Received: 21 January 2023 | Accepted: 3 March 2023

DOI: 10.1002/ijgo.14748

CLINICAL ARTICLE

Obstetrics

Obesity increases the odds of multiple pregnancies: A nationwide register-based cohort study in Finland

Matias Vaajala[1] | Rasmus Liukkonen[1] | Ilari Kuitunen[2,3] | Ville Ponkilainen[4] | Maiju Kekki[5,6] | Ville M. Mattila[1,7]

[1]Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

[2]Department of Pediatrics, Mikkeli Central Hospital, Mikkeli, Finland

[3]Institute of Clinical Medicine and Department of Pediatrics, University of Eastern Finland, Kuopio, Finland

[4]Department of Surgery, Central Finland Central Hospital Nova, Jyväskylä, Finland

[5]Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland

[6]Center for Child, Adolescent and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

[7]Department of Orthopedics and Traumatology, Tampere University Hospital, Tampere, Finland

Correspondence
Matias Vaajala, Arvo, Arvo Ylpön katu 34, Tampere, Pirkanmaa, 33520, Finland.
Email: matias.vaajala@tuni.fi

Abstract

Objective: To investigate the effects of increased pre-pregnancy body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) on the risk of having spontaneous multiple pregnancies using a nationwide register-based study sample.

Methods: Data from the National Medical Birth Register (MBR) (2004–2018) were used to evaluate the effects of a higher pre-pregnancy BMI on the risk of multiple pregnancies. Lower and higher pre-pregnancy BMI classes, using the WHO classification, were compared with a normal weight class. A logistic regression model was used to assess the primary outcomes. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) between the groups were compared. The model was adjusted by maternal age, maternal height, and maternal smoking status.

Results: The odds of multiple pregnancies were higher among women in the overweight group (aOR 1.07, 95% CI 1.02–1.12), obesity class I group (aOR 1.11, 95% CI 1.04–1.18), and obesity class II group (aOR 1.15, 95% CI 1.03–1.28) compared with women in the non-overweight BMI class. Women in the underweight group had lower odds for multiple pregnancies (aOR 0.82, 95% CI 0.73–0.93).

Conclusion: The odds of multiple pregnancies slightly increase with pre-pregnancy obesity, and this should be acknowledged as a minor risk factor for multiple pregnancies.

KEYWORDS
body mass index, multiple pregnancies, obesity, twin studies

1 | INTRODUCTION

The effects of overweight and obesity on the risk of multiple pregnancies have been studied. Multiple pregnancies are relatively rare, making the phenomenon challenging to study without proper data. Only a few studies have investigated the effects of a higher body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) on the risk of multiple pregnancies. A 2005 study that analyzed the US population found that women with a higher BMI had an increased risk of having twins.[1] The same study found that the risk of dizygous twins was higher, but the risk of homozygous twins was not increased.[1] Another study using a twin register in the Netherlands also found higher risk for multiple pregnancies in the obese population.[2] According to a large National

Birth Cohort in Denmark, in which women were recruited early in pregnancy and responded to two questionnaires before delivery, increasing BMI and height correlated with twinning among women without fertility treatment.[3] A Swedish cohort study reported a higher rate of multiple pregnancies in higher BMI groups when compared with a normal weight population.[4] However, to the best of our knowledge after these studies, no other study has focused on the association between a higher BMI and the risk of multiple pregnancies.

Women with higher BMI are known to be at higher risk for infertility.[5] Overweight women have a higher incidence of menstrual dysfunction and anovulation.[5] According to a review of the literature, obese women are more likely to have ovulatory dysfunction due to dysregulation of the hypothalamic–pituitary-ovarian axis.[6] Therefore, assisted reproductive technologies are more common among women with obesity and also a poorer outcome has been reported among these women.[7,8]

Based on our hypothesis, the possible increased risk of multiple pregnancies might be caused by disorders in hormonal activity due to obesity.[9] In obese women, spontaneous multiple pregnancies are suggested to be related to the increased levels of follicle-stimulating hormone.[10] Additionally, the prevalence of obesity and rates of obese parturients giving birth are increasing, meaning that obesity-related risks must be more thoroughly studied and acknowledged.[11] Hence, the aim of this study is to investigate the effects of increased BMI on the risk of having multiple pregnancies using a nationwide register-based study sample.

2 | MATERIALS AND METHODS

In this nationwide retrospective register-based cohort study, data from the National Medical Birth Register (MBR) was used to evaluate the effects of a higher pre-pregnancy BMI on the risk of multiple pregnancies. Multiple pregnancy was defined as a pregnancy with two or more fetuses. The MBR is maintained by the Finnish Institute for Health and Welfare. The study period was from 1 January 2004 to 31 December 2018.

