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## Reduction in stillbirths at term after new birth induction paradigm. Results of a national intervention

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## Reduction in stillbirths at term after new birth induction paradigm.

### Results of a national intervention

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8 29 **Abstract**

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10 30 **Objective.** Fetal deaths are still a key challenge for obstetricians worldwide. The risk of fetal death  
11 31 increases steeply after 42 gestational weeks. From 2009, Danish national guidelines  
12 32 recommended pregnant women to be offered induction to ensure delivery before 42 weeks. The  
13 33 aim of this study was to describe the development in fetal deaths with this more proactive birth  
14 34 induction practice, and to identify and quantify contributing factors for this development.

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17 35 **Design.** National cohort study.

18 36 **Setting.** Denmark

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20 37 **Participants.** Delivering women in Denmark, January 1, 2000 to December 31, 2012.

21  
22 38 **Outcome measures.** Stillbirths per 1,000 women at risk (prospective risk of stillbirth) and per  
23 39 1,000 new-born from 37 and 40 gestational weeks, respectively, through the study period.

24  
25 40 **Results.** During the study period, 829,165 children were live-born and 3,770 (0.45%) stillborn.

26 41 Induction of labour increased from 12.4 % in year 2000 to 25.1 % in 2012 ( $p<0.001$ ), and the per  
27 42 cent of children born at or after 42 weeks decreased from 8.0 % to 1.5 % ( $p<0.001$ ).

28  
29 43 Through the same period, the prospective risk of stillbirth after 37 weeks fell from 0.70 to 0.41 per  
30 44 1,000 ongoing pregnancies ( $p<0.001$ ), and from 2.4 to 1.4 per 1,000 new-born ( $p<0.001$ ).

31  
32 45 The regression analysis confirmed the inverse association between year of birth and risk of  
33 46 stillbirth. The lowest risk was observed in the years 2011-2012 as compared to years 2000-2002  
34 47 with a fully adjusted hazard ratio of 0.69 (95% CI 0.57-0.83). The general earlier induction, the  
35 48 focused earlier induction of women with body mass index  $>30$ , twins, and of women above 40  
36 49 years, and a halving of smoking pregnant women were all independent contributing factors for the  
37 50 decrease.

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40 51 **Conclusion.** A gradually more proactive and a differential earlier labour induction practice are  
41 52 likely to have the main responsibility for the substantial reduction in stillbirths in Denmark.

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43 53  
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45 54 **Key words:** Birth induction, fetal death, stillbirth, misoprostol

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47 55 **Abbreviations:** None.

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**Strengths and limitations**

**Strengths**

- Complete national data through a 13-year long study period
- Data analysed for all births after 37 weeks and after 40 weeks, respectively
- Access to important confounders
- Complete follow-up on all children born during the study period
- Advanced regression analysis
- A clear clinical message

**Limitations**

- Several clinical improvements have been undertaken during the study period
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## Introduction

Fetal death is still a dreaded complication of pregnancy, not least when occurring at term. The worldwide number of stillborn infants is estimated to 2.6 million per year, and the causes of a substantial part of these deaths are still unknown.[1] Identified risk factors include high maternal age, adiposity, fetal asphyxia, infections, and different maternal medical diseases.[2-5] Randomised studies have suggested a potential for prevention of fetal deaths by earlier induction of deliveries.[6]

Over the last two decades, the discussion of induction of labour versus expectant management has been prevalent among obstetricians.[7] A national Danish guideline in 2009 recommended induction of pregnant women ensuring delivery before 42 weeks.[8] Generally, pregnant women have since been offered labour induction at 41+3-5, while women at risk (body mass index >30 or age >40 years) have been offered induction at 41 weeks. Lastly, women at a high risk such as women with multiple pregnancies, preeclampsia or intrauterine growth restriction are often recommended induction before term.

The aim of this study was to describe birth induction practice in Denmark since year 2000, the corresponding development in post-term deliveries, and the stillbirth rates from 37 and 40 weeks of gestation (prospective stillbirth rate) and per 1,000 new-born. Secondly, to adjust these trends in rates of stillbirth for important risk factors of stillbirth.

## Methods

### *Design and setting*

In a historical cohort design data were collected from the Danish Birth Register, covering the period January 2000 through December 2012. The Registry is considered complete through this period. In order to reduce random variation, the 13-year study period was subdivided into five sub-periods of three, three, three, two, and two years length, respectively.

### *Participants*

All live births and stillbirths during the study period were included. For each gestational day after 37 weeks, the number and distribution of all new-born and stillbirths were assessed. The gestational ages were generally assessed from first trimester ultrasound examinations. For few women not attending this routine offer to all pregnant women in Denmark, the last menstrual period was used.

### *Outcome measures*

Rates of stillbirth per 1,000 ongoing pregnancies, also called the prospective risk of stillbirth, were calculated with a daily update from 37 weeks of gestation, accounting for the rapidly declining denominator especially after term. [9] The proportion of deliveries and of stillbirths after 37, 40, 41,

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8 104 and 42 weeks per 1,000 new-born were calculated annually from year 2000 through 2012, and in  
9 105 different sub-periods within this study period.

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11 106 The gestational age was recorded in 99.4 % of all new-born during the study period. Of 146  
12 107 missing gestational ages among stillborn infants, we sought in medical charts and local registers  
13 108 and achieved this information in 42 women, all of whom had ended their pregnancy before 37  
14 109 weeks. Therefore, all with a missing gestational age were allocated to the premature group.  
15 109 Gestational ages were however achieved for all stillbirths in 2011 and 2012.

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18 111 From 2004 a birth has in Denmark been defined as any pregnancy that ends after 22 weeks of  
19 112 gestation, and live-born before 22 weeks. Before 2004 only live-births between 22 and 28 weeks  
20 113 were considered as births, while delivery of dead fetuses before 28 weeks and live-born before 22  
21 114 weeks were considered as abortions. This technicality explains a minor increase in stillbirths before  
22 114 37 weeks of gestation from 2003 to 2004.

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25 116 Deaths within the first week after delivery was assessed for all included live-born, and rates of  
26 117 death were calculated in each study year.

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28 118 In the analytical assessment, analyses of the cumulative risk of stillbirth with increasing gestational  
29 119 age per 1,000 ongoing pregnancies was estimated using Nielson Aalen estimator with gestational  
30 120 age (in days) as the time scale.[10] By cox regression analyses, the hazard ratios of stillbirth by  
31 121 year of birth were estimated using year 2000-2002 as the reference group. Gestational age was  
32 122 underlying time scale in these analyses. The following potential confounders were included in the  
33 123 model: Plurality, parity, maternal age, year, smoking, and body mass index. The regression model  
34 123 aimed to quantify the contribution from each of the potential confounders for the association  
35 124 between calendar year and rates of stillbirth.[10] Hazard ratios with 95% confidence limits were  
36 124 calculated, and p-values below 0.05 were considered significant. Logistic regression was used to  
37 125 generate crude odds ratios.

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41 128 The main analysis was done on all deliveries from 37 weeks of gestation. As body mass index was  
42 129 not routinely recorded in the birth registry until 2004, additional sensitivity analyses were done for  
43 129 the sub-period 2004-2012, in order to quantify specifically the influence of body mass index on the  
44 130 decreasing stillborn rate. Finally, sensitivity analyses were conducted restricted to singletons.

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## Results

During the study period, 832,935 children were born. Of these were 3,770 (0.45 %) stillbirths and 829,165 (99.55 %) live-born. The distribution of new-born and stillborn infants in different pregnancy weeks, the crude rate of stillborn per 1,000 ongoing pregnancies and per 1,000 new-born in different gestational weeks, from different gestational ages and in different periods are shown in Table 1.

The frequency of birth induction increased from 12.4 % in year 2000 to 25.1 % in 2012, with a steep increase after 2010 (**Figure 1**). The earlier birth induction reduced the per cent of children born from 42 weeks of gestation from 8.0 % in year 2000 to 1.5 % in 2012 (**Figure 1**). The increasing induction rate and fall in deliveries from 42 weeks was, however, already observable from 2001.

### *Stillbirths with increasing gestational age.*

The background for the new induction paradigm in Denmark is illustrated for the period 2000-2008 in **Figure 2**. With increasing gestational age the risk of fetal death rises, peaking after 43 weeks of gestation with more than 14 deaths per 1,000 ongoing pregnancies, a risk more than ten times higher than in the weeks before term.

During the period 2009-2012, the stillborn rates were reduced 21-39%, and from 41+3 stillbirths were eliminated (**Figure 2**).

The crude rates of fetal deaths with increasing gestational age were reduced by 30-66% when adjusting for age, year, parity, plurality, and smoking (**Figure 3**). Adjustment for body mass index did not change the estimates significantly.

### *Stillbirths by time.*

The rate of stillborn infants from 37 weeks of gestation decreased from 0.70 (95% confidence interval 0.64-0.77) per 1,000 ongoing pregnancies (prospective stillbirth rate) during the period 2000-2002 to 0.41 (0.35-0.48) during the period 2011-2012 (**Figure 4**). The corresponding rate of stillborn infants from 40 weeks fell from 1.8 (1.6-2.1) during the period 2000-2002 to 0.74 (0.56-0.98) during 2011-2012, a reduction of 60 % ( $p<0.001$ ). The fall was steepest from 2009-10 to 2011-12.

The rate of stillborn infants per 1,000 new-born after 37 weeks demonstrated a similar decrease from 2.4 (2.2-2.6) during the period 2000-2002 to 1.4 (1.2-1.6) during 2011-2012, a fall of 43% (**Figure 4**). Among children born from 40 weeks, the corresponding stillborn rates fell from 2.1 (1.9-2.4) per 1,000 new-born to 0.77 (0.58-1.0) or by 63% ( $p<0.001$ ) (**Figure 4**).

**Comment [KA1]:** Jeg er lidt usikker på hvad du mener med sidste halvdel af sætningen?

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8 167 *Regression analysis*

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10 168 Several conditions, which may have influenced the risk of fetal death, changed during the study  
11 169 period (**Table 2**). The mean age of delivering women after 37 weeks of gestation increased from  
12 170 30.1 years in 2000-2002 to 30.9 years in 2011-12, and the proportion of delivering women  $\geq 40$   
13  
14 171 years increased from 2.0 % to 3.5 % ( $p < 0.001$ ).

15 172 The mean body mass index increased from 24.1 kg/m<sup>2</sup> in 2003-2005 to 24.4 kg/m<sup>2</sup> during 2011-  
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17 173 2012, and delivering women with a body mass index above 25 kg/m<sup>2</sup> increased from 32.0 % to  
18 174 34.4 % through the same period ( $p < 0.001$ ).

19  
20 175 While these changes are expected to increase the risk of fetal death, the proportion of pregnant  
21 176 smokers decreased from 20.5 % in 2000-2002 to 11.5 % in 2011-2012, almost a halving ( $p < 0.001$ ).

22 177 The proportion of primiparous increased slightly from 43.0 % to 44.5 % through the study period,  
23 178 while the proportion of multiple pregnancies after 37 weeks was almost stable; 2.4 % in 2000-2002,  
24 179 2.6 % in 2006-2008, and 2.5 % in 2011-12 (**Table 2**). The proportion of multiple deliveries after 40  
25 180 weeks of gestation from already low 0.12 % decreased to 0.04 %. Thereby, post term multiple  
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27 181 deliveries almost disappeared through the study period.

29  
30 182 In the fully adjusted model the following hazard ratios of fetal death were demonstrated: Smoking  
31 183 1.4 (1.2-1.6), body mass index  $> 25$  kg/m<sup>2</sup>; 1.5 (1.3-1.7), decreasing from 1.7 (1.4-2.0) during the  
32 184 period 2004-2008 to 1.3 (1.0-1.6) in 2009-2012. Primiparous had a relative risk of stillbirth of 1.2  
33 185 (1.1-1.3), and multiple pregnancy of 51.5 (44.4-59.6).

35 186 With adjustment for gestational age at delivery, the decline in stillbirths was reduced from -41.5 %  
36 187 to -35.5 % suggesting that the general earlier induction in it self accounted for about 15 % of the  
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38 188 reduction. Further adjustment for smoking, age at delivery, and parity increased the fall from -35.5  
39 189 % to -37.6 %, because the decrease in smoking counterbalanced the influence of the slightly  
40 190 increasing age and proportion of primiparous by time. By additional adjustment for plurality, the  
41 191 relative risk of stillbirth by time was reduced from -37.6 % to -31.4 %, suggesting that the changes  
42 192 in the management of twin pregnancies accounted for approximately 16 % of the decrease.

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45 193 In the sub-analysis covering the period 2004-2012, during which information about body mass  
46 194 index was available, the decreasing risk of stillbirth among women with high body mass index by  
47 195 time implied a further non significant four per cent reduction in overall stillbirth rates by time.

48  
49 196 The rest of the reduction in stillbirths is thus apparently due to the differential induction practice,  
50 197 where women with high-risk pregnancies are induced more proactively (earlier) than low-risk  
51 198 pregnancies,

53 199 The risk of fetal death in the week after term was reduced by 33-38 % ( $p < 0.01$ ), in the week after  
54 200 41 weeks by 30-33 % ( $p < 0.01$ ), and after 42 weeks by 30-33 % ( $p < 0.05$ )(**Figure 2**). Thus, the new



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8 201 induction paradigm firstly moved deliveries from late weeks with a high risk of stillbirth to earlier  
9 202 weeks with a lower risk. Secondly, in particular moved high-risk pregnancies to earlier induction,  
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11 203 but thirdly, also reduced the risk of fetal death in each post term week.

12 204 The decrease in the rate of stillbirth corresponds to a reduction in absolute numbers of stillborn  
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14 205 infants after 37 weeks from 136 stillbirths per year to now about 75 per year, a reduction of  
15 206 approximately 60 per year ( $p < 0.001$ ), corresponding to one saved stillborn infant per 1,000 new-  
16 207 born.

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18 208 During gestational weeks 37 to 40, the annual number of stillbirths fell from around 80 per year  
19 209 during the period 2000-2008 to 50 per year during 2009-2012. This reduction coincided with an  
20 210 increase in second trimester induced abortions on fetal indication from annually 292 during the  
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22 211 period 2000-2008 to 410 per year during the period 2009-2012, an increase of 118 induced  
23 212 abortions per year.[11]

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25 213 The risk of dying during the first week of life was reduced among children born after 37 weeks from  
26 214 1.7 (1.4-2.0) per 1,000 new-born in 2000 to 0.8 (0.6-1.0) per 1,000 live-born in 2012.[12]

27  
28 215 The Caesarean section rate in Denmark has after a steady increase over more than 40 years been  
29 216 stable throughout the last ten years at about 20 % of all deliveries, even with a slight reduction  
30 217 from 20.4 % in 2009 to 19.8 % in 2012 ( $p < 0.01$ ).[12]

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32 218 The sensitivity analysis excluding women with unknown gestational age did not change anything  
33 219 after 37 weeks, but decreased slightly the risk of fetal deaths before 37 weeks (data not shown).

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35 220 Sensitivity analyses restricted to singletons enhanced the fall in stillbirth rates by time. For all  
36 221 deliveries, the adjusted fall by time was -31% and for singletons -43%.

## 37 38 222 39 40 223 41 224 **Discussion**

42  
43 225 We report a decrease in risk of fetal death after 37 weeks to 0.14 % on a national level, which is  
44 226 the lowest risk ever reported in Denmark. Nor have any similar rate to our knowledge been  
45 227 published elsewhere.

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47 228 Ever since the 1990's, there has been an ongoing discussion of induction of labour versus  
48 229 expectant management of women after term.[7] Through the last ten years, a gradually more  
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50 230 proactive induction practice has gained ground over expectant management in several countries,  
51 231 including Denmark. The decision to make a Danish guideline in 2009 was stimulated by the NICE-  
52 232 guideline on induction of labour published in 2008 and the ACOG practice bulletin from 2009.[13,  
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8 234 Before 2009, many women were still not offered induction until after they passed 42 weeks of  
9 235 gestation. From 2009, the recommended induction regimen prevented many pregnancies from  
10 236 reaching post term gestational weeks of a high risk of fetal death. This change reduced the number  
11 237 of fetal deaths after term, but should in principle not influence the rate of deaths per 1,000 ongoing  
12 238 pregnancies in a certain post term week. The gestational age specific stillbirth rate after 41 weeks  
13 239 was, however, also reduced. This reduction could not be explained by the general earlier induction  
14 240 practice, but is according to our analyses a result of an even more proactive induction practice in  
15 241 women at an increased risk of stillbirth, such as women with body mass index >30, and women  
16 242 over 40 years. An increased fetal monitoring after term by time may also have influenced the  
17 243 decrease.

18 244 Through the last ten years, the majority of Danish units have used misoprostol for induction of  
19 245 labour, either applied vaginally or orally. It has been questioned, if induction by misoprostol could  
20 246 increase the risk of uterine hyperstimulation, asphyxia, and ultimately of neonatal death. In theory,  
21 247 an initiative to reduce the risk of fetal death could lead to neonatal complications and neonatal  
22 248 death. It is therefore important that the reduction in stillbirths was not associated with an increase  
23 249 in early neonatal deaths. On the contrary, the early neonatal deaths were halved during the study  
24 250 period, a circumstance, which undoubtedly was also influenced by an improved neonatal care  
25 251 through the study period.

26 252 It has been discussed, if induction of labour causes more Caesarean sections.[15] Some have  
27 253 argued that expectant management of labour increases the Caesarean section rate due to the  
28 254 risks associated with prolonged pregnancy.[16] The slight reduction in Caesarean sections with the  
29 255 new induction paradigm demonstrates that a proactive induction practice not necessarily increases  
30 256 the frequency of surgical interventions.

31 257 The offer of first trimester combined screening (double test and nuchal translucency scan), has in  
32 258 Denmark been widened to all pregnant women from year 2005-2006.[17] Before then, only women  
33 259 at 35 years or older were routinely offered first trimester screening. With the new routine, a majority  
34 260 of chromosomal abnormalities are detected and pregnancy most often terminated, accounting for  
35 261 the increase of approximately 118 annual second trimester induced abortions. Before the general  
36 262 screening was fully implemented, some fetuses with undetected abnormalities died later in  
37 263 pregnancy. From 20 weeks of gestation until term, 13 % of trisomy 21, 75 % of trisomy 18, and 35  
38 264 % of trisomy 13 experience fetal death [18], a majority of these before 37 gestational weeks. This  
39 265 circumstance may explain a reduction of about 15 fetal deaths per year, but only about seven after  
40 266 37 weeks corresponding to 12 % (7/60) of the observed reduction in stillborn infants.

41 267 During the study period, the quality of screening for structural abnormalities (offered in general  
42 268 throughout the period) and Doppler ultrasound both improved the monitoring of fetuses in utero,

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8 269 making it easier to detect threatened fetuses and to intervene to avoid further complications  
9 270 including fetal death. However, these circumstances are probably of minor importance for the  
10 271 decrease in stillbirths, as other countries with the same technical improvement have not observed  
11 272 a similar decrease in stillbirths. In Sweden, the proportion of deliveries after 42 weeks was 7.5 % in  
12 273 year 2000 and 6.5 % in 2011. During the same period, the stillbirth rate after 37 gestational weeks  
13 274 was stable between 1.6 and 1.9 per 1,000 new-born.[19] In Norway, 4.8 % of deliveries occurred at  
14 275 42 weeks or later, and the stillbirth rate after 37 weeks was 1.47 per 1,000 new-born [20], figures  
15 276 close to Danish figures in 2010.

16 277 The earlier induction of multiple pregnancies explained about 15 % of the reduction in stillbirths.

17 278 The selective early induction of high-risk pregnancies such as pregnancies in women with high  
18 279 body mass index, women above 40 years, and women with multiple pregnancies explains, why the  
19 280 impact of these risk factors decreased by time. Worldwide, maternal age at delivery has increased  
20 281 over the last five decades, and Denmark is no exception.[21] As high maternal age is associated  
21 282 with stillbirth, this increase should have increased the stillbirth rates slightly by time.[5, 22, 23]

22 283 Determining the optimal time to deliver necessarily involves balancing induction risks and benefits.  
23 284 According to earlier studies, the risks of post-term deliveries include an increased perinatal  
24 285 mortality, meconium aspiration, macrosomia, low umbilical cord artery pH, and low Apgar score at  
25 286 five minutes.[24] Inducing labour too early, on the other hand, may cause iatrogenic prematurity  
26 287 and respiratory complications.[25, 26]

27 288 When considering the overall risk of either fetal or infant death, previous studies have suggested  
28 289 the risk of expectant management to be lower than the risk of delivery until about 38 weeks.

29 290 Passing 38 weeks, the risk of expectant management was found to be higher than the risk of  
30 291 delivery, and the risk difference increases substantially after 40 and 41 weeks of gestation,  
31 292 favouring delivery over expectant management.[27]

32 293 Among the strengths of this study are the almost complete coverage of deliveries [28], and access  
33 294 to data making an evaluation of circumstances, which might have influenced the stillbirth rates  
34 295 possible. The main limitation is the observational design, and the difficulty to account effectively for  
35 296 all potential confounders. The significant reduction in fetal deaths seen in Denmark has not been  
36 297 observed in Sweden, where the handling of post term pregnancies has undergone less  
37 298 change.[19]

38 299 In conclusion, the striking decrease in risk of late fetal deaths through recent years is likely  
39 300 primarily to be due to the earlier and increased induction rate. The additional health costs to save  
40 301 these lives were low, and the reduction was obtained without an increase in surgical interventions.

