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ORIGINAL PAPER

Maternal Underweight is Associated with Lower Fracture Risk after Pregnancy: A Nationwide Register-Based Study in Finland

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Abstract

Lower body mass index (BMI) is associated with a higher risk for osteoporotic fractures in the postmenopausal population. However, in the fertile-aged population, the association between BMI and risk for fracture is not well studied. Our aim, therefore, is to investigate whether lower BMI (<18.5 kg/m^2) affects the risk for fractures requiring hospitalization after delivery in fertile-aged women when compared to women of normal weight (18.5 ≤ BMI < 25 kg/m^2). In this nationwide registry-based cohort study, all pregnancies were gathered from the National Medical Birth Register. The data were linked with data from the Care Register for Health Care, which includes information of all fractures leading to hospitalization or treated as outpatients for fertile-aged females (15–49 years), for the period 2004–2018. The annual rate of pregnancies with maternal pre-pregnancy underweight in a high-income country was calculated. Cox regression was used to calculate adjusted hazard ratios (aHR) of lower BMI for the risk for fracture within 5 years after delivery. The association between the risk of fracture and continuous BMI was assessed using logistic regression and presented with adjusted odds ratios (aORs) with 95% CIs. In total, 20,784 women were included in the underweight group and 344,753 in the normal weight group. Women in the underweight group had a lower overall risk for any fractures during the 5-year follow-up (aHR 0.75, CI 0.61–0.94). The odds for all fractures (aOR 1.07, CI 1.04–1.09 per BMI-unit upwards for all fractures) increased as pre-pregnancy BMI increased. Despite previous findings of a higher risk for fractures for underweight patients in the older population, the risk for fractures after pregnancy was lower among fertile-aged women with lower BMI.

Keywords Fracture risk · Underweight · Epidemiology

Introduction

In 2015, it was estimated that 9% of the world's adult population were underweight [1]. According to a study in the UK, approximately 3–4% of women enter pregnancy underweight [2]. However, the annual rate of underweight women entering pregnancy has not previously been studied. Low body mass index (BMI) is known to be associated with an increased risk for osteoporotic fractures in the postmenopausal population [3]. For example, a large nationwide Korean cohort study found that in patients over 40 years of age, severely underweight participants had a 28% increased fracture risk, moderately underweight patients had a 14% increased risk, and mild underweight patients had a 9% increased risk for osteoporotic fractures [3].

The main etiology behind the fracture risk caused by underweight has been hypothesized in the literature. In the first place, underweight is associated with low bone mineral density. The association between lower BMI and low bone mineral density is explained, along with the effects of body fat and lean body mass, by the gravitational effects of weight on skeletal system [4]. Secondly, lower BMI is associated with less soft tissue, especially around the bones [5]. Thus, as subcutaneous fat acts as a buffer against damage, it is advantageous for the maintenance of bone structure and

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strength [5]. Third, based on previous study, lower BMI is associated with nutrient deficiency and lack of nutrients, especially vitamin D and protein [6]. According to the findings of a large study in Korea that investigated the bone mineral density of premenopausal women, premenopausal women with low BMI are at notably higher risk for lower bone mass [7].

To date, most studies have focused on the effects of increased BMI on fracture risk. In overweight women, the rate of bone loss is significantly lower than in women of normal weight, probably related to higher plasma estrogen concentration [8]. A recent study in Finland reported a higher risk for fractures among overweight and obese fertile-aged females after pregnancy, but this study did not focus on underweight women [9]. Although the effect of underweight on bone health and general fracture risk is well studied in the elderly population, large studies in younger populations, such as in fertile-aged population, are lacking. Therefore, the association between BMI and risk for fracture in the fertile-aged population is not well understood. The authors hypothesize that the risk for fractures might be increased among the underweight population after pregnancy due to lower bone mineral density and less protective soft tissue around the bones. In addition, the possible relationship between behavioral and social factors, such as lower physical activity among women with lower BMI, might have an effect on the fracture risk. In the present study, we aimed to investigate whether lower BMI affects the risk for fracture leading to hospitalization after delivery in fertile-aged women using data from nationwide health care registers.

