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Adiposity change and mortality in middle-aged to older Chinese: an 8-year follow-up of the Guangzhou Biobank Cohort Study

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ABSTRACT

Objective To examine the associations of change in body mass index (BMI) and waist circumference (WC) over an average of 4 years with subsequent mortality risk in middle-aged to older Chinese.

Design Prospective cohort study based on the Guangzhou Biobank Cohort Study.

Setting Community-based sample.

Participants 17 773 participants (12 956 women and 4817 men) aged 50+ years.

Primary and secondary outcome measures Primary outcome measure was all-cause mortality. Secondary outcome measures were cardiovascular disease (CVD) and cancer mortality. Causes of death were obtained via record linkage, and coded according to the International Classification of Diseases (tenth revision).

Results 1424 deaths (53.4% women) occurred in the 17 773 participants (mean age 61.2, SD 6.8 years) during an average follow-up of 7.8 (SD=1.5) years, and 97.7% of participants did not have an intention of weight loss . Compared with participants with stable BMI, participants with BMI loss (>5%), but not gain, had a higher risk of all-cause mortality (HR=1.49, 95% CI 1.31 to 1.71), which was greatest in those who were underweight (HR=2.45, 95% CI 1.31 to 4.59). Similar patterns were found for WC. In contrast, for participants with a BMI of ≥27.5 kg/m^2, BMI gain, versus stable BMI, was associated with 89% higher risk of all-cause mortality (HR=1.89, 95% CI 1.25 to 2.88), 72% higher risk of CVD mortality (HR=1.72, 95% CI 0.80 to 3.72) and 2.27-fold risk of cancer mortality (HR=2.27, 95% CI 1.26 to 4.10).

Conclusion In older people, unintentional BMI/WC loss, especially in those who were underweight was associated with higher mortality risk. However, BMI gain in those with obesity showed excess risks of all-cause and cancer mortality, but not CVD mortality. Frequent monitoring of changes in body size can be used as an early warning for timely clinical investigations and interventions and is important to inform appropriate health management in older Chinese.

Strengths and limitations of this study

- ► This is a large population-based longitudinal study incorporating adiposity assessed at two time points and comprehensive measurements of potential confounders.
- ► The relatively short follow-up period might lead to insufficient number of deaths and thus a null association.
- ► Due to the lack of sufficient data on intentional weight loss, the association of intentional weight loss and mortality in our study could not be examined.
- ► Due to the observational nature of the study, biases from survival effects and residual confounding could not be ruled out, and hence the observed associations should not be interpreted causally.
- ► Generalisability to younger populations might be limited because all participants were older Chinese.

INTRODUCTION

Obesity is a rapidly expanding public health problem worldwide. The prevalence of overweight and obesity has been increasing sharply in most countries over the past few decades.[1] A four stages of obesity epidemic model proposed that in most countries obesity is in the early stages (stages 1 and 2) with increasing prevalence.[2] China is now in stage 1, with a relatively low (<10%) prevalence of obesity, and the morbidity and mortality outcomes attributed to obesity are not yet evident.[2] Previous studies have shown that individuals with obesity at baseline had higher risks of mortality during follow-up.[3 4] However, the relative mortality risk associated with obesity at baseline only might be biassed because body weight might have changed before baseline and/or during follow-up. Such issues had been highlighted by the controversy on whether overweight was protective or harmful in terms of its association with all-cause mortality.[3 4] Assessment of weight fluctuation at multiple time points might partly clarify these problems. Two recent systematic reviews of prospective cohort studies with data at two time points showed that both weight loss and

weight gain from baseline were associated with higher risks of all-cause mortality.[5 6] Most of the studies included in these two reviews were from high-income countries in Europe and North America, and only five studies were from Asia published before 2015.[7–11] Meanwhile, due to the lack of information on lifestyle, health and weight loss intention, residual confounding might be substantial, and reverse causality might counteract or overwhelm the associations of weight changes with mortality risk.[12] Moreover, baseline obesity might have modified the associations of subsequent adiposity change with the risks of mortality,[13 14] highlighting the importance of stratifying by baseline obesity status.

Rapid economic growth is often followed by increasing adiposity which is compounded by the ageing of the population. The prevalence of obesity in China has been increasing since the open-door policy in 1978. However, we found only two cohort studies from China examining the mortality risk due to adiposity changes. Both cohorts were small (n=1696 or 2090), and body mass index (BMI) changes during the early economic development (1976–1994 or 1992–2000) could not represent adiposity changes over recent years,[10 15] as the prevalence of overweight and obesity has been increasing dramatically together with ageing in China since 2000.[16] Moreover, using BMI alone could not distinguish body fat distribution and may lead to misclassification of adiposity.

Hence, in the present study, we used data from the Guangzhou Biobank Cohort Study (GBCS) to examine the associations of BMI and waist circumference (WC) change over an average of 4 years with subsequent mortality risk. We hypothesised that in older people, BMI/WC loss would be associated with higher risks of mortality, while BMI/WC gain, indicating real adiposity increase, in the obese group would be associated with higher mortality risks.

METHODS

Study subjects

At baseline of GBCS, 30 430 participants aged 50 years or above were recruited from 2003 to 2008. All surviving participants were invited for a repeated physical examination from March 2008 to December 2012 (ie, the first follow-up). Details of baseline examination and some results from the first follow-up examination have been reported previously.[17–20] Briefly, the GBCS is a three-way collaboration among the Guangzhou 12th Hospital and the Universities of Hong Kong and Birmingham. Participants were recruited from 'The Guangzhou Health and Happiness Association for the Respectable Elders' (GHHARE), a community social and welfare organisation. GHHARE is unofficially aligned with the municipal government. Membership is open to permanent Guangzhou residents aged 50 years or above for a nominal fee of ¥4 (~50 US cents) per month. GHHARE includes about 7% of Guangzhou residents in this age group, and has branches in all 10 districts of Guangzhou. The baseline and the first follow-up examinations included a face-to-face interview by trained nurses using a computer-assisted standardised questionnaire that included demographic characteristics, lifestyle factors, family and personal medical history, and assessment of height, weight, WC, blood pressure, fasting plasma glucose and lipids, and inflammatory markers. Weight loss intention was ascertained by the question 'have you tried to reduce your weight in the past 12 months?'. The first follow-up examinations did not include height. We assumed that the height of participants did not change within the past few years. All participants gave written, informed consent before participation.

