

Association of body mass index in early adulthood and middle age with future site-specific cancer mortality: the Harvard Alumni Health Study

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Background: The association between adiposity in early adulthood and subsequent development of specific malignancies is unclear. Further, the potential for mediation by adiposity in middle age has not been well examined. In a rare study, we investigated the association of body mass index (BMI) in early adulthood with mortality from several site-specific cancers.

Design: In the Harvard Alumni Health Study cohort, 19 593 males had a physical examination at the university between 1914 and 1952 (mean age: 18.4 years) and returned a questionnaire in 1962 or 1966 (mean age = 45.1 years). BMI was computed using weight (kg)/height² (m²) at both time points. Vital status follow up continued for a maximum of 82 years.

Results: Positive early adulthood cancer mortality gradients by BMI were found for all malignancies combined (adjusted hazard ratio [HR] = 1.11; 95% confidence interval [CI]: 1.05–1.17 for a one standard deviation increase in early adulthood BMI), and for lung (HR = 1.24; 95% CI = 1.10–1.40) and skin (HR = 1.29; 95% CI = 0.96–1.75) cancers. There were also apparent associations for cancers of the oesophagus and urogenital sites. Mediation by BMI in middle age was found to be minimal.

Conclusion: Higher BMI in early adulthood appears to be a direct risk factor for selected malignancies several decades later.

Key words: body mass index, Harvard, cohort study, mortality

introduction

A series of studies have examined the link between adiposity, measured in middle- and older-aged adults, and subsequent cancer development [1, 2]. Positive associations between body mass index (BMI), the most commonly used index of adiposity, and some site-specific malignancies—including colon, rectum, kidney, melanoma and pancreas—have been shown [2]. Physiological mechanisms including metabolic disturbance have been posited as plausible explanations for these observed associations [3]. However, despite the growing prevalence of obesity earlier in life, the long-term health consequences of obesity in early adulthood have not been well examined. This is due to a paucity of cohorts of young persons with BMI measurement who are then followed for several decades for the occurrence of cancer.

In the few studies relating body weight during early adulthood with future cancer risk, the number of events is low and statistical power is therefore sub-optimal [1, 4–6]. Other methodological constraints exist. Some studies [1, 5] suffer from an absence of

covariate data to assess the effect of confounding [7], while in others, the potentially mediating role of adiposity in middle age has not been explored [8]. This latter issue is particularly important since overweight young adults tend to remain overweight into middle age [9], such that the influence of excess weight during early adulthood on future cancer risk could simply be a result of perpetuated middle-aged adiposity.

The Harvard Alumni Health Study is a large prospective cohort with data collected across the entire adult life course. It therefore represents a rare opportunity to examine the associations of BMI during both early and middle adulthood with the risk of total and site-specific cancer mortality.

methods

study population

The Harvard Alumni Health Study is an ongoing cohort study of chronic disease risk factors in male undergraduates at the Harvard University, Boston, USA who matriculated between 1916 and 1950. A total of 33 415 men took part in a standardised, routine medical examination at ~18 years of age ('early adulthood') [10, 11]. Measurements of height and weight were made and students responded to enquiries regarding smoking habits (never, past or current) [10, 12]. Details on physical activity (<2, 2 to <5, ≥5 h/week

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or varsity athletics) were ascertained from athletic records documented during their undergraduate years [11].

Health questionnaires have been mailed to surviving alumni on a periodic basis since either 1962 or 1966 (hereafter referred to as 1962/1966), when they were aged, on average, 46 years ('middle age'). These questionnaires included questions about height and weight; it has been previously shown that these self-reported data have a high level of agreement with direct measurement of height and weight [12]. A total of 21 582 men (68% of surviving alumni) responded to the 1962/1966 questionnaire [13].

ascertainment of cancer mortality

We used documentation maintained by the Harvard University Alumni office to periodically identify decedents during follow-up and obtained copies of official death certificates from the state health departments through the end of 1998 to determine cause of death. Records are over 99% complete for vital status in this cohort [14]. Cancer deaths were coded according to the Seventh Revision of the International Classification of Disease (ICD 420) [15]. Deaths from any cancer were identified by ICD-7 codes 140-239. The cancer sites selected were those with at least 50 deaths for the purposes of model stability. We therefore considered the following individual cancer sites: trachea, bronchus and lung (ICD-7: 162-163; referred to as 'lung cancer'); colon (153); colorectal (153-154); stomach (151); liver (155-156); pancreas (157); prostate (177); kidney (180); bladder (181); oesophageal (150); brain (193); skin (190-191); lymphoma (200-202); multiple myeloma (203) and leukaemia (204). Additionally, cancers of the kidney, bladder, prostate and testis were considered in a group (177-181; referred to as 'urogenital'), as were neoplasms from lymphatic and haematopoietic tissues (200-205).

