Latent Class Trajectory Modeling of Adult Body Mass Index and Risk of Obesity-Related Cancer: Findings from the Melbourne Collaborative Cohort Study

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ABSTRACT

Background: Obesity increases the risk of 13 cancer types. Given the long process of carcinogenesis, it is important to determine the impact of patterns of body mass over time.

Methods: Using data from 30,377 participants in the Melbourne Collaborative Cohort Study, we identified body mass index (BMI) trajectories across adulthood and examined their association with the risk of obesity-related cancer. Participants completed interviews and questionnaires at baseline (1990–1994, age 40–69 years), follow-up 1 (1995–1998), and follow-up 2 (2003–2005). Body mass was recalled for age 18 to 21 years, measured at baseline, self-reported at follow-up 1, and measured at follow-up 2. Height was measured at baseline. Cancer diagnoses were ascertained from the Victorian Cancer Registry and the Australian Cancer Database. A latent class trajectory model was used to identify BMI trajectories that were not defined *a priori*. Cox regression was used to estimate HRs and 95% confidence intervals (CI) of obesity-related cancer risks by BMI trajectory.

Results: Six distinct BMI trajectories were identified. Compared with people who maintained lower normal BMI, higher risks of developing obesity-related cancer were observed for participants who transitioned from normal to overweight (HR, 1.29; 95% CI, 1.13–1.47), normal to class I obesity (HR, 1.50; 95% CI, 1.28–1.75), or from overweight to class II obesity (HR, 1.66; 95% CI, 1.32–2.08).

Conclusions: Our findings suggest that maintaining a healthy BMI across the adult lifespan is important for cancer prevention.

Impact: Categorization of BMI by trajectory allowed us to identify specific risk groups to target with public health interventions.

Introduction

In 2016, an International Agency for Research on Cancer (IARC) expert working group concluded that body fatness [operationalized as overweight or obesity; body mass index (BMI) ≥25 kg/m^2] increases the risk of 13 cancer types: esophagus, postmenopausal breast, liver, gallbladder, kidney, colorectal, multiple myeloma, meningioma, thyroid, gastric cardia, pancreatic, ovary, and corpus uteri (hereafter uterus; ref. 1). Between 1982 and 2017, the incidence of these cancers in Australia increased, especially for thyroid, liver, and kidney cancer. In women, increases have also been observed for postmenopausal breast cancer and uterine cancer, while men have also experienced increasing rates of esophageal cancer (2). In 2013, overweight and obesity were estimated to cause 4% of incident cancer cases and 5% of cancer deaths in Australia (3); these proportions are likely to increase if obesity continues to rise. Cross-sectional data collected between 1995 and 2015 in Australia indicate that, across most ages, more recent birth cohorts are experiencing higher prevalence of overweight and obesity than cohorts born 20 years earlier (4). Recent simulations of interventions have estimated that, over a 25-year period (2013–2037), 10% to 13% of obesity-related cancers in men and 7% to 11% in women could be avoided if all Australians had a BMI <25 kg/m^2 (5).

Given that the carcinogenic processes usually take many years, it is important to determine the possible impact of patterns of body size across the lifepath on cancer risk (6). Adults currently included in cohort studies of body size and cancer risk may not have experienced overweight and obesity in childhood, making patterns of weight over adulthood of particular interest. Some studies have assessed changes in body mass using predefined categories of change (e.g., increasing BMI, stable BMI, decreasing BMI; ref. 7). This approach may miss more complex patterns of change in body mass (8).

We have previously used data from the Melbourne Collaborative Cohort Study (MCCS) to identify groups of people whose BMI followed specific trajectories across adulthood, and examined the associations of these trajectories with mortality (9). Here, we applied the same method to examine the association of BMI trajectories with the risk of obesity-related cancer.

Materials and Methods

Study sample

The MCCS is a prospective cohort study of 41,513 residents of the Melbourne metropolitan area, with a mean age of 55 years (99% ages between 40 and 69 years) at recruitment from 1990 to 1994. Details of the cohort have been presented elsewhere (10). Southern European migrants were oversampled to broaden the range of lifestyle exposures. Baseline data were collected by interviewer-administered

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questionnaires on demographics, lifestyle and medical conditions, physical measurements, and a self-administered food frequency questionnaire (11). Further collections occurred between 1995 and 1998 (88% responded by telephone or mail) and between 2003 and 2007 (68% attended a study center). The research protocol was approved by Cancer Council Victoria's Human Research Ethics Committee.

