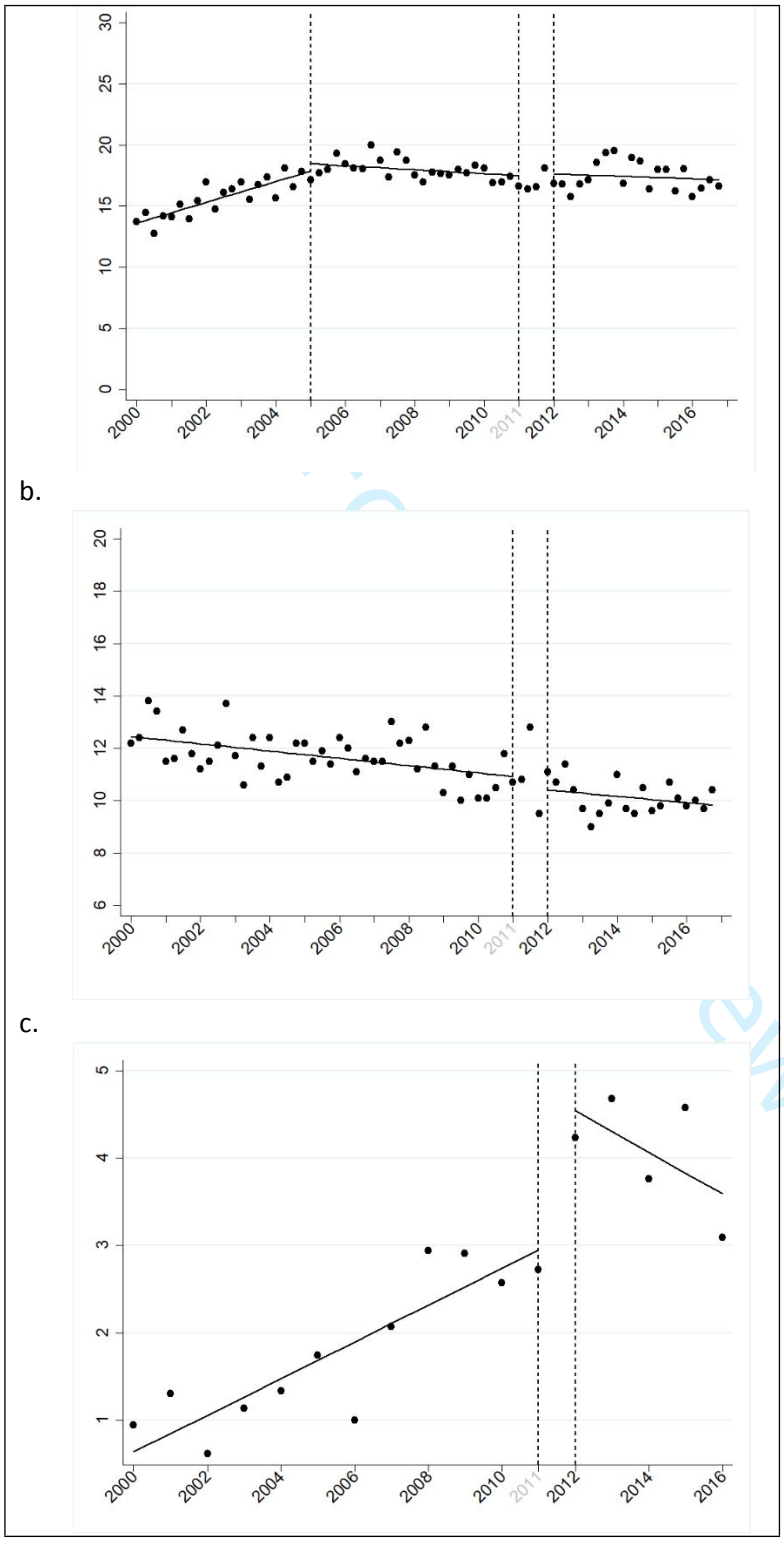




Induction of labour increased during the pre-intervention period with an annual average increase of 1.7% and rates rising from 25% to 41%. By 2011, a significant jump from 41% to 65% annual inductions was seen (p<0.00). After the substantial jump in the rate in 2011, the annual decline of 2.4% in the 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 pre-intervention 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 delivery (%). (c) Uterine ruptures per 1000 births.

a.



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 pre-intervention period, a steady increase of 0.2 ‰ yearly was observed. It 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).

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

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% 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.

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 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 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]. Due to a change in the definition of PPH, we considered PPH data to be unreliable in its present form. Information on labour dystocia is not available in the registry and instead labour augmentation was used as a proxy measure. Information on hyperstimulation of the uterus and precipitate labour was not available, but uterine rupture may be a severe consequence of an over-stimulated uterus.

