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The relationship between a uterine fibroid diagnosis and the risk of preterm birth, a cohort study.

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Title page

Title

The relationship between a uterine fibroid diagnosis and the risk of preterm birth, a cohort study.

Running title

Uterine fibroids and preterm birth

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Abstract

Objective: The aim was to investigate the association between clinically significant uterine fibroids and preterm birth, caesarean section (CS), postpartum haemorrhage (PPH), placental abruption, intrauterine growth restriction (IUGR), and uterine rupture.

Methods, participants, and setting: A historical cohort study based on data from the Danish National Birth Cohort (DNBC), the Danish National Patient Registry (DNPR), and the Danish National Birth Registry (DNBR). The final study population consisted of 92,696 pregnancies and was divided into four groups for comparison. Group 1: pregnancies of women without a fibroid diagnosis code or fibroid operation code; Group 2: pregnancies of women with a fibroid diagnosis code before pregnancy, during pregnancy, or up to one year after delivery, and no fibroid operation code before pregnancy; Group 3: pregnancies of women with a fibroid diagnosis code given more than one year after delivery; and Group 4: pregnancies of women with a fibroid operation code given before pregnancy.

Results: A diagnosis of fibroids before pregnancy gives an increased risk of preterm birth ≤ gestational age (GA) of 37 weeks (OR 2.3 (1.30–3.96)) and extreme preterm birth (GA 22+0–27+6 weeks, OR 20.1 (8.04–50.22)). The risk of CS was increased (OR 1.8 (1.23–2.72)) for women with a fibroid diagnosis code given before pregnancy; i.e., increased risk of elective CS (OR 1.9 (1.11–3.32)), but not acute CS (OR 1.5 (0.94–2.52)). The risks of PPH, placental abruption or IUGR were not increased in any of the groups.

Conclusion: We found a strong association between uterine fibroid diagnosis and preterm birth -–extreme preterm birth in particular.

Strengths and limitations of this study:

- This study explores an area with inconsistent evidence.
- This study is a large cohort study with data from 92,696 pregnancies.
- Limitations include a low prevalence of uterine fibroids and a small number of events.

Introduction

As many as 10 % of pregnant women may have uterine fibroids [1], and the incidence is likely to be even higher in populations with high maternal age and obesity [2, 3]. Fibroids may affect the uterine cavity, the placenta, and the foetus directly, but may also cause the myometrium to be more inflexible and less responsive to oxytocin [4, 5]. Overall, fibroids are associated with obstetrical complication rates of 10–40 % [6, 7], many of which have severe consequences. Due to the clinical impact on the mother and child, outcomes such as preterm birth, caesarean section (CS), postpartum haemorrhage (PPH), placental abruption, intrauterine growth restriction (IUGR), and uterine rupture have been evaluated in relation to uterine fibroids [6-11]. Some studies showed an association between fibroids and preterm birth, CS, PPH, and placental abruption [8, 9, 12-14], whereas other studies showed no association with preterm birth, CS, PPH, and IUGR [7, 13, 15].

To address these discrepancies, we conducted a large historical cohort study of unselected pregnant women. We focused on women with clinically significant fibroids and compared women with a uterine fibroid diagnosis code to a reference group of women without a uterine fibroid diagnosis code. The aim was to investigate the association between clinically significant uterine fibroids and obstetrical outcomes with a specific focus on preterm birth, CS, PPH, placental abruption, IUGR, and uterine rupture. Moreover, we analysed the association between myomectomy and the risk of uterine rupture.

Materials and methods

This historical cohort study is based on data from the Danish National Birth Cohort (DNBC), the Danish National Birth Registry (DNBR), and the Danish National Patient Registry (DNPR).

Study population

The DNBC is a pregnancy cohort consisting of data from 92,840 women and 101,042 pregnancies. All registered pregnancies were included. Enrolment was performed in early pregnancy during the period between 1996–2002. Inclusion criteria were the intention to carry a pregnancy to term, residency in Denmark, and sufficient Danish proficiency to participate in telephone interviews. Data was collected by computer-assisted telephone interviews twice during pregnancy, and subsequently when the children were six and eighteen months old. The DNBC data collection was approved by the Danish National Ethics Board. More details about this cohort have previously been described in detail [16].

The DNPR holds diagnosis and operation codes from all in-patients since 1977 and out-patients since 1995. The codes are classified according to the International Classification of Diseases ICD10 since 1994. Diagnosis and operation codes regarding fibroids were collected for this study.

The DNBR contains information about live births and complications of all registered births in Denmark since 1973.

Selected relevant data from the DNPR and the DNBR was linked to data from the DNBC, using the unique personal identification number given to all residents in Denmark.

Data

We collected data on maternal age, height, weight, smoking habits, expected date of birth, fertility treatment, and time to pregnancy (TTP) from the DNBC. Maternal body mass index (BMI) (kg/m^2) was calculated based on self-reported pre-pregnancy weight and height.

Fibroid diagnosis codes (DD25–DD259) and fibroid operation codes were collected from the DNPR. Operation codes were: myomectomy (KLCB10), laparoscopic myomectomy (KLCB11), hysteroscopic myomectomy (KLCB20), hysteroscopic resection of pathological tissue (KLCB22), hysteroscopic excision of pathological tissue (KLCB25), and hysteroscopic excision of other pathological tissue (KLCB98). We categorised operation codes into laparoscopic or open myomectomy (KLCB10, KLCB11) and hysteroscopic myomectomy (KLCB20, KLCB22, KLCB25, and KLCB98). Operation codes of the resection and excision of pathological tissue were pooled into one group of myomectomy since we assumed that many use these codes for hysteroscopic myomectomy.

Gestational age (GA), birth weight of the child, and data on obstetrical outcomes (caesarean section (KMCA10A, KMCA10D, KMCA10E, and KMCA10B), placental abruption (DO450, DO451, DO452, DO453, DO458, and DO459)), and PPH (DO720, DO721, DO721A, and DO721B) were collected from the DNBR.

Exposure definition

The study population was divided into four groups for comparison. Group 1: pregnancies of women without a fibroid diagnosis code or operation code; Group 2: pregnancies of women with a fibroid diagnosis code before pregnancy, during pregnancy, or up to one year after delivery, and no operation code before pregnancy; Group 3: pregnancies of women with a fibroid diagnosis code given more than one year after delivery; and Group 4: pregnancies of women with an operation code given before pregnancy.

Outcome definition

The outcomes were preterm birth, CS, placental abruption, PPH, IUGR and uterine rupture.

Preterm birth was defined as delivery at GA 22+0–36+6 weeks. We divided preterm birth into three categories according to the international classifications. Moderate preterm: GA 34+0–36+6 weeks, very preterm: GA 28+0–33+6 weeks, and extreme preterm: GA 22+0–27+6 weeks. Due to the small number of events, we merged the groups into clinically relevant binary outcomes: moderate preterm: GA 34+0–36+6 weeks and very and extreme preterm GA 22+0–33+6 weeks.

CS was categorised as acute (KMCA10A, KMCA10D, and KMCA10E) or elective (KMCA10B).

Placental abruption was reported under several diagnosis codes (DO450, DO451, DO452, DO453, DO458, and DO458) and pooled into one group.

PPH was defined as bleeding during delivery and up to 24 hours postpartum (DO720, DO721, DO721A, and DO721B).

We followed the international classification of small of gestational age/IUGR as a birth weight below -22% of the expected weight at a given GA. This classification was originally developed by the 1995 World Health Organization (WHO) expert committee [17]. We used a lower limit of -60 % based on clinical reasoning; all births with an expected birth weight below -60% were excluded due to potential misclassification.

Data from the group of women who had a myomectomy before pregnancy was used to analyse the association between myomectomy and the risk of uterine rupture (DO710, DO711).