statistical analyses

BMI was calculated ($\text{weight [kg]/height}^2 [\text{m}^2]$) for early adulthood and middle age, and we categorised values into quartiles. We also utilised current World Health Organisation (WHO) classifications for underweight ($<18.5 \text{ kg/m}^2$), normal weight (18.5 to $<25 \text{ kg/m}^2$; referent), overweight (25 to $<30 \text{ kg/m}^2$) and obesity ($\geq 30 \text{ kg/m}^2$) [16].

Of the 33 415 men who were medically examined in early adulthood, 2663 (8%) died before 1962 and 10 902 were not traced or did not respond to the questionnaire mailing. This resulted in a total of 19 850 men who had both records of a physical examination at college entry and returned a mailed questionnaire in 1962/1966 (Figure 1). Data on participants were discarded on the basis of data errors with recorded dates for university entry and death ($n = 29$), and missing information on height and weight at the medical examination ($n = 228$), leaving 19 593 men in the present study. In further analyses, we limited the sample to men with complete data on height and weight from the 1962/1966 questionnaire and potentially confounding variables ($n = 15 781$). The subjects excluded from the analysis had similar distribution of BMI at college entry to the analytical sample (mean = 21.7 kg/m^2 , standard deviation [SD] = 2.6 kg/m^2 and mean = 21.7 kg/m^2 , SD = 2.5 kg/m^2 , respectively).

Having determined that the proportional hazards assumption had not been violated, hazard ratios (HRs) and 95% confidence intervals (CIs) were computed using Cox regression models [17] to summarise the relationship of BMI in early and middle adulthood with subsequent total and site-specific cancer mortality; deaths from any other cause (including alternative cancers) were censored. In these analyses, we explored the association of BMI expressed as both a categorical variable and a 1 SD increase in relation to the site-specific cancers. In model 1, we adjusted for age only; we then adjusted for BMI at middle age in model 2, and finally, in model 3, we also controlled for cigarette smoking status and physical activity during early adulthood. We also obtained estimates from joint models to establish the

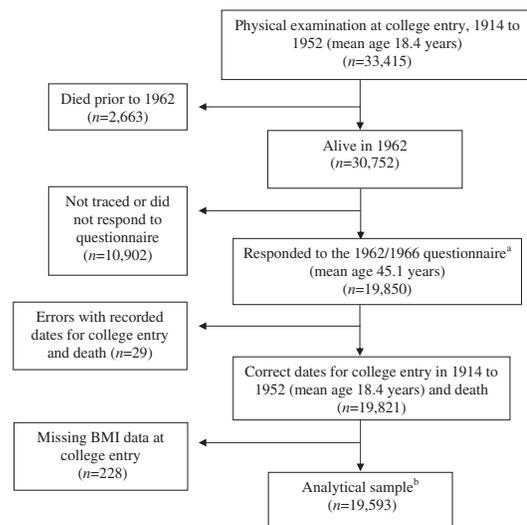


Figure 1. Participants in the Harvard Alumni study. a indicates 1732 men of the total 21 582 alumni responding in 1962/1966 were not examined at college entry. b indicates analytical sample for Model 1 that consisted of 19 593 men; 598 men had missing BMI data in 1962/1966, resulting in $n = 18 995$ in the analytical sample for Model 2; 3214 men had missing cigarette smoking status and physical activity in college leaving $n = 15 781$ in the analytical sample for Model 3.

direct effects of BMI in early adulthood. To guard against the possibility of middle-age BMI findings being affected by reverse causality—whereby potential bias would arise from possible weight loss caused by occult disease impacting on BMI—we carried out sensitivity analyses excluding 161 deaths occurring within 3 years following questionnaire return [18]. Also, all analyses were reconducted accounting for parental history of cancer (present for 308 men). To account for missing data—affecting at least one variable for 4040 men—survival analyses were also carried out on 21 multiply imputed datasets (corresponding to the percentage with missing data [19]). This was based on the chained equations procedure [20] and included all 19 821 men with valid dates and records for physical examination at university entry and 1962/1966 questionnaire. Finally, we produced effect estimates based on a subset of men with no missing data on BMI and potential confounders ($n = 15 781$).

results

The overall mean BMI increased by 2.7 kg/m^2 from 21.7 kg/m^2 in early adulthood (mean age = 18.4, SD = 1.8) to 24.4 kg/m^2 in middle adulthood (mean age = 46.1, SD = 9.4), and the two measures were significantly correlated ($r = 0.49$, $P < 0.001$). In Table 1, we show the relationships between early adulthood BMI and the study members' characteristics.

