Body size during adulthood, but not in childhood, associates with endometriosis, specifically in the peritoneal subtype—population-based life-course data from birth to late fertile age

Henna-Riikka Rossi1,2 | Rozenn Nedelec3 | Marjo-Riitta Jarvelin3,4,5,6 | Sylvain Sebert3 | Outi Uimari1,2 | Terhi T. Piltonen1,2

1Department of Obstetrics and Gynecology, Oulu University Hospital, Oulu, Finland
2PEDEGO Research Unit & Medical Research Center, University of Oulu, Oulu, Finland
3Center for Life course Health Research, University of Oulu, Oulu, Finland
4Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, UK
5MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, UK
6Department of Life Sciences, College of Health and Life Sciences, Brunel University, London, UK

Abstract

Introduction: Endometriosis is a common gynecological condition causing chronic pain and infertility. Only limited data exist on body size during childhood and adolescence in affected women. A leaner body shape has been associated with endometriosis in adults. However, longitudinal follow-up data from birth to adulthood are lacking. The aim of this study was to assess the association between body size and endometriosis from birth to age 46 years. We also performed in-depth analysis of the endometriosis subtypes.

Material and Methods: This was a population-based study including 96% of the children born in Northern Finland in 1966. Endometriosis case identification was based on (a) the World Health Organization's International Statistical Classification of Diseases code documentation from national hospital discharge registers and (b) self-reported diagnosis. A total of 348 women with endometriosis (203 in subtype analysis) and 3487 women without endometriosis were identified. Pregnancy, birth, and growth data up to adolescence were collected from welfare clinical records. Follow-up data of the Northern Finland Birth Cohort 1966 were collected at ages 14, 31, and 46 years through postal questionnaires and clinical examinations and included height, weight, and waist and hip circumference measurements. The associations between endometriosis and body size were assessed using logistic regression models.

Results: Body sizes in childhood and adolescence were comparable between women developing endometriosis and those not developing endometriosis. On average, the risk for endometriosis was 2% lower for every kilogram of weight (odds ratio [OR] 0.98, 95% CI 0.97-1.00) and 6% lower for every body mass index unit (OR 0.94, 95% CI 0.90-0.99) at age 31. By age 46, a lower risk for peritoneal endometriosis was observed with greater weight (OR 0.95, 95% CI 0.92-0.98), weight gain from age 14

Abbreviations: BMI, body mass index; HC, hip circumference; ICD, International Classification of Diseases; IGF-1, insulin-like growth factor 1; NFBC1966, Northern Finland Birth Cohort 1966; OR, odds ratio; SD, standard deviation; WC, waist circumference; WHR, waist-hip ratio.

Outi Uimari and Terhi T. Piltonen contributed equally.

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Endometriosis is a common chronic gynecological condition causing pelvic pain and infertility. Its etiology is multifactorial, including genetic, environmental, and lifestyle components. Endometriosis is characterized by the presence of functional endometrial tissue outside the uterus, most commonly on the peritoneal wall and ovaries. As in the eutopic endometrium, the proliferation of ectopic endometriosis lesions is promoted by the action of estrogen; so the onset of symptoms usually occurs post menarche during the reproductive years. The pathophysiology of endometriosis is complex, including steroidogenic linkage and abnormalities in immune response, angiogenesis, inflammation, and apoptosis. All these factors may lead to adhesion and the growth of ectopic lesions.

The link between endometriosis and weight and adiposity has been the subject of several studies. Findings indicate that early life factors such as prematurity and low birthweight may be associated with the disease. Interestingly, however, body size in childhood and from early to late adulthood seems to be inversely associated with endometriosis. Moreover, a body fat distribution characterized by a low waist-hip ratio (WHR) has more often been observed in affected women, which is also supported by genetic studies. These results, however, have been obtained from multiple study populations and with no distinction between endometriosis subtypes. Their reliability may further be limited due to small sample sizes and/or the use of self-reported endometriosis diagnosis and body size measurement data, which may be subject to recall bias.

The possible inverse association between endometriosis and body size has yet to be confirmed in a larger study setting including multiple life-course stages.

The aim of this study was to explore the association between endometriosis and its subtypes (peritoneal, ovarian, and deep infiltrating endometriosis) and body size development at several life-course stages from birth to adolescence to adulthood. The analysis was based on data of 5889 females, which included (a) longitudinal data on weight and height from birth to age 20 years and (b) cross-sectional data on weight and height at menarche and at ages 14, 31, and 46 years and waist and hip circumference data at ages 31 and 46 years.

**Conclusions:** This study provides further evidence of the associations between endometriosis and body size and adiposity, specifically in women with peritoneal endometriosis. The associations are evident in adulthood but not in childhood or adolescence.

**Keywords**

Adiposity, body mass index, body size, body weight, endometriosis, subtype, waist, waist-hip ratio

**Key message**

This population-based birth cohort study showed that endometriosis, specifically peritoneal subtype, associates with leaner habitus in adulthood only.