Data purification

During the data purification, we made some assumptions. If a uterine fibroid diagnosis code was given once, the woman was categorised as having at least one uterine fibroid during the study period, unless she had a fibroid operation code. A fibroid diagnosis code given more than 90 days after a fibroid operation code was interpreted as a new uterine fibroid. We assumed the fibroid to be present also before

pregnancy, if a fibroid diagnosis code was given during pregnancy or up to one year postpartum, and data were included in the fibroid group.

Missing values were identified and analysed. We had an 87% complete dataset. Missing values were imputed by multiple imputations of multiple variables (MICE) assuming that values were missing at random. Analyses were made before and after imputation.

We identified the potential confounders for each outcome based on the DAG (directed acyclic graph) [18]. For preterm birth, CS, and PPH, we identified maternal age and BMI to be possible confounders. For placental abruption, we identified maternal age to be a possible confounder. For IUGR and uterine rupture, we did not identify any possible confounders.

We found that 317 women had a myomectomy before pregnancy (205 by hysteroscopy and 112 by laparoscopy).

Statistical analyses

A one-way ANOVA was used for comparison of normally distributed data such as age. The Kruskal–Wallis test was used for comparison of non-normally distributed data such as BMI and parity. Smoking habits and fertility treatment were compared using the Chi–square test.

We used logistic regression analysis to compare the binary outcomes; preterm birth, CS, PPH, placental abruption, IUGR, and uterine rupture. We adjusted for potential confounders identified by DAGs in all analyses. By using robust standard errors, we accounted for some women being included with more than one pregnancy in the analyses.

We found the tests acceptable based on the Hosmer–Lemeshow goodness of fit test.

Subgroup analyses of women with a fibroid operation code before pregnancy were performed.

We performed stratified analyses for preterm birth regarding fertility treatment and multiple pregnancies.

All analyses were performed in STATA 15.

Patient and Public involvement statement

Participant in the DNBC are involved in all research based on data from the DNBC. A member of the DNBC ambassadors, which is a group of selected participants representing all participants, is represented in the DNBC reference group. There was no other patient or public involvement in this study.

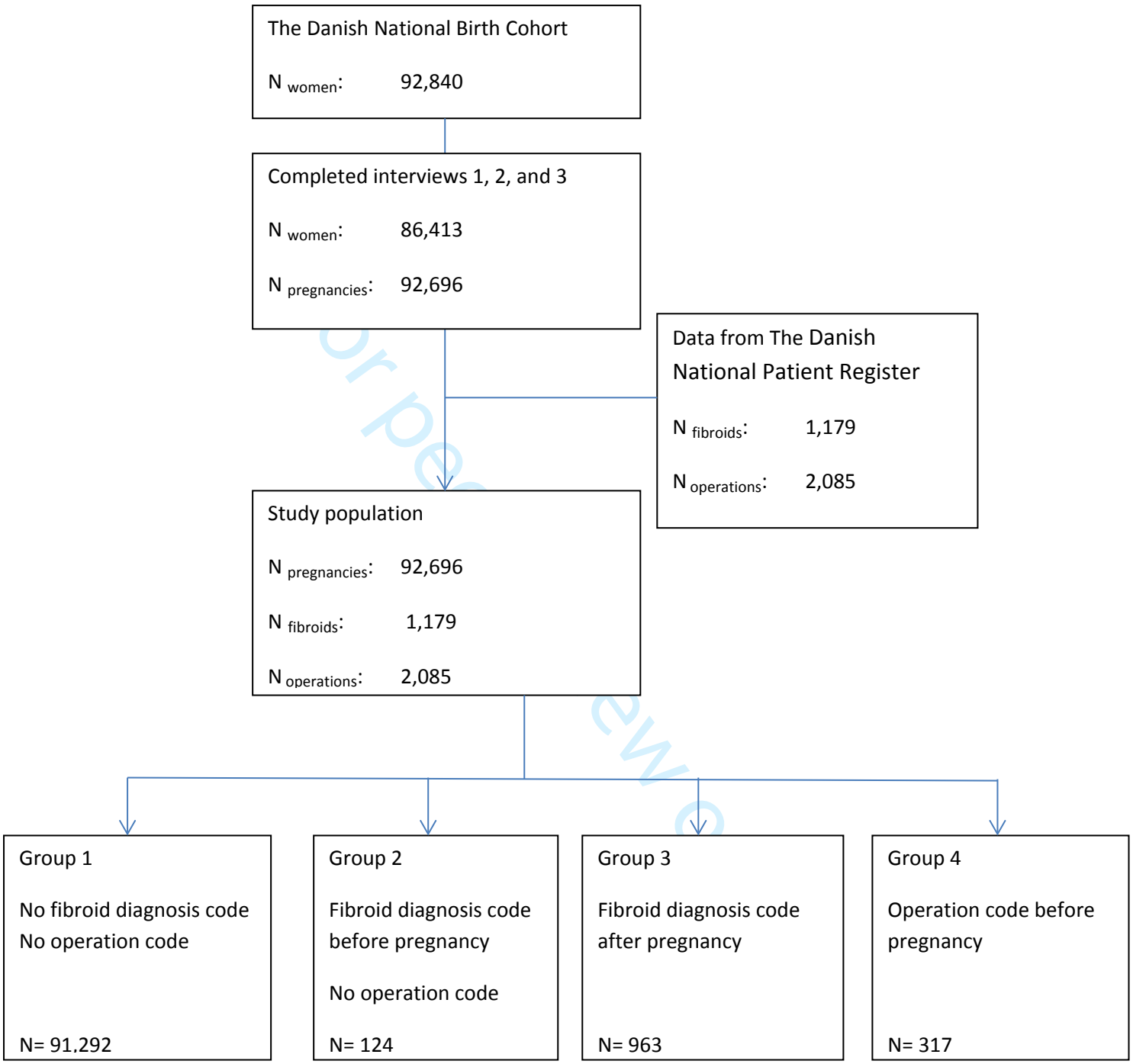
Ethical approval

This study was approved by the Danish Data Protecting Agency (registration number; 2012-58-0018). According to Danish law, ethical approval is not required for registry-based studies.

Results

Our final study population consisted of 86,323 women and 92,696 pregnancies, divided into the four exposure groups. (Fig. I)

Figure 1: Flowchart of the study population



Population characteristics for the four exposure groups are shown in Table I. The groups did not differ regarding BMI, but they differed regarding age, smoking habits, parity, multiple pregnancies, and proportion of fertility treatment.

Table 1: Population characteristics

	No fibroids	**Fibroids before pregnancy No operation**	**Fibroids after pregnancy**	**Fibroid operation before pregnancy**
Population, N	91,292	124	963	317
Age ,years Mean(SD)	30 (4.29)	34 (4.15)	32 (3.96)	34 (4.16)
BMI, kg/m² median(range)	23 (10-64)	23 (16-40)	23 (16-49)	22 (18-35)
Parity median (range)	1 (0-14)	1 (0-3)	1 (0-5)	0 (0-3)
Smoking, %	16.43	11.82	16.04	13.15
Fertility treatment, %	6.32	18.48	9.76	39.39
Multiple pregnancy,%	2.14	4.03	3.95	7.89

Preterm birth

The risk of overall preterm birth was increased among the group of women who had a fibroid diagnosis code before pregnancy compared to women without a fibroid diagnosis code, OR 2.3 (1.30–3.96). The risk of moderately preterm birth was not increased, OR 0.6 (0.20–1.96), whereas the risk of very preterm, extreme preterm, and the pooled group of very and extreme preterm birth, was significantly increased, OR 4.00 (1.75–9.13), OR 20.1 (8.04–50.22), and OR 6.5 (3.51–12.19), respectively. For the group of women with a fibroid diagnosis code after pregnancy, the risk of preterm birth was not increased. The group of women who had an operation before pregnancy had an increased risk of overall preterm birth of OR 1.8 (1.24–2.65) and very preterm birth OR 2.8 (1.55–5.22). None delivered extremely preterm (Table II).

