

# Childhood body mass index growth trajectories and endometrial cancer risk

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Previously, we found that excess weight already in childhood has positive associations with endometrial cancer; however, associations with changes in body mass index (BMI) during childhood are not well understood. Therefore, we examined whether growth in childhood BMI is associated with endometrial cancer and its sub-types. A cohort of 155,505 girls from the Copenhagen School Health Records Register with measured weights and heights at the ages of 6–14 years and born 1930–1989 formed the analytical population. BMI was transformed to age-specific z scores. Using linear spline multilevel models, each girl's BMI growth trajectory was estimated as the deviance from the average trajectory for three different growth periods (6.25–7.99, 8.0–10.99, 11.0–14.0 years). *Via* a link to health registers, 1,020 endometrial cancer cases were identified, and Cox regressions were performed. A greater gain in BMI during childhood was positively associated with endometrial cancer but no differences between the different growth periods were detected in models adjusted for baseline BMI. The hazard ratios for the associations with overall growth during childhood per 0.1 z score increase were 1.15 (95% confidence interval [CI]: 1.07–1.24) for all endometrial cancers, 1.12 (95% CI: 1.04–1.21) for estrogen-dependent cancers, 1.16 (95% CI: 1.06–1.26) for endometrioid adenocarcinomas and 1.46 (95% CI: 1.16–1.84) for non-estrogen-dependent cancers. Growth in BMI in early life is positively linked to later endometrial cancer risk. We did not identify any sensitive childhood growth period, which suggests that excess gain in BMI during the entire childhood period should be avoided.

Endometrial cancer is a common gynecologic malignancy among women, especially in developed countries.<sup>1</sup> It is estimated that >319,000 women worldwide are diagnosed with this disease per year,<sup>2</sup> and the number is likely to increase

**Key words:** body weights and measures, child, endometrial neoplasms, growth and development, obesity

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with the ageing of populations and the current pandemic levels of overweight and obesity. Greater adult adiposity is a key risk factor for endometrial cancer, especially tumors that are estrogen dependent.<sup>1,3</sup> In a previous study, we showed that excess adiposity already in childhood has positive associations with endometrial cancer later in life,<sup>4</sup> suggesting that body size development in early life may contribute to the associations found for adult adiposity.

Weight gain in adulthood is positively linked to the risk of endometrial cancer.<sup>5,6</sup> Previous studies have found associations between childhood body mass index (BMI) growth patterns and morbidity and mortality in adult life.<sup>7–11</sup> Thus, it is plausible that BMI growth trajectories in early life may be associated with long-term health consequences such as endometrial malignancies, either through an early establishment of carcinogenic processes or through tracking of BMI into adult life.<sup>12</sup>

A better understanding of such patterns, if they exist, is important for establishing the timing at which associations with excess adiposity emerge. Additionally, investigations of early life BMI growth and its impact on later disease risk add to the potential for identifying whether there exist sensitive periods during childhood for the development of endometrial malignancies.

Therefore, using repeated measured values of height and weight at different childhood ages from a population-based cohort, we investigated if growth in childhood BMI is associated with endometrial cancer and its sub-types.

**What's new?**

High body mass index (BMI) early in life is linked to an increased risk of endometrial cancer in adulthood. Potentially influencing that association are the amount by which BMI increases in childhood, as well as the timing of BMI increase. Here, analyses of data from the Copenhagen School Health Records Register for girls ages 6 to 14 shows that endometrial cancer risk is increased by greater BMI gain across ages, while the specific age at which BMI increases occurs has little impact. Excess BMI gain at any time during childhood could set the stage for endometrial carcinogenesis.

**Material and Methods****Study population**

Women came from the Copenhagen School Health Records Register (CSHRR), which has previously been described in detail elsewhere.<sup>13</sup> In brief, school children in the municipality of Copenhagen, born 1930–1989, underwent annual mandatory health examinations through 1983 and thereafter only at school entrance and exit. These examinations were performed by a medical doctor or a nurse who measured the children's heights and weights. This information has been computerized, and there was a maximum of 12 measures entered per child.<sup>13</sup> BMI was calculated and transformed into *z* scores using the Lamda, Median, Sigma (LMS) method,<sup>14</sup> based upon an internal age- and sex-specific reference.<sup>15</sup>

**Data linkage**

All Danish residents alive or born after 2 April 1968 were assigned a unique identification number by the Danish Civil Registration System.<sup>16</sup> Children who attended school at this time or later had their identification number recorded on their health card and identification numbers were retrieved for those who left school prior to this time. Identification numbers were successfully linked for 88% of the children.<sup>13</sup> These identification numbers enable linkages to national health registers for follow-up.