**2 | MATERIAL AND METHODS**

This study was based on the Northern Finland Birth Cohort 1966 (NFBC1966). It was a prospective birth cohort study consisting of 96.3% of all expected births during 1966 in Northern Finland (12,055 mothers, 12,058 live-born children, 5889 females, all Finnish Caucasian). Enrollment in the cohort began during the 24th gestational week, and birth, childhood, and adolescence growth measurements were collected by professionals through the Finnish health system. Specific time-points for the NFBC1966 data collection were planned about 15 years apart at ages 14, 31, and 46 years via postal questionnaires and clinical examinations. All data were collected by trained study nurses and doctors according to unified protocols. All individuals included in this study provided informed consent for the NFBC1966 study and for the use of their register-level data.

**2.1 | Identification of women with endometriosis**

Women with endometriosis were identified from the NFBC1966 population using two different data sources. First, self-reported cases were identified from the 46-year follow-up study. In the health questionnaire, women were asked to report whether they had been diagnosed with endometriosis (“Have you ever been diagnosed with endometriosis by a clinical doctor?”). The self-reported endometriosis diagnosis has been validated previously. Second, the NFBC1966 population was linked to the national outpatient and inpatient hospital discharge register (available from 1968 to 2012). The hospital discharge register is considered a reliable data source and has been widely used in scientific studies. It includes World Health Organization International Classification of Diseases (ICD) code.
standards for each hospital visit. In Finland, these codes are entered by clinical doctors. The ICD-9 and ICD-10 codes for endometriosis (617.1-617.9 and N80.1-N80.9, respectively; ICD-8 codes were converted to ICD-9) were used for medically confirmed case identification. These cases were categorized into the following endometriosis subtypes: peritoneal endometriosis (617.2, 617.3, N80.2, and N80.3), ovarian endometriosis (617.1 and N80.1), and deep infiltrating endometriosis (617.4, 617.5, 617.8, N80.4, N80.5, and N80.8). Some diagnosis overlap was observed. In these cases, peritoneal diagnosis was accepted only if the individual had no diagnosis of ovarian or deep infiltrating endometriosis. Cases of overlapping ovarian and deep infiltrating endometriosis diagnoses were classified as deep infiltrating endometriosis. There were also 21 diagnoses of unspecified/scar endometriosis (N80.9, N80.6), which were not included in the subtype analysis. Women who did not have an ICD code for endometriosis and replied "no" to the self-reported endometriosis question were considered to be women without endometriosis. A flow chart of the study population is shown in Figure 1.

2.2 Pregnancy and birth data

Birthweight data of the cohort individuals were collected from the hospital and welfare records. Individuals whose birthweight was below the 10th centile with respect to their gestational age were considered small for gestational age, whereas those whose birthweight was above the 90th centile were considered large for gestational age.

2.3 Growth data in childhood and adolescence

Childhood weight and height from early infancy until 6 years of age were measured by nurses at welfare clinics and from age 7 to age 17 years in school as part of the national child health screening program, which is free and available to all children born in Finland (coverage: 99% of the population). Between ages 17 and 20 years, body mass indices (BMIs) were measured in the context of the general healthcare system. The BMIs at age 14 years were calculated from height and weight measures reported by the parents. Women reported their age at menarche in the 46-year postal questionnaire, and the corresponding BMIs were calculated from the fitted BMI growth curves. The childhood growth data were divided into two age periods: from 2 weeks to 18 months (infancy) and from 18 months to 13 years (childhood). The longitudinal BMI linear mixed-effects model was fitted using the logarithmically transformed BMI as the outcome, and the predicted timing of adiposity peak (maximum weight during this period, around 9 months) and adiposity rebound point (nadir of the BMI curve, usually around 5 years) were calculated using estimated fixed and random coefficients.

The long-term BMI patterns of the cohort individuals between ages 2 and 20 years were assessed with group-based modeling using Nagin’s approach. The model identifies clusters or subpopulations exhibiting the same patterns of change or behavior over time. For modeling purposes, 16 age windows were created. Ages 17 to 20 years were grouped together to increase the number of measurements for this window. BMIs (expressed as weight in kg/height in m² for each age window) and BMI z-scores were internally calculated. Multiples and individuals with fewer than three BMI measures were excluded from the analysis. The model created four clusters of women with similar BMI trends between ages 2 and 20 years.

2.4 Body measurements in adulthood

Weight (in kilograms), height (in centimeters), waist circumference (WC; in centimeters), and hip circumference (HC; in centimeters) were measured at the NFBC1966 clinical examinations at ages 31 and 46 years. The BMI was calculated as weight (kg)/height (m)², and the WHR was calculated as WC/HC. The weight, height, waist, and hip measurement protocols have been described previously.