Materials and Methods

Data from the Care Register for Health Care and the National Medical Birth Register (MBR) was used to perform a nationwide retrospective cohort study. Both registers are nationwide registers and maintained by the Finnish Institute for Health and Welfare. The data from the registers was linked using the pseudonymised identification number for each individual. The study period in our data was from 1 January 2004 to 31 December 2018. The quality of the MBR has been well studied, and the quality and coverage have been found to be high (current coverage is reported to be nearly 100%) [10, 11]. Also, the quality of the Care Register for Health Care is good. According to a systematic review about the quality of the Care Register for Health Care, the coverage was found to be over 95% [12].

The Care Register for Health Care, which contains information on all visits to public secondary and tertiary level health care units. We included all fractures leading to hospitalization from 2004 to 2018. Hospitalization includes all patients treated as outpatients or inpatients, operatively or non-operatively treated. Finland has social tax-funded universal health care, with low costs to patients [13]. International Classification of Diseases 10th revision (ICD-10) codes were used to identify fracture patient. Fractures of the upper extremity, spine and pelvis, and lower extremity were included in the study. The specific ICD-10 codes with definitions for each group are shown in supplementary Table 1. The dates of the fracture hospitalization periods were collected from the Care Register for Health Care.

The data found in the Care Register for Health Care was linked with the data found in the MBR. The MBR is a high-quality register that contains information on all pregnancies with a birthweight of ≥500 grams or a gestational age of $\geq 22^{+0}$ weeks, delivery statistics, and the perinatal outcomes [14]. In addition to the basic information about the pregnancy and delivery, the MBR is the most extensive registry in Finland containing information on weight, making it ideal for a cohort study based on BMI. All pregnancies leading to birth recorded in the MBR between 2004 and 2013 in women aged between 15 and 44 were included. The pre-pregnancy weights and heights of the mothers were collected, and the maternal BMI was calculated. The weights collected were either the pre-pregnancy weight or the weight measured at the first visit to the maternity clinic during weeks 6 to 8 of pregnancy. The study groups were formed using the classification given by the World Health Organization (WHO) [15]. A total of 365,573 pregnant women were included in this study. During the years 2004–2013, BMI status was missing in 31,027 (5.3%) pregnancies. This excluded population has similar background information as women with BMI status included (mean age 30.1 years, proportion of smokers 12.4%, proportion of gestational diabetes 3.4%). Overweight women, obese women, and women with missing BMI status were excluded. After the exclusion of these patients, the study population was divided according to their BMI into the normal weight group ($18.5\ \mathrm{kg/m^2} \leq \mathrm{BMI} < 25.0\ \mathrm{kg/m^2}$) and the underweight group ($\mathrm{BMI} < 18.5\ \mathrm{kg/m^2}$). Dates of the fracture hospitalizations found in the Care Register for Health Care and dates of pregnancies in the MBR 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.

Statistics

Continuous variables were reported as mean with standard deviation or as median with interquartile range based on the distribution of the data. The annual rates for mothers entering pregnancy as underweight from all pregnancies were calculated. The rates were interpreted with 95% confidence intervals (CI). The CIs for the rates were calculated using Poisson regression.