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An important issue, which needs further studies, is the morbidity in new-born through the same study period, to confirm that the reduced mortality is not at the expense of an increased morbidity in new-born.

Denmark already had a low stillbirth rate a decade ago.[1] With the further reduction in stillbirths, we may now have achieved the lowest stillbirth rate ever reported. We see no reason why a similar more proactive induction paradigm could not be implemented in other countries, with a succeeding further reduction in late stillbirths worldwide.

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The study was approved by the Danish Data Protection Agency (J.no: 2013-41-2063) and the National Board of Health (J.no, FSEID 00000579). Ethical approval is not requested for registry based studies in Denmark

### **Contributions**

Hedegaard, Hedegaard and Lidegaard planned the study, Skovlund retrieved data from the National Birth Registry and National Health Registry. Mørch, Lidegaard, and Skovlund analysed the data. Hedegaard and Lidegaard wrote the manuscript. All authors revised the manuscript and accepted the final version. Morten Hedegaard is the guarantor.

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### **Conflict of interests**

All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare that Lidegaard within the last three years received honoraria for speeches in pharmacoepidemiological issues. Hedegaard, Hedegaard, Mørch and Skovlund did not declare any conflicts.

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### **Data Sharing Statement**

No additional data available

## References

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8 435 **Legends for tables and figures**

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10 436 **Table 1**

11 437 *Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-*  
12 438 *2012.*

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14 439 **Table 2**

15 440 *Characteristics of women giving birth at term and relative risk of stillbirth by time.*

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17 441 **Figure 1**

18  
19 442 *Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks,*  
20 443 *respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.*

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22 444 **Figure 2**

23  
24 445 *Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-*  
25 446 *2008 and 2009-2012. Number of weeks: 3,406,615. Number of fetal deaths: 3,770. Lower part the*  
26 447 *same in a semi-logarithmic plot*

27  
28 448 **Figure 3**

29  
30 449 *Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period*  
31 450 *2000-2012 and after adjustment for different confounders\*. Lower part the same in a semi-*  
32 451 *logarithmic plot.*

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34 452 **Figure 4**

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36 453 *Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new-born (lower) after 37 and*  
37 454 *40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95%*  
38 455 *confidence limits indicated,*

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40 456 **Supplementary online appendix (optional)**

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42 457 **Table 1S**

43 458 *Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-*  
44 459 *2012.*

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Table 1

Rates\* of born and stillborn in and from different gestational weeks  
and periods in Denmark 2000-2012.

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
<b>Number of born and stillborn infants</b>								
<b>Born (n)</b>	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
<b>Stillborn (n)</b>	835	915	992	539	489	2,742	1,028	3,770
<b>Stillbirths per 1,000 ongoing pregnancy weeks (prospective risk of stillbirth)</b>								
<b>&lt;37</b>	0.22	0.20	0.21	0.17	0.17	0.21	0.17	0.20
<b>37+0-6</b>	0.39	0.46	0.39	0.27	0.23	0.41	0.25	0.37
<b>38+0-6</b>	0.36	0.51	0.46	0.41	0.34	0.44	0.38	0.42
<b>39+0-6</b>	0.56	0.54	0.63	0.44	0.46	0.57	0.45	0.54
<b>40+0-6</b>	1.20	0.95	0.97	0.93	0.76	1.04	0.85	0.98
<b>41+0-6</b>	2.29	2.40	1.73	1.35	0.54	2.15	0.98	1.82
<b>42+</b>	15.55	6.09	11.16	6.60	7.83	11.60	6.96	10.86
<b>Total</b>	0.35	0.29	0.28	0.23	0.21	0.30	0.22	0.27
<b>From 37 w</b>	0.70	0.67	0.63	0.50	0.41	0.67	0.46	0.61
<b>From 40 w</b>	1.84	1.43	1.30	1.10	0.74	1.54	0.93	1.36
<b>From 41 w</b>	3.12	2.46	2.09	1.51	0.69	2.60	1.14	2.21
<b>Stillborn per 1.000 new-born</b>								
<b>From 37 w</b>	2.39	2.21	2.07	1.68	1.36	2.23	1.52	2.02
<b>From 40 w</b>	2.11	1.59	1.41	1.20	0.77	1.71	0.99	1.50
<b>From 41 w</b>	2.43	1.82	1.46	1.04	0.41	1.93	0.73	1.57
<b>From 42 w</b>	3.16	1.05	1.55	0.82	0.95	2.04	0.86	1.79

\*) Absolute numbers given in supplementary appendix Table 1S.

Table 2

*Characteristics of women giving birth at term and  
relative risk of stillbirth by time.*

	2000-02	2003-05	2006-08	2009-10	2011-12
<b>Mean age</b>	30.1	30.6	30.8	30.9	30.9
<b>Mother ≥40 yrs</b>	3,584	4,366	5,436	3,740	3,777
<b>% ≥40 years</b>	2.0	2.4	3.0	3.2	3.5
<b>BMI recorded (n)</b>	na	112,635	167,962	111,972	106,201
<b>Mean BMI</b>	na	24.1	24.2	24.3	24.4
<b>BMI &gt;25</b>	na	36,076	54,903	37,616	36,528
<b>% BMI &gt;25</b>	na	32.0	32.7	33.6	34.4
<b>BMI &gt;30</b>	na	12,480	19,683	13,946	13,720
<b>% BMI &gt;30</b>	na	11.1	11.7	12.5	12.9
<b>BMI &gt;35</b>	na	4,032	6,813	4,880	4,689
<b>% BMI &gt;35</b>	na	3.6	4.1	4.4	4.4
<b>Smoker</b>	37,540	30,782	25,656	14,891	12,527
<b>% smokers</b>	20.5	17.1	14.2	12.6	11.5
<b>Multiple pregnancies</b>	4,353	4,617	4,727	3,116	2,747
<b>% multiples</b>	2.4	2.6	2.6	2.6	2.5
<b>Stillborn multiples</b>	51	111	61	40	29
<b>% stillborn multiples</b>	1.2	2.4	1.3	1.3	1.1
<b>Para 0</b>	78,718	77,231	77,685	51,675	48,584
<b>% Para 0</b>	43.0	42.9	43.0	43.8	44.5
<b>Regression analysis</b>	<b>Hazard ratio<sup>§</sup> of stillborn (2000-2002 reference)</b>				
<b>Crude<sup>#</sup></b>	1	0.95	0.89	0.72	0.59
<b>Adjusted for GA<sup>¶</sup></b>	1	1.02	0.98	0.78	0.65
95% confidence intervals		0.89-1.17	0.85-1.12	0.66-0.92	0.53-0.78
<b>Adjusted exopt, Plurality<sup>**</sup></b>	1	1.03	0.89	0.73	0.62
95% confidence intervals		0.90-1.18	0.78-1.03	0.61-0.86	0.52-0.75
<b>Fully Adjusted<sup>**¶</sup></b>	1	1.07	0.96	0.78	0.69
95% confidence intervals		0.93-1.23	0.83-1.11	0.65-0.92	0.57-0.83

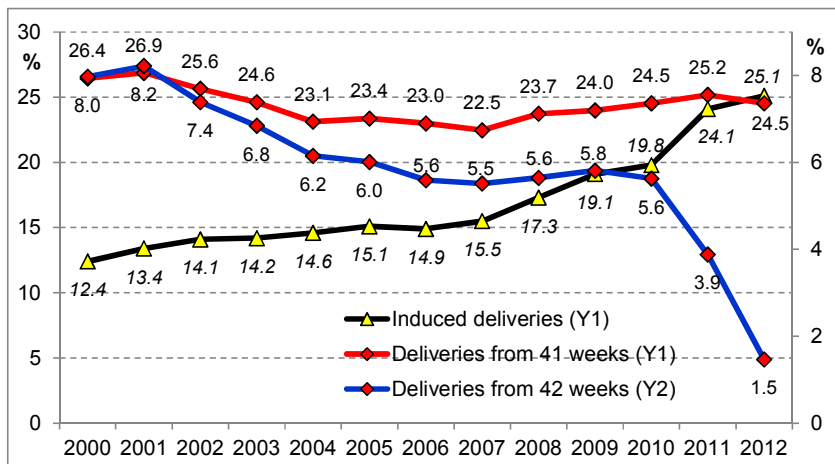
\*) Adjusted only for age, smoking, and parity \*\*\*) Additionally adjusted for plurality

§) Hazard ratios by cox regression. The crude estimates were calculated by logistic regression, and the risk estimates were odds ratios

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**Figure 1**

Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks, respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.



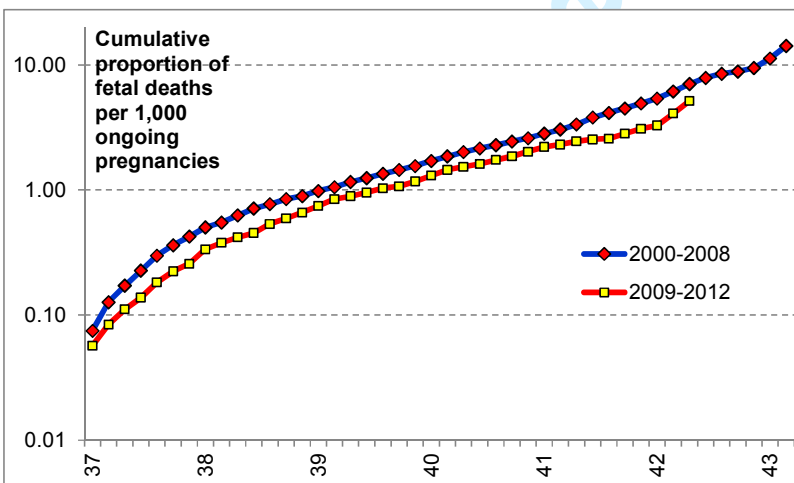
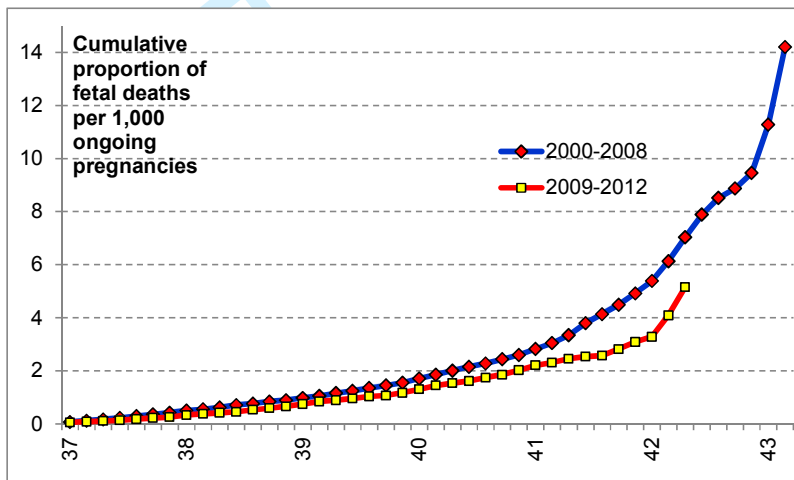
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Figure 2

Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-2008 and 2009-2012.

Number of weeks: 3,406,615, Number of fetal deaths: 3,770.

Lower part the same in a semi-logarithmic plot.

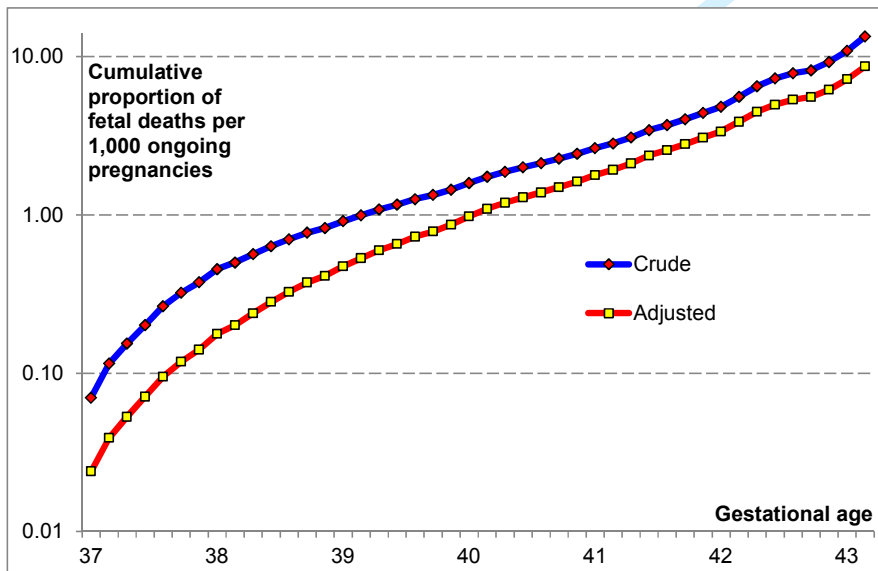
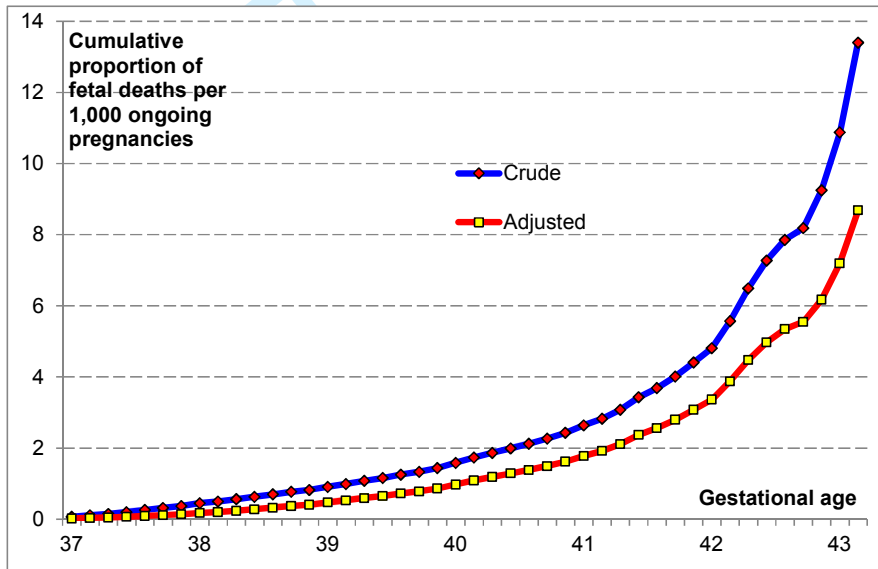


**Figure 3**

Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period 2000-2012 and after adjustment for different confounders\*.

Number of weeks: 3,406,615. Number of fetal deaths: 3,770.

Lower part the same in a semi-logarithmic plot

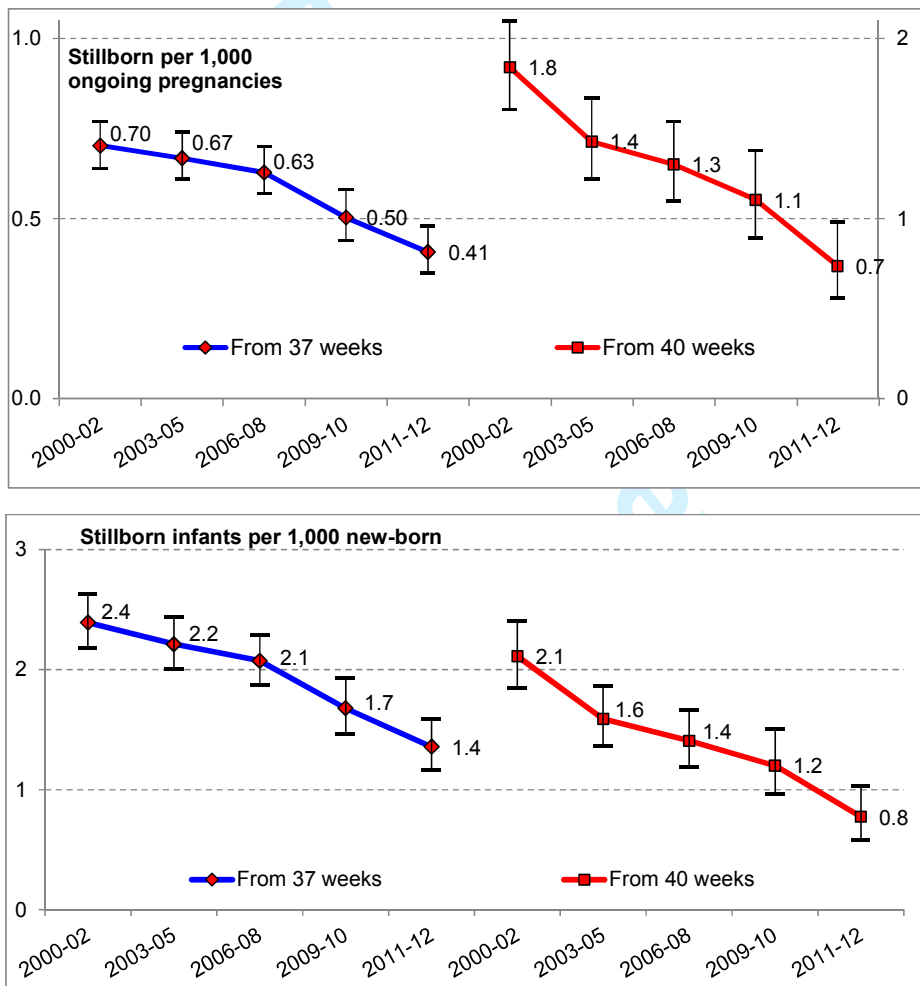


\*) Adjusted for age, calendar year, parity, plurality, and smoking

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**Figure 4**

Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new born (lower) after 37 and 40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95% confidence limits indicated.



## Online supplement

Table 1S

*Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.*

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
<b>New-born</b>								
<b>&lt;37</b>	14,127	14,806	15,171	9,212	8,693	44,104	17,905	62,009
<b>37+0-6</b>	10,964	12,129	11,533	7,066	6,369	34,626	13,435	48,061
<b>38+0-6</b>	24,807	27,976	28,521	17,757	16,121	81,304	33,878	115,182
<b>39+0-6</b>	42,212	42,303	42,711	27,282	24,523	127,226	51,805	179,031
<b>40+0-6</b>	53,193	51,410	52,874	35,005	32,777	157,477	67,782	225,259
<b>41+0-6</b>	36,415	33,813	34,267	23,570	26,106	104,495	49,676	154,171
<b>42+</b>	15,504	12,337	10,946	7,273	3,162	38,787	10,435	49,222
<b>Total</b>	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
<b>37+</b>	183,095	179,968	180,852	117,953	109,058	543,915	227,011	770,926
<b>40+</b>	105,112	97,560	98,087	65,848	62,045	300,759	127,893	428,652
<b>41+</b>	51,919	46,150	45,213	30,843	29,268	143,282	60,111	203,393
<b>Number of stillborn infants</b>								
<b>&lt;37</b>	397	517	617	341	341	1,531	682	2,213
<b>37+0-6</b>	72	83	70	32	25	225	57	282
<b>38+0-6</b>	62	85	78	46	35	225	81	306
<b>39+0-6</b>	82	75	89	41	40	246	81	327
<b>40+0-6</b>	96	71	72	47	36	239	83	322
<b>41+0-6</b>	77	71	49	26	9	197	35	232
<b>42+</b>	49	13	17	6	3	79	9	88
<b>Total</b>	835	915	992	539	489	2,742	1,028	3,770
<b>37+</b>	438	398	375	198	148	1211	346	1557
<b>40+</b>	222	155	138	79	48	515	127	642
<b>41+</b>	126	84	66	32	12	276	44	320

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

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract: <i>Line 35</i> (b) Provide in the abstract an informative and balanced summary of what was done and what was found: <i>Line 38-43</i>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported: <i>Line 66-76</i>
Objectives	3	State specific objectives, including any prespecified hypotheses: <i>Line 73-76</i>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper: <i>Page 3 line 79</i>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection: <i>Line 79-80</i>
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up: <i>Line 81-86</i> (b) For matched studies, give matching criteria and number of exposed and unexposed: <i>This study was not matched</i>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable: <i>Line 88-93</i>
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: <i>Line 79-87</i>
Bias	9	Describe any efforts to address potential sources of bias: <i>Line 106-119</i>
Study size	10	Explain how the study size was arrived at: <i>Line 84</i>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: <i>Line 88-119</i>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding: <i>Line 106-119</i> (b) Describe any methods used to examine subgroups and interactions: <i>116-119</i> (c) Explain how missing data were addressed: <i>Line 94-98</i> (d) If applicable, explain how loss to follow-up was addressed: <i>Line 94-98</i> (e) Describe any sensitivity analyses: <i>Line 119</i>
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals included in the study, completing follow-up, and analysed: <i>Line 94-98, 123-127</i> (b) Give reasons for non-participation at each stage: <i>Not relevant</i> (c) Consider use of a flow diagram: <i>Not relevant in this case</i>
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders: <i>Table 1</i> (b) Indicate number of participants with missing data for each variable of interest: <i>Line 94-98</i> (c) Summarise follow-up time (eg, average and total amount): <i>Not relevant</i>
Outcome data	15*	Report numbers of outcome events or summary measures over time: <i>Table 1, Table 2 and Table 1S, Line 133-152</i>



1 2 3 4 5 6 7 8 9 10 11	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: <i>Fig. 2 and Fig. 3</i> (b) Report category boundaries when continuous variables were categorized: <i>Line Table 1</i> (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period: <i>Line 144-152, 191-193</i>
12 13 14	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses: <i>Line 206-207</i>
15	<b>Discussion</b>		
16	Key results	18	Summarise key results with reference to study objectives: <i>Line 211-2123</i>
17 18 19 20 21 22 23	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. <i>Line 280-283</i>
24 25 26	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. <i>Line 252-261</i>
27	Generalisability	21	Discuss the generalisability (external validity) of the study results: <i>Line 239-242</i>
28	<b>Other information</b>		
29 30 31 32	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: <i>Line 299-306</i>

\*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>.