2.5 Covariates

Several potentially confounding variables were considered for possible associations with weight development and endometriosis: maternal weight gain during pregnancy, mother’s smoking status at pregnancy, gestational age at birth, age at menarche, socioeconomic and relationship status, smoking, physical activity, and hormonal contraceptive use. Maternal and gestational data were collected from hospital and welfare records. The gestational age at birth was classified according to the World Health Organization’s criteria for gestational weeks: very preterm, 33¹⁄₇; preterm, 34⁰⁰/₇ to 36⁰⁶/₇; and at term, 37⁰⁶/₇. Data on age at menarche were collected from the 46-year follow-up questionnaire. The socioeconomic status was determined based on the education level (basic, secondary, or tertiary/higher) reported in the questionnaire. The relationship status was determined as “in relationship” based on self-reported marriage or cohabitation at ages 31 and 46 years. Data on smoking habits were collected from self-reports at age 46 years. Individuals reported

![Flowchart of the data collection and study population. The population of women with endometriosis and women without endometriosis formed in the Northern Finland Birth Cohort 1966 for the present study are marked in grey. ICD, International Classification of Diseases](image-url)
never, formerly/occasionally, or currently smoking. Intensity and duration of physical activity data collected from the questionnaires were calculated as metabolic equivalent of task minutes per week.\textsuperscript{14} Parity data were collected from the questionnaires at ages 31 and 46 years. At age 46 years, respondents were asked if they had ever used hormonal contraceptives. Potential mediation for each confounder was tested using the Sobel test. Analytical models were constructed separately for four time-points: birth and ages 14, 31, and 46 years.

2.6 Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics software version 22 for Windows (IBM Corp.). Differences in continuous variables were analyzed using the independent samples t test or the Mann-Whitney U test and the chi-squared test was used to analyze differences in categorical parameters. Pearson correlation was used to test for correlation between BMI and the age at first endometriosis diagnosis. Binary logistic regression analysis was used to explore anthropometrics/body size associations between those with endometriosis and those without. Appropriate confounding factors were included in the multivariate analysis models. Analytical models were constructed separately for four available time-points: birth and ages 14, 31, and 46 years.

The results are reported as odds ratios (ORs) with 95% CIs. To exclude possible outliers in WC and HC measures, a 2 standard deviation (SD) threshold was used as a sensitivity analysis in the logistic regression calculation. A two-sided P value less than 0.05 was considered statistically significant. Bonferroni correction was conducted to reduce the risk of Type I Error: the P value of \( \frac{0.05}{4} \) \( (P < .0125) \) denotes statistical significance. Sobel test was used to explore for possible mediation between endometriosis and confounders. Group-based trajectory modeling from the Proc Traj procedure in SAS software version 9.4 (SAS Institute Inc.) was used.

2.7 Ethical approval

This study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District on 14 December 2011, registration number ETTMK: 94/2011.

3 RESULTS

The total endometriosis population consisted of 348 women, of whom 124 only self-reported endometriosis diagnosis and 224 had medically confirmed endometriosis (Figure 1). Other female cohort members were considered women without endometriosis (n = 3487). We categorized the medically confirmed cases into the following endometriosis subtypes: peritoneal endometriosis (n = 59; 26.3%), ovarian endometriosis (n = 107; 47.8%), and deep infiltrating endometriosis (n = 37; 16.5%). The participation rates in the follow-up data collection at ages 31 and 46 years did not differ between the endometriosis and non-endometriosis groups.

3.1 Baseline characteristics

Mothers of cohort members with and without endometriosis exhibited similar early-pregnancy weight and weight gain during pregnancy, as well as similar smoking rates. Women with and without endometriosis were born at similar gestational ages, and there were no distribution differences among those born as small-for-gestational age and those born as large for gestational age (Table 1). The mean age at menarche of women with endometriosis (12.6 ± 1.2 years) did not differ significantly from that of women without endometriosis (12.9 ± 1.2 years; \( P = .898 \)). Likewise, the BMI at menarche did not differ significantly (18.3 ± 2.3 vs 18.5 ± 2.7 kg/m\(^2\)). The mean age at endometriosis diagnosis was 31.6 ± 7.3 years (Table 1). As expected, the infertility rate of women with endometriosis was higher than that of women without endometriosis (31% vs 13%; \( P = .014 \)). Women with endometriosis had significantly lower parity at age 46 years (1.9 ± 1.2 vs 2.33 ± 1.8; \( P < .001 \)) and were more likely to have used hormonal contraceptives (93.5% vs 89.3%; \( P = .014 \); Table 1). No significant differences were observed between the two groups in terms of socioeconomic and relationship status, smoking, or physical activity (Table 1). According to the Sobel test, none of the confounding factors showed mediation for body size measures in adulthood or endometriosis risk.

3.2 Associations between lifelong body measurements and endometriosis

There were no associations between endometriosis and birthweight, adiposity peak, and adiposity rebound (Table 2). No associations were observed between endometriosis and weight, height, and BMI at age 14 years. The growth trajectory analysis revealed no significantly different trends between women who developed endometriosis and those who did not, and the proportions of women in each trajectory cluster were comparable (Figure S1).

