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High BMI and the risk of lower extremity fractures in fertile-aged women: A nationwide register-based study in Finland

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ABSTRACT

Objectives: Both high and low body mass index (BMI) is known to be associated with increased risk for osteoporotic fractures in the postmenopausal population. However, the association between BMI and risk for fracture in the fertile-aged (15–49 years) population is not well studied. We aim to examine how increased BMI affects the risk for fracture leading to hospitalization after delivery in fertile-aged women.

Material and methods: In this nationwide registry-based study, data on all women aged 15–49 years with fractures leading to hospitalization were retrieved from the Care Register for Health Care for the years 2004–2018. The data were linked with data from the National Birth Register, where the BMI status is collected for each pregnancy. Cox regression was used to examine the effect of increased BMI on the risk for fracture within five years after delivery. Risks were analyzed separately for upper extremity, spine and pelvis, and lower extremity fractures. The results were interpreted with hazard ratios (HR), adjusted hazard ratios (aHR), and 95% confidence intervals (CI).

Results: A total of 529 992 pregnant women with 3276 fractures leading to hospitalization within 5-year follow-up were included in this study. Of these, a total of 548 fractures required surgical treatment. Patients with BMI of 30 kg/m^2 or more had a higher rate of fractures in the lower extremity (≥50%). In lower extremity fractures, risk for fracture increased with increasing BMI. The risk fracture was highest in the group with BMI of 35–40 kg/m^2 (overall lower extremity aHR 2.43 95% CI 1.92–3.06; knee aHR 2.04, 95% CI 1.45–2.87; ankle aHR 3.01, 95% CI 2.16–4.20).

Conclusions: Higher BMI was associated to the increased risk for lower extremity fractures, especially ankle fractures, within five years of delivery. Information gained from this study is important in the clinical setting, as patients can be informed of the negative effect of obesity on the post-delivery risk for fractures.

Introduction

Increased body mass index (BMI) is one of the biggest threats to global health because it is associated with an increased risk for other comorbidities, such as type II diabetes and cardiovascular diseases [1]. Globally, a mean increase in BMI has been reported since 1980 [1,2]. In addition to the increase in BMI, an increasing trend has also been observed in the proportion of obesity. Indeed, it has been predicted that almost 80% of all adults in the United States will be overweight or obese by 2030 [3,4]. In Finland, the proportion of people in the female population with obesity is approximated to be ca. 20%, but this figure is expected to increase to 26% by 2050. Similar trends of increasing obesity within the female population are also expected throughout Europe [5].

In the older population, the relationship between BMI and risk of fracture is complex, as both the low and high BMI are reported to be risk factors for osteoporotic fractures [6]. In addition to BMI, risk of fractures is deniably affected by several other factors too, such as bone mineral density (BMD) [7]. In addition, despite the increased risk and other negative effects high BMI has on the health of individuals, higher BMI has also been associated with a decreased risk for hip fractures in the older population, also known as the “obesity paradox” [8]. Osteoporotic

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fractures are, however, generally associated with older, postmenopausal women [9].

In a previous survey-based study in Thailand, obesity was reported to increase the risk for fracture in any part of the body in the younger (19–50 years) female population [10]. According to the same study, the increase in risk was highest for fractures of the lower limb, where obesity increased the risk for lower limb fractures by over two fold compared to women of normal weight [10]. A similar trend was not, however, observed in the young male population [10].

Pregnancy and the postpartum period represent key moments in women's lives in which the risk for obesity is real [11]. According to a study in the United States, one in five women who were normal weight in their first pregnancy were in the overweight or obese BMI categories in their second pregnancy [12]. To our best knowledge, no previous studies have examined how BMI affects the risk for fracture in the fertile-aged (15–49 years) female population at the national level.

Higher BMI might increase the risk for fractures, especially fractures of the lower body, as increased body mass places higher stress and weight bearing on the biomechanics of the joints. The aim of this study is, therefore, to examine the effects of increased BMI on the risk for different types of fractures after delivery in fertile-aged women using nationwide registers.

Material and methods

In this nationwide retrospective register-based cohort study, data from the National Medical Birth Register (MBR) was combined with data from the Care Register for Health Care. Both registers are maintained by the Finnish Institute for Health and Welfare. Data from the registers were then combined using the pseudonymized identification number of the mother. The study period was from January 1st, 2004 to December 31st, 2018.

