Endocrine (2019) 64:82–89
https://doi.org/10.1007/s12020-019-01892-2

ORIGINAL ARTICLE

Check for updates

Weight change is associated with increased all-cause mortality and non-cardiac mortality among patients with type 2 diabetes mellitus

Zhenhua Xing[1] · Junyu Pei[1] · Jiabing Huang[1] · Xiaofan Peng[1] · Pengfei Chen[1] · Xinqun Hu[1] · Shan Gao[2]

Received: 24 October 2018 / Accepted: 5 March 2019 / Published online: 12 March 2019

Abstract

Background It is unclear whether changes in weight affect subsequent adverse events in patients with type 2 diabetes mellitus (T2DM) already at high risk of cardiovascular disease (CVD).

Methods and results This is a post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study data to examine the relationship between changes in weight and adverse events. Patients were divided into groups based on changes in body mass index (BMI): stable weight, gain or loss of BMI ≤1.5 kg/m^2; moderate weight gain, BMI gain of 1.5–5 kg/m^2; pronounced weight gain, BMI gain >5 kg/m^2; moderate weight loss, BMI loss of 1.5–5 kg/m^2; and pronounced weight loss, BMI loss >5 kg/m^2. The primary endpoint of the present study was all-cause mortality. Secondary endpoints were cardiac death, non-fatal myocardial infarction (MI), and non-cardiac mortality. A total of 9372 T2DM patients with a mean follow-up of 8.08 ± 3.00 years were included for analysis. The average change in weight across the entire study population was 1.80 ± 9.00%, representing ~0.448 ± 2.98 kg/m^2. Patients with pronounced weight loss had the highest risk of all-cause mortality (hazard ratio (HR) 2.07, 95% confidence interval (CI): 1.68–2.55), followed by patients with pronounced weight gain (HR 1.23, 95% CI: 1.02–1.56); patients with stable weight had the lowest risk. An asymmetric V-shaped relationship was observed between changes in BMI and all-cause mortality and non-cardiac mortality. Although no statistical significance was observed in terms of cardiac death and non-fatal MI, a flat V-shaped relationship may exist.

Conclusions Weight was stable in most T2DM patients with high risk of CVD. Weight loss and gain is associated with increased all-cause mortality and non-cardiac mortality. Pronounced weight loss and weight gain is associated with a slight increase in cardiac death and non-fatal MI incidence, which does not reach statistical significance.

Keywords Type 2 diabetes mellitus · Body mass index · Weight change · All-cause mortality · Cardiac death

Background

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by increased blood glucose levels, insulin resistance, and progressively insufficient insulin secretion [1]. In 2017, there were 425 million people with diabetes in the world, as estimated by the International Diabetes Federation (IDF) Diabetes Atlas, and there will be 629 million people with diabetes in 2045 [2]. Diabetes mellitus is associated with micro- and macrovascular complications, as well as cancer, renal disease, liver disease, and infection [3, 4]. T2DM patients tend to be overweight or obese. Obesity is associated with an increased risk of coronary atherosclerotic heart disease, hypertension, and hyperlipidemia [5–8]. However, body weight is modifiable, and changes in body weight have been associated with changes in these risk factors. Reducing body weight can improve blood glucose control, alleviate cardiovascular risk factors, and reduce the need for medicine [9]. However, weight loss has been found to be related to an increased risk of all-cause mortality and cardiovascular mortality in many studies [10–12]. These studies had relatively small sample sizes and assessed changes in weight over a short period (<2 years). No relevant study has been performed to investigate changes in weight among T2DM patients at high risk of cardiovascular disease (CVD). By understanding

✉ Shan Gao
xing2012x@csu.edu.cn

[1] Department of Cardiovascular Medicine, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China

[2] Department of Geriatrics, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China

current patterns of weight change in this population, new interventions can be developed to improve patient outcome. We examined the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study to assess changes in weight and subsequent outcomes among T2DM patients at high risk of CVD.

Methods

Study population

We retrospectively analyzed data from the ACCORD study, derived from the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). The design of the ACCORD trial has been described previously and the results have been published [13, 14]. Briefly, the ACCORD study was a multicenter randomized controlled trial performed to determine whether enhanced control of blood glucose, blood pressure, and lipids could reduce the incidence of CVD in T2DM patients with high risk of CVD. The study recruited 10,251 T2DM patients with previous CVD or CVD risk factors (dyslipidemia, hypertension, current smoker, or obesity) from 77 clinical centers across the United States and Canada; mean age was 62 years, median duration of T2DM disease was 10 years, and mean glycated hemoglobin (HbA1c) level was 8.3%. The study found that enhanced control of blood glucose, blood pressure, and blood lipid levels had a neutral effect on risk of overall death and non-fatal cardiovascular events but increased cardiac death risk.

