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8.6.2020

Stillbirth rates doubled after decrease in post-term inductions. A national cohort study.

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Abstract: 366 words

Main text: 1860 words

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What is already known on this topic.

- Stillbirth rate increases after term
- A more pro-active post-term induction practice was in Denmark associated with a substantial fall in stillbirth rates from 41+0 gestational weeks reaching a record low level of 0.38 per 1000 new-borns in 2011-2012
- Other improvements in obstetrical practice such as better surveillance of post-term pregnant women have been suggested as alternative explanations for the substantial decrease in stillbirth rates.

What this study adds.

- From 2012 to 2018 the induction rates from 41+0 gestational weeks fell in Denmark from 44.4% to 38.6%.
- During the same period, the stillbirth rates from 41+0 weeks doubled in Denmark. As the obstetrical practice and equipment did not degrade during the same period, this observation strongly suggests post-term induction practice to have a main responsibility for post-term risk of stillbirth.
- These observations are in line with a recent Swedish randomised trial.

Key words

Birth induction, stillbirth, foetal death, post-term pregnancies.

Abstract (366 words)

Objectives. After introduction of a more pro-active post-term induction practice, stillbirth rates have decreased substantially throughout the first decade of this century in Denmark. The aim was to follow up on induction and stillbirth rates in Denmark.

Design. Historical cohort study.

Setting. Denmark, all maternity wards.

Participants. We included all delivering women in Denmark during the period 2007 to 2018.

Intervention. Assessment of induction rates from 41 weeks of gestation.

Main outcome measure. Stillbirth rate from 41+0 gestational weeks. Potential confounding factors assessed were proportion of primiparous, maternal age, body mass index, and smoking in pregnancy. Rate differences were calculated with 95% CI, and p <0.05 indicated significant differences.

Results. Of 739,570 delivered children, 179,734 (24.3%) were born from 41+0 gestational weeks. The proportion of deliveries after 41 completed weeks which were induced increased from 2007 to 2010 from 25.4% to 29.3%, and from 2010 to 2012 to 44.4%. From 2012 to 2016 the induction rates decreased from 44.4% to 38.5%. After 2016 induction rates were stable.

During the same period, stillbirth rates decreased from 2007/08 to 2009/10 from 1.30 to 0.82 per 1000 new-born. From 2009/10 to 2011/12, the stillbirth rates fell further to 0.38 per 1000 new-born, a decrease of 54%, From 2012, however, the rates were doubled from 0.38 per 1000 in 2011/12 to 0.74 per 1000 in 2015/18; RR 1.97 (95% CI 1.02-3.81), p=0.033.

Changes in the included potential confounders cannot explain neither the substantial fall in stillbirth rates from 2007-08 to 2011-12, nor the doubling in stillbirth rates after 41 weeks since 2012.

During the whole study period, the cumulated risk of intrauterine foetal death increased from week 41+0 to 41+6 from 0.16 to 1.25 per 1000 on-going pregnancies or 7.8 folds. Going beyond 42 weeks further increased the risk to 2.46 per 1000 on-going pregnancies, or 15.5 times the risk of intrauterine deaths at 41+0.

Conclusion. We found a consistent inverse correlation between the proportion of women with induction of labour after 41 weeks of gestation and the stillbirth rates during the same period and same gestational ages. This Danish update on post-term inductions and corresponding stillbirth rates thus confirm previous findings suggesting a causal link between these two parameters.

Strengths and limitations

- Nationwide complete data covering the 12-year period 2007-2018
- Includes 179,734 new-born from 41 weeks of gestation
- Detailed deaths statistics on each day from 41+0 and cumulated by time
- Inclusion of other potential confounding factors in analysis
- Principal limitation: Observational non-experimental data.

Introduction

We previously reported a close temporal association between post term birth induction regimen and stillbirth rate i.e. with more frequent and earlier induction regime, the stillbirth rate went down (1). Danish obstetricians decided in 2010 to recommend deliveries to be completed before 42 weeks of gestation, with effective guidelines from 2011. This more pro-active induction practice increased the induction rate from 20 to 25%, while the stillbirth rates declined from 1.2 to record low 0.77 per 1000 new-born after 40 weeks of gestation (1). We also demonstrated improved perinatal outcomes and unchanged caesarean section rates with the more pro-active induction practice (2). Recently, a Swedish randomized study confirmed a higher risk of prenatal foetal death with postponing birth induction until 42 weeks of gestation as compared to induction at 41+0 weeks (3).

Some have questioned the association between induction scheme and stillbirth rates to be an expression of a causal influence of induction on stillbirth rates and have suggested other changes in obstetrical practice by time to be responsible for the temporal association, e.g. better surveillance of post-term pregnant women, better screening for women at risk of obstetrical complications, and declining smoking frequencies in pregnant women by time. Recently it has been questioned whether an association between induction regime and stillbirth rates exists at all (4).

One of the challenges with a more frequent and earlier induction regime, is the demand of an expanded staff to take care of these inductions, needs which often conflict with attempts to reduce staff as maternity wards are merged and centralized in order to ensure e.g. at site neonatal care facilities.

This study aimed to analyse induction frequencies and national stillbirth rates from 41 completed weeks during the period 2007 through 2018.

Material and methods

Study design

In a historical ecological design, deliveries from January 1, 2007 until December 31, 2018 were assessed.

Data sources

Data were retrieved from the Danish Birth Registry, which collects data on all deliveries in Denmark, including home-deliveries, deliveries in private clinics, and public maternity wards (5).

Time trend figures were based on publicly available data to ensure same data source as a recently published study (4). The detailed figures according to gestational ages were not publicly available. This analysis was restricted to delivering women with a permanent Danish pin-code and singleton delivery during the same study period.