The MBR contains information on pregnancies, delivery statistics and the perinatal outcomes of all births with a birthweight of 500 g or more or a gestational age of 22^{+0} weeks or longer. The MBR has high coverage and quality (the current coverage is nearly 100%).[12,13] We included all pregnancies recorded in the MBR between 2004 and 2018. Stillbirths were also included. A total of 697 710 pregnancies with a known BMI status were included in this study. Cases with missing BMI statuses were excluded. The weights collected were either the pre-pregnancy weight or the weight measured at the first visit to the maternity clinic during weeks 6–8 of pregnancy. The study groups were formed using the classifications given by the World Health Organization.[14] Based on their pre-pregnancy BMI, women were divided into six groups: underweight (BMI less than 18.5), overweight (BMI 25.0–29.9), obesity class I (BMI 30.0–34.9), obesity class II (BMI 35.0–39.9), obesity class III (BMI more than 40.0), and a reference group comprising normal weight women (BMI 18.5–24.9). A total of 20 784 (4.2%) women in the reference group were underweight. Pregnancies that were started using fertility treatments were excluded from the analysis, as the chances of multiple pregnancies are higher among these pregnancies.[15] The process used to form the study groups is shown as a flowchart in Figure 1.

The Ethical Committee of Tampere University Hospital waived the ethical committee evaluation of all retrospective studies using routinely collected healthcare data; 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 informed written consent was required because of the retrospective register-based study design and the patients were not contacted. Both the National MBR and the Care Register for Health Care have the same unique pseudonymized identification number for each patient. The pseudonymization was made by the Finnish data authority Findata. The authors did not have access to the pseudonymization key, as it is maintained by Findata. Permission for use of these data was granted by Findata after evaluation of the study protocol (Permission number: THL/1756/14.02.00/2020).

Continuous variables were interpreted as means with standard deviations or as a median with an interquartile range based on the distribution of the data. The categorical variables are presented as absolute numbers and percentages. A logistic regression model was used to assess the primary outcomes. The exposure variable was the categorized BMI class, and the primary outcome was multiple pregnancies. Women in higher BMI classes were compared with women in the non-overweight BMI class. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) between the groups were compared. The model was adjusted for maternal age (continuous), maternal height (continuous), and maternal smoking status during pregnancy (yes/no), as these are known to be possible risk factors for multiple pregnancies.[3,16,17] 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).[18] The DAG approach can be used to help choose which covariates should be included in traditional statistical approaches to minimize the magnitude of the bias in the estimate produced.[19] The variables included in the DAGs were chosen based on known risk factors and by hypothesized causal pathways. DAGitty automatically suggests possible adjustment variable sets that can influence the main outcome (see Figure S1). A *P* value less than 0.05 was considered statistically significant in all analyses. Statistical analyses were performed using R version 4.0.3 for Windows (R Foundation for Statistical Computing).

3 | RESULTS

A total of 464 983 pregnancies were included in the reference group, 28 991 in the underweight group, 174 776 in the overweight group, 66 592 in the obesity class I group, 23 130 in the obesity class II group, and 10 170 in the obesity class III group. A

