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RESEARCH ARTICLE

Epidemiology

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 hormonal replacement therapy 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 to identify homogeneous BMI trajectories over six decades of age, with a polynomial function of age. Odds ratios (ORs) and the corresponding 95% 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 five 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 with, 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 hormonal replacement therapy 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 a lifetime is associated with an increased risk of endometrial cancer. Weight during adulthood also appears to play an important role.

KEYWORDS
body mass index, body mass index trajectories, endometrial cancer, latent class growth models, prevention

Tweetable abstract: Longer exposure to overweight and obesity across a lifetime is associated with an increased risk of endometrial cancer.

1 | INTRODUCTION

Overweight and obesity are leading risk factors for disease and death globally. Elevated body mass index (BMI) has been associated not only with an increased risk of cardiovascular diseases and type 2 diabetes, but also with selected neoplasms.[1] One of the major public health concerns worldwide has been the continuing increases in obesity prevalence over the past decades and its consequences for chronic diseases.

Obesity is strongly associated with an increased risk of endometrial cancer (EC).[2,3] Most of the main recognised risk factors for EC act via an excessive and prolonged exposure to estrogens unopposed by progesterone. Post menopause, the adipose tissue provides endogenous estrogens through aromatisation of androgens secreted by the adrenal glands. Moreover, decreased sex hormone binding globulin concentration leads to increased bioavailable estrogens.[4] Another relevant risk factor for EC is hormonal replacement therapy (HRT), which provides exogenous estrogens, 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 on EC risk of overweight and obesity during the life course 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.

2 | METHODS

2.1 | Study population

A case–control study on EC was conducted between 1988 and 1998 in the Swiss Canton of Vaud and in metropolitan Milan, northern Italy. In Vaud, cases recruitment was population based, because 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 recognised risk factors for EC or to any long-term modification in diet. Women admitted for gynaecological, 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, a problem-oriented medical and reproductive history, including ever use of oral contraceptives or HRT. Patients were not involved in the development of the research.

2.2 | BMI assessment

The questionnaire collected information on current height and on 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 participant from 20 to 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 categorised into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30.0 kg/m^2).

2.3 | Statistical analysis

We performed a latent class growth model (LCGM) in order to identify homogeneous BMI trajectories over six 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 change 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 one (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 participants 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, participants 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 participants to each class with a weight equal to their posterior membership probability for that class.

In a third step, odds ratios and the corresponding 95% 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 oral contraceptive use, ever HRT use and smoking. The classical approach, which first identifies latent classes, then assigns the participant 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 those participants 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 'missing at random' 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.

We also analysed 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, MA, USA) and Latent Gold 6.0[15] statistical software.

3 | RESULTS

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

3.1 | BMI trajectories over adult lifetime

We identified five 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 participants was highest up to their 40s, and the proportion of normal weighted gradually increased over time. During their 70s and 80s, the proportion of underweighted participants slightly increased. Participants in the 'Normal weight-stable' trajectory showed a constant permanence in the normal weight category of BMI over adult lifetime. Participants in the 'Normal weight increasing to overweight' were in the normal weight range up to their middle age when they gradually changed to an overweight status that was maintained through their older years. The 'Overweight-stable' trajectory presented a change between their 20s and 30s and their 30s and 40s, where the proportion of normal weighted shifted towards overweight. More than 80% of the participants in this trajectory were overweight from their 30s on. A constant increase over time in obese participants was also reported. The 'Overweight increasing to obese' trajectory had the highest proportion of obese participant since age 20–30 years, with a steady increase of participants in the highest category of BMI.

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

The latent BMI trajectories showed specific traits in participants' demographics and health/lifestyle characteristics (Table 3). Women in trajectories associated with 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, versus less than 22% in the other trajectories). Pluriparae were more likely to be in the 'Overweight-stable' and 'Overweight increasing to obese' trajectories (more than 81% versus less than 77% in other trajectories). Less frequent use of oral contraceptives and HRT was reported among women in the 'Overweight-stable' and 'Overweight increasing to obese' trajectories. Smokers were leaner.

TABLE 1 Evolution of BMI trajectories over years of age; Italy and Switzerland, 1988–98

Age	BMI	Underweight increasing to normal weight (%)	Normal weight-stable (%)	Normal weight increasing to overweight (%)	Overweight-stable (%)	Overweight increasing to obese (%)
20–30 years	Underweight	82.60	7.22	8.78	1.86	3.10
	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 years	Underweight	66.81	2.36	0.02	0.06	0.54
	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 years	Underweight	44.89	1.31	0.00	0.01	0.03
	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 years	Underweight	29.01	1.06	0.00	0.00	0.00
	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 years	Underweight	26.56	1.02	0.00	0.00	0.00
	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 years	Underweight	43.68	0.92	0.00	0.00	0.00
	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

Abbreviation: BMI, body mass index.