Patient and public involvement

No patients or public were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Measures of adiposity change

Anthropometric measurements were performed by trained nurses using standard protocols in the morning before breakfast, including weight, standing height and WC, with light clothing and no shoes. WC was measured horizontally around the smallest circumference between the ribs and iliac crest, or at the navel, if no natural waistline was present. BMI was calculated as weight divided by height squared (kg/m^2). As the body build varies by ethnicity, we used the Chinese-specific cut-offs recommended by the WHO. Underweight was defined as BMI lower than 18.5 kg/m^2, normal weight as BMI 18.5–24.9 kg/m^2, overweight as BMI 25.0–27.4 kg/m^2 and obesity as BMI ≥27.5 kg/m^2.[21] Central adiposity was defined as WC ≥90 cm in men and ≥80 cm in women.[22]

BMIs measured at baseline (BMI_1) and at the first follow-up examination (BMI_2) were used to calculate the proportional change for each individual: $\Delta BMI=((BMI_2-BMI_1)/BMI_1)*100\%$. As definitions of substantial weight change ranged from 3% to 5% in previous studies (for example, a stable weight was defined as weight changes within ±3% by Lee *et al*[23] and within ±5% by Pan *et al*[24] and Dahl *et al*[25]), we chose a relatively conservative definition (ie, 5% as the cut-off) for BMI change. Participants were classified into three groups based on their proportional BMI change: BMI loss (ΔBMI <–5%), BMI stable (–5%to 5%), and BMI gain (ΔBMI >5%). The same classification method was used for WC change.[11]

Mortality

Information on underlying causes of deaths up to December 2017 was mostly obtained via record linkage with the Death Registry Department of the Guangzhou Centre for Disease Control and Prevention. The methods have been described in detail elsewhere.[26 27] Briefly, causes of death were coded according to the International Classification of Diseases (tenth revision) by trained medical staff in each hospital. In addition, verbal

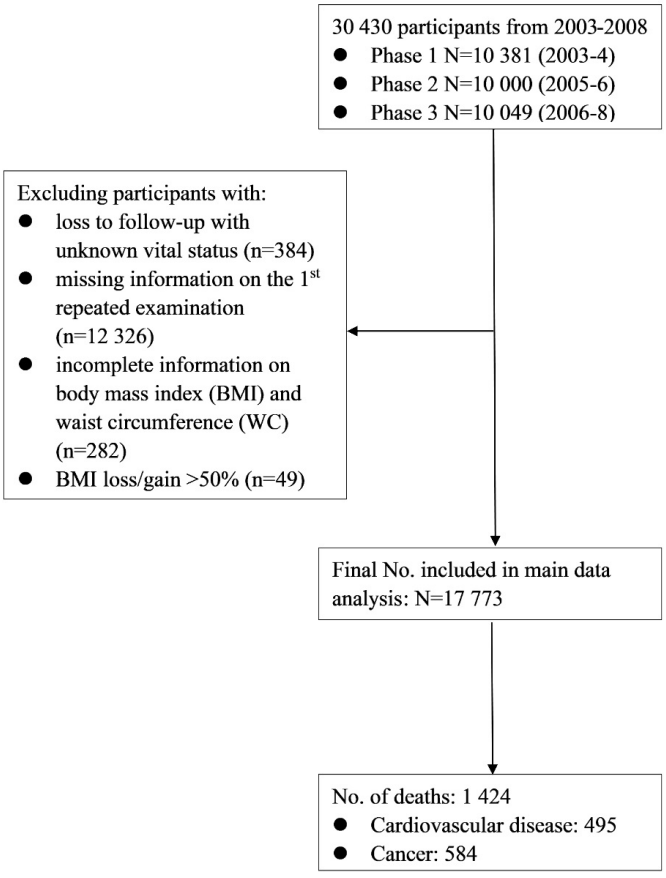

Figure 1 Flow diagram.

autopsy meetings were conducted in the Guangzhou 12th Hospital to further clarify the deaths with unclear causes. In the present study, we analysed all-cause mortality, and mortality due to all cardiovascular diseases (CVDs) and all cancers.

Statistical analysis

The Pearson χ^2 tests and one-way analysis of variance were used to compare baseline characteristics of groups according to BMI/WC change. Cox regression was used to analyse associations of mortality with BMI/WC change, giving crude and adjusted HRs and 95% CIs. Potential confounders included sex, age (continuous), education (primary, middle school and college), occupation (manual, non-manual and others), personal income (<¥10 000/year, ¥10 000–15 000/year, ≥¥15 000/year and not known, US$1 ≈ ¥8), physical activity assessed by International Physical Activity Questionnaire (inactive, moderate and active),[28] alcohol drinking (never, former and current drinkers), smoking (never, former and current smokers) and self-rated health (very good, good, poor and very poor). The study period used in the calculation of person years started from the first follow-up examination. To alleviate the effect of the time interval between the two examinations, we conducted subgroup analysis by time interval between the baseline and follow-up measurements (<4 years/≥4 years). To limit biases from underlying illnesses, analyses were also done after excluding participants who had poor health status at baseline and deaths within the first 3 years. Poor health status at baseline was defined by the presence of any of the following: (1) Regular use of medications for chronic diseases, such as diabetes, hypercholesterolaemia or CVDs, or (2) Any hospital admission in the past 6 months before baseline examination, or (3) Self-reported CVD history, or (4) Self-reported cancer history.[29] We also evaluated if the associations varied by age, baseline obesity status or weight loss intention between two examinations. Moreover, to avoid the issue of setting arbitrary cut-offs and increase statistical power, we also analysed associations of mortality with proportional BMI/WC change as continuous variables. Participants who died of any other causes after the first follow-up examination were regarded as censored at the date of death.[30 31] All analyses were done using STATA/IC V.14.0 (StataCorp LP, CollegeStation, Texas, USA). All p values were two-sided, and statistical significance was defined as p<0.05.