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 explanation may be that, in a country like Denmark with a generally high standard in public 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 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]. Changed screening policies, early termination of pregnancies with lethal abnormalities, 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 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 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 associated with offering routine inductions 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. Induction interferes with the physiological birth, as induction may prolong time in labour and in hospital, confine the woman to the bed attached to monitoring devices and an 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

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

Since induction has been found to be a risk factor for hyperstimulation and heavy 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 doubling of the risk of uterine rupture (RR 1.97, 95% CI 1.54-2.52) [2]. This study found a significant increase in uterine rupture (p<0,02) with a change from 2,6 to 4,2‰ after the intervention. A long term trend toward increasing use of epidural analgesia for pain relief leveled off after the new protocol (Figure 2c). In the present study, the need for augmentation of labour increased slightly after a long period of a decreased use (Figure 2b). Knowledge of risks associated with augmentation at 41 GW versus 42 GW is limited. One cohort study of 51,473 women found an increase in labour dystocia when induction of labour was performed at 41 GW (RR=1.29, 95% 1.22-1.37) [35] while a randomised trial of 508 women found no difference (RR 0.55, 95% CI 0.20-1.45) [36]. Conflicting results have been published regarding induction of labour and risk of CS [2,37,38]. In this study, no 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 have found 70-75% of the women went into spontaneous labour before 42 GW. The rest were induced due to medical reasons or induced at 42 GW [36,37,39,40].

Possible implications for clinicians and policymakers

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

Unanswered questions and future research

The intention behind implementation of a new induction of labour protocol was an expected reduction in stillbirth and perinatal mortality. Based on the results from this present study, the expected reduction in mortality after introducing earlier induction of labour was not achieved. As low stillbirth rates already exist in Scandinavian countries, medicalisation of a large group of low risk women may be ineffective or even provide more

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

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

Conclusion

The aim of this study was to evaluate changes in maternal and neonatal outcomes after implementing earlier routine induction of labour after 41+3 GW in the entire Danish population of pregnant women. No change in trend was found in low Apgar scores, stillbirths or perinatal deaths after implementation of earlier routine inductions of labour. The most substantial impact was the number of inductions of otherwise low risk pregnancies and an increased number of uterine ruptures. The use of epidural analgesia, augmentation of labour, instrumental births, and CSs remained stable. The study highlights a need for a more balanced discussion among health providers on routine induction at late term.

Author contribution

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

Competing interests

GD, RM and MJ have nothing to disclose.

ER was supported by a shared scholarship from Aarhus University and University College Copenhagen. Further, a grant from the Danish Association of Midwifery and Herlev Hospital supported the scholarship. Supporters had no influence on current research.

Funding

ER received a grant from Danish Association of Midwifery and Herlev Hospital supported the scholarship.

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information (Appendix 2 and 3)

