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Article

Young adulthood adiposity in relation to all-cause and cause-specific mortality: a prospective study of 0.5 million Chinese adults

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ABSTRACT

Obesity is a well-established risk factor for early death, but the exact shapes of associations between young adulthood body mass index (BMI) and mortality in later life were not well characterised. Using data from the prospective China Kadoorie Biobank study of 430,373 participants (~57% being women, with a median follow-up duration of 12 years), Cox regression analysis was performed to yield adjusted hazard ratios (HRs) relating BMI at ~25 years old (BMI_{25}) with different mortality outcomes including total mortality ($n = 36{,}814$), cardiovascular mortality ($n = 13{,}620$), cancer mortality ($n = 13{,}394$) and respiratory mortality ($n = 2929$). Mean BMI_{25} of participants was 21.9 (SD = 2.5) kg/m^2, and 1.9% participants were obese at young adulthood (i.e., $\text{BMI}_{25} \geq 28.0$ kg/m^2). Independent of baseline BMI, higher BMI_{25} was associated with much higher levels of blood glucose and diabetes prevalence at baseline. After adjusting for potential confounders e.g., age, smoking, and baseline measured BMI, BMI_{25} had a strong positive log-linear association with all above-mentioned mortality outcomes, those being obese at young adulthood had a HR of 1.85 (95% CI: 1.75–1.95), 1.85 (1.71–2.00), 1.40 (1.26–1.56) and 2.34 (1.96–2.81), respectively, compared with participants having BMI_{25} of 18.5–20.0 kg/m^2. The association with cancer mortality was more pronounced in men than in women, but no such heterogeneity was observed for total, cardiovascular diseases (CVD), and respiratory mortality. To conclude, the observed strong monotonically positive associations between young adulthood BMI and various mortality outcomes, independent of BMI in later life, support the need for early and stringent body weight control to prevent early death.

1. Introduction

High body mass index (BMI), or obesity, is a well-established risk factor for a range of chronic diseases, including type 2 diabetes, cardiovascular diseases (CVD), and certain cancers, which are the main contributors to premature mortality. Many studies have reported a J-shaped or U-shaped association between BMI and mortality from all causes and several specific causes, including CVD, cancer, respiratory diseases and other diseases [1–4]. An important contributor to excess deaths in the low BMI groups is widely speculated to be preexisting chronic diseases (e.g., cancer and chronic obstructive pulmonary disease), which could lead to both low BMI and early deaths. Unfortunately, it is difficult to address this so-called reverse causality problem in observational studies conducted in midlife or later, even after excluding those with a known status of prevalent chronic diseases at the start of the study [5–7]. BMI at young adulthood has been used as an

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instrumental variable for midlife BMI to assess the non-biased association between BMI and mortality [8], as most people at this period are at their physical peaks and healthiest stage; therefore, the possibilities of having weight-related illness and illness-related weight loss are minimal.

In addition to predicting late adulthood adiposity status, BMI in early life has been suggested to have potential long-term consequences on health and mortality independent of later life adiposity, although findings have not been entirely consistent [9–13]. For instance, in the Harvard Alumni Health Study of nearly 20,000 men, BMI at college entry (mean age ~18 years) was positively associated with cancer mortality and the association was not mediated by BMI at middle life (mean age ~46 years) [13]. In a similar but smaller study of male participants in the Glasgow Alumni Cohort, BMI in early adulthood (~22 years), but at mid-adulthood (~38 years), was positively associated with all-cause and CVD mortality [14]. However, it remains unclear whether the shape and strength of associations are similar across various population subgroups (e.g., by sex, smoking status and by diabetes status), particularly for some specific causes of mortality (e.g., site-specific cancers and respiratory diseases) and in populations outside high-income Western countries (e.g., China), where a large majority of the populations at that stage had BMI within normal range. Moreover, despite a myriad of metabolic pathways that have been suggested underlying the associations of adiposity with health conditions, disease risks and mortality [15], no previous study reported the associations of young adulthood BMI with proteomic profiles assessed decades later.

To fill in the knowledge gap, we analysed data from the China Kadoorie Biobank (CKB) study, a prospective cohort study of 0.5 million Chinese adults, aged 30–79 years at baseline, to evaluate the associations of BMI at ~25 years old (BMI_{25}) with overall and cause-specific mortality, with and without taking into account BMI assessed at baseline, and to explore the associations of BMI_{25} with blood-based protein biomarkers.

2. Methods

2.1. Study population

Details of the CKB study design and survey methods have been reported previously [16]. Briefly, the baseline survey took place between June 2004 and July 2008, involving five urban and five rural regions in China, chosen based on local disease patterns, risk exposures, population stability and infrastructural capacity. All residents without known major disabilities from 100–150 pre-selected administrative units were invited to attend the study. A total of 512,715 people aged 30–79 years were enrolled in the CKB study. Ethical approval of the study was obtained from the University of Oxford (025-04 or 5109-17 in later, updated approvals), China National and Regional Center for Disease Control and Prevention (CDC) (005/2004 or 2018-1038 in later, updated approvals) and the Chinese Academy of Medical Sciences (X1303262001). The CKB complied with the *Declaration of Helsinki* and all participants provided written informed consent.

2.2. Baseline data collection

At local study assessment clinics, participants completed an interviewer-administered laptop-based questionnaire on sociodemographic characteristics, lifestyle factors, prior disease history, self-reported health status and recalled body weight at ~25 years old ($weight_{25}$, n = 82,349 with missing data). As shown in the Table S1 and Table S2 (online), those participants with missing data on $weight_{25}$ were slightly older, more prone to be women, from rural area and with a lower education level.

A range of physical measurements were recorded by trained technicians, including height, weight, lung function, and blood pressure, using calibrated instruments with standard protocols, and non-fasting blood samples were collected from participants (with reported time since last meal, i.e., fasting time, recorded) for long-term storage as well as on-site measurements of random blood glucose (RBG) [17]. BMI_{25} was calculated as kg/m^2 using $weight_{25}$ and height measured at baseline. Baseline BMI was calculated similarly using measured body weight and height at baseline.

After the completion of the baseline survey, CKB randomly selected 5%–6% of baseline participants for periodic resurveys, using procedures similar to those at baseline. The first resurvey took place from July through October 2008, with 19,788 participants resurveyed. Among those participants who provided twice $weight_{25}$ data during the baseline survey and the first resurvey (n = 14,833), the correlation coefficient of two times BMI_{25} was 0.70 (95% CI 0.69–0. 71), similar across different age groups.

2.3. Mortality follow-up

Vital status of participants and causes of death were determined periodically through registration of deaths of China Disease Surveillance Points, checked annually against local residential, medical and health insurance records and confirmed through street committee or village administrators. All deaths were coded using the International Classification of Diseases, 10th Revision (ICD-10) by trained staff who were blinded to baseline information. By 31 December 2018, only 4028 (<1%) CKB participants were lost to follow-up. Except for all-cause mortality, our main outcomes also included CVD mortality (I00–I99), cancer mortality (C00–C97), and respiratory mortality (J00–J99). Secondary outcomes included mortality from IHD (I20–I25), ischaemic stroke (I63), and intracerebral hemorrhage (ICH, I61), which were the major subtypes of CVD; and lung cancer (C33–C34), liver cancer (C22) stomach cancer (C16), esophageal cancer (C15), and colorectal cancer (C18–C20), which were the top 5 contributors of cancer mortality. In addition, mortality from traffic accidents (V01–V99) was also studied as a negative control (Table S1 online).

