Adult lifetime body mass index trajectories and endometrial cancer risk

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ADULT LIFETIME BODY MASS INDEX TRAJECTORIES AND ENDOMETRIAL CANCER RISK

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ABSTRACT

Objective: To identify body mass index (BMI) trajectories in adult life and to examine their association with endometrial cancer (EC) risk, also exploring whether relations differ by HRT use.

Design: Pooled analysis of two case control studies.

Setting: Italy and Switzerland.

Population: A total of 458 EC cases and 782 controls.

Methods: We performed a latent class growth model in order to identify homogenous BMI trajectories over 6 decades of age, with a polynomial function of age. Odds Ratios (ORs) and the corresponding 95% confidence intervals (CI) for EC risk were derived through a multiple logistic regression model, correcting for classification error.

Main outcome measures: The relation of BMI trajectories with endometrial cancer.

Results: We identified 5 BMI trajectories. Compared with women in the 'Normal weight-stable' trajectory, a reduction by about 50% in the risk of EC emerged for those in the 'Underweight increasing to normal weight' (95% CI=0.28-0.99). The 'Normal weight increasing to overweight' and the 'Overweight-stable' trajectories were associated to, respectively, an excess of 3% (95% CI=0.66-1.60) and of 71% (95% CI= 1.12-2.59) in cancer risk. The OR associated to the trajectory 'Overweight increasing to obese' was 2.03 (95% CI= 1.31-3.13). Stronger effects emerged among HRT never users (OR= 2.19 for the 'Overweight-stable' trajectory and OR=2.49 for the 'Overweight increasing to obese' trajectory).

Conclusions: Our study suggests that longer exposure to overweight and obesity across lifetime is associated with an increased risk of endometrial cancer. Weight during adulthood also appears to play an important role.

Keywords: Endometrial cancer; body mass index; latent class growth models; body mass index trajectories; prevention.

INTRODUCTION

Overweight and obesity are leading risk factors for disease and death globally. Elevated body mass index (BMI) has been associated with an increased risk of cardiovascular diseases and type 2 diabetes, but also selected neoplasms (1). One of the major public health concern worldwide has been the continuing increases in obesity prevalence over the past decades and its consequences on chronic diseases.

Obesity is strongly associated with an increased risk of endometrial cancer (EC) (2, 3). Most of the main recognized risk factors for EC act via an excessive and prolonged exposure to oestrogens unopposed by progesterone. In post menopause, the adipose tissue provides endogenous oestrogens through aromatization of androgens secreted by adrenal glands. Moreover, decreased sex hormone binding globulin (SHBG) concentration leads to increased bioavailable oestrogens (4). Another relevant risk factor for EC is hormonal replacement therapy (HRT), which provides exogenous oestrogens, particularly when not opposed by progestin. With the substantial reduction in HRT use over the last two decades (5), body size has achieved a greater impact on EC risk.

The relationship between BMI and EC risk has been investigated. Most studies, however, rely on cross-sectional exposure information on BMI, typically at recruitment. The relation between weight change over time and EC risk is less well understood, and evidence on the cumulative impact of overweight and obesity during the life course on EC risk is scarce. Moreover, insights into whether the effect of body mass lifetime trajectories on the risk for EC differs by HRT use are still limited. Given that the carcinogenic processes usually take several decades, it is important to determine the possible impact of patterns of BMI lifetime changes on EC risk.

The aim of this study is to identify BMI trajectories in adult life and to examine their association with EC risk pooling data from two case control studies from Italy and Switzerland (6, 7). We also explored in detail whether relations differed by HRT use.

METHODS

Study population

A case-control study on EC was conducted between 1988 and 1998 in the Swiss Canton of Vaud and in the metropolitan Milan, Northern Italy. In Vaud, cases recruitment was population based, since identified cases were cross checked with incident cases reported to the local cancer registry. Overall, more than 80% of identified cases were interviewed. In Milan, case recruitment was hospital based, because the area was not covered by cancer registration schemes. Controls were women aged 75 years or less who were

admitted to the same networks of hospitals of cases, with a primary diagnosis unrelated to any of the recognized risk factors for EC or to any long-term modification in diet. Women admitted for gynaecologic, hormonal, metabolic or neoplastic conditions, or with a history of hysterectomy were also excluded. Less than 5% of patients refused to participate. Overall, 466 cases of histologically confirmed EC and 792 controls were included.