Methodological considerations

The new induction regime became national guidelines from 2011. It attempted to ensure delivery before 42 completed gestational weeks. The more pro-active induction policy was not, however, implemented over night from January 2011. It implied a more pro-active obstetrical practice also earlier after term in case of foetal growth stagnation or maternal complaint, with inductions soon after term. The focus for this analysis is, however, non-complicated pregnancies passing 41 weeks of gestation, which therefore became our cut-off for the present analysis.

Two further attempts influenced our methods. First transparency. While induction figures can easily be calculated annually, the number of stillbirths from 41 weeks became during the study period rather low. As figures below five are not allowed to be reported in scientific papers, all stillbirth figures were calculated for two consecutive years, beginning with 2007-08, ending with 2017-18.

The other attempt was to reduce random variation, which makes interpretations more difficult. This goal was also achieved by the two-year reporting of stillbirths.

Potential confounders considered were age of delivering women, body mass index, smoking in pregnancy and parity. These data were also made up for the same two-year periods.

Deaths within the first week of life have also been assessed, although we do not expect the same protection with the more pro-active induction practice as for stillbirths. The sum of stillbirths and deaths within first week of life allowed calculation of perinatal deaths and perinatal death rates.

For the whole study period, we calculated cumulated risk of foetal death per 1000 on-going pregnancies from 41+0 weeks to explore how much the cumulated risk increases for each day a pregnancy is prolonged from 41+0 weeks. These calculations were made on only Danish citizens, that is with a personal identification number (excluding recent immigrants or visitors to Denmark)

Generally, the trends presented are highly significant due to the large number of included deliveries. Differences in death rates were calculated with 95% confidence intervals (CI) by chi square test, and level of significance between rates was set at $p < 0.05$.

Ethics

Most data are publicly available at e-sundhed.dk. Data for the detailed analysis on different gestational days were delivered by permission from Danish Data Protection Agency j.no: 2013-41-2063

Results

During the study period, 739,570 children were delivered, and of these 731,446 (98.9%) had recorded gestational age. Of those with known gestational age, 179,734 (24.6%) were born from 41+0 gestational weeks.

The proportion of deliveries after 41 completed weeks which were induced increased from 2007 to 2010 from 25.4% to 29.3%, and from 2010 to 2012 further to 44.4% (Figure 1). From 2012 to 2016 the induction rates fell from these 44.4% to 38.5% of by 13%. After 2016 induction rates were stable.

During the same period, stillbirth rates decreased from 2007/08 to 2009/10 from 1.30 to 0.82 per 1000 new-borns, a decrease of 37% (Table 1 and Figure 2). From 2009/10 to 2011/12, the stillbirth rates fell further to 0.38 per 1000 births, a decrease of 54%.

From 2012, however, after more than a decade of consistent decrease in stillbirth rates, the rates have increased and were doubled from 2011/12 to 0.74 per 1000 in 2015/18; RR 1.97 (95% CI 1.02-3.81), p=0.033.

Thus, we observed a close inverse correlation between induction rates from 41 weeks and stillbirth rates during the same years.

The cumulated risk of intrauterine death during the period 2007-2018 according to gestational day from week 41+0 is illustrated in Table 2 and Figure 3. It appears that risk of intrauterine death increases exponentially with increasing gestational age, from 0.16 per 1000 pregnant women at 41+0 to 1.25 per 1000 pregnant women at 41+6, a 7.8-fold increase. The risk increased further if the pregnancy goes beyond 42 weeks to 2.46 per 1000 pregnancies or by 15 folds when compared to delivering at 41+0 weeks.

For the included potential confounders, the proportion of delivering women with an age of 35 years or older was rather stable around 20% throughout the study period as was a proportion of around 35% with body mass index above 25 kg/m^2. The percentage of primiparous women decreased from 51.4% in 2007-08 to 47.7% in 2017-18. This decrease should have decreased the stillbirth rates a little through the last part of the study period. The only potential confounder

which showed a substantial change was the percentage of smokers in pregnancy declining from 11.3% in 2007-08 to 5.9% in 2017-18. This decrease was most prominent from 2012 onwards and should therefore have contributed to a slight decrease in stillbirth rates during the period after 2012.

The perinatal mortality figures fell significantly from 2007-08 (1.8 per 1000) to 2011-12 (0.79 per 1000). After 2012, the perinatal mortality was slightly increasing from 0.92 in 2013-14 to 0.99 per 1000 in 2017-18 (NS).

Discussion

In this historical ecological study, we found a strong relationship between induction rates after 41 weeks of gestation and stillbirth rates. During the period of uninterrupted increase in inductions, the stillbirth rates decreased consistently, and most so from 2009-10 to 2011-12, coinciding with the new pro-active induction practice. It has been argued that other factors such as better ultrasound equipment or better surveillance of women with post-term pregnancies contributed substantially to the decrease in stillbirths from 2009 to 2012. The significantly increasing trend in stillbirths after 2012, coinciding with a decrease in induction rates after 41 weeks, contradicts such ideas as it is unlikely that the obstetrical surveillance or our technical equipment should have gotten worse over the last six years, on the contrary if anything. The declining proportion of smokers and the fewer primiparous women would tend to decrease our stillbirth rates. Nevertheless, we saw a significant doubling in these rates. No other factor seems to be able to explain this increase.

We do not claim, that the pro-active induction paradigm alone was responsible for the fall in stillbirth rates until 2012, and that the reduced induction rates alone are responsible for the increase in stillbirth after 2012, but our data strongly suggest that the induction paradigm has a *main responsibility* for this development.

An increase from 0.38 per 1000 to 0.74 per 1000 born (the average from 2015-2018) corresponds to five to six more stillbirths per year among pregnant women after 41 gestational weeks. In other words, the Danish data suggests that five to six more pregnant women experience a stillbirth today than in 2012, due to the 13% percent decrease in induction rates (=9.6 percent points decrease).

Thus, the present update to our last publication covering the period 2000 to 2012 (1) fully supports our earlier interpretation. The background for the decreased induction percentage after 2012 could be lack of resources at the maternity wards due to a general increase in the national

birth rate forcing the staff to postpone induction. From year 2000 until year 2012 the stillbirth rates among women delivering from 41 weeks fell by 82% or by an annual 30 stillborn per year. With the new increase, we have lost five of these 30 prevented deaths and are now back at the level of 2009-2010.