Exposure variable

Of the 10,251 patients with T2DM in the ACCORD trial, we excluded 192 patients for whom no body mass index (BMI) data were available. We also excluded another 687 patients because of limited weight change follow-up (<2 years). BMI is defined as the weight in kilograms divided by height in meters squared. Change in BMI is here defined as BMI at the last follow-up minus the baseline BMI. Patients were classified according to changes in their BMI: stable weight, change in BMI ≤±1.5 kg/m^2; moderate weight gain, BMI gain of 1.5–5 kg/m^2; pronounced weight gain, BMI gain >5 kg/m^2; moderate weight loss, BMI loss of 1.5–5 kg/m^2; and pronounced weight loss, BMI loss >5 kg/m^2. We also classified patients into five groups based upon the National Heart, Lung, and Blood Institute clinical guidelines to assess the difference in changes in BMI (normal, BMI 18.5–24.9 kg/m^2; overweight, BMI 25–29.9 kg/m^2; class I obesity, BMI 30–34.9 kg/m^2; class II obesity, BMI 35–39.9 kg/m^2; and class III obesity, BMI ≥40 kg/m^2). The primary endpoint of the study was all-cause mortality. Secondary endpoints were cardiac death, non-fatal myocardial infarction (MI), and non-cardiac mortality, which have been defined previously [13, 14].

The following were considered statistically significant covariates and clinically meaningful confounders: age, sex, smoking status, hypertension, hyperlipidemia, previous cardiovascular events, proteinuria, depression, HbA1c level, and fasting blood glucose level.

Statistical analysis

Baseline characteristics of patients across the categories were summarized as frequencies and percentages for categorical variables, and as means and standard deviations or interquartile range for continuous variables, depending on whether data distribution was normal as assessed by Q–Q plots. Categorical variables were compared by χ^2 analysis and continuous variables by analysis of variance or the Mann–Whitney U test depending on distribution type. Cox proportional hazards regression models that included statistically significant covariates and clinically meaningful confounders were constructed to determine hazard ratios (HRs) and 95% confidence interval (CI) of predefined endpoints based on change in BMI. The HRs associated with each change in the BMI group were compared with those of the stable BMI group. Survival curves of the five BMI change groups defined earlier were created from the Cox regression models, with statistically significant covariates and clinically meaningful confounders as co-covariates. Restricted cubic splines [15] of change in BMI were used to graphically assess the association between change in BMI and our predefined outcomes after adjusting for statistically significant covariates and clinically meaningful confounders. The correlation between baseline BMI and BMI at last follow-up was determined using Pearson's correlation coefficient (r). All of the statistical tests were two-sided and $P < 0.05$ was considered statistically significant. All of the statistical analyses were performed using IBM-SPSS Software (version 22) and R Statistical Software R (version 3.4.3).

Results

Patient characteristics among weight change groups

A total of 9372 T2DM patients with a mean follow-up of 8.08 ± 3.00 years were included in the present study. Table 1 shows the characteristics of patients according to change in BMI. The mean duration of T2DM was 10.75 ± 7.56 years. The proportion of patients in each change in BMI group were as follows: stable weight group, 45.2%; moderate weight gain group, 27.9%; pronounced weight

Table 1 Baseline demographic, clinical, and laboratory examination characteristics