Centrally trained interviewers administered the same structured questionnaire, in the same settings, to cases and controls. The questionnaire included information on demographics, a validated food frequency questionnaire (FFQ), a problem-oriented medical and reproductive history, including ever use of oral contraceptives (OC) or HRT. Patients were not involved in the development of the research.

BMI assessment

The questionnaire collected information on current height and weight at the following ages, if applicable: 20-29, 30-39, 40-49, 50-59, 60-69, and 70-74 years. Therefore, repeated weight measures were collected for each subject from 20-29 years up to their current age. BMI was computed at each time point as weight divided by squared height (kg/m^2). Current height was used in each calculation. BMI was then categorized in underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), and obese (>=30.0).

Statistical analysis

We performed a latent class growth model (LCGM) in order to identify homogenous BMI trajectories over 6 decades of age, with a polynomial function of age. The LCGM identifies latent classes of BMI that differ in the initial state and in the way they changes over time. The model evaluates similarities in BMI measurements over time so that individuals in the same class present similar trajectories of BMI changes. The relation between latent classes and BMI was specified via an ordinal regression model. Class parity was determined by subsequently increasing the number of latent classes from 1 (where all individuals belong to the same trajectory) until the value of the Bayesian information criterion (BIC) ceased to monotonically decrease or until the last solution according to BIC with a minimum of 5% of subjects in each latent class. We also checked coherence with other studies about BMI trajectory groups that used between four and six groups (8-12). Multiple LCGM with different trajectory shapes including linear, quadratic and cubic parameters for age were tested, using BIC and Wald test for each age term to select optimal shapes.

BMI trajectories were named and interpreted according to the estimated values for their evolution over ages and conditional distribution of BMI (class-specific response probabilities) were reported. In order to

complement the description of the BMI trajectories, we also examined their associations with a selected set of variables.

In a second step, subjects were assigned to latent classes based on their posterior class membership probabilities, obtained from the estimated parameters of the LCGM model and their observed responses. Proportional allocation was chosen to permit a "soft" classification, assigning subjects to each class with a weight equal to their posterior membership probability for that class.

In a third step, Odds Ratios (ORs) and the corresponding 95% confidence intervals (Cis) for EC risk were derived through multiple logistic regression models using the class assignments to evaluate the effect of BMI trajectories on the risk of EC. To account for known and potential risk factors, the model included terms for age, country, education, diabetes, family history of EC, age at menarche, menopausal status, parity, ever OC use, ever HRT use and smoking. The classical approach, which first identifies latent classes, then assigns subject to each class and finally builds the prediction model, underestimates the associations between the outcome and the class membership (13). As classification errors occur even with proportional assignment (14), we used a maximum likelihood-based correction method which incorporates uncertainty about classification in the estimation procedure and performs best with categorical outcomes (13).

We excluded from the analysis subjects with missing information on height or weight at every time point (n=18), leading to a total of 458 cases and 782 controls. Sparse missing values in BMI measurements were not excluded in the analysis, yielding maximum likelihood estimates under MAR missingness assumption. To assess the robustness of the selected latent class growth model, we compared it with the results obtained on complete cases only. A few (<5%) missing values on adjustment factors were replaced by the most frequent response according to age group and country. (13)

In a latter analysis, we assessed the risk of EC according to BMI trajectories in strata of HRT ever use.Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA), RStudio version 1.2.5019 (RStudio, Inc., Boston, Massachusetts, USA) and Latent Gold 6.0 (Vermunt & Magidson, 2021) statistical software.

RESULTS

The study population is described in Table S1. Controls were somewhat younger (11.3% vs 4.2% women under 45 years of age), had a higher proportion of women with age at menarche >15 (14.1% vs 9.0%), more frequent use of OC (17.3% vs 10.5%) and less frequent use of HRT (15.5% vs 22.9%).