2.4. Proteomics assays

Details of the CKB proteomics assays have been provided previously [15,18]. Among the study population of the current analysis, 1786 had been included in the randomly selected sub-cohort of a nested case-cohort study of IHD in CKB. Stored baseline plasma samples from these participants were analysed for levels of 2939 proteins using the Olink Explore 3072 platform in Olink laboratories in Uppsala, Sweden, and in Boston, USA, and 7289 SOMAmers targeting 6597 human proteins (with 2168 proteins also included in the Olink protein list) using the SomaLogic platform in SomaLogic laboratory in Colorado, USA. A total of 9332 protein measurements, corresponding to 7164 unique proteins, were included in the analysis.

2.5. Statistics analyses

This study excluded participants with missing information on baseline measured BMI (n = 2) or recalled $weight_{25}$ (n = 82,349), leaving 430,373 participants in the analysis.

The percentages or means and standard deviations of baseline characteristics were calculated across six categories of BMI_{25} (cut-off points: 18.5, 20.0, 23.0, 25.0, 28.0 kg/m^2), standardised by sex, 5-year age group and 10 study regions. The cutoff points were chosen to cover different thresholds to define overweight and obesity and to ensure a reasonable number of participants in each group. Multiple linear regression analyses were performed to examine the associations of BMI_{25} with physical measurements collected at baseline, including systolic blood pressure (SBP), diastolic blood pressure (DBP), RBG and lung function (i.e., FEV1/FVC ratio), with adjustment for age, sex, region, education, smoking, alcohol consumption, and with or without baseline BMI (Variance Inflation Factor [VIF] between baseline BMI and BMI_{25} was 1.11, indicating no multicollinearity between them). Logistic regression analysis, adjusting for the same covariates, was conducted to examine the association of BMI_{25} with baseline prevalence of diabetes, hypertension, cancer, and chronic obstructive pulmonary disease (COPD).

Cox proportional hazards models were used to estimate hazard ratios (HRs) for all-cause and cause-specific mortality by BMI_{25} categories or per 2 kg/m^2 BMI_{25}, with follow-up duration starting from the date of baseline entry until death, lost to follow-up (<1% in total), or the global censoring date (i.e., 31st December 2018), whichever came first. All models were stratified by sex, age-at-risk (5-year groups) and study region, and adjusted for education, smoking, alcohol intake, and with/without baseline BMI in deciles. The floating absolute risk method was used to estimate standard errors of log HR for all exposure categories, including the reference category, which is the group with BMI_{25} being 18.5–20 kg/m^2 in the current study [19]. Linear trend was examined through Wald tests with the median of BMI_{25} in each group used in models. The proportional hazards assumption for each covariate was met based on Schoenfeld residuals and log-log plots.

In our hypothesis-generating analysis associating BMI_{25} with proteomic markers, multiple linear regression models were used to analyse the associations of BMI_{25}, as an independent variable, with standardized level of each plasma protein (NPX [Normalised Protein eXpression] for Olink proteins and RFU [Relative Fluorescence Units] for SomaLogic proteins) as a dependent variable, adjusting for age and age^2, sex, study area, fasting time, fasting $time^2$, ambient temperature, ambient $temperature^2$, and plate ID. Multiple testing was corrected using the Bonferroni method across 7164 unique proteins, and results were compared with the list of proteins in significant association with baseline BMI [15,18] to identify proteins potentially underlying the observed associations of BMI_{25} with mortality, independent of baseline BMI.

Sensitivities analyses were conducted to assess risks of reverse causality through (1) excluding participants with baseline self-reported IHD or stroke/TIA (n = 19,582) for CVD mortality, chronic bronchitis, emphysema or COPD (n = 29,733) for respiratory mortality, cancer (n = 2254) for cancer mortality, or any baseline-prevalent diseases (n = 49,351) for all-cause mortality; (2) excluding the first 5 years of follow-up; (3) additional adjustment for physical activity and key dietary variables (i.e., the consumption of fresh fruit and red meat). Statistical analyses and relevant plots were performed in R version 4.4.3.

3. Results

3.1. Participant characteristics

Among the 430,373 participants included in the analysis, the mean age was 51.5 (SD 10.3) years, and 57.1% were women (Table 1). Overall, 48.3% of participants resided in urban regions, and 53.9% with at least 6 years of formal education. Mean BMI_{25} was 21.9 (SD 2.5) kg/m^2, with 7.5% of participants being underweight (i.e., BMI_{25} <18.5 kg/m^2) and 1.9% being obese (i.e., BMI_{25} ≥28 kg/m^2). Participants with lower BMI_{25} were more likely to be younger at baseline, reside in urban regions, and have a higher level of socioeconomic status (i.e., longer duration of formal education & higher household income). Mean BMI measured baseline was 23.8 (SD 3.2) kg/m^2, i.e., 1.9 kg/m^2 higher than BMI_{25}, which was positively correlated with each other (r = 0.31, Fig. S1 online). However, annual weight increase was inversely correlated with BMI_{25} (r = −0.37). Comparing the top with the bottom group of BMI_{25}, baseline BMI was 5.2 kg/m^2 higher, but BMI-change was 6.9 kg/m^2 lower (Table 1). Among those participants who had BMI_{25} ≥25 kg/m^2, 57.1% were still overweight at baseline survey (on average, ~25 years later), in contrast to 31.6% among those with BMI_{25} <25 kg/m^2.

3.2. Associations of young adulthood BMI with blood pressure, random blood glucose, and lung function

BMI_{25} was clearly and positively associated with SBP, DBP, and RBG but not FEV1/FVC ratio before correcting for baseline BMI (Table 1 and Fig. 1). However, additional adjustment for baseline BMI greatly attenuated the associations with SBP and DBP, while the strong positive association with RBG remained essentially unchanged. Compared to those with the lowest BMI_{25}, participants in the highest BMI_{25} group had approximately 1.0 mmol/L higher RBG levels. Similarly, BMI_{25} was clearly and positively associated with baseline prevalence rates of diabetes, and this association was largely independent of baseline BMI. Those who were obese at ~25 years old had nearly three times higher chance to have diabetes at baseline, with an odds ratio (OR) of 2.81 (95% CI: 2.65–2.98), than those in the reference group (i.e., BMI_{25} between 18.5 and 20 kg/m^2) regardless of baseline BMI status (Fig. S2 online). On the other hand, although BMI_{25} was also positively associated with hypertension prevalence before adjusting for baseline BMI, taking into account baseline BMI largely attenuated the association to a weak U shape. In addition, BMI_{25} was not clearly associated with the prevalence rates of cancer. About COPD prevalence, although there was a mild inverse association with BMI_{25}, additional adjusting for baseline BMI twisted the association to be positively significant; those with BMI_{25} ≥28 kg/m^2 had 26% higher risk of COPD prevalence (1.26, 95% CI: 1.16–1.35) than the reference group (Fig. S2 online).