The MBR contains information on pregnancies, delivery statistics, and the perinatal outcomes of all births with a birthweight of ≥ 500 g or a gestational age of ≥ 22^{+0} weeks. The MBR has high coverage and quality (the current coverage is nearly 100%), [13,14] and it is the most extensive registry in Finland that contains information on weight, making it ideal for a BMI-based study. It is well-known that BMI is a rather poor indicator of body composition among people of normal weight [15]. However, for the overweight and obesity, BMI is a good and valid indicator that can even underestimate the prevalence of obesity, making it a good variable for this study [16]. We included all pregnancies recorded in the MBR between 2004 and 2013 that led to birth in women aged between 15 and 44. The weights of the mothers were collected. A total of 529 992 pregnant women were included in this study. During the years 2004–2013, BMI status was missing in 31 027 (5.3%) pregnancies. Women with missing BMI status were excluded. The weights collected were either the pre-pregnancy weight or the weight measured at the first visit to the maternity clinics during weeks 6–8 of pregnancy. The study groups were formed using the classification given by the World Health Organization (WHO) [17]. Women were divided into five groups, depending on their BMI classification: overweight (BMI 25.0 – <30.0 kg/m^2), obesity class I (BMI 30 – <35 kg/m^2), obesity class II (BMI 35 – <40 kg/m^2), obesity class III (BMI over 40 kg/m^2), and control group (normal weight, BMI 18.5 – <25.0 kg/m^2). As the objective of our study was to investigate the effects of overweight and obesity on the risk for fractures, women who were underweight during pregnancy were excluded from the analysis.

The groups were linked with data found in the Care Register for Health Care. The register contains information on all fractures leading to hospitalization that took place during the years 2004–2018. Hospitalization includes all patients treated as outpatients or inpatients and includes both non-operatively and operatively treated fractures. International Classification of Diseases 10th revision (ICD-10) codes were used to identify fracture patients. Fractures of the upper extremity, spine and pelvis, and lower extremity were included in the study. Further, fractures of the lower extremity were further divided into three subgroups: hip and thigh, knee and lower leg, and ankle. Patients who underwent surgery were identified by NOMESCO (Nordic Medico-Statistical Committee) operation codes, which were also found in the Care Register for Health Care. The specific ICD-10 codes and NOMESCO operation codes with definitions for each fracture included in this study are presented in supplementary Tables 1 and 2. The dates of the fracture hospitalization periods found in the Care Register for Health Care were used to compare the risk for a woman sustaining a fracture after giving birth. The formation of the study groups is presented in Fig. 1. The results of this study are reported according to the STROBE guidelines [18].

Statistics

Continuous variables were reported as mean with standard deviation or as median with interquartile range based on distribution of the data. As 49 is the maximum age for the data in the Care Register for Health Care, the required 5-year follow-up condition for fractures is only met by those women who gave birth before the age of 45. Categorized variables were presented as absolute numbers and percentages and the rate for fractures as incidence rates (IR) per 10 000 person-years with 95% confidence intervals (CI).

The Cox regression model was used to evaluate the risk for fracture in women with higher BMI. Women with BMI of 18.5 – < 25.0 kg/m^2 formed the control group. The follow-up period was 5 years, starting from the event of giving birth found in the MBR. The endpoint of the follow-up was the first fracture after giving birth, start of the next pregnancy, or the common endpoint of the follow-up, which was 5 years after giving birth. The results were interpreted with hazard ratios (HR), adjusted hazard ratios (aHR), and 95% CI. Proportional hazards assumption was tested using Schoenfeld residuals, and the assumption was not violated in any tested model. Models were adjusted with the age and smoking status of the mother during pregnancy [19,20]. Adjustments were made by choosing the variables for a multivariate model using directed acyclic graphs (DAG) constructed using the free online software DAGitty (dagitty.net) [21]. The variables included in the DAG were chosen based on known risk factors and by hypothesized causal pathways (Supplementary Fig. 1).

As a supplementary analysis, the association between the risk of fracture and continuous BMI was assessed using the logistic regression. In addition to the known risk factors, the logistic models were adjusted with the follow-up time, because of the duration of the was not the same for all patients, and therefore the results would have been biased. Results from those analyses were interpreted with adjusted odds ratios (aORs) with 95% CIs. Statistical analyses were performed using R version 4.0.3.