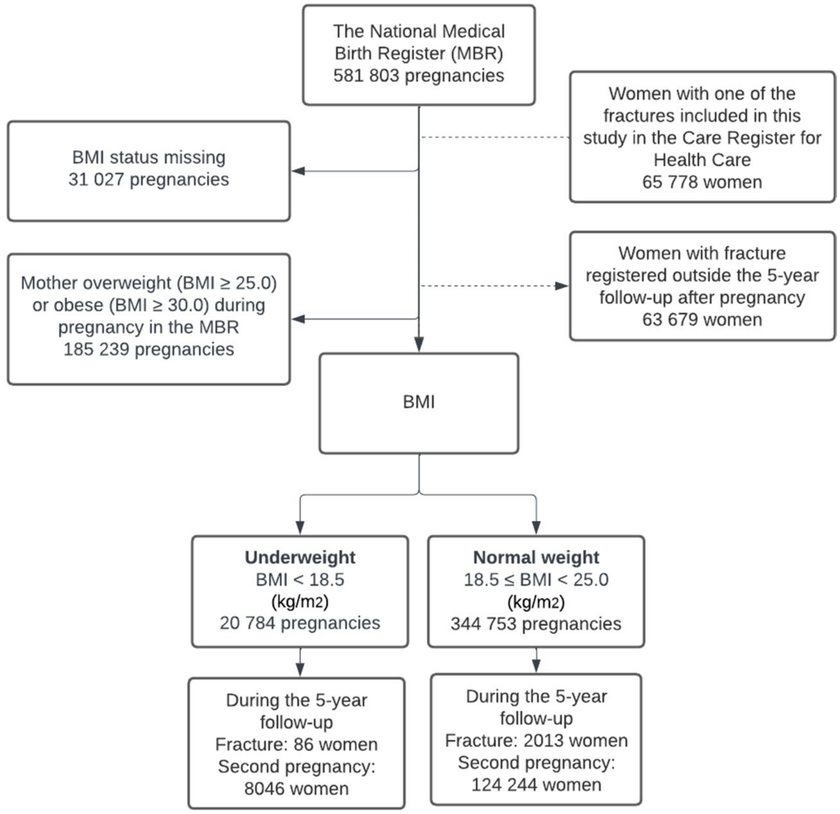

Fig. 1 Flowchart of the study population. Data from the National Medical Birth Register (MBR) were combined with data on the fracture hospitalizations recorded in the Care Register for Health Care

The risk for fracture in women with lower BMI was evaluated using the Cox regression model. Women with normal weight BMI (18.5–<25.0 kg/m^2) formed the control group. The start date of the follow-up was the day of giving birth. The endpoint of the follow-up was one of the following events: the 1st fracture hospitalization after giving birth, beginning of the next pregnancy, or the end point of the follow-up 5 years after giving birth. The required 5-year follow-up condition for fractures was only met by those women who gave birth before the age of 45, which is why no older women were included from the Care Register for Health Care. The risk for upper extremity fractures, fractures of spine or pelvis, and lower extremity fractures was analyzed separately. The results were interpreted with adjusted hazard ratios (aHR) and 95% confidence intervals (CI). Schoenfeld residuals were used to test the proportional hazard assumption. However, the assumption was not violated in any tested model. Models were adjusted with the age, gestational diabetes, and smoking status of the mother, as these are known to be possible risk factors for fractures [16–18]. The proportion of patients with missing smoking status is truly low in the MBR.

The association between the risk for fracture and continuous BMI was assessed using logistic regression. The uncategorized model was also created because, based on the previous literature, the categorized BMI might sometimes be a problematic exposure variable [19], and this excludes the possible scenario where the differences in the risk for fractures are caused by extremes in the BMI in both categorized cohorts. In addition to the known risk factors, the logistic regression models were adjusted with the follow-up time because the length of follow-up time was not the same for all patients, and the results would have been biased. The follow-up time was the adjustment in the model as a continuous variable. Thereafter, the results from these analyses were interpreted with adjusted odds ratios (aORs) with 95% CIs.

Adjustments for a multivariable model were made by choosing the variables using directed acyclic graphs (DAG). The DAGs were constructed using the online software DAGitty [20]. The variables in the DAGs were chosen based on known risk factors and hypothesized causal pathways (Supplementary Figure 1). Statistical analyses were performed using R version 4.0.3 (R Core Team: A Language and Environment for Statistical Computing, Vienna, Austria). The results of this study are reported according to the STROBE guidelines [21].