TABLE 2 Size and BMI marginal distribution over time conditioned on BMI trajectories; Italy and Switzerland, 1988–98

	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

Abbreviation: BMI, body mass index.

3.2 | BMI trajectories and EC risk

Table 4 reports odds ratios and the corresponding 95% CIs for EC according to the identified BMI trajectories. A monotonic increase in the odds ratios emerged for higher BMI and longer exposure to higher BMI. When participants 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 with 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 odds ratios among HRT never users emerged, as in the general case. Stronger associations emerged with trajectories related to higher BMI: odds ratio 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.

4 | DISCUSSION

4.1 | 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 with 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 for 'Normal to overweight' and 'Overweight' women displayed similar BMI composition after their 60s, 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.

4.2 | Interpretation

These results are consistent with those reported in literature.[16-30] Excess adiposity leads to hormonal and metabolic perturbations by producing estrogen through the aromatisation of androgens from the adrenal glands to estrogens in the adipose tissue.[30] This is the main source of

TABLE 3 Description of BMI trajectories according to selected health and lifestyle characteristics and demographics; Italy and Switzerland, 1988–98

	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 (years)					
<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 (years)					
<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 status					
Premenopause	14.51	17.00	15.30	13.82	19.07
In menopause	5.10	6.34	6.14	7.96	6.68
Postmenopause	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

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

estrogens in postmenopausal women.[4,7] Adipose tissue also increases levels of insulin and insulin-like growth factor I, which reduce synthesis and circulating levels of sex hormone binding globulin.[31] A systematic review reported that premenopausal obese women are exposed to prolonged unopposed estrogens during early adulthood, resulting in an increased risk of EC.[30] This is due to frequent anovulation in obese premenopausal women.[32-37] 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.[19] A longitudinal study from the USA reported that the intensity of overweight over time was associated with 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

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TABLE 4 Odds ratios (ORs) and related 95% CI for endometrial cancer according to body mass index trajectories; Italy and Switzerland, 1988–98

	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

Abbreviations: EC, endometrial cancer; HRT, hormonal replacement therapy; OC, oral contraceptive.

NoteModels 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.

inflammation, oxidative DNA damage, and mainly alterations in endogenous hormone metabolism.[17] Diabetes is a consequence of overweight and obesity, but it is also independently related to EC risk.[38]

Most studies analysed and reported separately single measures assessed at different ages. A study using a subset of our data set[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.[8,17,39] In particular, the Nurses' Health Study cohort analysed trajectories of body shape across the lifespan and risks of several cancers with a similar methodological approach.[8] There was a cubic relation of body shape with time, with a significant deviation from linearity, as we found for BMI. They identified five 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 weight increasing to overweight, Overweight-stable, Normal-stable and Overweight increasing to obese. The difference between their Lean-stable and our Underweight increasing to normal weight is at least in part ascribable to the different study population, and the higher weight of American women. Similar 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,[5,17,19,40,41,42,43], we observed that HRT use modified the association between BMI trajectories and EC risk. Among never HRT users, the positive association between BMI trajectories characterised 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 estrogens in women using HRT may obscure the effect of overweight and obesity. Estrone and serum estradiol levels among HRT users were reported to be around three to four times higher than among non-users, and about 1.4–1.6 times higher in obese women compared with normal weight women.[44,45]

4.3 | 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 measurements at selected time-points. Our analysis was more robust against the influence of confounding because studies based on a cross-sectional measure of BMI at a point in time are susceptible to confounding by previous body size. Working with categorised BMI allows us to relax strong, and sometimes unrealistic, model assumptions, such as normality of the distributions. LCGM has the advantage of not restricting the analysis on complete information. Incomplete information in our case derives from missing values and right censoring in participants younger than 74 years of age. We assigned participants to trajectories using proportional assignment, lessening the classification errors derived from univocal assignment of women to the trajectory where the posterior membership probability was highest. To further minimise classification errors,[14] we used a correction approach that incorporates uncertainty about classification in the estimation procedure and accounts for participants contributing to the analysis with fewer than six measurements (i.e. participant 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 participants tend to underestimate their body weight.[46]

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, categorising BMI shall reduce potential misclassification. Still, our results need to be interpreted with caution because of the relatively small sample size in some strata.

5 | CONCLUSION

This study contributes to 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 with an increased risk of EC. Given that the prevalence of unopposed HRT has decreased,[47] 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. Hence, it is never too late to control weight in order to reduce individual EC risk.

CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting information.

AUTHOR 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 management and revised the manuscript. FL organised data collection and revised the manuscript. All authors approved the final version of the manuscript.

ETHICS APPROVAL

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

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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