3.3. Young adulthood BMI and risk of all-cause and cause-specific mortality

During ~4 million person-years of follow-up (median 12.0 years), 36,814 deaths occurred, including 13,620 deaths from CVD, 13,394 deaths from cancers, 2929 deaths from respiratory diseases (Fig. 2), 1137 from traffic accidents and 5734 from other causes (Table S3 online). A positive and approximately log-linear association was observed of BMI_{25} with all-cause mortality and mortality from CVD, despite a slightly higher but not significant HR at the lowest end of the BMI_{25} category (Fig. 2). For total, CVD and cancer mortality, the shapes of associations were essentially unchanged with and without the adjustment for baseline BMI. Compared to this reference group, the HRs for all-cause mortality were 1.09 (1.07–1.11), 1.26 (1.23–1.29), 1.37 (1.33–1.41), and 1.85 (1.75–1.95) respectively in those with BMI_{25} levels of 20–23, 23–25, 25–28 and ≥28 kg/m^2 with baseline BMI included in the model. The corresponding HR for CVD mortality was 1.02 (1.00–1.05), 1.20 (1.16–1.25), 1.35 (1.29–1.41) and 1.85 (1.71–2.00), respectively. The association of BMI_{25} with cancer mortality was much weaker, although still significant. As compared to the reference group, being obese at ~25 years old was associated with 24% (18%–31%) and 40% (26%–56%), respectively, higher risk of cancer mortality before and after adjusting for baseline BMI. For respiratory mortality, however, additional adjusting for baseline BMI (which was inversely associated with respiratory mortality, Fig. S3 online) greatly strengthened the association with BMI_{25}, i.e., HR in the highest BMI_{25} group increased from 1.49 (1.25–1.78) to 2.34 (1.96–2.81) (Fig. 2).

The association between BMI_{25} and all-cause mortality was largely similar across age-at-risk groups. Overall, each 2 kg/m^2 increment was associated with 10% (HR 1.10; 1.08–1.10) higher mortality. However, this linear association was slightly stronger in men than in women, particularly in younger age groups (Fig. 3). This gender difference was driven mainly by cancer mortality, which was more than 3 times stronger on average in men than in women (Fig. S4 online). In those younger than 70 years old, the association of BMI_{25} with cancer mortality was 5 times stronger than that in women. However, the overall association of BMI_{25} with CVD mortality (Fig. S5 online) and respiratory mortality (Fig. S6 online) was not significantly different in men and women. Despite these statistically significant different linear associations in men and women, the dose-response relationship of BMI_{25} with all-cause mortality, CVD mortality and respiratory mortality were of similar strength and shape in men and women (Fig. 4). Contrast the highest BMI_{25} and the reference group, HRs for these mortality outcomes were 1.80 (1.66–1.95) vs. 1.87 (1.74–2.02), 1.74 (1.55–1.97) vs. 1.93 (1.73–2.15) and 2.13 (1.62–2.82) vs. 2.64 (2.08–3.35), respectively, in men and women. For cancer mortality, however, a clear dose-response relationship was only observed in men but not in women, despite the HR for the top vs the reference group being similar in men and women [1.45 (1.24–1.69) vs. 1.33 (1.15–1.54)].

The shapes of all these associations were also broadly similar in rural and urban areas (Fig. S7 online), in those with and without baseline prevalent diabetes (Fig. S8 online), and in never-regular and ever-regular smokers (Fig. S9 online). However, the strength of association of BMI_{25} with respiratory mortality was more than 2 times stronger in rural participants (HR of the obese group being 2.73 in rural areas and 1.77 in urban areas), while the strength of associations with other mortality outcomes was similar between rural and urban participants. Moreover, the associations with total, CVD and respiratory mortality were about 40% to 70% stronger among those with prevalent diabetes; and the association with respiratory disease mortality was nearly 3 times stronger in never-regular smokers, compared with the associations in their respective counterpart groups.

Among the specific CVD diseases investigated, BMI_{25} was in a strongest association with ICH mortality was the strongest (HR for top vs. reference BMI_{25} group was 1.92, 1.64–2.23), followed by IHD mortality (1.78, 1.55–2.04), and ischaemic stroke mortality (1.50, 1.17–1.93) (Fig. 5). Among the major cancer types, a higher BMI_{25} was clearly and positively associated with mortality from liver cancer (1.68, 1.30–2.18), stomach cancer (2.04, 1.55–2.67), esophageal cancer (1.53, 1.08–2.18) and colorectal cancer (1.52, 1.05–2.19), but not clearly associated with lung cancer mortality.

Stratified analyses by other socio-demographic and lifestyle factors found significant heterogeneity or trend across various strata (Figs. S10–S13 online), but qualitatively, most of the associations were consistent among subgroups of participants except for the associations with cancer mortality and respiratory mortality, which became non-significant among those who were overweight or obese at baseline. Sensitivity analyses, including the exclusion of those participants with baseline prevalent chronic diseases and the first five years of follow-up and the additional adjustment for physical activity and dietary variables, did not essentially change the results (Figs. S14–S16 online). BMI_{25} was not in a clear association with risk of death due to traffic accidents, which served as a negative control in our analysis (Fig. S17 online).

3.4. Associations of young adulthood BMI and proteins

A total of 27 proteins were significantly associated with BMI_{25}, among them 10 were not significantly associated with baseline BMI (Fig. S18, Table S4 online), including SEMA7A (Semaphorin 7A), SEMA5A, CD163 (Cluster of differentiation 163), SIGLEC1 (Sialoadhesin, or CD169), CD79B, CSF1R (Colony-stimulating factor 1 receptor), CRTAM (Class-I restricted T cell-associated molecule), TIMD4 (T-cell membrane protein 4) and two members of TAM family of receptor tyrosine kinases, AXL and TRYO3. In addition, another 6 proteins were significantly associated with both BMI_{25} and baseline BMI, but in opposite directions, including GAL (Galanin) and RBP (Retinol binding protein), which were inversely associated with BMI_{25} but positively associated with baseline BMI, and VCAM1 (Vascular cell adhesion molecule 1), CD48, LIFR (Leukemia inhibitory factor receptor), and GAS6 (Growth arrest-specific 6), which were positively associated with BMI_{25} but inversely association baseline BMI.