Ethics

All methods were carried in accordance with Finnish regulations. The Ethical Committee of Tampere University Hospital waived the ethical committee evaluation of all retrospective studies utilizing routinely collected healthcare data, and this decision is based on the law of medical research 488/1999 and the law of patient rights 785/1992. In accordance with Finnish regulations (the law of secondary use of routinely collected healthcare data 552/2019), no ethical informed written consent was required because of the retrospective register-based study design, and the patients were not contacted. Both the National Medical Birth Register (MBR) and the Care Register for Health Care have the same unique pseudonymised identification number for each patient. Permission for the use of this data was granted by Findata after the evaluation of the study protocol (Permission number: THL/1756/14.02.00/2020).

Results

The rates of pre-pregnancy underweight have remained stable during the last decades, ranging between 2.8 and 3.9%. However, since 2014, the trend has decreased slightly from 3.6 to 2.8% (Supplementary figure 2). In the present study, 20,784 pregnancies were placed in the underweight group and 344,753 pregnancies in the normal weight group. Women in the underweight group were younger than women in the normal weight group (mean 27.1 vs 29.5 years). A notably higher rate of smokers was observed in the underweight group when compared to the control group (22.3% vs 14.3%). Also, a lower rate of women in the underweight group had gestational diabetes when compared to the normal weight group (3.1% vs 5.3%). A total of 72.2% of women in the underweight group had mild underweight ($17.5 \leq BMI < 18.5$ kg/m^2), 21.6% had moderate underweight (16.5 kg/m^2 $\leq BMI < 17.5$ kg/m^2), and 6.1% had severe underweight ($BMI < 16.5$ kg/m^2). A lower rate for fractures was observed during the 5-year follow-up in the underweight group when compared to the control group (0.4% vs 0.6%) (Table 1). In the underweight group, the most common fracture types were fracture of the lower end of radius (n = 18), and fracture of clavicle (n = 5). No other fracture occurred more than 5 times. In normal weight group, the most common fracture types were fracture of lower end of radius (n = 494), fracture of lateral malleolus (n = 212), and other fractures of lower leg (n = 101) (Supplementary table 2).

Women in the underweight group had a lower total risk for fractures during the 5-year follow-up (aHR 0.75, CI 0.61–0.94). In addition, a lower risk for fractures of the lower extremity was observed in the underweight group (aHR 0.63, CI 0.42–0.95) when compared to women of a normal weight. However, no evidence of a difference in risk was found for fractures of the upper extremity (aHR 0.86, CI 0.65–1.16) or the spine or pelvis (aHR 1.07, CI 0.49–1.78) (Table 2). The odds for all fractures (aOR 1.07, CI 1.04–1.09 per BMI-unit upwards for all fractures) and fractures of the lower extremity (aOR 1.12, CI 1.08–1.18) increased markedly as pre-pregnancy BMI increased (Table 3).

Table 1 Background characteristics on the study groups and the number of fractures during the 5-year follow-up in these groups

	Underweight (BMI < 18.5 kg/m^2)		Normal weight (BMI 18.5–<25.0 kg/m^2)	
	n	%	*n*	%
Total number of patients	20,784		344,753	
Age (mean; sd)	27.1 (5.5)		29.5 (5.3)	
Smoking during pregnancy	4628	22.3	49,290	14.3
Gestational diabetes	637	3.1	18,389	5.3
Severity of underweight				
Mild underweight*	15,015	72.2	-	-
Moderate underweight**	4499	21.6	-	-
Severe underweight***	1270	6.1	-	-
Number of patients with fracture	86	0.4	2013	0.6
Years from giving birth to fracture (mean; sd)	2.3 (1.6)		2.5 (1.5)	
Fracture location				
Upper extremity	48	55.8	1024	50.9
Spine or pelvis	10	11.6	176	8.7
Lower extremity	24	27.9	661	32.8