At age 31 years, women with endometriosis exhibited lower mean weight than women without endometriosis (63.4 ± 9.8 vs 65.5 ± 13.0 kg; \( P = .016 \)). They had gained less weight since age 14 years (12 ± 8.2 vs 13.6 ± 9.3 kg; \( P = .004 \)), and their BMI was lower (22.9 ± 4.2 vs 23.6 ± 3.5 kg/m\(^2\); \( P = .016 \)). Women with endometriosis also had a smaller WC (76.3 ± 9.3 vs 78.9 ± 12.0 cm; \( P = .006 \)) and a lower WHR (0.79 ± 0.07 vs 0.81 ± 0.08; \( P = .002 \); Table 2). The multivariate analysis revealed inverse associations between several body size measures and endometriosis. Lower weight (OR 0.98, 95% CI 0.97-1.00), less weight gain between ages 14 and 31 years (OR 0.98, 95% CI 0.96-0.99), lower BMI (OR 0.94, 95% CI 0.90-0.98), smaller WC (OR 0.98, 95% CI 0.97-1.00), and smaller WHR (OR 0.79, 95% CI 0.63-1.00) were associated with a higher risk of endometriosis.
In contrast, HC showed no inverse association (Table 2). The endometriosis subtype analysis showed that women with peritoneal endometriosis had a lower mean BMI (22.7 ± 4.1 vs 23.6 ± 3.5 kg/m²; \( P = .043 \)) and a smaller mean WC (74.7 ± 9.4 vs 78.9 ± 12.0 cm; \( P = .046 \)) and HC (93.9 ± 6.6 vs 97.1 ± 8.8 cm; \( P = .039 \)) than women without endometriosis, but associations were not significant with the other two subtypes. After adjusting for confounders, the multivariate analysis indicated consistency in terms of OR estimates and effect directionality, although the results were not statistically significant (Table 3). There were no associations between body size measures and ovarian or deep infiltrating endometriosis. The results remained unchanged when the analysis was restricted to ±2SD for WC and HC data.

At age 46 years, women who had developed endometriosis still had a lower mean weight than women without endometriosis (70.4 ± 13.6 vs 72.2 ± 15.0 kg, \( P = .049 \)). However, weight gain since ages 14 and 31 years did not differ significantly between the two groups (Table 2). There were no significant differences in BMI, WC, and HC, but the WHR was slightly lower in women with endometriosis (0.86 ± 0.06 vs 0.87 ± 0.06; \( P = .012 \)).

| TABLE 1 Characteristics of the study population in the Northern Finland Birth Cohort 1966 |
|-----------------------------------------------|-------------------------------|------------------|
|                                               | No endometriosis (n = 3487)   | Endometriosis (n = 348) | \( P \) value |
| Mother’s prepregnancy weight (kg), mean (SD)  | 56.8 (15.1)                   | 56.9 (14.7)         | .856         |
| Mother’s pregnancy weight gain (kg), mean (SD)| 11.9 (4.0)                    | 12.1 (4.2)          | .654         |
| Mother’s smoking at the end of pregnancy, % (n)| 4.6 (161)                     | 4.9 (17)            | .966         |
| Gestational age at birth                      |                               |                   |
| Very preterm birth (<34 weeks), % (n)         | 4.0 (14)                      | 2.9 (10)           | .360         |
| Preterm birth (34-37 weeks), % (n)            | 3.8 (132)                     | 4.5 (1579)         |              |
| Birth at term (>37 weeks), % (n)              | 91.7 (3198)                   | 93.1 (324)         |              |
| Small for gestational age, % (n)              | 8.4 (277)                     | 8.2 (27)           | .882         |
| Large for gestational age, % (n)              | 11.3 (371)                    | 7.9 (26)           | .064         |
| Age at menarche, mean (SD)                    | 12.9 (1.2)                    | 12.6 (1.2)         | .898         |
| BMI at menarche (kg/m²), mean (SD)            | 18.5 (2.7)                    | 18.3 (2.3)         | .577         |
| Parity at age 31 years, mean (SD)             | 1.6 (1.3)                     | 1.3 (1.1)          | <.001        |
| Parity at age 46 years, mean (SD)             | 2.33 (1.8)                    | 1.9 (1.2)          | <.001        |
| Mean age at the time of first endometriosis diagnosis (years) | NA                            | 31.6 (7.3)         | NA           |
| Infertility by age 46 years, % (n)            | 13.0 (454)                    | 31.0 (108)         | <.001        |
| Hormonal contraceptive use (ever), % (n)      | 89.3 (2981)                   | 93.5 (315)         | .014         |

| Socioeconomical status defined as education level |
|---------------------------------------------------|
| Basic, % (n)                                      | 6.2 (209)                     | 4.4 (15)           |
| Secondary, % (n)                                 | 63.8 (2143)                   | 61.2 (207)         |
| Tertiary, % (n)                                   | 30.0 (1006)                   | 34.3 (116)         |

| Relationship status:                              |
|---------------------------------------------------|
| Lives in relationship at age 31 years, % (n)      | 77.9 (2450)                   | 77.5 (252)         |
| Lives in relationship at age 46 years, % (n)      | 76.8 (2574)                   | 79.3 (268)         |

| Smoking:                                           |
|---------------------------------------------------|
| Never, % (n)                                      | 56.0 (1861)                   | 59.8 (199)         |
| Former/Occasional, % (n)                          | 26.6 (885)                    | 21.3 (71)          |
| Active, % (n)                                     | 17.3 (575)                    | 18.9 (63)          |

| Physical activity: MET min/week                    |
|---------------------------------------------------|
| Light at age 31, mean (SD)                         | 508 (487)                     | 521 (490)          |
| Brisk at age 31, mean (SD)                         | 418 (501)                     | 456 (516)          |
| Light at age 46, mean (SD)                         | 519 (487)                     | 538 (485)          |
| Brisk at age 46, mean (SD)                         | 573 (608)                     | 523 (492)          |

Note: Data reported as mean(SD) or percentages (n). Significance tests for continuous variables were performed by using the independent samples t test or the Mann–Whitney U test, as appropriate. \( P \) value <.05 was considered significant.