The men were followed for cause-specific mortality for a mean of 56.5 years from university entry. In total, 2395 men died of a malignancy of some kind (mortality rate of 217 per 100 000 person years): 469 (42) of the lung, 228 (21) of the colon, 270 (24) of colorectal, 145 (13) of pancreas, 417 (38) of prostate, 535 (48) of urogenital, 66 (6) of skin, 82 (7) of oesophageal, 67 (7) of stomach, 69 (21) of liver, 55 (6) of kidney, 60 (5) of bladder, 85 (8) of brain, 149 (13) of lymphoma, 58 (52) of multiple myeloma, 119 (11) of leukaemia and 328 (30) of lymphatic and haematopoietic tissues. These results broadly accord with cancer mortality statistics for the

general USA white male population (222 cancers compared with 217 in our cohort), although for some individual sites, e.g. lung cancer, deaths are fewer due to the relatively low-smoking prevalence in the cohort [21].

Table 2 gives the relative risk estimates for the associations between BMI at both early and middle adulthood and mortality from any malignancy. For BMI at early adulthood, the age-adjusted BMI at university entry was associated with death from all malignancies combined, with an 8% (95% CI 4% to 13%) increased risk for every 1 SD BMI increase. Elevation in risk was stepwise across quartiles of BMI ($P_{\text{trend}} < 0.001$) such that men in the highest quartile, with a BMI $>23 \text{ kg/m}^2$, had a 27% (13% to 43%) increased risk compared with those with a BMI $<20 \text{ kg/m}^2$. Adjusting for BMI in middle age (Model 2) did not

change the magnitude of the relation between early BMI and later cancer risk. Further adjustment for smoking and physical activity at university entry (Model 3) also did not impact these results. In comparison to early BMI, associations were weaker for middle-age BMI in relation to any malignancy risk (Table 2).

A 1 SD increase in early adulthood BMI resulted in a 11% (2%–20%) increased risk of lung cancer mortality (Table 3). Results for quartiles of early adulthood BMI are shown for all malignancies in supplemental Table S1 (available at *Annals of Oncology* online). Men in the third and fourth quartiles had an ~50% elevated risk of lung cancer mortality compared with those in the first quartile of BMI ($P_{\text{trend}} = 0.001$). HRs strengthened after adjustment for middle-age BMI, early adulthood smoking and physical activity. Results for quartiles of middle-age BMI are

Table 1. Characteristics of study participants according to BMI at university entry ($N = 19\,593$)

	University entry BMI quartile				Total ($N = 19\,821$)
	$<20.0 \text{ kg/m}^2$ ($n = 4754$)	$20.0\text{--}21.3 \text{ kg/m}^2$ ($n = 4915$)	$21.3\text{--}23.0 \text{ kg/m}^2$ ($n = 5011$)	$>23.0 \text{ kg/m}^2$ ($n = 4913$)	
University entry					
Age (years), mean (SD)	18.1 (1.5)	18.2 (1.6)	18.4 (1.8)	18.8 (2.2)	18.4 (1.8)
Physical activity, n (%): <1 h/week	3.1 (140)	3.0 (142)	3.2 (152)	3.2 (153)	3.1 (587)
Current smoker, n (%):	33.9 (1337)	34.9 (1462)	34.7 (1481)	34.7 (1491)	34.6 (5771)
Yes					
Middle age					
Age (years), mean (SD)	48.0 (9.4)	47.0 (9.5)	45.6 (9.3)	43.8 (8.9)	46.1 (9.4)
BMI quartile, n (%)					
<22.8 kg/m^2	45.9 (2182)	28.7 (1,410)	17.2 (864)	6.5 (321)	24.4 (4777)
22.8 to <24.3 kg/m^2	25.3 (1204)	28.6 (1404)	27.5 (1377)	15.1 (740)	24.1 (4725)
24.3 to <25.8 kg/m^2	16.9 (803)	24.1 (1186)	29.3 (1467)	26.6 (1305)	24.3 (4761)
$\geq 25.8 \text{ kg/m}^2$	8.9 (422)	15.4 (756)	23.3 (1166)	48.6 (2388)	24.2 (4732)
Unknown	3.0 (143)	3.2 (159)	2.7 (137)	3.2 (159)	3.1 (598)

BMI, body mass index; SD, standard deviation.