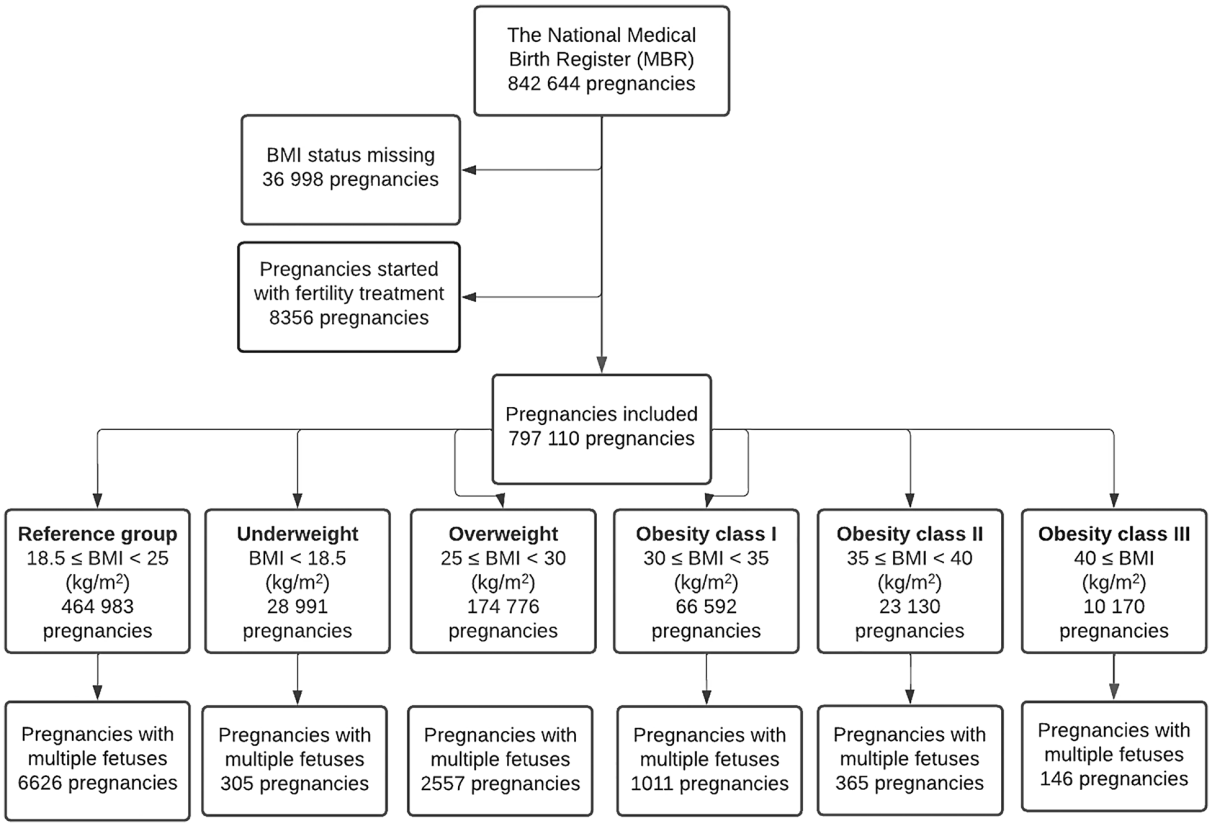

FIGURE 1 Flowchart of the study population. Women with different classes of obesity were compared with women with normal body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters).

total of 6626 (1.4%) multiple pregnancies were found in the reference group, 305 (1.1%) in the underweight group, 2557 (1.5%) in the overweight group, 1011 (1.5%) in the obesity class I group, 365 (1.6%) in the obesity class II group, and 146 (1.4%) in the obesity class III group. A higher rate of smokers was observed in higher BMI classes and the underweight class, when compared with the reference group. (Table 1) A total of 8356 pregnancies (1.0%) were started using fertility treatments and 36 998 pregnancies (4.4%) were excluded because of missing BMI.

The odds of multiple pregnancies were higher among women in the overweight group (aOR 1.07, 95% CI 1.02–1.12), obesity class I group (aOR 1.11, 95% CI 1.04–1.18), and obesity class II group (aOR 1.15, 95% CI 1.03–1.28) compared with women in a normal BMI class. Women in the obesity class III group did not have higher odds of multiple pregnancies (aOR 1.03, 95% CI 0.87–1.21) than women with a normal BMI. The odds for multiple pregnancies were lower among underweight women (aOR 0.82, 95% CI 0.73–0.93), when compared with normal BMI (Table 2).

4 | DISCUSSION

The main finding of this study is that the odds of multiple pregnancies increase with increasing BMI. The odds of multiple pregnancies were a little higher with a higher BMI, except for obesity class III, where the odds were not increased. However, the number of patients in this group was relatively small, and the results may be imprecise.

Based on previous studies, a higher BMI increases the risk of multiple pregnancies,[1,3,4] which is also supported by our results featuring a large nationwide register-based study sample. The increase in risk for multiple pregnancies was relatively restrained in our study when compared with these previous studies. The Swedish study with a large national birth cohort reported adjusted odds of 1.44 (95% CI 1.13–1.83) among women with BMI greater than 30,[3] which is higher than observed in our results. However, because of the crude nature of our data, the exact reason for this slightly increased risk remains unknown, and more research is warranted. The results of this study should provide important information regarding the risks of multiple pregnancies in overweight and obese mothers.

The research behind the association between obesity and multiple pregnancies is important, because obesity and multiple pregnancies are known to be risk factors for adverse pregnancy outcomes, both for the neonate and the mother.[20,21] According to a large cohort study consisting of only twin pregnancies, higher BMI was associated with gestational hypertension, pre-eclampsia, and gestational diabetes.[22] In addition, as multiple pregnancies are associated with increased risk for gestational diabetes[23,24] and obesity is known to be one of the biggest risk factors for the development of gestational diabetes,[25] studies assessing the association among these factors are important in the prevention of adverse maternal and fetal outcomes.