BMI trajectories over adult lifetime

We identified 5 BMI trajectories, conceived as latent classes with a different initial body size and a different evolution over life course. The best form of the relationship between BMI and time (i.e., age) was a cubic function, i.e., BMI increases over time but proportionally strongly over elderly ages.

Table 1 presents BMI trajectories, i.e., the evolution of BMI over time according to the five latent classes. We labelled the first one 'Underweight increasing to normal weight' trajectory, because the prevalence of underweighted subjects was highest up to their '40, and the proportion of normal weighted gradually increased over time. During their '70-'80, the proportion of underweighted subjects slightly increased. Subjects in the 'Normal weight-stable' trajectory showed a constant permanence in the normal weight category of BMI over adult lifetime. Subjects in the 'Normal weight increasing to overweight' were in the normal weight range up to their middle age when they gradually turned to an overweight status that was maintained over their older years. The 'Overweight-stable' trajectory presented a change between their 20'-30' and their '30-'40 where the proportion of normal weighted shifted towards overweight. More than 80% of the subjects in this trajectory were overweight from their '30 on. A constant increase over time in obese subjects was also reported. The 'Overweight increasing to obese' trajectory had the highest proportion of obese subject since age '20-'30, with a steady increase of subjects in the highest category of BMI.

Table 2 reports the conditional marginal distribution of BMI in the 5 latent classes over the whole period. The 'Underweight increasing to normal weight' trajectory (estimated size=8.3% of subjects) was mainly composed by subjects with BMI<25. In the 'Normal weight-stable' class (estimated size=43.2% of subjects) more of 93% of subjects were in the range 18.5-<25. In the 'Normal weight increasing to overweight' class (estimated size=23.1% of subjects), 57% of subject had normal BMI. More than 74% of subjects in the 'Overweight-stable' class were in the BMI range 25-30 (estimated size for this class=13.7% of subjects). People in the 'Overweight increasing to obese' class (estimated size=11.8% of subjects) reported BMI from 18.5 on, with a gradual increase in conditional probabilities up to the highest category of BMI that was composed by more than 56% of subjects.

The latent BMI trajectories showed specific traits in subjects' demographics and health/lifestyle characteristics (Table 3). Women in trajectories associated to lower BMI tended to be more educated (proportions of over 11 years of education were 34.1% and 33.9% respectively in the 'Underweight increasing to normal weight' and in the 'Normal weight-stable' trajectories, vs less than 22% in the other ones). Pluriparae were more likely to be in the 'Overweight-stable' and 'Overweight increasing to

obese'trajectories (more than 81% vs less than 77% in other trajectories). Less frequent use of OC and HRT was reported among women in the 'Overweight-stable' and 'Overweight increasing to obese' trajectories. Smokers were leaner.

BMI trajectories and EC risk

Table 4 reports ORs and the corresponding 95% CIs for EC according to the identified BMI trajectories. A monotonic increase in the ORs emerged for higher BMI and longer exposure to higher BMI. When subjects in the trajectory in 'Normal weight-stable' were set as reference, a reduction by about 50% in EC risk emerged for those in the 'Underweight to normal' (95%CI=0.28-0.99). The 'Normal weight increasing to overweight' and the 'Overweight-stable' trajectories showed, respectively, an increase of 3% (95% CI=0.66-1.60) and of 71% (95% CI= 1.12-2.59) in cancer risk. The OR associated to the trajectory 'Overweight increasing to obese' was 2.03 (95% CI= 1.31-3.13).

Table 4 also shows the results according to HRT use. No consistent trend in the BMI trajectories on EC risk emerged among ever HRT users. A monotonic increase in the ORs among HRT never users emerged, as in the general case. Stronger associations emerged with trajectories related to higher BMI: OR was 2.19 (95% CI: 1.36-3.51) for the 'Overweight-stable' trajectory and 2.49 (95% CI=1.56-3.99) for the 'Overweight increasing to obese' trajectory. No significant difference in risk emerged for the 'Underweight increasing to normal weight' and the 'Normal weight to overweight', with respect to the 'Normal weight-stable' trajectory.