Tabel 2 Results

	No fibroids	Fibroids before pregnancy No operation		Fibroids after pregnancy		Fibroid operation before pregnancy	
	(N=91,292)	(N=124)	Odds ratio (95%CI)	(N=963)	Odds ratio (95%CI)	(N=317)	Odds ratio (95%CI)
Preterm birth* (week)							
≤ 37	4,939 (5.4%)	14 (11.3%)	2.27 (1.30-3.96)	55 (5.7%)	1.08 (0.82-1.42)	29 (9.1%)	1.81 (1.24-2.65)
≥ 34 < 37	3,506 (3.9%)	3 (2.4%)	0.62 (0.20-1.96)	41 (4.3%)	1.11 (0.81-1.53)	18 (5.7%)	1.52 (0.94-2.43)
≥ 28 < 34	1,159 (1.2%)	6 (4.8%)	3.99 (1.75-9.13)	11 (1.4%)	0.90 (0.50-1.64)	11 (5.5%)	2.84 (1.55-5.22)
≥ 22 < 28	176 (0.2%)	5 (4.0%)	20.09 (8.04-50.22)	3 (0.3%)	1.56 (0.50-4.89)	0 (0%)	Empty
≥ 22 < 34	1,335 (1.5%)	11 (8.9%)	6.54 (3.51-12.19)	14 (1.5%)	0.99 (0.58-1.69)	11 (3.5%)	2.44 (1.33-4.48)
Caesarean section*							
Overall	14,542 (16%)	36 (29%)	1.83 (1.23-2.72)	164 (17%)	0.99 (0.84-1.19)	110 (35%)	2.48 (1.94-3.16)
Acute	9,901 (11%)	21 (17%)	1.54 (0.94-2.52)	116 (12%)	1.08 (0.88-1.32)	62 (20%)	1.91 (1.44-2.52)
Planned	4,641 (5%)	15 (12%)	1.92 (1.11-3.32)	48 (5%)	0.85 (0.64-1.14)	48 (15%)	2.58 (1.85-3.60)
IUGR*	3,731 (4.1%)	6 (4.8%)	1.27 (0.57-2.85)	35 (3.6%)	0.91 (0.65-1.28)	13 (4.1%)	1.05 (0.60-1.83)
PPH*	3,364 (3.7%)	7 (5.7%)	1.70 (0.70-3.65)	36 (3.7%)	1.06 (0.76-1.47)	15 (4.7%)	1.40 (0.84-2.35)
Abruption placentae**	490 (0.5%)	1 (0.8%)	1.41 (0.20-10.15)	6 (0.6%)	1.13 (0.50-2.53)	3 (0.9%)	1.66 (0.53-5.21)
Uterus rupture	7 (0.1%)	0 (0%)	Empty	2 (0.2%)	2.84 (0.39-20.56)	0 (0%)	Empty

* adjusted for age and BMI

** adjusted for age

We stratified accordingly to fertility treatment and found an increased risk of extremely preterm birth (OR 25.6 (7.95–82.43)) among women treated for infertility and among spontaneously pregnant women (OR 8.4 (1.08–15.76)). The same was applicable for the pooled group of very and extreme preterm birth where increased risk was found for women with fertility treatment OR 5.6 (2.24–13.85) and spontaneous pregnancy OR 4.5 (1.28–15.76). In women with a fibroid diagnosis code before pregnancy, the risk of preterm birth was not increased in any other groups (Table III).

Table 3: Results, stratified analyses, OR

	Fibroids before pregnancy No operation Odds ratio(95%CI)	Odds ratio(95%CI)	Fibroids after pregnancy Odds ratio(95%CI)	Odds ratio(95%CI)	Operation before pregnancy Odds ratio(95%CI)	Odds ratio(95%CI)
	No fertility treatment N=81,836	Fertility treatment N=5,522	No fertility treatment N=81,836	Fertility treatment N=5,522	No fertility treatment N=81,836	Fertility treatment N=5,522
Preterm birth (week)						
≤ 37	1.74(0.75-4.02)	1.37(0.39-4.76)	1.04(0.77-1.41)	0.93(0.51-1.72)	1.05(0.49-2.25)	1.06(0.59-1.92)
≥ 34 < 37	0.37(0.05-2.69)	Empty	1.02(0.71-1.47)	1.20(0.62-2.33)	1.24(0.55-2.80)	0.97(0.47-2.02)
≥ 28 < 34	2.45(0.60-10.02)	3.37(0.77-14.85)	0.94(0.48-1.81)	0.55(0.13-2.25)	0.64(0.09-4.61)	1.47(0.59-3.60)
≥ 22 < 28	25.60(7.95-82.43)	8.36(1.08-64.50)	2.13(0.68-6.69)	Empty	Empty	Empty
≥ 22 < 34	5.57(2.24-13.85)	4.5(1.28-15.76)	1.09(0.62-1.93)	0.46(0.17-1.87)	1.09(0.62-1.93)	1.22(0.49-3.04)
	Singleton pregnancy N= 89,338	Multiple pregnancies N=1,964	Singleton pregnancy N= 89,338	Multiple pregnancies N=1,964	Singleton pregnancy N= 89,338	Multiple pregnancies N=1,964
Preterm birth (week)						
≤ 37	1.90 (0.32-11.45)	2.18 (1.17-4.05)	0.66 (0.34-1.30)	1.02 (0.75-1.39)	1.17(0.53-2.59)	1.33(0.81-2.16)
≥ 34 < 37	0.76 (0.24-2.40)	Empty	0.99 (0.68-1.42)	0.99 (0.49-2.03)	1.26(0.68-1.42)	0.77(0.31-1.95)
≥ 28 < 34	3.41(1.25-9.28)	4.40 (0.73-26.48)	0.96 (0.50-1.86)	0.37 (0.09-1.53)	1.71(0.70-4.15)	2.09(0.82-5.27)
≥ 22 < 28	22.32 (8.18-60.92)	12.95 (1.41-118.77)	2.08 (0.66-6.56)	Empty	Empty	Empty
≥ 22 < 34	6.11 (2.99-12.51)	8.4 (1.41-50.93)	1.11 (0.63-1.98	0.31 (0.75-1.31)	1.48(0.61-3.59)	1.78(0.71-4.50)

We also stratified according to singleton pregnancies. Among singleton pregnant women with a fibroid diagnosis code before pregnancy, we found an increased risk of very preterm of OR 3.4 (1.25–9.28), extreme preterm of; OR 22.3 (8.18–60.92), and the pooled group of very and extreme preterm birth of OR 6.1 (2.99–12.51). Apart from that, the risk of preterm birth was not increased in any other groups (Table III). For multiple pregnancy women with a fibroid diagnosis code before pregnancy, we found an increased risk of overall preterm of OR 2.2 (1.17–4.05), very preterm OR 4.4 (0.73–26.48), extreme preterm OR 13.0 (1.41–118.77), and pooled very and extreme preterm birth OR 8.5 (1.41–50.93). Apart from that, the risk of preterm birth was not increased in any other groups (Table III). The risk of preterm birth was increased regardless of stratification according to fertility treatment (with and without) and type of pregnancy (singleton or multiple) (data not shown).

Caesarean section

The overall risk of CS was increased in women with a fibroid diagnosis code before pregnancy, OR 2.2 (1.50–3.21). The same applied after adjusting for age and BMI of OR 1.8 (1.23–2.72). The risk of acute CS was not increased in the adjusted analyses, OR 1.5 (0.94–2.52). The risk of elective CS was increased, OR 2.6 (1.50–4.41), and the same applied after adjusting for age and BMI, OR 1.9 (1.11–3.32). For the group of women with an operation code before pregnancy, the risk of CS was also increased; OR 2.6 (1.85–3.60) for elective CS and OR 1.9 (1.44–2.52) for acute CS. The risk of CS was not increased in women with a fibroid diagnosis code after pregnancy (Table II).

PPH, placental abruption, and IUGR

The risk of PPH, placental abruption and IUGR was not increased in women with a fibroid diagnosis code; PPH OR 1.7 (0.70–3.65), placental abruption OR 1.4 (0.20–10.15), and IUGR OR 1.3 (0.57–2.85) (Table II).