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**Adverse perinatal outcomes following an earlier post-term  
labour induction policy: a historical cohort study.**

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*Short title: Perinatal outcomes with labour induction at 41+3-5 weeks (57 characters).*

1  
2  
3 28 **Abstract**

4  
5 29 **Objective.** To assess the changes in adverse perinatal outcomes in children born from 37  
6  
7 30 weeks' gestation after implementing an earlier (41+3-5) post-term labour induction practice.

8  
9 31 **Design.** Register-based cohort study.

10  
11 32 **Setting.** Denmark, 2000-12.

12  
13 33 **Population.** Newborns from 37 weeks' gestation.

14  
15 34 **Methods.** Hazard ratios (HRs) of adverse perinatal outcomes were estimated using a Cox  
16  
17 35 regression analysis with gestational age as the underlying time, and adjusted for maternal  
18  
19 36 age, parity, plurality, smoking, and body mass index.

20  
21 37 **Outcome measures.** Adverse perinatal outcomes.

22  
23 38 **Results.** 770,926 infants were included in total. The use of labour induction increased from  
24  
25 39 9.7% in 2000-02 to 22.5% in 2011-12. From 2003-05 to 2011-12, the risk of umbilical cord  
26  
27 40 pH <7.0 decreased by 23% (HR 0.77, 95% confidence interval (CI) 0.67-0.89), and the  
28  
29 41 adjusted risk of Apgar score <7 at five minutes was stable. The risk of admission to neonatal  
30  
31 42 intensive care units increased by 56% (HR 1.56, 95% CI 1.47-1.66), whereas the risk of  
32  
33 43 neonatal deaths decreased by 44% (HR 0.56, 95% CI 0.45-0.70). The risk of cerebral palsy  
34  
35 44 was reduced by 26% (HR 0.74, 95% CI 0.60-0.90) from 2000-02 to 2009-10. The proportion  
36  
37 45 of infants born with fetal weight  $\geq$ 4500 grams decreased by one-third (HR 0.68, 95% CI  
38  
39 46 0.65-0.71). However, the risk of shoulder dystocia increased by 32% (HR 1.32, 95% CI 1.21-  
40  
41 47 1.44), and the risk of peripheral nerve injuries was reduced by 43% (HR 0.57, 95% CI 0.45-  
42  
43 48 0.73).

44  
45 49 **Conclusion.** The results suggest an overall improvement in perinatal outcomes as a result  
46  
47 50 of a more proactive approach to post-term labour induction.

48  
49 51 **Keywords.** Asphyxia, birth induction, misoprostol, perinatal outcome

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## 55 Introduction

56 In 2008, the National Institute for Health and Clinical Excellence published a guideline on  
57 post-term labour induction, stating that uncomplicated pregnancies should be induced in  
58 weeks 41-42; this guideline was followed by a similar practice bulletin issued by the  
59 American Congress of Obstetricians and Gynaecologists in 2009.<sup>1,2</sup> The same year, the  
60 national Danish guidelines were changed accordingly to recommend induction at week  
61 41+3-5 for low-risk pregnant women and even earlier for high-risk pregnant women (with a  
62 body mass index >30, age ≥40 years or certain medical conditions) even earlier.<sup>3</sup> The goal  
63 was to ensure delivery before 42 weeks.<sup>4</sup> In Denmark, no uncomplicated pregnancies are  
64 induced before gestational week 41+3-5, unless there is a clear medical indication for labour  
65 induction. This guideline on prolonged pregnancy led to an increase in post-term labour  
66 induction, which was followed by a significant reduction in the number of stillborn infants at  
67 term with no increase in operative intervention.<sup>5</sup> Studies have also suggested that maternal  
68 morbidity may be improved by a more proactive post-term induction practice.<sup>6</sup> However,  
69 recent meta-analyses found only a few studies that addressed the impact of different  
70 induction practices on neonatal mortality and morbidity;<sup>4, 7, 8</sup> thus, further studies are  
71 required.<sup>9</sup>

72 When examining rare outcomes, such as neonatal death, it is often difficult to achieve  
73 statistically significant correlations in clinical trials.<sup>10</sup> Under such circumstances, large  
74 observational studies may provide useful information.<sup>11, 12</sup>

75 This study aimed to investigate the national changes in different adverse perinatal outcomes  
76 over a period, during which a more proactive approach to post-term labour induction was  
77 implemented.

78

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81

## 82 **Methods**

### 83 *Design and setting*

84 This historical cohort study included all newborns in Denmark delivered from January 1,  
85 2000 to December 31, 2012. To reduce the random year-to-year variation, the 13-year study  
86 period was subdivided into five intervals of three, three, three, two and two years.

87 Data were retrieved in October 2013 from the Danish National Health Register and the  
88 Medical Birth Register, which contains information on all deliveries in Denmark since 1973.<sup>13</sup>  
89 Approval was obtained from the Danish Data Protection Agency (J.no: 2013-41-2063) and  
90 the National Board of Health (J.no. FSEID 00000579). According to the Danish Research  
91 Ethics Committee Law (§ 8, section 3), ethical approval is not required for register-based  
92 studies in Denmark.

### 93 *Participants*

94 Infants born from 37 gestational weeks were included, irrespective of maternal parity or  
95 plurality, because Cox regression analyses demonstrated only limited confounding due to  
96 these factors. As the focus of this study was post-term labour induction, it seemed logical to  
97 set the limit for inclusion at >40 gestational weeks. After careful consideration, however, the  
98 limit was set at >37 gestational weeks to avoid excluding the outcomes of high-risk  
99 pregnancies, which are often induced before 40 weeks. Gestational age was generally  
100 calculated based on first-trimester ultrasound examinations. For the few women who did not  
101 attend this routine offer to all pregnant women in Denmark, the date of their last menstrual  
102 period was used.

103 Based on diagnostic and surgical codes, the study population was subdivided according to  
104 the intentional mode of delivery as follows: a) an induction of labour cohort, b) a planned  
105 spontaneous vaginal delivery cohort, and c) an elective Caesarean section cohort. The  
106 specific codes identifying the cohorts are listed in the supplementary appendix (Table 1S).

107

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2  
3 108 *Outcomes*  
4

5 109 Eight outcomes were defined based on different criteria or clusters of diagnosis codes from  
6  
7 110 the International Classification of Diseases (ICD 10). The outcomes were categorised into  
8  
9 111 three groups (Appendix, Table 2S): asphyxia indicators (umbilical cord pH <7.0 and Apgar  
10  
11 112 score <7 at five minutes), potential manifestations of asphyxia (admission to neonatal  
12  
13 113 intensive care units within 28 days after birth, neonatal death, and cerebral palsy), and  
14  
15 114 prevention of macrosomia (fetal weight  $\geq$ 4500 grams, shoulder dystocia, and peripheral  
16  
17 115 nerve injury). A neonate could potentially have more than one outcome.

18  
19  
20 116 Prior to 2003, umbilical cord pH was not routinely recorded in the register. In this study we  
21  
22 117 intended to use arterial pH, but in the few cases where this information was not available,  
23  
24 118 either venous or unspecified pH was used. All pH values not in the range of 6.6-7.9 were  
25  
26 119 considered invalid, and were consequently excluded from the analysis.

27  
28  
29 120 There is often a long latency from birth until cerebral palsy is diagnosed. Therefore, a follow-  
30  
31 121 up time of three years was used, and the most recent years, 2011 and 2012, were excluded  
32  
33 122 from the analysis of this specific outcome.

34  
35 123 In accordance with the World Health Organisation (WHO), neonatal death was defined as  
36  
37 124 death within 28 days after birth.<sup>14</sup>

38  
39  
40 125 Shoulder dystocia and nerve injury were only assessed in vaginal deliveries.

41  
42 126 *Potential confounders*  
43

44  
45 127 To describe the timing of potential confounders, we gathered information on maternal age,  
46  
47 128 parity, plurality, smoking, and body mass index. The definitions are presented in the  
48  
49 129 appendix (Table 3S).

50  
51 130 *Calculations*  
52

53  
54 131 To calculate the crude and adjusted hazard ratios (HRs), Cox regression analyses were  
55  
56 132 performed with gestational age as the underlying time scale. The period from 2000-02 was  
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2  
3 133 used as the reference period. Adjustments were made for maternal age, parity, plurality, and  
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5 134 smoking. Because body mass index was not registered until 2004, we assessed the  
6  
7 135 influence of body mass index in a sub-analysis that was restricted to the years 2004-12.  
8  
9 136 Because the results changed by less than 5%, body mass index was not included in the  
10  
11 137 main analyses.

12  
13 138 Incidence rates in the total population and within the three delivery cohorts were calculated.  
14  
15 139 A chi-square test was used to analyse differences in incidence rates, with a p-value of less  
16  
17 140 than 0.05 considered significant.  
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20 141

## 21 22 142 **Results**

23  
24  
25 143 During the 13-year study period, a total of 832,935 children were born in Denmark. Of these,  
26  
27 144 770,926 children (92.6%) were born after 37 gestational weeks, constituting the study group.  
28  
29 145 Within the group, 104,107 (13.5%) children were born after labour induction, 602,219  
30  
31 146 (78.1%) were born after planned vaginal delivery, and 64,600 (8.4%) were born after elective  
32  
33 147 Caesarean section (Table 1).

34  
35  
36 148 The use of medical induction of labour within our study group (>37 weeks) increased from  
37  
38 149 9.1% in 2000 to 26.0% in 2012 ( $p<0.001$ ) (Figure 1). A steep increase was observed,  
39  
40 150 especially in 2010-11. Correspondingly, the percentage of pregnancies that continued  
41  
42 151 beyond 42 gestational weeks decreased from 8.0% in 2000 to 1.5% in 2012 ( $p<0.001$ )  
43  
44 152 (Figure 1).

45  
46  
47 153 The percentage of women with planned spontaneous vaginal delivery decreased linearly  
48  
49 154 from 84.5% in 2000-02 to 67.7% in 2011-12 ( $p<0.001$ ), whereas the elective Caesarean  
50  
51 155 section rate increased from 5.9% to 9.8% ( $p<0.001$ ) (Table 1).

## 52 53 156 *Asphyxia indicators*

54  
55  
56 157 The adjusted risk of umbilical cord pH <7.0 decreased by 23% (HR 0.77, 95% confidence  
57  
58 158 interval (CI) 0.67-0.89) when comparing 2003-04 with 2011-12 (Table 1 and Figure 2).  
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3 159 Subdivision into the three delivery cohorts revealed that the frequency of low pH decreased  
4  
5 160 significantly in all cohorts and was similar in the induced and spontaneous vaginal delivery  
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7 161 cohorts in 2011-12 at 4.9‰ (Table 2).

8  
9 162 Except from the changes in the crude incidence rate of Apgar scores <7 at five minutes  
10  
11 163 (<7/5) within the total population, all other results indicated that the rate of Apgar scores <7  
12  
13 164 was stable over time and across all study groups (Table 1, Figure 2, and Table 2).

#### 15 165 *Potential manifestations of asphyxia*

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17  
18 166 Throughout the study period, the adjusted risk of admission to a neonatal intensive care unit  
19  
20 167 increased by 56% (HR 1.56, 95% CI 1.47-1.66) (Table 1, and Figure 2). In the three cohorts,  
21  
22 168 admission rates were stable in the induced labour cohort, whereas the incidence rates of  
23  
24 169 children born after planned vaginal delivery and elective Caesarean section increased  
25  
26 170 significantly (Table 2).

27  
28  
29 171 The adjusted risk of neonatal death was almost halved (HR 0.56, 95% CI 0.45-0.70) (Table  
30  
31 172 1 and Figure 2). Although significant decreases were observed in all three cohorts, the  
32  
33 173 steepest decrease in risk was observed among children born after elective Caesarean  
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35 174 section, from 2.7‰ in 2000-02 to 1.0‰ in 2011-12 ( $p<0.001$ ) (Table 2).

36  
37  
38 175 The adjusted risk of cerebral palsy decreased by 26% (HR 0.74, 95% CI 0.60-0.90) from  
39  
40 176 2000-02 to 2009-10 (Table 1 and Figure 2). Only the planned vaginal delivery group  
41  
42 177 experienced a significant reduction in incidence rate from 1.6‰ in 2000-02 to 1.1‰ in 2009-  
43  
44 178 10 ( $p=0.003$ ) (Table 2).

#### 45 179 *Prevention of macrosomia*

46  
47  
48 180 Throughout the study period, the adjusted risk of birth weight  $\geq 4500$  grams decreased by  
49  
50 181 one-third (HR 0.68, 95% CI 0.65-0.71), from 4.2% in 2000-02 to 2.8% in 2011-12 ( $p<0.001$ )  
51  
52 182 (Table 1, Table 2 and Figure 3).

53  
54  
55 183 Despite the presence of fewer children with macrosomia, the risk of shoulder dystocia  
56  
57 184 increased by 32% (HR 1.32, 95 % CI 1.21-1.44) during the same period (Table 1 and Figure  
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3 185 3). In contrast, the adjusted risk of peripheral nerve injury decreased by 43% overall (HR  
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5 186 0.57, 95% CI 0.45-0.73), and decreases were observed in both vaginal delivery cohorts  
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7 187 (Table 1 and Figure 3).  
8

9  
10 188 *Time trends in potential confounders*

11  
12 189 Mean maternal age increased linearly from 30.1 years in 2000-02 to 30.9 years in 2010-11  
13  
14 190 (Appendix, Table 4S) but has stagnated since then. The prevalence of pregnant women >40  
15  
16 191 years of age increased considerably from 2.0% in 2000-02 to 3.5% in 2011-12 ( $p<0.001$ )  
17  
18 192 (Appendix, Table 4S).  
19

20  
21 193 The prevalence of smokers in the study population was almost halved from 21.1% to 11.6%  
22  
23 194 ( $p<0.001$ ) (Appendix, Table 4S). However, Cox regression analyses with and without  
24  
25 195 adjustments for smoking demonstrated, that this factor did not explain the reported  
26  
27 196 decreases in perinatal outcomes.  
28

29  
30 197 Body mass index was relatively constant, with a mean of 24.3 kg/m<sup>2</sup> (Appendix, Table 4S).  
31  
32 198 However, the prevalence of severely obese pregnant women (body mass index >35 kg/m<sup>2</sup>)  
33  
34 199 increased from 3.6% in 2003-05 to 4.4% in 2011-12 ( $p<0.001$ ) (Appendix, Table 4S).  
35

36  
37 200 Although statistically significant, the incidence rate of multiple pregnancies changed only  
38  
39 201 minimally, ranging from 2.4% to 2.6% ( $p<0.001$ ) (Appendix, Table 4S). The proportion of  
40  
41 202 nulliparous women increased slightly from 43.0% in 2000-03 to 44.5% in 2011-12 ( $p<0.001$ )  
42  
43 203 (Appendix, Table 4S).  
44

45 204

46  
47 205 **Discussion**

48  
49 206 *Main findings*

50  
51  
52 207 More than one quarter of Danish women who are pregnant beyond 37 weeks now  
53  
54 208 experience induced labour, and our recent study demonstrated a simultaneous reduction in  
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56 209 stillbirths.<sup>5</sup>  
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3 210 The results of the present study demonstrate that the reduction in the number of stillborn  
4  
5 211 infants was not at the expense of increased perinatal morbidity or neonatal mortality. On the  
6  
7 212 contrary, we detected significant reductions in newborn asphyxia, neonatal mortality,  
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9 213 newborn macrosomia, and peripheral nerve injuries. The incidence rate of admission to  
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11 214 neonatal intensive care units increased, but only in neonates born after planned vaginal  
12  
13 215 delivery or elective Caesarean section and not in neonates born after labour induction.

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15 216 Consistent with the decrease in asphyxia, the incidence rate of cerebral palsy decreased,  
16  
17 217 although this reduction was only statistically significant in the planned vaginal delivery  
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19 218 cohort.

#### 219 *Strengths and limitations*

22  
23  
24 220 The unique personal identity number that every individual in the Nordic countries carries is  
25  
26 221 the cornerstone of the Nordic medical registers. The Nordic registry's tradition of gathering  
27  
28 222 data for decades offers unique possibilities for research that are difficult to find anywhere  
29  
30 223 else in the world.<sup>13</sup> These data enable researchers to include a broad and unselected  
31  
32 224 sample of individuals, to achieve high external validity, which is one of the strengths of this  
33  
34 225 study. However, one of the limitations of register-based studies such as ours is their  
35  
36 226 observational and retrospective design, which makes it difficult to effectively account for all  
37  
38 227 confounders. Moreover, it is difficult to ensure that the data reporting is constant throughout  
39  
40 228 the study period.

#### 41 229 *Interpretation*

42  
43  
44 230 Before interpreting the results, it is important to remember that the reason for labour  
45  
46 231 induction often involves some type of pregnancy complication and is not necessarily limited  
47  
48 232 to post-term pregnancy. Secondly, it is essential to keep in mind that, due to more proactive  
49  
50 233 induction practices, the induced group has become gradually less burdened by pathological  
51  
52 234 pregnancies, as more women are now induced with prolonged pregnancy as the only reason  
53  
54 235 for labour induction. The size of the planned vaginal delivery group has consequently been  
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3 236 reduced, and includes less overborne and fewer high-risk deliveries. To summarise,  
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5 237 overborne pregnant women are generally transferred from the planned vaginal delivery  
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7 238 group, where they constitute a high-risk group, to the labour induction group, where they  
8  
9 239 constitute a low-risk group compared to the rest of the women in the induction group.  
10  
11 240 Hypothetically, if the decrease in adverse perinatal outcomes in the planned vaginal delivery  
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13 241 group were associated with an increase in adverse outcomes in the induced delivery group,  
14  
15 242 then an earlier induction practice would be questionable. However, simultaneous reductions  
16  
17 243 in adverse perinatal outcomes in both the labour induction group and the vaginal delivery  
18  
19 244 group would support a more proactive induction practice.  
20  
21 245 The stable risk of Apgar scores <7 at 5 minutes corresponds well with the findings of earlier  
22  
23 246 studies,<sup>4, 15, 16</sup> including a thorough Cochrane review from 2012, which suggested no  
24  
25 247 increase in newborn asphyxia with an earlier birth induction practice.<sup>8</sup> Although the decrease  
26  
27 248 in asphyxia may have been reflected in fewer Apgar scores <7 at 5 minutes, this outcome  
28  
29 249 was also influenced by a range of other factors, such as drug use, trauma, congenital  
30  
31 250 abnormalities, infections, and hypervolemia, problems that have not been resolved by an  
32  
33 251 earlier labour induction policy.<sup>17</sup> Because umbilical cord pH is more objective than Apgar  
34  
35 252 score assessments,<sup>18</sup> cord pH is our preferred indicator of asphyxia in newborns.<sup>19</sup>  
36  
37  
38 253 The increased risk of admission to neonatal intensive care units among children born after  
39  
40 254 planned vaginal delivery is worrisome. A lowered threshold for transfer to such units most  
41  
42 255 likely explains this increase, as a similar increase was observed in the elective Caesarean  
43  
44 256 section group. Furthermore, the increase in referrals to neonatal units was associated with a  
45  
46 257 substantial reduction in the risk of neonatal deaths. Earlier studies have encountered  
47  
48 258 difficulties achieving sufficient statistical power to demonstrate any difference between  
49  
50 259 children born after labour induction and those born according to expectant management,<sup>4, 8</sup>  
51  
52 260 but recent studies suggest that labour induction significantly reduces perinatal mortality,  
53  
54 261 which agrees with our results.<sup>7, 20</sup> However, the reduction in neonatal deaths was  
55  
56 262 undoubtedly also influenced by improved neonatal care throughout the study period.<sup>21, 22</sup>  
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3 263 The reduction in cerebral palsy corroborates with the decrease in asphyxia. Through the last  
4  
5 264 decade, our capacity to more precisely diagnose neurological pathologies has improved,  
6  
7 265 especially with the increased use of magnetic resonance imaging.<sup>23</sup> In addition, the  
8  
9 266 treatment regimen has also improved, resulting in enhanced neuroprotection.<sup>24, 25</sup> For  
10  
11 267 example, since 2006, Danish neonatal units have initiated moderate hypothermia in cases of  
12  
13 268 severe asphyxia,<sup>26</sup> which has improved the rate of survival without cerebral palsy or other  
14  
15 269 disabilities by 40%.<sup>24, 27</sup>

16  
17 270 The proportion of newborns  $\geq 4500$  grams has increased over the last several decades in  
18  
19 271 Denmark.<sup>28, 29</sup> The proactive induction practice reversed this development. While this  
20  
21 272 improvement was not the primary aim of the post-term labour induction guideline, it  
22  
23 273 constitutes an additional positive side effect.