Ethics

Both the National Medical Birth Register (MBR) and the Care Register for Health Care had the same unique pseudonymized identification number for each patient. The pseudonymization was done by the Finnish data authority Findata. The authors did not have access to the pseudonymization key, as it is maintained by Findata. In accordance with Finnish regulations, no informed written consent was required because of the retrospective register-based study design and the patients were not contacted. Permission for the use of the data was granted by Findata after evaluation of the study protocol. (Permission number: THL/1756/14.02.00/2020).

Results

A total of 529 992 pregnancies were included in the present study. In 5-year follow-up after delivery, we observed 3276 fractures leading to hospitalization. Of these, 548 fractures required surgical treatment. The mean age of the patients at the time of fracture was 33.6 (sd 5.5) for

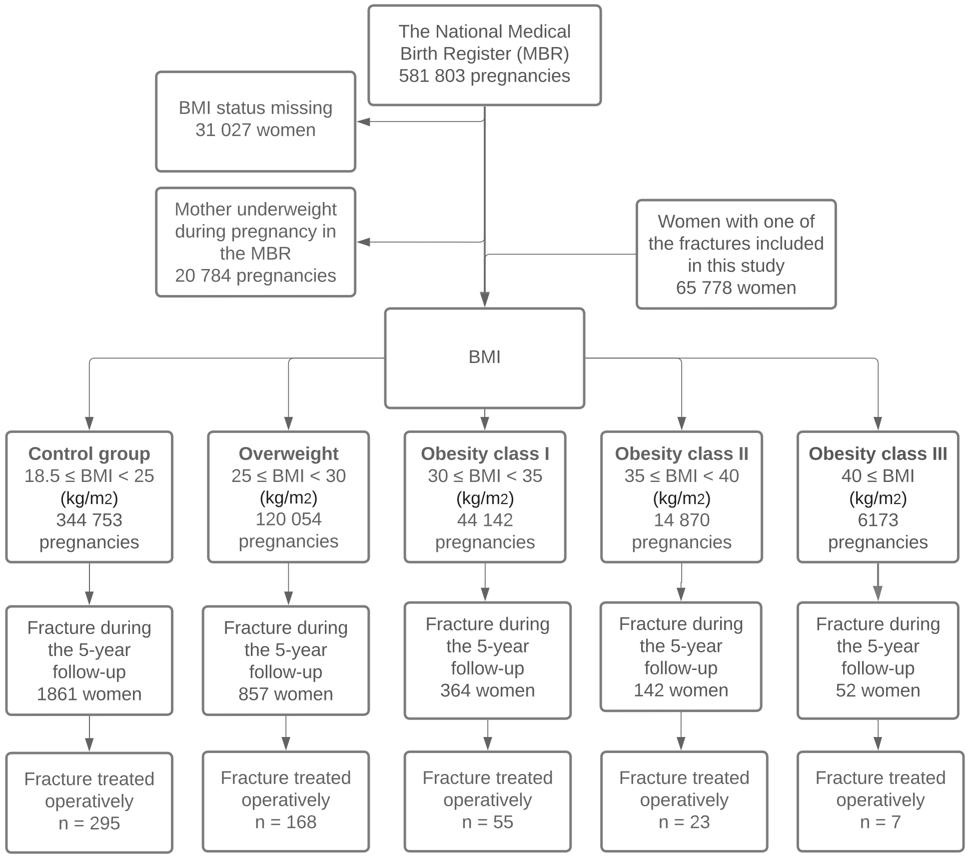

Fig. 1. Flowchart of the study population. Data from the MBR were combined with data on the diagnosed fracture hospitalizations recorded in the Care Register for Health Care. The study groups were created using the BMI classification given by the WHO.

upper extremity fractures, 32.2 (sd 5.8) for spine or pelvis fractures, and 33.2 (sd 5.7) for lower extremity fractures. Fractures in the upper extremity were more common than lower extremity fractures in patients with BMI of less than 30 kg/m^2, but fractures in the lower extremity were the most common in patients with BMI of more than 30 kg/m^2. Each study group had similar incidence rates of fractures requiring operative treatment (Table 1).