	BMI change (kg/m^2)					*P* value
	<−5	−5 to −1.5	−1.5 to −1.5	1.5 to −5	>5	
N (%)	344 (3.7)	1636(17.4)	4227(45.0)	2627 (28.0)	538 (5.9)	
Age (year; mean ± SD)	63.7 ± 6.92	64.1 ± 6.72	62.9 ± 6.63	62.0 ± 6.40	60.8 ± 5.79	0.000
Female (*n*, %)	193 (56.1)	751 (45.9)	1421 (33.6)	967 (36.8)	46.2 (46.2)	0.000
Race (*n*, %)						0.221
White	222 (64.5)	1041 (63.6)	2611 (61.8)	1645 (62.6)	367 (66.4)	
Non-white	122 (35.5)	595 (36.4)	1616 (38.2)	982 (37.4)	186 (33.6)	
Current smoker (*n*, %)	48 (14.0)	225 (13.8)	559 (13.2)	354 (13.5)	90 (16.3)	0.409
Mean duration of diabetes (year; mean ± SD)	11.6 ± 8.4	10.7 ± 7.9	10.7 ± 7.6	11.0 ± 7.4	10.7 ± 7.0	0.026
Hypertension (*n*, %)	270 (78.5)	1232 (75.3)	3147 (74.4)	1982 (75.4)	436 (78.8)	0.122
Hyperlipidemia (*n*, %)	249 (72.4)	1128 (68.9)	2999 (70.9)	1799 (68.5)	405 (73.2)	0.056
Previous cardiovascular events (*n*, %)	123 (35.8)	574 (35.1)	1421 (33.6)	906 (34.5)	202 (36.5)	0.577
Previous heart failure (*n*, %)	23 (6.67)	75 (4.6)	164 (3.9)	125 (4.8)	30 (5.4)	0.057
Education (*n*, %)						0.115
Less than high school	54 (15.7)	232 (14.2)	586 (13.9)	388 (14.8)	79 (14.3)	
High-school graduate	85 (26.4)	447 (27.4)	1070 (25.3)	721 (27.4)	150 (27.1)	
Some college	129 (37.5)	545 (33.4)	1389 (32.9)	843 (32.1)	193 (34.9	
College degree or higher	76 (22.1)	410 (25.1)	1179 (27.9)	675 (25.7)	131 (23.7)	
Proteinuria (%)	81 (23.5)	303 (18.5)	781 (18.5)	545 (20.7)	135 (24.4)	0.001
Depression (%)	99 (28.8)	414 (25.3)	899 (21.3)	617 (23.5)	155 (28.0)	0.000
HR (bpm, mean ± SD)	73 ± 11.6	72 ± 11.6	72 ± 11.7	73 ± 11.6	75 ± 11.6	0.980
SBP (mmHg, mean ± SD)	136 ± 17.0	137 ± 17.0	136 ± 16.7	136 ± 17.2	137 ± 17.4	0.140
DBP (mmHg, mean ± SD)	75 ± 10.7	74 ± 10.6	75 ± 10.7	75 ± 10.7	77 ± 10.7	0.881
BMI (kg/m^2, mean ± SD)	37 ± 4.80	33.1 ± 5.03	31.3 ± 5.22	32.3 ± 5.46	33.9 ± 5.22	0.000
Waist circumference (cm, mean ± SD)	116 ± 12.6	107 ± 13.3	104 ± 13.3	107 ± 13.7	111 ± 13.3	0.382
Glycated hemoglobin (%, mean ± SD)	8.21 ± 1.02	8.11 ± 0.960	8.21 ± 1.00	8.48 ± 1.10	8.70 ± 1.19	0.000
GFR (ml/min, mean ± SD)	86 ± 22.8	90.4 ± 29.1	91.3 ± 26.6	91.6 ± 26.8	91.8 ± 29.0	0.000
FBG (mg/dl, mean ± SD)	167 ± 54.9	169 ± 51.8	173 ± 54.6	181 ± 58.6	191 ± 59.8	0.000
Cholesterol (mg/dl, mean ± SD)						
Total	184 ± 39.5	184 ± 40.4	182 ± 41.1	184 ± 43.6	189 ± 43.3	0.068
Low-density lipoprotein	107 ± 33.8	105 ± 32.1	104 ± 33.5	104 ± 34.7	109 ± 35.8	0.043
High-density lipoprotein	42.8 ± 11.9	42.1 ± 11.5	41.7 ± 11.3	41.7 ± 11.7	41.5 ± 11.8	0.669
Urinary albumin (mg/dl ± SD)	10.5 ± 31.7	9.8 ± 33.0	8.89 ± 34.4	9.93 ± 31.5	13.5 ± 40.9	0.011
Medications (*n*, %)						
Meglitinides	9 (3.7)	42 (2.6)	116 (2.7)	67 (2.6)	9 (1.6)	0.654
Metformin	178 (51.7)	947 (57.9)	2714 (64.2)	1809 (68.9)	391 (70.7)	0.000
Insulin	60 (17.4)	181 (11.1)	429 (10.1)	308 (11.7)	68 (12.3)	0.001
Sulfonylurea	160 (46.5)	895 (54.7)	2285 (54.1)	1383 (52.6)	315 (57.0)	0.020
β-Blockers	117 (33.3)	540 (32.2)	1246 (28.7)	796 (29.8)	181 (32.6)	0.028
Statin	221 (64.2)	1051 (64.5)	2720 (64.5)	1661 (63.6)	337 (61.1)	0.573
ACEI	184 (53.5)	863 (52.9)	2247 (53.2)	1483 (56.6)	339 (61.6)	0.000
Aspirin	185 (53.8)	922 (56.6)	2286 (54.3)	1430 (54.8)	311 (56.5)	0.497

HR heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *GFR* glomerular filtration rate, *FBG* fasting blood glucose, *ACEI* angiotensin-converting enzyme inhibitors

gain group, 5.8%; moderate weight loss group, 17.5%; and pronounced weight loss group, 3.7%. The mean age was 62.7 ± 6.6 years, and the majority (61.8%) of patients were male. The individuals in the pronounced weight gain group tended to be younger. Female patients were more likely to gain weight. The pronounced weight gain and pronounced weight loss groups had more patients with depression and proteinuria. Patients with pronounced weight gain had higher glomerular filtration rate, HbA1c level, and fasting blood glucose level. Patients in the pronounced weight gain group were more likely to take metformin, and more patients with weight loss accepted insulin treatment. As a percentage of total body weight, the average weight change for the entire population (Fig. 1a) was 1.80 ± 9.00%,