Participants selected for this analysis

For this analysis, we excluded participants if they were ages <40 or >70 years at baseline ($n = 298$), were underweight (BMI <18.5 kg/m^2) at baseline or had extreme BMI values (BMI <15 or >45 kg/m^2; $n = 616$), were diagnosed with invasive or metastatic cancer other than basal cell or squamous cell skin cancers (i.e., keratinocyte skin cancer) before their last BMI measurement ($n = 5{,}647$), had missing data for any confounding variables ($n = 496$), or had BMI measured or reported for fewer than three time points to allow estimation of potentially nonlinear trajectories ($n = 4{,}079$). These exclusions left 30,377 eligible participants. A flowchart of the participant selection is presented in **Fig. 1**.

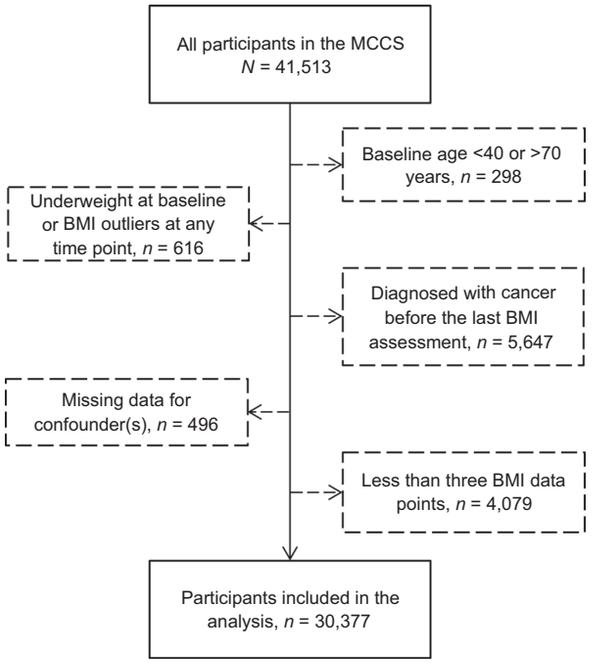

Figure 1.
Flowchart of participants in the MCCS.

BMI assessment

Each participant's body mass was recorded at up to four time points: at age 18 to 21 years, baseline (age 40–69 years), follow-up 1 (age 43–77 years), and follow-up 2 (age 48–85 years). At baseline, participants were asked to recall their body mass when ages 18 to 21 years. Height and body mass at baseline were measured by study staff following standard protocols (12). Body mass at follow-up 1 was self-reported. It was measured by study staff at follow-up 2 (12). To adjust for measurement error arising from having body mass self-reported at follow-up 1, a correction was applied to data based on sex- and age-specific comparison of self-reported and measured body mass in the Australian National Nutrition Survey (13, 14). Recalled body mass at age 18 to 21 years was not adjusted because the correction formula may not be applicable to it. For each time point, BMI was calculated as body mass (kg) divided by baseline height squared (m^2).

Obesity-related cancer assessment

Incident cancers were ascertained from the Victorian Cancer Registry and the Australian Cancer Database and defined as the earliest diagnosis of an invasive or metastatic primary cancer (we excluded *in situ* and benign tumors). Obesity-related cancers were those defined in the recent evaluation carried out by the IARC Handbooks of Cancer Prevention program: esophagus adenocarcinoma, postmenopausal breast, liver, gallbladder, renal cell, colon and rectum, multiple myeloma, meningioma, thyroid, gastric cardia, pancreas, ovary, and corpus uteri (Supplementary Table S1; ref. 1).

Statistical analysis

BMI trajectories

The statistical methods, which have been described previously, followed the recommendations of Nagin and colleagues (8, 9). In brief, we used a latent class trajectory model to identify latent homogeneity in BMI trajectories from age 18 to 21 years to late adulthood. Longitudinal BMI data were fitted as a mixture of several latent trajectories in a censored normal model, with a polynomial function for age (15). Because other studies of BMI trajectory groups have used between four and six groups (16–21), we first compared up to six groups. Assuming all had quadratic patterns, we used the Bayesian information criterion (BIC) and the log Bayes factor as a guide to select the number of groups. We then compared linear and quadratic patterns of the chosen number of trajectories, also using the BIC and the log Bayes factor to select optimal shapes. Participants were assigned to the group that had the highest posterior predicted probability calculated from the final model. We evaluated the adequacy of the final model using recommended diagnostic measures: an average posterior probability of assignment for each group of 0.7 or higher; odds of correct classification of 5.0 or higher; the proportion of a sample assigned to a certain group close to the proportion estimated from the model; and a reasonably narrow confidence interval around each trajectory (22).