24  
25  
26 274 In theory, the reduction in vaginal deliveries of macrosomic children should reduce the risk of  
27  
28 275 shoulder dystocia.<sup>30-33</sup> However, we detected increases in shoulder dystocia in both vaginal  
29  
30 276 delivery cohorts. The total incidence rate of shoulder dystocia of 0.8% in 2006-08 is still low  
31  
32 277 compared to a 2006 American study, which reported an incidence rate of shoulder dystocia  
33  
34 278 of 1.6% in 2006.<sup>34</sup> Thus, shoulder dystocia may previously have been underreported, an  
35  
36 279 explanation that is further supported by the reduction in peripheral nerve injuries. Recently,  
37  
38 280 many obstetrical units in Denmark have focused on the management of shoulder dystocia,  
39  
40 281 resulting in more thorough diagnosis and training of medical staff. This increased attention  
41  
42 282 could explain why more cases of shoulder dystocia are being diagnosed, even though fewer  
43  
44 283 children suffer from nerve injuries.

45  
46  
47 284 Children born after labour induction demonstrated the highest incidence rates of the majority  
48  
49 285 of the adverse outcomes. If this effect were a consequence of the intervention itself, one  
50  
51 286 would expect more complications following the increased use of labour induction. However,  
52  
53 287 most adverse outcomes actually decreased in frequency with the increased induction rate.  
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55 288 This disparity suggests that the higher incidence rates in the labour induction cohort are a  
56  
57 289 consequence of selection bias, with high-risk pregnant women being induced more often  
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3 290 than women awaiting spontaneous delivery.  
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5 291 However, the improved perinatal outcomes might also be influenced by other factors not  
6  
7 292 related to labour induction. Awareness of the dangers related to smoking has grown,<sup>35</sup>  
8  
9 293 explaining the significant reduction in pregnant smokers; this reduction contributed  
10  
11 294 significantly to the decrease in stillbirths but only marginally contributed to reductions in the  
12  
13 295 perinatal outcomes described in this study.  
14

15  
16 296 The increased maternal age, greater nulliparity, and higher body mass index indicated that  
17  
18 297 more women were at risk according to time in our study population, which suggests that the  
19  
20 298 crude results reported have underestimated the positive effect of labour induction.<sup>36</sup>  
21  
22 299 However, adjusting for these factors only minimally changed the results (Table 1).  
23

24  
25 300 *Conclusion*  
26

27 301 This study assessed the changes in different perinatal outcomes over a decade during which  
28  
29 302 the management of post-term pregnancies changed considerably. The results suggest an  
30  
31 303 overall improvement in perinatal outcomes in children born from 37 weeks' gestation.  
32  
33 304 Although smoking, maternal age and parity changed significantly over our study period,  
34  
35 305 adjusting for these factors did not change the estimates substantially.  
36

37  
38 306 Our results are in accordance with earlier studies, but reporting on the effects of an earlier  
39  
40 307 post-term labour induction policy on a national level is unique; such effects have not been  
41  
42 308 previously reported. Labour induction is a simple and inexpensive intervention that can be  
43  
44 309 implemented in countries throughout the world, to improve perinatal outcomes.  
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5  
6 312 **Contribution to authorship**  
7

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9  
10 314 Health Register and The Medical Birth Register. L.S.M, C.W.S, M.H, M.H, and Ø.L analysed the data.  
11  
12 315 M.H, M.H, and Ø.L. wrote the manuscript. All authors revised the manuscript and accepted the final  
13  
14 316 version. Morten Hedegaard is the guarantor.

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21  
22 320 **Disclosure of interests**  
23

24  
25 321 All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf)  
26  
27 322 (available on request from the corresponding author) and declare that Ø.L. within the last three years  
28  
29 323 received honoraria for speeches in pharmacoepidemiological issues. M.H, M.H, C.W.S and L.S.M did  
30  
31 324 not declare any conflicts.

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440 **Table 1**

441 *Absolute number of individuals in the three delivery cohorts and changes in overall hazard*  
 442 *ratios for adverse perinatal outcomes in children born from 37 weeks' gestation in Denmark*  
 443 *from 2000 to 2012.*

444 *Ratios adjusted for maternal age, smoking, parity and plurality.*

	<b>2000- 2002</b>	<b>2003- 2005</b>	<b>2006- 2008</b>	<b>2009- 2010</b>	<b>2011- 2012</b>
<b>Number of deliveries</b>					
Induced delivery	17,673	20,060	23,066	18,788	24,520
Planned vaginal	15,4681	145,118	140,747	87,829	73,844
Elective Caesarean	10,741	14,790	17,039	11,336	10,694
Total	183,095	179,968	180,852	117,953	109,058
<b>Umbilical cord pH &lt;7.0</b>					
Hazard ratio, crude	-	1.00	0.88	0.71*	0.76*
Hazard ratio, adjusted	-	1.00	0.89	0.72*	0.77*
Confidence intervals, adjusted	-	<i>Reference</i>	<i>0.77-1.02</i>	<i>0.62-0.84</i>	<i>0.67-0.89</i>
<b>Apgar scores &lt;7/5 min</b>					
Hazard ratio, crude	1.00	0.97	0.95	0.95	1.09
Hazard ratio, adjusted	1.00	0.97	0.93	0.93	1.07
Confidence intervals, adjusted	<i>Reference</i>	<i>0.89-1.05</i>	<i>0.86-1.02</i>	<i>0.84-1.02</i>	<i>0.97-1.18</i>
<b>Admission to neonatal intensive care units</b>					
Hazard ratio, crude	1.00	1.10*	1.12*	1.47*	1.60*
Hazard ratio, adjusted	1.00	1.08*	1.11*	1.45*	1.56*
Confidence intervals, adjusted	<i>Reference</i>	<i>1.02-1.14</i>	<i>1.04-1.17</i>	<i>1.37-1.54</i>	<i>1.47-1.66</i>
<b>Neonatal death</b>					
Hazard ratio, crude	1.00	0.81*	0.71*	0.52*	0.54*
Hazard ratio, adjusted	1.00	0.82*	0.69*	0.52*	0.56*
Confidence intervals, adjusted	<i>Reference</i>	<i>0.70-0.96</i>	<i>0.59-0.82</i>	<i>0.42-0.64</i>	<i>0.45-0.70</i>
<b>Cerebral palsy</b>					
Hazard ratio, crude	1.00	0.81*	0.79*	0.74*	-
Hazard ratio, adjusted	1.00	0.81*	0.79*	0.74*	-
Confidence intervals, adjusted	<i>Reference</i>	<i>0.68-0.95</i>	<i>0.66-0.93</i>	<i>0.60-0.90</i>	-
<b>Birth weight ≥4500g</b>					
Hazard ratio, crude	1.00	0.95*	0.81*	0.75*	0.65*
Hazard ratio, adjusted	1.00	0.99	0.85*	0.76*	0.68*
Confidence intervals, adjusted	<i>Reference</i>	<i>0.96-1.03</i>	<i>0.82-0.88</i>	<i>0.73-0.80</i>	<i>0.65-0.71</i>
<b>Shoulder dystocia</b>					
Hazard ratio, crude	1.00	0.97	1.13*	1.34*	1.30*
Hazard ratio, adjusted	1.00	0.99	1.15*	1.36*	1.32*
Confidence intervals, adjusted	<i>Reference</i>	<i>0.91-1.07</i>	<i>1.07-1.25</i>	<i>1.25-1.48</i>	<i>1.21-1.44</i>
<b>Nerve injury</b>					
Hazard ratio, crude	1.00	0.77*	0.73*	0.83	0.59*
Hazard ratio, adjusted	1.00	0.77*	0.71*	0.80*	0.57*
Confidence intervals, adjusted	<i>Reference</i>	<i>0.64-0.93</i>	<i>0.58-0.86</i>	<i>0.65-0.99</i>	<i>0.45-0.73</i>

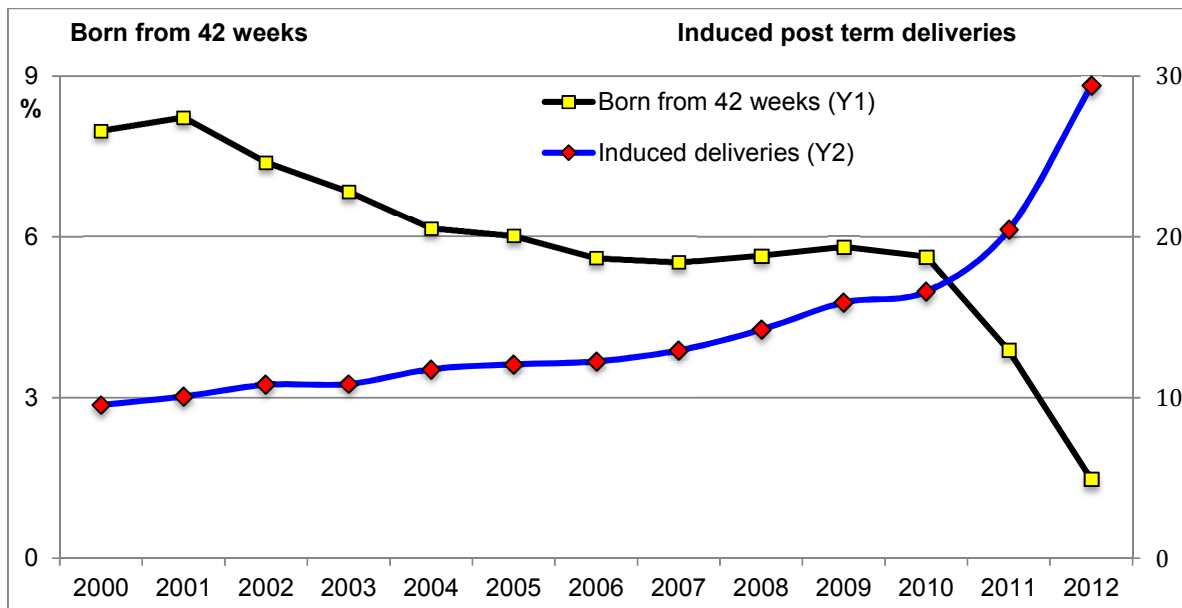
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448 **Figure 1**

449 *Percentages of deliveries induced after 37 weeks and of children born after 42 weeks in*  
 450 *Denmark from 2000-2012.*



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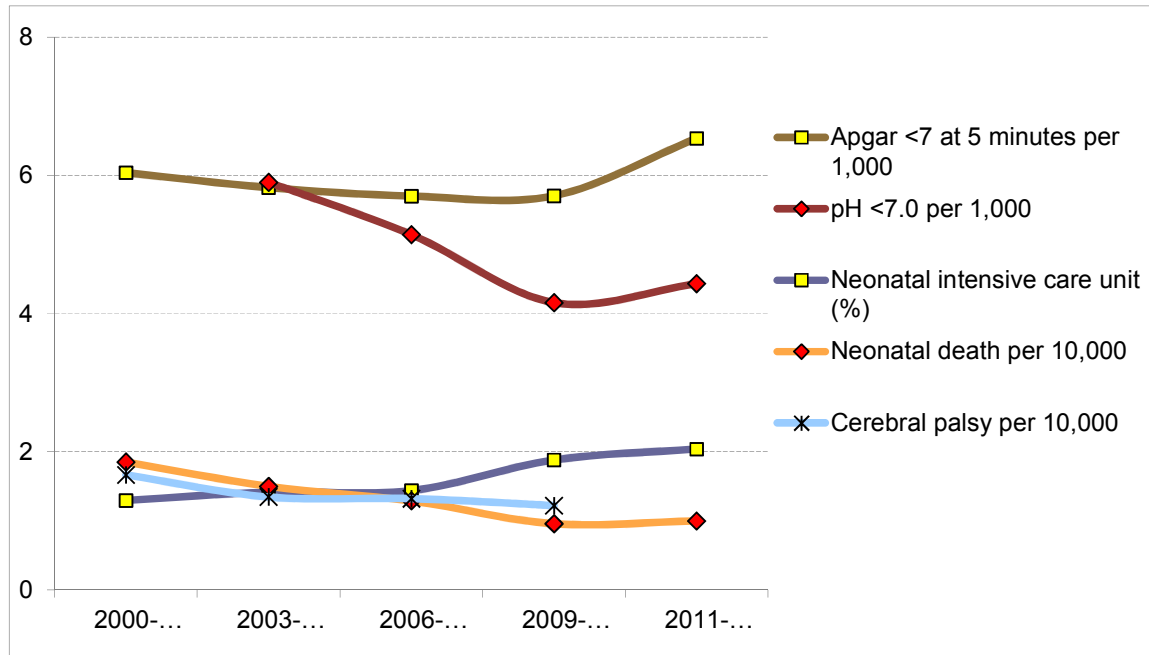
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466 **Figure 2**

467 *Incidence rates of asphyxia indicators and their potential manifestations from 37 weeks'*  
 468 *gestation in Denmark from 2000 to 2012.*

469 *Incidence rates are expressed per 1,000 newborns, unless otherwise specified\*.*



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 471 \*) All results are significant. However, the significance for Apgar scores <7/5 disappears after  
 472 adjusting for potential confounders.  
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491 **Table 2**

492 *Incidence rates of morbidity indicators among children born after a) induced delivery, b)*  
 493 *planned spontaneous vaginal delivery, and c) elective Caesarean section*  
 494 *from 37 weeks' gestation in Denmark from 2000 to 2012.*

495 *Incidence rates are expressed per 1,000 newborns unless otherwise specified*

	2000- 2002	2003- 2005	2006- 2008	2009- 2010	2011- 2012	P- value*	Total
<b>Umbilical cord pH &lt;7.0</b>							
Induced delivery	-	8.0	7.9	5.7	4.9	<0.001	6.3
Planned vaginal	-	6.0	5.1	4.3	4.9	0.002	5.0
Elective Caesarean	-	2.2	1.5	0.4	0.5	0.002	1.0
Total	-	5.9	5.1	4.2	4.4	<0.001	4.8
<b>Apgar scores &lt;7/5 min</b>							
Induced delivery	9.7	7.9	9.3	8.5	8.2	0.259	8.7
Planned vaginal	5.7	5.8	5.4	5.5	6.3	0.153	5.7
Elective Caesarean	4.7	3.4	2.9	3.0	4.5	0.051	3.6
Total	6.0	5.8	5.7	5.7	6.5	0.037	5.9
<b>Admission to neonatal intensive care units (%)</b>							
Induced delivery	2.5	2.6	2.5	2.7	2.6	0.738	2.6
Planned vaginal	1.1	1.2	1.2	1.6	1.7	<0.001	1.3
Elective Caesarean	2.2	1.9	1.7	2.4	2.7	<0.001	2.1
Total	1.3	1.4	1.4	1.9	2.0	<0.001	1.6
<b>Neonatal death</b>							
Induced delivery	2.4	1.5	1.8	1.3	1.0	0.005	1.6
Planned vaginal	1.7	1.5	1.3	0.9	1.0	<0.001	1.4
Elective Caesarean	2.7	1.8	0.7	0.5	1.0	<0.001	1.3
Total	1.9	1.5	1.3	1.0	1.0	<0.001	1.4
<b>Cerebral palsy</b>							
Induced delivery	2.2	1.6	1.3	1.7	-	0.178	1.7
Planned vaginal	1.6	1.2	1.3	1.1	-	0.003	1.4
Elective Caesarean	1.9	2.0	1.6	1.7	-	0.804	2.0
Total	1.7	1.3	1.3	1.2	-	0.005	1.5
<b>Birth weight ≥4500g (%)</b>							
Induced delivery	6.2	5.6	4.6	4.2	3.7	<0.001	4.8
Planned vaginal	4.0	3.8	3.3	3.0	2.5	<0.001	3.5
Elective Caesarean	3.7	3.7	2.9	3.1	2.6	<0.001	3.2
Total	4.2	4.0	3.4	3.2	2.8	<0.001	3.6
<b>Shoulder dystocia</b>							
Induced delivery	8.4	8.8	9.4	11.8	12.1	<0.001	10.2
Planned vaginal	7.1	6.9	8.3	9.7	9.0	<0.001	7.9
Total	6.8	6.6	7.6	9.1	8.8	<0.001	7.6
<b>Nerve injury</b>							
Induced delivery	2.3	1.6	1.5	1.9	1.2	0.076	1.7
Planned vaginal	1.3	1.1	1.0	1.1	0.8	0.003	1.1
Total	1.4	1.1	1.0	1.1	0.8	<0.001	1.1

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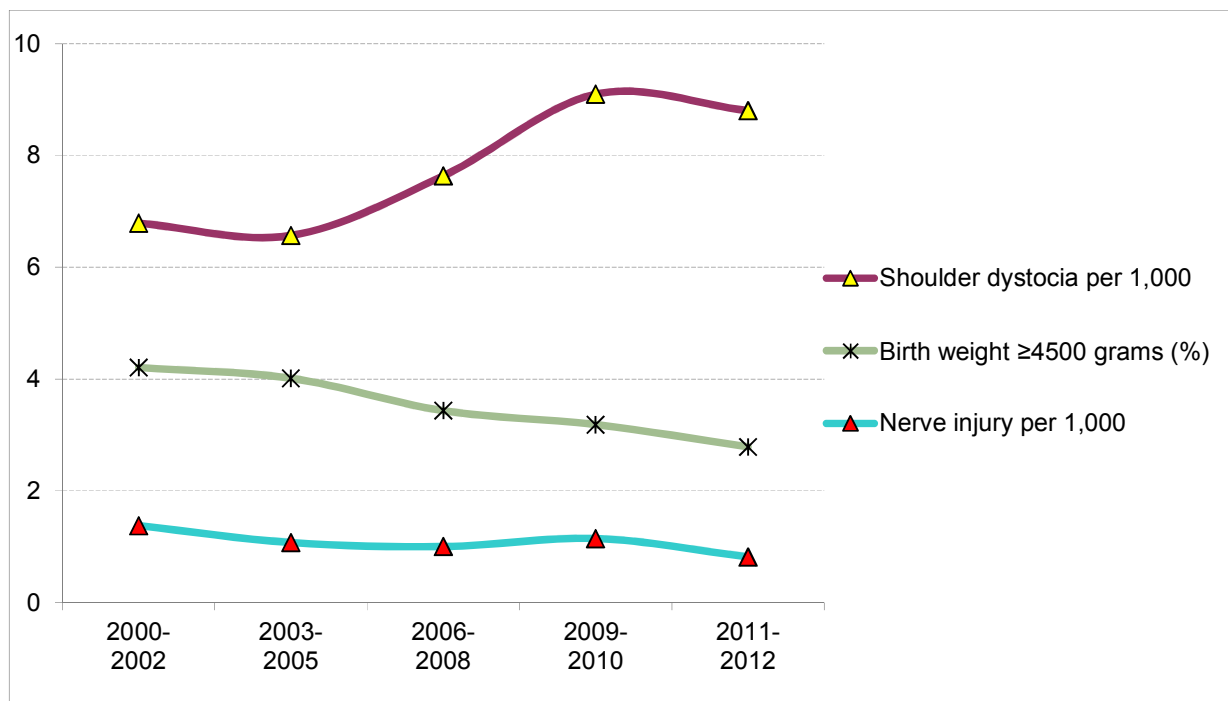
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501 **Figure 3**  
502 *Incidence rates of macrosomia from 37 weeks in Denmark from 2000 to 2012. Incidence*  
503 *rates are expressed per 1,000 newborns, unless otherwise specified\*.*



\*) All results are significant.

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507 **Appendix**508 **Table 1S**

509 *Diagnosis codes defining groups of women who had a) induced delivery, b) planned*  
 510 *spontaneous vaginal delivery, and c) elective Caesarean section in Demark from 2000 to*  
 511 *2012.*

**Medically induced delivery (group A)**Diagnosis-codes

DO499 Duration of pregnancy as main indication for induction of labour.

DO838A Assisted single delivery after induction of labour.

DO848A Assisted multiple deliveries after induction of labour.

Procedure-codes

BKHD2 Labour induced by medications.

BKHD20 Labour induced by prostaglandins.

BKHD20A Labour induced by Misoprostol.

BKHD21 Labour induced by Oxytocin.

**Planned vaginal delivery (Group C)**

Defined as all deliveries minus group A and B.

**Elective Caesarean Section (Group B)**Diagnosis-codes

DO820 Delivery by elective Caesarean Section.

DO842 Multiple deliveries, all by Caesarean Section.