TABLE 1 Background information on the study groups used in the analyses; in each study group, the smoking status of approximately 1.8%–2.6% of patients was unknown.[a]

	Reference group (BMI <25)	Underweight (BMI <18)	Overweight (25 ≤ BMI < 30)	Obesity class I (30 ≤ BMI < 35)	Obesity class II (35 ≤ BMI < 40)	Obesity class III (BMI ≥40)
Total number	464 983	28 991	174 776	66 592	23 130	10 170
Age at the time of pregnancy, y	29.6 ± 5.3	27.3 ± 5.5	30.1 ± 5.4	30.1 ± 5.4	29.9 ± 5.4	30.2 ± 5.4
Smoking status						
Smoker	65 033 (14.0%)	6229 (21.5%)	27 528 (16.3%)	12 483 (19.5%)	4767 (21.1%)	2137 (21.1%)
Maternal height, cm	165.6 ± 6.0	165.4 ± 6.3	165.4 ± 6.1	165.3 ± 6.1	165.4 ± 6.2	165.6 ± 6.3
Stillbirths						
Multiple pregnancy	6639 (1.4%)	305 (1.1%)	2557 (1.5%)	1011 (1.5%)	365 (1.6%)	146 (1.4%)
Twins	6566 (1.4%)	302 (1.0%)	2523 (1.5%)	999 (1.5%)	361 (1.6%)	144 (1.4%)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

[a]Data are presented as mean ± standard deviation or as number (percentage).

TABLE 2 Adjusted odds for multiple pregnancy among different BMI classes.[a]

BMI class	aOR (95% CI)
Underweight (BMI ≤18.5)	0.82 (0.73–0.93)
Overweight (BMI 25.0 to <30.0)	1.07 (1.02–1.12)
Obesity class I (BMI 30 to <35)	1.11 (1.04–1.18)
Obesity class II (BMI 35 to <40)	1.15 (1.03–1.28)
Obesity class III (BMI ≥40)	1.03 (0.87–1.21)

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval.

[a]Pregnancies in women with BMI class higher than normal were compared with pregnancies among normal weight women (BMI 18.5–25.0). The model was adjusted for maternal age (continuous), maternal height (continuous), and maternal smoking status during pregnancy (yes/no).

In addition, the rapidly increasing prevalence of obese parturients makes this an important research topic.[11,26]

Compared with previous studies, the unique strength of our study is the large nationwide register with a BMI variable registered for nearly all pregnancies that occurred during the study period, making it the most comprehensive data set on the BMI of women.[12,13] Compared with previous studies in which BMI was assessed using questionnaires that are inevitably vulnerable to recall or reporting bias, the register data used in our study are routinely collected using structured forms and national instructions, which ensures good coverage and reduces possible reporting and selection biases. Furthermore, the coverage of both registers included in this study was high. The main limitation for this study is that we do not have information on the type of multiple pregnancy (e.g. homozygous and dizygous). In addition, the information on the fertility treatments is not routinely collected, meaning that only treatments brought up by the mother or treatment providers are registered in the MBR. However, as our study sample is large and the need for fertility treatments is still a relatively small percentage of all pregnancies,[27] we believe that this does not have an important effect on the main results. However, it is good to acknowledge that the total number of fertility treatments reported by the Finnish Institute for Wealth and Welfare is higher than observed in the MBR, meaning that all fertility treatments are not available in the register.

In summary, based on our results, the odds of multiple pregnancies increase slightly with obesity, and it should be acknowledged as a minor risk factor for multiple pregnancies.

AUTHOR CONTRIBUTIONS

Matias Vaajala and Rasmus Liukkonen wrote the initial manuscript. Ilari Kuitunen and Ville M. Mattila designed the study. Ville M. Mattila supervised the study. Ville Ponkilainen helped in planning appropriate statistical analysis. Maiju Kekki provided clinical expertise. Each author commented on the manuscript during the process and confirmed the final version to be submitted.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Matias Vaajala https://orcid.org/0000-0002-1294-6173

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SUPPORTING INFORMATION

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How to cite this article: Vaajala M, Liukkonen R, Kuitunen I, Ponkilainen V, Kekki M, Mattila VM. Obesity increases the odds of multiple pregnancies: A nationwide register-based cohort study in Finland. *Int J Gynecol Obstet*. 2023;00:1-5. doi:10.1002/ijgo.14748