Table 2. HRs (95% CIs) for mortality from all malignancies in relation to BMI in early adulthood and middle age

	BMI range (kg/m^2)	Deaths	Total	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)
Early adulthood (18.4 years)						
Per 1 SD (2.56) increase		2395	19 593	1.08 (1.04–1.13)	1.08 (1.03–1.13)	1.11 (1.05–1.17)
Quartiles						
	<20.0	606	4754	1.00 (ref)	1.00	1.00
	20.0 to 21.3	598	4915	1.01 (0.90–1.13)	1.01 (0.90–1.14)	1.03 (0.90–1.17)
	21.4 to 23.0	608	5011	1.11 (0.99–1.24)	1.11 (0.99–1.25)	1.10 (0.96–1.26)
	>23.0	583	4913	1.27 (1.13–1.43)	1.26 (1.11–1.43)	1.35 (1.17–1.56)
P_{trend}^a				<0.001	<0.001	<0.001
Middle age (46.1 years)						
Per 1 SD (2.55) increase		2363	19 209	1.05 (1.01–1.10)	—	—
Quartiles						
	<22.8	605	4837	1.00 (ref)	—	—
	22.8 to <24.3	513	4764	0.84 (0.75–0.95)	—	—
	24.3 to <25.8	620	4816	1.02 (0.91–1.14)	—	—
	≥ 25.8	625	4792	1.04 (0.93–1.16)	—	—
P_{trend}^a				0.103	—	—

Model 1: Adjusted for age (total number of subjects and deaths as tabulated); Model 2: Adjusted for age and BMI in 1962/66 ($n = 18\,995$; 2337 cancer deaths); Model 3: Adjusted for age, cigarette smoking status and physical activity at college entry and BMI in 1962/66 ($n = 15\,781$; 1855 cancer deaths).

^aP-value of test for trend.

BMI, body mass index; CI, confidence intervals; HR, hazard ratio; SD, standard deviation; ref, reference.

Table 3. HRs (95% CIs) for mortality from site-specific malignancies in relation to a 1 standard deviation (2.56 kg/m²) increase in BMI in early adulthood (mean age 18.4 years)

	Deaths	Deaths per 1000 men	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)
Lung cancer	469	23.9	1.11 (1.02–1.20)	1.18 (1.09–1.27)	1.24 (1.10–1.40)
Colorectal cancer	270	13.8	1.08 (0.96–1.21)	1.03 (0.90–1.18)	1.09 (0.93–1.27)
Colon cancer	228	11.6	1.09 (0.97–1.23)	1.05 (0.91–1.21)	1.11 (0.94–1.31)
Stomach cancer	67	3.4	0.97 (0.74–1.26)	0.93 (0.69–1.26)	0.94 (0.68–1.30)
Liver cancer	69	3.5	1.07 (0.86–1.35)	1.11 (0.87–1.41)	0.98 (0.68–1.40)
Pancreatic cancer	145	7.4	1.03 (0.87–1.22)	1.01 (0.84–1.23)	1.08 (0.87–1.34)
Prostate cancer	417	21.3	1.06 (0.97–1.17)	1.04 (0.93–1.16)	1.04 (0.91–1.19)
Kidney cancer	55	2.8	1.23 (1.07–1.41)	1.12 (0.91–1.39)	1.17 (0.84–1.62)
Bladder cancer	60	3.1	1.05 (0.81–1.36)	1.00 (0.73–1.37)	0.91 (0.63–1.60)
Urogenital cancer	535	27.3	1.09 (1.01–1.18)	1.05 (0.96–1.16)	1.05 (0.93–1.18)
Oesophageal cancer	82	4.2	1.14 (0.97–1.35)	1.17 (0.99–1.37)	1.21 (0.91–1.60)
Brain cancer	85	4.3	1.00 (0.80–1.25)	1.03 (0.80–1.33)	1.05 (0.78–1.42)
Skin cancer	66	3.4	1.19 (1.01–1.39)	1.34 (0.99–1.80)	1.29 (0.96–1.75)
Lymphoma	149	7.6	1.11 (0.96–1.28)	1.04 (0.87–1.25)	1.08 (0.87–1.34)
Multiple myeloma	58	3.0	1.19 (1.03–1.38)	1.17 (0.99–1.37)	1.23 (0.90–1.60)
Leukaemia	119	6.1	0.98 (0.80–1.19)	0.98 (0.79–1.23)	1.12 (0.88–1.42)
Lymphatic and haematopoietic tissue malignancies	328	16.7	1.09 (0.98–1.20)	1.06 (0.94–1.19)	1.12 (0.97–1.30)