**Study outcomes**

Incident endometrial cancers were identified through linkage to the national Danish Cancer Registry and classified using the International Classification of Disease (ICD)-10 codes, which were available from 1978 onward due to a recording project at the Registry.<sup>17</sup> The following codes were used to define endometrial cancer: C54.0–C54.1, C54.3–C54.6, C54.9 and C55.9. Based on ICD-O-3 morphology codes, endometrial cancers were further classified as estrogen-dependent, including the sub-type of endometrioid adenocarcinoma, and non-estrogen-dependent cancers.<sup>4</sup> Few tumors could not be classified as either type ( $N = 8$ ). Vital status was obtained by linkage to the national Danish Civil Registration System<sup>16</sup> and hysterectomy information by linkage to the Danish National Patient Register, which contains computerized information on all hospital discharge diagnoses from 1977 onwards.<sup>18</sup>

Women eligible for our study were born from 1930 to 1989, had an identification number, were alive and living in Denmark on 1 January 1978 and were aged 18 years or older.

From the starting population of 184,276 women, 158,751 women fulfilled these criteria. The largest reason for ineligibility was lacking an identification number ( $n = 21,717$ ), and this was due to reasons including death before 1968, emigration or spelling errors in the records that precluded us from retrieving the number.<sup>13</sup> From the eligible women, exclusions were made for those with a hysterectomy prior to 1978 ( $n = 525$ ) or age 18 ( $n = 5$ ), an endometrial cancer diagnosis prior to 1978 ( $n = 10$ ) or missing a date at diagnosis ( $n = 1$ ), no height and/or weight measures in childhood ( $n = 2,701$ ) or an outlying BMI or height value at all childhood ages ( $z$  scores  $< -4.5$  or  $> 4.5$ ;  $n = 4$ ). Each woman was followed from the age of 18 years or from her age in 1978, whichever came later. Women were followed up until a diagnosis of endometrial cancer, hysterectomy, death, emigration, loss to follow-up, or 31 December 2012, whichever came first.

**Statistical analyses**

Linear spline multilevel models<sup>19</sup> were used to estimate childhood BMI growth trajectories from age 6.25 years to 14.0 years for all girls with at least one weight and height measurement between these ages under a missing at random assumption. The multilevel model has two levels: measurement occasion (Level 1) and individual (Level 2). The occasion-level residuals estimate the measurement error in the BMI values and the individual-level residuals represent an individual's BMI growth pattern.

The rate of change in BMI *z* scores was modeled as three linear splines with knot points positioned at ages 8.0 and 11.0 years as these are approximately mid-way through the age range included in our study. Additionally, these knot points allowed for a sufficient number of girls in each age group. The baseline level was set at 7.0 years in all models. The deviance from average for each child (*i.e.*, individual-level residuals) was estimated for every age period as defined by the knot points (6.25–7.99, 8.0–10.99 and 11.0–14.0 years). Furthermore, we included an interaction with birth cohort (10-year intervals), thus allowing the baseline and slopes of the linear splines to vary by birth cohort.

We evaluated how well the model fitted the data by calculating the BMI *z* scores predicted by the model and comparing these with observed values (Supporting Information Table S1). We found a high agreement for all three growth periods. Further, we conducted sensitivity tests excluding women with few or many childhood measures ( $\leq 5$  or  $\geq 10$ ). We found that the results were generally similar to those

**Table 1.** Point estimates for the associations between young childhood body size (baseline size only, age 7 years) and all endometrial cancers, estrogen-dependent cancers and endometrioid adenocarcinomas<sup>1</sup>

Type	BMI z scores						p-Value <sup>2</sup>
	-1.0		0	1.0			
	HR	95% CI	HR	HR	95% CI		
All combined	0.98	0.88–1.08	1.00 (ref.)	1.18	1.08–1.30	0.009	
Estrogen-dependent	0.99	0.89–1.10	1.00 (ref.)	1.19	1.09–1.31	0.001	
Endometrioid adenocarcinoma	0.95	0.84–1.08	1.00 (ref.)	1.27	1.13–1.42	0.01	

<sup>1</sup>Stratified by 5-year birth cohorts. BMI baseline level was modeled using linear splines with two knots at z scores of  $\pm 0.68$ .