4. Discussion

In this large prospective study among Chinese adults, young adulthood BMI was positively associated with all-cause mortality, as well as mortalities from CVD, cancer and respiratory diseases, independent of baseline BMI. The strength of associations was much stronger than previously reported in the literature, and the shapes of associations were largely log-linear, with no significant excess of mortality at the lowest end of BMI_{25}. Comparing with participants with BMI_{25} between 18.5 and 20 kg/m^2, those who had $BMI_{25} \geq 28$ kg/m^2 had 85% (75%–95%) higher all-cause mortality, 84% (71%–200%) higher CVD mortality, 40% (26%–56%) higher cancer mortality and 134% (96%–181%) respiratory disease mortality. Each 2 kg/m^2 higher BMI_{25} was associated with HRs of 10% higher risk of all-cause and CVD mortality, 6% higher cancer mortality, and 13% higher respiratory mortality. Most of these associations were of similar strength in both genders, except for the much weaker association between BMI_{25} and cancer mortality in women than in men, due at least partially to the inverse association between BMI_{25} and breast cancer mortality. In addition, the associations of BMI_{25} with total, CVD and respiratory mortality were much stronger among people with prevalent diabetes at baseline.

It is well-known that early life adiposity could track or persist to adulthood and is a strong predictor of metabolic health in later life [20]. However, previous evidence was equivocal on the extent to which obesity at later ages could explain the health impacts of early life adiposity. In our study, we found that BMI_{25} exhibited a strong positive association with diabetes but not hypertension, after accounting for baseline BMI. This was in line with the results from a previous meta-analysis of 6 studies involving over 128,000 adults from the US, Europe, Australia and China, which demonstrated that people who had excess weight in childhood but were normal weight in adulthood had a significantly higher risk of diabetes but not hypertension [20]. Similarly, in a prospective cohort study of over 1100 white adult men in the US, the risk of hypertension was not increased in those participants who were overweight or obese at 25 years but returned to normal weight at age 45 years [21]. In a pooled analysis of data from 6 US prospective cohorts involving more than 30,000 participants, young adulthood BMI was also significantly and positively associated with diabetes risk after controlling for later life BMI [22]. Such residual impact of young adulthood BMI on diabetes after accounting for midlife BMI suggests a need to prevent the onset of obesity across the life course to lower the risk of developing diabetes [23]. Furthermore, the observed interaction between BMI_{25} and baseline prevalence of diabetes, similar to that previously reported in a study with data

Table 1
Baseline characteristics of participants by young adulthood BMI (BMI$_{25}$) categories

Characteristics	BMI$_{25}$, kg/m^2						All (*n* = 430,373)
	<18.5 (*n* = 32,260)	18.5 to <20 (*n* = 66,002)	20 to <23 (*n* = 199,815)	23 to <25 (*n* = 83,096)	25 to <28 (*n* = 40,959)	$\geq$28 (*n* = 8241)	
BMI$_{25}$, kg/m^2 (SD)	17.6 (1.1)	19.3 (0.4)	21.5 (0.8)	23.9 (0.6)	26.1 (0.9)	29.6 (2.1)	21.9 (2.5)
Young adulthood weight, kg (SD)	45.7 (4.7)	49.9 (3.7)	54.7 (4.1)	60.1 (4.4)	65.2 (5.6)	73.7 (8.5)	55.7 (6.9)
Age and socioeconomic factors							
Age, years (SD)	50.7 (11.7)	49.8 (10.3)	50.9 (10.1)	52.8 (10.4)	54.6 (11.0)	56.1 (12.0)	51.5 (10.3)
Female, %	70.1	59.6	52.2	57.0	65.3	61.7	57.1
Urban, %	55.9	53.2	47.9	44.7	44.8	47.3	48.3
$\geq$6 years of education, %	57.1	57.0	54.5	51.9	49.1	47.3	53.9
Household income >20 000 yuan per year, %	48.8	49.7	47.7	46.0	44.8	43.4	47.5
Lifestyle factors							
Male ever-regular smoker, %	72.5	72.8	74.2	74.9	75.8	73.9	74.3
Female ever-regular smoker, %	3.3	2.8	2.8	3.1	3.7	4.5	3.1
Male ever-regular alcohol drinker, %	36.9	37.4	38.2	39.0	40.1	39.1	38.4
Female ever-regular alcohol drinker, %	3.1	2.7	2.5	2.5	2.6	3.5	2.6
Physical activity, MET h/day (SD)	20.2 (14.1)	20.6 (12.4)	21.1 (11.6)	21.6 (12.4)	21.5 (13.9)	20.8 (15.8)	21.1 (11.8)
Physical measurements, mean (SD)							
Baseline BMI, kg/m^2	22.1 (3.5)	22.7 (3.1)	23.6 (3.0)	24.7 (3.1)	25.7 (3.5)	27.3 (4.4)	23.8 (3.2)
Difference between baseline and young adulthood BMI, kg/m^2	4.6 (3.7)	3.4 (3.1)	2.1 (3.1)	0.8 (3.2)	-0.4 (3.5)	-2.3 (4.5)	1.9 (3.4)
Systolic blood pressure, mmHg	128.7 (21.9)	129.4 (20.0)	130.2 (19.3)	131.4 (19.6)	133.0 (21.5)	136.4 (25.2)	130.4 (19.1)
Diastolic blood pressure, mmHg	77.1 (12.2)	77.3 (11.1)	77.6 (10.7)	78.2 (11.2)	79.0 (12.4)	80.7 (14.3)	77.8 (10.7)
Random blood glucose, mmol/L	6.0 (2.3)	6.0 (2.2)	6.0 (2.2)	6.1 (2.3)	6.3 (3.0)	7.2 (4.9)	6.0 (2.2)
FEV1/FVC ratio x 100	84.3 (8.8)	84.5 (7.9)	84.6 (7.4)	84.7 (7.6)	84.8 (7.6)	84.7 (8.5)	84.6 (7.3)
Medical history and health status, %							
Self-reported CVD[*]	4.6	4.4	4.3	4.7	5.2	6.7	4.6
Self-reported hypertension	10.9	11.0	11.2	12.0	13.9	19.0	11.6
Self-reported diabetes	2.7	2.6	2.7	3.5	5.2	11.8	3.2
Baseline prevalent diabetes[**]	5.2	5.1	5.3	6.3	8.9	17.8	6.0
Self-reported cancer	0.5	0.5	0.5	0.5	0.6	0.5	0.5
Baseline prevalent COPD[†]	7.6	7.1	6.9	6.9	6.5	7.3	6.9
Self-reported poor health status	10.6	9.8	9.5	10.3	11.6	15.5	10.1

BMI: Body Mass Index; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; MET: metabolic equivalent of tasks; SD: standard deviation.

Values were standardized to age, sex and region structure of the study population.

[*] Defined as self-reported physician-diagnosed coronary heart disease, stroke or TIA.

[**] Including self-reported physician-diagnosed diabetes, fasting blood glucose level $\geq$7.0 mmol/L or non-fasting blood glucose level $\geq$11.1 mmol/L.

[†] Including self-reported physician-diagnosed COPD or those with FEV1/FVC <0.7.

from US nurses and health professionals [24], indicates the importance of diabetes prevention alongside body weight control.