A recent attempt to extrapolate unidirectional trend curves appears to be unsuited to evaluate the influence of induction and implied at total miss of the significant increase in stillbirths over last six years (4). On the other hand, our results are in line with the newly published randomised Swedish study suggesting significantly higher stillbirth rates with postponing induction to 42 weeks instead of at 41 weeks of gestation (3).

The main limitation of this study is its ecological design implying that even a strong correlation is not an ultimate prove of a causal relationship between induction regime and stillbirth rates. The few missing deliveries without recorded gestational age (1.1%) are mainly very preterm deliveries, demonstrated by journal check in a sample of deliveries without this information in our previous study (1). This small lack is thus unlikely to have influenced our main results materially.

Among strengths are the nationwide design including all delivering women over a period of 12 years, ensuring a fair external validity, the generally good data quality in the birth registry, and the high percentage with complete data.

The current Danish recommendation is to initiate induction between 41+3 and 41+5 weeks in order to accomplish birth no later than 41+6 weeks of gestation. Following to the new Swedish data it is considered to revise our national guidelines and offer induction to all women at 41+0 weeks. The data in Table 2 and Fig. 3 may be helpful in these reflections.

In conclusion, this follow-up confirms that timely post-term inductions still seem to play a key role for stillbirth rates in women with uncomplicated pregnancies passing 41 gestational weeks. We recommend all obstetrical units to adhere to the national guidelines to ensure record low stillbirth rates as we achieved in 2012.

Acknowledgements

None of the authors had any conflict of interest. Expenses were covered by department of Gynaecology. Steen Rasmussen is thanked for data management of the detailed figures for Table 2 and Figure 3.

Contributions

ØLi, LK and AT conceptualised the study, ØLi made the analyses and wrote first draft of paper. All authors interpreted the results, revised the manuscript and accepted the final version.

Patient or public were not involved in this register study. The press will be informed about the results when published. Danish legislation prevents data sharing, but annual stillbirth rates are publicly available on www.e-sundhed.dk.

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Table 1

Characteristics of women delivering from 41+0 gestational weeks in Denmark 2007-2018

		2007-08	2009-10	2011-12	2013-14	2015-16	2017-18
Deliveries	41+	29,957	30,616	29,149	28,254	30,318	31,440
Stillbirths	41+ (n)	39	25	11	18	24	22
	per 1000	1.30	0.82	0.38	0.64	0.79	0.70
Neonatal deaths*		15	5	12	8	5	9
Perinatal deaths#	41+ (n)	54	30	23	26	29	31
	per 1000	1.80	0.98	0.79	0.92	0.96	0.99
Age	% 35+	19.7	20.5	20.5	20.6	20.5	20.1
BMI	% 25+	35.2	35.3	35.4	34.9	34.8	36.6
Smoking	in pregn	11.3	9.9	8.7	7.7	6.9	5.9
Parity	% P0	51.4	51.7	50.5	49.5	47.8	47.7

*) *Neonatal deaths are deaths within first week of life.*

#) *Perinatal mortality = stillbirths + neonatal deaths*

Table 2

Intrauterine deaths per 1000 pregnant women from 41+0 gestational weeks through the period 2007-2018 in Denmark

2007-18	41+0	41+1	41+2	41+3	41+4	41+5	41+6	42+
Pregnant	177,334	149,139	123,520	101,677	79,868	60,451	40,896	24,800
Born	28,195	25,619	21,843	21,809	19,417	19,555	16,096	24,800
Risk time (days)#	163,237	136,330	112,599	90,773	70,160	50,674	32,848	12,400
Foetal deaths	26	16	12	14	14	15	7	15
Deaths/1000	0.16	0.12	0.11	0.15	0.20	0.30	0.21	1.21
Cumulated	0.16	0.28	0.38	0.54	0.74	1.03	1.25	2.46
Relative risk*	1	1.7	1.4	1.4	1.4	1.4	1.2	2.0
Relative risk"	1	1.7	2.4	3.4	4.6	6.5	7.8	15.4

)# Calculated at the number of pregnant women at start of day minus half of deliveries that day. *) As compared with the day before ") As compared to rate at 41+0.