Risk of obesity-related cancer

Cox regression with age as the time scale was used to estimate HRs and 95% confidence intervals (CI) for the risk of any obesity-related cancer in relation to trajectory. Follow-up began at the last BMI assessment and ended at the first of: date of obesity-related cancer diagnosis; other cancer with invasive, metastatic, or uncertain behavior; date of death; or May 31, 2017, which was the date of the most recent complete cancer data linkage. Models included potential confounders (selected using a causal diagram presented in Supplementary Fig. S1): year of birth (<1930, 1930–39, 1940–49, ≥1950); height (cm); sex (male, female); country of birth (Australia/New Zealand/Northern Europe, Southern Europe); an area-based measure of socioeconomic position (SEIFA: socio-economic indexes for areas) from the Australian Census (quintiles); highest education attained (primary school or lower, some high or technical school, completed high or technical school, completed tertiary education); smoking status at last BMI assessment (never, former, current); alcohol drinking status at baseline [lifetime abstainer, former, current low (1–39 g/day for male; 1–19 g/day for female), current high (≥40 g/day for male; ≥20 g/day for female)]; physical activity score at baseline (none, low, moderate, high; computed from frequency of walking, vigorous and less vigorous exercise over the last 6 months; ref. 23); and Mediterranean diet score (0–3, 4–6, 7–9)

details of which are described elsewhere (24). Because smoking can be a strong confounder, we performed a further analysis restricted to never smokers.

Tests based on Schoenfeld residuals were used to examine the proportional hazards assumption and the Cox models were stratified on covariates that did not satisfy the proportional hazards assumption.

We also examined associations between trajectories of BMI and each of colorectal and postmenopausal breast cancer as these were the two types for which enough cases had accrued to be examined separately. In addition, we undertook sensitivity analyses for all models: (i) we excluded the first 2 years of follow-up to account for potential reverse causation; (ii) we excluded participants without data from follow-up 2 ($n = 8{,}008$), so that the final data points contributing to the trajectories were not extrapolated and the beginning of follow-up were the same for all participants; (iii) we compared our findings with the HRs obtained from a one time point assessment of BMI (last measured BMI); and (iv) finally, we modeled sex-specific trajectories and examined their associations with risk of obesity-related cancer for men and women separately, as suggested by a reviewer.

Statistical analyses were performed using Stata version 14.2 (Stata Corp.).

Results

Six trajectories of BMI across adulthood were identified (**Fig. 2**). Almost all participants (94%) had normal BMI at age 18 to 21 years (TR1, TR2, TR3, and TR5). For two thirds, BMI increased later in life to higher normal (TR2) or overweight (TR3). A smaller proportion (19%) maintained a lower normal BMI (TR1) throughout adulthood. Thirteen percent of participants became obese in midlife (TR5 and TR6) and 3% were consistently borderline obese over the adult years considered (TR4). Model adequacy diagnostics are presented in Supplementary Table S2.

The characteristics of participants within each trajectory were essentially the same as reported in our analysis of mortality (9) and are presented in **Table 1**. Mediterranean diet score, physical activity, and alcohol consumption decreased across TR1 to TR6. A higher proportion of participants in the borderline obesity trajectory (TR4) compared with other trajectories had prevalent diabetes and heart disease at baseline.

Table 2 presents the HRs for BMI trajectories in relation to risk of obesity-related cancer in all participants and in never-smokers at last BMI assessment, using stable lower normal BMI trajectory (TR1) as the reference category. We observed no meaningfully increased risk for the stable higher-normal BMI trajectory (TR2: HR, 1.04; 95% CI, 0.92–1.18). Increased risk was observed for all other trajectories, although the HR for chronic borderline obesity (TR4) had a wide CI. As the higher normal trajectory (TR2) showed evidence of nonproportional hazards for never-smokers ($P = 0.02$), we fitted an interaction between this trajectory and attained age and presented HRs for age 67, 74, and 80 (25th, 50th, and 75th percentiles of age at diagnosis). For this trajectory, the HR was slightly lower at younger attained age than at older attained age. In all participants, while the proportional hazards assumption was not violated, the same pattern (i.e., larger HRs with increasing age) was seen for TR2. The HRs for BMI trajectories were similar for never-smokers and the whole cohort.