Uterine rupture

We found no uterine ruptures in the group with an operation code before pregnancy (N=317, 112 laparoscopic myomectomies, and 205 hysteroscopic myomectomies). Uterine rupture was diagnosed in 67 of the 91,292 (0.1%) women without a fibroid diagnosis code. Two women out of the 963 with a fibroid diagnosis code after pregnancy (0.21%) were diagnosed with uterine rupture, and no women out of 124 (0%) had uterine rupture and a fibroid diagnosis code before pregnancy.

Discussion

Women with a uterine fibroid diagnosis code had a significantly higher risk of preterm birth in general, extreme preterm birth in particular. The fact that the association persisted through all the analyses, irrespective of the mode of conception, number of foetuses, age, and BMI enhances the robustness and significance of our results.

Previous studies that differed in design in terms of exposure and outcome found weaker associations. A previous systematic review from 2008 reported a cumulative preterm birth rate (before GA 37 weeks) of 16% among women with fibroids corresponding to an OR of 1.5 (1.3–1.7). None of the included studies, however, adjusted for potential confounders such as age and BMI [8]. A recent case series from 2018 reported a preterm birth rate of 28% in women with uterine fibroids. This study did not include a reference group without fibroids, and a calculation of the estimated risk was not possible [19]. All previous studies used different classifications of preterm birth, which further complicates comparison. Three historical cohort studies all showed an increased risk of preterm birth (GA <37 weeks), but they used different categorisation regarding GA. Thus, Arisoy et al. reported an OR 4.7 (1.9–11.6) for preterm birth <37, OR 4.3 (2.0–13.9) for preterm birth <34 weeks, decreasing to OR 3.3 (0.8–13.4) for preterm birth <32 weeks [20]. Blitz et al also categorized preterm birth into groups depending on GA and found OR 1.61 (1.16–2.23) for preterm birth 34–36 weeks, OR 2.99 (1.65–5.40) for preterm birth 32–33 weeks, OR 1.47 (0.59–3.67) for 28–31 weeks, and OR 1.81 (1.49–2.19) for 20–27 weeks[21]. In contrast, Lai et al. found an increased risk of preterm birth with decreasing gestational age; OR 1.70 (1.12–2.58) for 24–34 weeks, OR 1.99 (1.05–3.75)

for 24–28 weeks and OR 2.48 (1.38–4.44) for 20–27 weeks [22]. All three cohort studies included women who had undergone a routine second-trimester obstetrical ultrasound, which was the basis for inclusion into the exposure or control group. Women in our cohort study were included based on a fibroid diagnosis code and we assume that many clinical insignificant fibroids with no symptoms were never diagnosed. Therefore, women in our cohort are likely to be different from women with fibroids diagnosed by routine ultrasound in pregnancy.

In line with previous studies, women with a fibroid diagnosis code had an increased risk of elective caesarean section. A review from 2016 based on 13 studies reported a cumulative CS frequency of 49% corresponding to an unadjusted OR of 3.7 (3.5–3.9) [23]. These findings are in line with the clinical guidelines of elective CS if the uterine fibroids are evaluated to infer a risk of mechanical obstruction or malpresentation. Further, we found that women with a fibroid diagnosis code intended for vaginal delivery had the same risk of acute CS as women without a fibroid diagnosis code.

With regard to the risk of PPH, placental abruption, or IUGR, we found no differences between groups. In contrast, a review from 2016, based on historical cohort studies, and a systematic review from 2008, suggested an increased risk of all three outcomes [23]. However, other studies, which for different reasons were not included in the systematic review, are consistent with our findings [9, 13, 20, 22, 24].

We found no uterine ruptures following laparoscopic myomectomy (N = 112). The risk of uterine rupture following laparoscopic myomectomy has been compared to the risk following uterine surgery such as CS [23, 25, 26], and some authors have reported an increased risk of uterine rupture after myomectomy [27]. Based on clinical reasoning it is believed that surgical skills and techniques such as the use of bipolar diathermy, and timespan from operation to pregnancy are essential factors for the risk of uterine rupture after myomectomy. Our study did not allow the analysis for these factors. In Denmark, complex laparoscopic myomectomy is preferentially performed by experienced surgeons and six months from

operation to pregnancy is recommended. Both factors are likely to have contributed to the low rate of uterine rupture found in our study.

In a review from 2016, it was suggested that fibroid treatment minimises the risk of adverse negative obstetrical outcomes. However, they also concluded that more clinical studies are needed to draw firm conclusions as findings are still inconsistent [28]. Our results support a strategy of removing the fibroid prior to pregnancy in order to minimise the risk of preterm birth. A Randomized Controlled Trial, which would be optimal for firm conclusions, is not possible due to ethical considerations. At best, a large cohort study with detailed exposure and outcome information can give further information.

Limitations

Our results are based on retrospective data, and the number of events was small despite the large size of the cohort. We found a low prevalence of uterine fibroid diagnosis codes in our study population compared to previous reports [29]. It might indicate that women participating in DNBC consisted of a selected group of women [30].

Our exposure registration was based on clinical diagnosis coding, which may be incorrect or missing and lead to exposure misclassification. We found that some women had an operation code, but no diagnosis code, substantiating this hypothesis. In Denmark, operation codes are more closely connected to hospital budgets than clinical diagnosis codes. Diagnosis codes may be underreported and explain the relatively few numbers of diagnosed uterine fibroids in our study. We did not have the possibility to validate the data from the DNPR. However, others previously did so and concluded that the data were suitable for clinical quality control [31].

A short cervix in early pregnancy has been associated with uterine fibroids and may represent part of the mechanism behind the risk of preterm birth among women with uterine fibroids [7, 21]. Unfortunately, we

did not have the opportunity to investigate the contribution of cervical length on preterm birth due to the lack of a specific diagnosis code.

Conclusions

The present study, including 92,696 pregnancies, found a strong association between a uterine fibroid diagnosis and the risk of preterm birth in general and extreme preterm birth in particular. We suggest that future clinical studies focus on the relationship between obstetrical outcomes and fibroids in terms of anatomical location, growth throughout pregnancy, and cervical length.

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Disclosure of Interests

Completed ICMJE disclosure of interest forms are available to view online as supporting information.

Author statement

K.K: Project development, Data management, Data analysis, Manuscript writing/editing

U.S.K: Project development, Data analysis, Manuscript writing

O.M: Project development, Data analysis, Manuscript writing

P.H: Project development, Data analysis, Manuscript writing

P.R: Project development, Data analysis, Manuscript writing

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results			
Participants	13*	√	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		√	(b) Give reasons for non-participation at each stage
		√	(c) Consider use of a flow diagram
Descriptive data	14*	√	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		√	(b) Indicate number of participants with missing data for each variable of interest
		√	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	√	*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
			Cross-sectional study—Report numbers of outcome events or summary measures
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
			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	√	Summarise key results with reference to study objectives
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
Interpretation	20	√	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	√	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	√	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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Title page

Title

The relationship between a uterine fibroid diagnosis and the risk of adverse obstetrical outcomes, a cohort study.

Running title

Uterine fibroids and preterm birth

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Abstract

Objective: The aim was to investigate the association between clinically significant uterine fibroids and preterm birth, caesarean section (CS), postpartum haemorrhage (PPH), placental abruption, intrauterine growth restriction (IUGR), and uterine rupture.

Methods, participants, and setting: A historical cohort study based on data from the Danish National Birth Cohort (DNBC), the Danish National Patient Registry (DNPR), and the Danish National Birth Registry (DNBR). The final study population consisted of 92,696 pregnancies and was divided into four groups for comparison. Group 1: pregnancies of women without a fibroid diagnosis code or fibroid operation code; Group 2: pregnancies of women with a fibroid diagnosis code before pregnancy, during pregnancy, or up to one year after delivery, and no fibroid operation code before pregnancy; Group 3: pregnancies of women with a fibroid diagnosis code given more than one year after delivery; and Group 4: pregnancies of women with a fibroid operation code given before pregnancy.