RESULTS

Of the 30 430 participants at baseline, 12 657 were excluded, and of them, 384 were lost to follow-up with unknown vital status, 12 326 did not return for the first repeated examination, 282 had incomplete information on BMI or WC, and 49 had BMI loss/gain >50% (in this cohort, as mean BMI increased only slightly,[29] change >50% was over the 99th centile and might be due to measurement errors), giving 17 773 participants (12 956 women and 4 817 men) in the present analysis (figure 1). The mean age was 61.2 (SD=6.8) years. During the average follow-up of 7.8 (SD=1.5) years since the first follow-up examination in 2008–2012 to December 2017, 1424 (761 (53.4%) women and 663 (46.6%) men) deaths were recorded.

Table 1 shows that during baseline and the first follow-up examination, most of the participants (68.4%) had stable BMI with ±5% change; 13.7% had BMI loss of >5% and 17.9% had BMI gain of >5%. For WC, more participants (50.0%) had a gain of >5% than having stable WC within ±5% change (42.6%), and few (7.4%) had WC loss of >5%. At baseline, compared with those with stable BMI, those with BMI loss were older, more likely to be women, with poor health status, intentional weight loss and type 2 diabetes (p from <0.001 to 0.024), and with lower socioeconomic position indicated by low education, manual occupation and low family income (p from <0.001 to 0.032). Those with BMI gain were younger, more likely to be women, manual workers and with good health status (p from <0.001 to 0.001), and less likely to be with intentional weight loss and type 2 diabetes (p from <0.001 to 0.024). Those with BMI loss or BMI gain were less likely to be physically active and alcohol users than those with stable BMI (p from <0.001 to 0.004). Even though statistically significant, the differences were small. Baseline characteristics by WC change showed similar patterns (table 1). Among those with BMI gain,

Table 1 Baseline characteristics of 17 773 participants aged 50+ years in the Guangzhou Biobank Cohort Study first examined in 2003–2008 and followed up until December 2017

	BMI change			
	Loss (<–5%)	Stable (–5% to 5%)	Gain (>5%)	P value for difference
Number of participants (n, %)	2435 (13.7)	12 165 (68.4)	3173 (17.9)	
Age, years, mean (SD)	62.2 (7.3)	61.1 (6.8)	60.8 (6.6)	<0.001
Sex, % men	26.5	28.0	24.1	<0.001
Education, % primary or below	39.0	38.7	40.6	<0.001
Occupation, % manual	60.8	59.8	61.4	<0.001
Family income (¥/year), % <30 000	38.9	36.3	37.9	0.032
Personal income (¥/year), % <10 000	31.2	31.2	35.2	<0.001
Physical activity, % active	51.8	52.4	51.7	0.004
Alcohol use, % current	23.2	26.2	23.1	<0.001
Smoking, % current	9.0	9.3	10.0	0.199
Self-rated health, % poor	16.9	16.2	18.5	0.012
Health status, % poor	21.0	18.7	17.2	0.001
Intentional weight loss,* %	3.0	2.3	1.9	0.024
Type 2 diabetes, % yes	7.8	5.5	5.4	<0.001
	Waist circumference change			
	Loss (<–5%)	Stable (–5% to 5%)	Gain (>5%)	P value for difference
Number of participants (n, %)	1310 (7.4)	7573 (42.6)	8890 (50.0)	
Age, years, mean (SD)	62.9 (6.7)	61.7 (6.7)	60.5 (6.9)	<0.001
Sex, % men	31.2	32.0	22.2	<0.001
Education, % primary or below	39.5	39.3	38.8	<0.001
Occupation, % manual	58.1	60.4	60.3	<0.001
Family income (¥/year), % <30 000	41.3	36.3	36.8	<0.001
Personal income (¥/year), % <10 000	32.4	31.2	32.4	<0.001
Physical activity, % active	56.5	55.0	49.1	<0.001
Alcohol use, % current	22.9	25.6	25.3	0.001
Smoking, % current	10.8	10.6	8.0	<0.001
Self-rated health, % poor	17.2	16.3	17.0	0.480
Health status, % poor	21.2	20.1	17.2	<0.001
Intentional weight loss,* %	3.4	2.6	2.0	0.001
Type 2 diabetes, % yes	8.0	6.8	4.6	<0.001

¥ ≈ 12.5 US cents, US$1 ≈ ¥8
*Based on weight loss intention between two examinations
BMI, body mass index.

the prevalence of underweight (7.06%) at baseline was higher than those with stable BMI or BMI loss (prevalence 3.58% and 2.87%, respectively). A similar pattern was seen among WC change groups. However, those with BMI loss had higher prevalence of overweight (23.33%) or obesity (15.93%) at baseline than those with stable BMI (22.22% and 12.91%, respectively) or BMI gain (15.73% and 8.07%, respectively) (see online supplemental table 1).

BMI change and mortality

Table 2 shows that after adjusting for sex, age, education, occupation, personal income, physical activity, drinking, smoking and self-rated health, compared with participants with stable BMI, those with BMI loss showed a 49% higher risk for all-cause mortality (HR=1.49, 95% CI 1.31 to 1.71), 45% higher risk for CVD mortality (HR=1.45, 95% CI 1.16 to 1.81) and 40% higher risk for cancer mortality (HR=1.40, 95% CI 1.13 to 1.74). No significant association with all-cause mortality risk was found for BMI gain (HR=0.99, 95% CI 0.84 to 1.05). The results were similar after excluding those with poor health at baseline. BMI loss, but not BMI gain, showed higher risks for all-cause, CVD and cancer mortality (HR=1.58, 95% CI 1.36 to 1.85; 1.54, 95% CI 1.17 to 2.02, and 1.57, 95% CI 1.23

Table 2 HRs for all-cause, cardiovascular disease (CVD) and cancer mortality by changes in body mass index (BMI) and waist circumference from 2003–2008 (baseline) to 2012 (first repeated examination) and followed up till December 2017 in the Guangzhou Biobank Cohort Study