<sup>2</sup>Test for linearity using a likelihood ratio test.

BMI: Body mass index, CI: Confidence interval, HR: Hazard ratio.

from the entire sample (not shown), suggesting that the missing at random assumption underlying the multilevel models is likely to hold.

The individual-level estimates (baseline and BMI growth parameters) were then included in Cox proportional hazard regressions to investigate the associations with endometrial cancer in adulthood. We used age as the underlying time scale and analyses were stratified by 5-year birth cohorts. We performed a series of conditional analyses using the following models: (i) the baseline level only (indicating young childhood body size), (ii) the baseline level plus the first (6.25–7.99 years) childhood BMI growth period, (iii) the baseline level plus the first and second (8.0–10.99 years) childhood BMI growth periods and (iv) the baseline level plus the first, second and third (11.0–14.0 years) BMI growth periods.

The linearity of the associations was assessed by linear splines with two knots at BMI z scores of  $\pm 0.68$ . We detected statistically significant non-linearity for associations between the BMI baseline level (in models unadjusted and adjusted for childhood BMI growth) and all endometrial cancers, estrogen-dependent cancers and endometrioid adenocarcinomas. Therefore, we modeled the non-linearity using linear splines with a z score of 0 as reference and we present point estimates for z scores of  $\pm 1.0$  equivalent to approximately the 16<sup>th</sup> and 84<sup>th</sup> percentiles. Deviations from linearity were not detected in the associations between the BMI baseline level and non-estrogen-dependent cancers. Similarly, we did not identify indications of non-linearity in the associations between childhood BMI growth parameters and all endometrial cancer forms. Therefore, the associations between BMI growth and endometrial cancer are shown per 0.1 z score increase as this was approximately the standard deviation in BMI growth for each age period.

Using a Chi-squared test, we investigated if the associations between each of the three BMI growth parameters (6.25–7.99, 8.0–10.99, 11.0–14.0 years) and endometrial cancer differed from each other. As we did not find indications of significant differences (all confidence intervals included 1) we additionally constructed a combined BMI growth estimate (averaging the three BMI growth residuals adjusting for the baseline level) to express average BMI growth during

childhood. We then examined the associations with endometrial cancer using a model including the BMI baseline level and the combined BMI growth estimate.

We examined the proportional hazards assumptions underlying the Cox models by testing if associations between baseline BMI and growth in childhood BMI, respectively, and endometrial cancer differed within categories of age at diagnosis (quartiles with approximately the same number of cases in each category) using likelihood ratio tests. Interactions of birth cohort with the associations between baseline BMI and growth in childhood BMI, respectively, and endometrial cancers were similarly investigated using likelihood ratio tests. We did not identify violations of the proportional hazards assumption or birth cohort effects in any of the associations.

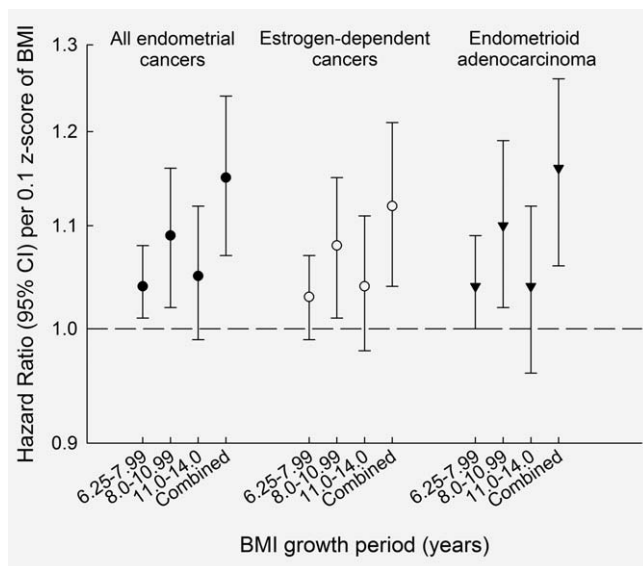
Statistical analyses were performed using Stata (version 12.1, StataCorp LP College Station, TX) and MLwiN (version 2.26) via Stata.