Results: A diagnosis of fibroids before pregnancy yielded an increased risk of preterm birth (gestational age (GA) ≤37 weeks) (OR 2.27 (1.30–3.96)) and extreme preterm birth (GA 22+0–27+6 weeks, OR 20.09 (8.04–50.22)). The risk of CS was increased (OR 1.83 (1.23–2.72)) for women with a fibroid diagnosis code given before pregnancy; significantly increased risk of elective CS (OR 1.92 (1.11–3.32)), but not acute CS (OR 1.54 (0.94–2.52)). The risks of PPH, placental abruption or IUGR were not increased in any of the groups.

Conclusion: We found a strong association between clinically significant uterine fibroids and preterm birth, and an association between clinically significant uterine fibroids and CS. In contrast, no association between clinically significant uterine fibroids and PPH, placental abruption, or IUGR was seen.

Strengths and limitations of this study:

- This study explores an area with inconsistent evidence.
- This study is a large cohort study with data from 92,696 pregnancies.
- Limitations include a low prevalence of uterine fibroids and a small number of events.

Introduction

As many as 10 % of pregnant women may have uterine fibroids [1], and the incidence is likely to be even higher in populations with high maternal age and obesity [2, 3]. Fibroids may affect the uterine cavity, the placenta, and the foetus directly, but may also cause the myometrium to be more inflexible and less responsive to oxytocin [4, 5]. Overall, fibroids are associated with obstetrical complication rates of 10–40 % [6, 7], many of which have severe consequences. Due to the clinical impact on the mother and child, outcomes such as preterm birth, caesarean section (CS), postpartum haemorrhage (PPH), placental abruption, intrauterine growth restriction (IUGR), and uterine rupture have been evaluated in relation to uterine fibroids [6-11]. Some studies showed an association between fibroids and preterm birth, CS, PPH, and placental abruption [8, 9, 12-14], whereas other studies showed no association with preterm birth, CS, PPH, and IUGR [7, 13, 15].

To address these discrepancies, we conducted a large historical cohort study of unselected pregnant women. We focused on women with clinically significant fibroids and compared women with a uterine fibroid diagnosis code to a reference group of women without a uterine fibroid diagnosis code. The aim was to investigate the association between clinically significant uterine fibroids and obstetrical outcomes with a

specific focus on preterm birth, CS, PPH, placental abruption, IUGR, and uterine rupture. Moreover, we analysed the association between myomectomy and the risk of uterine rupture.

Materials and methods

This historical cohort study is based on data from the Danish National Birth Cohort (DNBC), the Danish National Birth Registry (DNBR), and the Danish National Patient Registry (DNPR).

Study population

The DNBC is a pregnancy cohort consisting of data from 92,840 women and 101,042 pregnancies. All registered pregnancies were included. Enrolment was performed in early pregnancy during the period between 1996–2002. Inclusion criteria were the intention to carry a pregnancy to term, residency in Denmark, and sufficient Danish proficiency to participate in telephone interviews. Data was collected by computer-assisted telephone interviews twice during pregnancy, and subsequently when the children were six and eighteen months old. The DNBC data collection was approved by the Danish National Ethics Board. More details about this cohort have previously been described in detail [16].

The DNPR holds diagnosis and operation codes from all in-patients since 1977 and out-patients since 1995. The codes are classified according to the International Classification of Diseases ICD10 since 1994. Diagnosis and operation codes regarding fibroids were collected for this study.

The DNBR contains information about live births and complications of all registered births in Denmark since 1973.

Selected relevant data from the DNPR and the DNBR was linked to data from the DNBC, using the unique personal identification number given to all residents in Denmark.

Data

We collected data on maternal age, height, weight, smoking habits, expected date of birth, and fertility treatment (regardless of mode of assisted reproductive technique) from the DNBC. Maternal body mass index (BMI) (kg/m^2) was calculated based on self-reported pre-pregnancy weight and height.

Fibroid diagnosis codes (DD25–DD259) and fibroid operation codes were collected from the DNPR. Operation codes were: myomectomy (KLCB10), laparoscopic myomectomy (KLCB11), hysteroscopic myomectomy (KLCB20), hysteroscopic resection of pathological tissue (KLCB22), hysteroscopic excision of pathological tissue (KLCB25), and hysteroscopic excision of other pathological tissue (KLCB98). We categorised operation codes into laparoscopic or open myomectomy (KLCB10, KLCB11) and hysteroscopic myomectomy (KLCB20, KLCB22, KLCB25, and KLCB98). Operation codes of the resection and excision of pathological tissue were pooled into one group of myomectomy since we assumed that many use these codes for hysteroscopic myomectomy.

Gestational age (GA), birth weight of the child, and data on obstetrical outcomes (caesarean section (KMCA10A, KMCA10D, KMCA10E, and KMCA10B), placental abruption (DO450, DO451, DO452, DO453, DO458, and DO459)), and PPH (DO720, DO721, DO721A, and DO721B) were collected from the DNBR.

Exposure definition

The study population was divided into four groups for comparison. Group 1: pregnancies of women without a fibroid diagnosis code or operation code; Group 2: pregnancies of women with a fibroid diagnosis code before pregnancy, during pregnancy, or up to one year after delivery, and no operation code before pregnancy; Group 3: pregnancies of women with a fibroid diagnosis code given more than one year after delivery; and Group 4: pregnancies of women with an operation code given before pregnancy.

Outcome definition

The outcomes were preterm birth, CS, placental abruption, PPH, IUGR and uterine rupture.

Preterm birth was defined as delivery at GA 22+0–36+6 weeks. We divided preterm birth into three categories according to the international classifications. Moderate preterm: GA 34+0–36+6 weeks, very preterm: GA 28+0–33+6 weeks, and extreme preterm: GA 22+0–27+6 weeks. Due to the small number of events, we merged the groups into clinically relevant binary outcomes: moderate preterm: GA 34+0–36+6 weeks and very and extreme preterm GA 22+0–33+6 weeks.

CS was categorised as acute (KMCA10A, KMCA10D, and KMCA10E) or elective (KMCA10B).

Placental abruption was reported under several diagnosis codes (DO450, DO451, DO452, DO453, DO458, and DO458) and pooled into one group.

PPH was defined as bleeding during delivery and up to 24 hours postpartum (DO720, DO721, DO721A, and DO721B).

We followed the international classification of small of gestational age/IUGR as a birth weight below -22% of the expected weight at a given GA. This classification was originally developed by the 1995 World Health Organization (WHO) expert committee [17]. We used a lower limit of -60 % based on clinical reasoning; all births with an expected birth weight below -60% were excluded due to potential misclassification.

Data from the group of women who had a myomectomy before pregnancy was used to analyse the association between myomectomy and the risk of uterine rupture (DO710, DO711).

Data purification

During the data purification, we made some assumptions. If a uterine fibroid diagnosis code was given once, the woman was categorised as having at least one uterine fibroid during the study period, unless she had a fibroid operation code. A fibroid diagnosis code given more than 90 days after a fibroid operation code was interpreted as a new uterine fibroid. We assumed the fibroid to be present also before

pregnancy, if a fibroid diagnosis code was given during pregnancy or up to one year postpartum, and data were included in the fibroid group.

Missing values were identified and analysed. We had an 87% complete dataset. Missing values were imputed by multiple imputations of multiple variables (MICE) assuming that values were missing at random. Analyses were made before and after imputation.

We identified the potential confounders for each outcome based on the DAG (directed acyclic graph) [18]. For preterm birth, CS, and PPH, we identified maternal age and BMI to be possible confounders. For placental abruption, we identified maternal age to be a possible confounder. For IUGR and uterine rupture, we did not identify any possible confounders.

We found that 317 women had a myomectomy before pregnancy (205 by hysteroscopy and 112 by laparoscopy).