For colorectal cancer, no strong associations were observed for any trajectory except overweight to class II obesity (TR6), for which the HR was 1.47 (95% CI, 0.98–2.20); however, only 30 people in this trajectory were diagnosed with colorectal cancer (**Table 3**). For postmenopausal breast cancer, the HRs for each trajectory followed a similar pattern to that observed for all obesity-related cancers. The largest HRs were observed for women whose BMI changed from normal to overweight (TR3: HR, 1.31; 95% CI, 1.05–1.62) and from normal BMI to class I obesity (TR5: HR, 1.55; 95% CI, 1.20–2.00; **Table 3**).

The results from sensitivity analyses (excluding the first 2 years of follow-up; and excluding participants who did not attend follow-up 2) were not materially different from the main results (see Supplementary Tables S3 and S4). Models including BMI trajectories were almost identical to those with last measured BMI in terms of the BIC and

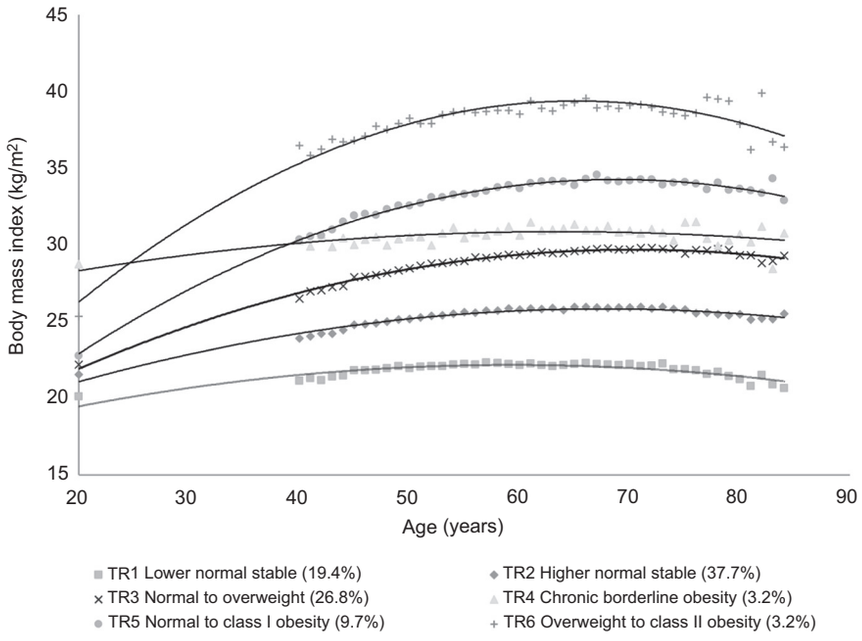

Figure 2.
BMI trajectories estimated in the MCCS using a latent class trajectory model.

Table 1. Characteristics of participants by BMI trajectory groups in the MCCS.