Figure 1

Induction rates *from 41 gestational weeks in Denmark 2007-2018 (red Y1).*

Proportion of non-induced *women also shown (blue Y2)*

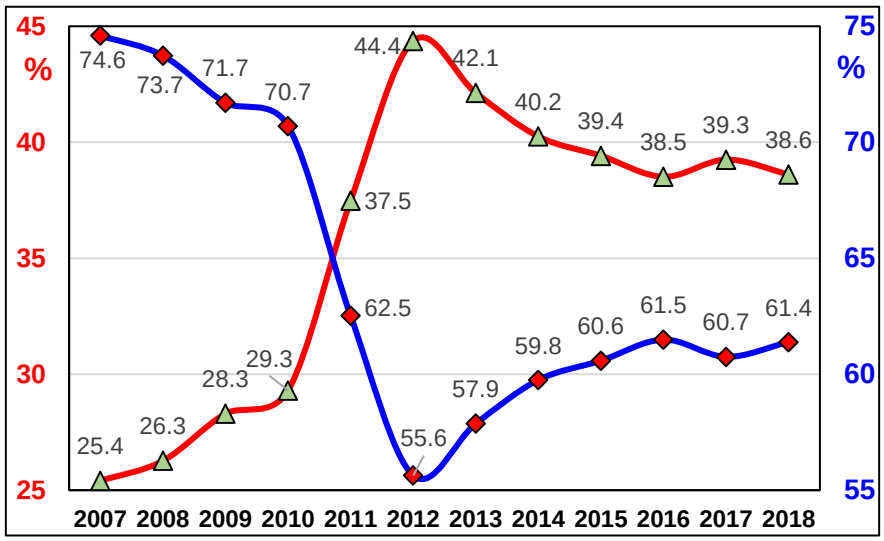


Figure 2

Stillbirth rates per 1000 born from 41 gestational weeks from 2007 through 2018

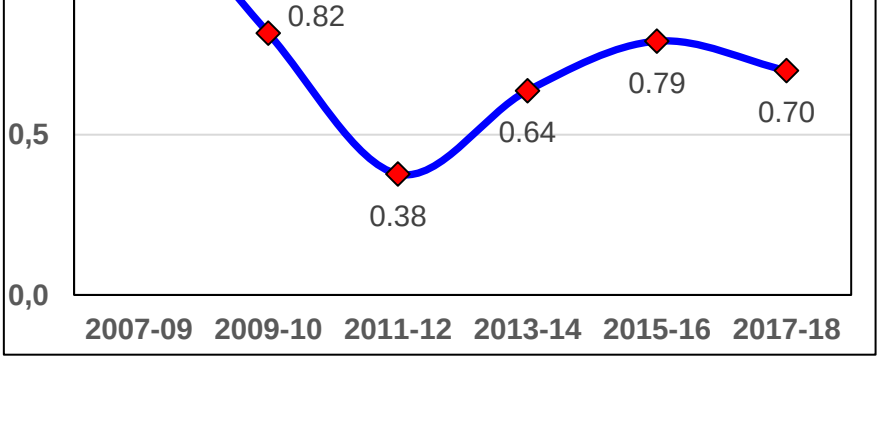
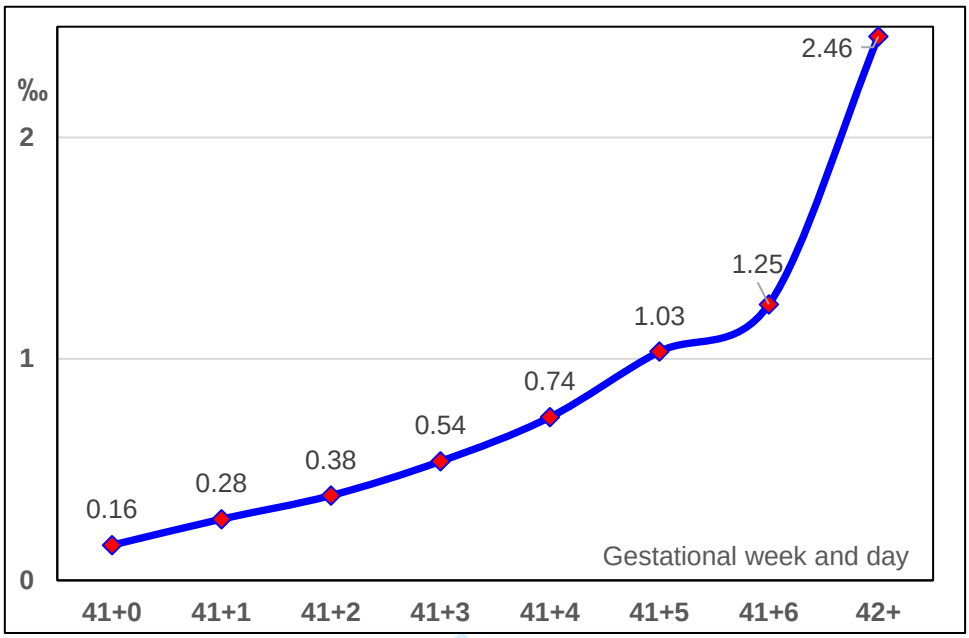


Figure 3

Cumulated risk of intrauterine death from 41+0 gestational weeks per 1000 on-going pregnancies. Denmark 2007-2018



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Yes**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. **Yes, page 4**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Yes, page 5**
Objectives	3	State specific objectives, including any prespecified hypotheses **p5 line 23-24**
Methods		
Study design	4	Present key elements of study design early in the paper **p5 line 28-29**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Abstract line 6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **p5, 31-32, p6 line 5-12**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **not availale**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **p6 line 5-25**
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 more than one group **p5 line 30-32 and p6 line 1-4**
Bias	9	Describe any efforts to address potential sources of bias **p6 line 20-21**
Study size	10	Explain how the study size was arrived at **p5 line 27-23**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **p6 line 5-19**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **p6 line 20-21 and line 31-33.**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed **p6 line 2-4**
		(*d*) If applicable, explain how loss to follow-up was addressed **na**
		(*e*) Describe any sensitivity analyses **None conducted**
Results		
Participants	13*	(a) 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 **p5 28-32, p7 line 7-9 and 22-27, Table 1, Table 2**
		(b) Give reasons for non-participation at each stage **p5, 28-30**
		(c) Consider use of a flow diagram **will not provide further as compared with the text (in this particular case).**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **p7 line 7-9**
		(c) Summarise follow-up time (eg, average and total amount) **p5 line 28**

Outcome data	15*	Report numbers of outcome events or summary measures over time **p7 and table 1 + 2.**
Main results	16	(*a*) 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 **Only unadjusted figures were reported. Separate confounder description was made.**
		(*b*) Report category boundaries when continuous variables were categorized **Table 1 and 2 and Fig 1-3.**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **p8 line 26-30, p9 line 1-4**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **na**
Discussion		
Key results	18	Summarise key results with reference to study objectives **p 8 line 10-13**
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 **p 9 line 10-15**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **p8 line 31-33 and p9 line 1-18**
Generalisability	21	Discuss the generalisability (external validity) of the study results **p9 line 16-18.**
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 **P 9 line 29-30**

*Give information separately for exposed and unexposed groups.

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BMJ Open

Are the Danish stillbirth rates still record low? A nationwide ecological study.

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Abstract (291 words)

Objectives. After introduction of a more pro-active post-term induction practice, stillbirth rates have decreased substantially throughout the first decade of this century in Denmark. The aim was to follow up on induction and stillbirth rates in Denmark.