Model 1: Adjusted for age (number and percentage of deaths as tabulated); Model 2: Adjusted for age and BMI in 1962/1966 ($n = 18\,995$); Model 3: Adjusted for age, cigarette smoking status and physical activity at college entry and BMI in 1962/1966 ($n = 15\,781$). BMI, body mass index; CI, confidence intervals; HR, hazard ratio; SD, standard deviation.

shown in supplemental Table S2 (available at *Annals of Oncology* online). Higher middle-age BMI was inversely but nonsignificantly associated with a decreased risk of lung cancer mortality across quartiles ($P_{\text{trend}} = 0.070$) (Table 4).

Results in Table 3 and supplemental Table S1 (available at *Annals of Oncology* online) indicate that BMI during early adulthood was not associated with the risk of colorectal cancer mortality, although a 1 SD increase in middle-age BMI was associated with a 12% increase in risk (Table 4). Results for colon cancer mortality were similar to those found for colorectal cancer mortality.

There were associations between higher BMI in early adulthood and kidney cancer mortality with a 23% increased risk for every 1 SD BMI increase (Table 3). Those in the fourth quartile experienced more than double the risk compared with the lowest quartile ($P_{\text{trend}} = 0.025$). Adjusting for middle-age BMI and early adulthood smoking and physical activity attenuated the results. Each 1 SD increase in BMI during middle adulthood was associated with a 46% increase in kidney cancer mortality. Associations for all urogenital cancers were similar to those of kidney. Oesophageal cancer mortality exhibited an association across quartiles of BMI in early adulthood, which remained upon adjustment for middle-age BMI, smoking and physical activity ($P = 0.030$); there were no associations of middle-age BMI with this malignancy (Table 4 and supplemental Table S2, available at *Annals of Oncology* online). There was a suggestion of association of higher BMI in early adulthood with skin cancer.

There was no apparent relation of either early- or later-life BMI with any of the remaining malignancies: stomach, pancreas, liver, brain, prostate, bladder, lymphatic and haematopoietic tissue malignancies (lymphoma, multiple

Table 4. Age-adjusted HRs (95% CIs) for mortality from site-specific malignancies in relation to a 1 standard deviation (2.55 kg/m²) increase in body mass index in middle age (mean age 46.1 years)

	Deaths	Deaths per 1000 men	HR (95% CI)
Lung cancer	459	23.9	0.93 (0.84–1.02)
Colorectal cancer	269	14.0	1.12 (1.00–1.26)
Colon cancer	227	11.8	1.14 (1.00–1.29)
Stomach cancer	67	3.5	1.10 (0.87–1.39)
Liver cancer	68	3.5	0.96 (0.75–1.23)
Pancreatic cancer	148	7.7	1.03 (0.87–1.21)
Prostate cancer	409	21.3	1.08 (0.98–1.19)
Kidney cancer	55	2.9	1.46 (1.17–1.82)
Bladder cancer	58	3.0	1.04 (0.80–1.35)
Urogenital cancer	525	27.3	1.12 (1.03–1.22)
Oesophageal cancer	81	4.2	1.05 (0.84–1.30)
Brain cancer	83	4.3	0.94 (0.75–1.18)
Skin cancer	63	3.3	1.14 (0.90–1.44)
Lymphoma	145	7.5	1.19 (1.02–1.39)
Multiple myeloma	58	3.0	1.15 (0.90–1.48)
Leukaemia	121	6.3	0.98 (0.81–1.18)
Lymphatic and haematopoietic tissue malignancies	326	17.0	1.10 (0.99–1.18)

CI, confidence intervals; HR, hazard ratio; SD, standard deviation.

myeloma and leukaemia) (Tables 3 and 4 and supplemental Tables S1 and S2, available at *Annals of Oncology* online).