	BMI trajectory groups											
	TR1 Lower normal stable		TR2 Higher normal stable		TR3 Normal to overweight		TR4 Chronic borderline obesity		TR5 Normal to class I obesity		TR6 Overweight to class II obesity	
Characteristics of participants	***N* = 5,905**		***N* = 11,455**		***N* = 8,146**		***N* = 975**		***N* = 2,933**		***N* = 963**	
Baseline age, mean (SD)	54.3	(8.9)	55.3	(8.7)	54.7	(8.3)	55.2	(8.5)	53.7	(8.1)	52.3	(7.9)
Age at last BMI assessment, mean (SD)	64.1	(9.2)	65.0	(9.0)	64.4	(8.7)	64.7	(9.1)	63.5	(8.5)	62.0	(8.6)
BMI age 18–21, kg/m^2, mean (SD)	20.1	(2.0)	21.5	(2.3)	22.2	(2.3)	28.7	(2.6)	22.8	(2.5)	25.3	(3.9)
BMI 1990–1994, kg/m^2, mean (SD)	21.8	(1.4)	25.1	(1.5)	28.5	(1.8)	30.4	(2.3)	32.6	(2.2)	37.5	(2.7)
BMI 1995–1998, kg/m^2, mean (SD)	22.4	(1.4)	25.8	(1.5)	29.4	(1.7)	31.0	(2.2)	33.6	(2.1)	38.7	(2.4)
BMI 2003–2007, kg/m^2, mean (SD)	22.0	(1.7)	25.7	(1.6)	29.5	(1.8)	30.9	(2.3)	34.1	(2.2)	39.0	(2.7)
Sex, *N* (%)												
Male	1,457	(24.7)	5,073	(44.3)	3,884	(47.7)	558	(57.2)	989	(33.7)	217	(22.5)
Female	4,448	(75.3)	6,382	(55.7)	4,262	(52.3)	417	(42.8)	1,944	(66.3)	746	(77.5)
Country of birth, *N* (%)												
Australia/New Zealand/Northern Europe	5,538	(93.8)	9,489	(82.8)	5,669	(69.6)	598	(61.3)	1,861	(63.5)	616	(64.0)
Southern Europe	367	(6.2)	1,966	(17.2)	2,477	(30.4)	377	(38.7)	1,072	(36.5)	347	(36.0)
SEIFA 5 quintiles, *N* (%)												
1—Least advantaged	740	(12.5)	1,754	(15.3)	1,555	(19.1)	208	(21.3)	674	(23.0)	239	(24.8)
2	931	(15.8)	2,167	(18.9)	1,817	(22.3)	253	(25.9)	700	(23.9)	235	(24.4)
3	870	(14.7)	1,788	(15.6)	1,349	(16.6)	145	(14.9)	487	(16.6)	181	(18.8)
4	1,204	(20.4)	2,262	(19.7)	1,523	(18.7)	157	(16.1)	531	(18.1)	146	(15.2)
5—Most advantaged	2,160	(36.6)	3,484	(30.4)	1,902	(23.3)	212	(21.7)	541	(18.4)	162	(16.8)
Level of education, *N* (%)												
Primary or lower	299	(5.1)	1,397	(12.2)	1,831	(22.5)	290	(29.7)	798	(27.2)	264	(27.4)
Some high/technical school	2,300	(39.0)	4,432	(38.7)	3,038	(37.3)	335	(34.4)	1,158	(39.5)	409	(42.5)
Completed high/technical school	1,372	(23.2)	2,591	(22.6)	1,658	(20.4)	189	(19.4)	562	(19.2)	167	(17.3)
Completed tertiary education	1,934	(32.8)	3,035	(26.5)	1,619	(19.9)	161	(16.5)	415	(14.1)	123	(12.8)
Mediterranean diet score 1990–1994, *N* (%)												
0–3	1,800	(30.5)	3,712	(32.4)	2,761	(33.9)	368	(37.7)	1,042	(35.5)	322	(33.4)
4–6	3,322	(56.3)	6,202	(54.1)	4,384	(53.8)	508	(52.1)	1,598	(54.5)	548	(56.9)
7–9	783	(13.3)	1,541	(13.5)	1,001	(12.3)	99	(10.2)	293	(10.0)	93	(9.7)
Mediterranean diet score 2003–2007, *N* (%)												
0–3	991	(23.3)	1,780	(23.2)	1,249	(24.3)	132	(23.9)	429	(24.2)	154	(26.5)
4–6	2,594	(60.9)	4,737	(61.7)	3,203	(62.4)	346	(62.7)	1,158	(65.3)	369	(63.4)
7–9	675	(15.8)	1,156	(15.1)	685	(13.3)	74	(13.4)	185	(10.4)	59	(10.1)
Physical activity score 1990–1994, *N* (%)												
0	886	(15.0)	2,099	(18.3)	1,990	(24.4)	245	(25.1)	863	(29.4)	325	(33.7)
>0 and <4	1,096	(18.6)	2,233	(19.5)	1,652	(20.3)	183	(18.8)	661	(22.5)	241	(25.0)
≥4 and <6	2,121	(35.9)	4,110	(35.9)	2,849	(35.0)	354	(36.3)	987	(33.7)	284	(29.5)
≥6	1,802	(30.5)	3,013	(26.3)	1,655	(20.3)	193	(19.8)	422	(14.4)	113	(11.7)
METs 2003–2007, median (IQR)	21.5	(9.9–39.8)	19.3	(8.2–36.9)	14.9	(6.0–29.7)	14.2	(5.0–32.1)	11.2	(3.7–24.4)	9.0	(2.8–19.8)
Drinking status 1990–1994, *N* (%)												
Lifetime abstainers	1,474	(25.0)	2,786	(24.3)	2,301	(28.2)	303	(31.1)	1,084	(37.0)	441	(45.8)
Ex-drinkers	506	(8.6)	1,087	(9.5)	826	(10.1)	110	(11.3)	274	(9.3)	99	(10.3)
Current [1–39 g (male), 1–19 (female)]	3,246	(55.0)	6,376	(55.7)	4,209	(51.7)	484	(49.6)	1,358	(46.3)	374	(38.8)
Current [≥ 40 (male), ≥20 (female)]	679	(11.5)	1,206	(10.5)	810	(9.9)	78	(8.0)	217	(7.4)	49	(5.1)
Smoking status at last BMI measurement, *N* (%)												
Never	3,681	(62.3)	6,681	(58.3)	4,532	(55.6)	514	(52.7)	1,775	(60.5)	606	(62.9)
Former	1,756	(29.7)	3,994	(34.9)	2,999	(36.8)	374	(38.4)	955	(32.6)	280	(29.1)
Current	468	(7.9)	780	(6.8)	615	(7.5)	87	(8.9)	203	(6.9)	77	(8.0)
Had angina before 1990–1994, *N* (%)	190	(3.4)	528	(4.9)	426	(5.6)	65	(7.1)	140	(5.1)	54	(6.0)
Had heart attack before 1990–1994, *N* (%)	102	(1.7)	292	(2.5)	234	(2.9)	31	(3.2)	74	(2.5)	21	(2.2)
Had stroke before 1990–1994, *N* (%)	37	(0.6)	127	(1.1)	92	(1.1)	14	(1.4)	25	(0.9)	12	(1.2)
Had diabetes before 1990–1994, *N* (%)	76	(1.3)	254	(2.2)	324	(4.0)	65	(6.7)	150	(5.1)	59	(6.1)
Birth cohort, *N* (%)												
Before 1930	1,295	(21.9)	2,772	(24.2)	1,667	(20.5)	246	(25.2)	480	(16.4)	117	(12.1)
After 1930, before 1940	1,706	(28.9)	3,757	(32.8)	2,906	(35.7)	317	(32.5)	1,046	(35.7)	317	(32.9)
After 1940, before 1950	2,058	(34.9)	3,578	(31.2)	2,638	(32.4)	314	(32.2)	1,046	(35.7)	379	(39.4)
After 1950	846	(14.3)	1,348	(11.8)	935	(11.5)	98	(10.1)	361	(12.3)	150	(15.6)