Operational-codes

KMCA11 Elective Caesarean Section in uterine isthmus (from 2000-01)

KMCA10B Elective Caesarean Section in uterine isthmus (from 2001-12)

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523 **Table 2S**524 *Diagnosis codes and other criteria defining eight adverse perinatal outcomes.*

<b>Asphyxia indicators</b>	
<b>Umbilical cord pH &gt; 7.0</b>	
	Arterial, venous or unspecified pH.
<b>Apgar scores &gt;7/5</b>	
	Apgar score less than 7 after five minutes.
<b>Potential manifestations of asphyxia</b>	
<b>Neonatal intensive care unit</b>	
	Admission to neonatal intensive care unit within 28 days after birth.
<b>Neonatal death</b>	
	Death of neonate within 28 days after birth.
<b>Cerebral palsy</b>	
DG800	Spastic quadriplegic cerebral palsy.
DG801	Spastic diplegic cerebral palsy.
DG802	Spastic hemiplegic cerebral palsy.
DG803	Dyskinetic cerebral palsy.
DG803A	Athetoid cerebral palsy.
DG803B	Dystonic cerebral palsy.
DG804	Ataxic cerebral palsy.
DG808	Other cerebral palsy.
DG808A	Mixed cerebral palsy syndromes.
DG809	Cerebral palsy, unspecified.
<b>Prevention of macrosomia</b>	
<b>Fetal weight ≥4500 grams</b>	
	Fetal weight ≥4500 grams.
<b>Shoulder dystocia</b>	
DO660	Delivery complicated by shoulder dystocia.
<b>Nerve injury</b>	
DP140	Erb paralysis due to birth injury.
DP141	Klumpke paralysis due to birth injury.
DP143	Other brachial plexus injuries.

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529 **Table 3S**530 *Diagnosis codes and other criteria defining possible confounders.*

<b>Maternal age</b>	Using personal registration number and day of delivery
<b>Parity</b>	Number of prior pregnancies
<b>Plurality</b>	Single or multiple gestation
<b>Smoker</b>	Smoker or non-smoker, registered at first contact with doctor
<b>Body mass index</b>	Using maternal height and weight.

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557 **Table 4S**

558 *Maternal age, parity, plurality, smoking, and body mass index among pregnant women from*  
 559 *37 weeks' gestation in Denmark from 2000 to 2012.*

Possible confounders	2000-2002	2003-2005	2006-2008	2009-2010	2011-2012	P-value*	Total
<b>Maternal age</b>							
Mean maternal age, years	30.1	30.6	30.8	30.9	30.9		30.7
Numbers of mothers >40 years	3,584	4,366	5,436	3,740	3,777		20,903
Incidence rate	2.0	2.4	3.0	3.2	3.5	<0.001	2.7
<b>Parity</b>							
Number of nulliparous women	78,718	77,231	77,685	51,675	48,584		333,893
Incidence rate	43.0	42.9	43.0	43.8	44.5	<0.001	43.3
<b>Plurality (‰)</b>							
Number of multigravidas	4,353	4,617	4,727	3,116	2,747		19,560
Incidence rate	2.4	2.6	2.6	2.6	2.5	<0.001	2.5
<b>Smoker</b>							
Number of smokers	37,540	30,782	25,656	14,891	12,527		121,396
Incidence rate	21.1	17.5	14.5	12.9	11.6	<0.001	16.1
<b>Body mass index</b>							
Mean body mass index	-	24.1	24.2	24.4	24.4		24.3
Number of women with BMI >35	-	4,032	6,813	4,880	4,689		20,414
Incidence rate	-	3.6	4.1	4.4	4.4	<0.001	4.1

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# BMJ Open

## Reduction in stillbirths at term after new birth induction paradigm. Results of a national intervention

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## Reduction in stillbirths at term after new birth induction paradigm.

### Results of a national intervention

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4 29 **Abstract**

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6 30 **Objective.** The risk of fetal death increases steeply after 42 gestational weeks. Since 2009, a more  
7  
8 31 proactive policy including prevention of prolonged pregnancy, and early intervention of women with  
9  
10 32 diabetes, preeclampsia, high body mass index, and high age. The aim of this study was to describe  
11  
12 33 the development in fetal deaths with this more proactive birth induction practice, and to identify and  
13  
14 34 quantify contributing factors for this development.

15  
16 35 **Design.** National cohort study.

17  
18 36 **Setting.** Denmark

19  
20 37 **Participants.** Delivering women in Denmark, January 1, 2000 to December 31, 2012.

21  
22 38 **Outcome measures.** Stillbirths per 1,000 women at risk (prospective risk of stillbirth) and per  
23  
24 39 1,000 new-born from 37 and 40 gestational weeks, respectively, through the study period.

25  
26 40 **Results.** During the study period, 829,165 children were live-born and 3,770 (0.45%) stillborn.

27  
28 41 Induction of labour increased from 12.4 % in year 2000 to 25.1 % in 2012 ( $p<0.001$ ), and the per  
29  
30 42 cent of children born at or after 42 weeks decreased from 8.0 % to 1.5 % ( $p<0.001$ ).

31  
32 43 Through the same period, the prospective risk of stillbirth after 37 weeks fell from 0.70 to 0.41 per  
33  
34 44 1,000 ongoing pregnancies ( $p<0.001$ ), and from 2.4 to 1.4 per 1,000 new-born ( $p<0.001$ ).

35  
36 45 The regression analysis confirmed the inverse association between year of birth and risk of  
37  
38 46 stillbirth. The lowest risk was observed in the years 2011-2012 as compared to years 2000-2002  
39  
40 47 with a fully adjusted hazard ratio of 0.69 (95% CI 0.57-0.83). The general earlier induction, the  
41  
42 48 focused earlier induction of women with body mass index  $>30$ , twins, and of women above 40  
43  
44 49 years, and a halving of smoking pregnant women were all independent contributing factors for the  
45  
46 50 decrease.

47  
48 51 **Conclusion.** A gradually more proactive and a differential earlier labour induction practice are  
49  
50 52 likely to have the main responsibility for the substantial reduction in stillbirths in Denmark.

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54 54 **Key words:** Birth induction, fetal death, stillbirth, misoprostol

55  
56 55 **Abbreviations:** None.

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59 **Strengths and limitations**

60 **Strengths**

- 61 • Complete national data through a 13-year long study period
- 62 • Data analysed for all births after 37 weeks and after 40 weeks, respectively
- 63 • Access to important confounders
- 64 • Complete follow-up on all children born during the study period
- 65 • Advanced regression analysis
- 66 • A clear clinical message

67 **Limitations**

- 68 • Several clinical improvements have been undertaken during the study period
- 69 •
- 70

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## 71 Introduction

72 Fetal death is still a dreaded complication of pregnancy, not least when occurring at term. The  
73 worldwide number of stillborn infants is estimated to 2.6 million per year, and the causes of a  
74 substantial part of these deaths are still unknown.[1] Identified risk factors include high maternal  
75 age, adiposity, fetal asphyxia, infections, and different maternal medical diseases.[2-5]  
76 Randomised studies have suggested a potential for prevention of fetal deaths by earlier induction  
77 of deliveries.[6]

78 Over the last two decades, the discussion of induction of labour versus expectant management  
79 has been prevalent among obstetricians.[7] A national Danish guideline in 2009 recommended  
80 induction of pregnant women ensuring delivery before 42 weeks.[8] Generally, pregnant women  
81 have since been offered labour induction at 41+3-5, while women at risk (body mass index >30 or  
82 age >40 years) have been offered induction at 41 weeks. Lastly, women at a high risk such as  
83 women with multiple pregnancies, preeclampsia or intrauterine growth restriction are often  
84 recommended induction before term.

85 The aim of this study was to describe birth induction practice in Denmark since year 2000, the  
86 corresponding development in post-term deliveries, and the stillbirth rates from 37 and 40 weeks of  
87 gestation (prospective stillbirth rate) and per 1,000 new-born. Secondly, to adjust these trends in  
88 rates of stillbirth for important risk factors of stillbirth.

## 89 Methods

### 90 *Design and setting*

91 In a historical cohort design data were collected from the Danish Birth Register, covering the period  
92 January 2000 through December 2012. The Registry is considered complete through this period. In  
93 order to reduce random variation, the 13-year study period was subdivided into five sub-periods of  
94 three, three, three, two, and two years length, respectively.

### 95 *Participants*

96 All live births and stillbirths during the study period were included. For each gestational day after 37  
97 weeks, the number and distribution of all new-born and stillbirths were assessed. The gestational  
98 ages were generally assessed from first trimester ultrasound examinations. For few women not  
99 attending this routine offer to all pregnant women in Denmark, the last menstrual period was used.

### 100 *Outcome measures*

101 Rates of stillbirth per 1,000 ongoing pregnancies, also called the prospective risk of stillbirth, were  
102 calculated with a daily update from 37 weeks of gestation, accounting for the rapidly declining  
103 denominator especially after term. [9] The proportion of deliveries and of stillbirths after 37, 40, 41,

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4 104 and 42 weeks per 1,000 new-born were calculated annually from year 2000 through 2012, and in  
5 105 different sub-periods within this study period.

7 106 The gestational age was recorded in 99.4 % of all new-born during the study period. Of 146  
8 107 missing gestational ages among stillborn infants, we sought in medical charts and local registers  
9 108 and achieved this information in 42 women, all of whom had ended their pregnancy before 37  
10 109 weeks. Therefore, all with a missing gestational age were allocated to the premature group.  
11 110 Gestational ages were however achieved for all stillbirths in 2011 and 2012.

12 111 From 2004 a birth has in Denmark been defined as any pregnancy that ends after 22 weeks of  
13 112 gestation, and live-born before 22 weeks. Before 2004 only live-births between 22 and 28 weeks  
14 113 were considered as births, while delivery of dead fetuses before 28 weeks and live-born before 22  
15 114 weeks were considered as abortions. This technicality explains a minor increase in stillbirths before  
16 115 37 weeks of gestation from 2003 to 2004.

17 116 Deaths within the first week after delivery was assessed for all included live-born, and rates of  
18 117 death were calculated in each study year.

19 118 In the analytical assessment, analyses of the cumulative risk of stillbirth with increasing gestational  
20 119 age per 1,000 ongoing pregnancies was estimated using Nielson Aalen estimator with gestational  
21 120 age (in days) as the time scale.[10] By cox regression analyses, the hazard ratios of stillbirth by  
22 121 year of birth were estimated using year 2000-2002 as the reference group. Gestational age was  
23 122 underlying time scale in these analyses. The following potential confounders were included in the  
24 123 model: Plurality, parity, maternal age, year, smoking, and body mass index. The regression model  
25 124 aimed to quantify the contribution from each of the potential confounders for the association  
26 125 between calendar year and rates of stillbirth.[10] Hazard ratios with 95% confidence limits were  
27 126 calculated, and p-values below 0.05 were considered significant. Logistic regression was used to  
28 127 generate crude odds ratios.

29 128 The main analysis was done on all deliveries from 37 weeks of gestation. As body mass index was  
30 129 not routinely recorded in the birth registry until 2004, additional sensitivity analyses were done for  
31 130 the sub-period 2004-2012, in order to quantify specifically the influence of body mass index on the  
32 131 decreasing stillborn rate. Finally, sensitivity analyses were conducted restricted to singletons.

33 132  
34 133

## 134 Results

135 During the study period, 832,935 children were born. Of these were 3,770 (0.45 %) stillbirths and  
136 829,165 (99.55 %) live-born. The distribution of new-born and stillborn infants in different  
137 pregnancy weeks, the crude rate of stillborn per 1,000 ongoing pregnancies and per 1,000 new-  
138 born in different gestational weeks, from different gestational ages and in different periods are  
139 shown in Table 1.

140 The frequency of birth induction increased from 12.4 % in year 2000 to 25.1 % in 2012, with a  
141 steep increase after 2010 (**Figure 1**). The earlier birth induction reduced the per cent of children  
142 born from 42 weeks of gestation from 8.0 % in year 2000 to 1.5 % in 2012 (**Figure 1**). The  
143 increasing induction rate and fall in deliveries from 42 weeks was, however, already observable  
144 from 2001.

### 145 *Stillbirths with increasing gestational age.*

146 The background for the new induction paradigm in Denmark is illustrated for the period 2000-2008  
147 in **Figure 2**. With increasing gestational age the risk of fetal death rises, peaking after 43 weeks of  
148 gestation with more than 14 deaths per 1,000 ongoing pregnancies, a risk more than ten times  
149 higher than in the weeks before term.

150 During the period 2009-2012, the stillborn rates were reduced 21-39%, and from 41+3 stillbirths  
151 were eliminated (**Figure 2**).

152 The crude rates of fetal deaths with increasing gestational age were reduced by 30-66% when  
153 adjusting for age, year, parity, plurality, and smoking (**Figure 3**). Adjustment for body mass index  
154 did not change the estimates significantly.

### 155 *Stillbirths by time.*

156 The rate of stillborn infants from 37 weeks of gestation decreased from 0.70 (95% confidence  
157 interval 0.64-0.77) per 1,000 ongoing pregnancies (prospective stillbirth rate) during the period  
158 2000-2002 to 0.41 (0.35-0.48) during the period 2011-2012 (**Figure 4**). The corresponding rate of  
159 stillborn infants from 40 weeks fell from 1.8 (1.6-2.1) during the period 2000-2002 to 0.74 (0.56-  
160 0.98) during 2011-2012, a reduction of 60 % ( $p < 0.001$ ). The fall was steepest from 2009-10 to  
161 2011-12.

162 The rate of stillborn infants per 1,000 new-born after 37 weeks demonstrated a similar decrease  
163 from 2.4 (2.2-2.6) during the period 2000-2002 to 1.4 (1.2-1.6) during 2011-2012, a fall of 43%  
164 (**Figure 4**). Among children born from 40 weeks, the corresponding stillborn rates fell from 2.1 (1.9-  
165 2.4) per 1,000 new-born to 0.77 (0.58-1.0) or by 63% ( $p < 0.001$ ) (**Figure 4**).

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4 167 *Regression analysis*

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6 168 Several conditions, which may have influenced the risk of fetal death, changed during the study  
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8 169 period (**Table 2**), The mean age of delivering women after 37 weeks of gestation increased from  
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10 170 30.1 years in 2000-2002 to 30.9 years in 2011-12, and the proportion of delivering women  $\geq 40$   
11  
12 171 years increased from 2.0 % to 3.5 % ( $p < 0.001$ ).

13  
14 172 The mean body mass index increased from 24.1 kg/m<sup>2</sup> in 2003-2005 to 24.4 kg/m<sup>2</sup> during 2011-  
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16 173 2012, and delivering women with a body mass index above 25 kg/m<sup>2</sup> increased from 32.0 % to  
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18 174 34.4 % through the same period ( $p < 0.001$ ).

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20 175 While these changes are expected to increase the risk of fetal death, the proportion of pregnant  
21  
22 176 smokers decreased from 20.5 % in 2000-2002 to 11.5 % in 2011-2012, almost a halving ( $p < 0.001$ ).

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24 177 The proportion of primiparous increased slightly from 43.0 % to 44.5 % through the study period,  
25  
26 178 while the proportion of multiple pregnancies after 37 weeks was almost stable; 2.4 % in 2000-2002,  
27  
28 179 2.6 % in 2006-2008, and 2.5 % in 2011-12 (**Table 2**). The proportion of multiple deliveries after 40  
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30 180 weeks of gestation from already low 0.12 % decreased to 0.04 %. Thereby, post term multiple  
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32 181 deliveries almost disappeared through the study period.

33  
34 182 In the fully adjusted model the following hazard ratios of fetal death were demonstrated: Smoking  
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36 183 1.4 (1.2-1.6), body mass index  $> 25$  kg/m<sup>2</sup>; 1.5 (1.3-1.7), decreasing from 1.7 (1.4-2.0) during the  
37  
38 184 period 2004-2008 to 1.3 (1.0-1.6) in 2009-2012. Primiparous had a relative risk of stillbirth of 1.2  
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40 185 (1.1-1.3), and multiple pregnancy of 51.5 (44.4-59.6).

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42 186 With adjustment for gestational age at delivery, the decline in stillbirths was reduced from -41.5 %  
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44 187 to -35.5 % suggesting that the general earlier induction in it self accounted for about 15 % of the  
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46 188 reduction. Further adjustment for smoking, age at delivery, and parity increased the fall from -35.5  
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48 189 % to -37.6 %, because the decrease in smoking counterbalanced the influence of the slightly  
49  
50 190 increasing age and proportion of primiparous by time. By additional adjustment for plurality, the  
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52 191 relative risk of stillbirth by time was reduced from -37.6 % to -31.4 %, suggesting that the changes  
53  
54 192 in the management of twin pregnancies accounted for approximately 16 % of the decrease.

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56 193 In the sub-analysis covering the period 2004-2012, during which information about body mass  
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58 194 index was available, the decreasing risk of stillbirth among women with high body mass index by  
59  
60 195 time implied a further non significant four per cent reduction in overall stillbirth rates by time.

196  
197 196 The rest of the reduction in stillbirths is thus apparently due to the differential induction practice,  
198  
199 197 where women with high-risk pregnancies are induced more proactively (earlier) than low-risk  
200  
201 198 pregnancies,

202  
203 199 The risk of fetal death in the week after term was reduced by 33-38 % ( $p < 0.01$ ), in the week after  
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205 200 41 weeks by 30-33 % ( $p < 0.01$ ), and after 42 weeks by 30-33 % ( $p < 0.05$ )(**Figure 2**). Thus, the new

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4 201 induction paradigm firstly moved deliveries from late weeks with a high risk of stillbirth to earlier  
5 202 weeks with a lower risk. Secondly, in particular moved high-risk pregnancies to earlier induction,  
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7 203 but thirdly, also reduced the risk of fetal death in each post term week.  
8

9 204 The decrease in the rate of stillbirth corresponds to a reduction in absolute numbers of stillborn  
10 205 infants after 37 weeks from 136 stillbirths per year to now about 75 per year, a reduction of  
11 206 approximately 60 per year ( $p < 0.001$ ), corresponding to one saved stillborn infant per 1,000 new-  
12 207 born.  
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16 208 During gestational weeks 37 to 40, the annual number of stillbirths fell from around 80 per year  
17 209 during the period 2000-2008 to 50 per year during 2009-2012. This reduction coincided with an  
18 210 increase in second trimester induced abortions on fetal indication from annually 292 during the  
19 211 period 2000-2008 to 410 per year during the period 2009-2012, an increase of 118 induced  
20 212 abortions per year.[11]  
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24 213 The risk of dying during the first week of life was reduced among children born after 37 weeks from  
25 214 1.7 (1.4-2.0) per 1,000 new-born in 2000 to 0.8 (0.6-1.0) per 1,000 live-born in 2012.[12]  
26

27 215 The Caesarean section rate in Denmark has after a steady increase over more than 40 years been  
28 216 stable throughout the last ten years at about 20 % of all deliveries, even with a slight reduction  
29 217 from 20.4 % in 2009 to 19.8 % in 2012 ( $p < 0.01$ ).[12]  
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32 218 The sensitivity analysis excluding women with unknown gestational age did not change anything  
33 219 after 37 weeks, but decreased slightly the risk of fetal deaths before 37 weeks (data not shown).  
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36 220 Sensitivity analyses restricted to singletons enhanced the fall in stillbirth rates by time. For all  
37 221 deliveries, the adjusted fall by time was -31% and for singletons -43%,  
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## 43 224 **Discussion**

44  
45 225 We report a decrease in risk of fetal death after 37 weeks to 0.14 % on a national level, which is  
46 226 the lowest risk ever reported in Denmark. Nor have any similar rate to our knowledge been  
47 227 published elsewhere.  
48

49 228 Ever since the 1990's, there has been an ongoing discussion of induction of labour versus  
50 229 expectant management of women after term.[7] Through the last ten years, a gradually more  
51 230 proactive induction practice has gained ground over expectant management in several countries,  
52 231 including Denmark. The decision to make a Danish guideline in 2009 was stimulated by the NICE-  
53 232 guideline on induction of labour published in 2008 and the ACOG practice bulletin from 2009.[13,  
54 233 14]  
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4 234 Before 2009, many women were still not offered induction until after they passed 42 weeks of  
5 235 gestation. From 2009, the recommended induction regimen prevented many pregnancies from  
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7 236 reaching post term gestational weeks of a high risk of fetal death. This change reduced the number  
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9 237 of fetal deaths after term, but should in principle not influence the rate of deaths per 1,000 ongoing  
10 238 pregnancies in a certain post term week. The gestational age specific stillbirth rate after 41 weeks  
11 239 was, however, also reduced. This reduction could not be explained by the general earlier induction  
12 240 practice, but is according to our analyses a result of an even more proactive induction practice in  
13 241 women at an increased risk of stillbirth, such as women with body mass index >30, and women  
14 242 over 40 years. An increased fetal monitoring after term by time may also have influenced the  
15 243 decrease.

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20 244 Through the last ten years, the majority of Danish units have used misoprostol for induction of  
21 245 labour, either applied vaginally or orally. It has been questioned, if induction by misoprostol could  
22 246 increase the risk of uterine hyperstimulation, asphyxia, and ultimately of neonatal death. In theory,  
23 247 an initiative to reduce the risk of fetal death could lead to neonatal complications and neonatal  
24 248 death. It is therefore important that the reduction in stillbirths was not associated with an increase  
25 249 in early neonatal deaths. On the contrary, the early neonatal deaths were halved during the study  
26 250 period, a circumstance, which undoubtedly was also influenced by an improved neonatal care  
27 251 through the study period.