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Appendix

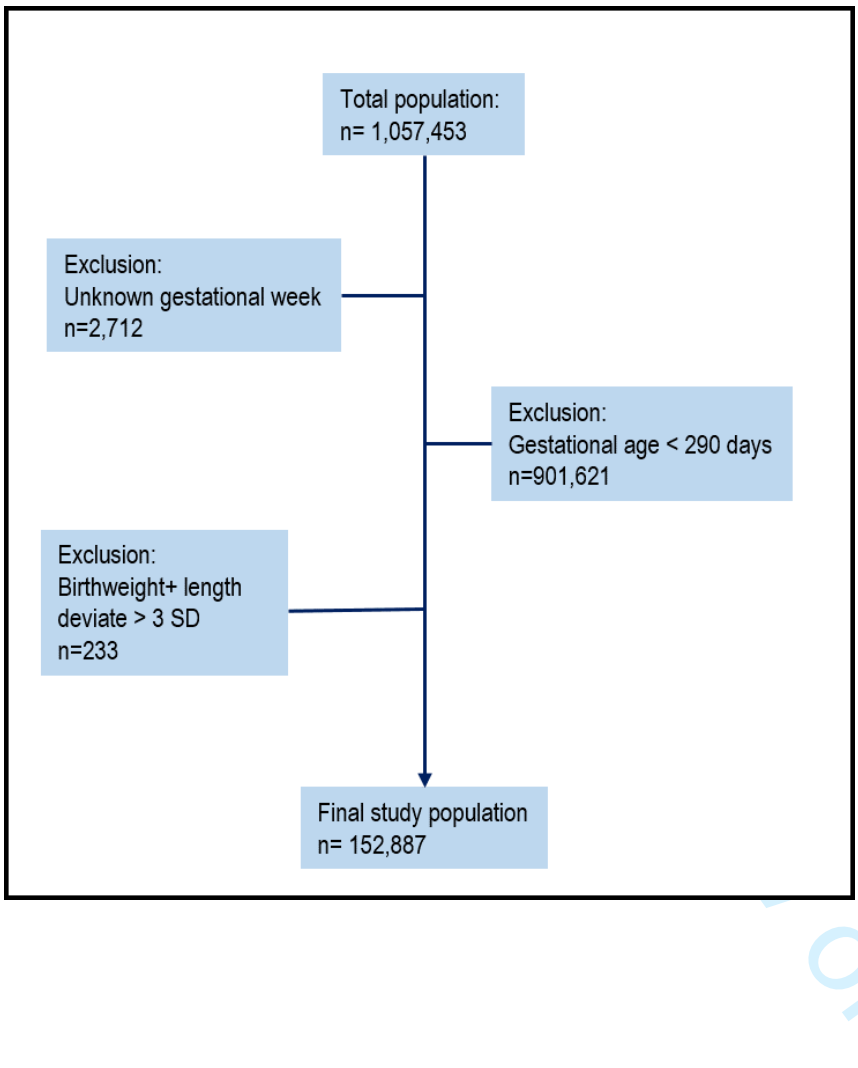
Appendix 1

Appendix 2

Appendix 3

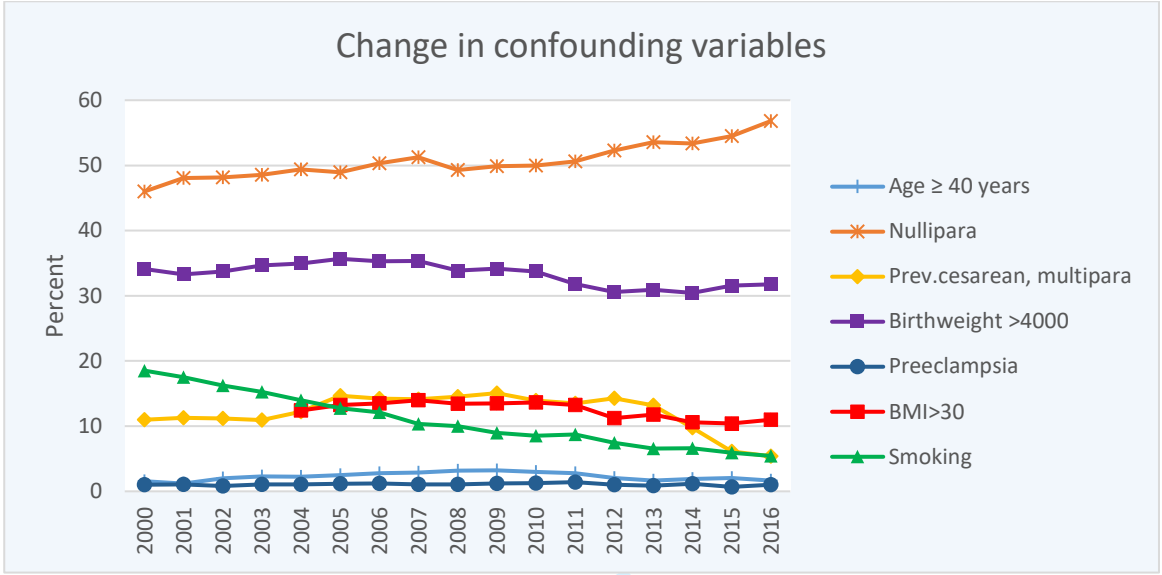
Appendix 1

Flowchart



Appendix 2

Maternal characteristics. From 41+3 gestational weeks and beyond. 2000-2016



Appendix 3.

Number of births, interventions and maternal outcome

Year	Quarter	No. births	Instrumental	Induction	epidural	Augment	Cesarean	Epis	Tears 3&4	Ruptures	No. births Apgar	Apgar<7/5
2000	2000q1	2598	318	631	27	760	357	376	98	2	2567	18
	2000q2	2686	334	577	33	845	388	357	88	1	2666	22
	2000q3	2716	375	663	41	815	346	365	104	1	2676	13
	2000q4	2670	357	653	36	871	379	345	108	1	2632	16
2001	2001q1	2699	310	658	82	822	381	349	113	2	2659	20
	2001q2	2802	324	685	68	806	424	303	140	1	2766	15
	2001q3	2780	354	691	88	831	387	341	108	1	2741	19
	2001q4	2484	292	691	78	759	383	299	109	1	2450	19
2002	2002q1	2378	266	675	121	712	403	242	86	6	2344	24
	2002q2	2472	285	705	183	758	364	300	103	1	2433	19
	2002q3	2659	323	794	208	816	429	285	112	1	2632	17
	2002q4	2378	325	719	225	770	390	279	100	1	2350	16
2003	2003q1	2285	267	671	224	726	387	277	93	11	2255	10
	2003q2	2369	251	706	227	731	368	253	101	1	2331	19
	2003q3	2728	337	799	243	869	457	339	97	1	2684	25
	2003q4	2320	261	761	242	706	403	267	65	1	2292	17
2004	2004q1	2299	286	802	276	692	360	247	93	12	2269	15
	2004q2	2168	232	723	288	692	392	223	82	1	2143	15
	2004q3	2377	260	744	290	729	394	228	84	1	2351	13

	2004q4	2181	265	745	282	696	389	254	100		2164	9
2005	2005q1	2191	267	771	384	704	376	197	75	16	2171	10
	2005q2	2305	265	741	422	736	408	247	97		2273	24
	2005q3	2526	300	868	488	825	455	231	88		2490	18
	2005q4	2159	247	752	442	675	417	208	106		2132	5
2006	2006q1	2043	253	745	445	610	377	186	84		2009	18
	2006q2	2366	283	851	492	713	428	197	113		2330	18
	2006q3	2403	267	845	520	747	433	194	102		2361	27
	2006q4	2229	258	793	524	719	446	168	86		2191	12
2007	2007q1	2067	237	741	443	646	387	188	93		2036	19
	2007q2	2092	241	794	472	617	363	159	85		2066	11
	2007q3	2335	303	874	604	730	453	198	109		2297	27
	2007q4	2187	266	806	587	659	409	147	82		2159	17
2008	2008q1	2176	268	800	505	670	382	160	87	27	2148	18
	2008q2	2267	254	832	497	663	384	149	92		2237	15
	2008q3	2536	325	955	598	754	451	165	111		2509	15
	2008q4	2194	248	852	533	668	387	157	103		2173	11
2009	2009q1	2155	222	859	514	618	378	118	84	26	2127	15
	2009q2	2273	257	920	571	669	409	114	95		2245	12
	2009q3	2431	244	965	623	700	430	127	102		2400	20
	2009q4	2084	230	850	557	597	382	112	89		2054	14
2010	2010q1	2262	229	854	623	642	410	108	104	24	2231	18
	2010q2	2388	240	991	599	638	404	128	112		2364	17
	2010q3	2485	260	1005	705	637	422	134	94		2459	14