DISCUSSION

Main findings

The results of this study confirm not only a role of elevated BMI in the aetiology of EC but also the impact of duration of exposure across lifetime. A longer exposure to overweight and obesity was associated with an increased risk of EC and the level of weight during adulthood also seemed to play an important role. In general, greater BMI was associated to higher cancer risk, even within the low to normal reference range for BMI. The difference in risk between the 'Underweight to normal weight' and 'Normal weight' trajectories confirms that lean women have the lowest risk. The trajectories 'Normal to overweight' and 'Overweight' displayed similar BMI composition after their '60, but in the last group the over representation of overweight people started earlier. The difference in risk of EC between these two groups indicates that women exposed to prolonged overweight/obesity during adulthood have higher risk.

Interpretation

These results are consistent with those reported in literature (15-29). Excess adiposity leads to hormonal and metabolic perturbations by producing oestrogen through the aromatization of androgens from adrenals to oestrogens in the adipose tissue (29). This is the main source of oestrogens in post-menopausal women (4, 7). Adipose tissue also increases levels of insulin and insulin-like growth factor 1 (IGF-1), which reduce synthesis and circulating levels of SHBG (30). A systematic review reported that premenopausal obese women are exposed to prolonged unopposed oestrogens during early adulthood, resulting in an increased risk of EC (29). This is due to frequent anovulation in obese pre-menopausal women (31-36). The NIH-AARP Diet and Health Study cohort suggested that long term adiposity throughout adulthood was associated with increased risk of EC, beyond current adiposity (18). A longitudinal study from the United States reported that the intensity of overweight over time was associated to additional risk and found a dose-risk relationship. The authors suggested that earlier and long term exposure to overweight are likely related to mechanisms associated with increased risk of cancer, such as chronic inflammation, oxidative DNA damage, and mainly alterations in endogenous hormone metabolism (16). Diabetes is a consequence of overweight and obesity, but it is also independently related to EC risk (37).

Most studies analysed and reported separately single measures assessed at different ages. A study using a subset of our dataset (7) reported a greater effect of recent BMI but also a role of fat accumulated among overweight and obese women at diagnosis. However, only a few studies considered lifetime body size changes and EC risk (8, 16, 38). In particular, the Nurses' Health Study cohort analysed trajectories of body shape across the lifespan and several cancer risk with a similar methodological approach (8). There was a cubic relation of body shape with time, with a significant deviation from linearity, like we found for BMI. They identified 5 body shape trajectories that were similar to ours. Their Lean-moderate increase, Lean-marked increase, Medium-stable and Heavy-stable/increase were comparable, respectively to our Normal to overweight, Overweight, Normal, and Overweight to obese. The difference between their Lean-stable and our Under-to normal weight is at least in part ascribable to the different study population, and the higher weight of American women. Similarly to our results, they reported increasing hazard ratios for EC according to higher body size and its longer duration of exposure.

Consistently with the Nurses' Health Study cohort finding and previous evidence (5, 16, 18, 39-42), we observed that HRT use modified the association between BMI trajectories and EC risk. Among never HRT users, the positive association between BMI trajectories characterized by higher weight and its longer duration, and EC was monotonic. In contrast, no consistent trend of life trajectories of BMI emerged

among women who had used HRT. High levels of exogenous oestrogens in women using HRT may obscure the effect of overweight and obesity. Oestrone and serum estradiol levels among HRT users were reported to be around 3 to 4 times higher than among non-users, and about 1.4 to 1.6 times higher in obese women compared to normal weight women (43, 44).

Strengths and Limitations

Strengths of our analysis include the unique conceptual and methodological approach that allowed us to examine trajectories of BMI across the adult life course in a case-control setting, overpassing the well-known strategy that analyses separately different measurement at selected time point. Our analysis was more robust against the influence of confounding since studies based on a cross-sectional measure of BMI at a point in time are susceptible to confounding by previous body size. Working with categorized BMI allows to relax strong, and sometimes unrealistic, models assumption, such as normality of the distributions. LCGM has the advantage to not restrict the analysis on complete information. Incomplete information in our case derives from missing values and right censoring in subject younger than 74 years of age. We assigned subjects to trajectories using proportional assignment, lessening the classification errors derived from univocally assignment of women to the trajectory where the posterior membership probability was highest. To further minimize classification errors(14), we used a correction approach that incorporates uncertainty about classification in the estimation procedure and accounts for subjects contributing to the analysis with less than six measurement (i.e., subject with missing and/or with right censored information). We were also able to control for selected demographics and health, and lifestyle conditions, and had adequate power to assess the potential effect modification of HRT use.