Our findings on all-cause and CVD mortality were in broad agreement with results from several previous studies suggesting that excess weight at a young age has an independent (i.e., regardless of obesity status in later life) detrimental role on later-life mortality [9,14,25]. For instance, in the PROCAS study of nearly 60,000 British women, it was found that being overweight and obese at 20 years had a ~30% higher or more than doubled risk of premature all-cause mortality compared with a healthy weight, after adjustment for BMI in later adulthood [26]. In another analysis involving nearly 80,000 men and women in the Southern Community Cohort study (SCCS) in the US, being overweight at around 21 years was associated with 29% higher risk of premature death and being obese was associated with 91% higher mortality risk than their normal-weighted counterparts, regardless of middle adulthood BMI status [9]. More importantly, the small and non-significant excess of morality at the lowest end of young adulthood BMI observed in our study and PROCAS, SCCS corroborated the previous notion that reverse causality should be the main cause of the J- or U-shaped association between late adulthood adiposity and mortality [1]. In addition, our results indicate that young adulthood BMI between 18.5 and 20 kg/m^2 was associated with the lowest all-cause and cause-specific mortality, replicating what has been found in SCCS as well as several other studies [27]. This suggests that the optimal BMI lies towards the lower end of the recommended normal range of BMI, and entering adulthood with a lower but healthy BMI would help in preventing early deaths from major chronic diseases in later life.

Young adulthood obesity has been related to cancer mortality in some but not all previous studies [9,11–13,28]. For instance, the association between BMI$_{21}$ and cancer mortality in SCCS was not statistically significant, which might be caused by a low statistical power due to a relatively smaller number of cancer deaths involved (*n* = 1721) [9], as compared to what we have in our current study (i.e., >13,000 deaths). However, previous evidence is limited about whether early life adiposity is related to a higher cancer mortality independently of later life BMI; therefore, the strength of associations observed in the current study could not be directly compared with the literature. In the Harvard Alumni Health Study cohort, early adulthood BMI of male students was positively associated with mortality of total cancer as well as lung cancer and oesophagus cancer, independent of BMI in middle age [13], but the association between BMI$_{25}$ and lung cancer mortality in our current study was not significant. Interestingly, in the current study, BMI$_{25}$ had a much weaker (despite still significant) association with cancer mortality than with CVD and respiratory mortalities, particularly in women. This might be partially related to the potentially protective role of early life obesity in preventing breast cancer [29–32], which could compensate for the potential detrimental impact of adiposity on other types of cancers. In our data, only a small number of deaths were caused by breast cancer, but still, a clearly significant inverse association was observed. Exact pathways (either biological or social/environmental) through

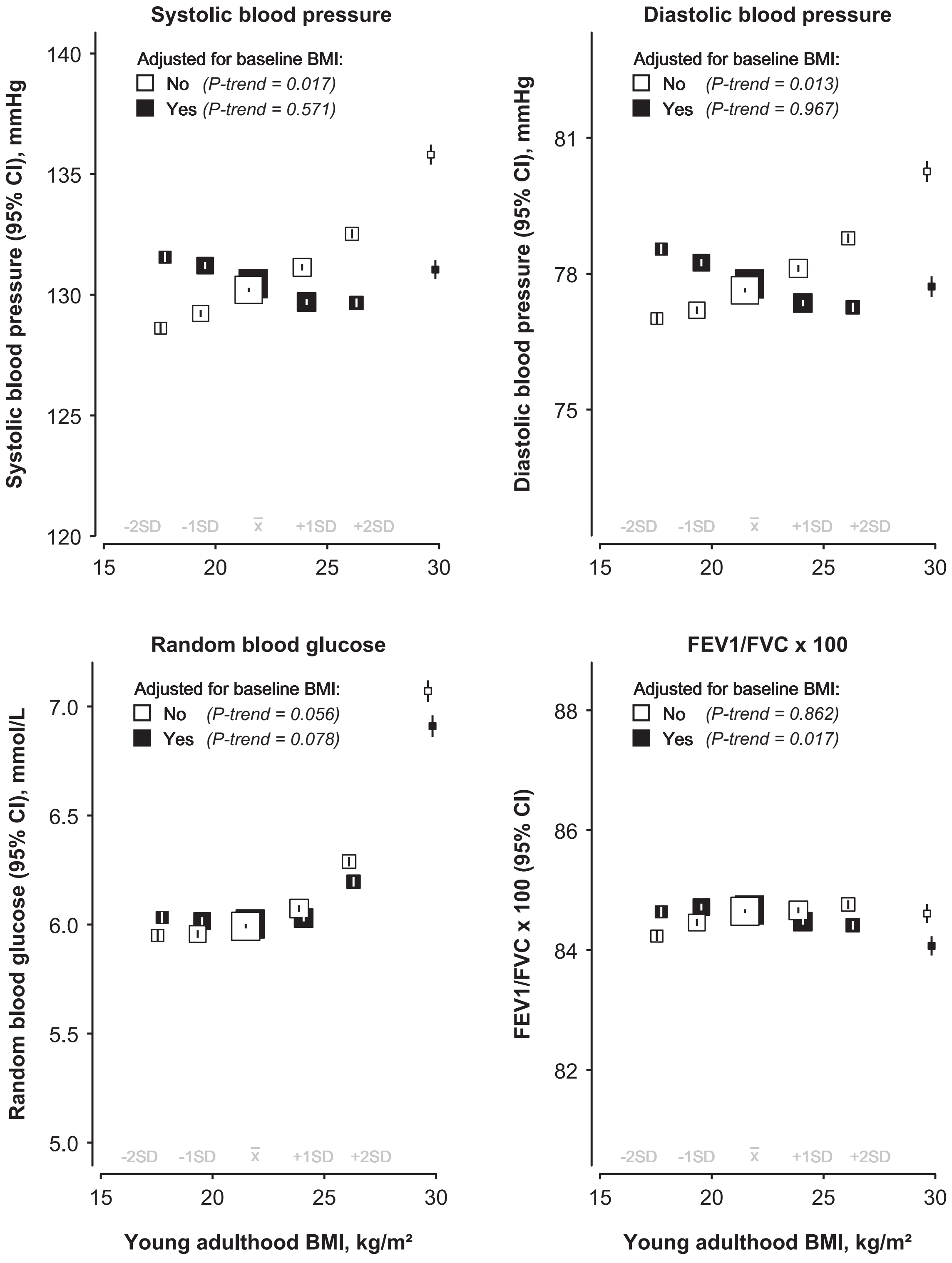
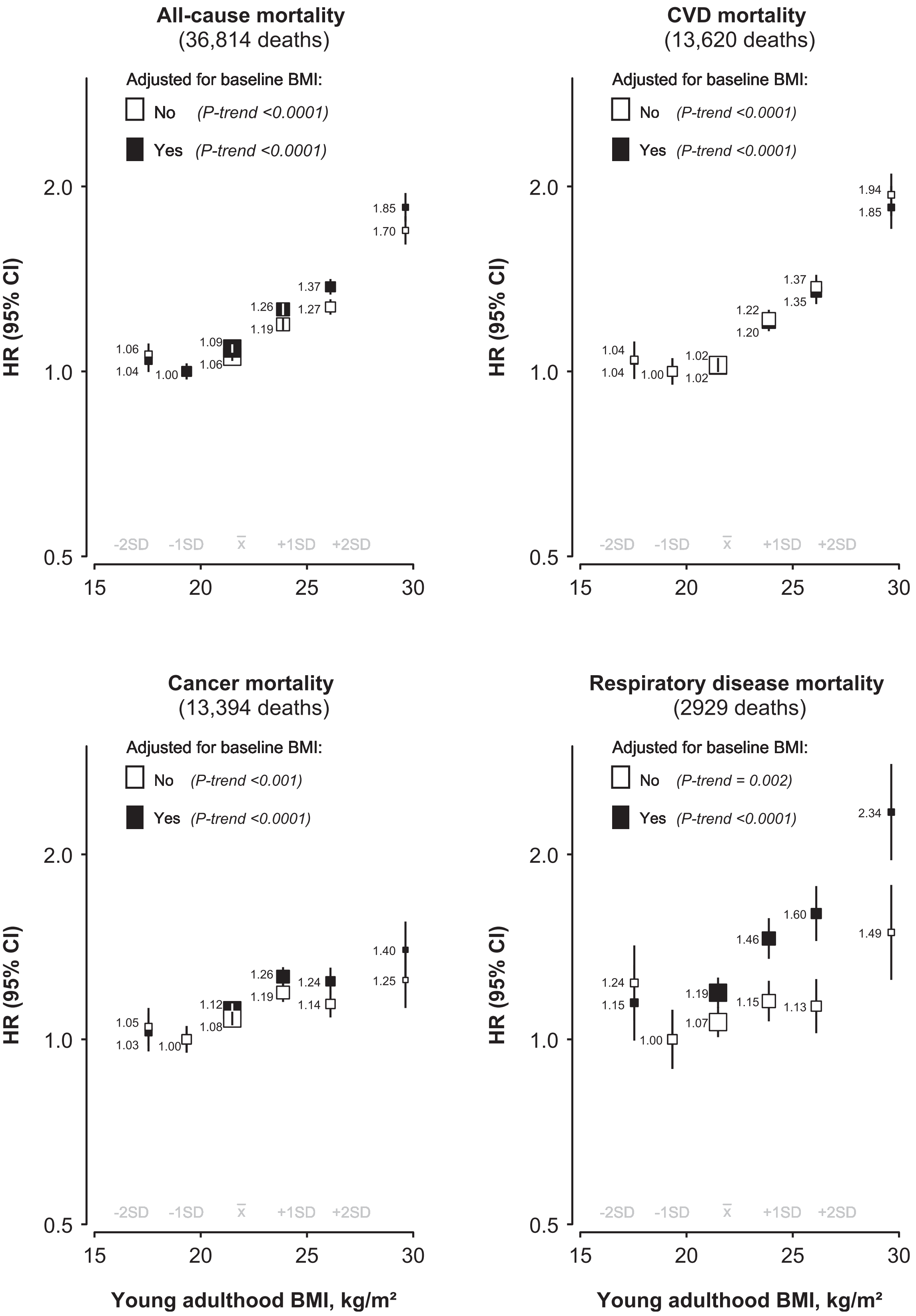