	2010q4	2191	258	979	660	594	382	117	108		2153	26
2011	2011q1	2115	227	907	658	538	351	104	118	23	2094	5
	2011q2	2150	232	1090	700	511	352	87	103		2121	13
	2011q3	2313	296	1230	813	569	383	110	96		2285	16
	2011q4	1884	179	1064	617	403	341	71	84		1862	15
2012	2012q1	1879	208	1168	692	465	317	88	96		1861	12
	2012q2	1932	206	1292	633	467	324	88	95		1913	11
	2012q3	2090	239	1380	730	530	330	89	94		2064	18
	2012q4	1900	197	1242	654	474	319	89	78		1882	9
2013	2013q1	1865	180	1222	689	449	319	69	75		1839	12
	2013q2	1979	179	1227	684	435	367	79	81		1952	11
	2013q3	2095	199	1274	749	482	405	84	77		2070	16
	2013q4	1761	174	1044	688	440	344	85	60		1737	11
2014	2014q1	1810	200	1117	655	420	305	103	60	29	1776	15
	2014q2	1878	182	1114	717	457	356	80	62		1852	8
	2014q3	2108	200	1258	773	510	394	87	78		2079	13
	2014q4	1920	201	1064	688	472	315	92	63		1891	13
2015	2015q1	1847	177	1069	705	436	332	107	59	37	1820	13
	2015q2	1937	190	1087	702	466	348	103	52		1896	14
	2015q3	2247	240	1299	832	548	364	107	71		2220	15
	2015q4	2041	206	1154	769	534	368	126	60		2005	19
2016	2016q1	2032	200	1127	719	479	320	108	76	27	2001	18
	2016q2	2185	219	1205	770	551	359	116	72		2144	17
	2016q3	2445	237	1329	820	578	419	107	71		2405	20

2016q4	2080	217	1193	750	535	346	108	81	2048	13	

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

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

		more than one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	5-6
Study size	#10	Explain how the study size was arrived at	5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a according to ITSA design
Statistical methods	#12c	Explain how missing data were addressed	6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical methods	#12e	Describe any sensitivity analyses	6-7
Results			
Participants	#13a	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
Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	Appendix 1
Descriptive data	#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.	Appendix 2
Descriptive data	#14b	Indicate number of participants with missing data for each	6

		variable of interest	
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	#15	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	#16a	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
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 1
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	14
Limitations	#19	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
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	16-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17-18
Other Information			
Funding	#22	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

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032815.R1
Article Type:	Original research
Date Submitted by the Author:	17-Oct-2019
Complete List of Authors:	Rydahl, Eva; University College Copenhagen, Midwifery; Aarhus Universitet, Clinical Medicine Declercq, Eugene; Boston University School of Public Health, Department of Community Health Sciences Juhl, Mette ; University College Copenhagen, Midwifery Maimburg, Rikke; Aarhus Universitet, Department of Clinical Medicine; Aarhus Universitetshospital, Department of Gynaecology Obstetrics
Primary Subject Heading:	Obstetrics and gynaecology
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]

Title page:

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

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Keywords

Labour, induced [MeSH], Medicalization [MeSH], Adverse events [MeSH], Stillbirth [MeSH], Perinatal death [MeSH]

Word count: 4058 words

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

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 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, chorioamnionitis, precipitate labour, and uterine rupture [2].

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

Material and Methods

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

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

The exposure of interest was the new protocol from March 2011 and implemented during 2011 at Danish hospitals offering routine induction at 41+3-41+5 GW [10].
The outcomes of interest were stillbirth, perinatal death (stillborn or dead within the first 7 days), and low Apgar score (<7 after 5 minutes). We also analysed trends in birth interventions such as induction of labour (medical and/or mechanical), augmentation of labour (synthetic oxytocin), epidural analgesia (pain relief during vaginal birth), and maternal outcomes such as instrumental birth (forceps or vacuum extraction), CS and uterine rupture.
Potential confounding variables of interest included advanced maternal age (≥ 40 years), nulliparity, previous CS (among multiparous), light/moderate preeclampsia (blood pressure

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

The variables in the dataset 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%. The STROBE cohort reporting guidelines were used [15]

Patient and Public Involvement

Patients were not directly involved in the study, as it was based on register data. However, in the inial phase of the study, the consumer organisation for Parenthood and Childbirth was contacted to discuss relevance of the aim of this present study. The results from the study will be published in the consumer organisation´s journal as well as in other relevant sites of public interest.

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 auto-correlation [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.

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 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 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 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. 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 "<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

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.

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

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 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 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 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. Table 1 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 fit before and after 2011 is shown as an IRR and a significance test for difference in IRR.

Table 1 presents trend before and after intervention, together with interruption jump (2011)

Outcomes	Interruption jump 2011	Pre-intervention trend % per year (95% CI)	Post-intervention trend % per year (95% CI)	Difference in trends[a] 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:				

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

[a]IRR, Incidence Rate Ratio
[b]GOF, Goodness-of-fit test.

Primary outcome: Perinatal mortality and morbidity

Table 2 presents stillbirths and perinatal death in absolute numbers per 1000 births. A general decline of intrauterine deaths was observed during the study period, with an initial risk of stillbirth at 2.3 per 1000 births in the year 2000 dropping to a rate of <1 per 1000 from approximately 2009, after which it has generally remained between 1.0 and 0.5 per 1,000 births.