Design. Historical ecological study.

Participants. We included all delivering women in Denmark during the period 2007 to 2018.

Intervention. Induction rates from 41 weeks of gestation.

Main outcome measure. Stillbirth rates from 41+0 weeks.

Results. Of 739,570 delivered children, 179,734 (24.3%) were born from 41+0 weeks. The proportion of deliveries after 41 weeks which were induced increased from 25.4% in 2007 to 44.4% in 2012. From 2012 to 2015 the induction rates decreased from 44.4% to 39.4%. After 2015 rates were stable.

During the same period, stillbirth rates decreased from 1.30 in 2007/08 to 0.38 per 1000 new-born in 2011/12; -54%. From 2012, however, the rates were doubled from 0.38 per 1000 in 2011/12 to 0.74 per 1000 in 2015/18; RR 1.97 (95% CI 1.02-3.81), p=0.033.

Changes in the included potential confounders cannot explain neither the substantial fall in stillbirth rates from 2007/08 to 2011/12, nor the doubling in stillbirth rates after 41 weeks since 2012.

During the whole study period, the cumulated risk of intrauterine foetal death increased from week 41+0 to 41+6 from 0.16 to 1.25 per 1000 on-going pregnancies or 7.8 folds. Going beyond 42 weeks further increased the risk to 2.46 per 1000 on-going pregnancies.

Conclusion. We found a consistent inverse correlation between the proportion of women with induction of labour after 41 weeks of gestation and the stillbirth rates during the same period and same gestational ages. This Danish update on post-term inductions and corresponding stillbirth rates thus confirm previous findings suggesting a causal link between these two parameters.

Key words: Birth induction, stillbirth, foetal death, post-term pregnancies.

Strengths and limitations

- Nationwide complete data covering the 12-year period 2007-2018
- Includes 179,734 new-born from 41 weeks of gestation
- Detailed deaths statistics on each day from 41+0 and cumulated by time
- Inclusion of other potential confounding factors in analysis
- Principal limitation: Observational non-experimental data.

Introduction

We previously reported a close temporal association between post term birth induction regimen and stillbirth rate i.e. with more frequent and earlier induction regime, the stillbirth rate went down (1). Danish obstetricians decided in 2010 to recommend deliveries to be completed before 42 weeks of gestation, with effective guidelines from 2011. This more pro-active induction practice increased the induction rate from 20 to 25%, while the stillbirth rates declined from 1.2 to record low 0.77 per 1000 new-born after 40 weeks of gestation (1). We also demonstrated improved perinatal outcomes and unchanged caesarean section rates with the more pro-active induction practice (2). Recently, a Swedish randomized study confirmed a higher risk of prenatal foetal death with postponing birth induction until 42 weeks of gestation as compared to induction at 41+0 weeks (3).

Some have questioned the association between induction scheme and stillbirth rates to be an expression of a causal influence of induction on stillbirth rates and have suggested other changes in obstetrical practice by time to be responsible for the temporal association, e.g. better surveillance of post-term pregnant women, better screening for women at risk of obstetrical complications, and declining smoking frequencies in pregnant women by time. Recently it has been questioned whether an association between induction regime and stillbirth rates exists at all (4).

One of the challenges with a more frequent and earlier induction regime, is the demand of an expanded staff to take care of these inductions, needs which often conflict with attempts to reduce staff as maternity wards are merged and centralized in order to ensure e.g. at site neonatal care facilities.

This study aimed to analyse induction frequencies and national stillbirth rates from 41 completed weeks during the period 2007 through 2018.

Material and methods

Study design

In a historical ecological design, deliveries from January 1, 2007 until December 31, 2018 were assessed.

Data sources

Data were retrieved from the Danish Birth Registry, which collects data on all deliveries in Denmark, including home-deliveries, deliveries in private clinics, and public maternity wards (5). Time trend figures were based on publicly available data to ensure same data source as a

recently published study (4). The detailed figures according to gestational ages were not publicly available. For these analyses we had access only to delivering women with a permanent Danish pin-code, and this detailed analysis was restricted to singleton deliveries. Ethnicity was operationalised as country of origin and was achieved from Statistics Denmark (6).

Methodological considerations

The new induction regime became national guidelines from 2011. It attempted to ensure delivery before 42 completed gestational weeks. The more pro-active induction policy was not, however, implemented over night from January 2011. It implied a more pro-active obstetrical practice also earlier after term in case of foetal growth stagnation or maternal complaint, with inductions soon after term. The focus for this analysis is, however, non-complicated pregnancies passing 41 weeks of gestation, which therefore became our cut-off for the present analysis.

Two further attempts influenced our methods. First transparency. While induction figures can easily be calculated annually, the number of stillbirths from 41 weeks became during the study period rather low. As figures below five are not allowed to be reported in scientific papers, all stillbirth figures were calculated for two consecutive years, beginning with 2007-08, ending with 2017-18.

The other attempt was to reduce random variation, which makes interpretations more difficult. This goal was also achieved by the two-year reporting of stillbirths.

Potential confounders considered were age of delivering women, body mass index, smoking in pregnancy, parity, and ethnicity. These data were also made up for the same two-year periods.

Deaths within the first week of life have also been assessed, although we do not expect the same protection with the more pro-active induction practice as for stillbirths. The sum of stillbirths and deaths within first week of life allowed calculation of perinatal deaths and perinatal death rates.

For the whole study period, we calculated cumulated risk of foetal death per 1000 on-going pregnancies from 41+0 weeks to explore how much the cumulated risk increases for each day a pregnancy is prolonged from 41+0 weeks. These calculations were made on only Danish citizens, that is with a personal identification number (excluding recent immigrants or visitors to Denmark)

Generally, the trends presented are highly significant due to the large number of included deliveries. Differences in death rates were calculated with 95% confidence intervals (CI) by chi square test, and level of significance between rates was set at $p < 0.05$.