Fig. 1. Association of young adulthood BMI (BMI_{25}) with blood pressure, random blood glucose, and lung function. Mean values were adjusted for age (5-year groups), sex, study area, education, smoking and alcohol consumption. Each solid or open square represents the mean value. The vertical lines indicate 95% CIs. *P*-trend reflects the trend test at $BMI_{25} \geq 20$ kg/m^2. BMI: body mass index, CI: confidence interval, FEV1/FVC: forced expiratory volume in one second to forced vital capacity ratio.

which young adulthood BMI is positively associated with risks of digestive cancers but inversely associated with breast cancer risk deserve exploration. Such knowledge would provide valuable information for cancer aetiology and prevention.

Mortality of respiratory diseases has been less studied for its association with early life BMI. In a large-scale follow-up study of 230,000 Norwegian adolescents, significantly higher respiratory mortality was observed among those with either lower or higher BMI measured at ages 14–19 years [33]. This U-shaped association was different from the significant linear positive association of BMI_{25} with respiratory death observed in our current study, and the difference might be related to the confounding effect of smoking in their analyses. Previous findings from studies utilising robust methodologies to appropriately control for the confounding of



All-cause mortality (36,814 deaths)

CVD mortality (13,620 deaths)

Cancer mortality (13,394 deaths)

Respiratory disease mortality (2929 deaths)

Fig. 2. Adjusted HRs for all-cause, CVD, cancer, and respiratory disease mortality by young adulthood BMI (BMI_{25}). The adjusted HRs (95% CIs) were stratified by age-at-risk (5-year groups) and study area, and adjusted for education, smoking, alcohol consumption, and baseline BMI (deciles), with those participants having BMI_{25} between 18.5–20 kg/m^2 as reference. Squares represent the HRs with area inversely proportional to the variance of the log HRs, and error bars indicate their 95% CIs. HRs are plotted against mean BMI_{25} in each category. *P*-trend reflects the trend test at BMI_{25} ≥20 kg/m^2. BMI: body mass index, CI: confidence interval, CVD: cardiovascular disease, HR: hazard ratio.

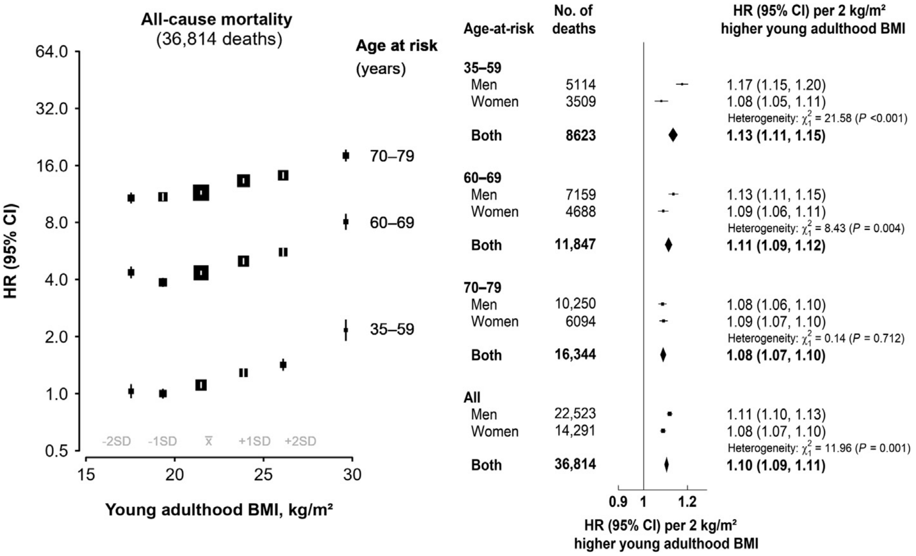
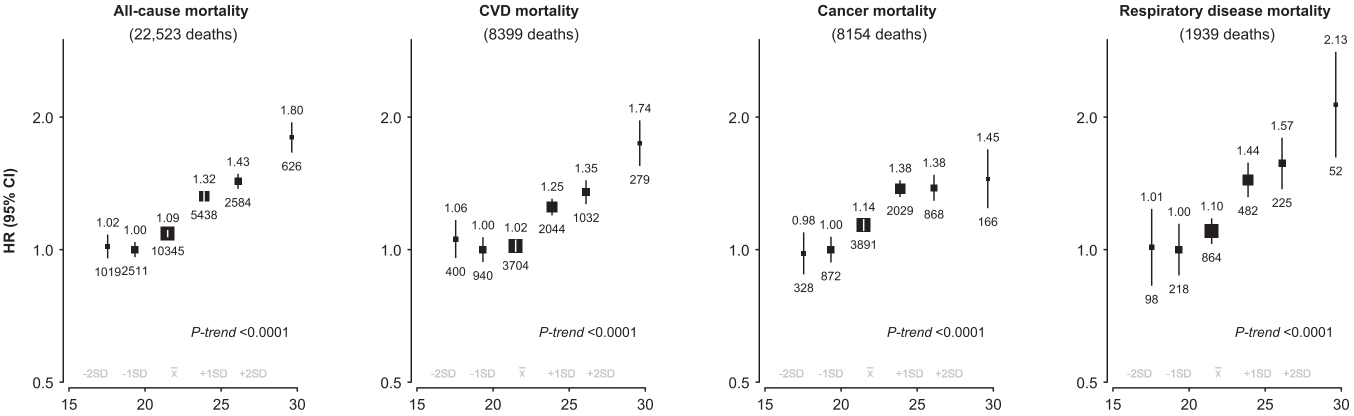