Table 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.

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- 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 (%).

a	(Fig 1a-c perinatal outcomes)
b	
c	

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.

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) Labour induction (b) Augmentation (c) Epidural analgesia.

a	(Fig 2a-c interventions in childbirth)
b	
c	

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 pre-intervention 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.

a	(Fig 3a-c maternal outcomes)
b	
c	

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 pre-intervention 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).

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

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.

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 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 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]. Due to a change in the definition of PPH, we considered the PPH data in the study period to be unreliable. Information on labour dystocia is not available in the registry, instead labour augmentation was used as a proxy measure. Information on hyperstimulation of the uterus and precipitate labour was not available, but uterine rupture may be a severe consequence of an over-stimulated uterus.

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 explanation may be that, in a country like Denmark with a generally high standard in public 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 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]. Changed screening policies, early termination of pregnancies with lethal abnormalities,

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 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 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 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. 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 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 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 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 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

implementation of the new protocol (Figure 2c). In the present study, the use of augmentation of labour increased slightly after a long period of a decreased use (Figure 2b). Knowledge of risks associated with augmentation at 41 GW versus 42 GW is limited. One cohort study of 51,473 women found an increase in labour dystocia after induction of labour was performed at 41 GW (RR=1.29, 95% 1.22-1.37) [35] while a randomised trial of 508 women found no difference (RR 0.55, 95% CI 0.20-1.45) [36]. Conflicting results have been published regarding induction of labour and risk of CS [2,37,38]. In this study, no 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 found 70-75% of the women went into spontaneous labour before 42 GW. The rest were induced due to medical reasons or induced at 42 GW [36,37,39,40].

Possible implications for clinicians and policymakers

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

Unanswered questions and future research

The intention behind implementation of a new induction of labour protocol was an expected reduction in stillbirth and perinatal mortality. Based on the results from this present study, the expected reduction in mortality after introducing earlier induction of labour was not achieved. As low stillbirth rates already exist in Scandinavian countries, medicalisation of a large group of low risk women may be ineffective or even provide more harms than benefits. As most register studies only provide the numbers of adverse outcomes, a more detailed study of case fatality is needed not only taking into account congenital abnormalities, but also underlying social mechanisms and suboptimal care, to provide knowledge on how to reduce adverse outcomes in counties with a low stillbirth rate [41].

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

Conclusion

The aim of this study was to evaluate changes in maternal and neonatal outcomes after implementing earlier routine induction of labour after 41+3 GW in the entire Danish population of pregnant women. No change in trend was found in low Apgar scores, stillbirths or perinatal deaths after implementation of earlier routine inductions of labour. The most substantial impact was the number of inductions of labour in women with otherwise low risk pregnancies and an increased number of uterine ruptures. The use of epidural analgesia, augmentation of labour, instrumental births, and CSs remained stable. The study highlights a need for a more balanced discussion among health providers on routine induction at late term.

Author contribution

ER and RM planned the study. ER & RM analysed data. ER wrote the manuscript in close correspondence with RM, MJ, and ED. ER, RM; MJ, and ED revised the manuscript and accepted the final version. ER is the guarantor.

Acknowledgement

We are grateful for Danish midwives and physician's contribution to collect data from courses of pregnancy and childbirth to be used for research. Further, we acknowledge fruitful discussions with the Parenthood and Childbirth Organisation in the initial planning of the study.

Competing interests

ED, RM and MJ have nothing to disclose. ER was supported by a shared scholarship from Aarhus University and University College Copenhagen. Further, a grant from the Danish Association of Midwifery and Herlev Hospital supported the scholarship. Supporters had no influence on current research.

Funding

ER received a grant from Danish Association of Midwifery and Herlev Hospital supported the scholarship.

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information (Appendix 2 and 3)

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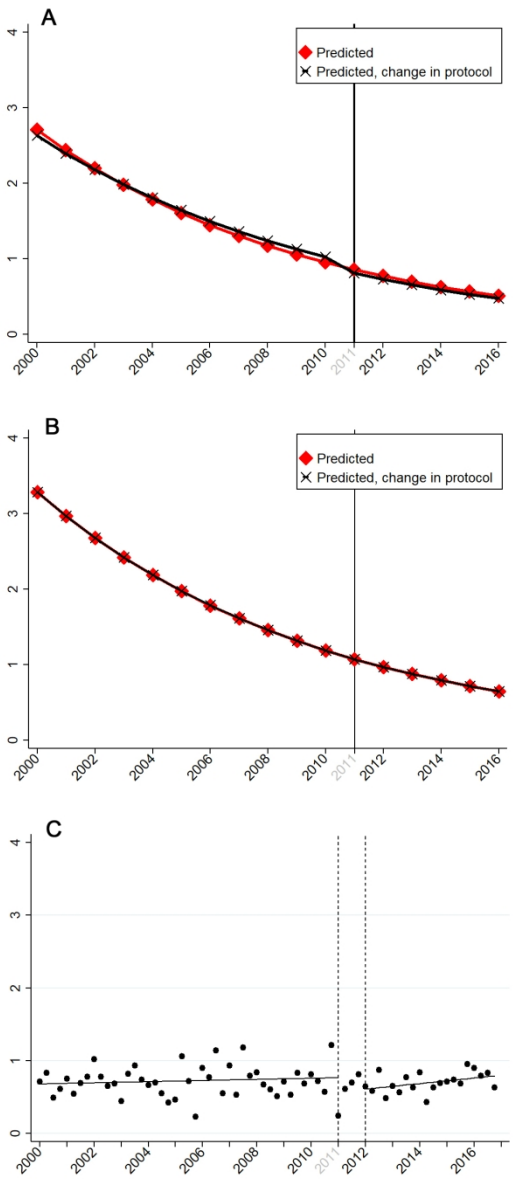
Appendix