Ethics

Most data are publicly available at e-sundhed.dk. Data for the detailed analysis on different gestational days were delivered by permission from the Regional Data Protection Agency: J no P-2020-217.

Patient and public involvement

Patient or public were not involved in this register study. The press will be informed about the results when published. Danish legislation prevents data sharing, but annual stillbirth rates are publicly available on www.e-sundhed.dk.

Results

During the study period, 739,570 children were delivered, and of these 731,446 (98.9%) had recorded gestational age. Of those with known gestational age, 179,734 (24.6%) were born from 41+0 gestational weeks.

The proportion of deliveries after 41 completed weeks which were induced increased from 2007 to 2010 from 25.4% to 29.3%, and from 2010 to 2012 further to 44.4% (Figure 1). From 2012 to 2018 the induction rates fell from these 44.4% to 38.6% of by 13%. After 2015 induction rates were stable.

During the same period, stillbirth rates decreased from 2007/08 to 2009/10 from 1.30 to 0.82 per 1000 new-borns, a decrease of 37% (Table 1 and Figure 2). From 2009/10 to 2011/12, the stillbirth rates fell further to 0.38 per 1000 births, a decrease of 54%.

From 2012, however, after more than a decade of consistent decrease in stillbirth rates, the rates have increased and were doubled from 2011/12 to 0.74 per 1000 in 2015/18; rate ratio 1.97 (95% CI 1.02-3.81), p=0.033. Comparing 2017-18 with 2011-12 provided an incidence rate ratio of 1.85 (95% CI 0.90-3.82), p=0.089.

Thus, we observed a close inverse correlation between induction rates from 41 weeks and stillbirth rates during the same years.

The cumulated risk of intrauterine death during the period 2007-2018 according to gestational day from week 41+0 is illustrated in Table 2 and Figure 3. It appears that risk of intrauterine death increases exponentially with increasing gestational age, from 0.16 per 1000 pregnant

women at 41+0 to 1.25 per 1000 pregnant women at 41+6, a 7.8-fold increase. The risk increased further if the pregnancy goes beyond 42 weeks to 2.46 per 1000 pregnancies or by 15 folds when compared to delivering at 41+0 weeks.

For the included potential confounders, the proportion of delivering women with an age of 35 years or older was rather stable around 20% throughout the study period as was a proportion of around 35% with body mass index above 25 kg/m^2. The percentage of primiparous women decreased from 51.4% in 2007-08 to 47.7% in 2017-18. This decrease should have decreased the stillbirth rates a little through the last part of the study period. The only potential confounder which showed a substantial change was the percentage of smokers in pregnancy declining from 11.3% in 2007-08 to 5.9% in 2017-18. This decrease was most prominent from 2012 onwards and should therefore have contributed to a slight decrease in stillbirth rates during the period after 2012. Finally, the proportion of delivering women with origin from Africa, South America or Asia increased during the period 2011-12 to 2017-18 from 8.2% to 11.4%.

The perinatal mortality figures fell significantly from 2007-08 (1.8 per 1000) to 2011-12 (0.79 per 1000). After 2012, the perinatal mortality was slightly increasing from 0.92 in 2013-14 to 0.99 per 1000 in 2017-18 (NS).

Discussion

In this historical ecological study, we found a strong relationship between induction rates after 41 weeks of gestation and stillbirth rates. During the period of uninterrupted increase in inductions, the stillbirth rates decreased consistently, and most so from 2009-10 to 2011-12, coinciding with the new pro-active induction practice.

Evaluation of results

It has been argued that other factors such as better ultrasound equipment or better surveillance of women with post-term pregnancies contributed substantially to the decrease in stillbirths from 2009 to 2012. The significantly increasing trend in stillbirths after 2012, coinciding with a decrease in induction rates after 41 weeks, contradicts such ideas as it is unlikely that the obstetrical surveillance or our technical equipment should have deteriorated over the last six years, on the contrary if anything. The declining proportion of smokers and the fewer primiparous women would tend to decrease our stillbirth rates. As all Danish citizens have equal and free access to obstetrical care, prenatal diagnosis and public delivery wards, the modest increase in non-Caucasian delivering women is not expected to have influenced the stillbirth rates more than marginally, partly counter balancing the decreasing influence from fewer

smokers and fewer primiparous women. Nevertheless, we saw a significant doubling in these rates. We could not identify any other factor, which could explain the observed increase in stillbirths after 2012.

We do not claim, that the pro-active induction paradigm alone was responsible for the fall in stillbirth rates until 2012, and that the reduced induction rates alone are responsible for the increase in stillbirth after 2012, but our data strongly suggest that the induction paradigm has a *main responsibility* for this development.

Implication of findings

An increase from 0.38 per 1000 to 0.74 per 1000 born (the average from 2015-2018) corresponds to five to six more stillbirths per year among pregnant women after 41 gestational weeks. In other words, the Danish data suggests that five to six more pregnant women experience a stillbirth today than in 2012, due to the 13% percent decrease in induction rates (=9.6 percent points decrease).

Thus, the present update to our last publication covering the period 2000 to 2012 (1) supports our earlier interpretation. The background for the decreased induction percentage after 2012 could be lack of resources at the maternity wards due to a general increase in the national birth rate forcing the staff to postpone induction. From year 2000 until year 2012 the stillbirth rates among women delivering from 41 weeks fell by 82% or by an annual 30 stillborn per year. With the new increase, we have lost five of these 30 prevented deaths and are now back at the level of 2009-2010.

A recent attempt to extrapolate unidirectional trend curves appears to be unsuited to evaluate the influence of induction and implied at total miss of the significant increase in stillbirths over last six years (4). On the other hand, our results are in line with the newly published randomised Swedish study suggesting significantly higher stillbirth rates with postponing induction to 42 weeks instead of at 41 weeks of gestation (3).