	All-cause			CVD			Cancer		
	Loss (<–5%)	Stable (–5% to 5%)	Gain (>5%)	Loss (<–5%)	Stable (–5% to 5%)	Gain (>5%)	Loss (<–5%)	Stable (–5% to 5%)	Gain (>5%)
In the whole sample (n=17 773)									
	BMI change								
Person years	18 709	95 503	24 655	18 709	95 503	24 655	18 709	95 503	24 655
No. of deaths	296	905	223	103	311	81	109	377	98
Crude HR (95% CI)	1.66 (1.46 to 1.90)*	Ref.	0.97 (0.83 to 1.12)	1.67 (1.34 to 2.09)*	Ref.	1.03 (0.80 to 1.31)	1.48 (1.20 to 1.83)*	Ref.	1.01 (0.81 to 1.26)
AHR§ (95% CI)	1.49 (1.31 to 1.71)*	Ref.	0.99 (0.85 to 1.15)	1.45 (1.16 to 1.81)†	Ref.	1.08 (0.84 to 1.38)	1.40 (1.13 to 1.74)†	Ref.	1.02 (0.81 to 1.28)
	Waist circumference change								
Person years	10 344	59 806	68 717	10 344	59 806	68 717	10 344	59 806	68 717
No. of deaths	164	664	596	63	239	193	57	264	263
Crude HR (95% CI)	1.40 (1.18 to 1.66)*	Ref.	0.81 (0.72 to 0.90)*	1.47 (1.11 to 1.94)†	Ref.	0.74 (0.61 to 0.90)†	1.24 (0.93 to 1.66)	Ref.	0.88 (0.74 to 1.04)
AHR§ (95% CI)	1.28 (1.08 to 1.52)†	Ref.	0.94 (0.84 to 1.05)	1.33 (1.00 to 1.76)‡	Ref.	0.87 (0.72 to 1.05)	1.19 (0.89 to 1.59)	Ref.	1.02 (0.86 to 1.22)
After excluding those with poor health at baseline (n=14 446)									
	BMI change								
Person years	14 808	77 852	20 448	14 808	77 852	20 448	14 808	77 852	20 448
No. of deaths	222	657	160	71	207	55	90	285	77
Crude HR (95% CI)	1.77 (1.52 to 2.06)*	Ref.	0.94 (0.79 to 1.11)	1.78 (1.36 to 2.33)*	Ref.	1.03 (0.77 to 1.39)	1.66 (1.31 to 2.11)*	Ref.	1.03 (0.80 to 1.33)
AHR§ (95% CI)	1.58 (1.36 to 1.85)*	Ref.	1.00 (0.84 to 1.19)	1.54 (1.17 to 2.02)†	Ref.	1.11 (0.83 to 1.50)	1.57 (1.23 to 2.00)*	Ref.	1.10 (0.85 to 1.42)
	Waist circumference change								
Person years	8167	47 900	57 040	8167	47 900	57 040	8167	47 900	57 040
No. of deaths	120	475	444	46	156	131	42	204	206
Crude HR (95% CI)	1.45 (1.19 to 1.77)*	Ref.	0.81 (0.71 to 0.93)†	1.66 1.20 to 2.31)†	Ref.	0.75 (0.59 to 0.95)	1.20 (0.86 to 1.68)	Ref.	0.86 (0.71 to 1.04)
AHR§ (95% CI)	1.31 (1.07 to 1.60)†	Ref.	0.96 (0.84 to 1.10)	1.49 (1.07 to 2.08)‡	Ref.	0.87 (0.69 to 1.11)	1.13 (0.80 to 1.58)	Ref.	1.02 (0.84 to 1.25)

Continued

Table 2 Continued

	All-cause			CVD			Cancer		
	Loss (<−5%)	Stable (−5% to 5%)	Gain (>5%)	Loss (<−5%)	Stable (−5% to 5%)	Gain (>5%)	Loss (<−5%)	Stable (−5% to 5%)	Gain (>5%)

*p<0.001
†p<0.01
‡p<0.05
§Adjusted for sex, age, education, occupation, personal income, physical activity, drinking, smoking and self-rated health
AHR, adjusted HR; Ref, reference.

to 2.00, respectively). The results did not vary substantially after excluding deaths within the first 3 years, or those with intentional weight loss, or stratifying by age at baseline or time interval (<4years/≥4 years) (see online supplemental tables 2–6). However, the HR for mortality risk due to BMI loss was slightly lower after excluding deaths within the first 3 years and in participants aged under 70 years (see online supplemental tables 2and 3). Moreover, when BMI change was used as a continuous variable, for those with BMI loss, less BMI change showed lower mortality risks (HR=0.97, 95% CI 0.96 to 0.99, per 1% change in BMI), indicating that greater BMI loss was associated with higher mortality risks, while for those with BMI gain, no association with mortality risks was found for BMI change (HR=1.01, 95% CI 0.99 to 1.03, per 1% change in BMI) (see online supplemental table 7).

Stratified analyses by baseline BMI status showed different patterns of mortality risk associated with BMI change. Table 3 and figure 2 show that in all four groups with different baseline BMI status, compared with stable BMI, BMI loss showed higher risks for all-cause mortality. In the underweight group, those with BMI loss, versus those with stable BMI, had a high risk for all-cause mortality (HR=2.45, 95% CI 1.31 to 4.59). Compared with the underweight group, the HRs for all-cause mortality in the normal weight, overweight and obese groups were attenuated and became non-significant in the obese group (HR and 95% CI 1.46 (1.23 to 1.74), 1.52 (1.15 to 2.02) and 1.41 (0.98 to 2.02), respectively).

Table 3 and figure 2 also show that in those with obesity at baseline, BMI gain versus stable BMI showed 82% higher risk of all-cause mortality (HR=1.89, 95% CI 1.25 to 2.88) and more than twofold risk of cancer mortality (HR=2.27, 95% CI 1.26 to 4.10). However, when baseline adiposity, ignoring adiposity change, was analysed, the associations were weak and non-significant, with the HR (95% CI) being 1.17 (0.99 to 1.37) for all-cause mortality and 1.17 (0.91 to 1.51) for cancer mortality (see online supplemental table 8). Similar results were observed after excluding those with poor health at baseline (see online supplemental table 9).