Differences in numbers vary in different analyses as a result of some missing data.

Abbreviations: BMI, body mass index; MET min/week: metabolic equivalent of task score.
| Age 14 years<sup>b</sup> | No endometriosis (n = 3487), mean (SD) | Endometriosis (n = 348), mean (SD) | Univariate OR (95% CI) | Multivariate OR (95% CI) | P value |
|-------------------------|---------------------------------------|-------------------------------------|------------------------|-------------------------|---------|
| Weight (kg)             | 50.7 (7.9)                            | 50.5 (7.3)                          | 1.00 (0.98-1.01)       | 0.99 (0.98-1.01)         | .506    |
| Height (cm)             | 161.5 (6.1)                           | 161.5 (5.9)                         | 1.00 (0.98-1.02)       | 1.00 (0.98-1.02)         | .979    |
| BMI (kg/m<sup>2</sup>)  | 19.4 (2.5)                            | 19.3 (2.3)                          | 0.98 (0.94-1.03)       | 0.98 (0.93-1.03)         | .322    |

| Age 31 years<sup>c</sup> | No endometriosis (n = 3487), mean (SD) | Endometriosis (n = 348), mean (SD) | Univariate OR (95% CI) | Multivariate OR (95% CI) | P value |
|-------------------------|---------------------------------------|-------------------------------------|------------------------|-------------------------|---------|
| Weight (kg)             | 65.5 (13.0)                           | 63.4 (9.8)                          | 0.99 (0.97-1.00)       | 0.98 (0.97-1.00)         | .012<sup>*</sup> |
| Weight gain from age 14 to 31 years (kg) | 13.6 (9.3)                          | 12.0 (8.2)                          | 0.98 (0.97-0.99)       | 0.98 (0.96-0.99)         | .004<sup>+</sup> |
| Height (cm)             | 164.7 (6.1)                           | 164.7 (6.2)                         | 1.00 (0.98-1.02)       | 0.99 (1.00-1.02)         | .492    |
| BMI (kg/m<sup>2</sup>)  | 23.6 (3.5)                            | 22.9 (4.2)                          | 0.95 (0.92-0.99)       | 0.94 (0.90-0.98)         | .001<sup>+</sup> |
| WC (cm)                 | 78.9 (12.0)                           | 76.3 (9.3)                          | 0.98 (0.97-0.99)       | 0.98 (0.97-1.00)         | .024    |
| HC (cm)                 | 97.1 (8.8)                            | 96.1 (7.1)                          | 0.99 (0.97-1.00)       | 0.99 (0.97-1.00)         | .121    |
| WHR                     | 0.81 (0.08)                           | 0.79 (0.07)                         | 0.71 (0.58-0.88)       | 0.79 (0.63–1.00)         | .051    |

| WHR by categories       |                                      |                                     |                        |                         |         |
| BMI <18.5 kg/m<sup>2</sup> | 0.45 (0.06-3.19)                   | NA**                                | NA**                   | NA**                   |         |
| BMI 18.5-25 kg/m<sup>2</sup> | 0.71 (0.53-0.97)                  | 0.85 (0.62-1.15)                   | .292                   |                         |         |
| BMI >25 kg/m<sup>2</sup>  | 0.69 (0.46-1.02)                   | 0.67 (0.43-1.04)                   | .071                   |                         |         |

| Age 46 years<sup>d</sup> | No endometriosis (n = 3487), mean (SD) | Endometriosis (n = 348), mean (SD) | Univariate OR (95% CI) | Multivariate OR (95% CI) | P value |
|-------------------------|---------------------------------------|-------------------------------------|------------------------|-------------------------|---------|
| Weight (kg)             | 72.2 (15.0)                           | 70.4 (13.6)                         | 0.99 (0.98-1.00)       | 0.99 (0.98-1.00)         | .262    |
| Weight gain from age 14 to 46 years (kg) | 20.7 (12.5)                          | 19.4 (11.6)                         | 0.99 (0.98-1.00)       | 1.01 (0.99-1.03)         | .235    |
| Weight gain from age 31 to 46 years (kg) | 7.0 (8.2)                            | 7.4 (7.8)                           | 0.99 (0.98-1.00)       | 0.99 (0.98-1.00)         | .223    |
| Height (cm)             | 164.8 (6.0)                           | 164.6 (6.2)                         | 1.00 (0.98-1.02)       | 1.00 (0.98-1.02)         | .980    |
| BMI (kg/m<sup>2</sup>)  | 26.2 (5.2)                            | 25.7 (4.7)                          | 0.98 (0.96-1.00)       | 0.98 (0.95-1.01)         | .126    |
| WC (cm)                 | 87.3 (12.1)                           | 85.8 (12.7)                         | 0.99 (0.98-1.00)       | 0.99 (0.98-1.01)         | .231    |
| HC (cm)                 | 100.5 (11.1)                          | 99.9 (10.6)                         | 0.99 (0.98-1.01)       | 1.00 (0.98-1.01)         | .700    |
| WHR                     | 0.87 (0.06)                           | 0.86 (0.06)                         | 0.77 (0.62-0.94)       | 0.80 (0.62-1.03)         | .083    |