Strengths and limitations of study

The main limitation of this study is its ecological design implying that even a strong correlation is not an ultimate prove of a causal relationship between induction regime and stillbirth rates. The few missing deliveries without recorded gestational age (1.1%) are mainly very preterm deliveries, demonstrated by journal check in a sample of deliveries without this information in our previous study (1). This small lack is thus unlikely to have influenced our main results materially.

Among strengths are the nationwide design including all delivering women over a period of 12 years, ensuring a fair external validity, the generally good data quality in the birth registry, and the high percentage with complete data.

The current Danish recommendation is to initiate induction between 41+3 and 41+5 weeks in order to accomplish birth no later than 41+6 weeks of gestation. Following to the new Swedish data it is considered to revise our national guidelines and offer induction to all women at 41+0 weeks. The data in Table 2 and Fig. 3 may be helpful in these considerations.

Conclusion

In conclusion, this follow-up confirms that timely post-term inductions still seem to play a key role for stillbirth rates in women with uncomplicated pregnancies passing 41 gestational weeks. We recommend all obstetrical units to adhere to the national guidelines to ensure record low stillbirth rates as we achieved in 2012.

Data sharing

All data relevant to the study are included in the article. Only authorized scientists can after relevant permissions from the Danish Data Protection Agency get access to individual medical data in Danish registries.

Acknowledgements

Steen Rasmussen is thanked for data management of the detailed figures for Table 2 and Figure 3.

Competing interests

None of the authors had any conflict of interest.

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Contributions

ØLi, LK and AT conceptualised the study, ØLi made the analyses and wrote first draft of paper.
All authors ØLi, LK, AT, PD, and OBP interpreted the results, revised the manuscript and accepted the final version.

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Table 1

Characteristics of women delivering from 41+0 gestational weeks in Denmark 2007-2018

		2007-08	2009-10	2011-12	2013-14	2015-16	2017-18
Deliveries	41+	29,957	30,616	29,149	28,254	30,318	31,440
Stillbirths	41+ (n)	39	25	11	18	24	22
	per 1000	1.30	0.82	0.38	0.64	0.79	0.70
Neonatal deaths*		15	5	12	8	5	9
Perinatal deaths#	41+ (n)	54	30	23	26	29	31
	per 1000	1.80	0.98	0.79	0.92	0.96	0.99
Age	% 35+	19.7	20.5	20.5	20.6	20.5	20.1
BMI	% 25+	35.2	35.3	35.4	34.9	34.8	36.6
Smoking	in pregnancy	11.3	9.9	8.7	7.7	6.9	5.9
Parity	% P0	51.4	51.7	50.5	49.5	47.8	47.7
Ethnicity	% AASA"	7.1	7.6	8.2	9.3	10.6	11.4

*) *Neonatal deaths are deaths within first week of life.*
#) *Perinatal mortality = stillbirths + neonatal deaths*
") *AASA = African, Asian or South American origin*

Table 2

Intrauterine deaths per 1000 pregnant women from 41+0 gestational weeks through the period 2007-2018 in Denmark

2007-18	41+0	41+1	41+2	41+3	41+4	41+5	41+6	42+
Pregnant	177,334	149,139	123,520	101,677	79,868	60,451	40,896	24,800
Born	28,195	25,619	21,843	21,809	19,417	19,555	16,096	24,800
Risk time (days)#	163,237	136,330	112,599	90,773	70,160	50,674	32,848	12,400
Foetal deaths	26	16	12	14	14	15	7	15
Deaths/1000	0.16	0.12	0.11	0.15	0.20	0.30	0.21	1.21
Cumulated	0.16	0.28	0.38	0.54	0.74	1.03	1.25	2.46
Relative risk*	1	1.7	1.4	1.4	1.4	1.4	1.2	2.0
Relative risk"	1	1.7	2.4	3.4	4.6	6.5	7.8	15.4

*)# Calculated as the number of pregnant women at start of day minus half of deliveries that day. *) As compared with the day before ") As compared to rate at 41+0.*

Legends for figures

Figure 1

Induction rates from 41 gestational weeks in Denmark 2007-2018 (red Y1). Proportion of non-induced women also shown (blue Y2)

Figure 2

Stillbirth rates per 1000 born from 41 gestational weeks from 2007 through 2018

Figure 3

Cumulated risk of intrauterine death from 41+0 gestational weeks per 1000 on-going pregnancies. Denmark 2007-2018