Statistical analyses

A one-way ANOVA was used for comparison of normally distributed data such as age. The Kruskal–Wallis test was used for comparison of non-normally distributed data such as BMI and parity. Smoking habits and fertility treatment were compared using the Chi–square test.

We used logistic regression analysis to compare the binary outcomes; preterm birth, CS, PPH, placental abruption, IUGR, and uterine rupture. We adjusted for potential confounders identified by DAGs in all analyses (maternal age and body mass index). By using robust standard errors, we accounted for some women being included with more than one pregnancy in the analyses.

We found the tests acceptable based on the Hosmer–Lemeshow goodness of fit test.

Subgroup analyses of women with a fibroid operation code before pregnancy were performed.

We performed stratified analyses for preterm birth regarding fertility treatment and multiple pregnancies.

All analyses were performed in STATA 15.

Patient and Public involvement statement

Participant in the DNBC are involved in all research based on data from the DNBC. A member of the DNBC ambassadors, which is a group of selected participants representing all participants, is represented in the DNBC reference group. There was no other patient or public involvement in this study.

Ethical approval

This study was approved by the Danish Data Protecting Agency (registration number; 2012-58-0018). According to Danish law, ethical approval is not required for registry-based studies.

Results

Our final study population consisted of 86,323 women and 92,696 pregnancies, divided into the four exposure groups. (Fig. 1)

Population characteristics for the four exposure groups are shown in Table 1. The groups did not differ regarding BMI, but they differed regarding age, smoking habits, parity, multiple pregnancies, and proportion of fertility treatment.

Table 1: Population characteristics

	No fibroids **Group 1 (reference group)**	**Fibroids before pregnancy** **No operation** **Group 2**	**Fibroids after pregnancy** **Group 3**	**Fibroid operation before pregnancy** **Group 4**
Population, N	91,292	124	963	317

Age ,years Mean(SD)	30 (4.29)	34 (4.15)	32 (3.96)	34 (4.16)
BMI, kg/m² median(range)	23 (10-64)	23 (16-40)	23 (16-49)	22 (18-35)
Parity median (range)	1 (0-14)	1 (0-3)	1 (0-5)	0 (0-3)
Smoking, %	16.43	11.82	16.04	13.15
Fertility treatment, %	6.32	18.48	9.76	39.39
Multiple pregnancy,%	2.14	4.03	3.95	7.89

Preterm birth

The risk of overall preterm birth was increased among the group of women who had a fibroid diagnosis code before pregnancy (group 2) compared to women without a fibroid diagnosis code (group 1), OR 2.3 (1.30–3.96). The risk of moderately preterm birth was not increased, OR 0.6 (0.20–1.96), whereas the risk of very preterm, extreme preterm, and the pooled group of very and extreme preterm birth, was significantly increased, OR 4.00 (1.75–9.13), OR 20.1 (8.04–50.22), and OR 6.5 (3.51–12.19), respectively. For the group of women with a fibroid diagnosis code after pregnancy (group 3), the risk of preterm birth was not increased. The group of women who had an operation before pregnancy (group 4) had an

increased risk of overall preterm birth of OR 1.8 (1.24–2.65) and very preterm birth OR 2.8 (1.55–5.22).

None delivered extremely preterm (Table 2).

Tabel 2 Results

	No fibroids **Group 1 (reference group)**	**Fibroids before pregnancy No operation Group 2**		**Fibroids after pregnancy Group 3**		**Fibroid operation before pregnancy Group 4**	
	(N=91,292)	(N=124)	Odds ratio (95%CI)	(N=963)	Odds ratio (95%CI)	(N=317)	Odds ratio (95%CI)
Preterm birth* (week)							
≤ 37	4,939 (5.4%)	14 (11.3%)	2.27 (1.30-3.96)	55 (5.7%)	1.08 (0.82-1.42)	29 (9.1%)	1.81 (1.24-2.65)
≥ 34 < 37	3,506 (3.9%)	3 (2.4%)	0.62 (0.20-1.96)	41 (4.3%)	1.11 (0.81-1.53)	18 (5.7%)	1.52 (0.94-2.43)
≥ 28 < 34	1,159 (1.2%)	6 (4.8%)	3.99 (1.75-9.13)	11 (1.4%)	0.90 (0.50-1.64)	11 (5.5%)	2.84 (1.55-5.22)
≥ 22 < 28	176 (0.2%)	5 (4.0%)	20.09 (8.04-50.22)	3 (0.3%)	1.56 (0.50-4.89)	0 (0%)	Empty
≥ 22 < 34	1,335 (1.5%)	11 (8.9%)	6.54 (3.51-12.19)	14 (1.5%)	0.99 (0.58-1.69)	11 (3.5%)	2.44 (1.33-4.48)
Caesarean section*							
Overall	14,542 (16%)	36 (29%)	1.83 (1.23-2.72)	164 (17%)	0.99 (0.84-1.19)	110 (35%)	2.48 (1.94-3.16)
Acute	9,901 (11%)	21 (17%)	1.54 (0.94-2.52)	116 (12%)	1.08 (0.88-1.32)	62 (20%)	1.91 (1.44-2.52)
Planned	4,641 (5%)	15 (12%)	1.92 (1.11-3.32)	48 (5%)	0.85 (0.64-1.14)	48 (15%)	2.58 (1.85-3.60)

IUGR*	3,731 (4.1%)	6 (4.8%)	1.27 (0.57-2.85)	35 (3.6%)	0.91 (0.65-1.28)	13 (4.1%)	1.05 (0.60-1.83)
PPH*	3,364 (3.7%)	7 (5.7%)	1.70 (0.70-3.65)	36 (3.7%)	1.06 (0.76-1.47)	15 (4.7%)	1.40 (0.84-2.35)
Abruption placentae**	490 (0.5%)	1 (0.8%)	1.41 (0.20-10.15)	6 (0.6%)	1.13 (0.50-2.53)	3 (0.9%)	1.66 (0.53-5.21)
Uterus rupture	7 (0.1%)	0 (0%)	Empty	2 (0.2%)	2.84 (0.39-20.56)	0 (0%)	Empty

* adjusted for age and BMI

** adjusted for age

We stratified accordingly to fertility treatment and found an increased risk of extremely preterm birth (OR 25.6 (7.95–82.43)) among women treated for infertility and among spontaneously pregnant women (OR 8.4 (1.08–15.76)). The same was applicable for the pooled group of very and extreme preterm birth where increased risk was found for women with fertility treatment OR 5.6 (2.24–13.85) and spontaneous pregnancy OR 4.5 (1.28–15.76). In women with a fibroid diagnosis code before pregnancy, the risk of preterm birth was not increased in any other groups (Table 3).

Table 3: Results, stratified analyses,

	Fibroids before pregnancy No operation Group 2 Odds ratio(95%CI)		**Fibroids after pregnancy Group 3 Odds ratio(95%CI)**		**Operation before pregnancy Group 4 Odds ratio(95%CI)**	
	No fertility treatment N=75/81,836	Fertility treatment N=17/5,522	No fertility treatment N=869/81,836	Fertility treatment N=94/5,522	No fertility treatment N=140/81,836	Fertility treatment N=91/5,522

Preterm birth (week)						
≤ 37	1.74(0.75-4.02)	1.37(0.39-4.76)	1.04(0.77-1.41)	0.93(0.51-1.72)	1.05(0.49-2.25)	1.06(0.59-1.92)
≥ 34 < 37	0.37(0.05-2.69)	Empty	1.02(0.71-1.47)	1.20(0.62-2.33)	1.24(0.55-2.80)	0.97(0.47-2.02)
≥ 28 < 34	2.45(0.60-10.02)	3.37(0.77-14.85)	0.94(0.48-1.81)	0.55(0.13-2.25)	0.64(0.09-4.61)	1.47(0.59-3.60)
≥ 22 < 28	25.60(7.95-82.43)	8.36(1.08-64.50)	2.13(0.68-6.69)	Empty	Empty	Empty
≥ 22 < 34	5.57(2.24-13.85)	4.5(1.28-15.76)	1.09(0.62-1.93)	0.46(0.17-1.87)	1.09(0.62-1.93)	1.22(0.49-3.04)