Within lower extremity fractures, BMI was associated with increased risk of fracture in every BMI group. The biggest increase in risk was observed in patients with BMI of more than 35 kg/m^2 but less than 40 kg/m^2 (aHR 2.43, 95%CI 1.92–3.06) (Table 2). Subgroup analyses for different types of lower extremity fractures were performed. The risk for fracture was highest in the group with BMI of 35–40 kg/m^2 (knee aHR 2.04, 95%CI 1.45–2.87; ankle aHR 3.01, 95%CI 2.16–4.20), and increased as the BMI increased, with the exception of the group with BMI of ≥ 40 kg/m^2 (knee aHR 1.80, 95% CI 1.00–3.08; ankle aHR 2.61, 95% CI 1.55–4.39) (Table 3).

The results from logistic regression analyses using continuous BMI were similar to those from the analyses of categorious BMI; the higher BMI increased the risk of fractures of the lower extremity (aOR 1.05, CI

Table 1
Background information on the study groups used in the survival analysis and incidence rates (IR) per 10 000 person-years of fractures during the 5-year follow-up with 95% confidence intervals (CI) in each group. In each study group, the smoking status of approximately 1.8–2.0% of patients was unknown.

	Control group BMI < 25 (kg/m^2)		Pre-obesity 25 ≤ BMI < 30 (kg/m^2)		Obesity class I 30 ≤ BMI < 35 (kg/m^2)		Obesity class II 35 ≤ BMI < 40 (kg/m^2)		Obesity class III 40 ≤ BMI (kg/m^2)	
Total number	344 753		120 054		44 142		14 870		6173	
	n	%	n	%	n	%	n	%	n (%)	%
Age at the time of pregnancy (mean; sd)	29.4 (5.2)		30.1 (5.4)		30.1 (5.4)		29.9 (5.4)		30.2 (5.4)	
Smoking status (%)										
smoker*	47 293	13.7	19 625	16.3	8590	19.5	3139	21.1	1303	21.1
Fracture during 5-year follow-up (%)	1861	0.5	857	0.7	364	0.8	142	1.0	52	0.8
Fracture location (%)										
upper extremity	1024	55.0	430	50.2	159	43.7	54	38.0	17	32.7
operatively treated	98	9.6	48	11.2	12	7.5	5	9.3	0	0.0
spine or pelvis	176	9.5	54	6.3	23	6.3	7	4.9	6	11.5
operatively treated	21	11.9	< 5**	7.4	< 5**	8.7	0	0.0	0	0.0
lower extremity	661	35.5	373	43.5	182	5.0	81	57.0	29	55.8
operatively treated	167	25.3	116	31.1	41	22.5	18	22.2	7	24.1

* Includes women who smoked during 1st semester and/or in later semesters
** The Finnish legislation prevents to report the exact event rate if the rate is lower than five.

Table 2
Hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for the event of a woman sustaining a fracture of different anatomic regions after giving birth during 5-year follow-up. Women with higher BMI were compared to women with BMI of 18.5–24.9 kg/m^2. Models were adjusted for smoking status and the age of the mother during pregnancy. Control group consisted of 344 753 pregnancies. Of these 1024 women suffered fracture of upper extremity, 176 suffered a fracture of spine or pelvis, and 661 suffered a fracture of lower extremity.

	Pre-obesity 25 ≤ BMI < 30 (kg/m^2)	Obesity class I 30 ≤ BMI < 35 (kg/m^2)	Obesity class II 35 ≤ BMI < 40 (kg/m^2)	Obesity class III 40 ≤ BMI (kg/m^2)
Total number of pregnancies	120 054	44 142	14 870	6173
Upper extremity				
Total number of fractures	430	159	54	17
HR (CI)	1.11 (0.99–1.24)	1.10 (0.93–1.30)	1.10 (0.83–1.44)	0.80 (0.50–1.30)
aHR (CI)	1.09 (0.97–1.22)	1.02 (0.89–1.25)	1.02 (0.80–1.38)	0.76 (0.47–1.23)
Spine or pelvis				
Total number of fractures	54	23	7	6
HR (CI)	0.82 (0.60–1.11)	0.93 (0.60–1.44)	0.84 (0.39–1.78)	1.67 (0.74–3.78)
aHR (CI)	0.81 (0.60–1.10)	0.87 (0.56–1.35)	0.77 (0.36–1.65)	1.52 (0.67–3.44)
Lower extremity				
Total number of fractures	373	182	81	29
HR (CI)	1.50 (1.32–1.70)	1.96 (1.67–2.31)	2.58 (2.04–3.24)	2.17 (1.50–3.15)
aHR (CI)	1.47 (1.29–1.66)	1.87 (1.59–2–21)	2.43 (1.92–3.06)	2.03 (1.40–2.94)

1.04 – 1.05), especially fractures of the knee (aOR 1.05, CI 1.04–1.05). or ankle (aOR 1.05, CI 1.04–1.05) (Table 4).