WC change and mortality

Table 2 shows that after adjusting for potential confounding factors as above, WC loss versus WC stable group showed higher risks for all-cause (HR=1.28, 95% CI 1.08 to 1.52) and CVD (HR=1.33, 95% CI 1.00 to 1.76) mortality. No significant associations with mortality risks (HR=0.94, 95% CI 0.84 to 1.05) were found for WC gain. The results were similar after excluding those with poor health at baseline, deaths within the first 3 years or intentional weight loss, or stratifying by age at baseline or time interval (<4years/≥4 years) (table 2, online supplemental tables 2–6). Moreover, when WC change was used as a continuous variable, for those with WC loss, less WC change appeared to be associated with a lower risk of all-cause mortality, although the association was

Table 3 HRs for all-cause, cardiovascular disease (CVD) and cancer mortality by changes in body mass index (BMI) from 2003–2008 (baseline) to 2012 (first repeated examination), and followed up till December 2017 in 17 773 participants of the Guangzhou Biobank Cohort Study, stratified by groups of baseline BMI

	All-cause			CVD			Cancer		
	Loss (<–5%)	Stable (–5% to 5%)	Gain (>5%)	Loss (<–5%)	Stable (-5% to 5%)	Gain (>5%)	Loss (<–5%)	Stable (–5% to 5%)	Gain (>5%)
Person years	18 709	95 503	24 655	18 709	95 503	24 655	18 709	95 503	24 655
Underweight									
No. of deaths	15	48	16	6	11	6	5	21	5
Crude HR (95% CI)	2.14 (1.20 to 3.83)‡	Ref.	0.64 (0.36 to 1.13)	3.86 (1.42 to 10.50)†	Ref.	1.04 (0.38 to 2.81)	1.62 (0.61 to 4.29)	Ref.	0.46 (0.17 to 1.22)
AHR§ (95% CI)	2.45 (1.31 to 4.59)†	Ref.	0.77 (0.43 to 1.40)	5.16 (1.63 to 16.37)†	Ref.	1.30 (0.44 to 3.80)	1.52 (0.54 to 4.29)	Ref.	0.61 (0.22 to 1.70)
Normal									
No. of deaths	170	546	147	59	181	52	61	238	65
Crude HR (95% CI)	1.68 (1.42 to 2.00)*	Ref.	0.94 (0.78 to 1.12)	1.75 (1.30 to 2.35)*	Ref.	1.01 (0.74 to 1.37)	1.39 (1.05 to 1.85)‡	Ref.	0.94 (0.72 to 1.24)
AHR§ (95% CI)	1.46 (1.23 to 1.74)*	Ref.	0.93 (0.78 to 1.13)	1.44 (1.07 to 1.94)‡	Ref.	1.03 (0.76 to 1.40)	1.29 (0.97 to 1.72)	Ref.	0.92 (0.70 to 1.22)
Overweight									
No. of deaths	68	201	32	23	80	15	29	72	13
Crude HR (95% CI)	1.63 (1.23 to 2.14)†	Ref.	0.88 (0.60 to 1.27)	1.37 (0.86 to 2.18)	Ref.	1.04 (0.60 to 1.81)	1.96 (1.27 to 3.02)†	Ref.	0.99 (0.55 to 1.78)
AHR§ (95% CI)	1.52 (1.15 to 2.02)†	Ref.	1.02 (0.70 to 1.48)	1.28 (0.80 to 2.06)	Ref.	1.26 (0.72 to 2.20)	1.89 (1.21 to 2.94)†	Ref.	1.13 (0.62 to 2.05)
Obese									
No. of deaths	43	110	28	15	39	8	14	46	15
Crude HR (95% CI)	1.60 (1.13 to 2.28)†	Ref.	1.64 (1.08 to 2.48)‡	1.55 (0.86 to 2.82)	Ref.	1.33 (0.62 to 2.85)	1.26 (0.69 to 2.29)	Ref.	2.09 (1.16 to 3.74)‡
AHR§ (95% CI)	1.41 (0.98 to 2.02)	Ref.	1.89 (1.25 to 2.88)†	1.38 (0.75 to 2.54)	Ref.	1.72 (0.80 to 3.72)	1.08 (0.59 to 1.98)	Ref.	2.27 (1.26 to 4.10)†

Underweight: BMI <18.5 kg/m^2; normal: 18.5 kg/m^2 ≤ BMI <25 kg/m^2; overweight: 25 kg/m^2 ≤ BMI < 27.5 kg/m^2; obese: BMI ≥ 27.5 kg/m^2
*p<0.001
†p<0.01
‡p<0.05
§Adjusted for sex, age, education, occupation, personal income, physical activity, drinking, smoking and self-rated health
AHR, adjusted HR; Ref, reference.