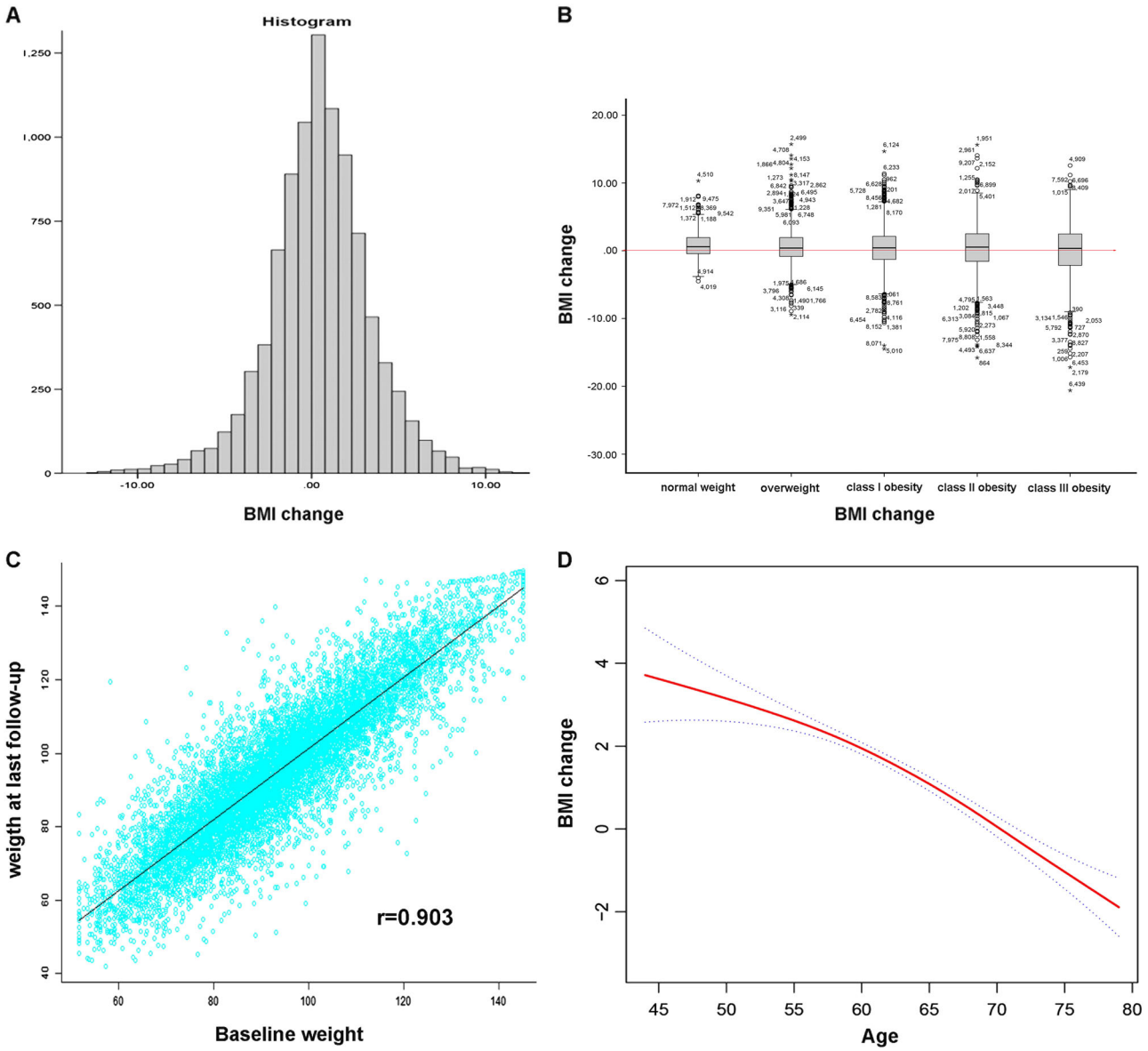

Fig. 1 Change in body mass index (BMI) during follow-up **a**; change in BMI among predefined BMI categories **b**; correlation and agreement between baseline BMI and BMI at last follow-up **c**; relationship between BMI and age after adjusting for race, sex, smoking, education level, and depression **d**

representing ~approximately $0.448 \pm 2.98\ kg/m^2$. A significant correlation was found between baseline BMI and BMI at last follow-up (Fig. 1c, $r = 0.903$). The weight change among different BMI categories is presented in Fig. 1b. Normal weight patients were more likely to gain weight than obese patients. Another finding was the effect of age on weight loss, with older patients losing more weight as a percentage of their original body weight than younger patients. After adjusting for confounding factors including race, sex, smoking status, education level, and depression, we found an inverse relationship between age and weight gain (Fig. 1d)

Multivariate-adjusted analyses

After adjusting for statistically significant covariates and clinically meaningful confounders, patients with pronounced weight loss (BMI loss $>5\ kg/m^2$) had the highest risk of all-cause mortality, followed by patients with pronounced weight gain (BMI $> kg/m^2$); patients with stable weight had the lowest risk (Fig. 2a). The same pattern was also observed for non-cardiac mortality (Fig. 2d). No significant differences were noted between groups with respect to the incidence of cardiac death and non-fatal MI (Fig. 2b, c). HRs and absolute risk for primary and second endpoints are presented in Table 2.