Discussion

The main finding of the present study was that higher BMI was associated to the higher risk for lower extremity fractures in fertile-aged women. Moreover, the risk were highest for fractures of the ankle, and the risk increased along with increased BMI. In addition, the risk for fractures of the knee and other parts of the lower leg was markedly higher for women with higher BMI.

Within the five-year follow-up after delivery, the risk for lower extremity fracture increased among those women with higher BMI than in women in the normal-weight population. However, no increase in risk was observed in fractures of the upper extremity or spine and pelvis. This finding might be explained by the biomechanics of the lower extremity, as the weight-bearing joints are under increased stress due to obesity compared to the normal-weight population [22,23]. It has also been reported, that people with obesity are more prone to sustain distal extremity injuries, which might be due to the fact that obesity definitely increases the mechanical energy when i.e. falling after to misstep or slip [24,25]. This same trend of increased risk of lower extremity fractures was observed by Jordan et. al (2013) in their self-report study. They observed a 2.35-fold risk for lower limb fractures in women with BMI of 30 kg/m^2 or higher compared to people of a normal weight [10]. However, since their study was based on a self-report survey, it might be prone to selection and reporting bias. Furthermore, they failed to differentiate between the types of fractures in the lower limb. In our study, the risk for any lower extremity fracture was ca. twofold in patients with BMI of more than 30 kg/m^2 compared to the normal-weight population. In particular, the risk for ankle fractures increased markedly in patients with BMI of more than 30 kg/m^2 when compared to the normal-weight population. Although the association between increased risk for ankle fracture and higher BMI has previously been reported in the literature, [26,27] the findings reported in our study have confirmed this association for the first time in fertile-aged women in a nationwide registry based setting.

The risk for knee, proximal tibial, or fibular fracture increased almost twofold in people with BMI of 30 kg/m^2 or higher compared to the normal-weight population. This increase in risk might also be due to the biomechanics of the knee [22]. Previously, higher BMI has been associated with increased rates of osteoarthritis of the knee [28]. Even the increased rates of knee osteoarthritis reported since the mid-20th century have been explained by increased rates of obesity [29]. However, the effect of BMI on the risk for knee or lower leg fractures in fertile-aged women has not previously been investigated. In the present study, the risk for both knee or ankle fractures increased in line with increases in

Table 3
Hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for the event of a woman sustaining a fracture of different parts of the lower extremity after giving birth during 5-year follow-up. Women with higher BMI during pregnancy were compared to women with BMI of 18.5–24.9 kg/m^2. Models were adjusted for smoking status and the age of the mother during pregnancy. Control group consisted of 344 753 pregnancies. Of these, 52 women suffered a fracture of hip or thigh, 350 women suffered a fracture of lower leg, and 268 women suffered a fracture of ankle.

	Pre-obesity 25 ≤ BMI < 30 (kg/m^2)	Obesity class I 30 ≤ BMI < 35 (kg/m^2)	Obesity class II 35 ≤ BMI < 40 (kg/m^2)	Obesity class III 40 ≤ BMI (kg/m^2)
Total number of pregnancies	120 054	44 142	14 870	6173
Hip or thigh				
Total number of fractures	13	6	5	0
HR (CI)	0.67 (0.36–1.23)	0.83 (0.36–1.93)	2.04 (0.81–5.10)	–
aHR (CI)	0.67 (0.36–1.23)	0.95 (0.34–1.86)	1.89 (0.75–4.75)	–
Knee or lower leg				
Total number of fractures	208	96	37	14
HR (CI)	1.58 (1.33–1.88)	1.96 (1.56–2.45)	2.22 (1.58–3.12)	1.98 (1.12–3.37)
aHR (CI)	1.53 (1.19–1.82)	1.83 (1.46–2.30)	2.04 (1.45–2.87)	1.80 (1.00–3.08)
Ankle				
Total number of fractures	154	85	40	13
HR (CI)	1.52 (1.24–1.85)	2.24 (1.76–2.86)	3.10 (2.22–4.32)	2.71 (1.61–4.56)
aHR (CI)	1.49 (1.22–1.82)	2.18 (1.71–2.79)	3.01 (2.16–4.20)	2.61 (1.55–4.39)