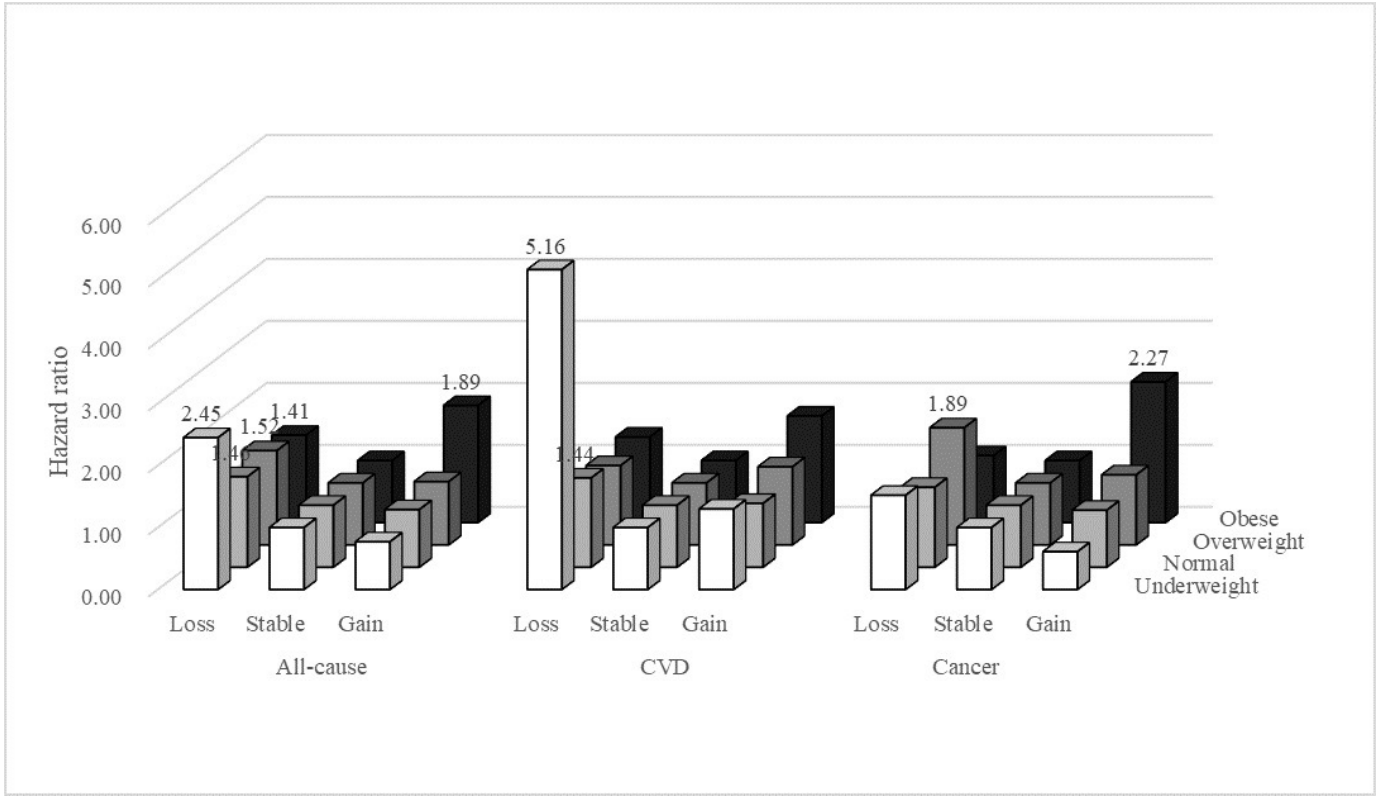

Figure 2 Adjusted HRs* for all-cause, cardiovascular disease (CVD) and cancer mortality by changes in body mass index (BMI) from 2003–2008 (baseline) to 2012 (first repeated examination), and followed up till December 2017 in 17 773 participants of the Guangzhou Biobank Cohort Study, stratified by groups of baseline BMI. *: adjusted for sex, age, education, occupation, personal income, physical activity, drinking, smoking and self-rated health. Underweight: BMI <18.5 kg/m^2; normal: 18.5 kg/m^2≤ BMI <25 kg/m^2; overweight: 25 kg/m^2 ≤BMI < 27.5 kg/m^2; obese: BMI ≥27.5 kg/m^2.

not statistically significant (HR=0.98, 95% CI 0.96 to 1.00, per 1% change in WC) (see online supplemental table 7).

Table 4 and figure 3 show that, in men with WC level of 80–90 cm and women with WC of 70–80 cm, those with WC loss had higher risks for all-cause mortality (HR=1.61, 95% CI 1.21 to 2.13) and CVD mortality (HR=1.76, 95% CI 1.12 to 2.79). No significant associations between WC gain and mortality risks in all subgroups were found with HR (95% CI) being 0.87 (0.69 to 1.10), 1.05 (0.87 to 1.27) and 0.97 (0.79 to 1.18) (table 4, online supplemental table 10).

DISCUSSION

To our knowledge, the current study is the largest population-based prospective study in China examining the association of adiposity change with the risks of mortality in middle-aged and older people. The findings in our study are similar to those in the western populations. We found that in participants who were obese (BMI ≥27.5 kg/m^2) at baseline, BMI gain during follow-up was associated with a higher risk of all-cause and cancer mortality, but not CVD mortality, although the null association for CVD mortality could be due to the lack of statistical power. Notably, when adiposity change was ignored, no significant associations of baseline obesity with the risks of all-cause and cause-specific mortality were observed. BMI/WC loss versus stable BMI showed increased risks of all-cause, CVD and cancer mortality. Moreover, the risks for all-cause and CVD mortality related to BMI loss appeared to be the highest in those who were underweight, followed by those with normal or overweight. Such results which have not been reported before, indicate that reverse causality effects might be likely, and such effects could not be completely eliminated after adjusting for self-rated health and excluding those with poor health at baseline.

Our study's positive associations of BMI loss with all-cause, CVD and cancer mortality, and WC loss with all-cause mortality are generally consistent with those from two meta-analyses of studies mainly from the West.[5 6] The findings could be explained by the reduction of lean body mass with ageing and adiposity loss, which could increase the risk of sarcopenia and frailty.[32 33] Another possible explanation is due to reverse causality, because adiposity loss in older people is usually indicative of underlying diseases. In our commentary on the more recent meta-analysis on adiposity change,[12] we highlight that the association of adiposity loss with higher risks of all-cause mortality in middle-aged to older people might be most likely due to reverse causality.[12] To address reverse causality, the two meta-analyses above conducted subgroup analyses by baseline age and

Table 4 HRs for all-cause, cardiovascular disease (CVD) and cancer mortality by changes in waist circumference from 2003–2008 (baseline) to 2012 (first repeated examination), and followed up till December 2017 in 17 773 participants of the Guangzhou Biobank Cohort Study, stratified by groups of baseline waist circumference