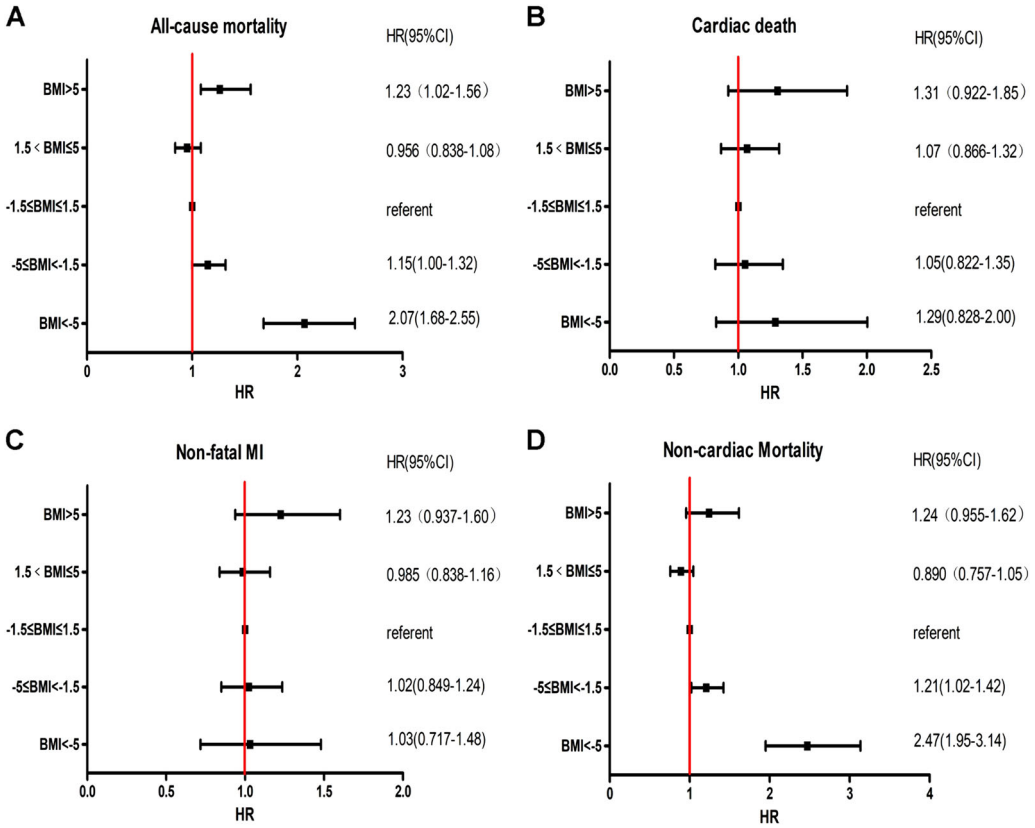

Fig. 2 Primary and secondary endpoints according to predefined body mass index (BMI) change groups. The following were considered statistically significant covariates and clinically meaningful confounders: age, sex, smoking status, hypertension, hyperlipidemia, previous cardiovascular events, proteinuria, depression, glycated hemoglobin level, and fasting blood glucose level

Table 2 Hazard ratios for primary endpoint and secondary endpoints

	BMI change (kg/m^2)				
Outcome	<−5	−5 to −1.5	−1.5 to 1.5	1.5–5	>5
Person-years	3147	14,964	38,664	24,029	4921
All-cause mortality, no.	122	368	839	450	108
Absolute risk (%)[a]	33.5	21.2	18.0	16.3	19.3
HR (95% CI)[b]	2.07 (1.68–2.55)	1.15 (1.00–1.32))	Referent	0.956 (0.838–1.08)	1.23 (1.02–1.56)
Cardiac death, no.	26	106	293	175	42
Absolute risk (%)[a]	7.1	6.1	6.3	6.4	7.5
HR (95% CI)[b]	1.29 (0.828–2.00)	1.05 (0.822–1.35)	Referent	1.07 (0.866–1.32)	1.31 (0.922–1.85)
No-fatal death, no.	32	164	411	254	66
Absolute risk (%)[a]	8.8	9.5	8.8	9.2	11.8
HR (95% CI)[b]	1.03 (0.717–1.48)	1.02 (0.849–1.24)	Referent	0.985 (0.838–1.16)	1.23 (0.937–1.60)
No-cardiac death	96	262	546	275	66
Absolute risk (%)[a]	26.4	15.1	11.7	10.0	11.8
HR (95% CI)[b]	2.47 (1.95–3.14)	1.21 (1.02–1.42)	Referent	0.890 (0.757–1.05)	1.24 (0.955–1.62)

BMI body mass index, *HR* hazard ratio

[a]Calculated by the rate of events in percentage (number events per number of participants) during follow-up

[b]Calculated by Cox proportional hazards regression analysis adjusted for age, sex, race, smoking, hypertension, hyperlipidemia, previous cardiovascular events, previous heart failure, proteinuria, depression, glycated hemoglobin, fasting blood glucose, glomerular filtration rate