Appendix 1

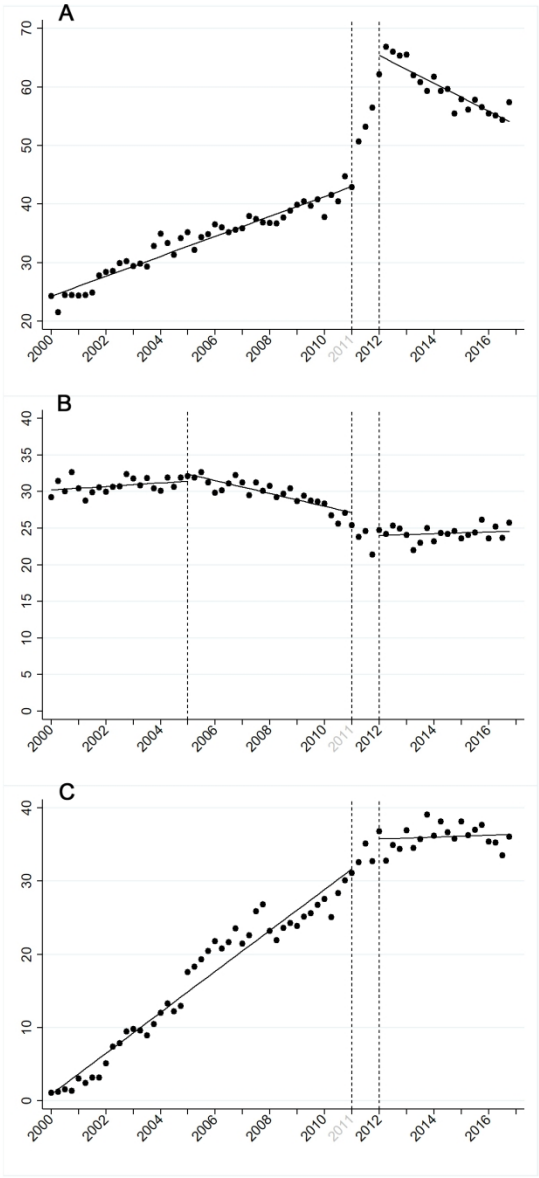
Appendix 2

Appendix 3



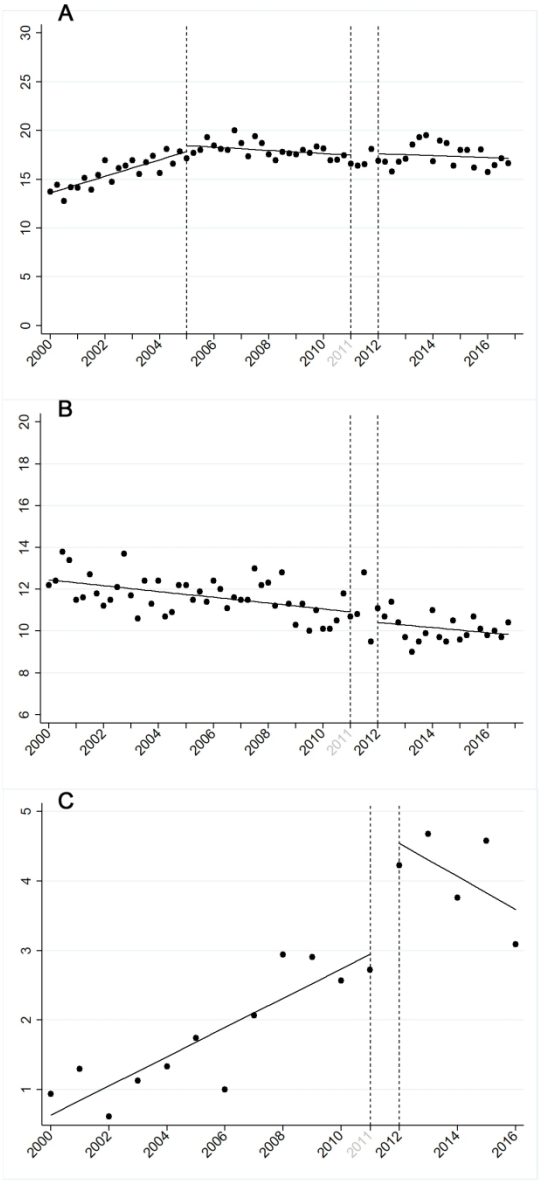
Perinatal outcomes

98x208mm (300 x 300 DPI)



Interventions in childbirth

98x207mm (300 x 300 DPI)