	All-cause			CVD			Cancer		
Waist circumference, cm	**Loss (<–5%)**	**Stable (–5% to 5%)**	**Gain (>5%)**	**Loss (<–5%)**	**Stable (–5% to 5%)**	**Gain (>5%)**	**Loss (<–5%)**	**Stable (–5% to 5%)**	**Gain (>5%)**
Person years	10 344	59 806	68 717	10 344	59 806	68 717	10 344	59 806	68 717
<80 for M; <70 for F									
No. of deaths	22	137	197	8	37	58	11	61	91
Crude HR (95% CI)	1.20 (0.76 to 1.88)	Ref.	0.73 (0.58 to 0.90)†	1.55 (0.72 to 3.34)	Ref.	0.81 (0.54 to 1.23)	1.38 (0.73 to 2.63)	Ref.	0.74 (0.53 to 1.02)
AHR (95% CI)	1.08 (0.68 to 1.70)	Ref.	0.87 (0.69 to 1.10)	1.54 (0.71 to 3.33)	Ref.	0.98 (0.64 to 1.51)	1.25 (0.65 to 2.39)	Ref.	0.88 (0.63 to 1.24)
80–90 for M; 70–80 for F									
No. of deaths	62	237	249	24	83	83	18	93	111
Crude HR (95% CI)	1.85 (1.40 to 2.44)*	Ref.	0.84 (0.71 to 1.01)	2.01 (1.28 to 3.17)†	Ref.	0.82 (0.61 to 1.12)	1.38 (0.83 to 2.29)	Ref.	0.94 (0.71 to 1.24)
AHR (95% CI)	1.61 (1.21 to 2.13)†	Ref.	1.05 (0.87 to 1.27)	1.76 (1.12 to 2.79)‡	Ref.	1.04 (0.76 to 1.42)	1.21 (0.72 to 2.03)	Ref.	1.15 (0.86 to 1.54)
90+ for M; 80+ for F									
No. of deaths	80	290	150	31	119	52	28	110	61
Crude HR (95% CI)	1.20 (0.94 to 1.54)	Ref.	0.83 (0.68 to 1.01)	1.12 (0.76 to 1.67)	Ref.	0.71 (0.51 to 0.99)*	1.13 (0.75 to 1.72)	Ref.	0.87 (0.63 to 1.19)
AHR§ (95% CI)	1.15 (0.90 to 1.48)	Ref.	0.97 (0.79 to 1.18)	1.02 (0.69 to 1.53)	Ref.	0.82 (0.59 to 1.14)	1.18 (0.78 to 1.80)	Ref.	1.06 (0.77 to 1.45)

*p<0.001
†p<0.01
‡p<0.05
§Adjusted for sex, age, education, occupation, personal income, physical activity, drinking, smoking and self-rated health
AHR, adjusted hazard ratio; F, female; M, male; Ref, reference.

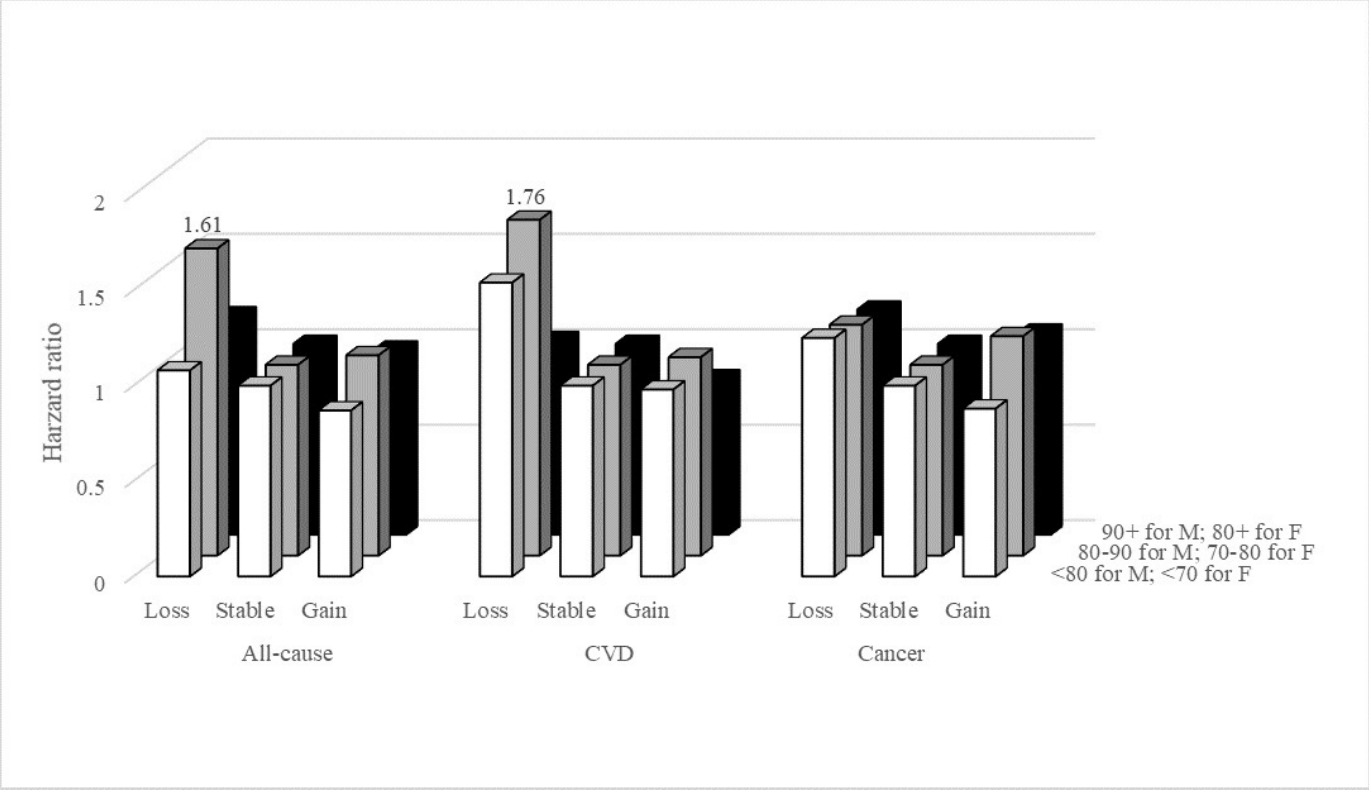

Figure 3 Adjusted HRs* for all-cause, cardiovascular disease (CVD) and cancer mortality by changes in waist circumference from 2003–2008 (baseline) to 2012 (first repeated examination), and followed up till December 2017 in 17 773 participants of the Guangzhou Biobank Cohort Study, stratified by groups of baseline waist circumference (cm). F, female; M, male. *: adjusted for sex, age, education, occupation, personal income, physical activity, drinking, smoking and self-rated health.