Our study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for register-based studies.

## Results

In total, 155,505 women were included in our study and there were 994,287 childhood body size measurements. The median number of routine weight and height measures was 7 (5–95 percentiles: 2–9). Across the birth years included in our study, average-sized 7-year-old girls (approximately 23 kg, median heights of 120–124 cm) gained 20–23 kg and increased in height by 32–35 cm from 7 to 13 years of age. During 4.1 million person-years of follow-up, 1,020 women were diagnosed with endometrial cancer, of which 920 were estrogen-dependent cancers (among these 659 were endometrioid adenocarcinomas), 92 were non-estrogen-dependent cancers and 8 cancers could not be classified as either type.

Body size at the youngest childhood ages (expressed by the baseline only model) had non-linear associations with endometrial cancer, except for non-estrogen-dependent endometrial cancer (Table 1). Thus, girls with a BMI z score of 1 or above at the youngest childhood ages had a higher risk of all endometrial cancers, estrogen-dependent cancers and endometrioid adenocarcinoma compared to girls with a BMI



**Figure 1.** Childhood BMI ( $\text{kg}/\text{m}^2$ ) growth in each of the three age periods adjusted for baseline size and the preceding growth period(s) and combined growth during childhood (6.25–14.0 years) and associations with all endometrial cancers, estrogen-dependent cancers and endometrioid adenocarcinomas per 0.1 z score increase in each period and for the combined growth estimate (Cox model stratified by 5-year birth cohorts).

**Table 2.** Young childhood body size (baseline size only) and childhood BMI growth adjusted for baseline size and previous growth periods and the associations with non-estrogen-dependent endometrial cancer per 0.1 z score increase in each period<sup>1</sup>

	Hazard ratio	95% Confidence interval
Baseline (7 years)	1.01	0.98–1.03
Growth period (years)		
6.25–7.99	1.17	1.05–1.30
8.0–10.99	1.15	0.94–1.40
11.0–14.0	1.10	0.90–1.34
Combined growth (6.25–14.0 years)	1.46	1.16–1.84

BMI: Body mass index.

<sup>1</sup>Stratified by 5-year birth cohorts.

z score of 0 (Table 1). In contrast, no associations with endometrial cancer were found for girls with a BMI z score below 0 (Table 1).

Associations between BMI growth at the three different periods during childhood and all endometrial cancers, estrogen-dependent cancers and endometrioid adenocarcinomas were consistently positive but several of the confidence intervals included 1 (Fig. 1). Although the second period of BMI growth (8.0–10.99 years) had positive associations with all cancer types, these associations did not differ significantly from the other BMI growth periods (all confidence intervals for the tests of the comparisons included 1) that we investigated (Fig. 1). When averaging the childhood BMI growth

parameters into a combined estimate (modeled by the combined growth parameter adjusted for baseline size), the associations with all types of endometrial cancer were positive and the confidence intervals did not include 1 (Fig. 1).

For the rare ( $N = 92$ ) type of non-estrogen-dependent endometrial cancer, we found indications of associations with young childhood body size (Table 2). Furthermore, although some evidence supported that childhood BMI growth had positive associations with non-estrogen-dependent endometrial cancers, and the first BMI growth period in particular, the associations were not significantly different from each other ( $p$  values = 0.84). Additionally, due to the low number of cases the confidence intervals were wide (Table 2).

## Discussion

In our study, we prospectively assessed the associations between BMI growth trajectories in childhood and adult endometrial cancer. Our results indicate that a greater gain in childhood BMI is positively associated with later endometrial cancer. Aside from the overall BMI gain from 6.25 to 14.0 years, we did not identify any sensitive BMI growth periods during this age span which had associations with adult endometrial cancer.