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32 252 It has been discussed, if induction of labour causes more Caesarean sections.[15] Some have  
33 253 argued that expectant management of labour increases the Caesarean section rate due to the  
34 254 risks associated with prolonged pregnancy.[16] The slight reduction in Caesarean sections with the  
35 255 new induction paradigm demonstrates that a proactive induction practice not necessarily increases  
36 256 the frequency of surgical interventions.

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40 257 The offer of first trimester combined screening (double test and nuchal translucency scan), has in  
41 258 Denmark been widened to all pregnant women from year 2005-2006.[17] Before then, only women  
42 259 at 35 years or older were routinely offered first trimester screening. With the new routine, a majority  
43 260 of chromosomal abnormalities are detected and pregnancy most often terminated, accounting for  
44 261 the increase of approximately 118 annual second trimester induced abortions. Before the general  
45 262 screening was fully implemented, some fetuses with undetected abnormalities died later in  
46 263 pregnancy. From 20 weeks of gestation until term, 13 % of trisomy 21, 75 % of trisomy 18, and 35  
47 264 % of trisomy 13 experience fetal death [18], a majority of these before 37 gestational weeks. This  
48 265 circumstance may explain a reduction of about 15 fetal deaths per year, but only about seven after  
49 266 37 weeks corresponding to 12 % (7/60) of the observed reduction in stillborn infants.

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56 267 During the study period, the quality of screening for structural abnormalities (offered in general  
57 268 throughout the period) and Doppler ultrasound both improved the monitoring of fetuses in utero,

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4 269 making it easier to detect threatened fetuses and to intervene to avoid further complications  
5 270 including fetal death. However, these circumstances are probably of minor importance for the  
6 271 decrease in stillbirths, as other countries with the same technical improvement have not observed  
7 272 a similar decrease in stillbirths. In Sweden, the proportion of deliveries after 42 weeks was 7.5 % in  
8 273 year 2000 and 6.5 % in 2011. During the same period, the stillbirth rate after 37 gestational weeks  
9 274 was stable between 1.6 and 1.9 per 1,000 new-born.[19] In Norway, 4.8 % of deliveries occurred at  
10 275 42 weeks or later, and the stillbirth rate after 37 weeks was 1.47 per 1,000 new-born [20], figures  
11 276 close to Danish figures in 2010.

12 277 The earlier induction of multiple pregnancies explained about 15 % of the reduction in stillbirths.  
13 278 The selective early induction of high-risk pregnancies such as pregnancies in women with high  
14 279 body mass index, women above 40 years, and women with multiple pregnancies explains, why the  
15 280 impact of these risk factors decreased by time. Worldwide, maternal age at delivery has increased  
16 281 over the last five decades, and Denmark is no exception.[21] As high maternal age is associated  
17 282 with stillbirth, this increase should have increased the stillbirth rates slightly by time.[5, 22, 23]

18 283 Determining the optimal time to deliver necessarily involves balancing induction risks and benefits.  
19 284 According to earlier studies, the risks of post-term deliveries include an increased perinatal  
20 285 mortality, meconium aspiration, macrosomia, low umbilical cord artery pH, and low Apgar score at  
21 286 five minutes.[24] Inducing labour too early, on the other hand, may cause iatrogenic prematurity  
22 287 and respiratory complications.[25, 26]

23 288 When considering the overall risk of either fetal or infant death, previous studies have suggested  
24 289 the risk of expectant management to be lower than the risk of delivery until about 38 weeks.  
25 290 Passing 38 weeks, the risk of expectant management was found to be higher than the risk of  
26 291 delivery, and the risk difference increases substantially after 40 and 41 weeks of gestation,  
27 292 favouring delivery over expectant management.[27]

28 293 A Scottish historical cohort study by Stock et al. demonstrated similarly a substantial lower  
29 294 perinatal mortality in women induced at 41 weeks as compared with expectant management; OR  
30 295 0.30 (95% CI 0.20-0.46).[28]

31 296 Among the strengths of this study are the almost complete coverage of deliveries [29], and access  
32 297 to data making an evaluation of circumstances, which might have influenced the stillbirth rates  
33 298 possible. The main limitation is the observational design, and the difficulty to account effectively for  
34 299 all potential confounders. The significant reduction in fetal deaths seen in Denmark has not been  
35 300 observed in Sweden, where the handling of post term pregnancies has undergone less  
36 301 change.[19]

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4 302 In conclusion, the striking decrease in risk of late fetal deaths through recent years is likely  
5 303 primarily to be due to the earlier and increased induction rate. The additional health costs to save  
6 304 these lives were low, and the reduction was obtained without an increase in surgical interventions.

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9 305 An important issue, which needs further studies, is the morbidity in new-born through the same  
10 306 study period, to confirm that the reduced mortality is not at the expense of an increased morbidity  
11 307 in new-born.

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14 308 Denmark already had a low stillbirth rate a decade ago.[1] With the further reduction in stillbirths,  
15 309 we may now have achieved the lowest stillbirth rate ever reported. We see no reason why a similar  
16 310 more proactive induction paradigm could not be implemented in other countries, with a succeeding  
17 311 further reduction in late stillbirths worldwide.

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### 22 313 **Acknowledgements**

23  
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26 316 Denmark

### 27 317 **Contributions**

28  
29 318 Hedegaard, Hedegaard and Lidegaard planned the study, Skovlund retrieved data from the National Birth  
30 319 Registry and National Health Registry. Mørch, Lidegaard, and Skovlund analysed the data. Hedegaard and  
31 320 Lidegaard wrote the manuscript. All authors revised the manuscript and accepted the final version. Morten  
32 321 Hedegaard is the guarantor.

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### 36 325 **Conflict of interests**

37 326 All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf)  
38 327 (available on request from the corresponding author) and declare that Lidegaard within the last three years  
39 328 received honoraria for speeches in pharmacoepidemiological issues. Hedegaard, Hedegaard, Mørch and  
40 329 Skovlund did not declare any conflicts.

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10 340 **Data sharing**

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12 341 No additional data available.  
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415 **Table 1**

416 *Rates\* of born and stillborn in and from different gestational weeks*  
 417 *and periods in Denmark 2000-2012.*

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
<b>Number of born and stillborn infants</b>								
<b>Born (n)</b>	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
<b>Stillborn (n)</b>	835	915	992	539	489	2,742	1,028	3,770
<b>Stillbirths per 1,000 ongoing pregnancy weeks (prospective risk of stillbirth)</b>								
<b>&lt;37</b>	0.22	0.20	0.21	0.17	0.17	0.21	0.17	0.20
<b>37+0-6</b>	0.39	0.46	0.39	0.27	0.23	0.41	0.25	0.37
<b>38+0-6</b>	0.36	0.51	0.46	0.41	0.34	0.44	0.38	0.42
<b>39+0-6</b>	0.56	0.54	0.63	0.44	0.46	0.57	0.45	0.54
<b>40+0-6</b>	1.20	0.95	0.97	0.93	0.76	1.04	0.85	0.98
<b>41+0-6</b>	2.29	2.40	1.73	1.35	0.54	2.15	0.98	1.82
<b>42+</b>	15.55	6.09	11.16	6.60	7.83	11.60	6.96	10.86
<b>Total</b>	0.35	0.29	0.28	0.23	0.21	0.30	0.22	0.27
<b>From 37 w</b>	0.70	0.67	0.63	0.50	0.41	0.67	0.46	0.61
<b>From 40 w</b>	1.84	1.43	1.30	1.10	0.74	1.54	0.93	1.36
<b>From 41 w</b>	3.12	2.46	2.09	1.51	0.69	2.60	1.14	2.21
<b>Stillborn per 1.000 new-born</b>								
<b>From 37 w</b>	2.39	2.21	2.07	1.68	1.36	2.23	1.52	2.02
<b>From 40 w</b>	2.11	1.59	1.41	1.20	0.77	1.71	0.99	1.50
<b>From 41 w</b>	2.43	1.82	1.46	1.04	0.41	1.93	0.73	1.57
<b>From 42 w</b>	3.16	1.05	1.55	0.82	0.95	2.04	0.86	1.79

419 \*) Absolute numbers given in supplementary appendix Table 1S.

420

421 **Table 2**

422 *Characteristics of women giving birth at term and*  
 423 *relative risk of stillbirth by time.*

	2000-02	2003-05	2006-08	2009-10	2011-12
<b>Mean age</b>	30.1	30.6	30.8	30.9	30.9
<b>Mother ≥40 yrs</b>	3,584	4,366	5,436	3,740	3,777
<b>% ≥40 years</b>	2.0	2.4	3.0	3.2	3.5
<b>BMI recorded (n)</b>	na	112,635	167,962	111,972	106,201
<b>Mean BMI</b>	na	24.1	24.2	24.3	24.4
<b>BMI &gt;25</b>	na	36,076	54,903	37,616	36,528
<b>% BMI &gt;25</b>	na	32.0	32.7	33.6	34.4
<b>BMI &gt;30</b>	na	12,480	19,683	13,946	13,720
<b>% BMI &gt;30</b>	na	11.1	11.7	12.5	12.9
<b>BMI &gt;35</b>	na	4,032	6,813	4,880	4,689
<b>% BMI &gt;35</b>	na	3.6	4.1	4.4	4.4
<b>Smoker</b>	37,540	30,782	25,656	14,891	12,527
<b>% smokers</b>	20.5	17.1	14.2	12.6	11.5
<b>Multiple pregnancies</b>	4,353	4,617	4,727	3,116	2,747
<b>% multiples</b>	2.4	2.6	2.6	2.6	2.5
<b>Stillborn multiples</b>	51	111	61	40	29
<b>% stillborn multiples</b>	1.2	2.4	1.3	1.3	1.1
<b>Para 0</b>	78,718	77,231	77,685	51,675	48,584
<b>% Para 0</b>	43.0	42.9	43.0	43.8	44.5
<b>Regression analysis</b>	<b>Hazard ratio<sup>§</sup> of stillborn (2000-2002 reference)</b>				
<b>Crude<sup>#</sup></b>	1	0.95	0.89	0.72	0.59
<b>Adjusted for GA<sup>†</sup></b>	1	1.02	0.98	0.78	0.65
95% confidence intervals		0.89-1.17	0.85-1.12	0.66-0.92	0.53-0.78
<b>Adjusted excpt, Plurality<sup>**</sup></b>	1	1.03	0.89	0.73	0.62
95% confidence intervals		0.90-1.18	0.78-1.03	0.61-0.86	0.52-0.75
<b>Fully Adjusted<sup>**†</sup></b>	1	1.07	0.96	0.78	0.69
95% confidence intervals		0.93-1.23	0.83-1.11	0.65-0.92	0.57-0.83

425 \*) Adjusted only for age, smoking, and parity \*\*\*) Additionally adjusted for plurality

426 §) Hazard ratios by cox regression. The crude estimates were calculated by logistic regression,  
 427 and the risk estimates were odds ratios

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4 434 **Legends for tables and figures**

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6 435 **Table 1**

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8 436 *Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-*  
9 437 *2012.*

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11 438 **Table 2**

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13 439 *Characteristics of women giving birth at term and relative risk of stillbirth by time.*

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15 440 **Figure 1**

16  
17 441 *Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks,*  
18 442 *respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.*

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20 443 **Figure 2**

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22 444 *Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-*  
23 445 *2008 and 2009-2012. Number of weeks: 3,406,615. Number of fetal deaths: 3,770. Lower part the*  
24 446 *same in a semi-logarithmic plot*

25  
26 447 **Figure 3**

27  
28 448 *Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period*  
29 449 *2000-2012 and after adjustment for different confounders\*. Lower part the same in a semi-*  
30 450 *logarithmic plot.*

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32 451 **Figure 4**

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34 452 *Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new-born (lower) after 37 and*  
35 453 *40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95%*  
36 454 *confidence limits indicated,*

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38 455 **Supplementary online appendix (optional)**

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40 456 **Table 1S**

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42 457 *Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-*  
43 458 *2012.*

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July 11, 2014

**Reduction in stillbirths at term after new birth induction paradigm.****Results of a national intervention***Mette Hedegaard<sup>1</sup>, scholar researcher**Øjvind Lidegaard<sup>1</sup>, professor in Obstetrics and Gynaecology,**Charlotte Wessel Skovlund<sup>1</sup>, data manager**Lina Steinrud Mørch, epidemiologist, and**Morten Hedegaard<sup>2</sup>, head of dept, of obstetrics,***Word counts:***Title: 15 words, 102 characters including space**Abstract: 300 words**Text: 3,054 words (excl, abstract, references, tables and figures)**Tables: 2**Figures: 4**Supplementary online appendix: One with one table*

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8 29 **Abstract**

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10 30 **Objective.** ~~Fetal deaths are still a key challenge for obstetricians worldwide.~~ The risk of fetal death  
11 31 increases steeply after 42 gestational weeks. ~~From~~Since 2009, ~~Danish national guidelines~~  
12 32 ~~recommended a more proactive policy including prevention of prolonged pregnancy, and early~~  
13 33 ~~intervention of women with diabetes, preeclampsia, high body mass index, and high age pregnant~~  
14 34 ~~women to be offered induction to ensure delivery before 42 weeks.~~ The aim of this study was to  
15 35 describe the development in fetal deaths with this more proactive birth induction practice, and to  
16 36 identify and quantify contributing factors for this development.

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18 36  
19 37 **Design.** National cohort study.

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21 38 **Setting.** Denmark

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23 39 **Participants.** Delivering women in Denmark, January 1, 2000 to December 31, 2012.

24 40 **Outcome measures.** Stillbirths per 1,000 women at risk (prospective risk of stillbirth) and per  
25 41 1,000 new-born from 37 and 40 gestational weeks, respectively, through the study period.

26 41  
27 42 **Results.** During the study period, 829,165 children were live-born and 3,770 (0.45%) stillborn.

28 43 Induction of labour increased from 12.4 % in year 2000 to 25.1 % in 2012 ( $p<0.001$ ), and the per  
29 44 cent of children born at or after 42 weeks decreased from 8.0 % to 1.5 % ( $p<0.001$ ).

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32 45 Through the same period, the prospective risk of stillbirth after 37 weeks fell from 0.70 to 0.41 per  
33 46 1,000 ongoing pregnancies ( $p<0.001$ ), and from 2.4 to 1.4 per 1,000 new-born ( $p<0.001$ ).

34  
35 47 The regression analysis confirmed the inverse association between year of birth and risk of  
36 48 stillbirth. The lowest risk was observed in the years 2011-2012 as compared to years 2000-2002  
37 49 with a fully adjusted hazard ratio of 0.69 (95% CI 0.57-0.83). The general earlier induction, the  
38 50 focused earlier induction of women with body mass index  $>30$ , twins, and of women above 40  
39 51 years, and a halving of smoking pregnant women were all independent contributing factors for the  
40 52 decrease.

41 52  
42  
43 53 **Conclusion.** A gradually more proactive and a differential earlier labour induction practice are  
44 54 likely to have the main responsibility for the substantial reduction in stillbirths in Denmark.

45  
46 55  
47 56 **Key words:** Birth induction, fetal death, stillbirth, misoprostol

48 56  
49 57 **Abbreviations:** None.  
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**Strengths and limitations**

**Strengths**

- Complete national data through a 13-year long study period
- Data analysed for all births after 37 weeks and after 40 weeks, respectively
- Access to important confounders
- Complete follow-up on all children born during the study period
- Advanced regression analysis
- A clear clinical message

**Limitations**

- Several clinical improvements have been undertaken during the study period
-

## Introduction

Fetal death is still a dreaded complication of pregnancy, not least when occurring at term. The worldwide number of stillborn infants is estimated to 2.6 million per year, and the causes of a substantial part of these deaths are still unknown.[1] Identified risk factors include high maternal age, adiposity, fetal asphyxia, infections, and different maternal medical diseases.[2-5] Randomised studies have suggested a potential for prevention of fetal deaths by earlier induction of deliveries.[6]

Over the last two decades, the discussion of induction of labour versus expectant management has been prevalent among obstetricians.[7] A national Danish guideline in 2009 recommended induction of pregnant women ensuring delivery before 42 weeks.[8] Generally, pregnant women have since been offered labour induction at 41+3-5, while women at risk (body mass index >30 or age >40 years) have been offered induction at 41 weeks. Lastly, women at a high risk such as women with multiple pregnancies, preeclampsia or intrauterine growth restriction are often recommended induction before term.

The aim of this study was to describe birth induction practice in Denmark since year 2000, the corresponding development in post-term deliveries, and the stillbirth rates from 37 and 40 weeks of gestation (prospective stillbirth rate) and per 1,000 new-born. Secondly, to adjust these trends in rates of stillbirth for important risk factors of stillbirth.

## Methods

### *Design and setting*

In a historical cohort design data were collected from the Danish Birth Register, covering the period January 2000 through December 2012. The Registry is considered complete through this period. In order to reduce random variation, the 13-year study period was subdivided into five sub-periods of three, three, three, two, and two years length, respectively.

### *Participants*

All live births and stillbirths during the study period were included. For each gestational day after 37 weeks, the number and distribution of all new-born and stillbirths were assessed. The gestational ages were generally assessed from first trimester ultrasound examinations. For few women not attending this routine offer to all pregnant women in Denmark, the last menstrual period was used.

### *Outcome measures*

Rates of stillbirth per 1,000 ongoing pregnancies, also called the prospective risk of stillbirth, were calculated with a daily update from 37 weeks of gestation, accounting for the rapidly declining denominator especially after term. [9] The proportion of deliveries and of stillbirths after 37, 40, 41,

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and 42 weeks per 1,000 new-born were calculated annually from year 2000 through 2012, and in different sub-periods within this study period.

The gestational age was recorded in 99.4 % of all new-born during the study period. Of 146 missing gestational ages among stillborn infants, we sought in medical charts and local registers and achieved this information in 42 women, all of whom had ended their pregnancy before 37 weeks. Therefore, all with a missing gestational age were allocated to the premature group.

Gestational ages were however achieved for all stillbirths in 2011 and 2012.

From 2004 a birth has in Denmark been defined as any pregnancy that ends after 22 weeks of gestation, and live-born before 22 weeks. Before 2004 only live-births between 22 and 28 weeks were considered as births, while delivery of dead fetuses before 28 weeks and live-born before 22 weeks were considered as abortions. This technicality explains a minor increase in stillbirths before 37 weeks of gestation from 2003 to 2004.

Deaths within the first week after delivery was assessed for all included live-born, and rates of death were calculated in each study year.

In the analytical assessment, analyses of the cumulative risk of stillbirth with increasing gestational age per 1,000 ongoing pregnancies was estimated using Nielson Aalen estimator with gestational age (in days) as the time scale.[10] By cox regression analyses, the hazard ratios of stillbirth by year of birth were estimated using year 2000-2002 as the reference group. Gestational age was underlying time scale in these analyses. The following potential confounders were included in the model: Plurality, parity, maternal age, year, smoking, and body mass index. The regression model aimed to quantify the contribution from each of the potential confounders for the association between calendar year and rates of stillbirth.[10] Hazard ratios with 95% confidence limits were calculated, and p-values below 0.05 were considered significant. Logistic regression was used to generate crude odds ratios.

The main analysis was done on all deliveries from 37 weeks of gestation. As body mass index was not routinely recorded in the birth registry until 2004, additional sensitivity analyses were done for the sub-period 2004-2012, in order to quantify specifically the influence of body mass index on the decreasing stillborn rate. Finally, sensitivity analyses were conducted restricted to singletons.

## Results

During the study period, 832,935 children were born. Of these were 3,770 (0.45 %) stillbirths and 829,165 (99.55 %) live-born. The distribution of new-born and stillborn infants in different pregnancy weeks, the crude rate of stillborn per 1,000 ongoing pregnancies and per 1,000 new-born in different gestational weeks, from different gestational ages and in different periods are shown in Table 1.

The frequency of birth induction increased from 12.4 % in year 2000 to 25.1 % in 2012, with a steep increase after 2010 (**Figure 1**). The earlier birth induction reduced the per cent of children born from 42 weeks of gestation from 8.0 % in year 2000 to 1.5 % in 2012 (**Figure 1**). The increasing induction rate and fall in deliveries from 42 weeks was, however, already observable from 2001.

### *Stillbirths with increasing gestational age.*

The background for the new induction paradigm in Denmark is illustrated for the period 2000-2008 in **Figure 2**. With increasing gestational age the risk of fetal death rises, peaking after 43 weeks of gestation with more than 14 deaths per 1,000 ongoing pregnancies, a risk more than ten times higher than in the weeks before term.

During the period 2009-2012, the stillborn rates were reduced 21-39%, and from 41+3 stillbirths were eliminated (**Figure 2**).

The crude rates of fetal deaths with increasing gestational age were reduced by 30-66% when adjusting for age, year, parity, plurality, and smoking (**Figure 3**). Adjustment for body mass index did not change the estimates significantly.