Abbreviations: IQR, interquartile range; MET, metabolic equivalent; SD, standard deviation.

Table 2. HRs for associations between BMI trajectory groups and risk of obesity-related cancers in all participants ($n = 30,377$) and never-smokers at last BMI assessment (17,789) in the MCCS.

	Obesity-related cancer in all participants ($n = 30,377$)			Obesity-related cancer in never-smokers at last BMI assessment ($n = 17,789$)		
BMI trajectory groups	**Person-years**	**Cases**	**HR (95% CI)**	**Person-years**	**Cases**	**HR (95% CI)**
TR1 Lower normal stable	70,139	451	1	44,359	290	1
TR2 Higher normal stable[a]	135,117	847	1.04 (0.92–1.18)	80,157	510	1.05 (0.91–1.22)
Age 67 years			1.00 (0.87–1.15)			0.94 (0.79–1.12)
Age 74 years			1.06 (0.93–1.20)			1.07 (0.92–1.24)
Age 80 years			1.11 (0.94–1.30)			1.19 (0.99–1.43)
TR3 Normal to overweight	97,088	702	1.29 (1.13–1.47)	55,309	408	1.28 (1.09–1.49)
TR4 Chronic borderline obesity	11,552	67	1.12 (0.85–1.48)	6,205	35	1.05 (0.74–1.50)
TR5 Normal to class I obesity	35,199	299	1.50 (1.28–1.75)	21,684	188	1.51 (1.25–1.83)
TR6 Overweight to class II obesity	11,772	108	1.66 (1.32–2.08)	7,481	64	1.53 (1.16–2.01)

Note: Adjusted for birth cohort, height, sex, country of birth, SEIFA, highest level of education, smoking status at latest BMI assessment, baseline Mediterranean diet score, alcohol drinking status, and physical activity score and with attained age as the time scale.
[a]As TR2 showed evidence of non-proportional hazards for never-smokers ($P = 0.02$), we fitted an interaction between this trajectory and attained age and presented HRs for age 67, 74, and 80 (25th, 50th, and 75th percentiles of age at diagnosis).

Akaike information criterion (Supplementary Table S5). The HRs estimated for the last measured BMI were, in general, somewhat lower than the HRs derived for trajectories ending at the equivalent category of BMI. For example, for all obesity-related cancers, TR3 normal to overweight HR, 1.29 (95% CI, 1.13–1.47); last measured BMI overweight HR, 1.14 (95% CI, 1.00–1.30). See Supplementary Table S6 for further details.

In the sex-specific analyses, we identified similar numbers and shapes of BMI trajectories in women and men (Supplementary Fig. S2). The risks of obesity-related cancer in men and in women were similar to the risk in the main analysis. For the "Overweight to class II obesity" trajectory, the HR was higher for men than for women. However, the HR was based on a small number of cases and had a wide CI (Supplementary Table S7).