Table 4
Results from the multivariable logistic regression analyses using BMI as a continuous variable. The results were interpreted as adjusted odds ratios (aORs) with 95% confidence intervals (Cis). The outcome was the fracture during the maximum of 5-years follow-up. The model was adjusted by maternal age, maternal smoking status, and follow-up time.

	aOR (CI)
Fractures of upper extremity	1.00 (0.99–1.00)
Fractures of spine or pelvis	0.99 (0.99–1.01)
Fractures of lower extremity	1.05 (1.04–1.05)
hip or thigh	1.01 (0.99–1.02)
knee or lower leg	1.05 (1.04–1.05)
ankle	1.05 (1.04–1.06)

BMI, with the exception of the group with BMI of 40 kg/m^2 or more. The results of these groups were, however, more imprecise due to the fewer number of patients.

The proportion of all classes of overweight and obesity increased during the study period, which has been reported in a recent study using the whole population of fertile-aged women in Finland [30]. Moreover, a similar increase in the prevalence of overweight and obesity has also been reported in other countries. According to a nationwide study in China, the prevalence of adults with overweight and obesity increased by 14.7% and 26.7%, respectively, during the years 1993–2015 [31]. Similar trends have also been reported in Europe [32,33]. Indeed, according to a forecasting study, the prevalence of obesity in Finland will undergo an absolute increase of 2% during the years 2015–2025 [34]. Based on current trends, it has been estimated that 38% of the world's adult population will be overweight and another 20% obese by the year 2030 [35]. According to the WHO, the main reasons behind the increasing prevalence of overweight and obesity are an increased intake of energy-dense foods and a decrease in physical inactivity due to the increasingly sedentary nature of many forms of work [36]. Based on our results and the rapidly increasing prevalence of overweight and obesity, these results might possibly indicate an increased incidence of fractures of the lower limb. Therefore, overweight and obesity should be regarded as clinically important risk factors for fractures in future.

The strength of our study is the large nationwide register with a BMI variable registered for nearly all pregnancies during the study period, making it the most comprehensive data on the BMI of women. Compared to previous studies in which BMI is mostly based on questionnaires that are vulnerable to bias, the register data used in our study are routinely collected with structured forms with national instructions, which ensures good coverage and reduces possible reporting and selection bias [37]. Furthermore, the coverage of both registers included in this study is high [13,38].

The main limitation of our study is the missing information on the BMD. It is evident, that lower BMD increases the risk of bone fractures. As we did not have an access to the information on BMD, as it is not routinely screened for whole population, we can not make definitive conclusions that the increased risk of fractures within people with obesity was not mediated by lower BMD. However, as our study population was relatively young and large, we believe that the potential bias that the missing information on BMD and possible other co-morbidities might have had on our results was minimal. Third limitation that our study has, is the missing clinical information on the fractures included in this study (e.g., radiological finding, trauma mechanisms, cause of fracture). In addition, women who died or migrated abroad during the follow-up are not available based on our data. Another limitation that our study might have, is the possible selection bias, as we only included pregnant females in our study, and therefore it does not reflect the whole population perfectly.

Conclusion

Higher BMI was associated with the increased risk for lower extremity fractures, especially ankle fractures, in fertile-aged women in five-year follow-up after delivery. The information gained from this study is important in the clinical setting, as patients can be informed of the effects of pre-pregnancy obesity on post-delivery risk for fractures.

Author contributions

MV and RL wrote the initial manuscript. IK and VM made the study design. VM supervised the study. VP helped planning appropriate statistical analysis. Each author commented the manuscript during the process and approved the final version to be submitted.

Ethical statement

Both the National Medical Birth Register (MBR) and the Care Register for Health Care had the same unique pseudonymized identification number for each patient. The pseudonymization was done by the Finnish data authority Findata. The authors did not have access to the pseudonymization key, as it is maintained by Findata. In accordance with Finnish regulations, no informed written consent was required because of the retrospective register-based study design and the patients were not contacted. Permission for the use of the data was granted by Findata after evaluation of the study protocol. (Permission number: THL/1756/14.02.00/2020).

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.orcp.2022.11.001.

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