	Singleton pregnancy N= 119/89,338	Multiple pregnancies N=5/1,964	Singleton pregnancy N= 925/89,338	Multiple pregnancies N=38/1,964	Singleton pregnancy N= 292/89,338	Multiple pregnancies N=25/1,964
Preterm birth (week)						
≤ 37	1.90 (0.32-11.45)	2.18 (1.17-4.05)	0.66 (0.34-1.30)	1.02 (0.75-1.39)	1.17(0.53-2.59)	1.33(0.81-2.16)
≥ 34 < 37	0.76 (0.24-2.40)	Empty	0.99 (0.68-1.42)	0.99 (0.49-2.03)	1.26(0.68-1.42)	0.77(0.31-1.95)
≥ 28 < 34	3.41 (1.25-9.28)	4.40 (0.73-26.48)	0.96 (0.50-1.86)	0.37 (0.09-1.53)	1.71(0.70-4.15)	2.09(0.82-5.27)
≥ 22 < 28	22.32 (8.18-60.92)	12.95 (1.41-118.77)	2.08 (0.66-6.56)	Empty	Empty	Empty
≥ 22 < 34	6.11 (2.99-12.51)	8.4 (1.41-50.93)	1.11 (0.63-1.98	0.31 (0.75-1.31)	1.48(0.61-3.59)	1.78(0.71-4.50)

We also stratified according to singleton pregnancies. Among singleton pregnant women with a fibroid diagnosis code before pregnancy, we found an increased risk of very preterm of OR 3.4 (1.25–9.28), extreme preterm of; OR 22.3 (8.18–60.92), and the pooled group of very and extreme preterm birth of OR 6.1 (2.99–12.51). Apart from that, the risk of preterm birth was not increased in any other groups (Table 3). For multiple pregnancy women with a fibroid diagnosis code before pregnancy, we found an increased risk of overall preterm of OR 2.2 (1.17–4.05), very preterm OR 4.4 (0.73–26.48), extreme preterm OR 13.0 (1.41–118.77), and pooled very and extreme preterm birth OR 8.5 (1.41–50.93). Apart from that, the risk of preterm birth was not increased in any other groups (Table 3). The risk of preterm birth was increased regardless of stratification according to fertility treatment (with and without) and type of pregnancy (singleton or multiple) (data not shown).

Caesarean section

The overall risk of CS was increased in women with a fibroid diagnosis code before pregnancy (group 2), OR 2.2 (1.50–3.21). The same applied after adjusting for age and BMI of OR 1.8 (1.23–2.72). The risk of acute CS was not increased in the adjusted analyses, OR 1.5 (0.94–2.52). The risk of elective CS was increased, OR 2.6 (1.50–4.41), and the same applied after adjusting for age and BMI, OR 1.9 (1.11–3.32). For the group of women with an operation code before pregnancy (group 4), the risk of CS was also increased; OR 2.6 (1.85–3.60) for elective CS and OR 1.9 (1.44–2.52) for acute CS. The risk of CS was not increased in women with a fibroid diagnosis code after pregnancy (group 3) (Table 2).

PPH, placental abruption, and IUGR

The risk of PPH, placental abruption and IUGR was not increased in women with a fibroid diagnosis code; PPH OR 1.7 (0.70–3.65), placental abruption OR 1.4 (0.20–10.15), and IUGR OR 1.3 (0.57–2.85) (Table 2).

Uterine rupture

We found no uterine ruptures in the group with an operation code before pregnancy (N=317, 112 laparoscopic myomectomies, and 205 hysteroscopic myomectomies). Uterine rupture was diagnosed in 67 of the 91,292 (0.1%) women without a fibroid diagnosis code. Two women out of the 963 with a fibroid diagnosis code after pregnancy (0.21%) were diagnosed with uterine rupture, and no women out of 124 (0%) had uterine rupture and a fibroid diagnosis code before pregnancy.

Discussion

Women with a uterine fibroid diagnosis code had a significantly higher risk of preterm birth in general, extreme preterm birth in particular. The fact that the association persisted through all the analyses, irrespective of the mode of conception, number of foetuses, age, and BMI enhances the robustness and significance of our results.

Previous studies that differed in design in terms of exposure and outcome found weaker associations. A previous systematic review from 2008 reported a cumulative preterm birth rate (before GA 37 weeks) of 16% among women with fibroids corresponding to an OR of 1.5 (1.3–1.7). None of the included studies, however, adjusted for potential confounders such as age and BMI [8]. A recent case series from 2018 reported a preterm birth rate of 28% in women with uterine fibroids. This study did not include a reference group without fibroids, and a calculation of the estimated risk was not possible [19]. All previous studies used different classifications of preterm birth, which further complicates comparison. Three historical cohort studies all showed an increased risk of preterm birth (GA <37 weeks), but they used different categorisation regarding GA. Arisoy et al. reported an OR 4.7 (1.9–11.6) for preterm birth <37, OR 4.3 (2.0–13.9) for preterm birth <34 weeks, decreasing to OR 3.3 (0.8–13.4) for preterm birth <32 weeks [20]. Blitz et al. also categorized preterm birth into groups depending on GA and found OR 1.61 (1.16–2.23) for preterm birth 34–36 weeks, OR 2.99 (1.65–5.40) for preterm birth 32–33 weeks, OR 1.47 (0.59–3.67) for

28–31 weeks, and OR 1.81 (1.49–2.19) for 20–27 weeks[21]. In contrast, Lai et al. found an increased risk of preterm birth with decreasing gestational age; OR 1.70 (1.12–2.58) for 24–34 weeks, OR 1.99 (1.05–3.75) for 24–28 weeks and OR 2.48 (1.38–4.44) for 20–27 weeks [22]. All three cohort studies included women who had undergone routine second-trimester obstetrical ultrasound, which was the basis for inclusion into the exposure or control group. Women in our cohort study were included based on a fibroid diagnosis code and we assume that many clinical insignificant fibroids with no symptoms were never diagnosed. Therefore, women in our cohort are likely to be different from women with fibroids diagnosed by routine ultrasound in pregnancy.

In line with previous studies, women with a fibroid diagnosis code had an increased risk of elective caesarean section. A review from 2016 based on 13 studies reported a cumulative CS frequency of 49% corresponding to an unadjusted OR of 3.7 (3.5–3.9) [23]. These findings are in line with the clinical guidelines of elective CS if the uterine fibroids are evaluated to infer a risk of mechanical obstruction or malpresentation. Further, we found that women with a fibroid diagnosis code intended for vaginal delivery had the same risk of acute CS as women without a fibroid diagnosis code.

With regard to the risk of PPH, placental abruption, or IUGR, we found no differences between groups. In contrast, a review from 2016, based on historical cohort studies, and a systematic review from 2008, suggested an increased risk of all three outcomes [23]. However, other studies, which for different reasons were not included in the systematic review, are consistent with our findings [9, 13, 20, 22, 24].

We found no uterine ruptures following laparoscopic myomectomy (N = 112). The risk of uterine rupture following laparoscopic myomectomy has been compared to the risk following uterine surgery such as CS [23, 25, 26], and some authors have reported an increased risk of uterine rupture after myomectomy [27]. Based on clinical reasoning it is believed that surgical skills and techniques such as the use of bipolar diathermy, and timespan from operation to pregnancy are essential factors for the risk of uterine rupture after myomectomy. Our study did not allow the analysis for these factors. In Denmark, complex

laparoscopic myomectomy is preferentially performed by experienced surgeons and six months from operation to pregnancy is recommended. Both factors are likely to have contributed to the low rate of uterine rupture found in our study.