Discussion

In all trajectories modeled in our study, BMI increased over adulthood and tended to decrease at older ages, but only trajectories that moved beyond a normal BMI were associated with an increased risk of obesity-related cancer, compared with a lifelong healthy BMI. BMI increasing from normal to overweight was associated with a 29% increased risk, whereas BMI increasing from normal to class I obesity was associated with a 50% increased risk. The trajectory with the greatest risk increase (66%) was overweight to class II obesity.

A key strength of this study is that we could derive trajectories of BMI across adulthood because body mass had been measured or reported at multiple times. Furthermore, we avoided bias by not grouping participants into categories of change between two time points (8). Our study had several limitations that are important to consider, including assessing weight at age 18 to 21 years based on recall at baseline (20–50 years later), which could be inaccurate. However, previous studies have typically reported moderate to strong correlation between body mass measured in young adulthood and recalled decades later (25, 26). Another limitation is the long period of time between age 18 to 21 years and baseline, which means that there may have been different patterns of BMI change over early and mid-adulthood that we could not identify. Information about potential confounders at age 18 to 21 years was missing. Creating trajectories using the latent class trajectory model required excluding participants who attended the baseline visit only (i.e., excluding those with no subsequent data due to nonattendance or death). In one study, this type of selection bias resulted in underestimation of rate ratios for higher BMI categories in the case of all-cause mortality (27). Some trajectories in the analyses of colorectal cancer and breast cancer had few cases, and the estimated HRs were imprecise as indicated by wide CIs.

Table 3. HRs for colorectal cancer and postmenopausal breast cancer according to BMI trajectory groups in participants of the MCCS.

	Colorectal cancer[a] ($n = 30,377$)			Postmenopausal breast cancer[b] ($n = 18,199$)		
BMI trajectory groups	**Person-years**	**Cases**	**HR (95% CI)**	**Person-years**	**Cases**	**HR (95% CI)**
TR1 Lower normal stable	70,139	151	1.00	54,342	184	1.00
TR2 Higher normal stable	135,117	285	0.86 (0.71–1.06)	78,374	239	0.93 (0.76–1.14)
TR3 Normal to overweight	97,088	251	1.10 (0.89–1.35)	52,814	202	1.31 (1.05–1.62)
TR4 Chronic borderline obesity	11,552	26	0.92 (0.60–1.41)	5,255	16	1.18 (0.68–2.04)
TR5 Normal to class I obesity	35,199	80	1.11 (0.84–1.46)	24,117	109	1.55 (1.20–2.00)
TR6 Overweight to class II obesity	11,772	30	1.47 (0.98–2.20)	9,174	39	1.49 (1.02–2.18)

[a]Adjusted for birth cohort, height, sex, country of birth, highest level of education, smoking status at latest BMI assessment, baseline Mediterranean diet score, and physical activity score; stratified by SEIFA and alcohol drinking status; and with attained age as the time scale.
[b]Adjusted for birth cohort, country of birth, SEIFA, highest level of education, smoking status at latest BMI assessment, baseline Mediterranean diet score, alcohol drinking status, and physical activity score; stratified by height; and with attained age as the time scale.

Only one study has examined the association of body shape trajectories with total cancer and obesity-related cancer. Song and colleagues used data from the Nurses' Health Study and the Health Professionals Follow-up Study to model trajectories using pictograms for early life and BMI for later life (28). Five trajectories were identified: for women, lean-moderate increase, lean-marked increase, and heavy-stable/increase trajectories were associated with a higher risk of total and obesity-related cancers compared with the lean-stable pattern. For men, all trajectories were associated with an increased risk of total and obesity-related cancer compared with the lean-stable group.

Studies of BMI trajectories (or body shape using diagrams) across a range of ages have examined associations with risk of specific cancers, including colorectal cancer and postmenopausal breast cancer. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial estimated BMI trajectories using data from ages 20, 50, and study entry at a mean age of 63 years. Four trajectories were identified (BMI remaining normal; normal to overweight; normal to obese; and overweight to obese). Compared with participants having stable normal BMI, those in the normal with obese trajectory had increased colorectal cancer risk (16). The French E3N study used self-reported body shape at age 8, at menarche, at 20 to 25, and at 35 to 40 years to define six body size trajectories. Women with a large body shape at menarche, irrespective of their shape before or after, tended to have reduced risk of estrogen receptor–positive or progesterone receptor–positive postmenopausal breast cancer, compared with women who were consistently lean (17). This is consistent with findings from the Nurses' Health Study, in which adiposity at age 10 was inversely associated with risk of postmenopausal breast cancer (29).