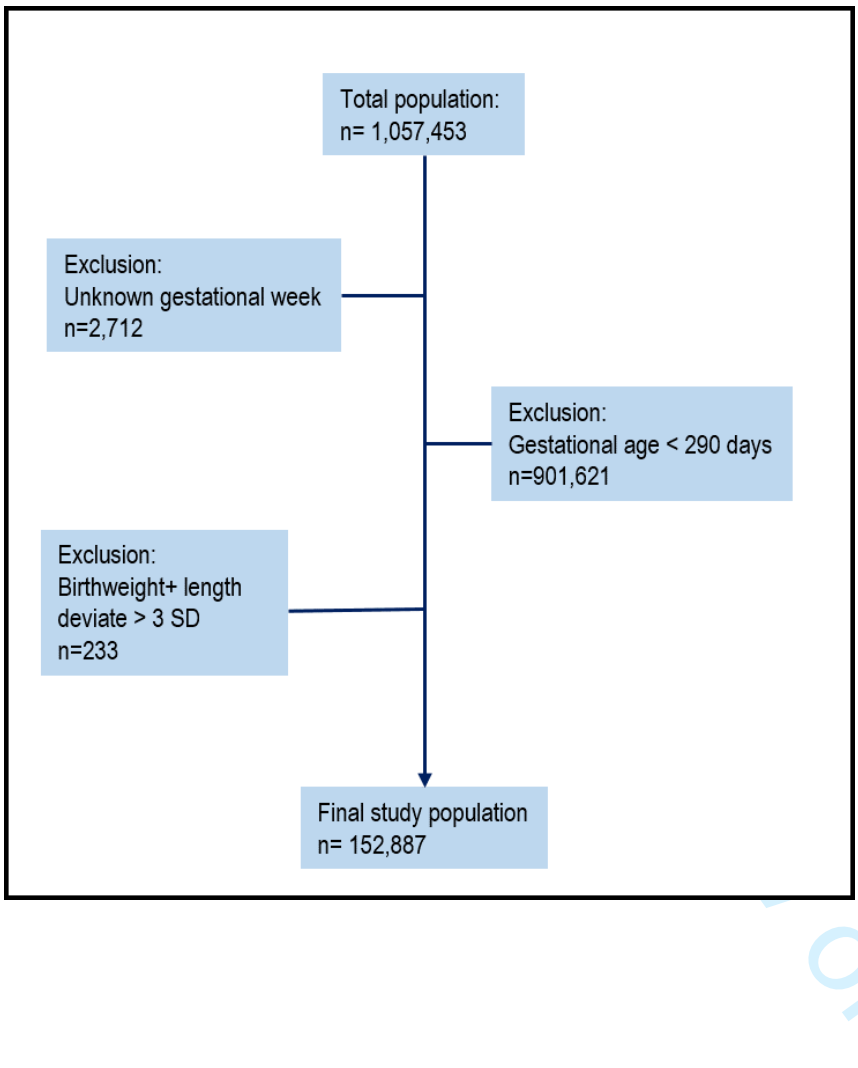


Maternal outcomes

98x207mm (300 x 300 DPI)

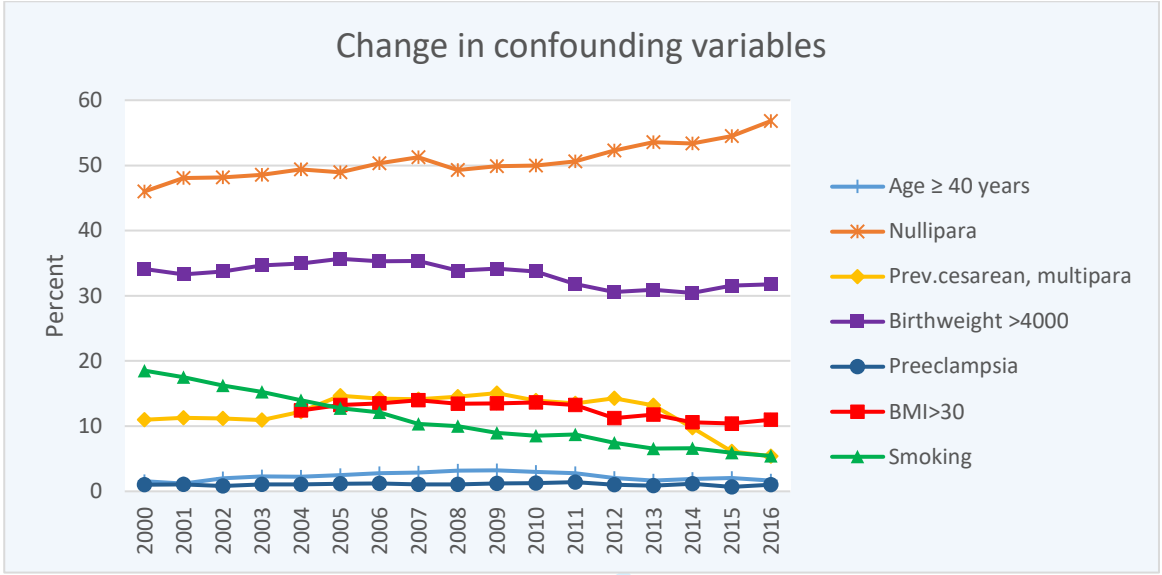
Appendix 1

Flowchart



Appendix 2

Maternal characteristics. From 41+3 gestational weeks and beyond. 2000-2016



Appendix 3.