Potential limitations of our study include information and selection bias. However, catchment area and the participation rates were similar between cases and controls. Controls were included in the studies according to a wide spectrum of conditions unrelated to cancer or the major risk factors for cancer, we excluded hysterectomised women from the control group (7), and overall participation was almost complete, thus reducing possible selection bias. Weight was self-reported, which might be subject to measurement error. It has been reported that particularly overweight and obese subjects tend to underestimate their body weight (45). However, little different recall is likely between cases and controls, given the same setting, and most women were unaware that elevated weight is a risk factor for EC. Moreover, categorizing BMI shall reduce potential misclassification. Still, our results need to be interpreted with cautions due to the relatively small sample size in some strata.

CONCLUSION

This study contributes to extend the accumulating evidence on the role of body size over adult life course on EC risk. Greater weight and longer exposure to higher BMI particularly among non HRT users is associated to an increased risk of EC. Given that the prevalence of unopposed HRT has decreased (46), excess body size is the leading preventable cause of EC. Prevention of weight gain across all weight categories, but particularly when leading to overweight and obesity, must be recommended, regardless of the age. Thus, it is never too late to control weight in order to reduce individual EC risk.

AUTHORS' CONTRIBUTIONS

MD conducted data analysis and released the first draft. JV supervised data analysis and revised the manuscript. CLV designed the study and the data collection and revised the manuscript. EN revised data collection and managements and revised the manuscript. FL organized data collection and revised the manuscript. All authors approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The participating studies were performed in accordance with laws, regulations and guidelines for the protection of human subjects (including consent from the participants) applicable at the time of study conduction, and in accordance with the Declaration of Helsinki.

DATA AVAILABILITY

Data are available upon reasonable request.

COMPETING INTEREST

The authors declare no competing interests.

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375 Table 1. Evolution of BMI trajectories over years of ages. Italy and Switzerland, 1988-1998.

Age	BMI	*Underweight increasing to normal weight %*	*Normal weight-stable %*	*Normal weight increasing to overweight %*	*Overweight-stable %*	*Overweight increasing to obese %*
20-30	**Underweight**	82.60	7.22	8.78	1.86	3.10
years	**Normal weight**	17.16	92.01	91.22	62.03	42.91
	Overweight	0.23	0.77	0.00	36.04	42.76
	Obese	0.01	0.00	0.00	0.07	11.23
30-40	**Underweight**	66.81	2.36	0.02	0.06	0.54
years	**Normal weight**	32.11	95.13	98.79	16.67	18.99
	Overweight	1.01	2.51	1.19	81.91	48.21
	Obese	0.07	0.00	0.00	1.36	32.26
40-50	**Underweight**	44.89	1.31	0.00	0.01	0.03
years	**Normal weight**	50.77	94.27	64.43	5.16	3.72
	Overweight	3.76	4.42	35.34	89.57	30.48
	Obese	0.58	0.00	0.23	5.27	65.76
50-60	**Underweight**	29.01	1.06	0.00	0.00	0.00
years	**Normal weight**	60.40	93.56	16.67	2.57	0.47
	Overweight	8.23	5.38	78.9	87.37	12.49
	Obese	2.35	0.00	4.44	10.06	87.04
60-70	**Underweight**	26.56	1.02	0.00	0.00	0.00
years	**Normal weight**	61.26	93.37	6.70	1.73	0.08
	Overweight	9.25	5.61	81.51	84.33	5.30
	Obese	2.93	0.00	11.79	13.94	94.62

70-80	**Underweight**	43.68	0.92	0.00	0.00	0.00
years	**Normal weight**	51.67	92.95	5.48	1.18	0.03
	Overweight	4.00	6.12	80.47	80.28	3.36
	Obese	0.65	0.00	14.05	18.54	96.61

376 BMI: body mass index.

Table 2. Size and BMI marginal distribution over time conditioned on BMI trajectories. Italy and Switzerland, 1988-1998.