Fig. 3. Adjusted HRs for all-cause mortality by young adulthood BMI (BMI_{25}), stratified by age at risk and sex. The left panel shows the adjusted HRs for all-cause mortality by BMI_{25}, across different age-at-risk groups. Analysis was stratified by sex and study area, and adjusted for education, smoking, alcohol consumption and baseline BMI (deciles). The group with age-at-risk being 35–59 years and BMI_{25} of 18.5–20 kg/m^2 was used as the reference. HRs are plotted against mean BMI_{25} in each category. Squares represent the HRs with area inversely proportional to the variance of the log HRs, and error bars indicate their 95% CIs. The right panel shows HRs for all-cause mortality per 2 kg/m^2 higher BMI_{25}, by age-at-risk and sex. BMI: body mass index; CI: confidence interval; HR: hazard ratio.

(a) Male



(b) Female

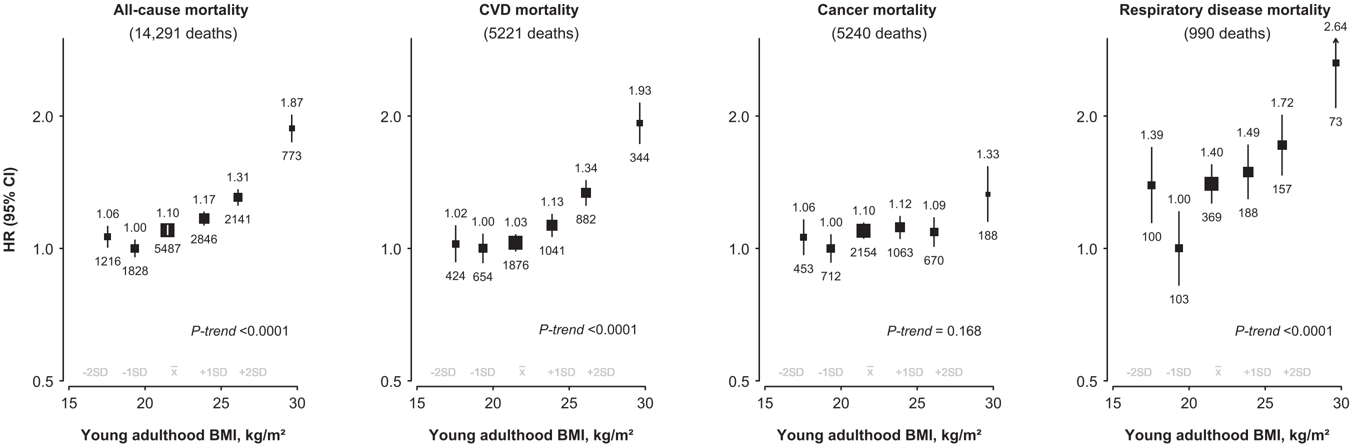


Fig. 4. Adjusted HRs for all-cause, CVD, cancer, and respiratory disease mortality by young adulthood BMI (BMI_{25}), by sex. The adjusted HRs (95% CIs) were stratified by age-at-risk (5-year groups) and study area, and adjusted for education, smoking, alcohol consumption, and baseline BMI (deciles), with those participants having BMI_{25} between 18.5–20 kg/m^2 as reference. Squares represent the HRs with area inversely proportional to the variance of the log HRs, and error bars indicate their 95% CIs. HRs are plotted against sex-specific mean BMI_{25} in each category. *P*-trend reflects trend test at BMI_{25} ≥20 kg/m^2. BMI: body mass index, CI: confidence interval, CVD: cardiovascular disease, HR: hazard ratio.