### *Stillbirths by time.*

The rate of stillborn infants from 37 weeks of gestation decreased from 0.70 (95% confidence interval 0.64-0.77) per 1,000 ongoing pregnancies (prospective stillbirth rate) during the period 2000-2002 to 0.41 (0.35-0.48) during the period 2011-2012 (**Figure 4**). The corresponding rate of stillborn infants from 40 weeks fell from 1.8 (1.6-2.1) during the period 2000-2002 to 0.74 (0.56-0.98) during 2011-2012, a reduction of 60 % ( $p<0.001$ ). The fall was steepest from 2009-10 to 2011-12.

The rate of stillborn infants per 1,000 new-born after 37 weeks demonstrated a similar decrease from 2.4 (2.2-2.6) during the period 2000-2002 to 1.4 (1.2-1.6) during 2011-2012, a fall of 43% (**Figure 4**). Among children born from 40 weeks, the corresponding stillborn rates fell from 2.1 (1.9-2.4) per 1,000 new-born to 0.77 (0.58-1.0) or by 63% ( $p<0.001$ ) (**Figure 4**).

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8 169 *Regression analysis*

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10 170 Several conditions, which may have influenced the risk of fetal death, changed during the study  
11 171 period (**Table 2**). The mean age of delivering women after 37 weeks of gestation increased from  
12 172 30.1 years in 2000-2002 to 30.9 years in 2011-12, and the proportion of delivering women  $\geq 40$   
13 173 years increased from 2.0 % to 3.5 % ( $p < 0.001$ ).

14 174  
15 174 The mean body mass index increased from 24.1 kg/m<sup>2</sup> in 2003-2005 to 24.4 kg/m<sup>2</sup> during 2011-  
16 175 2012, and delivering women with a body mass index above 25 kg/m<sup>2</sup> increased from 32.0 % to  
17 175 34.4 % through the same period ( $p < 0.001$ ).

18 176  
19 177 While these changes are expected to increase the risk of fetal death, the proportion of pregnant  
20 177 smokers decreased from 20.5 % in 2000-2002 to 11.5 % in 2011-2012, almost a halving ( $p < 0.001$ ).

21 178  
22 179 The proportion of primiparous increased slightly from 43.0 % to 44.5 % through the study period,  
23 179 while the proportion of multiple pregnancies after 37 weeks was almost stable; 2.4 % in 2000-2002,  
24 180 2.6 % in 2006-2008, and 2.5 % in 2011-12 (**Table 2**). The proportion of multiple deliveries after 40  
25 181 weeks of gestation from already low 0.12 % decreased to 0.04 %. Thereby, post term multiple  
26 182 deliveries almost disappeared through the study period.

27 183  
28 183 In the fully adjusted model the following hazard ratios of fetal death were demonstrated: Smoking  
29 184 1.4 (1.2-1.6), body mass index  $> 25$  kg/m<sup>2</sup>; 1.5 (1.3-1.7), decreasing from 1.7 (1.4-2.0) during the  
30 185 period 2004-2008 to 1.3 (1.0-1.6) in 2009-2012. Primiparous had a relative risk of stillbirth of 1.2  
31 186 (1.1-1.3), and multiple pregnancy of 51.5 (44.4-59.6).

32 186  
33 187 With adjustment for gestational age at delivery, the decline in stillbirths was reduced from -41.5 %  
34 187 to -35.5 % suggesting that the general earlier induction in it self accounted for about 15 % of the  
35 188 reduction. Further adjustment for smoking, age at delivery, and parity increased the fall from -35.5  
36 189 % to -37.6 %, because the decrease in smoking counterbalanced the influence of the slightly  
37 190 increasing age and proportion of primiparous by time. By additional adjustment for plurality, the  
38 190 relative risk of stillbirth by time was reduced from -37.6 % to -31.4 %, suggesting that the changes  
39 191 in the management of twin pregnancies accounted for approximately 16 % of the decrease.

40 192  
41 193 In the sub-analysis covering the period 2004-2012, during which information about body mass  
42 193 index was available, the decreasing risk of stillbirth among women with high body mass index by  
43 194 time implied a further non significant four per cent reduction in overall stillbirth rates by time.

44 195  
45 195 The rest of the reduction in stillbirths is thus apparently due to the differential induction practice,  
46 196 where women with high-risk pregnancies are induced more proactively (earlier) than low-risk  
47 197 pregnancies,  
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49 198  
50 199 The risk of fetal death in the week after term was reduced by 33-38 % ( $p < 0.01$ ), in the week after  
51 200 41 weeks by 30-33 % ( $p < 0.01$ ), and after 42 weeks by 30-33 % ( $p < 0.05$ )(**Figure 2**). Thus, the new  
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8 203 induction paradigm firstly moved deliveries from late weeks with a high risk of stillbirth to earlier  
9 204 weeks with a lower risk. Secondly, in particular moved high-risk pregnancies to earlier induction,  
10  
11 205 but thirdly, also reduced the risk of fetal death in each post term week.

12 206 The decrease in the rate of stillbirth corresponds to a reduction in absolute numbers of stillborn  
13  
14 207 infants after 37 weeks from 136 stillbirths per year to now about 75 per year, a reduction of  
15 208 approximately 60 per year ( $p < 0.001$ ), corresponding to one saved stillborn infant per 1,000 new-  
16 209 born.  
17

18 210 During gestational weeks 37 to 40, the annual number of stillbirths fell from around 80 per year  
19 211 during the period 2000-2008 to 50 per year during 2009-2012. This reduction coincided with an  
20 212 increase in second trimester induced abortions on fetal indication from annually 292 during the  
21  
22 213 period 2000-2008 to 410 per year during the period 2009-2012, an increase of 118 induced  
23 214 abortions per year.[11]  
24

25 215 The risk of dying during the first week of life was reduced among children born after 37 weeks from  
26 216 1.7 (1.4-2.0) per 1,000 new-born in 2000 to 0.8 (0.6-1.0) per 1,000 live-born in 2012.[12]  
27

28 217 The Caesarean section rate in Denmark has after a steady increase over more than 40 years been  
29 218 stable throughout the last ten years at about 20 % of all deliveries, even with a slight reduction  
30 219 from 20.4 % in 2009 to 19.8 % in 2012 ( $p < 0.01$ ).[12]  
31

32 220 The sensitivity analysis excluding women with unknown gestational age did not change anything  
33 221 after 37 weeks, but decreased slightly the risk of fetal deaths before 37 weeks (data not shown).  
34

35 222 Sensitivity analyses restricted to singletons enhanced the fall in stillbirth rates by time. For all  
36 223 deliveries, the adjusted fall by time was -31% and for singletons -43%,  
37

## 38 224 39 40 225 41 226 **Discussion**

42  
43 227 We report a decrease in risk of fetal death after 37 weeks to 0.14 % on a national level, which is  
44 228 the lowest risk ever reported in Denmark. Nor have any similar rate to our knowledge been  
45 229 published elsewhere.  
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47 230 Ever since the 1990's, there has been an ongoing discussion of induction of labour versus  
48 231 expectant management of women after term.[7] Through the last ten years, a gradually more  
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50 232 proactive induction practice has gained ground over expectant management in several countries,  
51 233 including Denmark. The decision to make a Danish guideline in 2009 was stimulated by the NICE-  
52 234 guideline on induction of labour published in 2008 and the ACOG practice bulletin from 2009.[13,  
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8 236 Before 2009, many women were still not offered induction until after they passed 42 weeks of  
9 237 gestation. From 2009, the recommended induction regimen prevented many pregnancies from  
10 238 reaching post term gestational weeks of a high risk of fetal death. This change reduced the number  
11 239 of fetal deaths after term, but should in principle not influence the rate of deaths per 1,000 ongoing  
12 240 pregnancies in a certain post term week. The gestational age specific stillbirth rate after 41 weeks  
13 241 was, however, also reduced. This reduction could not be explained by the general earlier induction  
14 242 practice, but is according to our analyses a result of an even more proactive induction practice in  
15 243 women at an increased risk of stillbirth, such as women with body mass index >30, and women  
16 244 over 40 years. An increased fetal monitoring after term by time may also have influenced the  
17 245 decrease.

18 246 Through the last ten years, the majority of Danish units have used misoprostol for induction of  
19 247 labour, either applied vaginally or orally. It has been questioned, if induction by misoprostol could  
20 248 increase the risk of uterine hyperstimulation, asphyxia, and ultimately of neonatal death. In theory,  
21 249 an initiative to reduce the risk of fetal death could lead to neonatal complications and neonatal  
22 250 death. It is therefore important that the reduction in stillbirths was not associated with an increase  
23 251 in early neonatal deaths. On the contrary, the early neonatal deaths were halved during the study  
24 252 period, a circumstance, which undoubtedly was also influenced by an improved neonatal care  
25 253 through the study period.

26 254 It has been discussed, if induction of labour causes more Caesarean sections.[15] Some have  
27 255 argued that expectant management of labour increases the Caesarean section rate due to the  
28 256 risks associated with prolonged pregnancy.[16] The slight reduction in Caesarean sections with the  
29 257 new induction paradigm demonstrates that a proactive induction practice not necessarily increases  
30 258 the frequency of surgical interventions.

31 259 The offer of first trimester combined screening (double test and nuchal translucency scan), has in  
32 260 Denmark been widened to all pregnant women from year 2005-2006.[17] Before then, only women  
33 261 at 35 years or older were routinely offered first trimester screening. With the new routine, a majority  
34 262 of chromosomal abnormalities are detected and pregnancy most often terminated, accounting for  
35 263 the increase of approximately 118 annual second trimester induced abortions. Before the general  
36 264 screening was fully implemented, some fetuses with undetected abnormalities died later in  
37 265 pregnancy. From 20 weeks of gestation until term, 13 % of trisomy 21, 75 % of trisomy 18, and 35  
38 266 % of trisomy 13 experience fetal death [18], a majority of these before 37 gestational weeks. This  
39 267 circumstance may explain a reduction of about 15 fetal deaths per year, but only about seven after  
40 268 37 weeks corresponding to 12 % (7/60) of the observed reduction in stillborn infants.

41 269 During the study period, the quality of screening for structural abnormalities (offered in general  
42 270 throughout the period) and Doppler ultrasound both improved the monitoring of fetuses in utero,

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8 271 making it easier to detect threatened fetuses and to intervene to avoid further complications  
9 272 including fetal death. However, these circumstances are probably of minor importance for the  
10 273 decrease in stillbirths, as other countries with the same technical improvement have not observed  
11 274 a similar decrease in stillbirths. In Sweden, the proportion of deliveries after 42 weeks was 7.5 % in  
12 275 year 2000 and 6.5 % in 2011. During the same period, the stillbirth rate after 37 gestational weeks  
13 276 was stable between 1.6 and 1.9 per 1,000 new-born.[19] In Norway, 4.8 % of deliveries occurred at  
14 277 42 weeks or later, and the stillbirth rate after 37 weeks was 1.47 per 1,000 new-born [20], figures  
15 278 close to Danish figures in 2010.

16 279 The earlier induction of multiple pregnancies explained about 15 % of the reduction in stillbirths.

17 280 The selective early induction of high-risk pregnancies such as pregnancies in women with high  
18 281 body mass index, women above 40 years, and women with multiple pregnancies explains, why the  
19 282 impact of these risk factors decreased by time. Worldwide, maternal age at delivery has increased  
20 283 over the last five decades, and Denmark is no exception.[21] As high maternal age is associated  
21 284 with stillbirth, this increase should have increased the stillbirth rates slightly by time.[5, 22, 23]

22 285 Determining the optimal time to deliver necessarily involves balancing induction risks and benefits.  
23 286 According to earlier studies, the risks of post-term deliveries include an increased perinatal  
24 287 mortality, meconium aspiration, macrosomia, low umbilical cord artery pH, and low Apgar score at  
25 288 five minutes.[24] Inducing labour too early, on the other hand, may cause iatrogenic prematurity  
26 289 and respiratory complications.[25, 26]

27 290 When considering the overall risk of either fetal or infant death, previous studies have suggested  
28 291 the risk of expectant management to be lower than the risk of delivery until about 38 weeks.

29 292 Passing 38 weeks, the risk of expectant management was found to be higher than the risk of  
30 293 delivery, and the risk difference increases substantially after 40 and 41 weeks of gestation,  
31 294 favouring delivery over expectant management.[27]

32 295 [A Scottish historical cohort study by Stock et al. demonstrated similarly a substantial lower](#)  
33 296 [perinatal mortality in women induced at 41 weeks as compared with expectant management; OR](#)  
34 297 [0.30 \(95% CI 0.20-0.46\).\[28\]](#)

35 298 Among the strengths of this study are the almost complete coverage of deliveries [298], and  
36 299 access to data making an evaluation of circumstances, which might have influenced the stillbirth  
37 300 rates possible. The main limitation is the observational design, and the difficulty to account  
38 301 effectively for all potential confounders. The significant reduction in fetal deaths seen in Denmark  
39 302 has not been observed in Sweden, where the handling of post term pregnancies has undergone  
40 303 less change.[19]

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8 304 In conclusion, the striking decrease in risk of late fetal deaths through recent years is likely  
9 305 primarily to be due to the earlier and increased induction rate. The additional health costs to save  
10 these lives were low, and the reduction was obtained without an increase in surgical interventions.  
11 306

12 307 An important issue, which needs further studies, is the morbidity in new-born through the same  
13 study period, to confirm that the reduced mortality is not at the expense of an increased morbidity  
14 308 in new-born.  
15 309

16 310 Denmark already had a low stillbirth rate a decade ago.[1] With the further reduction in stillbirths,  
17 we may now have achieved the lowest stillbirth rate ever reported. We see no reason why a similar  
18 311 more proactive induction paradigm could not be implemented in other countries, with a succeeding  
19 312 further reduction in late stillbirths worldwide.  
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22 314

### 23 315 **Acknowledgements**

24 316 The study was approved by the Danish Data Protection Agency (J.no: 2013-41-2063) and the National  
25 317 Board of Health (J.no, FSEID 00000579). Ethical approval is not requested for registry based studies in  
26 318 Denmark  
27 319

### 28 319 **Contributions**

29 320 Hedegaard, Hedegaard and Lidegaard planned the study, Skovlund retrieved data from the National Birth  
30 321 Registry and National Health Registry. Mørch, Lidegaard, and Skovlund analysed the data. Hedegaard and  
31 322 Lidegaard wrote the manuscript. All authors revised the manuscript and accepted the final version. Morten  
32 323 Hedegaard is the guarantor.  
33 324

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36 326 Department of Gynaecology, Rigshospitalet, University of Copenhagen.  
37 327

### 38 327 **Conflict of interests**

39 328 All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf)  
40 329 (available on request from the corresponding author) and declare that Lidegaard within the last three years  
41 330 received honoraria for speeches in pharmacoepidemiological issues. Hedegaard, Hedegaard, Mørch and  
42 331 Skovlund did not declare any conflicts.  
43 332

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## Legends for tables and figures

### Table 1

*Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.*

### Table 2

*Characteristics of women giving birth at term and relative risk of stillbirth by time.*

### Figure 1

*Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks, respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.*

### Figure 2

*Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-2008 and 2009-2012. Number of weeks: 3,406,615. Number of fetal deaths: 3,770. Lower part the same in a semi-logarithmic plot*

### Figure 3

*Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period 2000-2012 and after adjustment for different confounders\*. Lower part the same in a semi-logarithmic plot.*

### Figure 4

*Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new-born (lower) after 37 and 40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95% confidence limits indicated.*

### Supplementary online appendix (optional)

### Table 1S

*Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.*

Table 1

Rates\* of born and stillborn in and from different gestational weeks  
and periods in Denmark 2000-2012.

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
<b>Number of born and stillborn infants</b>								
<b>Born (n)</b>	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
<b>Stillborn (n)</b>	835	915	992	539	489	2,742	1,028	3,770
<b>Stillbirths per 1,000 ongoing pregnancy weeks (prospective risk of stillbirth)</b>								
<b>&lt;37</b>	0.22	0.20	0.21	0.17	0.17	0.21	0.17	0.20
<b>37+0-6</b>	0.39	0.46	0.39	0.27	0.23	0.41	0.25	0.37
<b>38+0-6</b>	0.36	0.51	0.46	0.41	0.34	0.44	0.38	0.42
<b>39+0-6</b>	0.56	0.54	0.63	0.44	0.46	0.57	0.45	0.54
<b>40+0-6</b>	1.20	0.95	0.97	0.93	0.76	1.04	0.85	0.98
<b>41+0-6</b>	2.29	2.40	1.73	1.35	0.54	2.15	0.98	1.82
<b>42+</b>	15.55	6.09	11.16	6.60	7.83	11.60	6.96	10.86
<b>Total</b>	0.35	0.29	0.28	0.23	0.21	0.30	0.22	0.27
<b>From 37 w</b>	0.70	0.67	0.63	0.50	0.41	0.67	0.46	0.61
<b>From 40 w</b>	1.84	1.43	1.30	1.10	0.74	1.54	0.93	1.36
<b>From 41 w</b>	3.12	2.46	2.09	1.51	0.69	2.60	1.14	2.21
<b>Stillborn per 1.000 new-born</b>								
<b>From 37 w</b>	2.39	2.21	2.07	1.68	1.36	2.23	1.52	2.02
<b>From 40 w</b>	2.11	1.59	1.41	1.20	0.77	1.71	0.99	1.50
<b>From 41 w</b>	2.43	1.82	1.46	1.04	0.41	1.93	0.73	1.57
<b>From 42 w</b>	3.16	1.05	1.55	0.82	0.95	2.04	0.86	1.79

\*) Absolute numbers given in supplementary appendix Table 1S.

Table 2

*Characteristics of women giving birth at term and  
relative risk of stillbirth by time.*

	2000-02	2003-05	2006-08	2009-10	2011-12
<b>Mean age</b>	30.1	30.6	30.8	30.9	30.9
<b>Mother ≥40 yrs</b>	3,584	4,366	5,436	3,740	3,777
<b>% ≥40 years</b>	2.0	2.4	3.0	3.2	3.5
<b>BMI recorded (n)</b>	na	112,635	167,962	111,972	106,201
<b>Mean BMI</b>	na	24.1	24.2	24.3	24.4
<b>BMI &gt;25</b>	na	36,076	54,903	37,616	36,528
<b>% BMI &gt;25</b>	na	32.0	32.7	33.6	34.4
<b>BMI &gt;30</b>	na	12,480	19,683	13,946	13,720
<b>% BMI &gt;30</b>	na	11.1	11.7	12.5	12.9
<b>BMI &gt;35</b>	na	4,032	6,813	4,880	4,689
<b>% BMI &gt;35</b>	na	3.6	4.1	4.4	4.4
<b>Smoker</b>	37,540	30,782	25,656	14,891	12,527
<b>% smokers</b>	20.5	17.1	14.2	12.6	11.5
<b>Multiple pregnancies</b>	4,353	4,617	4,727	3,116	2,747
<b>% multiples</b>	2.4	2.6	2.6	2.6	2.5
<b>Stillborn multiples</b>	51	111	61	40	29
<b>% stillborn multiples</b>	1.2	2.4	1.3	1.3	1.1
<b>Para 0</b>	78,718	77,231	77,685	51,675	48,584
<b>% Para 0</b>	43.0	42.9	43.0	43.8	44.5
<b>Regression analysis</b>	<b>Hazard ratio<sup>§</sup> of stillborn (2000-2002 reference)</b>				
<b>Crude<sup>#</sup></b>	1	0.95	0.89	0.72	0.59
<b>Adjusted for GA<sup>¶</sup></b>	1	1.02	0.98	0.78	0.65
95% confidence intervals		0.89-1.17	0.85-1.12	0.66-0.92	0.53-0.78
<b>Adjusted excpt, Plurality<sup>**</sup></b>	1	1.03	0.89	0.73	0.62
95% confidence intervals		0.90-1.18	0.78-1.03	0.61-0.86	0.52-0.75
<b>Fully Adjusted<sup>**¶</sup></b>	1	1.07	0.96	0.78	0.69
95% confidence intervals		0.93-1.23	0.83-1.11	0.65-0.92	0.57-0.83

\*) Adjusted only for age, smoking, and parity \*\*\*) Additionally adjusted for plurality

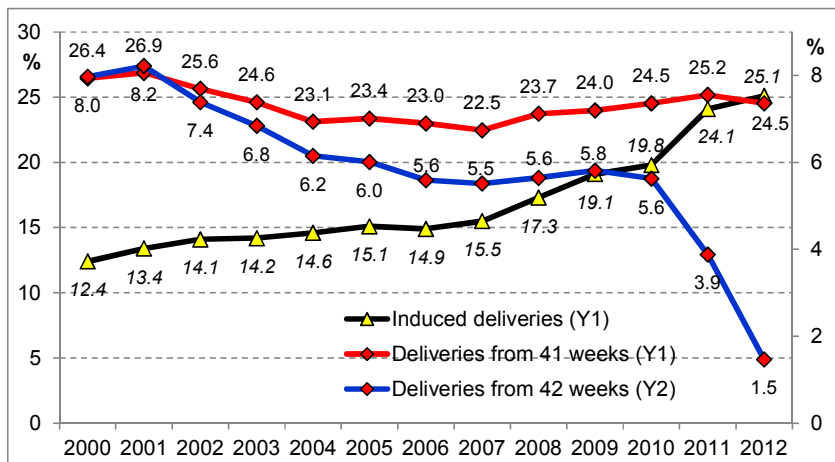
§) Hazard ratios by cox regression. The crude estimates were calculated by logistic regression, and the risk estimates were odds ratios



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**Figure 1**

Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks, respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.