| WHR by categories       |                                      |                                     |                        |                         |         |
| BMI <18.5 kg/m<sup>2</sup> | 1.36 (0.04-47.17)                  | NA**                                | NA**                   |                         |         |
| BMI 18.5-25 kg/m<sup>2</sup> | 0.58 (0.41-0.84)                  | 0.53 (0.34-0.82)                   | .005<sup>+</sup>       |                         |         |
| BMI >25 kg/m<sup>2</sup>  | 0.89 (0.65-1.22)                   | 0.91 (0.63-1.31)                   | .600                   |                         |         |

Note: The odds ratios were calculated per 1 unit change, except WHR per 0.1 unit change. Significant P values marked with bold.

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist to hip ratio.

In multivariate analysis:

- Mother’s weight gain during pregnancy, mother’s smoking at end of pregnancy, gestational age at birth.
- Age at menarche.
- Socioeconomical status, relationship status at age 31, smoking status, physical activity at age 31, age at menarche, parity at age 31, lifetime hormonal contraceptive use at age 46 years.
- Socioeconomical status, relationship status at age 46, smoking status, physical activity at age 46, age at menarche, parity at age 46, lifetime hormonal contraceptive use at age 46 years.
- *P value significant after the Bonferroni correction.
### TABLE 3  
Association between adulthood body size measurements and different endometriosis subtypes; multivariate binary logistic regression analysis model

|                  | No endometriosis (n = 3487) | Peritoneal endometriosis (n = 59) | Multivariate OR (95% CI) | P value | Ovarian endometriosis (n = 107) | Multivariate OR (95% CI) | P value | Deep infiltrating endometriosis (n = 37) | Multivariate OR (95% CI) | P value |
|------------------|-----------------------------|----------------------------------|--------------------------|---------|-------------------------------|--------------------------|---------|------------------------------------------|--------------------------|---------|
| **Age 31 years** |                             |                                  |                          |         |                               |                          |         |                                          |                          |         |
| Weight (kg)      | 65.5 (13.0)                 | 62.3 (9.7)                       | 0.98 (0.94-1.02)         | .324    | 65.0 (9.9)                    | 0.99 (0.96-1.01)         | .289    | 65.5 (11.5)                              | 1.00 (0.96-1.03)         | .702    |
| Weight gain from 14 to 31 years (kg) | 13.6 (9.3) | 13.6 (9.6) | 1.00 (0.95-1.04) | .993 | 13.0 (9.2) | 0.97 (0.94-1.00) | .979 | 15.4 (10.1) | 0.99 (0.95-1.04) | .853 |
| Height (cm)      | 164.7 (6.1)                 | 164.5 (6.5)                      | 0.98 (0.91-1.04)         | .490    | 165.8 (5.5)                   | 1.03 (0.90-1.01)         | .243    | 164.4 (7.8)                              | 1.00 (0.93-1.07)         | .640    |
| BMI (kg/m²)      | 23.6 (3.5)                  | 22.7 (4.1)                       | 0.93 (0.84-1.05)         | .269    | 23.2 (3.3)                    | 0.93 (0.88-1.01)         | .080    | 23.8 (4.2)                               | 0.98 (0.89-1.08)         | .827    |
| WC (cm)          | 78.9 (12.0)                 | 74.7 (9.4)                       | 0.96 (0.91-1.01)         | .132    | 77.1 (8.2)                    | 0.98 (0.96-1.01)         | .150    | 79.3 (10.8)                              | 0.99 (0.95-1.04)         | .743    |
| HC (cm)          | 97.1 (8.8)                  | 93.9 (6.6)                       | 0.94 (0.88-1.01)         | .073    | 97.1 (6.9)                    | 0.98 (0.95-1.01)         | .984    | 97.4 (7.3)                               | 1.00 (0.94-1.04)         | .900    |
| WHR              | 0.81 (0.08)                 | 0.79 (0.06)                      | 0.74 (0.35-1.53)         | .410    | 0.79 (0.06)                   | 0.71 (0.4-1.15)          | .162    | 0.81 (0.07)                              | 0.91 (0.46-1.81)         | .750    |
| **Age 46 years** |                             |                                  |                          |         |                               |                          |         |                                          |                          |         |
| Weight (kg)      | 72.2 (15.0)                 | 66.7 (12.5)                      | 0.95 (0.92-0.98)         | .014    | 71.3 (13.3)                   | 1.00 (0.99-1.02)         | .884    | 74.2 (14.9)                              | 1.01 (0.98-1.03)         | .638    |
| Weight gain from 14 to 46 years (kg) | 20.7 (12.5) | 16.7 (10.8) | 0.97 (0.94-1.00) | .049 | 20.2 (12.0) | 1.00 (0.98-1.02) | .966 | 23.5 (13.1) | 1.01 (0.98-1.04) | .838 |
| Weight gain from 31 to 46 years (kg) | 7.0 (8.2) | 6.8 (6.7) | 0.99 (0.95-1.04) | .791 | 7.3 (6.6) | 1.04 (0.98-1.05) | .405 | 6.2 (10.5) | 1.01 (0.95-1.07) | .676 |
| Height (cm)      | 164.8 (6.0)                 | 165.3 (6.1)                      | 1.01 (0.96-1.06)         | .795    | 165.5 (6.1)                   | 1.03 (0.99-1.07)         | .185    | 164.3 (6.7)                              | 1.00 (0.93-1.06)         | .317    |
| BMI (kg/m²)      | 26.2 (5.2)                  | 24.6 (4.5)                       | 0.91 (0.84-0.98)         | .009    | 26.1 (5.0)                    | 1.00 (0.95-1.04)         | .817    | 27.6 (5.9)                               | 1.04 (0.90-1.14)         | .943    |
| WC (cm)          | 87.3 (13.1)                 | 82.1 (12.2)                      | 0.96 (0.93-0.99)         | .006    | 86.2 (11.1)                   | 1.00 (0.99-1.02)         | .954    | 88.7 (13.3)                              | 1.02 (0.96-1.07)         | .578    |
| HC (cm)          | 100.5 (11.1)                | 98.1 (9.7)                       | 0.97 (0.94-1.01)         | .096    | 100.0 (9.7)                   | 1.00 (0.98-1.02)         | .956    | 102.5 (12.3)                             | 1.01 (0.98-1.05)         | .503    |
| WHR              | 0.87 (0.06)                 | 0.83 (0.06)                      | 0.37 (0.21-0.64)         | <.001*  | 0.86 (0.06)                   | 1.04 (0.68-1.58)         | .861    | 0.86 (0.05)                              | 1.05 (0.53-2.10)         | .884    |