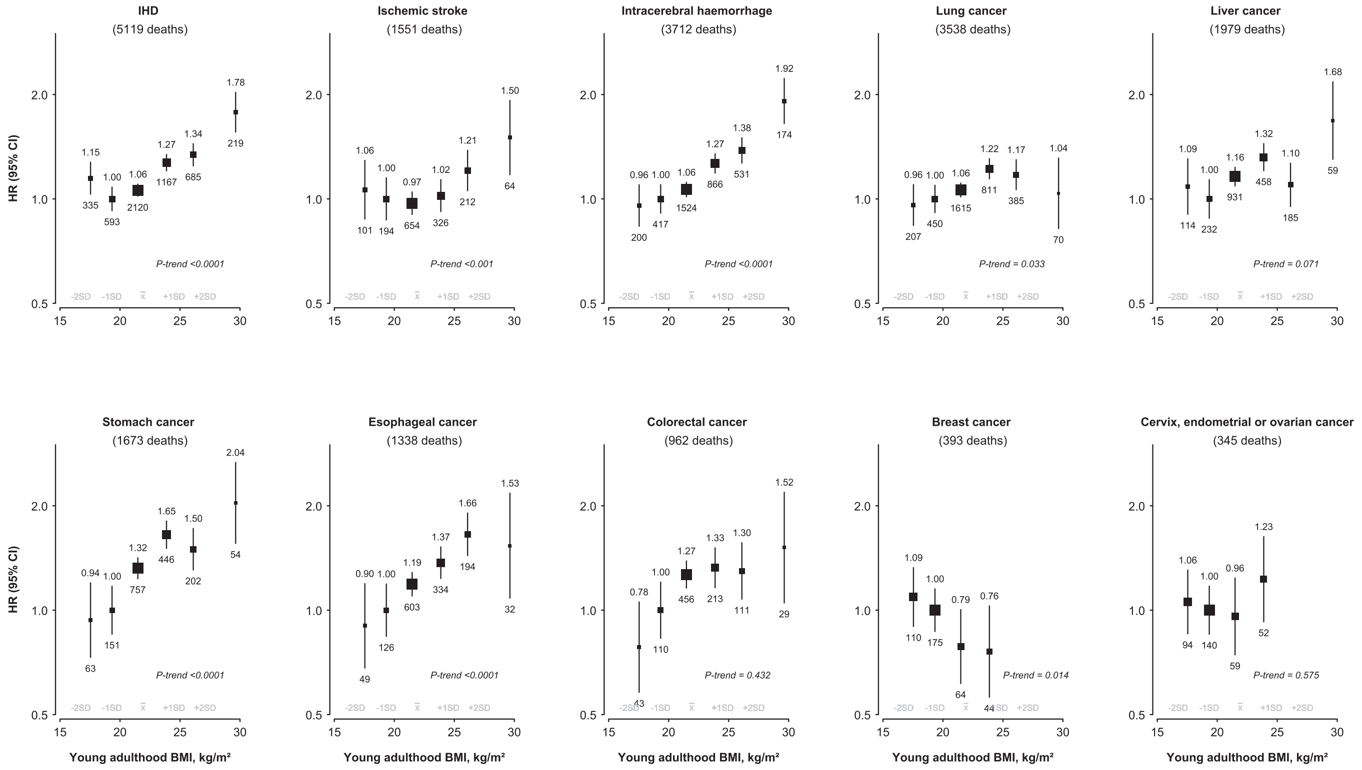


Fig. 5. Adjusted HRs for mortality from specific types of CVD and cancer by young adulthood BMI (BMI_{25}). The adjusted HRs (95% CIs) were stratified by age-at-risk (5-year groups) and study area, and adjusted for education, smoking, alcohol consumption, and baseline BMI (deciles), with those participants having BMI_{25} between 18.5–20 kg/m^2 as reference. Squares represent the HRs with area inversely proportional to the variance of the log HRs, and error bars indicate their 95% CIs. *P*-trend reflects the trend test at $\text{BMI}_{25} \geq 20$ kg/m^2, except for breast cancer and cervix, endometrial or ovarian cancers, where the full BMI range was used. BMI: body mass index, CI: confidence interval, CVD: cardiovascular disease, HR: hazard ratio, IHD: Ischaemic heart disease.

cigarette smoking support a positive association of BMI with respiratory disease risk. For instance, in a large intergenerational study by Smith et al. [7], which used offspring BMI as an instrument to assess the association of BMI with mortality in over 1 million Swedish participants, low BMI was not associated with a higher risk of respiratory diseases. In another Mendelian randomisation analysis of data from the UK Biobank and the FinnGen Biobank, it was found that obesity increases the risks of 20 out of 35 respiratory diseases [34]. Both mechanical and inflammatory mechanisms may contribute to the direct link between BMI and respiratory mortality [35,36], although the exact underlying mechanisms remain to be revealed.

No previous studies have reported associations between young adulthood adiposity and blood levels of proteins measured decades later. We identified 16 proteins as potential mediators linking BMI_{25} with mortality (independent of baseline BMI), of which 13 (except for CSF1R, TRYO3 and SEMA5A) have been associated with all-cause mortality in a separate analysis of CKB data [37], although their exact functions are largely unconfirmed. Existing literature tends to suggest that these proteins could regulate inflammation and immune homeostasis. For instance, SEMA7A has been found to have diverse roles in various physiological and pathological processes and has been recognised as having potential as both a diagnostic biomarker and a therapeutic target in neurodegenerative, autoimmune and cardiovascular diseases [38]. Likewise, AXL has multifaceted roles in regulating apoptosis, inflammation, oxidative stress, and vascular remodelling. Emerging pre-clinical evidence suggests that higher levels of circulating AXL and its ligand GAS6 could predict all-cause and cardiovascular mortality [39].

The strengths of our study included a large sample size, a prospective study design, and the high quality of outcome assessment. Although observed associations could not be interpreted as a causal relationship, as BMI_{25} is less likely to be influenced by pre-existing medical conditions, its associations with mortality are less likely to be biased by reverse causality. The monotonically positive associations found in our analyses are consistent with previous CKB reports from Mendelian Randomisation analysis [40], suggesting the U-shaped associations between mid-life BMI and mortality reported in the literature should be largely due to reverse causality bias by weight loss caused by illness and poor medical conditions.

This study has limitations, too. Firstly, we used recalled body weight_{25} and height measured at baseline to calculate BMI_{25}. It is well-known that human height may shrink with ageing. In our participants, baseline measured height was about 4 cm different between those younger than 40 years old and those older than 70 years old (Fig. S19 online). Therefore, using baseline height may lead to lower values of BMI_{25}, particularly among older age groups. Given the highly probable positive association between age and mortality, participant misclassification caused by using baseline height should have under-estimated the observed positive associations of BMI with mortality. Furthermore, we have tried to estimate height_{25} according to the height change rates by age and sex (Fig. S19 online) and used it to derive a new BMI_{25}, but the main results were not essentially altered. Secondly, information on participants' lifestyle factors when they were 25 years old was not available; therefore, the analyses were only adjusted for baseline status of smoking and alcohol consumption, which usually start at a young age and are highly addictive, but no other lifestyle factors (e.g., diet and physical activity). This could have increased the possibility of residual confounding, which is inevitable in observational studies. Thirdly, our cohort study might have recruited disproportionately fewer people who had been obese at young adulthood and survived to middle age or later, leading to potential survival bias, which can distort the association between

BMI_{25} and mortality. Finally, given the scope of the current observational study, we did not undertake genetic analyses and further functional analyses of proteins to clarify the causality and exact pathways underlying the observed associations.

In summary, our study provides further evidence that excess body fatness during young adulthood may increase the risks of death in later life, independent of later life BMI. The shapes of these associations were largely linear, and being obese at around 25 years old was associated with nearly doubled risk of early death from all-cause, CVD, cancer and respiratory diseases. These findings suggest that previously reported J-shaped or U-shaped associations between adult BMI and mortality should be mainly attributed to reverse causality, and population-based intervention strategies should be deployed early to control premature death.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Author contributions

Lei Fan, Andri Iona, and Huaidong Du have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Lei Fan, Andri Iona, Shixian Feng, Gang Zhou, Huarong Sun, Pang Yao, Canqing Yu, Yiping Chen, Dianjianyi Sun, Pei Pei, Ling Yang, Mingshu Yan, Xiaoming Yang, Jun Lv, Junshi Chen, Liming Li, Zhengming Chen, Huaidong Du were involved in the acquisition, analysis, or interpretation of data. Lei Fan, Andri Iona, and Huaidong Du drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. . Lei Fan and Andri Iona performed the statistical analysis. Liming Li and Zhengming Chen obtained funding. Shixian Feng, Gang Zhou, Huarong Sun, Canqing Yu, Yiping Chen, Dianjianyi Sun, Pei Pei, Ling Yang, Xiaoming Yang, Jun Lv, Junshi Chen, Liming Li, Zhengming Chen, and Huaidong Du provided the administrative, technical, or material support. Huaidong Du and Zhengming Chen supervised the study.

Appendix B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scib.2026.02.036.

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