follow-up duration, and sensitivity analyses by excluding studies that included potentially unhealthy participants and examining intentional weight loss. They found that the results did not change substantially. The positive associations above were also reported by some recent Asian cohort studies (in China,[15] Singapore[24] and Japan[9]). In the present study, to explore potential reverse causality, we excluded participants with poor health at baseline or intentional weight loss between two examinations and deaths during the first 3 years, conducted subgroup analyses by age groups (<70 years or ≥70 years), time interval (<4 years/≥4 years) and baseline BMI status, and found that the results did not vary substantially. Our subgroup analysis showed that the old and thin (underweight) participants had much higher risks of all-cause mortality, which could be an early indicator of frailty and would be of great clinical significance. Our results were consistent with previous studies.[13 15] However, as expected, the risk of all-cause mortality associated with BMI loss attenuated after excluding deaths within the first 3 years, and the risk in participants aged over 70 years was slightly higher than those aged under 70 years, implying strong reverse causality. As the HRs were the highest in those who were underweight, and almost all weight loss was unintentional, the results should have important clinical applications. Older and underweight people with unintentional BMI loss are at very high mortality risk and need urgent clinical interventions and treatments. For prevention and early detection, the weight of 'old and thin' people should be monitored frequently.

Previous findings on weight gain and mortality were inconsistent, with some studies showing positive associations,[9 10 15 24 25 34–36] while others found no association.[37–41] Our results of the higher risks of all-cause and cancer mortality in those with baseline obesity were consistent with some previous studies,[13 14] indicating modifying effect of baseline adiposity status. The associations might be explained by the increase in excess body fat and adiposity tissue, which lead to higher inflammation, alteration of immune response and subsequent risks for metabolic disorders.[42 43] The two meta-analyses above, without weight change data, showed consistently that obesity at baseline was associated with higher risks of all-cause mortality during follow-up.[3 4] Thus, BMI gain from baseline obesity would result in higher mortality risks. However, if participants with underweight atbaseline gained BMI, as a result of improved nutrition and health status from treatment, their BMI might approach a normal level, and the benefitof normal BMI level might counteract the adverse effect of BMI gain. Note that obesity as defined in our sample has a low BMI (≥27.5 kg/m^2) than the WHO definition (≥30.0 kg/m^2), and gross obesity is rare in China and was rare in previous meta-analyses. With increasing obesity and ageing in China and globally, in prevalence and in absolute BMI levels, future studies

would probably show greater relative risks of mortality and disease burdens due to adiposity.

The strengths of our study included the population-based longitudinal design incorporating adiposity measured at two time points, comprehensive measurements and analyses of a wide range of potential confounding factors, and large sample size. In addition, information of anthropometric measures at baseline and follow-up was collected by well-trained nurses using a standard protocol, which would minimise information errors and misclassification bias due to self-reporting or changes in measurement methods, and might enhance comparability of the adiposity measures between the two time points. Furthermore, in older adults, the body fat distribution may change with an increased centralisation of adiposity while total weight remains constant,[44] indicating that BMI and WC might not change simultaneously, and highlighting the importance of using a combination of BMI and WC to examine the associations of adiposity and mortality comprehensively.

Our study had several limitations. First, the number of all-cause and cause-specific deaths, that is, deaths due to CVD or cancer, was small, which could be due to relatively short follow-up time and might have led to an insufficient statistical power and the subsequent non-significant association. Mega cohorts with millions of subjects are needed for breaking down by several variables together (such as sex, age group, health status and adiposity at baseline, and weight loss/gain intention and treatment). Second, as all our participants were aged 50 years or above at baseline, generalisation of the results to younger populations might be limited. Moreover, women were oversampled in this study, as other population-based elderly cohorts. However, we adjusted for sex in data analysis to minimise its potential confounding effect. In addition, within sex and age group, the participants had similar prevalence of chronic diseases to nationally representative samples of the urban Chinese.[17] Thus, the unbalanced sex ratio might not be a major concern in the current study. Third, as very few participants (n=415) reported intentional weight loss, we could not further analyse the association of intentional weight loss and mortality in our study. Intentional weight loss in older Chinese people was uncommon. Although obesity is traditionally a symbol of wealth and fortune, the increased awareness of the harms of obesity and related problems such as hypertension, dyslipidaemia, diabetes would lead to increasing weight loss intention. Future studies must collect such information and analyse intentional and unintentional weight loss separately. Fourth, due to improving survival from most chronic diseases since the past few decades globally,[45] studies focusing on mortality only might be increasingly problematic due to the misclassification of the study outcomes. For example, some survivors of CVD or cancer may be misclassified as 'non-disease' and be used as the reference group, which would bias the relative risks towards the null. Finally, residual confounding due to unadjusted, unmeasured or poorly measured variables, such as self-reported physical activity and smoking, and unmeasured height at the first follow-up examination, could not be ruled out, and hence the observed associations should not be interpreted causally.

In conclusion, BMI gain in those with obesity was associated with a higher risk of all-cause and cancer mortality, suggesting keeping a stable weight at old age could be more beneficial. However, unintentional BMI/WC loss was associated with substantially higher risks of all-cause and CVD mortality, especially in those underweight. As attributable fraction in the exposed group can be calculated by using relative risk minus one, divided by the relative risk, based on an HR of 2.0 for all-cause mortality, an attributable fraction of 50% can be obtained, which means that of all deaths in older people with both baseline underweight and unintentional weight loss within a few years, half can be attributable to weight loss probably caused by underlying health conditions.[46] Such results indicate that older and underweight people should be monitored frequently for unintentional weight loss as an early warning for timely clinical investigations and interventions. Moreover, interventions for older people, such as nutrition education and promotion of physical activity, before the fluctuations in weight become evident are important. Future cohort studies should refocus from reverse causality to examine the factors for unintentional weight loss and the adverse health outcomes in the old and thin.

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Competing interests None declared.

Patient consent for publication All participants gave written, informed consent before participation.

Ethics approval The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study.

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