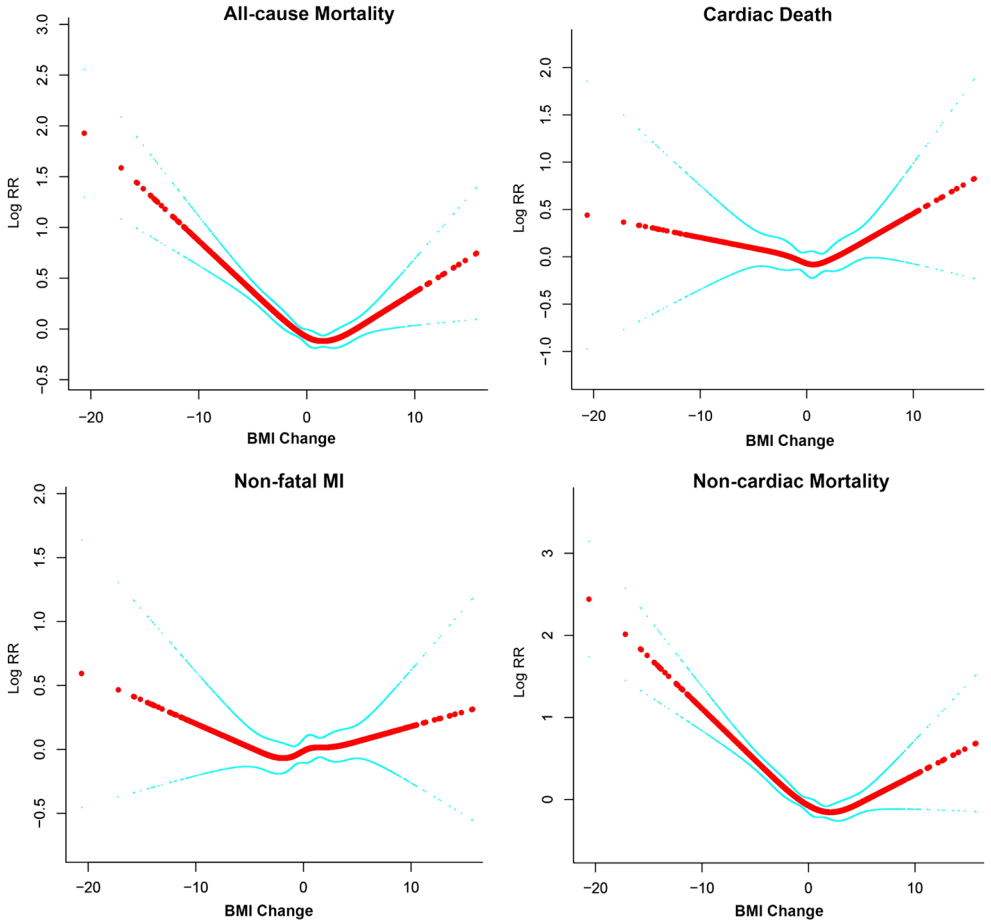

Fig. 3 Association between change in body mass index (BMI) and primary or secondary endpoints after multivariate adjustment. Red line denotes fitted curves and blue line represents 95% confidence intervals for the association between BMI and adverse events. All models were adjusted for cofounders in Fig. 2

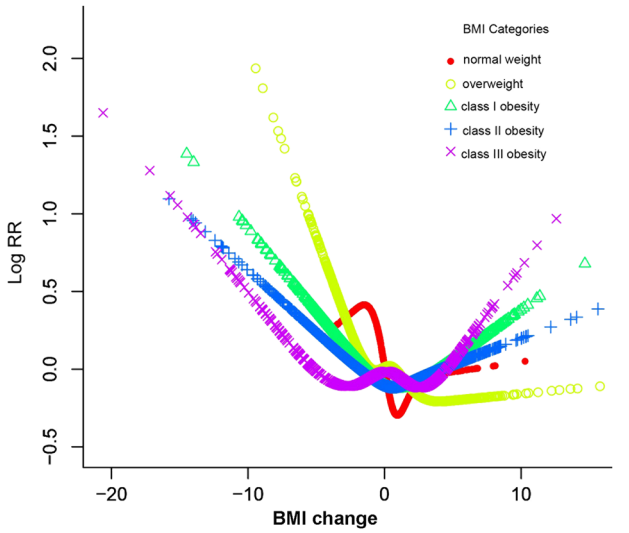

Fig. 4 Association between change in body mass index (BMI) and primary endpoint according to predefined BMI subgroups

Change in BMI as a continuous variable

Stable weight patients with lower risk of multivariate-adjusted rates across the entire group showed an asymmetric V-shaped pattern in terms of all-cause mortality and non-cardiac mortality, with the highest rates observed in the pronounced weight loss group (Fig. 3a, d). A flat V-shaped relationship was observed between BMI and cardiac death or non-fatal MI; patients with stable weight had the lowest rate of events, which then increased slowly as weight was either gained or lost (Fig. 3b, c).

When we categorized patients into five groups according to their baseline BMI, a V-shaped relationship between change in BMI and all-cause mortality was observed for all patients, except for overweight patients. As overweight patients gained weight, the risk of all-cause mortality remained unchanged (Fig. 4).