In a review from 2016, it was suggested that fibroid treatment minimizes the risk of adverse negative obstetrical outcomes. However, they also concluded that more clinical studies are needed to draw firm conclusions as findings are still inconsistent [28]. In the present study, the risk of preterm birth decreased whereas the risk of CS increased after myomectomy compared to the risks among women with untreated uterine fibroids. Our results contribute to the overall discussion about treatment prior to pregnancy, however, more studies are required. A Randomized Controlled Trial, which would be optimal for firm conclusions, is not possible due to ethical considerations. At best, a large cohort study with detailed exposure and outcome information can give further information.

Limitations

Our results are based on retrospective data, and the number of events was small despite the large size of the cohort. We found a low prevalence of uterine fibroid diagnosis codes in our study population compared to previous reports [29]. It might indicate that women participating in DNBC consisted of a selected group of women [30]. Our results cannot be used as an indicator of prevalence or incidence in the general population, but it is important to notice, that data are fully valid for analyses of associations[31].

Our exposure registration was based on clinical diagnosis coding, which may be incorrect or lacking due to various work-related distractions and a variable individual interpretation of clinical cases, leading to exposure misclassification. The low prevalence of uterine fibroids in our study population is likely to be a result of underreporting. A potential bias will lead towards exposed women being categorized as unexposed, and hence attenuation of the association between exposure (uterine fibroids) and outcomes [32]. Since the potential underreporting is independent of the outcome due to the prospective nature of

data collection in a cohort study, a potential misclassification could lead to non-differential information bias.

Further, we found that some women had an operation code, but no diagnosis code, substantiating the hypothesis of risk of exposure misclassification. In Denmark, operation codes are more closely connected to hospital budgets than clinical diagnosis codes. A detailed validation of data would most likely have solved discrepancies, but we did not have the possibility to validate the data from the DNPR, and we relied on previous studies, showing that reproductive gynecological coding in the DNPR is generally valid and suitable for clinical quality control [33].

Risk of misclassification related to the operation codes could have been cleared by post-operative histological diagnoses. As this data was not available, we minimized the risk by ensuring that none of the women in our exposure group had a diagnoses code for other uterine pathologies such as adenomyosis or polyps.

The DNBC mainly consist of white women with middle or high social status [30] and since uterine fibroids have different pathophysiology for e.g. Afro-American and Caucasian woman [34], our results can only reasonably be applied to the Scandinavian population.

A short cervix in early pregnancy has been associated with uterine fibroids and may represent part of the mechanism behind the risk of preterm birth among women with uterine fibroids [7, 21]. Unfortunately, we did not have the opportunity to investigate the contribution of cervical length on preterm birth due to the lack of a specific diagnosis code.

Conclusions

The present study, including 92,696 pregnancies, found a strong association between a uterine fibroid diagnosis and the risk of preterm birth in general and extreme preterm birth in particular. We suggest that future clinical studies focus on the relationship between obstetrical outcomes and fibroids in terms of anatomical location, growth throughout pregnancy, and cervical length.

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Data sharing statement

Data are available upon reasonable request.

Disclosure of Interests

Completed ICMJE disclosure of interest forms are available to view online as supporting information. There are no competing interests.

Author statement

K.K: Project development, Data management, Data analysis, Manuscript writing/editing

U.S.K: Project development, Data analysis, Manuscript writing

O.M: Project development, Data analysis, Manuscript writing

P.H: Project development, Data analysis, Manuscript writing

P.R: Project development, Data analysis, Manuscript writing

Figure legends

Fig. 1: Flowchart of the study population

Table 1: Population characteristics

Table 2: Results

Table 3: Results, stratified analyses, adjusted OR

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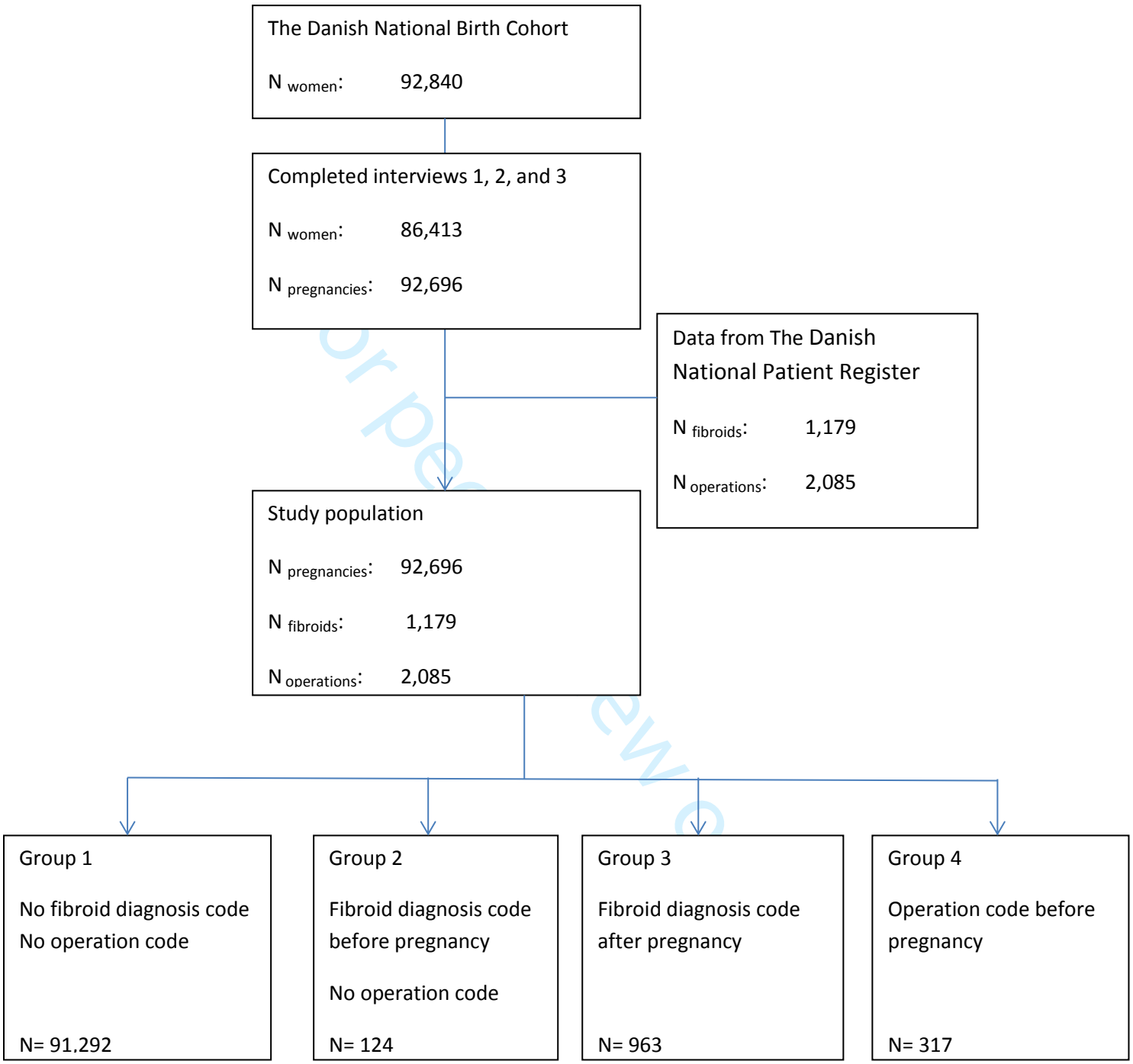
Figure 1: Flowchart of the study population



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

	Item No	Recommendation
Title and abstract **(Page 1)**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale (Page 3)	2	Explain the scientific background and rationale for the investigation being reported
Objectives (Page 3)	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design (Page 4)	4	Present key elements of study design early in the paper
Setting (Page 4)	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants (Page 4)	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables (Page 5+6)	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement (Page 5+6)	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
Bias (Page 7)	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables (Page 6)	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods (Page 6+7)	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants (Figure 1)	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data (Table 1) (Page 6)	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results (Page 11-16)	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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results (Page 16)	18	Summarise key results with reference to study objectives
Limitations (Page 18)	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation (Page 18-19)	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability (Page 18-19)	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding (Page 19)	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

*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.