Although the IARC review considered evidence for an association between overweight or obesity and risk of prostate cancer to be limited (1), analysis of the NIH-AARP Diet and Health Study reported that a trajectory increasing from normal body mass at age 18 years to obesity at study entry (mean age 63 years) was associated with a higher risk of fatal prostate cancer compared with stable normal weight (18). Combining data from the PLCO and NIH-AARP studies, Petrick and colleagues examined trajectories based on BMI at ages 20, 50, and study baseline (around age 63 years) in relation to esophageal adenocarcinoma and gastric cardia adenocarcinoma. Compared with a stable normal BMI, trajectories that reflected BMI increases from normal to overweight or obese, or from overweight to obese, were associated with an increased risk of both cancers, the risk being over three times higher for the latter trajectory (19). In a Canadian case–control study of pancreatic cancer, five BMI trajectories based on BMI in adolescence, 20s, 30s to 40s, 50s to 60s were identified; persistent overweight and progressive obesity were associated with an increased risk relative to stable normal weight (20). Data from the Nurses' Health Study and the Health Professionals Follow-up Study were used to determine body shape trajectories based on somatotype pictograms for age 5, 10, 20, 30, and 40 years, and self-reported height and weight to calculate BMI at age 45, 50, 55, and 60 years in relation to multiple myeloma risk. Four trajectories were identified, and the pattern that started out at a medium body size and increased, compared with remaining lean, was associated with an increased risk of multiple myeloma (21).

In the MCCS, trajectories gave slightly higher HRs than single BMI measures for associations with obesity-related cancers, although model fits were not notably better with the additional information provided by the trajectories. This comparison was based on BMI at the final measure so that the follow-up was the same for the trajectory and single time point analyses. Had the comparison been made on a single BMI measure at another time point, the results may have been different. Zheng and colleagues showed that the effect sizes of BMI at a single time point were smaller than the corresponding estimates using BMI trajectories in relation to mortality (30). Kelly and colleagues have provided data for BMI at ages 20, 50, and baseline (mean age 63 years) and prostate cancer, as well as associations for BMI trajectories combining these data points; at these ages the HR for prostate cancer mortality were 1.69 (95% CI, 0.75–3.82), 1.55 (1.05–2.29), and 1.46 (1.02–2.09), respectively, while the HRs for trajectories normal to obese, or overweight to obese were 1.95 (1.21–3.12) and 2.65 (1.35–5.18), respectively (31). These figures like our data show somewhat higher HRs for trajectories than single time points, and some evidence that obesity at average age 63 years was differently associated with prostate cancer mortality depending on BMI at age 20 years. We did not have any trajectories finishing at the same BMI but starting at very different BMIs. Participants in the MCCS mostly reported low BMI at age 18 to 21 years which is consistent with other Australian data showing that children ages 5 to 15 years had prevalence of overweight and obesity less than 10% up to the 1970s when the prevalence increased rapidly (32), and birth cohort data showing that the prevalence of overweight and obesity in people ages 18 to 21 years has increased for cohorts born between 1974 and 1977 and 1994 and 1997 (4). However, as people become overweight and obese at earlier ages, the potential extra information from using trajectories may become more important.

Overall, the research to date suggests that body mass trajectories that reflect increasing adiposity from young adulthood are associated with an increased risk of several obesity-related cancers in later life. Our study adds to this body of evidence and highlights the importance of maintaining a normal BMI into older ages to reduce the risk of cancer. To reduce the cancer burden associated with obesity, primary prevention targeting young adults to prevent weight gain over adulthood is vital.

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Authors' Contributions

Y. Yang: Formal analysis, methodology. **B.M. Lynch:** Conceptualization, supervision, writing–original draft, writing–review and editing. **P.-A. Dugué:** Supervision, writing–review and editing. **A. Karahalios:** Writing–review and editing. **R.J. MacInnis:** Writing–review and editing. **J.K. Bassett:** Writing–review and editing. **A. McAleese:** Conceptualization. **C. Sinclair:** Conceptualization. **G.G. Giles:** Conceptualization, resources. **R.L. Milne:** Conceptualization, resources, writing–review and editing. **A.M. Hodge:** Conceptualization, supervision, writing–original draft, writing–review and editing. **D.R. English:** Conceptualization, supervision, writing–review and editing.

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