Discussion

Our study of T2DM patients at high risk of CVD found that patients whose weight remained stable across a relatively long follow-up period had the lowest risk of adverse events. Weight gain and weight loss were associated with increased risk of all-cause mortality and non-cardiac mortality. However, there were no statistically significant differences between weight change groups in terms of cardiac death and non-fatal MI. Changes in weight, regardless of gain or loss, were associated with slightly increased risk.

Our study demonstrated that most T2DM patients with high risk of CVD had stable weight in a nearly 10-year follow-up period. Obese patients were more likely to lose weight than normal weight patients, though the change was small. Our findings were consistent with those of previous studies [16]. Older patients tended to lose weight and younger patients tended to gain weight. The mechanism accounting for the age-associated loss in weight is age-related loss of muscle mass [17].

Our study's findings are consistent with previous findings in terms of the relationship between weight loss and all-cause mortality [11, 18–20]. Some studies, although relatively few in number, have found that patients with weight loss may also suffer from preexisting diseases that affect both weight change and mortality [21, 22]. This phenomenon remained present even after excluding subjects with preexisting diseases [11, 12, 23, 24]; therefore, another factor should be considered in analyzing the association of weight loss and all-cause mortality. Intentional weight loss through exercise may not be associated with increased mortality [25, 26], but most studies have focused mainly on unintentional weight loss. Increased all-cause mortality has been shown to be associated with weight loss in most studies and meta-analyses [27]. Our study found that weight loss mainly increased the risk of non-cardiac mortality, though the risk of cardiac death also increased slowly. Our results were similar with the Look Action for Health in Diabetes (Look AHEAD study), which found that weight loss did not reduce the incidence of CVD [28]. Our study also raised questions similar to those raised by the Look AHEAD study, which evaluated whether weight loss is essential to the management of T2DM. For the elderly, weight loss is accompanied by loss of muscle mass even in obese individuals, which may explain the relationship between weight loss and mortality.

Our study also found weight gain to be associated with increased risk of all-cause mortality and non-cardiac death. The increased all-cause mortality is mainly attributable to non-cardiac mortality. The rate of cardiac death only increased slowly with weight gain. Previous studies have shown weight gain to be associated with increased risk of CVD, and weight loss to be associated with reduced risk of CVD [29–31]. The main reason for this difference may involve the unique characteristics of the population studied (T2DM patients with mean 10-year disease duration and high risk of CVD). Weight gain in young adults may be accompanied by other cardiovascular risk factors such as hypertension, diabetes, or hyperlipidemia, which may lead to CVD. However, reports of associations between weight gain and mortality have been conflicting. Some studies found the risk of mortality to be higher in patients who gained weight [19, 32]; other studies did not [8, 11, 23]. Different patient characteristics between study cohorts, including age, sex, rate of weight change, and accompanying diseases [33], may account for this discrepancy.

Conclusions

Weight was stable in most T2DM patients with high risk of CVD. Weight loss and gain is associated with increased all-cause mortality and non-cardiac mortality. Pronounced weight loss and weight gain is associated with a slight increase in cardiac death and non-fatal MI incidence, which does not reach statistical significance.

Data availability

The Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

Acknowledgements All authors read, provided critical feedback, and approved the final manuscript.

Authors' contributions S.G. and Z.X. designed the study and provided methodological expertise. J.H., X.H. and J.P. drafted the manuscript. P.C., and X.P. drafted the tables and figures.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent for publication All the authors listed have approved the manuscript and agree to publish.

References

1. P. Ambery, V.E. Parker, M. Stumvoll et al. MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study. Lancet **391**(10140), 2607–2618 (2018)