Figure 1

Induction rates *from 41 gestational weeks in Denmark 2007-2018 (red Y1).*

Proportion of non-induced *women also shown (blue Y2)*

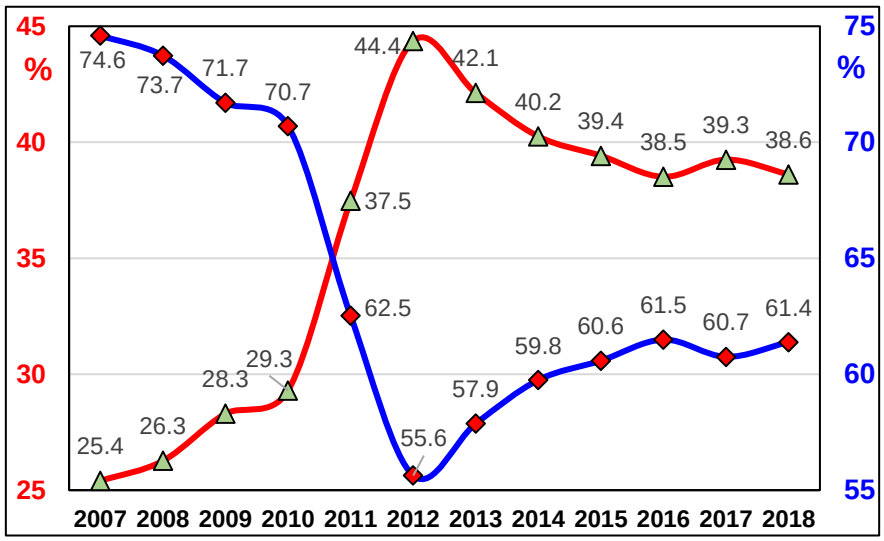


Figure 2

Stillbirth rates per 1000 born from 41 gestational weeks from 2007 through 2018

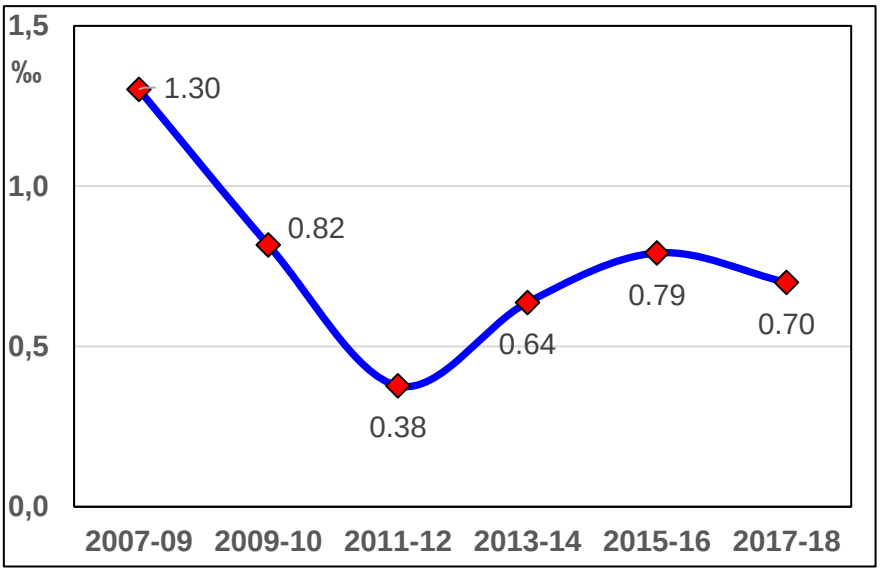
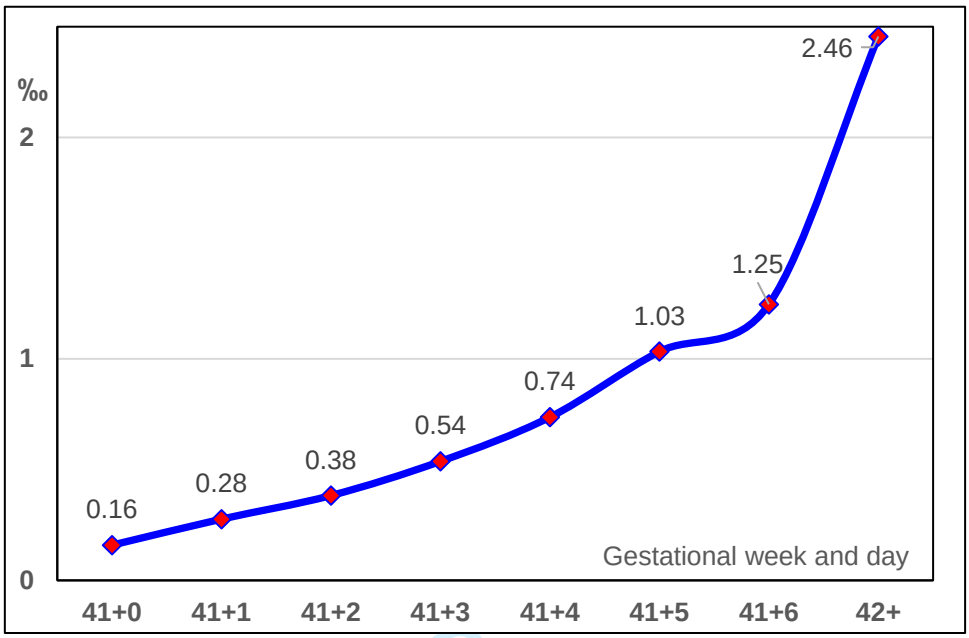


Figure 3

Cumulated risk of intrauterine death from 41+0 gestational weeks per 1000 on-going pregnancies. Denmark 2007-2018



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Yes**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. **Yes, page 4**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Yes, page 5**
Objectives	3	State specific objectives, including any prespecified hypotheses **p5 line 23-24**
Methods		
Study design	4	Present key elements of study design early in the paper **p5 line 28-29**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Abstract line 6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **p5, 31-32, p6 line 5-12**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **not availale**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **p6 line 5-25**
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 more than one group **p5 line 30-32 and p6 line 1-4**
Bias	9	Describe any efforts to address potential sources of bias **p6 line 20-21**
Study size	10	Explain how the study size was arrived at **p5 line 27-23**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **p6 line 5-19**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **p6 line 20-21 and line 31-33.**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed **p6 line 2-4**
		(*d*) If applicable, explain how loss to follow-up was addressed **na**
		(*e*) Describe any sensitivity analyses **None conducted**
Results		
Participants	13*	(a) 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 **p5 28-32, p7 line 7-9 and 22-27, Table 1, Table 2**
		(b) Give reasons for non-participation at each stage **p5, 28-30**
		(c) Consider use of a flow diagram **will not provide further as compared with the text (in this particular case).**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **p7 line 7-9**
		(c) Summarise follow-up time (eg, average and total amount) **p5 line 28**

Outcome data	15*	Report numbers of outcome events or summary measures over time **p7 and table 1 + 2.**
Main results	16	(*a*) 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 **Only unadjusted figures were reported. Separate confounder description was made.**
		(*b*) Report category boundaries when continuous variables were categorized **Table 1 and 2 and Fig 1-3.**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **p8 line 26-30, p9 line 1-4**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **na**
Discussion		
Key results	18	Summarise key results with reference to study objectives **p 8 line 10-13**
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 **p 9 line 10-15**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **p8 line 31-33 and p9 line 1-18**
Generalisability	21	Discuss the generalisability (external validity) of the study results **p9 line 16-18.**
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 **P 9 line 29-30**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.