*Note: The odds ratios were calculated per 1 unit change, except WHR per 0.1 unit change. Significant P values marked with bold.

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist to hip ratio.

In multivariate analysis:

*a Socioeconomic status, relationship status at age 31, smoking status, physical activity at age 31, age at menarche, parity at age 31, lifetime hormonal contraceptive use at age 46 years.

b Socioeconomic status, relationship status at age 46, smoking status, physical activity at age 46, age at menarche, parity at age 46, lifetime hormonal contraceptive use at age 46 years.

*P value significant after the Bonferroni correction.
multivariate analysis showed an inverse association between endometriosis and WHR among women with a BMI of 18.5-25 kg/m² (OR 0.53, 95% CI 0.34-0.82, Table 2). The subtype analysis revealed inverse associations between peritoneal endometriosis and weight (OR 0.95, 95% CI 0.92-0.98), weight gain from age 14 to 46 years (OR 0.97, 95% CI 0.94-1.00), BMI (OR 0.91, 95% CI 0.84-0.98), WC (OR 0.96, 95% CI 0.93-0.99), and WHR (OR 0.37, 95% CI 0.21-0.64; Table 3). In contrast, there was a tendency toward positive associations between all body size measures and ovarian and deep infiltrating endometriosis (OR > 1). The parameters of the model after adjustment were consistent in terms of effect size and directionality but were not statistically significant; therefore, independent effects could not be confirmed. The results remained unchanged when the analysis was restricted to ±2SD for WC and HC data.

4 DISCUSSION

This prospective population-based birth cohort study found an inverse association between endometriosis, specifically of the peritoneal subtype, and a smaller body size in terms of BMI, WC, and WHR. No associations were found between endometriosis and birthweight or adiposity from childhood to age 20 years.

A few studies have investigated body size in childhood and adolescence in women with endometriosis and have reported conflicting results. 5,15-17 Whereas we found no association between endometriosis and adiposity in childhood or adolescence, the Nurses’ Health Study II reported a lower incidence of endometriosis in females with a larger body size at ages 5, 10, and 20 years. 5,18 Farland et al found a lower likelihood of endometriosis in women reporting a large body size at the age of 8 years, at menarche, and at ages 20-25 years. 16 Interestingly, Nagle et al suggested that being overweight at age 10 years but also underweight at age 16 years was associated with a higher risk of endometriosis. 15 Possible explanations for these conflicting results are differences in study designs and between study populations’ ethnicities. Moreover, most previous studies used body shape illustrations in a retrospective manner, whereas our study mostly analyzed data obtained from measurements.

Several epidemiological studies have associated a taller or leaner habitus with endometriosis in adulthood. 7,17,19-24 A study assessing the BMIs of 84 patients undergoing laparoscopy for tubal sterilization or as a diagnostic procedure at 5-year intervals between ages 15 and 45 years reported a smaller body size in endometriosis patients. 17 A recent meta-analysis of 11 studies on the association between endometriosis and BMI found a pooled relative risk for endometriosis of 0.67 for every 5 kg/m². 22 Moreover, the Nurses’ Health Study II cohort data showed an inverse association between BMI and endometriosis, which was stronger in women with infertility. 23 Previous studies’ results are in line with our findings regarding adults. We found that lower weight and BMI at age 31 years were associated with a higher risk of endometriosis. The risk was 2% lower for each kilogram of weight and 6% lower for each BMI unit.