	Trajectory 1: Under increasing to normal weight %	***Trajectory 2: Normal weight-stable %***	***Trajectory 3: Normal increasing to overweight %***	***Trajectory 4: Overweight-stable %***	***Trajectory 5: Overweight increasing to obese %***
Size	8.28	43.17	23.06	13.66	11.83
BMI					
Underweight	51.98	2.78	2.07	0.45	0.83
Normal weight	42.94	93.58	57.40	19.44	14.33
Overweight	4.06	3.64	37.50	74.15	28.53
Obese	1.02	0.00	3.02	5.97	56.31

BMI: body mass index.

380 Table 3. Description of BMI trajectories according to selected health and lifestyle characteristics and
381 demographics. Italy and Switzerland, 1988-1998.

		Underweight increasing to normal weight %	*Normal weight-stable %*	*Normal weight increasing to overweight %*	*Overweight-stable %*	*Overweight increasing to obese %*
Case control status	**Case**	25.58	33.66	35.53	45.68	49.47
	Control	74.42	66.34	64.47	54.32	50.53
Country	**Italy**	36.45	32.04	34.59	36.39	42.61
	Switzerland	63.55	67.96	65.41	63.61	57.39
Age	**<45**	7.18	9.38	8.82	4.98	10.73
	45-54	15.26	19.27	17.60	19.85	19.25
	55-64	35.19	34.11	33.41	34.25	42.78
	≥65	42.37	37.24	40.17	40.92	27.24
Education	**<7 years**	19.41	16.07	22.77	26.20	34.48
	7-11 years	46.54	50.04	55.27	54.79	48.76
	>11	34.05	33.89	21.97	19.01	16.76
parity	**Nulliparae**	22.94	26.66	24.01	18.20	17.89
	Parae	77.06	73.34	75.99	81.80	82.11
Age at menarche	**<12**	12.66	12.03	13.36	12.64	17.05
	12-13	37.75	40.53	42.37	45.40	41.06
	14-15	36.88	34.62	32.09	33.03	28.71
	>15	12.72	12.82	12.18	8.93	13.17
Menopausal	**Pre menopause**	14.51	17.00	15.30	13.82	19.07

status	**In menopause**	5.10	6.34	6.14	7.96	6.68
	Post menopause	80.39	76.66	78.56	78.22	74.25
Ever use of OC	**No**	81.08	82.51	85.66	90.21	91.60
	Yes	18.92	17.49	14.34	9.79	8.40
Ever use of HRT	**No**	78.45	77.51	84.29	84.82	91.24
	Yes	21.55	22.49	15.71	15.18	8.76
Smoking	**Never**	63.04	65.00	73.77	77.11	68.71
	Former	9.92	11.61	10.76	11.12	12.98
	Current	27.04	23.39	15.47	11.77	18.31

382 BMI: body mass index; HRT: hormonal replacement therapy; OC: oral contraceptive.

Table 4. Odds ratios (OR) and related 95% confidence intervals (CI) for endometrial cancer according to BMI trajectories. Italy and Switzerland, 1988-1998.

	Overall		HRT ever use		HRT never use	
	OR[a]	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Underweight increasing to normal weight	0.52	(0.28-0.99)	0.23	(0.06 - 0.95)	0.70	(0.33 - 1.49)
Normal weight-stable	1[b]	-	1[b]	-	1[b]	-
Normal weight increasing to overweight	1.03	(0.66-1.60)	0.33	(0.12 - 0.91)	1.55	(0.93 - 2.57)
Overweight-stable	1.71	(1.12-2.59)	0.80	(0.31 - 2.05)	2.19	(1.36 - 3.51)
Overweight increasing to obese	2.03	(1.31-3.13)	0.90	(0.19 - 4.28)	2.49	(1.56 - 3.99)

Models adjusted for age, country, education, diabetes, family history of EC, smoking, age at menarche, menopausal status, parity, ever OC use. [a]Model also adjusted for ever HRT use. [b]Reference category. BMI: body mass index.