*$17.5 \leq BMI < 18.5$ kg/m^2; **16.5 kg/m^2 $\leq BMI < 17.5$ kg/m^2; ***$BMI < 16.5$ kg/m^2

Table 2 Adjusted hazard ratios (aHR) with 95% confidence intervals (CI) between underweight women (BMI < 18.5 kg/m^2) and normal weight women (18.5–25 kg/m^2) for the event of a woman suffering a fracture after giving birth during the 5-year follow-up

Fracture risk during the 5-year follow-up	aHR* (CI)
Total risk	0.75 (0.61–0.94)
Risk for different anatomic regions	
Upper extremity	0.86 (0.65–1.16)
Spine or pelvis	1.07 (0.49–1.78)
Lower extremity	0.63 (0.42–0.95)

*Adjusted with the age, gestational diabetes, and smoking status of the mother during pregnancy

Table 3 Adjusted odds ratios (aOR) with 95% confidence intervals (CI) for the association between continuous BMI and fracture risk

Odds for fracture per BMI-unit upwards	aOR* (CI)
Total odds	1.07 (1.04–1.09)
Odds for different anatomic regions	
Upper extremity	1.02 (0.98–1.05)
Spine or pelvis	1.06 (0.99–1.15)
Lower extremity	1.12 (1.08–1.18)

*Adjusted with the age, gestational diabetes, smoking status of the mother during pregnancy, and follow-up time

Discussion

The main finding of this study was that the total risk for fractures and risk for fractures of the lower extremity after pregnancy among underweight women was lower when compared with normal weight women.

Interestingly, in contrast to the postmenopausal female population [3], the risk for fractures among underweight women was not higher in Finnish fertile-aged females after pregnancy. Due to the crude nature of our data, however, the reason behind this decreased risk for fractures remains unknown. Therefore, interpretations to try to explain the data are mostly exploratory and speculative. One possible explanation might be that the weakening/decreasing effect of being underweight on bone mineral density is not as high as in the older populations. According to a longitudinal study in Denmark, when a small bone loss is observed at the hip and lumbar spine in women before menopause, this bone loss nearly triples during the early postmenopausal years, before decreasing to the premenopausal rate for the hip and to zero for the lumbar spine [22]. Furthermore, a study conducted in 2021 that examined the effects of obesity on bone mineral density reported that a strong positive association between BMI and bone mineral density existed in both sexes of obese cohorts in the older population. However, there was no significant difference in bone mineral density in men aged between 40 and 60 years and women aged <55 years with normal or low weight when compared to overweight or obese cohorts [23]. It is, therefore, possible that BMI has no important effect on bone mineral density in the younger populations, and this topic should be researched further.

Because the weights collected in Finland are either the pre-pregnancy weight or the weight measured at the first visit to the maternity clinics during weeks 6 to 8 of pregnancy, the post-pregnancy BMI might have increased from the weight collected at the beginning of the pregnancy. It is known, for example, that maternal underweight is associated with preterm births (both spontaneous and iatrogenic) and low birthweight, but an appropriate weight gain during pregnancy may mitigate low BMI [24]. Also, gaining weight during pregnancy is a normal physiological phenomenon. Indeed, according to the literature, the mean weight gain in pregnancy for women with normal weight is 16.8 kg [25]. Furthermore, an increase of 150, 200, and 300 kcal per day during the first, second, and third trimesters is recommended in the literature for women who are underweight [26]. Therefore, it is possible that some women with low pre-pregnancy weight might end up in the normal BMI class after pregnancy, and women with normal BMI might end up becoming overweight. This could explain the results, as overweight is known to increase the risk for all fractures that are largely independent of age and sex [27]. The latest study published in Finland found that based on pre-pregnancy BMI, women with higher BMI had a higher risk for fractures, especially in the lower extremity [9]. The risk for fractures was also increasing as the BMI increased [9]. Interestingly, however, based on the results of this study, it appears that women with low BMI have even lower risk for fractures than the normal weight population.