Although an association between BMI and endometriosis has been widely reported, data on adiposity distribution are scarce. Our results show a smaller WC and lower WHR among women with endometriosis at age 31 years and lower WHR at age 46 years, specifically in women with peritoneal endometriosis. Similarly, a pear-shaped body figure and concentration of adipose tissue below the waist have been associated with the condition. 17,20,23 Shah et al found that the risk of endometriosis in women with a WHR of less than 0.6 is almost three times higher than that in women with a WHR of 0.7-0.79. 22 McCann et al also reported an association between a low WHR and endometriosis, but only in women under the age of 30. 7

Overall, in our study, women with endometriosis appeared to gain less weight up to age 31 years and to have a smaller WC and a lower WHR at reproductive age. This could be explained by the natural course of endometriosis, whose symptoms usually appear a few years after menarche, intensify during the years of fertility, and start to recede toward menopause. The persistent association between peritoneal endometriosis and a lean habitus at age 46 years indicates a possible independent role of endometriosis in weight development. Moreover, our subtype analysis supports the usefulness of endometriosis classification, as well as the existence of shared biological processes between endometriosis and adiposity. 8 It should be noted, however, that our study did not consider chronic pain and fatigue affecting eating patterns, long-term calorie intake, or nutrition quality, which may play a role in the association between body size and endometriosis. 25 We were not able to analyze eating patterns, because such data were not available for the NFBC1966. Moreover, as the differences in absolute body size measurements were small, the long-term health outcomes remain elusive.

The association between a leaner habitus and endometriosis raises questions regarding the underlying mechanism. A recent study exploring endometriosis in a mouse model showed reduced body weight and body fat. Interestingly, the difference in body weight and fat was associated with altered expression of genes related to liver metabolism and weight control. 26 Human studies have reported altered expression of metabolism-related hormones such as leptin, which is known to modulate food intake and appetite control, so directly correlating with adiposity. 27 Leptin has been suggested to trigger early development of endometriosis in inflammatory status, and a high concentration may promote angiogenesis. 28 Indeed, some studies have reported leptin overexpression in the serum, peritoneal fluid, and endometrioma of women with endometriosis. 28-30 Another potential mechanism could involve insulin-like growth factor 1 (IGF-1), which exerts anabolic effects and modulates glucose metabolism. 31 Evidence suggests that high IGF-1 levels in plasma and peritoneal fluid are associated with a higher risk of endometriosis. 32 Moreover, a cross-sectional analysis of the Nurses’ Health Study II cohort found an inverse association between adult plasma levels of IGF-1 with body size at ages 5 and 10 years and BMI at age 18 years. 33 Further studies are warranted to elucidate the underlying mechanisms.
This study has several strengths. First, it analyzed a large set of population-based data with a homogeneous female population in terms of age, ethnicity, and access to health care. Second, it mostly included data obtained from measurements. Third, it used extensive national register data, including early life and gestational data. Fourth, it performed endometriosis subtype analyses. Overall, our data cover long-term development of weight and weight gain prospectively from birth to 46 years of age and waist and hip measurements in adulthood. Moreover, we included several covariates in our analysis. The self-reported endometriosis diagnosis may be considered a limitation. However, it has previously been validated from hospital records. Moreover, women also exhibited a typical endometriosis profile with regard to pain tolerance, infertility, parity, and oral contraceptive pill use. A Swedish study concluded that self-reported diagnosis is moderately accurate, and its accuracy is even higher when additional information is available. Another limitation is that as body size data at age 14 years were based on parents’ reports, they may not be as accurate as the measurements taken by healthcare professionals. Further, a certain degree of selection bias for the study groups cannot be ruled out, although the participation rate of the total NFBC1966 population was high (at age 31 years, the rate of the total NFBC1966 population was high (at age 31 years, the participation rate was 81%, and the clinical examination participation rate was 77%; at age 46 years, the rates were 72% and 64%, respectively), and the participation rate in the follow-up data collection was equal in the two study groups. The study population homogeneity, although a strength in some respects, constitutes a limitation in other respects, as it limits the generalizability of the findings to other ethnicities or purely hospital-derived populations. Finally, this study found significant correlations but could not establish causation between endometriosis and body size.

5 | CONCLUSION

This study provides further evidence of the association between endometriosis and a smaller body size and lower adiposity, specifically in peritoneal endometriosis, in adulthood but not in childhood or adolescence. Our findings indicate significant differences between endometriosis subtypes, suggesting the importance of classification in endometriosis research. To elucidate the mechanism underlying the association between a lean body shape and peritoneal endometriosis, future studies should explore the direction of causality and investigate the role of factors affecting body size development, such as metabolism and nutrition.

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CONFLICT OF INTEREST

None.

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ORCID

Henna-Riikka Rossi https://orcid.org/0000-0001-7886-4042
Outi Uimari https://orcid.org/0000-0002-8954-2900
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.