When we recategorised the BMI data into standard WHO groupings, our results were essentially unchanged. Weight gain between early and later adulthood was associated with an increased risk of total cancer mortality, as well as cancers of the

lung and oesophagus; weight loss also preceded development of lung cancer and malignancies of the lymphatic and haematopoietic tissue. Our results persisted in analyses excluding deaths within 3 years of the 1962/1966 questionnaire return and accounting for parental history of cancer. Joint model estimation also yielded similar results. In re-analyses of all models based on imputed data and confined to the subset of participants with completely observed data, results remained consistent with those presented here.

discussion

The main aim of the present analyses was to examine the relation of BMI in early adulthood with death from cancers. We found evidence of an association between increasing early adulthood BMI and cancer for all malignancies combined, and those of the lung, oesophagus, skin and urogenital sites. Conversely, BMI during middle-age BMI was inversely associated with lung cancer death.

comparisons with other studies

The few cohorts with sufficient length of follow-up (~20–40 years) to investigate the role of early adulthood BMI on the subsequent development of cancer [1, 4–6] have yielded conflicting results. In one study, null findings for cancer mortality were apparent in a small cohort of UK University students [4]. In other cohorts, a positive association with risk of prostate cancer (20%–22% excess risk in the overweight/obese) was found [5], and there was a doubling of risk of colon cancer together with null findings for larynx, lung and lymphatic system among an adolescent population [1].

Previously, studies have examined the associations of BMI with site-specific cancers in the Harvard Alumni Health Study [6, 18, 22, 23], with elevated BMI associated with an increased risk of breast cancer (in a subsample that included women) [6], kidney and bladder cancers [6, 23], and colon cancer [18], but null findings for other cancers including lung [6], prostate and testis [23], and pancreatic [22] malignancies). In these studies, follow-up extended until 1978 or 1988 with fewer cancer end points. For this paper, an extra 10–20 years of follow-up enabled us to re-examine these associations while accounting for the effect of BMI during middle-age.

mechanisms

Greater caloric intake alone or in combination with reduced physical activity has been implicated in the development of obesity [24]. Some credible mechanisms have been proposed to account for the relation between obesity and the increased risk of developing cancer [24]. Endogenous hormones such as sex steroids, insulin, and insulin-like growth factor-1 increase with the accumulation of body fat and are involved in the control of growth, differentiation and metabolism of cells, potentially linking energy-dense processed carbohydrate and animal fat consumption and cancer development. Alternative explanations include increases in the number of adipocytes along with associated obesity-related inflammatory markers (e.g. adipokines/cytokines), the nuclear factor kappa beta system and DNA-damaging oxidative stresses [25].

Additionally, given that birth weight is associated with weight in adult life, links between birth weight and cancer [26] point to the possible influence of the intrauterine environment. The ways in which such mechanisms may act in some, but not all, cancer subtypes are not currently clear. Alternatively, since elevated BMI corresponds (in the same way that taller stature does) to larger body size, there are simply more cells that may potentially undergo malignant transformation [27].

study strengths and limitations

With the combined advantages of a large number of subjects with measured height and weight, covariate data during early and middle adulthood, and long-term subsequent follow-up, this study overcomes any lack of power and unaccounted confounding and mediation affecting previous studies. However, our study does have some shortcomings. While we had measured height and weight at university entry that eliminated recall bias, the determination of BMI in middle age relies on self-reported height and weight, whereby the precision of self-reported values is lower than directly measured ones. Despite this limitation, contemporary self-reported measures are likely to be more accurate than recalled estimates. We still cannot rule out probable residual confounding as we lacked contemporaneous information on diet, alcohol and other covariates. Since the cancer outcomes were based on mortality, they reflect a combination of incidence and survival rather than disease aetiology *per se*. Additionally, death certificates may not accurately reflect the cancer site (e.g. colon versus rectal cancer). Our results persisted even after the exclusion of alumni dying within 3 years following the questionnaire return, indicating that this may not be explained by reverse causality.

In conclusion, BMI during early adulthood among Harvard undergraduates was associated with elevated rates of total cancer plus cancer of the lung, oesophagus, skin and urogenital sites. Unchecked, the increasing prevalence of obesity seen in Europe, North America and emerging economic areas will be likely to lead to an increase in the incidence of some cancers. Effective measures to tackle the persisting obesity epidemic are necessary to alleviate the burden of cancer and also other chronic diseases.

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disclosure

The authors declare no conflicts of interest.

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