Number of births, interventions and maternal outcome

Year	Quarter	No. births	Instrumental	Induction	epidural	Augment	Cesarean	Epis	Tears 3&4	Ruptures	No. births Apgar	Apgar<7/5
2000	2000q1	2598	318	631	27	760	357	376	98	2	2567	18
	2000q2	2686	334	577	33	845	388	357	88	1	2666	22
	2000q3	2716	375	663	41	815	346	365	104	1	2676	13
	2000q4	2670	357	653	36	871	379	345	108	1	2632	16
2001	2001q1	2699	310	658	82	822	381	349	113	2	2659	20
	2001q2	2802	324	685	68	806	424	303	140	1	2766	15
	2001q3	2780	354	691	88	831	387	341	108	1	2741	19
	2001q4	2484	292	691	78	759	383	299	109	1	2450	19
2002	2002q1	2378	266	675	121	712	403	242	86	6	2344	24
	2002q2	2472	285	705	183	758	364	300	103	1	2433	19
	2002q3	2659	323	794	208	816	429	285	112	1	2632	17
	2002q4	2378	325	719	225	770	390	279	100	1	2350	16
2003	2003q1	2285	267	671	224	726	387	277	93	11	2255	10
	2003q2	2369	251	706	227	731	368	253	101	1	2331	19
	2003q3	2728	337	799	243	869	457	339	97	1	2684	25
	2003q4	2320	261	761	242	706	403	267	65	1	2292	17
2004	2004q1	2299	286	802	276	692	360	247	93	12	2269	15
	2004q2	2168	232	723	288	692	392	223	82	1	2143	15
	2004q3	2377	260	744	290	729	394	228	84	1	2351	13

	2004q4	2181	265	745	282	696	389	254	100		2164	9
2005	2005q1	2191	267	771	384	704	376	197	75	16	2171	10
	2005q2	2305	265	741	422	736	408	247	97		2273	24
	2005q3	2526	300	868	488	825	455	231	88		2490	18
	2005q4	2159	247	752	442	675	417	208	106		2132	5
2006	2006q1	2043	253	745	445	610	377	186	84		2009	18
	2006q2	2366	283	851	492	713	428	197	113		2330	18
	2006q3	2403	267	845	520	747	433	194	102		2361	27
	2006q4	2229	258	793	524	719	446	168	86		2191	12
2007	2007q1	2067	237	741	443	646	387	188	93		2036	19
	2007q2	2092	241	794	472	617	363	159	85		2066	11
	2007q3	2335	303	874	604	730	453	198	109		2297	27
	2007q4	2187	266	806	587	659	409	147	82		2159	17
2008	2008q1	2176	268	800	505	670	382	160	87	27	2148	18
	2008q2	2267	254	832	497	663	384	149	92		2237	15
	2008q3	2536	325	955	598	754	451	165	111		2509	15
	2008q4	2194	248	852	533	668	387	157	103		2173	11
2009	2009q1	2155	222	859	514	618	378	118	84	26	2127	15
	2009q2	2273	257	920	571	669	409	114	95		2245	12
	2009q3	2431	244	965	623	700	430	127	102		2400	20
	2009q4	2084	230	850	557	597	382	112	89		2054	14
2010	2010q1	2262	229	854	623	642	410	108	104	24	2231	18
	2010q2	2388	240	991	599	638	404	128	112		2364	17
	2010q3	2485	260	1005	705	637	422	134	94		2459	14

	2010q4	2191	258	979	660	594	382	117	108		2153	26
2011	2011q1	2115	227	907	658	538	351	104	118	23	2094	5
	2011q2	2150	232	1090	700	511	352	87	103		2121	13
	2011q3	2313	296	1230	813	569	383	110	96		2285	16
	2011q4	1884	179	1064	617	403	341	71	84		1862	15
2012	2012q1	1879	208	1168	692	465	317	88	96		1861	12
	2012q2	1932	206	1292	633	467	324	88	95		1913	11
	2012q3	2090	239	1380	730	530	330	89	94		2064	18
	2012q4	1900	197	1242	654	474	319	89	78		1882	9
2013	2013q1	1865	180	1222	689	449	319	69	75		1839	12
	2013q2	1979	179	1227	684	435	367	79	81		1952	11
	2013q3	2095	199	1274	749	482	405	84	77		2070	16
	2013q4	1761	174	1044	688	440	344	85	60		1737	11
2014	2014q1	1810	200	1117	655	420	305	103	60	29	1776	15
	2014q2	1878	182	1114	717	457	356	80	62		1852	8
	2014q3	2108	200	1258	773	510	394	87	78		2079	13
	2014q4	1920	201	1064	688	472	315	92	63		1891	13
2015	2015q1	1847	177	1069	705	436	332	107	59	37	1820	13
	2015q2	1937	190	1087	702	466	348	103	52		1896	14
	2015q3	2247	240	1299	832	548	364	107	71		2220	15
	2015q4	2041	206	1154	769	534	368	126	60		2005	19
2016	2016q1	2032	200	1127	719	479	320	108	76	27	2001	18
	2016q2	2185	219	1205	770	551	359	116	72		2144	17
	2016q3	2445	237	1329	820	578	419	107	71		2405	20

2016q4	2080	217	1193	750	535	346	108	81	2048	13	

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

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

		more than one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	5-6
Study size	#10	Explain how the study size was arrived at	5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a according to ITSA design
Statistical methods	#12c	Explain how missing data were addressed	6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical methods	#12e	Describe any sensitivity analyses	6-7
Results			
Participants	#13a	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
Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	Appendix 1
Descriptive data	#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.	Appendix 2
Descriptive data	#14b	Indicate number of participants with missing data for each	6

		variable of interest	
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	#15	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	#16a	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
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 1
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	14
Limitations	#19	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
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	16-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17-18
Other Information			
Funding	#22	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