2. IDF Diabetes Atlas. http://www.diabetesatlas.org/across-the-globe.html.
3. E.W. Gregg, N. Sattar, M.K. Ali, The changing face of diabetes complications. Lancet Diabetes Endocrinol. **4**(6), 537–547 (2016)
4. K.S.S. Rao, S. Kaptoge, A. Thompson et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N. Engl. J. Med. **364**(9), 829–841 (2011)
5. D. Mozaffarian, E.J. Benjamin, A.S. Go et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation **133**(4), e38–e360 (2016)
6. F.B. Ortega, C.J. Lavie, S.N. Blair, Obesity and cardiovascular disease. Circ. Res. **118**(11), 1752–1770 (2016)
7. E.E. Calle, M.J. Thun, J.M. Petrelli, C. Rodriguez, C.W. Heath, Body-mass index and mortality in a prospective cohort of U.S. adults. N. Engl. J. Med. **341**(15), 1097–1105 (1999)
8. S. Maru, Y.T. van der Schouw, C.H. Gimbrère, D.E. Grobbee, P. H. Peeters, Body mass index and short-term weight change in relation to mortality in Dutch women after age 50 y. Am. J. Clin. Nutr. **80**(1), 231–236 (2004)
9. X. Pi-Sunyer, G. Blackburn, F.L. Brancati et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care **30**(6), 1374–1383 (2007)
10. C. Sauvaget, K. Ramadas, G. Thomas, J. Vinoda, S. Thara, R. Sankaranarayanan, Body mass index, weight change and mortality risk in a prospective study in India. Int. J. Epidemiol. **37**(5), 990–1004 (2008)
11. W.B. Drøyvold, N.T.I. Lund, S. Lydersen et al. Weight change and mortality: the Nord-Trøndelag Health Study. J. Intern. Med. **257**(4), 338–345 (2005)
12. I.M. Lee, R.S. Paffenbarger, Change in body weight and longevity. JAMA **268**(15), 2045–2049 (1992)
13. H.C. Gerstein, M.C. Riddle, D.M. Kendall et al. Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am. J. Cardiol. **99**(12A), 34i–43i (2007)
14. H.C. Gerstein, M.E. Miller, R.P. Byington et al. Effects of intensive glucose lowering in type 2 diabetes. N. Engl. J. Med. **358**(24), 2545–2559 (2008)
15. S. Durrleman, R. Simon, Flexible regression models with cubic splines. Stat. Med. **8**(5), 551–561 (1989)
16. I. Kunz, U. Schorr, S. Klaus, A.M. Sharma, Resting metabolic rate and substrate use in obesity hypertension. Hypertension **36**(1), 26–32 (2000)
17. Y.Y. Fadl, H.M. Krumholz, M. Kosiborod et al. Predictors of weight change in overweight patients with myocardial infarction. Am. Heart J. **154**(4), 711–717 (2007)
18. L.F. Amador, S.S. Al, K.S. Markides, J.S. Goodwin, Weight change and mortality among older Mexican Americans. Aging Clin. Exp. Res. **18**(3), 196–204 (2006)
19. R. Andres, D.C. Muller, J.D. Sorkin, Long-term effects of change in body weight on all-cause mortality. A review. Ann. Intern. Med. **119**(7 Pt 2), 737–743 (1993)
20. D.K. Dey, E. Rothenberg, V. Sundh, I. Bosaeus, B. Steen, Body mass index, weight change and mortality in the elderly. A 15 y longitudinal population study of 70 y olds. Eur. J. Clin. Nutr. **55**(6), 482–492 (2001)
21. S.G. Wannamethee, A.G. Shaper, M. Walker, Weight change, body weight and mortality: the impact of smoking and ill health. Int. J. Epidemiol. **30**(4), 777–786 (2001)
22. C. Iribarren, D.S. Sharp, C.M. Burchfiel, H. Petrovitch, Association of weight loss and weight fluctuation with mortality among Japanese American men. N. Engl. J. Med. **333**(11), 686–692 (1995)
23. A.B. Newman, D. Yanez, T. Harris, A. Duxbury, P.L. Enright, L. P. Fried, Weight change in old age and its association with mortality. J. Am. Geriatr. Soc. **49**(10), 1309–1318 (2001)
24. E.R. Pamuk, D.F. Williamson, M.K. Serdula, J. Madans, T.E. Byers, Weight loss and subsequent death in a cohort of U.S. adults. Ann. Intern. Med. **119**(7 Pt 2), 744–748 (1993)
25. A.A. Meltzer, J.E. Everhart, Unintentional weight loss in the United States. Am. J. Epidemiol. **142**(10), 1039–1046 (1995)
26. D.F. Williamson, T.J. Thompson, M. Thun, D. Flanders, E. Pamuk, T. Byers, Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care **23**(10), 1499–1504 (2000)
27. F.W. Cheng, X. Gao, G.L. Jensen, Weight change and all-cause mortality in older adults: a meta-analysis. J. Nutr. Gerontol. Geriatr. **34**(4), 343–368 (2015)
28. J.P. Wilding, The importance of weight management in type 2 diabetes mellitus. Int. J. Clin. Pract. **68**(6), 682–691 (2014)
29. S. Choi, K. Kim, S.M. Kim et al. Association of obesity or weight change with coronary heart disease among young adults in South Korea. JAMA Intern. Med. **178**(8), 1060–1068 (2018)
30. R. Selmer, A. Tverdal, Body mass index and cardiovascular mortality at different levels of blood pressure: a prospective study of Norwegian men and women. J. Epidemiol. Community Health **49**(3), 265–270 (1995)
31. Y. Zheng, J.E. Manson, C. Yuan et al. Associations of weight gain from early to middle adulthood with major health outcomes later in life. JAMA **318**(3), 255–269 (2017)
32. A. Nanri, T. Mizoue, Y. Takahashi, M. Noda, M. Inoue, S. Tsugane, Weight change and all-cause, cancer and cardiovascular disease mortality in Japanese men and women: the Japan Public Health Center-Based Prospective Study. Int. J. Obes. (Lond.). **34**(2), 348–356 (2010)
33. Z. Xing, J. Pei, J. Huang, X. Peng, P. Chen, X. Hu, Relationship of obesity to adverse events among patients with mean 10-year history of type 2 diabetes mellitus: results of the ACCORD study. J. Am. Heart Assoc. **7**(22), e010512 (2018)