Previously we found that childhood BMI at ages 7–13 years had positive associations with endometrial cancer risk and that the associations were particularly strong for the estrogen-dependent endometrial cancer forms and that these associations were unaffected by adjustment for adult hormone replacement therapy use.<sup>4</sup> In our study, we similarly found that body size at the youngest ages increased the risk of all endometrial cancers except for the rare non-estrogen-dependent cancers. Whether these associations operate through the early establishment of carcinogenic processes or by putting girls on a growth trajectory that leads to adult overweight remains to be elucidated. Nonetheless, in a previous study we found that childhood BMI is relatively poor at identifying later adult overweight at ages when most endometrial cancers emerge, suggesting that childhood BMI and growth may have independent associations with later endometrial cancer.<sup>12</sup>

Our results suggest that growth in childhood BMI is important for the future risk of endometrial cancer and its sub-types. All associations with the different growth periods were positive and did not differ from each other. Studies on adult body size suggest that weight gain after age 18 years is positively associated with endometrial cancer.<sup>5,6</sup> Nonetheless, we cannot disentangle if excess weight gain already in childhood or weight gain more proximal to an endometrial cancer diagnosis is most important for the future risk of endometrial cancer as we did not have adult size available in our study.

Growth in childhood BMI reflects genetics and the environment in which the child was born into and grew up in.<sup>20</sup> Thus growth in BMI is an indicator of risk and is not necessarily the causative factor for endometrial cancer. Our study included girls born from 1930 to 1989, thus although few



genetic changes occurred there were large environmental changes with improved nutrition, medical care and social conditions. We indirectly accounted for these factors by stratifying the analyses by birth cohort as information on these other factors was unavailable in our study. We found the associations between child BMI growth and endometrial cancer did not differ by birth cohort; thus they were the same for a girl born in 1930 as in 1940, and 1950 and so on. Taken together with the results from our earlier study in girls and those in women, these results suggest that the associations have biologic origins and do not only reflect social conditions.

The underlying biological pathways for an association between childhood BMI growth and endometrial cancer risk are only speculative. A faster gain in childhood BMI leading to a greater level of excess BMI is most likely associated with increased levels of endogenous sex hormones and insulin resistance as is suggested for adult adiposity.<sup>21,22</sup> Thus, girls with greater BMI gain already in childhood may be more susceptible to carcinogenic mechanisms through an enhanced cell proliferation caused by a prolonged exposure period resulting in an endometrial cancer diagnosis numerous years later.<sup>21,22</sup>

Strengths of our study include that it was undertaken in a large population-based cohort of girls. The large number of repeated measurements of height and weight allowed us to assess whether there existed specific periods during the ages of 6.25–14.0 years, which were associated with endometrial cancer development. We used multilevel models to obtain childhood BMI growth trajectories and these models have the advantage of not being restricted to include measures at specific ages or to individuals with complete information on the exposure variable.<sup>23</sup>

There are limitations to our study as well; children from this historic cohort are relatively lean compared to contemporary children with approximately 7% of the girls in our study being classified as overweight (including obesity) by the Centers for Disease Control (CDC) 2000 growth reference.<sup>24</sup> Accordingly, there is likely less variability in the BMI growth patterns among girls in our study than may be observed among more contemporary cohorts of girls. As a result, it is possible that although a sensitive period was not detected in our study, one may exist. Additionally, as the anthropometric information available was measured at ages 6.25–14 years, we are lacking information on very early childhood and late adolescent BMI growth. Therefore, we cannot rule out that a

sensitive period exists before or after the included age range. Further as information on early life factors which may be associated with childhood BMI and endometrial cancer was unavailable; we cannot explore what effect they may have on the associations that we observed. In our study, we did not have information available on the age at menarche or menopause, both of which may affect a woman's risk of endometrial cancer *via* exposure to endogenous sex hormones.<sup>25</sup> Finally, our study population is based on girls who attended school in Copenhagen and who are primarily Caucasian. As our follow-up was virtually complete and nationwide due to the register linkages, our findings are generalizable to all Danish women and likely other Caucasian populations, but they may not be generalizable to other ethnicities.

In conclusion, our findings suggest that a greater BMI gain during childhood is associated with future risk of endometrial malignancies. We did not detect a particularly sensitive period for excess BMI gain in childhood from the ages of 6.25–14.0 years. From a public health perspective our study suggests that excess BMI should be avoided during the entire childhood period to limit the later risk of adverse health outcomes such as endometrial malignancies.

### Authors' Contributions

The authors' responsibilities were as follows: JA and JLB conceived the research; JA, MG, KT, LU, TIAS and JLB designed the research; TIAS and JLB provided data; JA and JLB conducted the research; JA, MG, KT analyzed data; JA and JLB wrote the article and had primary responsibility for final content. All authors read and approved the submitted article. The corresponding author had full access to all data in the study and had the final responsibility for the decision to submit for publication.

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