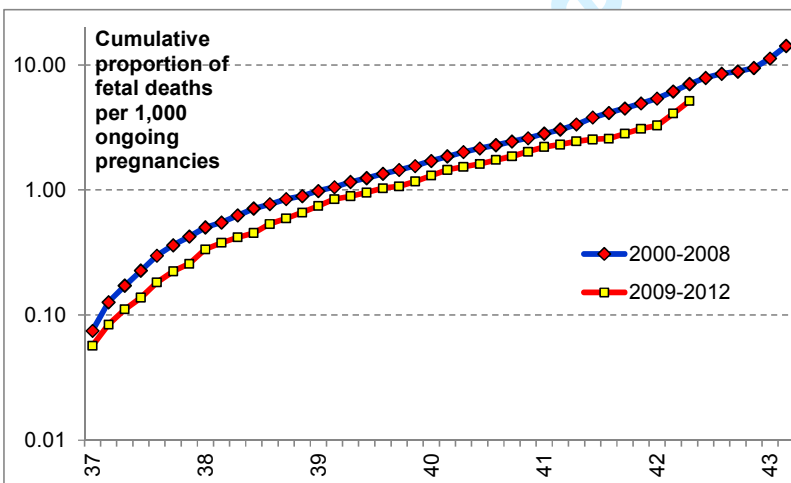
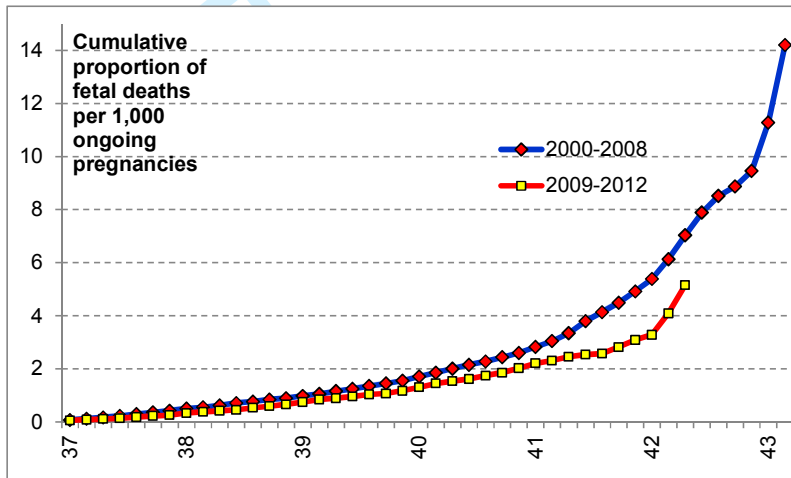
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Figure 2

Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-2008 and 2009-2012.

Number of weeks: 3,406,615, Number of fetal deaths: 3,770.

Lower part the same in a semi-logarithmic plot.

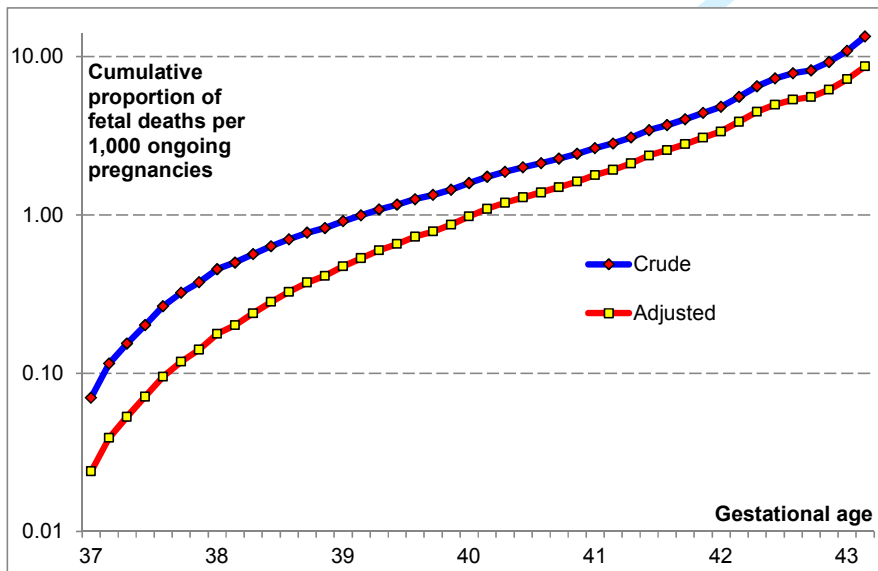
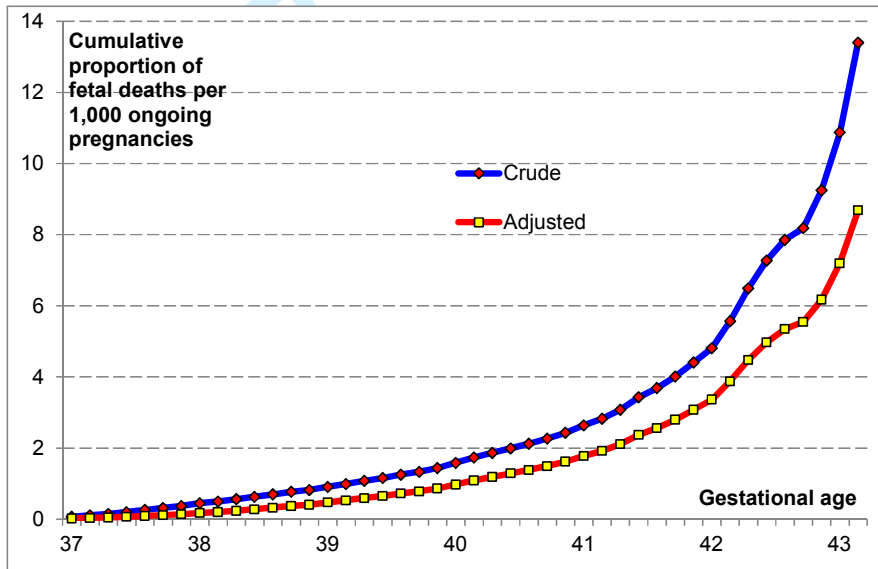


**Figure 3**

Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period 2000-2012 and after adjustment for different confounders\*.

Number of weeks: 3,406,615. Number of fetal deaths: 3,770.

Lower part the same in a semi-logarithmic plot

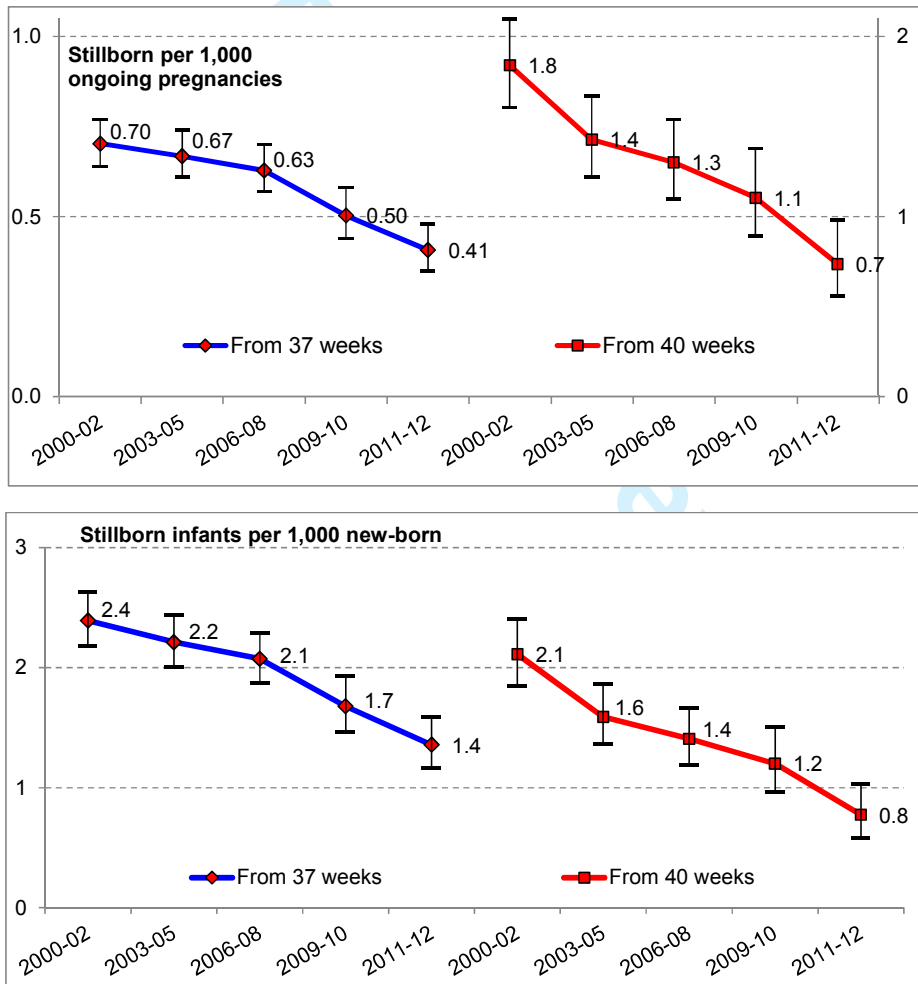


\*) Adjusted for age, calendar year, parity, plurality, and smoking

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**Figure 4**

*Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new born (lower) after 37 and 40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95% confidence limits indicated.*



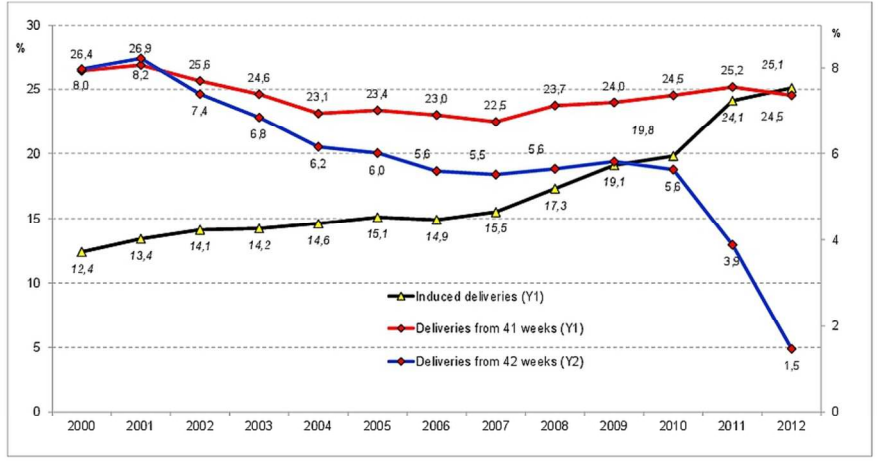
## Online supplement

Table 1S

*Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.*

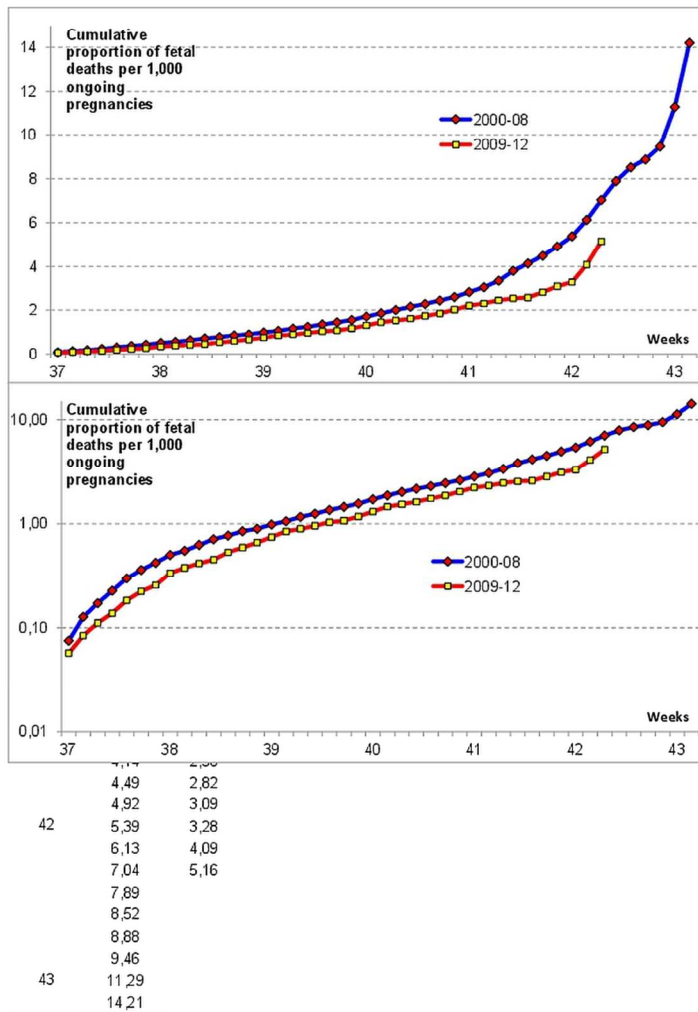
	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
<b>New-born</b>								
<b>&lt;37</b>	14,127	14,806	15,171	9,212	8,693	44,104	17,905	62,009
<b>37+0-6</b>	10,964	12,129	11,533	7,066	6,369	34,626	13,435	48,061
<b>38+0-6</b>	24,807	27,976	28,521	17,757	16,121	81,304	33,878	115,182
<b>39+0-6</b>	42,212	42,303	42,711	27,282	24,523	127,226	51,805	179,031
<b>40+0-6</b>	53,193	51,410	52,874	35,005	32,777	157,477	67,782	225,259
<b>41+0-6</b>	36,415	33,813	34,267	23,570	26,106	104,495	49,676	154,171
<b>42+</b>	15,504	12,337	10,946	7,273	3,162	38,787	10,435	49,222
<b>Total</b>	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
<b>37+</b>	183,095	179,968	180,852	117,953	109,058	543,915	227,011	770,926
<b>40+</b>	105,112	97,560	98,087	65,848	62,045	300,759	127,893	428,652
<b>41+</b>	51,919	46,150	45,213	30,843	29,268	143,282	60,111	203,393
<b>Number of stillborn infants</b>								
<b>&lt;37</b>	397	517	617	341	341	1,531	682	2,213
<b>37+0-6</b>	72	83	70	32	25	225	57	282
<b>38+0-6</b>	62	85	78	46	35	225	81	306
<b>39+0-6</b>	82	75	89	41	40	246	81	327
<b>40+0-6</b>	96	71	72	47	36	239	83	322
<b>41+0-6</b>	77	71	49	26	9	197	35	232
<b>42+</b>	49	13	17	6	3	79	9	88
<b>Total</b>	835	915	992	539	489	2,742	1,028	3,770
<b>37+</b>	438	398	375	198	148	1211	346	1557
<b>40+</b>	222	155	138	79	48	515	127	642
<b>41+</b>	126	84	66	32	12	276	44	320

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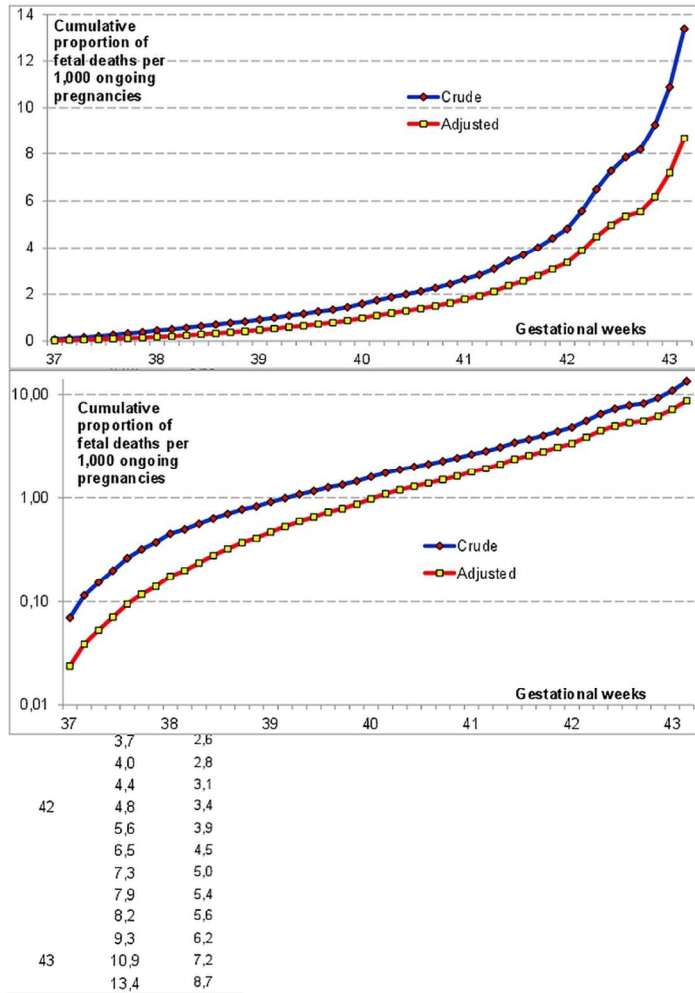
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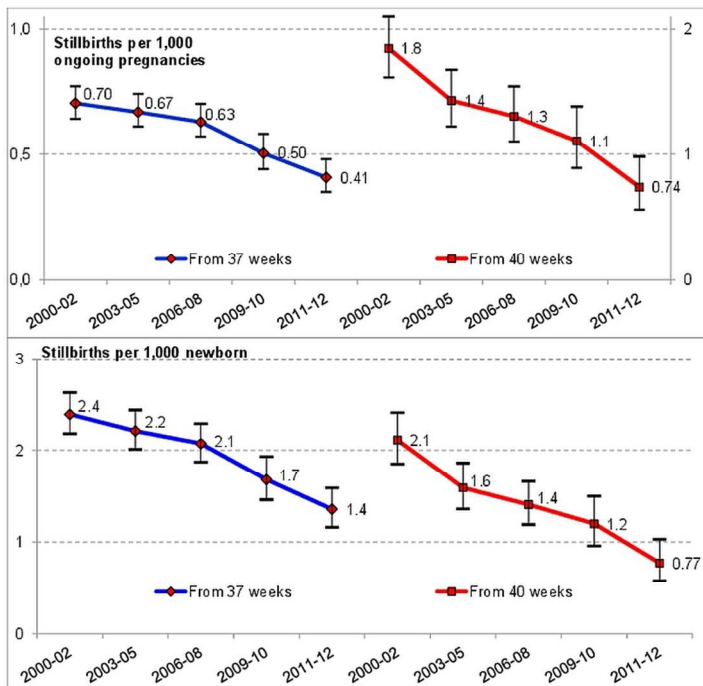
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## Online supplement

Table 1S

*Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.*

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<b>40+</b>	222	155	138	79	48	515	127	642
<b>41+</b>	126	84	66	32	12	276	44	320

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

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract: <i>Line 35</i> (b) Provide in the abstract an informative and balanced summary of what was done and what was found: <i>Line 38-43</i>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported: <i>Line 66-76</i>
Objectives	3	State specific objectives, including any prespecified hypotheses: <i>Line 73-76</i>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper: <i>Page 3 line 79</i>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection: <i>Line 79-80</i>
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up: <i>Line 81-86</i> (b) For matched studies, give matching criteria and number of exposed and unexposed: <i>This study was not matched</i>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable: <i>Line 88-93</i>
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: <i>Line 79-87</i>
Bias	9	Describe any efforts to address potential sources of bias: <i>Line 106-119</i>
Study size	10	Explain how the study size was arrived at: <i>Line 84</i>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: <i>Line 88-119</i>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding: <i>Line 106-119</i> (b) Describe any methods used to examine subgroups and interactions: <i>116-119</i> (c) Explain how missing data were addressed: <i>Line 94-98</i> (d) If applicable, explain how loss to follow-up was addressed: <i>Line 94-98</i> (e) Describe any sensitivity analyses: <i>Line 119</i>
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals included in the study, completing follow-up, and analysed: <i>Line 94-98, 123-127</i> (b) Give reasons for non-participation at each stage: <i>Not relevant</i> (c) Consider use of a flow diagram: <i>Not relevant in this case</i>
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders: <i>Table 1</i> (b) Indicate number of participants with missing data for each variable of interest: <i>Line 94-98</i> (c) Summarise follow-up time (eg, average and total amount): <i>Not relevant</i>
Outcome data	15*	Report numbers of outcome events or summary measures over time: <i>Table 1, Table 2 and Table 1S, Line 133-152</i>

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: <i>Fig. 2 and Fig. 3</i>
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7			(b) Report category boundaries when continuous variables were categorized: <i>Line Table 1</i>
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10			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period: <i>Line 144-152, 191-193</i>
11			
12	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses: <i>Line 206-207</i>
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15	<b>Discussion</b>		
16	Key results	18	Summarise key results with reference to study objectives: <i>Line 211-2123</i>
17	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. <i>Line 280-283</i>
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20	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. <i>Line 252-261</i>
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24	Generalisability	21	Discuss the generalisability (external validity) of the study results: <i>Line 239-242</i>
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27	<b>Other information</b>		
28	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: <i>Line 299-306</i>
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\*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>.