The lower risk for fractures of the lower extremity among underweight women might also be explained by the biomechanics of the lower extremity. Compared to the underweight population, the weight-bearing joints of women who have a higher BMI are under increased stress, leading to more fractures [28, 29]. It has also been reported that women with higher BMI are more likely to sustain distal extremity injuries because higher mass increases the mechanical energy when falling from height after a misstep or slip [30]. Even though the present study only examines women who are underweight compared with the normal weight population, our findings might be applicable in the situation where increased mass due to pregnancy is burdening the joints of the lower extremity more in the normal pre-pregnancy weight population than in the underweight population.

To date, the effects of underweight on bone health and general fracture risk are well studied in the elderly population, but large studies in younger populations are lacking. Furthermore, the etiology of this in both the postmenopausal population and the fertile-aged population remains partly unknown. Based on our results and the literature, it appears that the fracture risk among women might possibly change from negative to positive at the menopausal/postmenopausal age. This topic should, therefore, be studied in more detail both physiologically and clinically, using more precise datasets that include more confounding factors, such as comorbidities, bone mineral density, and the different age classes of women.

The advantage of this study is that it is based on two large nationwide registers with good quality and coverage (the current coverage of the MBR is nearly 100%) [10, 12] allowing us to perform analyses using a large dataset. In the MBR, the BMI variable is registered for nearly all pregnancies during our study period, providing the most comprehensive data on the BMI of women in Finland. In previous literature, BMI is mostly based on questionnaires, which are vulnerable to bias. The register data used in our study is routinely collected with structured forms with national instructions, which reduces possible reporting and selection bias, and ensures good coverage [14].

The main limitation of our study was the missing clinical information on the fractures. (e.g., cause of fracture and trauma mechanisms, radiological findings). Also, we had no information on the bone mineral density (BMD). It is known that lower BMD increases the risk of bone fractures. However, we did not have information on BMD because it is not routinely screened in the MBR. Therefore, we cannot make definitive conclusions that the lower risk of fractures among with underweight was not mediated by BMD. However, as the population used in our data was large and relatively young, we believe that the potential bias of the missing information on BMD and other possible co-morbidities does not play an important role in terms of our results. Also, fractures treated in private clinics are not available in our data. In addition, data on women who migrated abroad or died during the follow-up are not available in our dataset. Moreover, as only pregnant women were included in our study, a further limitation of our study might be possible selection bias because the study population does not reflect the whole population perfectly. MBR as a source for BMI means selection bias since being underweight can reduce fertility by causing hormonal imbalance. Thus, the study material can be lacking for the women who are most severely underweighted if they did not manage to get pregnant and/or carry pregnancy to over 22 weeks.

Conclusion

Despite previous findings about the higher risk for fractures for underweights in the older population, the risk for fractures after pregnancy was lower among fertile-aged women with lower BMI.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s42399-023-01548-3.

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

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Data availability The data that support the findings of this study are available from Findata, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Findata (url Findata.fi, email info@Findata.fi). The corresponding author (email matias.vaajala@tuni.fi) can be contacted for the data with a reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate All methods were carried in accordance with Finnish regulations. The Ethical Committee of Tampere University Hospital waived the ethical committee evaluation of all retrospective studies utilizing routinely collected healthcare data, and this decision is based on the law of medical research 488/1999 and the law of patient rights 785/1992. In accordance with Finnish regulations (the law of secondary use of routinely collected healthcare data 552/2019), no ethical informed written consent was required because of the retrospective register-based study design, and the patients were not contacted. Both the National Medical Birth Register (MBR) and the Care Register for Health Care have the same unique pseudonymised identification number for each patient. Permission for the use of this data was granted by Findata after the evaluation of the study protocol (Permission number: THL/1756/14.02.00/2020).

Consent for Publication Not applicable

Conflict of Interests The authors declare no competing interests.

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